SYNTHESES OF NOVEL FLUORINE-CONTAINING HETEROCYCLIC COMPOUNDS VIA TRIFLUOROACETYLATED ALKENES AS KEY INTERMEDIATES

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NORIO OTA

July 2009

The Graduate School of Science and Technology

Kobe University

DOCTORAL DISSERTATION

SYNTHESES OF NOVEL FLUORINE-CONTAINING HETEROCYCLIC COMPOUNDS VIA TRIFLUOROACETYLATED ALKENES AS KEY INTERMEDIATES

（トリフルオロアセチル化アルケン類を鍵中間体とする新規含フッ素ヘテロ環化合物の合成）

NORIO OTA

July 2009

The Graduate School of Science and Technology

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PREFACE

The studies presented in this thesis were carried out under the direction of Associate Professor Etsuji Okada (Department of Chemical Science and Engineering) from 2003 to 2009 and Visiting Professor Tsuneaki Sakata (Department of Life Science) from 2006 to 2009 at the Graduate School of Science and Technology at Kobe University. This thesis is mainly concerned with syntheses of novel fluorine-containing heterocyclic compounds via trifluoroacetylated alkenes as key intermediates for the exploration of novel pharmaceutical compounds.

The author wishes to express his sincere gratitude to Associate Professor Etsuji Okada for his constant guidance, valuable comments and hearty encouragement during the course of this work. Sincere thanks are also due to Associate Professor Yasuhiro Kamitori for his expert guidance and valuable discussions. In addition, the author is also much obliged to Professor Tsuneaki Sakata, Dr. Dai Shibata (Mitsubishi Gas Chemical Company, Inc.), and his colleagues for their generous support and helpful discussions throughout this work. Gratitude is also expressed to Dr. Reiji Takeda (Executive Director of The Cell Science Research Foundation, Consultant at Shionogi & Co., Ltd.) for his continuous support. The author is also grateful to Shionogi & Co., Ltd. for giving the chance of this work. The author expresses sincere appreciation to Professor Yasukiyo Ueda, Professor Atsunori Mori, and Professor Akihiko Kondo for their appropriate advice in the course of making this thesis.

Finally, the author wishes to express his deep appreciation to his wife, Mrs. Masami Ota for her assistance and encouragement.

Norio Ota

July, 2009

CONTENTS

PAGE

GENERAL INTRODUCTION 1

PART I

Facile Synthetic Methods for Novel Fluorine-Containing Heterocyclic Compounds and Building Blocks 9

CHAPTER 1 A Convenient Synthesis of Fluorine-Containing Dihydrobenzo-[*b*][1,4]diazepinols and its Application to a Synthesis of Novel *N*-Sulfinylanilines 10

CHAPTER 2 A Convenient Synthetic Method for Fluorine-Containing 4-Alkoxydihydrobenzo[*b*][1,4]diazepinols and 3*H*-Benzo[*b*][1,4]diazepines by the Reaction of β-Trifluoroacetylketene Acetals with 1,2-Phenylenediamines 28

CHAPTER 3 One Step Introduction of 4,4-Bis(trifluoroacetyl)-1,3-butadiene System to Aromatic Rings Using Fluorine-Containing 3,4-Dihydro-2*H*-pyrans. A Facile Synthetic Method for 1,1,1,5,5,5-Hexafluoro-3-[(*E*)-3-arylallylidene]pentane-2,4-diones 39

CHAPTER 4 A Facile and Convenient Synthetic Method for 2-Bis(trifluoroacetyl)methylene- and 2-Trifluoroacetylmethylene-2,3-dihydro-3-methylthiazoles 48

PART II

Molecular Orbital Calculation Studies Related to the Syntheses of Novel Fluorine-Containing Benzo[*b*][1,4]diazepines and Dihydropyrans 62

CHAPTER 5 Reaction of β,β-Bis(trifluoroacetyl)vinyl Ethers and β-Trifluoro-acetylvinyl Ethers with 1,2-Phenylenediamines Accessing Fluorine-Containing Benzo[*b*][1,4]diazepine Derivatives – A Study about the Reaction Based on Molecular Orbital Calculations 63

CHAPTER 6 Reaction of β-Trifluoroacetylketene Acetals and β-Trifluoroacetylvinyl Ethers with 1,2-Phenylenediamines Accessing Fluorine-Containing Benzo[*b*][1,4]diazepine Derivatives – A Molecular Orbital Calculation Study 75

CHAPTER 7 Hetero Diels-Alder Reaction of β-Trifluoroacetylated Vinyl Ethers With Vinyl Ethers to Access Fluorine-Containing Dihydropyran Derivatives – A Molecular Orbital Calculation Study 87

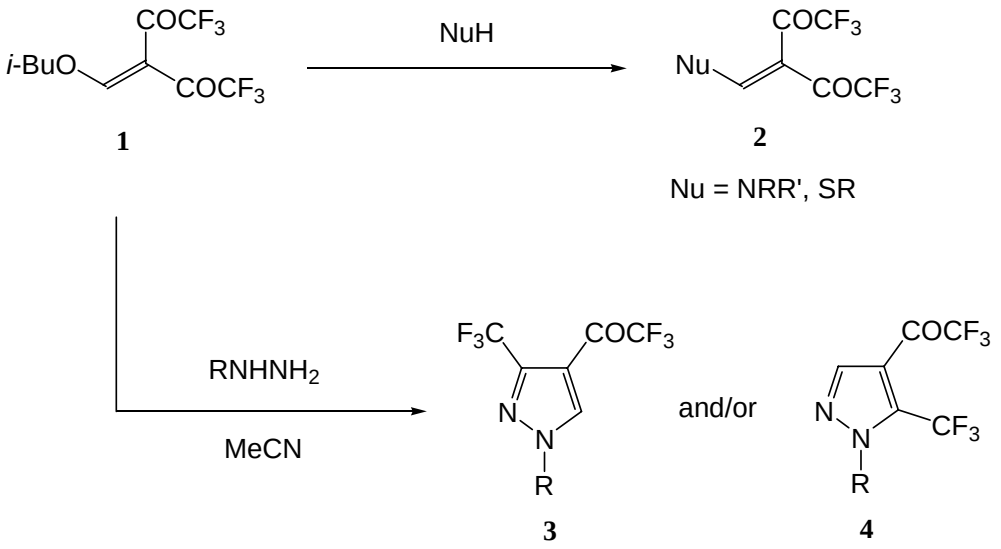
GENERAL CONCLUSION 100

PUBLICATION LIST 104

ORAL AND POSTER PRESENTATIONS LIST 106

GENERAL INTRODUCTION

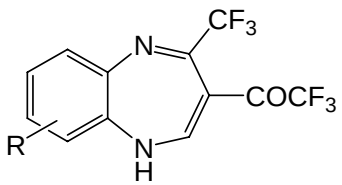
Previously, in the course of our investigations on the nucleophilic substitutions at olefinic carbon atoms,[1-6] it was found that β,β-bis(trifluoroacetyl)vinyl *iso*-butyl ether (**1**)[7] readily reacted with various amines and thiols under very mild conditions to give the corresponding *O*-*N* and *O*-*S* exchanged products **2** in high yields.[6] As an extension of this work, we used this type of nucleophilic exchange reaction and subsequent cyclodehydration with bifunctional *N*-nucleophiles such as hydrazines to prepare 3- and 5-trifluoromethyl-4-trifluoroacetylpyrazoles (**3** and **4**) which are hardly obtainable by other routes.[8]



1 **2** **3** **4**

Nu = NRR', SR

As similar example of the reaction with bifunctional *N*-nucleophiles, Reddy *et al*. reported that 1*H*-benzo[*b*][1,4]diazepines (**5**) were obtained by the microwave reaction of β,β-bis(trifluoroacetyl)vinyl ether (**1**) with 1,2-phenylenediamines.[9,10]



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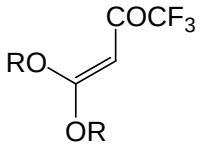
As is commonly known, benzo[*b*][1,4]diazepines are important noteworthy heterocyclic systems due to their application in the creation of useful bioactive substances.[11]

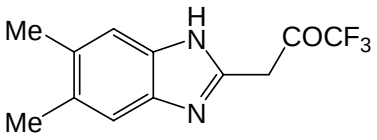
Additionally, β-trifluoroacetylketene acetals (**6**)[12,13] were also found to be quite convenient building blocks applicable to the syntheses of novel fluorine-containing heterocyclic compounds by reaction with bifunctional nucleophiles. For instance, fluorine-containing isoxazolines, 1*H*-pyrazolines, and imidazolines were easily obtained by reaction with hydroxylamine, hydrazines, and 1,2-ethylenediamine, respectively.[14,15] Moreover, it was found that β-trifluoroacetylketene acetal (**6b**) reacted with 4,5-dimethyl-1,2-phenylenediamine under microwave irradiation to produce the corresponding benzimidazoles (**7**) without any formation of benzodiazepines.[10]



6

a: R = Me

b: R = Et



7

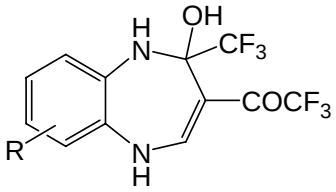
Meanwhile, it is well-known that various kinds of fluorine-containing heterocyclic compounds are assembled into new chemical entities given that these compounds are now widely recognized as important organic materials that demonstrate interesting bioactive functions in modern drug discovery and development.[16-19] Actually, many clinical agents containing fluorine-containing heterocyclic compounds have been widely recommended as first-line treatment up to now.[20] For instance, the first clinically useful quinolone was nalidixic acid, a non-fluorinated quinolone, which was of limited therapeutic utility mainly due to its relatively weak potency especially against gram-positive pathogens, and low serum drug levels as a result of rapid renal clearance. As a result of many studies on structure-activity relationships in this class of compounds, the

most important change towards improvement of antibacterial and pharmacokinetic properties was achieved by addition of a fluorine atom to position 6 of the ring.[21-25] Consequently, various second and third generation agents, so-called new quinolones, have become available for clinical use during the past three decades.[26-30] In the field of other antibiotics, some fluorinated third generation cephalosporins are quite popular as broad spectrum drugs that have further increased efficacy against gram-negative organisms.[31-33] Moreover, in many cases of chronic disease caused by hyperlipidemia, the famous statins are generally administered as typical treatment. The statins act by binding to the active site of HMG-CoA reductase and sterically preventing the substrate from binding. It was found that the type II statins containing a fluorophenyl group as one of the essential moieties are more effective than type I statins. This improvement in type II statins was explained by the additional binding interactions via the fluorophenyl group based on X-ray crystallography study of the complexes comprised of statins and HMG-CoA reductase.[34] Accordingly, the development of new methodologies for the syntheses of many kinds of fluorine-containing heterocyclic compounds is very fascinating research area for synthetic organic chemists.

In these situations, the author has started to research a novel methodology for the synthesis of fluorine-containing heterocyclic compounds using trifluoroacetylated alkenes **1** and **6** as suitable key intermediates. New class of fluorine-containing heterocyclic systems are necessary for the exploration of novel pharmacophore, and development of effective synthetic methods for these compounds is nowadays much desirable. Additionally, novel synthetic methods of versatile building blocks for the construction of CF_3-containing heterocyclic compounds, such trifluoroacetylated alkene analogues as **1** and **6**, have been also investigated.

The present study in PART I concerns the facile synthetic methods for novel fluorine-containing heterocyclic compounds and building blocks.

Chapter 1 describes convenient and selective syntheses of novel 1*H*-benzo[*b*][1,4]diazepinols (**8**) by the reaction of β,β-bis(trifluoroacetyl)vinyl ether (**1**) with various 1,2-phenylenediamines under mild conditions without microwave irradiation. These results show sharp contrast with those reported by Reddy *et al*.[9,10] In addition, it was found that **8** reacted with thionyl chloride under mild condition to afford the unexpected *N*-sulfinylanilines (**9**). Interestingly, it was also found that some of these 1*H*-benzo[*b*][1,4]diazepinols (**8**) and *N*-sulfinylanilines (**9**) exert remarkable antineoplastic efficacy.



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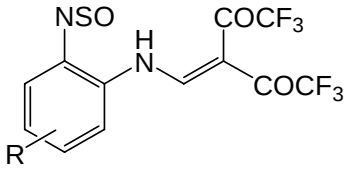
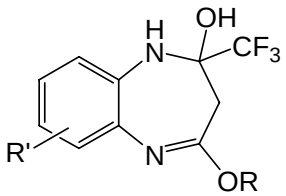


9

Our continuing interest in the synthesis of trifluoromethyl-containing benzodiazepines described in chapter 1, a new potential pharmacophore of antineoplastic efficacy, prompted us to synthesize the C-4 substituted analogues of **8**. The annulation reaction of β-trifluoroacetylketene acetals (**6a**, **6b**) with various 1,2-phenylenediamines were attempted for achievement of this purpose. Chapter 2 shows the facile syntheses of the desired fluorine-containing diazepinols (**10a**, **10b**) having an alkoxy group at the C-4 position.

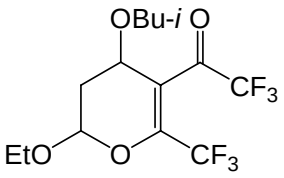


10

a: R = Me

b: R = Et

Chapter 3 demonstrates a facile and convenient 4,4-bis(trifluoroacetyl)-1,3-butadienylation method for various aromatic compounds by utilizing a fluorine-containing dihydropyran derivative (**11**),[35] which was accessible by the hetero Diels-Alder reaction of our key intermediate (**1**). This type of 4,4-bis(trifluoroacetyl)-1,3-butadienylation are expected to become the available tools for the construction of novel *CF_3*-containing heterocyclic compounds.



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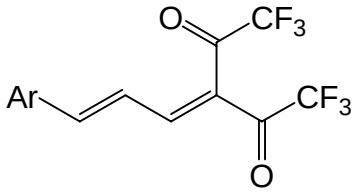
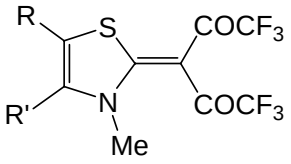
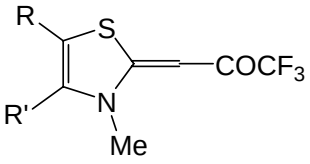


12

Chapter 4 is concerned with an efficient synthetic method for novel cyclic β-trifluoroacetylated ketene *S*,*N*-acetals, 2-bis(trifluoroacetyl)methylene- and 2-trifluoroacetylmethylene-2,3-dihydro-3-methylthiazoles (**13a**, **13b**). Moreover, the highly polarized structure of diacylated compounds (**13a**) is also described.



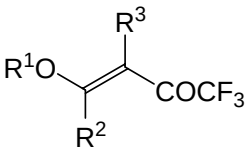
13a



13b

The present research in PART II concerns the molecular orbital calculation studies related to the syntheses of novel fluorine-containing benzo[*b*][1,4]diazepines and dihydropyrans based on the results of synthetic studies in PART I.

Chapters 5 and 6 demonstrate the molecular orbital calculation studies on the difference of products resulting from the reactions of β,β-bis(trifluoroacetyl)vinyl *iso*-butyl ether (**1**), β-trifluoroacetylketene



1, **6a**, **14**, **14'**

	R^1	R^2	R^3
1	*i*-Bu	H	$COCF_3$
6a	Me	MeO	H
14	*i*-Bu	H	H
14'	Me	Ph	H

dimethyl acetal (**6a**), β-trifluoroacetylvinyl *iso*-butyl ether (**14**), and β-trifluoroacetyl-α-phenylvinyl methyl ether (**14'**) with 1,2-phenylenediamine.

Chapter 7 is concerned with the molecular orbital calculation study related to the synthesis of fluorine-containing dihydropyran (**11**), which is the essential compound of the novel method for C_8-unit introduction to various aromatic compounds as described in chapter 3, by hetero Diels-Alder reaction of **1** with various vinyl ethers.

REFERENCES

1. Y. Kamitori, M. Hojo, R. Masuda, T. Fujitani, T. Kobuchi, and T. Nishigaki, *Synthesis*, 1986, 340.
2. M. Hojo, R. Masuda, E. Okada, S. Sakaguchi, H. Narumiya, and K. Moriomoto, *Tetrahedron Lett.*, 1989, **30**, 6173.
3. M. Hojo, R. Masuda, E. Okada, H. Yamamoto, K. Moriomoto, and K. Okada, *Synthesis*, 1990, 195.
4. M. Hojo, R. Masuda, and E. Okada, *Chem. Lett.*, 1990, 2095.
5. E. Okada, R. Masuda, M. Hojo, and R. Inoue, *Synthesis*, 1992, 533.
6. M. Hojo, R. Masuda, E. Okada, and Y. Mochizuki, *Synthesis*, 1992, 455.
7. M. Hojo, R. Masuda, and E. Okada, *Synthesis*, 1990, 347.
8. E. Okada, R. Masuda, and M. Hojo, *Heterocycles*, 1992, **34**, 791.
9. A. C. S. Reddy, P. S. Rao, and R. V. Venkataratnam, *Tetrahedron Lett.*, 1996, **37**, 2845.
10. A. C. S. Reddy, P. S. Rao, and R. V. Venkataratnam, *Tetrahedron*, 1997, **53**, 5847.
11. D. Lloyd and H. MacNab, *Adv. Heterocycl. Chem.*, 1998, **71**, 1.
12. M. Hojo, R. Masuda, and E. Okada, *Synthesis*, 1986, 1013.
13. M. Hojo, R. Masuda, and Y. Kamitori, *Tetrahedron Lett.*, 1976, 1009.
14. M. A. P. Martins, C. M. P. Pereira, N. E. K. Zimmermann, W. Cunico, S. Moura, P. Beck, N. Zanatta, and H. G. Bonacorso, *J. Fluorine Chem.*, 2003, **123**, 261.
15. A. Narsaiah, A. Sivaprasad, and R. V. Venkataratnam, *J. Fluorine Chem.*, 1994, **66**, 47.
16. R. Filler and Y. Kobayashi, 'Biomedicinal Aspects of Fluorine Chemistry,' Kodansha & Elsevier Biomedical, Tokyo, 1982.
17. R. Filler, 'Organofluorine Chemicals and Their Industrial Applications,' Ellis Horwood, London, 1979.

18. J. T. Welch, *Tetrahedron*, 1987, **43**, 3123.
19. R. Filler, Y. Kobayashi, and L. M. Yagupolskii, 'Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications,' Elsevier, Amsterdam, 1993.
20. T. Taguchi, 'Fussokei Seiri Kassei Busshitsu no Gousei to Oyo,' CMC Publishing, Tokyo, 2005.
21. R. Stahlmann, *Drugs of Today*, 1984, **24**, 529.
22. C. W. T. Daniel and F. B. Prabhavathi, *Antimicrob. Agents Chemother.*, 1989, **33**, 131.
23. C. Siporin, *Annu. Res. Microbiol.*, 1989, **43**, 601.
24. A. M. Emmerson and A. M. Jones, *J. Antimicrob. Chemother.*, 2003, **51**, 13.
25. P. M. Hawkey, *J. Antimicrob. Chemother.*, 2003, **51**, 29.
26. R. F. Grossman, *J. Antimicrob. Chemother.*, 1997, **40**, 59.
27. A. J. Schaeffer, *Am. J. Med.*, 2002, **113**(1A), 45S.
28. C. Carson and K. G. Kurt, *Drugs*, 2004, **64**, 1359.
29. H. H. Liu, *Curr. Ther. Res.*, 2004, **65**, 225.
30. T. D. Gootz and P. R. McGuirk, *Expert Opin. Invest. Drugs*, 1994, 93.
31. K. Shimizu, *Jpn. J. Antibiot.*, 1988, **41**, 1809.
32. H. Mikamo, K. Kawazoe, K. Izumi, S. Hachiya, M. Satoh, K. Munakata, and T. Tamaya, *Int. J. Antimicrob. Agents*, 1997, **8**, 7.
33. N. Watanabe, F. Ohba, M. Moriyama, J. Kimura, T. Toyosawa, Y. Sugihara, J. Kai, T. Suzuki, and Y. Yamanishi, *Jpn. Pharmacol. Ther.*, 1997, **25**, 1219.
34. E. Istvan, *Atherosclerosis Suppl.*, 2003, **4**, 3.
35. M. Hojo, R. Masuda, and E. Okada, *Synthesis*, 1990, 347.

PART I

Facile Synthetic Methods for Novel Fluorine-Containing Heterocyclic Compounds and Building Blocks

CHAPTER 1

A Convenient Synthesis of Fluorine-Containing Dihydrobenzo-[*b*][1,4]diazepinols and its Application to a Synthesis of Novel *N*-Sulfinylanilines

SUMMARY

The reactions of 1,1,1,5,5,5-hexafluoro-3-(isobutoxymethylene)-pentane-2,4-dione (**1**) with various benzene-1,2-diamines gave 2,5-dihydro-3-trifluoroacetyl-2-trifluoromethyl-1*H*-benzo[*b*][1,4]diazepines (**5**) in moderate to high yields under very mild conditions. Also, 2,5-dihydro-3-perhaloalkanoyl-2-perhaloalkyl-1*H*-benzo[*b*][1,4]diazepines (**7**) were synthesized successfully by quite similar manner. Reactions of thus obtained dihydrobenzo[*b*][1,4]-diazepinols (**5**) with thionyl chloride gave unexpected novel fluorine-containing *N*-sulfinylanilines (**9**).

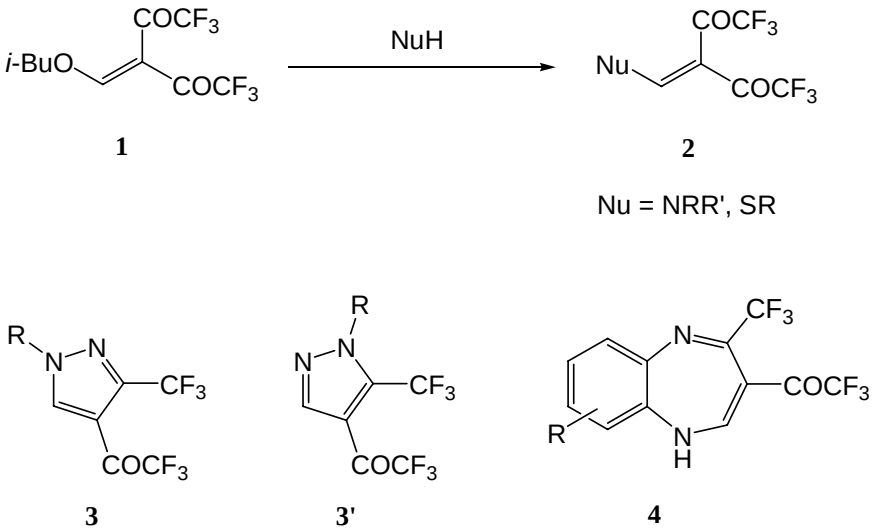
INTRODUCTION

Benzo[*b*][1,4]diazepines are attractive and important heterocycles because of being applicable to the creation of useful biologically active substances. In medicinal scientific fields, certain benzo[*b*][1,4]diazepines are useful for the antipsychotic therapy. For example, 2-amino-4-phenyl and 2-(*p*-fluorophenyl)-4-phenyl-8-chloro derivatives are known as tranquilizers[1] and antidepressants[2] respectively. It has been also reported that some 2-amino-4-methylthiobenzo[*b*][1,4]diazepines act as depressants of the central nervous system and anti-convulsants, whereas 2,4-diamino derivatives showed effects as stimulants and convulsants.[3] Moreover, some benzo[*b*][1,4]diazepines, in particular 2-thio derivatives, show antibacterial activity,[4-6] while 2,4-dimethyl derivatives are known as anti-sarcoma.[7] In agricultural scientific

fields, new herbicidal agents bearing a benzo[*b*][1,4]diazepine unit have been developed.[8]

On the other hand, much attention in recent years has been paid to the development of new methodologies for the syntheses of many kinds of fluorine-containing heterocycles, since these compounds are now widely recognized as important organic materials showing interesting biological activities useful in medicinal and agricultural fields.[9-12]

In the course of our investigations on the nucleophilic substitutions at olefinic carbon atoms,[13-18] it was found that 1,1,1,5,5,5-hexafluoro-3-(isobutoxymethylene)pentane-2,4-dione **1**[19] readily reacted with various amines and thiols under very mild conditions to give the corresponding *O*-*N* and *O*-*S* exchanged products **2** in high yields.[18] These findings prompted us to investigate about the application of above nucleophilic substitutions with the use of bifunctional nucleophiles to the syntheses of a variety of novel fluorine-containing heterocycles which have high potential leading to pharmacophores. For instance, using the reaction of **1** with hydrazines, we succeeded in the synthesis of 3- and 5-trifluoromethyl-4-trifluoroacetylpyrazoles (**3** and **3'**) which are hardly obtainable by other methods.[20] As for the synthesis of fluorine-containing benzo[*b*][1,4]diazepines, Reddy *et al*. reported the reaction of **1** with benzene-1,2-diamines



Scheme 1

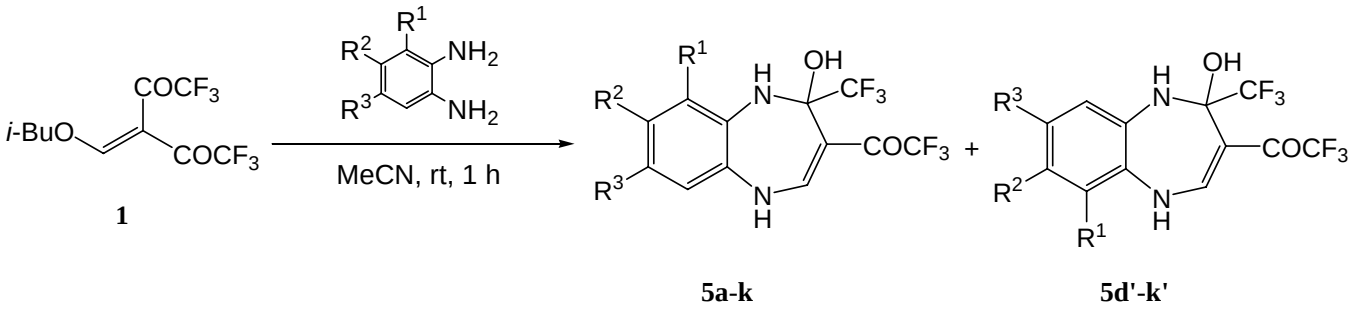
under microwave irradiation to give 1*H*-benzo[*b*][1,4]diazepines (**4**) (Scheme 1).[21,22]

In contrast to their results, we found the reaction of β,β-bis(perhaloalkanoyl)vinyl ethers

including **1** with benzene-1,2-diamines without microwave irradiation gave novel 2,5-dihydro-3-perhaloalkanoyl-2-perhaloalkyl-1*H*-benzo[*b*][1,4]diazepinols (**5** and **7**) selectively under very mild conditions. We here report an efficient and convenient synthetic method for these dihydrobenzo[*b*][1,4]diazepinols which are expected to have remarkable anti-tumor activities. Moreover, we describe in this chapter a facile synthesis of novel fluorine-containing *N*-sulfinylanilines (**9**), which were obtained unexpectedly from dihydrobenzo[*b*][1,4]diazepinols (**5**) by treatment with thionyl chloride. These *N*-sulfinylanilines (**9**) are also expected to have noticeable anti-tumor activities.

RESULTS AND DISCUSSION

We examined the reaction of β,β-bistrifluoroacetylvinyl ether (**1**) with various benzene-1,2-diamines (Scheme 2 and Table 1). The reaction of **1** with slightly excess amounts of benzene-1,2-diamine in acetonitrile readily occurred at ambient temperature to give dihydrobenzo[*b*][1,4]-



Scheme 2

diazepinol (**5a**) in 85% yield (entry 1). Under the same conditions, the reaction of **1** with 4,5-dimethylbenzene-1,2-diamine and 4,5-dichlorobenzene-1,2-diamine afforded the corresponding diazepinols **5b** and **5c** in high yields (entry 2 and 3). In the ^{13}C NMR spectra of **5b**, the ring carbon (C-2') substituted by a CF_3 group appeared at 86.4 ppm as a quartet signal due to C-F geminal coupling ($^2J_{CF}$ = 28.2 Hz) and a signal of the carbonyl carbon was observed at 178.7 ppm as quartet ($^2J_{CF}$ = 34.3 Hz).

The annulation reaction of **1** with mono-substituted benzene-1,2-diamine gave a mixture of two regioisomers of the corresponding diazepinol. Thus a mixture of two regioisomers (**5d**, **d'**) was obtained in 69% yield when **1** was reacted with 3-methylbenzene-1,2-diamine (entry 4). Quite similarly, the reactions of **1** with other benzene-1,2-diamines bearing various substituents on benzene ring proceeded successfully.

Table 1 Synthesis of 2,5-dihydro-3-trifluoroacetyl-2-trifluoromethyl-1*H*-benzo[*b*][1,4]-diazepinols **5a**-**k'** form **1** and benzene-1,2-diamines.[a]

Entry	R^1	R^2	R^3	Product	Yield (%)[b]
1	H	H	H	**5a**	85
2	H	Me	Me	**5b**	87
3	H	Cl	Cl	**5c**	82
4	Me	H	H	**5d**, **5d'**[c]	69[d]
5	H	Cl	H	**5e**, **5e'**[e]	71[d]
6	H	Me	H	**5f**, **5f'**[e]	80[d]
7	H	NO_2	H	**5g**, **5g'**[c]	76[d]
8	H	COPh	H	**5h**, **5h'**[e]	78[d]
9	H	CO_2H	H	**5i**, **5i'**[e]	74[d]
10	H	CO_2Me	H	**5j**, **5j'**[e]	82[d]
11	H	CO_2Bu-*n*	H	**5k**, **5k'**[e]	89[d]

[a] Benzene-1,2-diamines (1.1 times molar amounts) were used.

[b] Isolated yield.

[c] Ratio of regioisomers calculated by ^1H NMR spectra were 3.3/1 (**5d**/**5d'** or **5d'**/**5d**) and 2.5/1 (**5g**/**5g'** or **5g'**/**5g**) respectively.

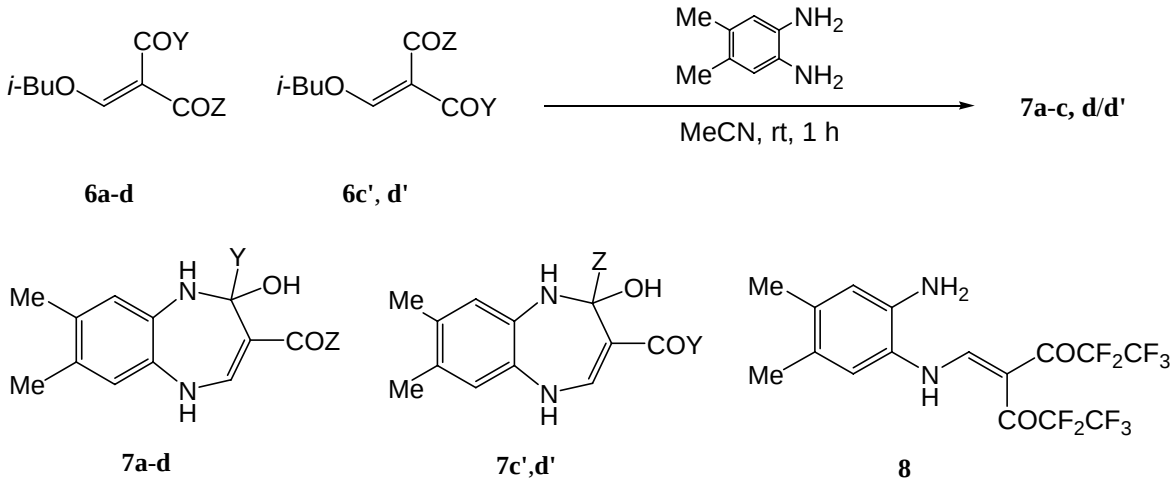
[d] Combined yield of two regioisomers.

[e] Ratio of regioisomers could not be determined.

The reaction of **1** with 4-chlorobenzene-1,2-diamine, 4-methylbenzene-1,2-diamine, 4-nitrobenzene-1,2-diamine, 3,4-diaminophenyl(phenyl)methanone, 3,4-diaminobenzoic acid,

methyl 3,4-diaminobenzoate and *n*-butyl 3,4-diaminobenzoate gave mixtures of the corresponding 7-substituted and 8-substituted dihydrobenzo[*b*][1,4]diazepinols (**5e-k'**) in 71-89% yields (entry 5-11). The results of our approaches on the reactions of **1** with benzene-1,2-diamines show sharp contrast with those reported by Reddy *et al*.[21,22] In all cases in Table 1, dihydrobenzo[*b*][1,4]diazepinols (**5a-k'**) were obtained selectively under very mild conditions in the absence of microwave irradiation without any formation of the corresponding 1*H*-benzo[*b*][1,4]diazepines (**4**).

Our method was applicable to the synthesis of fluorine-containing dihydrobenzo[*b*][1,4]diazepinols from several β,β-bisperhaloalkanoylvinyl ethers (**6a-d'**). As shown in Scheme 3 and Table 2, we attempted the reactions of **6a-d'** with 4,5-dimethylbenzene-1,2-diamine employing the same reaction condition for the synthesis of diazepinols **5a-k'** from **1**.



Scheme 3

The annulation reaction of β,β-bis(chlorodifluoroacetyl)vinyl ether (**6a**) with 4,5-dimethylbenzene-1,2-diamine easily proceeded at room temperature to give the corresponding diazepinol **7a** in 79% yield (entry 1). In contrast to this, the reaction of β,β-bis(pentafluoropropanoyl)vinyl ether (**6b**) with 4,5-dimethylbenzene-1,2-diamine afforded enamine **8** which is thought to be a precursor of **7b** together with equimolar amounts of the corresponding diazepinol **7b** (entry 2). Unfortunately, the ratio of **7b** and **8** almost unchanged by prolongation of reaction time, and **7b** could not be isolated from the mixture in spite of any

our effort. The formation of diazepinol **7b** was confirmed by ^{13}C NMR measurement of a mixture of **7b** and **8**. The ring carbon (C-2') binding a CF_2CF_3 group of **7b** appeared at 87.6 ppm as a triplet signal ($^2J_{CF}$ = 24.3 Hz). This chemical shift of C-2' is compatible with that (86.4 ppm) of diazepinol **5b** described above. The structures of **7c**, **7d** and **7d'** were also confirmed by ^{13}C NMR spectra. In the spectra of **7c**, the ring carbon (C-2') binding a CF_3 group appeared at 85.7 ppm as a quartet signal ($^2J_{CF}$ = 29.8 Hz), while the carbonyl carbon gave a triplet signal ($^2J_{CF}$ = 23.7 Hz) at 180.7 ppm. In the spectra of **7d**, the ring carbon (C-2') appeared at 86.7 ppm as a quartet signal ($^2J_{CF}$ = 29.8 Hz), while the carbonyl carbon was observed at 182.4 ppm as a singlet signal. Although **7d'** could not be isolated, in the spectra of a mixture of **7d** and **7d'**, the ring carbon (C-2') of **7d'** appeared at 100.3 ppm as a singlet signal, and the carbonyl carbon of **7d'** gave a quartet signal ($^2J_{CF}$ = 32.0 Hz) at 179.0 ppm.

Table 2 Synthesis of 2,5-dihydro-7,8-dimethyl-1*H*-benzo[*b*][1,4]diazepinols **7a-d'** from **6a-d'** and 4,5-dimethylbenzene-1,2-diamines.[a]

Entry	Substrate	Y	Z	Product	Yield (%)
1	**6a**	CF_2Cl	CF_2Cl	**7a**	79[b]
2	**6b**	CF_2CF_3	CF_2CF_3	**7b**[c]	46[d]
3	**6c**, **6c'**[e]	CF_3	CF_2CF_3	**7c**	73[b]
4	**6d**, **6d'**[e]	CF_3	CCl_3	**7d**, **7d'**	78[f]

[a] 4,5-Dimethylbenzene-1,2-diamines (1.1 times molar amounts) were used.

[b] Isolated yield.

[c] **7b** was obtained as a mixture with enamine **8** (**7b**/**8**= 1/1).

[d] The yield of **7b** was calculated from signal intensity in ^1H NMR spectra.

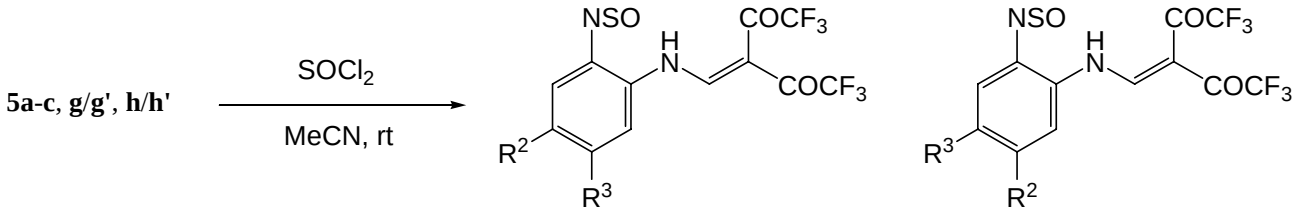
[e] A mixture of **6c** and **6c'** (**6c**/**6c'=** 1/4 or 4/1) or **6d** and **6d'** (**6d**/**6d'=** 1/1) was used as a substrate.

[f] Combined yield of two regioisomers.

Our attempts to dehydrate dihydrobenzo[*b*][1,4]diazepinol (**5a**) to the corresponding 1*H*-benzo[*b*][1,4]diazepine (**4**: R= H) by acid catalysis resulted in failure to give a complex mixture.

So, we tried dehydration of **5a** with the use of thionyl chloride.

As shown in Scheme 4 and Table 3, the reaction of **5a** with equimolar amounts of thionyl chloride in acetonitrile completed within 5 min at ambient temperature to afford unexpected *N*-sulfinylaniline **9a** in 86% yield (entry 1), and neither expected 1*H*-benzo[*b*][1,4]diazepine (**4**: R= H) nor its precursor, 2-chloro-2-trifluoromethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]diazepine, was obtained.



9a-c, **g**, **h** **9g'**, **h'**

Scheme 4

Table 3 Synthesis of *N*-sulfinylanilines **9a-c**, **g**/**g'** and **h**/**h'** from **5a-c**, **g**/**g'** and **h**/**h'**.

Entry	Substrate	R^2	R^3	$SOCl_2$ (mol equiv)	Time (min)	Product	Yield (%)[a]
1	**5a**	H	H	1	5	**9a**	86
2	**5b**	Me	Me	1	5	**9b**	100
3	**5c**	Cl	Cl	1	5	**9c**	79
4	**5g**, **5g'**[b]	NO_2	H	1	30	**9g**, **9g'**[c]	98[d]
5	**5h**, **5h'**[b,c]	COPh	H	2	30	**9h**, **9h'**[c]	94[d]

[a] Isolated yield.

[b] A mixture of **5g** and **5g'** (**5g**/**5g'**= 1/2.5 or 2.5/1) or **5h** and **5h'** was used as a substrate.

[c] Ratio of regioisomers could not be determined.

[d] Combined yield of two regioisomers.

Similarly 7,8-dimethyl- and 7,8-dichlorodihydrobenzo[*b*][1,4]diazepinols (**5b**, **c**) treated with thionyl choloride to give the corresponding *N*-sulfinylanilines (**9b**, **c**) in high yields (entry 2 and

3). In the cases of the reactions using a mixture of 7- and 8-nitrodihydrobenzo[*b*][1,4]diazepinol (**5g**, **g'**) and a mixture of 7- and 8-benzoyldihydrobenzo[*b*][1,4]diazepinol (**5h**, **h'**), prolonged reaction time and, in the latter case, use of 2 times molar amounts of thionyl chloride were necessary to obtain the corresponding *N*-sulfinylanilines (**9g**, **g'** and **9h**, **h'**) in high yields (entry 4 and 5).

In conclusion, we present here an efficient and convenient synthetic method accessing novel fluorine-containing dihydrobenzo[*b*][1,4]diazepinols which are not easily obtainable by other methods. Moreover, we can provide a facile and convenient method to synthesize novel *N*-sulfinylanilines via fluorine-containing dihydrobenzo[*b*][1,4]diazepinols.

In addition, we have found that dihydrobenzo[*b*][1,4]diazepinol (**5b**) and *N*-sulfinylaniline (**9b**) exert fine anti-tumor potency on carcinomas of lung, colon and ovary.[23] On the basis of our results, further biological evaluation of these novel dihydrobenzo[*b*][1,4]diazepinols (**5** and **7**) and *N*-sulfinylanilines (**9**) is now under way to fulfill our expectations for discovery of a new pharmacophore with antineoplastic efficacy.

EXPERIMENTAL

Mps were determined on an electrothermal digital melting point apparatus and are uncorrected. The ^{13}C NMR spectra were recorded on a VARIAN Unity INOVA 400 spectrometer using TMS as an internal standard. ^{1}H NMR spectra were obtained with a JEOL PMX 60SI spectrometer. IR spectra were taken with a PerkinElmer Spectrum ONE FT-IR spectrometer. Microanalyses were taken with a YANACO CHN-Corder MT-5 analyzer.

General procedure for the synthesis of 2,5-dihydro-3-trifluoroacetyl-2-trifluoromethyl-1*H*-benzo[*b*][1,4]diazepinols (5a-k') from 1,1,1,5,5,5-hexafluoro-3-(isobutoxymethylene)-pentane-2,4-dione (1).

To a solution of **1**[19] (293 mg, 1.0 mmol) dissolved in MeCN (4 mL) was added benzene-1,2-diamines (1.1 mmol) and the mixture was stirred for 1 h at ambient temperature. After evaporation of the solvent, purification of a residue by silica gel column chromatography using *n*-hexane-EtOAc (10:1) afforded **5a-k'**. In the cases of **5d**, **5d'**, and **5f-k'**, small amount of single isomer could be isolated, while the other isomer could not be separated from the mixture of two isomers by silica gel column chromatography. Neither **5e** nor **5e'** could be isolated from the mixture of two isomers by silica gel column chromatography.

2,2,2-Trifluoro-1-(2-hydroxy-2-trifluoromethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]diazepin-3-yl)-ethanone (5a): mp 86-87 °C (*n*-hexane-EtOAc); ^{1}H NMR ($CDCl_3$-CD_3CN) δ 9.60-9.05 (br, 1H, NH), 8.55 (br s, 1H, OH), 7.92 (d, J = 10.0 Hz, 1H, H-4'), 7.37-7.02 (m, 4H, H_{arom}), 4.98 (br s, 1H, NH); IR (KBr): 1551 (C=O) cm^{-1}. Anal. Calcd for $C_{12}H_8F_6N_2O_2$: C, 44.18; H, 2.47; N, 8.59. Found: C, 44.08; H, 2.63; N, 8.60.

2,2,2-Trifluoro-1-(2-hydroxy-7,8-dimethyl-2-trifluoromethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]-diazepin-3-yl)ethanone (5b): mp 126-127 °C (*n*-hexane-EtOAc); ^{13}C NMR (CD_3COCD_3) δ 18.8, 19.3 (CH_3), 86.4 ($^{2}J_{CF}$ = 28.2 Hz, C-2'), 102.9 (C-3'), 118.7 ($^{1}J_{CF}$ = 290.7 Hz, CO**C**F_3), 125.8 ($^{1}J_{CF}$ = 294.5 Hz, 2'-CF_3), 122.6, 123.3, 127.0, 131.3, 132.9, 136.7 (C_{arom}), 149.1 (C-4'), 178.7 ($^{2}J_{CF}$ = 34.3 Hz, **C**OCF_3); ^{1}H NMR ($CDCl_3$-CD_3CN) δ 9.32-8.73 (br, 1H, NH), 8.55 (br s, 1H,

OH), 7.82 (d, *J* = 10.0 Hz, 1H, H-4'), 6.78 (s, 2H, H_{arom}), 4.65-4.37 (br, 1H, NH), 2.22 (s, 6H, CH_3); IR (KBr): 1583 (C=O) cm^{-1}. Anal. Calcd for $C_{14}H_{12}F_6N_2O_2$: C, 47.47; H, 3.41; N, 7.91. Found: C, 47.24; H, 3.14; N, 7.90.

1-(7,8-Dichloro-2-hydroxy-2-trifluoromethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]diazepin-3-yl)-2,2,2-trifluoroethanone (5c): mp 163-164 °C (*n*-hexane-EtOAc); ^1H NMR ($CDCl_3$-CD_3CN) δ 9.65-9.05 (br, 1H, NH), 8.35 (br s, 1H, OH), 7.83 (d, *J* = 9.0 Hz, 1H, H-4'), 7.22 (s, 2H, H_{arom}), 5.18 (br s, 1H, NH); IR (KBr): 1544 (C=O) cm^{-1}. Anal. Calcd for $C_{12}H_6Cl_2F_6N_2O_2$: C, 36.48; H, 1.53; N, 7.09. Found: C, 36.18; H, 1.79; N, 7.13.

2,2,2-Trifluoro-1-(2-hydroxy-6-methyl-2-trifluoromethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]diazepin-3-yl)ethanone (5d) or 2,2,2-trifluoro-1-(2-hydroxy-9-methyl-2-trifluoromethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]diazepin-3-yl)ethanone (5d'): mp 131-132 °C (*n*-hexane-EtOAc); ^1H NMR ($CDCl_3$-CD_3CN) δ 9.48-8.82 (br, 1H, NH), 8.57 (br s, 1H, OH), 7.85 (d, *J* = 10.0 Hz, 1H, H-4'), 7.28-6.80 (m, 3H, H_{arom}), 4.52 (br s, 1H, NH), 2.33 (s, 3H, CH_3); IR (KBr): 1610 (C=O) cm^{-1}. Anal. Calcd for $C_{13}H_{10}F_6N_2O_2$: C, 45.89; H, 2.96; N, 8.23. Found: C, 45.62; H, 3.00; N, 8.23.

A mixture of 1-(7-chloro-2-hydroxy-2-trifluoromethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]-diazepin-3-yl)-2,2,2-trifluoroethanone (5e) and 1-(8-chloro-2-hydroxy-2-trifluormethyl-2,5-dihydro-1*H*-benzo-[*b*][1,4]diazepin-3-yl)-2,2,2-trifluoroethanone (5e'): ^1H NMR ($CDCl_3$-CD_3CN) δ 9.40-8.90 (br, 1H, OH), 8.63-8.28 (br, 1H, NH), 7.85 (d, *J* = 9.0 Hz, 1H, H-4'), 7.37-6.87 (m, 3H, H_{arom}), 4.87, 4.20 (br s, 1H, NH of two regioisomers); IR (KBr): 1555 (C=O) cm^{-1}. Anal. Calcd for $C_{12}H_7ClF_6N_2O_2$: C, 39.96; H, 1.96; N, 7.77. Found: C, 39.93; H, 2.02; N, 7.75.

2,2,2-Trifluoro-1-(2-hydroxy-7-methyl-2-trifluoromethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]diazepin-3-yl)ethanone (5f) or 2,2,2-trifluoro-1-(2-hydroxy-8-methyl-2-trifluoromethyl-2,5-dihydro-1*H*-benzo-[*b*][1,4]diazepin-3-yl)ethanone (5f'): mp 102-103 °C (*n*-hexane-EtOAc); ^1H NMR ($CDCl_3$-CD_3CN) δ 9.52-8.53 (br, 1H, NH), 8.53-7.90 (br, 1H, OH), 7.63 (br s, 1H, H-4'), 6.90-6.58 (m, 3H, H_{arom}), 4.97 (br s, 1H, NH), 2.25 (s, 3H, CH_3); IR (KBr): 1559 (C=O) cm^{-1}.

Anal. Calcd for $C_{13}H_{10}F_6N_2O_2$: C, 45.89; H, 2.96; N, 8.23. Found: C, 45.98; H, 3.07; N, 8.03.

2,2,2-Trifluoro-1-(2-hydroxy-7-nitro-2-trifluoromethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]-diazepin-3-yl)-ethanone (5g) or 2,2,2-trifluoro-1-(2-hydroxy-8-nitro-2-trifluoromethyl-2,5-dihydro-1*H*-benzo-[*b*][1,4]diazepin-3-yl)ethanone (5g'): mp 139-140 °C (*n*-hexane-EtOAc); ^{1}H NMR ($CDCl_3$-CD_3CN) δ 8.60-7.82 (m, 5H, NH, OH, H-4', H_{arom}), 7.25 (d, *J* = 10.0 Hz, 1H, H_{arom}), 5.98 (br s, 1H, NH); IR (KBr): 1623 (C=O) cm^{-1}. Anal. Calcd for $C_{12}H_7F_6N_3O_4$: C, 38.83; H, 1.90; N, 11.32. Found: C, 38.89; H, 2.10; N, 11.06.

1-(7-Benzoyl-2-hydroxy-2-trifluoromethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]diazepin-3-yl)-2,2,2-trifluoroethanone (5h) or 1-(8-benzoyl-2-hydroxy-2-trifluoromethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]-diazepin-3-yl)-2,2,2-trifluoroethanone (5h'): mp 166-167 °C (*n*-hexane-EtOAc); ^{1}H NMR ($CDCl_3$-CD_3CN) δ = 8.75-8.20 (br, 1H, NH), 8.00-7.50 (m, 9H, OH, H-4', C_6H_5CO), 7.22 (d, *J* = 9.0 Hz, 1H, H_{arom}), 5.80 (br s, 1H, NH); IR (KBr): 1568 (C=O) cm^{-1}. Anal. Calcd for $C_{19}H_{12}F_6N_2O_3$: C, 53.03; H, 2.81; N, 6.51. Found: C, 52.91; H, 2.91; N, 6.53.

2-Hydroxy-3-trifluoroacetyl-2-trifluoromethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]diazepine-7-carboxylic acid (5i) or 2-hydroxy-3-trifluoroacetyl-2-trifluoromethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]diazepine-8-carboxylic acid (5i'): mp 177-178 °C (*n*-hexane- EtOAc); ^{1}H NMR ($CDCl_3$-CD_3CN) δ 11.43-10.73 (br, 1H, NH), 8.61 (s, 1H, H-4'), 8.08-7.75 (m, 3H, H_{arom}, OH), 7.33 (d, *J* = 8.0 Hz, 1H, H_{arom}), 6.45 (br s, 1H, NH); IR (KBr): 1686 (C=O), 1611 (C=O) cm^{-1}. Anal. Calcd for $C_{13}H_8F_6N_2O_4$: C, 42.18; H, 2.18; N, 7.57. Found: C, 42.55; H, 2.26; N, 7.18.

2-Hydroxy-3-trifluoroacetyl-2-trifluoromethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]diazepine-7-carboxylic acid methyl ester (5j) or 2-hydroxy-3-trifluoroactyl-2-trifluoromethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]diazepine-8-carboxylic acid methyl ester (5j'): mp 160-161 °C (*n*-hexane-EtOAc); ^{1}H NMR ($CDCl_3$-CD_3CN) δ 9.67-9.15 (br, 1H, NH), 8.45 (s, 1H, OH), 8.09-7.79 (m, 3H, 4-H', H_{arom}), 7.22 (d, *J* = 8.8 Hz, 1H, H_{arom}), 5.70 (br s, 1H, NH), 3.93 (s, 3H, CH_3); IR (KBr): 1698 (C=O), 1627 (C=O) cm^{-1}. Anal. Calcd for $C_{14}H_{10}F_6N_2O_4$: C, 43.76; H, 2.62; N, 7.29. Found: C, 44.08; H, 2.74; N, 6.85.

2-Hydroxy-3-trifluoroacetyl-2-trifluoromethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]diazepine-7-carboxylic acid butyl ester (5k) or 2-hydroxy-3-trifluoroactyl-2-trifluoromethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]diazepine-8-carboxylic acid butyl ester (5k'): mp 158-159 °C (*n*-hexane-EtOAc); ^{1}H NMR ($CDCl_3$-CD_3CN) δ 9.93-9.13 (br, 1H, NH), 8.47 (s, 1H, OH), 8.13-7.81 (m, 3H, H-4', H_{arom}), 7.24 (d, *J* = 10.0 Hz, 1H, H_{arom}), 5.70 (br s, 1H, NH), 4.37 (t, 2H, C**H**$_2$(CH_2)$_2$$CH_3$), 1.83-0.80 (m, 7H, CH_2(C**H**$_2$)$_2$C**H**$_3$)); IR (KBr): 1687(C=O), 1630 (C=O) cm^{-1}. Anal. Calcd for $C_{17}H_{16}F_6N_2O_4$: C, 47.90; H, 3.78; N, 6.57. Found: C, 47.92; H, 3.71; N, 6.66.

General procedure for the synthesis of bisperhaloalkanoylated 2-methyl-1-(vinyloxy)-propane (6).

Method A (for 6a, b).

To an ice-cooled mixture of 2-methyl-1-(vinyloxy)propane (1.00 g, 10 mmol) and pyridine (2.37 g, 30 mmol) was added dropwise a solution of perhaloalkanoic anhydride (30 mmol) in dry $CHCl_3$ (1 mL) with continuous stirring. After stirring for 18 h at 50 °C, the crude mixture being poured into ice-cooled *n*-hexane (50 mL) resulted in the rapid precipitation of pyridinium salts. After filtration, the solution is dried over Na_2SO_4 and concentrated in vacuo to give **6a** (2.31 g, 71 %) or **6b** (3.18 g, 80 %).

1,5-Dichloro-1,1,5,5-tetrafluoro-3-(isobutoxymethylene)pentane-2,4-dione (6a): bp 110 °C / 3 mmHg; ^{1}H NMR ($CDCl_3$) δ 8.10 (s, 1H, CH=C), 4.20 (d, *J* = 7.0 Hz, 2H, CH_2), 2.47-1.78 (m, 1H, CH), 1.01 (d, *J* = 7.0 Hz, 6H, CH_3). Anal. Calcd for $C_{10}H_{10}Cl_2F_4O_3$: C, 36.95; H, 3.10. Found: C, 37.19; H, 2.79.

1,1,1,2,2,6,6,7,7,7-Decafluoro-4-(isobutoxymethylene)heptane-3,5-dione (6b): bp 150 °C / 5 mmHg; ^{1}H NMR ($CDCl_3$) δ 8.09 (s, 1H, CH=C), 4.19 (d, *J* = 6.4 Hz, 2H, CH_2), 2.43-1.76 (m, 1H, CH), 1.02 (d, *J* = 7.6 Hz, 6H, CH_3); IR (film): 1751 (C=O), 1682 (C=O) cm^{-1}. Anal. Calcd for $C_{12}H_{10}F_{10}O_3$: C, 36.75; H, 2.57. Found: C, 36.36; H, 2.41.

Method B (for 6c-d')

To an ice-cooled mixture of (*E*)-1,1,1-trihalo-4-isobutoxybut-3-en-2-one (2 mmol) and pyridine

(474 mg, 6 mmol) was added dropwise a solution of perhaloalkanoic anhydride (6 mmol) in dry $CHCl_3$ (0.5 mL) with continuous stirring. After stirring for 18 h at 50 °C, the mixture was dissolved in CH_2Cl_2 (10 mL). The whole mixture was washed with water (10 mL) and dried over Na_2SO_4. Removal of the solvent under vacuum afforded a mixture of **6c** and **6c'** (512 mg, 71 %), or that of **6d** and **6d'** (458 mg, 67 %).

A mixture of (*E*)- and (*Z*)-1,1,1,5,5,6,6,6-octafluoro-3-(isobutoxymethylene)hexane-2,4-dione (6c, c'): ^{1}H NMR ($CDCl_3$) δ 8.04, 8.00 (s, 1H, CH=C), 4.18 (d, *J* = 6.4 Hz, 2H, CH_2), 2.43-1.75 (m, 1H, CH), 0.98 (d, *J* = 7.2 Hz, 6H, CH_3); IR (film): 1750 (C=O), 1697 (C=O) cm^{-1}. Anal. Calcd for $C_{11}H_{10}F_8O_3$: C, 38.61; H, 2.95. Found: C, 38.42; H, 2.91.

A mixture of (*E*)- and (*Z*)-1,1,1-trichloro-5,5,5-trifluoro-3-(isobutoxymethylene)pentane-2,4-dione (6d, d'): ^{1}H NMR ($CDCl_3$) δ 8.09, 7.97 (s, 1H, CH=C), 4.25 (d, *J* = 6.4 Hz, 2H, CH_2), 2.45-1.78 (m, 1H, CH), 1.02 (d, *J* = 7.6 Hz, 6H, CH_3); IR (film): 1753 (C=O), 1692 (C=O) cm^{-1}. Anal. Calcd for $C_{10}H_{10}Cl_3F_3O_3$: C, 35.17; H, 2.95. Found: C, 34.99; H, 2.91.

General procedure for the synthesis of 2,5-dihydro-3-perhaloalkanoyl-2-perhaloalkyl-1*H*-benzo[*b*][1,4]diazepines (7a-d') from perhalo-(isobutoxymethylene)alkanediones (6).
To a solution of **6** (1.0 mmol) dissolved in MeCN (4 mL) was added 4,5-dimethylbenzene-1,2-diamine (143 mg, 1.1 mmol) and the mixture was stirred for 1 h at ambient temperature. After evaporation of the solvent, purification of a residue by silica gel column chromatography using *n*-hexane-EtOAc (10:1) afforded **7a-d'**. In the case of **7b**, pure **7b** could not be obtained by silica gel chromatography because of a contamination of small amounts of **8**. In the case of a mixture of **7d**, and **7d'**, small amount of single isomer **7d** could be isolated, while the other isomer **7d'** could not be separated from the mixture of two isomers by silica gel column chromatography.

2-Chloro-1-[2-(chlorodifluoromethyl)-2-hydroxy-7,8-dimethyl-2,5-dihydro-1*H*-benzo-[*b*][1,4]diazepin-3-yl]-2,2-difluoroethanone (7a): mp 123-124 °C (*n*-hexane-EtOAc); ^{1}H NMR ($CDCl_3$-CD_3CN) δ 9.38-8.88 (br, 1H, NH), 8.78 (br s, 1H, OH), 7.98 (d, *J* = 10.0 Hz, 1H, H-4'), 6.82 (s, 2H, H_{arom}), 4.95 (br s, 1H, NH), 2.18 (s, 6H, CH_3); IR (KBr): 1563 (C=O) cm^{-1}. Anal.

Calcd for $C_{14}H_{12}Cl_2F_4N_2O_2$: C, 43.43; H, 3.12; N, 7.24. Found: C, 43.59; H, 2.76; N, 7.44.

2,2,3,3,3-Pentafluoro-1-(2-hydroxy-7,8-dimethyl-2-pentafluoroethyl-2,5-dihydro-1*H*-benzo-[*b*][1,4]diazepin-3-yl)propanone (7b): ^{1}H NMR (CD_3CN) δ 9.45-8.98 (br, 1H, NH), 8.83 (s, 1H, OH), 7.93 (d, 1H, *J* = 10.0 Hz, H-4'), 6.82 (s, 2H, H_{arom}), 5.09 (br s, 1H, NH), 2.23 (s, 6H, CH_3).

2,2,3,3,3-Pentafluoro-1-(2-hydroxy-7,8-dimethyl-2-trifluoromethyl-2,5-dihydro-1*H*-benzo-[*b*][1,4]diazepin-3-yl)propanone (7c): mp 134-135 °C (*n*-hexane-EtOAc); ^{13}C NMR (CD_3CN) δ 18.8, 19.4 (CH_3), 86.7 ($^2J_{CF}$ = 29.8 Hz, C-2'), 104.3 (C-3'), 110.6-130.0 (m, **C**F_2**C**F_3), 125.7 ($^1J_{CF}$ = 293.7 Hz, 2'-CF_3), 122.7, 123.1, 126.8, 132.0, 132.4, 137.4 (C_{arom}), 149.0 (C-4'), 180.7 ($^2J_{CF}$ = 23.8 Hz, **C**OCF_2CF_3); ^{1}H NMR ($CDCl_3$-CD_3CN) δ 9.49-9.03 (br, 1H, NH), 8.46 (s, 1H, OH), 7.91 (d, *J* = 10.0 Hz, 1H, H-4'), 6.89 (s, 2H, H_{arom}), 5.00 (br s, 1H, NH), 2.20 (s, 6H, CH_3); IR (KBr): 1568 (C=O) cm^{-1}. Anal. Calcd for $C_{15}H_{12}F_8N_2O_2$: C, 44.57; H, 2.99; N, 6.93. Found: C, 44.55; H, 3.03; N, 6.92.

2,2,2-Trichloro-1-(2-hydroxy-7,8-dimethyl-2-trifluoromethyl-2,5-dihydro-1*H*-benzo[*b*][1,4]-diazepin-3-yl)ethanone (7d): mp 146-147 °C (*n*-hexane-EtOAc); ^{1}H NMR ($CDCl_3$-CD_3CN) δ 9.60-9.10 (br, 1H, NH), 8.57 (d, *J* = 10.0 Hz, 1H, H-4'), 8.34 (br s, 1H, OH), 7.87 (s, 2H, H_{arom}), 5.01 (br s, 1H, NH), 2.20 (s, 6H, CH_3); IR (KBr): 1567 (C=O) cm^{-1}. Anal. Calcd for $C_{14}H_{12}Cl_3F_3N_2O_2$: C, 41.66; H, 3.00; N, 6.94. Found: C, 41.66; H, 3.27; N, 6.66.

4-[(2-Amino-4,5-dimethylphenylamino)methylene]-1,1,1,2,2,6,6,7,7,7-decafluoroheptane-3,5-dione (8): mp 178-179 °C (aqueous MeCN); ^{1}H NMR ($CDCl_3$-CD_3CN) δ 11.67-10.90 (br, 1H, NH), 8.39 (br s, 1H, CH=C), 6.99 (s, 1H, H_{arom}), 6.74 (s, 1H, H_{arom}), 4.92-4.49 (br, 2H, NH_2), 2.20 (s, 6H, CH_3); IR (KBr): 1648 (C=O) cm^{-1}. Anal. Calcd for $C_{16}H_{12}F_{10}N_2O_2$: C, 42.30; H, 2.66; N, 6.17. Found: C, 42.30; H, 2.78; N, 5.69.

General procedure for the synthesis of *N*-sulfinylanilines 9 from diazepinols 5.

To a solution of **5** (1 mmol) was added dropwise a solution of thionyl chloride (119 mg, 1 mmol) in CH_3CN (4 mL) with continuous stirring (in the case of a mixture of **5h** and **5h'**, 2 mmol of

thionyl chloride was used). After stirring for 5 – 30 min at ambient temperature, removal of the solvent under vacuum afforded **9a-c**, **9g**, **g'** and **9h**, **h'**.

1,1,1,5,5,5-Hexafluoro-3-[[2-(*N*-sulfinylamino)phenylamino]methylene]pentane-2,4-dione (9a): mp 107-108 °C (*n*-hexane-CH_2Cl_2); ^{1}H NMR (CD_3COCD_3) δ 12.77 (br s, 1H, NH), 7.75-7.42 (m, 4H, H_{arom}, CH=C), 7.04-7.03 (m, 1H, H-6); IR (KBr): 1663 (C=O), 1608 (C=O) cm^{-1}. Anal. Calcd for $C_{12}H_6F_6N_2O_3S$: C, 38.74; H, 1.62; N, 7.53. Found: C, 38.66; H, 1.58; N, 7.72.

1,1,1,5,5,5-Hexafluoro-3-[[4,5-dimethyl-2-(*N*-sulfinylamino)phenylamino]methylene]pentane-2,4-dione (9b): mp 133-134 °C (*n*-hexane-CH_2Cl_2); ^{13}C NMR (CD_3COCD_3) δ 19.7, 20.4 (CH_3), 103.8 (**C**$(COCF_3)_2$), 117.2 ($^1J_{CF}$ = 287.6 Hz, CF_3), 117.6 ($^1J_{CF}$ = 292.2 Hz, CF_3), 118.2, 129.6, 130.6, 132.6, 138.0, 143.4 (C_{arom}), 177.0 ($^2J_{CF}$ = 34.3 Hz, **C**OCF_3), 180.8 ($^2J_{CF}$ = 38.1 Hz, **C**OCF_3); ^{1}H NMR (CD_3COCD_3) δ 13.33-12.50 (br, 1H, NH), 8.80 (d, 1H, *J* = 14.0 Hz, CH=C), 8.44 (s, 1H, H_{arom}), 7.73 (s, 1H, H_{arom}), 2.41, 2.33 (s, 6H, CH_3); IR (KBr): 1648 (C=O), 1619 (C=O) cm^{-1}. Anal. Calcd for $C_{14}H_{10}F_6N_2O_3S$: C, 42.01; H, 2.52; N, 7.00. Found: C, 42.02; H, 2.67; N, 6.80.

1,1,1,5,5,5-Hexafluoro-3-[[4,5-dichloro-2-(*N*-sulfinylamino)phenylamino]methylene]pentane-2,4-dione (9c): mp 116-118 °C (*n*-hexane-CH_2Cl_2); ^{1}H NMR (CD_3COCD_3) δ 12.60 (br s, 1H, NH), 8.53 (d, 1H, *J* = 14.0 Hz, CH=C), 8.43 (s, 1H, H_{arom}), 7.80 (s, 1H, H_{arom}); IR (KBr): 1658 (C=O), 1611 (C=O) cm^{-1}. Anal. Calcd for $C_{12}H_4Cl_2F_6N_2O_3S$: C, 32.67; H, 0.91; N, 6.35. Found: C, 32.52; H, 1.21; N, 6.20.

A mixture of 1,1,1,5,5,5-hexafluoro-3-[[4-nitro-2-(*N*-sulfinylamino)phenylamino]methylene]pentane-2,4-dione (9g) and 1,1,1,5,5,5-hexafluoro-3-[[5-nitro-2-(*N*-sulfinylamino)-phenylamino]methylene]pentane-2,4-dione (9g'): ^{1}H NMR (CD_3COCD_3) δ 12.72-12.13 (br, 1H, NH), 8.66-7.47 (m, 4H, H_{arom}, CH=C); IR (KBr): 1706 (C=O), 1657 (C=O), 1603 (C=O), 1585 (C=O) cm^{-1}. Anal. Calcd for $C_{12}H_5F_6N_3O_5S$: C, 34.54; H, 1.21; N, 10.07. Found: C, 34.32; H, 1.40; N, 10.08.

A mixture of 1,1,1,5,5,5-hexafluoro-3-[[4-benzoyl-2-(*N*-sulfinylamino)phenylamino]-methylene]pentane-2,4-dione (9h) and 1,1,1,5,5,5-hexafluoro-3-[[5-benzoyl-2-(*N*-sulfinyl-amino)phenylamino]methylene]pentane-2,4-dione (9h'): ^{1}H NMR (CD_3COCD_3) δ 13.28-12.11 (br, 1H, NH), 8.92-8.47 (m, 1H, H_{arom}), 8.47-8.25 (m, 1H, H_{arom}), 7.71-7.23 (m, 7H, H_{arom}, CH=C); IR (KBr): 1711 (C=O), 1655 (C=O), 1608 (C=O), 1589 (C=O) cm^{-1}. Anal. Calcd for $C_{19}H_{10}F_6N_2O_4S$: C, 47.91; H, 2.12; N, 5.88. Found: C, 48.16; H, 2.18; N, 5.57.

REFERENCES

1. A. Tajana, R. Pennini, and D. Nardi, *Farmaco Ed. Sci.*, 1980, **35**, 181.
2. K. C. Joshi, V. N. Pathak, P. Arya, and P. Chand, *Pharmazie*, 1979, **34**, 718.
3. G. Roma, E. Vigevani, A. Balbi, and A. Ermili, *Farmaco Ed. Sci.*, 1979, **34**, 62.
4. D. Nardi, E. Massarani, A. Tajana, R. Cappelletti, and M. Veronese, *Farmaco Ed. Sci.*, 1975, **30**, 727.
5. F. Giodano, C. Grieco, C. Silipo, and A. Vittoria, *Boll. Soc. Ital. Biol. Sper.*, 1975, **51**, 1069.
6. C. Grieco, C. Silipo, and A. Vittoria, *Farmaco Ed. Sci.*, 1977, **32**, 909.
7. A. I. Kravchenko, *Farmakol. Toksikol.*, 1974, **37**, 474.
8. D. P. Clifford, D. Jackson, R. V. Edwards, and P. Jeffrey, *Pestic. Sci.*, 1976, **7**, 453.
9. R. Filler and Y. Kobayashi, 'Biomedicinal Aspects of Fluorine Chemistry,' Kodansha & Elsevier Biomedical, Tokyo, 1982.
10. R. Filler, 'Organofluorine Chemicals and Their Industrial Applications,' Ellis Horwood, London, 1979.
11. J. T. Welch, *Tetrahedron*, 1987, **43**, 3123.
12. R. Filler, Y. Kobayashi, and L. M. Yagupolskii, 'Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications,' Elsevier, Amsterdam, 1993.
13. Y. Kamitori, M. Hojo, R. Masuda, T. Fujitani, T. Kobuchi, and T. Nishigaki, *Synthesis*, 1986, 340.
14. M. Hojo, R. Masuda, E. Okada, S. Sakaguchi, H. Narumiya, and K. Moriomoto, *Tetrahedron Lett.*, 1989, **30**, 6173.
15. M. Hojo, R. Masuda, E. Okada, H. Yamamoto, K. Moriomoto, and K. Okada, *Synthesis*, 1990, 195.
16. M. Hojo, R. Masuda, and E. Okada, *Chem. Lett.*, 1990, 2095.
17. E. Okada, R. Masuda, M. Hojo, and R. Inoue, *Synthesis*, 1992, 533.
18. M. Hojo, R. Masuda, E. Okada, and Y. Mochizuki, *Synthesis*, 1992, 455.
19. M. Hojo, R. Masuda, and E. Okada, *Synthesis*, 1990, 347.
20. E. Okada, R. Masuda, and M. Hojo, *Heterocycles*, 1992, **34**, 791.
21. A. C. S. Reddy, P. S. Rao, and R. V. Venkataratnam, *Tetrahedron Lett.*, 1996, **37**, 2845.
22. A. C. S. Reddy, P. S. Rao, and R. V. Venkataratnam, *Tetrahedron*, 1997, **53**, 5847.

23. E. Okada, N. Ota, T. Tomoda, M. Fujimoto, and H. Takenaka, Jpn. Kokai Tokkyo Koho 2006-273,844, 2006.

CHAPTER 2

A Convenient Synthetic Method for Fluorine-Containing 4-Alkoxy-dihydrobenzo[*b*][1,4]diazepinols and 3*H*-Benzo[*b*][1,4]diazepines by the Reaction of β-Trifluoroacetylketene Acetals with 1,2-Phenylene-diamines

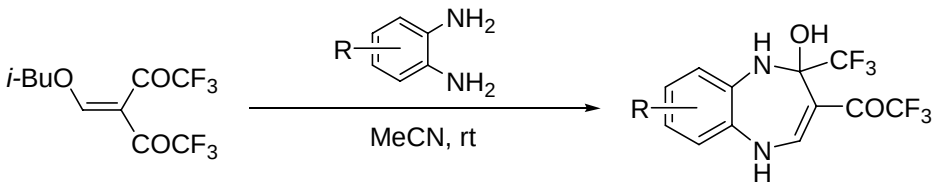
SUMMARY

β-Trifluoroacetylketene dialkyl acetals (**3** and **5**) reacted easily with various 1,2-phenylenediamines to give novel 4-alkoxy-2-trifluoromethyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepinols (**6** and **8**) in moderate to high yields. Dehydration of **6** and **8** proceeded thermally under reduced pressure to afford the corresponding fluorine-containing 3*H*- benzo[*b*][1,4]diazepines (**7** and **9**).

INTRODUCTION

Benzo[*b*][1,4]diazepines have attracted much attention as an important class of heterocycles in the field of medicinal and agricultural chemistries.[1] These compounds are widely used as powerful agents, especially for the antipsychotic therapy.[2] Very recently, we have reported the facile synthesis of novel fluorine-containing dihydrobenzo[*b*][1,4]diazepinols (**2**),[3] some of which showed remarkable antineoplastic efficacy,[4] by the reaction of β,β-bis(trifluoroacetyl)vinyl ethers (**1**) with various 1,2-phenylenediamines (Scheme 1). In our previous studies, it was found that ketene dithioacetals[5] and orthoacetates[6] reacted with trifluoroacetic anhydride quite easily to afford the corresponding β-trifluoroacetylated ketene *S*,*S*- and *O*,*O*-acetals, respectively, and that these acylated compounds cleanly underwent nucleophilic *S*-*N* and *O*-*N* exchange reactions[7,8] with aliphatic and aromatic amines to give β-trifluoroacetylated ketene *S*,*N*-, *O*,*N*-, and *N*,*N*-acetals. Thereafter, these β-trifluoroacetylketene acetals were found to be convenient

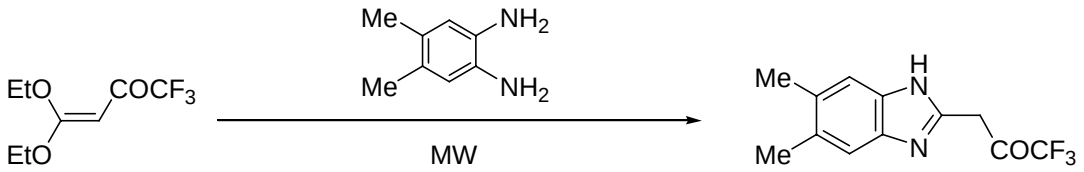
building blocks which are applicable to the syntheses of a variety of novel fluorine-containing heterocyclic compounds by the reactions with bifunctional nucleophiles. For instance, fluorine-containing isoxazolines, 1*H*-prrazolines, and imidazolines were easily obtained by the reactions with hydroxylamine, hydrazines, and 1,2-ethylenediamine, respectively.[9,10]



1 **2**

Scheme 1

Additionally, Reddy *et al.* reported the interesting reaction of β-trifluoroacetylketene acetal (**3**) with 4,5-dimethyl-1,2-phenylenediamine under microwave irradiation to give solely benzimidazoles (**4**) without any formation of benzodiazepines (Scheme 2).[11] These studies and



3 **4**

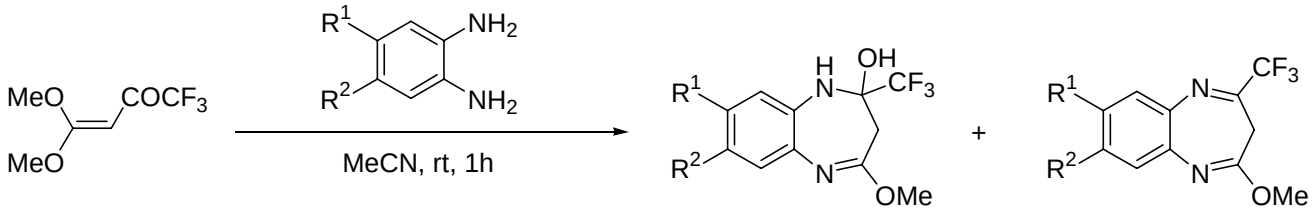
Scheme 2

our continuing interest in the synthesis of trifluoromethyl-containing benzodiazepines, a new potential pharmacophore of antineoplastic efficacy, prompted us to explore the feasibility of the benzodiazepine-ring construction by the non-microwave assisted cyclization reaction of β-trifluoroacetylketene acetals with 1,2-phenylenediamines. In this chapter we wish to report the annulation reaction of β-trifluoroacetylketene acetals (**3** and **5**) with various 1,2-phenylenediamines under very mild conditions without microwave irradiation to afford the desired fluorine-containing 2,3-dihydro-1*H*-benzo[*b*][1,4]diazepinols (**6** and **8**) having an alkoxy group at the C-4 position. In addition, the thermally induced dehydration of **6** and **8** under

reduced pressure leading to the formation of the corresponding 2-alkoxy-3*H*-benzo[*b*][1,4]diazepines (**7** and **9**) is presented.

RESULTS AND DISCUSSION

β-Trifluoroacetylketene dimethyl acetal (**5**) was easily prepared in 92% yield by the acylation of trimethyl orthoacetate with trifluoroacetic anhydride according to our method reported previously.[6,12] The results of the annulation reaction of **5** with 1,2-phenylenediamines are depicted in Scheme 3 and summarized in Table 1. Reaction of **5** with slightly excess amounts of



5 **6a-e'** **7a-e'**

Scheme 3

1,2-phenylenediamine readily occurred at room temperature in acetonitrile to give the desired 4-methoxy-2-trifluoromethyl-2,3- dihydro-1*H*-benzo[*b*][1,4]diazepin-2-ol (**6a**) in 68% yield with the formation of its dehydrated product, 2-methoxy-4-trifluoromethyl-3*H*-benzo[*b*][1,4]diazepine (**7a**), in 5% yield (Entry 1). Similarly, 4,5-dimethyl- and 4,5-dichloro-1,2-phenylenediamines reacted with **5** to afford the corresponding dihydrobenzodiazepinols (**6b**,**c**) - benzodiazepines (**7b**,**c**) mixtures in high combined yields (Entries 2 and 3). The annulation with unsymmetrical 1,2-phenylenediamines such as 4-benzoyl- and 4-nitro-1,2-phenylenediamines also proceeded cleanly to afford the mixtures of the four components, the two regioisomers of dihydrobenzodiazepinols (**6d**,**d'** and **6e**,**e'**) and those of benzodiazepines (**7d**,**d'** and **7e**,**e'**), in excellent combined yields (Entries 4 and 5). Although the attempted separation of mixtures of the two regioisomers was unsuccessful, all of the separation of the mixtures into **6a-e'** and **7a-e'** was easily performed by column chromatography.

Table 1 Reaction of β-trifluoroacetylketene dimethyl acetal (**5**) with 1,2-phenylenediamines.[a]

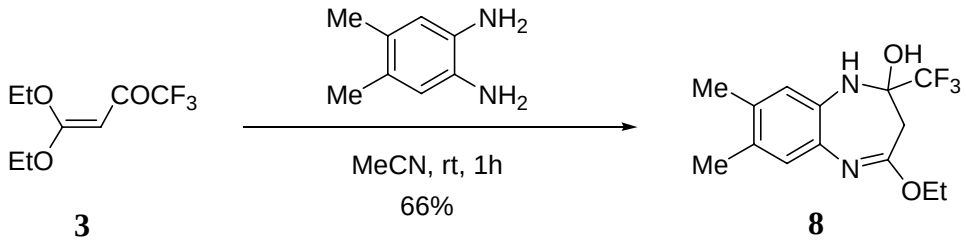
Entry	R^1	R^2	Product	Yield (%)[b]
1	H	H	**6a**	68
			7a	5
2	Me	Me	**6b**	63
			7b	13
3	Cl	Cl	**6c**	78
			7c	5
4	COPh or H	H or COPh	**6d** and **6d'**[c]	81[d]
			7d and **7d'**[c]	2[d]
5	NO_2 or H	H or NO_2	**6e** and **6e'**[c]	65[d]
			7e and **7e'**[c]	11[d]

[a] 1.1 equiv of 1,2-phenylenediamines was used.

[b] Isolated yield after chromatography.

[c] The mixture of the two regioisomers was placed on the column. The regio-chemistry and the ratio are not determined yet.

[d] Combined yield of two regioisomers.

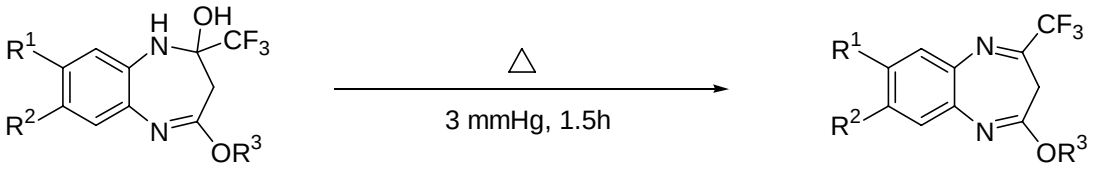


3 **8**

Scheme 4

These results of our approaches on the reactions of **5** with 1,2-phenylenediamines show sharp contrast with those reported by Reddy *et al* (see Scheme 2).[11] As shown in Scheme 3,

dihydrobenzodiazepinols (**6**) were obtained predominantly, together with the small amounts of the corresponding benzodiazepines (**7**) under very mild conditions in the absence of microwave irradiation in acetonitrile without any formation of the corresponding benzimidazoles (**4**). To verify no difference in reactivities between dimethyl derivative (**5**) and diethyl one (**3**), we then examined the reaction of **3** with 4,5-dimethyl-1,2-phenylenediamine, in which 4-ethoxy derivative of 2,3-dihydro-1*H*-benzo[*b*][1,4]diazepinols (**8**) was obtained solely in 66% yield with no accompanying benzimidazoles (**4**) as depicted in Scheme 4.



6a-e', **8** **7a-e'**, **9**

Scheme 5

Table 2 Dehydration of 2,3-dihydro-1*H*-benzo[*b*][1,4]diazepinols (**6a-e'** and **8**).

Entry	R^1	R^2	R^3	Temp (°C)[a]	Product	Yield (%)[b]
1	H	H	Me	110	**7a**	24
2	Me	Me	Me	120	**7b**	91
3	Cl	Cl	Me	120	**7c**	75
4[c]	COPh or H	H or COPh	Me	110	**7d** and **7d'**[d]	89[e]
5[c]	NO_2 or H	H or NO_2	Me	150	**7e** and **7e'**[d]	48[e]
6	Me	Me	Et	120	**9**	85

[a] Oven temperature (3 mmHg).

[b] Isolated yield after distillation.

[c] A mixture of two regioisomers (**6d**,**d'** or **6e**,**e'**) was used as a starting material.

[d] The mixture of two regioisomers was distilled. The regiochemistry and the ratio are not determined yet.

[e] Combined yield of two regioisomers.

Next we attempted the acid-catalyzed dehydration of 2,3-dihydro-1*H*-benzo[*b*][1,4]diazepin-2-ols (**6a-e'** and **8**) to 3*H*-benzo[*b*][1,4]diazepines (**7a-e'** and **9**), but this resulted in failure to give complex mixtures. So, we tried to carry out the present dehydration with the use of Kugelrohr distillation apparatus, namely, by heating under reduced pressure, as depicted in Scheme 5 and summarized in Table 2. All dihydrobenzodiazepinols (**6a-e'** and **8**) was thoroughly dehydrated at 110-150 °C under reduced pressure (3 mmHg) within 1.5 h to provide the corresponding benzodiazepines (**7a-e'** and **9**) in high yields except for the cases of **7a** and **7e**,**e'** with formation of large amounts of decomposition products.

In summary, we have developed a facile and convenient synthetic method for 4-alkoxy-2-trifluoromethyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepinols (**6** and **8**), which are not easily obtained by other methods. Moreover, the thermal dehydration of **6** and **8** was successfully carried out under reduced pressure to give 2-alkoxy-4-trifluoromethyl-3*H*-benzo[*b*][1,4]diazepines (**7** and **9**). Evaluation of biological activities, especially of antineoplastic efficacy, is now under way for novel fluorine-containing benzodiazepines (**6**-**9**).

EXPERIMENTAL

Mps were determined on an electrothermal digital melting point apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on a Bruker AVANCE500 spectrometer using TMS as an internal standard. IR spectra were taken with a PerkinElmer Spectrum ONE FT-IR spectrometer. Microanalyses were taken with a YANACO CHN-Corder MT-5 analyzer.

Synthesis of 1,1,1-trifluoro-4,4-dimethoxybut-3-en-2-one (5).[12]

To an ice-cooled stirred solution of 1,1,1-trimethoxyethane (4.81 g, 40 mmol) and pyridine (6.33 g, 80 mmol) in $CHCl_3$ (40 mL) was added dropwise trifluoroacetic anhydride (16.80 g, 80 mmol) and the mixture was stirred for 3 h at room temperature. Then, CH_2Cl_2 (100 mL) was added and the whole mixture was washed with aq. 10 % Na_2CO_3 (50 mL) and with water (50 mL), and dried over Na_2SO_4. The solvent and pyridine was removed in vacuo to give **5** (6.76 g, 92%). **5**: mp 67-68 °C (*n*-hexane-EtOAc); ^{1}H NMR ($CDCl_3$): δ 4.98 (s, 1H, =CH), 3.98 (s, 3H, CH_3), 3.92 (s, 3H, CH_3); IR (KBr): 1675 (C=O) cm^{-1}. Anal. Calcd for $C_6H_7F_3O_3$: C, 39.14; H, 3.83. Found: C, 39.16; H, 3.82.

General procedure for the synthesis of 4-methoxy-2-trifluoromethyl-2,3-dihydro-1*H*-benzo[*b*][1,4]-diazepin-2-ols (6a-e') and 4-methoxy-2-trifluoromethyl-3*H*-benzo[*b*][1,4]-diazepines (7a-e').

To a solution of **5** (184 mg, 1.0 mmol) in MeCN (4 mL) was added 1,2-phenylenediamines (1.1 mmol) and the mixture was stirred for 1 h at room temperature. The solvent was removed under reduced pressure and the crude mixture was chromatographed on silica gel column using *n*-hexane-EtOAc (9:1) as eluent to give **6a-e'** and **7a-e'**. In the case with 4-benzoyl-1,2-phenylenediamine, a mixture of **6d** and **6d'** and a mixture of **7d** and **7d'** were eluted respectively. Similarly, a mixture of **6e** and **6e'** and a mixture of **7e** and **7e'** were eluted respectively in the case with 4-nitro-1,2-phenylenediamine.

4-Methoxy-2-trifluoromethyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepin-2-ol (6a): mp 126-127 °C (*n*-hexane-EtOAc); ^{1}H NMR ($CDCl_3$): δ 7.10-6.81 (m, 4H, H_{arom}), 4.11 (s, 1H, OH or

NH), 3.91 (s, 3H, OCH_3), 3.27 (s, 1H, OH or NH), 2.82 (d, 1H, *J* = 14.0 Hz, CH_2), 2.61 (d, 1H, *J* = 14.0 Hz, CH_2); IR (KBr): 3326, 3112, 1652 cm^{-1}. Anal. Calcd for $C_{11}H_{11}F_3N_2O_2$: C, 50.77; H, 4.26; N, 10.77. Found: C, 50.72; H, 4.43; N, 10.65.

4-Methoxy-7,8-dimethyl-2-trifluoromethyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepin-2-ol (6b): mp 122-123 °C (*n*-hexane-EtOAc); ^1H NMR ($CDCl_3$): δ 6.89 (s, 1H, H_{arom}), 6.62 (s, 1H, H_{arom}), 4.05 (s, 1H, OH or NH), 3.88 (s, 3H, OCH_3), 3.14 (s, 1H, OH or NH), 2.81 (d, 1H, *J* = 14.0 Hz, CH_2), 2.59 (d, 1H, *J* = 14.0 Hz, CH_2), 2.20 (s, 3H, CH_3), 2.19 (s, 3H, CH_3); IR (KBr): 3321, 3082, 1652 cm^{-1}. Anal. Calcd for $C_{13}H_{15}F_3N_2O_2$: C, 54.16; H, 5.24; N, 9.72. Found: C, 54.10; H, 5.01; N, 9.47.

7,8-Dichloro-4-methoxy-2-trifluoromethyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepin-2-ol (6c): mp 117-118 °C (*n*-hexane-EtOAc); ^1H NMR ($CDCl_3$): δ 7.21 (s, 1H, H_{arom}), 6.97 (s, 1H, H_{arom}), 4.21 (s, 1H, OH or NH), 3.89 (s, 3H, OCH_3), 3.17 (s, 1H, OH or NH), 2.84 (d, 1H, *J* = 14.0 Hz, CH_2), 2.63 (d, 1H, *J* = 14.0 Hz, CH_2); IR (KBr): 3315, 3071, 1648 cm^{-1}. Anal. Calcd for $C_{11}H_9Cl_2F_3N_2O_2$: C, 40.14; H, 2.76; N, 8.51. Found: C, 40.28; H, 2.74; N, 8.40.

A mixture of (2-hydroxy-4-methoxy-2-trifluoromethyl-2,3-dihydro-1*H*-benzo[*b*][1,4]-diazepin-8-yl)phenylmethanone (6d) and (2-hydroxy-4-methoxy-2-trifluoromethyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepin-7-yl)phenylmethanone (6d'): ^1H NMR ($CDCl_3$): δ 7.74-6.82 (m, 8H, H_{arom}), 4.61 (s, 1H, OH or NH), 4.50 (s, 1H, OH or NH), 3.92, 3.86 (s, 3H, OCH_3), 2.89 (d, 1H, *J* = 14.0 Hz, CH_2), 2.73 (d, 1H, *J* = 14.0 Hz, CH_2); IR (KBr): 3372, 3324, 1662, 1646 cm^{-1}. Anal. Calcd for $C_{18}H_{15}F_3N_2O_3$: C, 59.34; H, 4.15; N, 7.69. Found: C, 59.49; H, 4.41; N, 8.02.

A mixture of 4-methoxy-8-nitro-2-trifluoromethyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepin-2-ol (6e) and 4-methoxy-7-nitro-2-trifluoromethyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepin-2-ol (6e'): ^1H NMR ($CDCl_3$ + CD_3CN): δ 8.20-7.73 (m, 2H, H_{arom}), 7.23-7.07 (m, 1H, H_{arom}), 5.60 (s, 1H, NH or OH), 5.50 (s, 1H, NH or OH), 4.00, 3.90 (s, 3H, OCH_3), 2.89 (d, 1H, *J* = 14.0 Hz, CH_2), 2.73 (d, 1H, *J* = 14.0 Hz, CH_2); IR (KBr): 3487, 3300, 3170, 1649 cm^{-1}. Anal. Calcd for

$C_{11}H_{10}F_3N_3O_4$: C, 43.29; H, 3.30; N, 13.77. Found: C, 43.38; H, 3.33; N, 13.65.

2-Methoxy-4-trifluoromethyl-3*H*-benzo[*b*][1,4]diazepine (7a): bp (oven temperature) 110 °C / 3 mmHg; ^{1}H NMR ($CDCl_3$): δ 7.63-7.13 (m, 4H, H_{arom}), 3.87 (s, 3H, OCH_3), 3.10 (s, 2H, CH_2); IR (KBr): 1646 cm^{-1}. Anal. Calcd for $C_{11}H_9F_3N_2O$: C, 54.55; H, 3.75; N, 11.57. Found: C, 54.79; H, 3.71; N, 11.37.

2-Methoxy-7,8-dimethyl-4-trifluoromethyl-3*H*-benzo[*b*][1,4]diazepine (7b): bp (oven temperature) 120 °C / 3 mmHg; ^{1}H NMR ($CDCl_3$): δ 7.32 (s, 1H, H_{arom}), 7.16 (s, 1H, H_{arom}), 3.90 (s, 3H, OCH_3), 3.08 (s, 2H, CH_2), 2.30 (s, 6H, CH_3); IR (KBr): 1648 cm^{-1}. Anal. Calcd for $C_{13}H_{13}F_3N_2O$: C, 57.78; H, 4.85; N, 10.37. Found: C, 57.96; H, 4.94; N, 10.10.

7,8-Dichloro-2-methoxy-4-trifluoromethyl-3*H*-benzo[*b*][1,4]diazepine (7c): mp 98-99 °C (*n*-hexane-EtOAc); ^{1}H NMR ($CDCl_3$): δ 7.66 (s, 1H, H_{arom}), 7.49 (s, 1H, H_{arom}), 3.93 (s, 3H, OCH_3), 3.16 (s, 2H, CH_2); IR (KBr): 1648 cm^{-1}. Anal. Calcd for $C_{11}H_7Cl_2F_3N_2O$: C, 42.47; H, 2.27; N, 9.01. Found: C, 42.87; H, 2.36; N, 8.68.

A mixture of (2-methoxy-4-trifluoromethyl-3*H*-benzo[*b*][1,4]diazepin-7-yl)phenylmethanone (7d) and (4-methoxy-2-trifluoromethyl-3*H*-benzo[*b*][1,4]diazepin-7-yl)phenylmethanone (7d'): bp (oven temperature) 140 °C / 3 mmHg; ^{1}H NMR (CD_3CN): δ 8.07-7.35 (m, 8H, H_{arom}), 3.94, 3.91 (s, 3H, OCH_3), 3.29 (s, 2H, CH_2); IR (KBr): 1657, 1642 cm^{-1}. Anal. Calcd for $C_{18}H_{13}F_3N_2O_2$: C, 62.43; H, 3.78; N, 8.09. Found: C, 62.39; H, 3.98; N, 7.93.

A mixture of 2-methoxy-7-nitro-4-trifluoromethyl-3*H*-benzo[*b*][1,4]diazepine (7e) and 4-methoxy-7-nitro-2-trifluoromethyl-3*H*-benzo[*b*][1,4]diazepine (7e'): bp (oven temperature) 150 °C / 3 mmHg; ^{1}H NMR ($CDCl_3$): δ 8.27-8.00 (m, 2H, H_{arom}), 7.73-7.57 (m, 1H, H_{arom}), 3.81 (br s, 3H, OCH_3), 3.24 (s, 2H, CH_2); IR (KBr): 1646 cm^{-1}. Anal. Calcd for $C_{11}H_8F_3N_3O_3$: C, 46.00; H, 2.81; N, 14.63. Found: C, 46.02; H, 2.98; N, 14.44.

Synthesis of 4-ethoxy-7,8-dimethyl-2-trifluoromethyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepin-2-ol (8).

To a solution of **3**[6] (214 mg, 1.0 mmol) in MeCN (4 mL) was added 4,5-dimethyl-1,2-phenylene-diamine (150 mg, 1.1 mmol) and the mixture was stirred for 1 h at room temperature. The solvent was removed under reduced pressure and the crude mixture was chromatographed on silica gel column using *n*-hexane-EtOAc (4:1) as eluent to give **8** (200 mg, 66%). **8**: mp 117-118 °C (*n*-hexane-EtOAc); ^{1}H NMR ($CDCl_3$): δ 6.79 (s, 1H, H_{arom}), 6.66 (s, 1H, H_{arom}), 4.35 (s, 1H, OH or NH), 4.24 (q, 2H, *J* = 7.0 Hz, $C\underline{H}_2CH_3$), 4.12 (s, 1H, OH or NH), 2.71 (d, 1H, *J* = 14.0 Hz, CH_2), 2.48 (d, 1H, *J* = 14.0 Hz, CH_2), 2.16 (s, 6H, CH_3), 1.30 (t, 3H, *J* = 7.0 Hz, $CH_2C\underline{H}_3$); IR (KBr): 3332, 3095, 1648 cm^{-1}. Anal. Calcd for $C_{14}H_{17}F_3N_2O_2$: C, 55.62; H, 5.67; N, 9.27. Found: C, 55.66; H, 5.66; N, 9.22.

General procedure for the dehydration of dihydrobenzodiazepinols (6 and 8) to benzodiazepines (7 and 9).

The dehydration of **6** and **8** was successfully carried out with the use of Kugelrohr distillation apparatus. The conditions are as follows: oven temperature, see Table 2; heating time, 1.5 h; reduced pressure, 3 mmHg.

2-Ethoxy-7,8-dimethyl-4-trifluoromethyl-3*H*-benzo[*b*][1,4]diazepine (9): mp 82-83 °C (*n*-hexane-EtOAc); ^{1}H NMR ($CDCl_3$): δ 7.26 (s, 1H, H_{arom}), 7.09 (s, 1H, H_{arom}), 4.30 (q, 2H, *J* = 7.0 Hz, $C\underline{H}_2CH_3$), 3.07 (s, 2H, CH_2), 2.31 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 1.32 (t, 3H, *J* = 7.0 Hz, $CH_2C\underline{H}_3$); IR (KBr): 1642, 1615 cm^{-1}. Anal. Calcd for $C_{14}H_{15}F_3N_2O$: C, 59.15; H, 5.32; N, 9.85. Found: C, 59.20; H, 5.36; N, 10.04.

REFERENCES

1. D. Lloyd and H. MacNab, *Adv. Heterocycl. Chem.*, 1998, **71**, 1.
2. (a) H. Schutz, 'Benzodiazepines,' Springer, Heidelberg, 1982. (b) R. I. Fryer, 'Comprehensive Heterocyclic Chemistry,' Wiley, New York, 1991. (c) L. Randall and B. Kappel, 'Benzodiazepines,' Raven Press, New York, 1973.
3. N. Ota, T. Tomoda, N. Terai, Y. Kamitori, D. Shibata, M. Médebielle, and E. Okada, *Heterocycles*, 2008, **76**, in press.
4. E. Okada, N. Ota, T. Tomoda, M. Fujimoto, and H. Takenaka, Jpn. Kokai Tokkyo Koho 2006-273844, 2006.
5. M. Hojo, R. Masuda, and Y. Kamitori, *Tetrahedron Lett.*, 1976, 1009.
6. M. Hojo, R. Masuda, and E. Okada, *Synthesis*, 1986, 1013.
7. M. Hojo, R. Masuda, E. Okada, H. Yamamoto, K. Moriomoto, and K. Okada, *Synthesis*, 1990, 195.
8. M. Hojo, R. Masuda, E. Okada, and Y. Mochizuki, *Synthesis*, 1992, 455.
9. M. A. P. Martins, C. M. P. Pereira, N. E. K. Zimmermann, W. Cunico, S. Moura, P. Beck, N. Zanatta, and H. G. Bonacorso, *J. Fluorine Chem.*, 2003, **123**, 261.
10. B. Narsaiah, A. Sivaprasad, and R. V. Venkataratnam, *J. Fluorine Chem.*, 1994, **66**, 47.
11. A. C. S. Reddy, P. S. Rao, and R. V. Venkataratnam, *Tetrahedron*, 1997, **53**, 5847.
12. Very recently, the synthesis of 1,1,1-trifluoro-4,4-dimethoxybut-3-en-2-one (**5**) was reported: M. Lubbe, A. Bunescu, M. Sher, A. Villinger, and P. Langer, *Synlett*, 2008, 1862.

CHAPTER 3

One Step Introduction of 4,4-Bis(trifluoroacetyl)-1,3-butadiene System to Aromatic Rings Using Fluorine-Containing 3,4-Dihydro-2*H*-pyrans. A Facile Synthetic Method for 1,1,1,5,5,5-Hexafluoro-3-[(*E*)-3-aryl-allylidene]pentane-2,4-diones

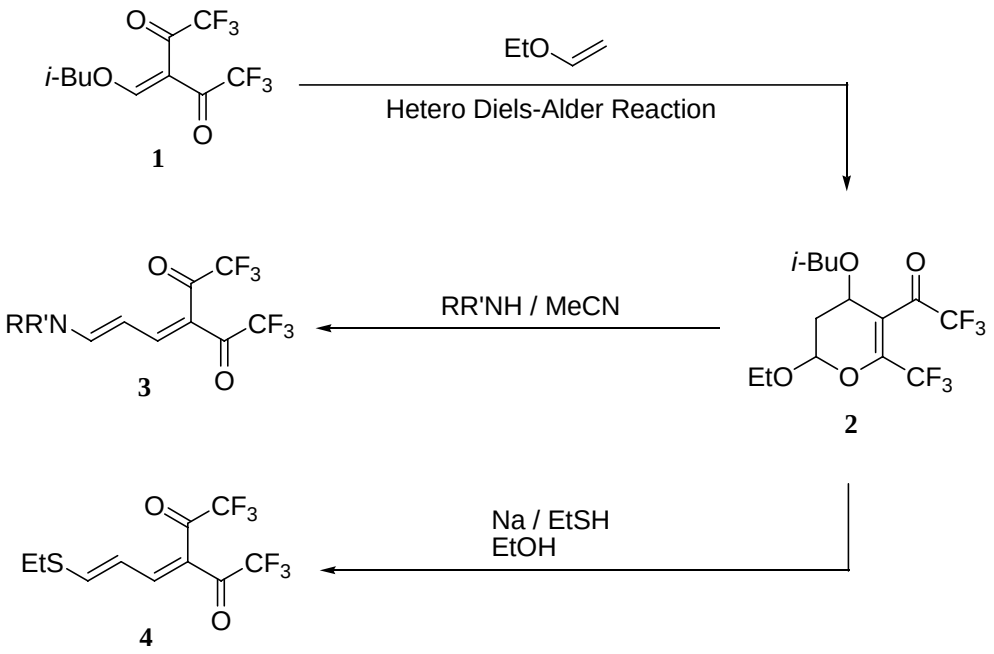
SUMMARY

New 1,1,1,5,5,5-hexafluoro-3-[(*E*)-3-arylallylidene]pentane-2,4-diones were synthesized in moderate to high yields by the ring-opening reaction of 1-(2-ethoxy-4-isobutoxy-6-trifluoromethyl-3,4-dihydro-2*H*-pyran-5-yl)-2,2,2-trifluoroethanone with aromatic compounds in refluxing trifluoroacetic acid.

INTRODUCTION

3-Allylidenepentane-2,4-diones and 2-allylidenepropane-1,3-dione systems are valuable building blocks for the synthesis of various heterocycles. It has been reported that the reaction of 3-allylidenepentane-2,4-diones with hydroxylamine give isoxazole, isoxazolone and 1,2-oxazepine derivatives.[1] Moreover, the syntheses of 3*H*-[1,2]dithioles,[2] pyrazolines[3] and dihydrofurans[4] from various 2-allylidenemalonates have been reported. 2-(3-Amidoallylidene)malonates and 2-(3-aminoallylidene)malonates are also known to undergo intramolecular cyclization reaction to give the corresponding pyridines or pyridones.[5] Recently much attention has been paid to the biological activities of fluorine-containing heterocycles because of their potential utility in medicinal and agricultural scientific fields.[6-9] Trifluoroacetylated alkenes could serve as versatile building blocks in the construction of functionalized heterocycles bearing trifluoromethyl groups, which are expected to show

interesting medicinal activities. On the other hand, the carbon-carbon bond formation has been one of the most significant and challenging subjects in organic chemistry. So, new methodologies for carbon-carbon bond forming reactions are of considerable interest in the field of organic synthesis.[10-12] Previously, we reported that the ring-opening reactions of fluorine-containing dihydropyran derivative **2**, which was easily prepared by the hetero Diels-Alder reaction of bis(trifluoroacetyl)vinyl ethers **1** with ethyl vinyl ether,[13] with amines and sodium ethanethilolate afforded the corresponding 4,4-bis(trifluoroacetyl)-1,3-butadienylamines **3**[14] and 4,4-bis(trifluoroacetyl)-1,3-butadienyl ethyl sulfide **4**[15], respectively (Scheme 1).



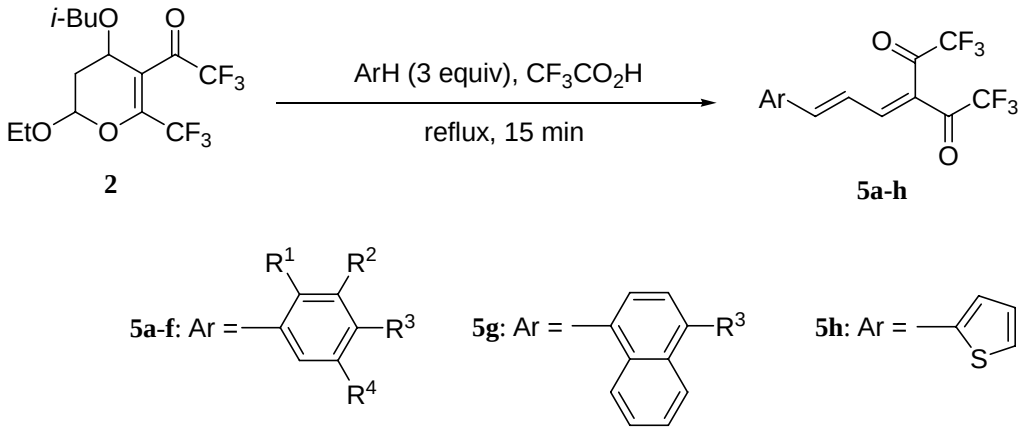
Scheme 1

In this chapter we wish to report a very facile and convenient synthetic method for 4,4-bis(trifluoroacetyl)-1,3-butadienylated aromatic compounds **5** through the acid-catalyzed C_8-unit introduction to aromatic rings by making use of fluorine-containing dihydropyran derivative **2**. Possibly, these new fluorinated 3-allylidenepentane-2,4-diones **5** can serve as versatile building blocks for the construction of CF_3 -containing heterocycles, which may be expected to show interesting biological activities.[6-9]

RESULTS AND DISCUSSION

The results of the present 4,4-bis(trifluoroacetyl)-1,3-butadienylation reaction of aromatics are shown in Scheme 2 and summarized in Table 1. Reaction of **2** with monosubstituted benzenes, anisole (3 equiv.), easily proceeded in refluxing trifluoroacetic acid within 15 min to give **5a**, 4,4-bis(trifluoroacetyl)butadienylated only at the *p*-position, in 66% yield (entry 1). Thioanisole also exhibited almost the same reactivity with anisole to afford the desired **5b** in 55% yield (entry 2).

Reaction of **2** with 1,3-disubstituted benzenes, for example, 1-methoxy-3-methylbenzene under the same conditions provided a mixture of two kinds of regioisomers **5c** (or **5c'**) and **5c'** (or **5c**) in



Scheme 2

42% and 21% yields, respectively (entry 3). Separation of the mixtures into **5c** and **5c'** was easily performed by column chromatography. In contrast to this, 4,4-bis(trifluoroacetyl)butadienylation reactions with 1,2-disubstituted benzenes such as 1-methoxy-2-methylbenzene and 1,2-dimethoxybenzene took place regioselectively to give the corresponding single isomers **5d** (or **5d'**) and **5e**, respectively, in good yields (entries 4 and 5). Similarly, trisubstituted benzenes, for example, 1,2-dimethoxy-4-methylbenzene reacted cleanly with **2** to afford the corresponding single regioisomer **5f** (or **5f'**) in 89% yield (entry 6).

It was, moreover, found that this type of 4,4-bis(trifluoroacetyl)-1,3-butadienylation had application to other aromatic compounds, as 1-methoxynaphthalene (naphthalenes) and thiophene

(heteroaromatics), to provide **5g** and **5h** in moderate yields (entries 7 and 8).

Table 1 Synthesis of 1,1,1,5,5,5-hexafluoro-3-[(*E*)-3-arylallylidene]pentane-2,4-diones (**5a-h**).

Entry	Compound	R^1	R^2	R^3	R^4	Product	Yield (%)[a]
1	**5a**	H	H	OMe	H	**5a**	66
2	**5b**	H	H	SMe	H	**5b**	55
3[b]	**5c**	OMe	H	Me	H	**5c** or **5c'**	42
	5c'	Me	H	OMe	H	**5c'** or **5c**	21
4[c]	**5d**	H	Me	OMe	H	**5d** or **5d'**	67
	5d'	H	OMe	Me	H		
5	**5e**	H	OMe	OMe	H	**5e**	72
6[c]	**5f**	Me	H	OMe	OMe	**5f** or **5f'**	89
	5f '	OMe	OMe	H	Me		
7	**5g**	-	-	OMe	-	**5g**	51
8	**5h**	-	-	-	-	**5h**	50

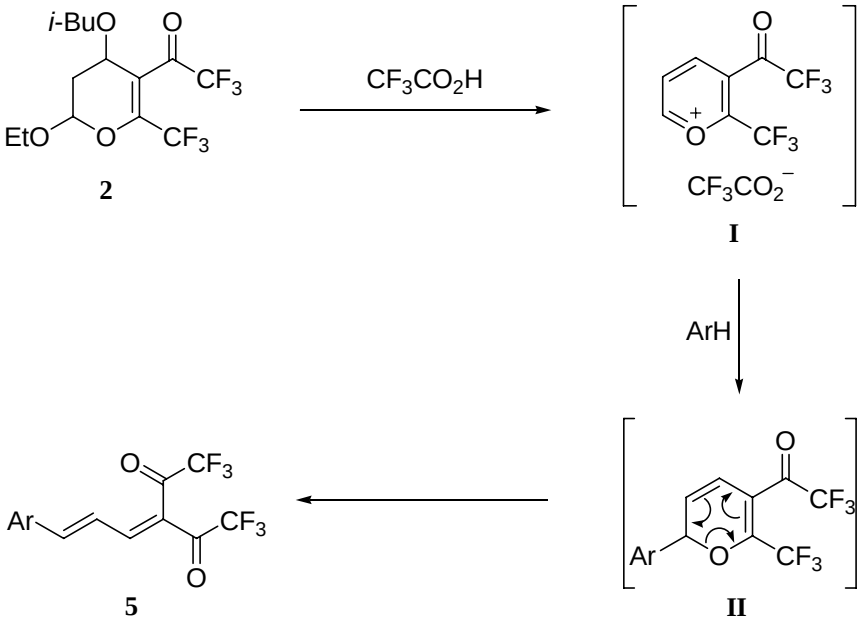
[a] Isolated yield.

[b] Two kinds of regioisomers **5c** and **5c'** were formed and each of them was separated by column chromatography. The regiochemical structure was not determined.

[c] Either of regioisomers was formed and the regiochemical structure was not determined.

A possible pathway for the formation of **5** is depicted in Scheme 3. Elimination of alcohols from **2** by trifluoroacetic acid occurs first to form pyrylium **I**, electrophilic substitution of aromatic compounds (ArH) with **I** gives 2*H*-pyran **II**, and finally **II** undergoes electrocyclic ring-opening reaction to afford **5**. The stereochemistry of all compounds **5a-h** was determined on the basis of ^{1}H-NMR spectral data. The large coupling constant $J_{CH=CH}$ (11-14 Hz) suggests

the *E* configuration. The regiochemical structure on benzene ring of **5c**/**5c'**, **5d**/**5d'** and **5f**/**5f '** was not determined.



Scheme 3

In conclusion, we have developed a very simple method for the introduction of fluorine-containing C_8-unit, 4,4-bis(trifluoroacetyl)-1,3-butadiene system, to aromatic rings and the novel fluorinated 3-(3-arylallylidene)pentane-2,4-diones **5**, which are not easily accessible by other methods, have been synthesized in one step by utilizing the acid-catalyzed ring-opening reaction of CF_3 - containing dihydropyran derivative **2** with aromatics. Further work is under progress in our laboratory on the synthetic application of **5** to the fluorine-containing heterocycles of potentially biological importance.

EXPERIMENTAL

Mps were determined on an electrothermal digital melting point apparatus and are uncorrected. The ^{13}C NMR spectra were recorded on a VARIAN Unity INOVA 400 spectrometer using TMS as an internal standard. ^{1}H NMR spectra were obtained with a JEOL PMX 60SI spectrometer. IR spectra were taken with a PerkinElmer Spectrum ONE FT-IR spectrometer. Microanalyses were taken with a YANACO CHN-Corder MT-5 analyzer.

General procedure for 4,4-bis(trifluoroacetyl)butadienylation of various aromatic compounds (ArH) by dihydropyran derivative 2.

To a mixture of **2**[9] (437 mg, 1.2 mmol) and ArH (3.6 mmol) was added trifluoroacetic acid (2 mL) and this solution was stirred at reflux temperature for 15 min. The mixture was washed with 10% aq. Na_2CO_3 (30 mL) and H_2O (30 mL), extracted with CH_2Cl_2 (30 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude mixture was chromatographed on silica gel column using *n*-hexane/benzene (1:1) as eluent to give **5**.

1,1,1,5,5,5-Hexafluoro-3-[(*E*)-3-(4-methoxyphenyl)allylidene]pentane-2,4-dione (4a): mp 86-87 °C (*n*-hexane/benzene); ^{1}H NMR: δ = 7.61 (d, 1H, *J* = 11.6 Hz, C<u>H</u>C($COCF_3$)$_2$), 7.39 (d, 2H, *J* = 8.6 Hz, H-3', H-5'), 7.24 (d, 1H, *J* = 12.8 Hz, C<u>H</u>CHCHC($COCF_3$)$_2$), 7.11 (dd, 1H, *J* = 12.8, 11.6 Hz, C<u>H</u>CHC($COCF_3$)$_2$), 6.78 (d, 2H, *J* = 8.6 Hz, H-2', H-6'), 3.79 (s, 3H, OCH_3); IR (KBr): 1679 (C=O) cm^{-1}. Anal. Calcd for $C_{15}H_{10}F_6O_3$: C, 51.15; H, 2.86; F, 32.36. Found: C, 50.88; H, 2.71; F, 32.24.

1,1,1,5,5,5-Hexafluoro-3-[(*E*)-3-(4-methylsulfanylphenyl)allylidene]pentane-2,4-dione (4b): mp 66-67 °C (*n*-hexane/benzene); ^{1}H NMR: δ = 7.68 (d, 1H, *J* = 11.0 Hz, C<u>H</u>C($COCF_3$)$_2$), 7.39 (d, 2H, *J* = 8.0 Hz, H-3', H-5'), 7.33 (d, 1H, *J* = 11.0 Hz, C<u>H</u>CHCHC($COCF_3$)$_2$), 7.13 (dd, 1H, *J* = 11.0, 11.0 Hz, C<u>H</u>CHC($COCF_3$)$_2$), 7.12 (d, 2H, J = 8.0 Hz, H-2', H-6'), 2.47 (s, 3H, SCH_3); IR (KBr): 1672 (C=O) cm^{-1}. Anal. Calcd for $C_{15}H_{10}F_6O_2S$: C, 48.92; H, 2.74; F, 30.95. Found: C, 48.36; H, 2.66; F, 30.53.

1,1,1,5,5,5-Hexafluoro-3-[(*E*)-3-(2-methoxy-4-methylphenyl)allylidene]pentane-2,4-dione (4c): mp 58-59 °C (*n*-hexane/benzene); ^{1}H NMR: δ = 7.63 (d, 1H, *J* = 12.0 Hz, C<u>H</u>C(COCF$_3$)$_2$), 7.48 (d, 1H, *J* = 12.0 Hz, C<u>H</u>CHCHC(COCF$_3$)$_2$), 6.88 (dd, 1H, *J* = 12.0, 12.0 Hz, C<u>H</u>CHC(COCF$_3$)$_2$), 6.67 (d, 1H, *J* = 6.4 Hz, H-6'), 6.63 (d, 1H, *J* = 6.4 Hz, H-5'), 6.58 (s, 1H, H-3'), 3.74 (s, 3H, OCH$_3$), 2.38 (s, 3H, CH$_3$); IR (KBr): 1689 (C=O) cm^{-1}. Anal. Calcd for C$_{16}$H$_{12}$F$_6$O$_3$: C, 52.47; H, 3.30; F, 31.12. Found: C, 52.47; H, 3.28; F, 29.26.

1,1,1,5,5,5-Hexafluoro-3-[(*E*)-3-(4-methoxy-2-methylphenyl)allylidene]pentane-2,4-dione (4c'): mp 93-94 °C (*n*-hexane/benzene); ^{1}H NMR: δ = 7.64 (d, 1H, *J* = 12.0 Hz, C<u>H</u>C(COCF$_3$)$_2$), 7.56 (d, 1H, *J* = 13.0 Hz, C<u>H</u>CHCHC(COCF$_3$)$_2$), 7.23 (dd, 1H, *J* = 13.0, 12.0 Hz, C<u>H</u>CHC(COCF$_3$)$_2$), 7.23 (d, 1H, *J* = 8.0 Hz, H-6'), 6.66 (d, 1H, *J* = 8.0 Hz, H-5'), 6.59 (s, 1H, H-3'), 3.81 (s, 3H, OCH$_3$), 2.35 (s, 3H, CH$_3$); IR (KBr): 1682 (C=O) cm^{-1}. Anal. Calcd for C$_{16}$H$_{12}$F$_6$O$_3$: C, 52.47; H, 3.30; F, 31.12. Found: C, 52.52; H, 3.30; F, 31.42.

1,1,1,5,5,5-Hexafluoro-3-[(*E*)-3-(4-methoxy-3-methylphenyl)allylidene]pentane-2,4-dione (4d): mp 111-112 °C (*n*-hexane/benzene); ^{1}H NMR: δ = 7.67 (d, 1H, *J* = 10.0 Hz, C<u>H</u>C(COCF$_3$)$_2$), 7.34 (d, 1H, *J* = 7.0 Hz, H-6'), 7.28 (d, 1H, *J* = 11.0 Hz, C<u>H</u>CHCHC(COCF$_3$)$_2$), 7.25 (s, 1H, H-2'), 7.19 (d, 1H, *J* = 7.0 Hz, H-5'), 6.80 (dd, 1H, *J* = 11.0, 10.0 Hz, C<u>H</u>CHC(COCF$_3$)$_2$), 3.83 (s, 3H, OCH$_3$), 2.20 (s, 3H, CH$_3$); IR (KBr): 1682 (C=O) cm^{-1}. Anal. Calcd for C$_{16}$H$_{12}$F$_6$O$_3$: C, 52.47; H, 3.30; F, 31.12. Found: C, 52.79; H, 3.38; F, 31.10.

3-[(*E*)-3-(3,4-Dimethoxyphenyl)allylidene]-1,1,1,5,5,5-hexafluoropentane-2,4-dione (4e): mp 119-120 °C (*n*-hexane/benzene); ^{1}H NMR: δ = 7.70 (d, 1H, *J* = 10.0 Hz, C<u>H</u>C(COCF$_3$)$_2$), 7.22 (s, 1H, H-2'), 7.15 (d, 1H, *J* = 8.0 Hz, H-6'), 7.12 (d, 1H, *J* = 13.0 Hz, C<u>H</u>CHCHC(COCF$_3$)$_2$), 6.98 (dd, 1H, *J* = 13.0, 10.0 Hz, C<u>H</u>CHC(COCF$_3$)$_2$), 6.83 (d, 1H, *J* = 8.0 Hz, H-5'), 3.90 (s, 6H, OCH$_3$); IR (KBr): 1678 (C=O) cm^{-1}. Anal. Calcd for C$_{16}$H$_{12}$F$_6$O$_4$: C, 50.27; H, 3.16; F, 29.82. Found: C, 50.27; H, 3.19; F, 29.33.

3-[(*E*)-3-(4,5-Dimethoxy-2-methylphenyl)allylidene]-1,1,1,5,5,5-hexafluoropentane-2,4-

dione (4f): mp 112-113 °C (*n*-hexane/benzene); ^{1}H NMR: δ = 7.72 (d, 1H, *J* = 12.0 Hz, C<u>H</u>C(COCF$_3$)$_2$), 7.57 (d, 1H, *J* = 12.0 Hz, C<u>H</u>CHCHC(COCF$_3$)$_2$), 6.98 (s, 1H, H-6'), 6.91 (dd, 1H, *J* = 12.0, 12.0 Hz, C<u>H</u>CHC(COCF$_3$)$_2$), 6.63 (s, 1H, H-3'), 6.36 (s, 1H, H-3'), 3.87 (s, 6H, OCH$_3$), 2.42 (s, 3H, CH$_3$); IR (KBr): 1710 (C=O) cm^{-1}. Anal. Calcd for $C_{17}H_{14}F_6O_4$: C, 51.52; H, 3.56; F, 28.77. Found: C, 51.46; H, 3.39; F, 28.72.

1,1,1,5,5,5-Hexafluoro-3-[(*E*)-3-(4-methoxynaphthalen-1-yl)allylidene]pentane-2,4-dione (4g): mp 125-126 °C (*n*-hexane/benzene); ^{1}H NMR: δ = 8.27-7.35 (m, 6H, H-5'-H-8', C<u>H</u>C(COCF$_3$)$_2$, C<u>H</u>CHCHC(COCF$_3$)$_2$), 7.57 (d, 1H, *J* = 8.2 Hz, 1H, H-2'), 7.08 (dd, 1H, *J* = 14.0, 12.0 Hz, 1H, C<u>H</u>CHC(COCF$_3$)$_2$), 6.72 (d, 1H, *J* = 8.2 Hz, H-3'), 3.97 (s, 3H, OCH$_3$); IR (KBr): 1648 (C=O) cm^{-1}. Anal. Calcd for $C_{19}H_{12}F_6O_3$: C, 56.73; H, 3.01; F, 28.33. Found: C, 56.56; H, 2.83; F, 28.05.

1,1,1,5,5,5-Hexafluoro-3-[(*E*)-3-thiophen-2-ylallylidene]pentane-2,4-dione (4h): mp 88-89 °C (*n*-hexane/benzene); ^{1}H NMR: δ = 7.61 (d, 1H, *J* = 14.4 Hz, C<u>H</u>C(COCF$_3$)$_2$), 7.56 (d, 1H, *J* = 4.8 Hz, H-5'), 7.46 (d, 1H, *J* = 12.0 Hz, C<u>H</u>CHCHC(COCF$_3$)$_2$), 7.34 (d, 1H, *J* = 5.6 Hz, H-3'), 7.06 (dd, 1H, *J* = 5.6, 4.8 Hz, H-4'), 6.83 (dd, 1H, *J* = 14.4, 12.0 Hz, C<u>H</u>CHC(COCF$_3$)$_2$); IR (KBr): 1686 (C=O) cm^{-1}. Anal. Calcd for $C_{12}H_6F_6O_2S$: C, 43.91; H, 1.84; F, 34.73. Found: C, 43.66; H, 1.76; F, 34.49.

REFERENCES

1. T. Kurihara, K. Nasu, Y. Mizuhara, and K. Hayashi, *Chem. Pharm. Bull.*, 1982, **30**, 2742; K. Huang, C. Li, Q. Liu, H. Bai, and Z. Mu, *Gaodeng Xuexiao Huaxue Xuebao*, 2004, **25**, 1264.
2. H. Quiniou and N. Lozac'h, *Bull. Soc. Chim. Fr.*, 1963, 1171.
3. H. Abdallah, R. Gree, and R. Carrie, *Can. J. Chem.*, 1985, **63**, 3031.
4. Z. Arnold, V. Kral, G. V. Kryshtal, and L. A. Yanovskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1983, 2162.
5. I. Shibuya and M. Kurabayashi, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 73; M. T. Cocco, C. Congiu, A. Maccioni, and A. J. Plumitallo, *Heterocycl. Chem.*, 1989, **26**, 1859.
6. R. Filler and Y. Kobayashi, 'Biomedicinal Aspects of Fluorine Chemistry,' Kodansha & Elsevier Biomedical, Tokyo, 1982.
7. R. Filler, 'Organofluorine Chemicals and Their Industrial Applications,' Ellis Horwood, London, 1979.
8. J. T. Welch, *Tetrahedron*, 1987, **43**, 3123.
9. R. Filler, Y. Kobayashi, and L. M. Yagupolskii, 'Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications,' Elsevier, Amsterdam, 1993.
10. B. M. Trost, *Angew. Chem., Int. Ed.*, 1995, **34**, 259.
11. B. M. Trost, F. D. Toste, and A. B. Pinkerton, *Chem. Rev.*, 2001, **101**, 2067.
12. V. Ritleng, V. C. Sirlin, and M. Pfeffer, *Chem. Rev.*, 2002, **102**, 1731.
13. M. Hojo, R. Masuda, and E. Okada, *Synthesis*, 1990, 347.
14. M. Hojo, R. Masuda, and E. Okada, *Synthesis*, 1990, 425.
15. M. Hojo, R. Masuda, and E. Okada, *Synthesis*, 1991, 46.

CHAPTER 4

A Facile and Convenient Synthetic Method for 2-Bis(trifluoroacetyl)-methylene- and 2-Trifluoroacetylmethylene-2,3-dihydro-3-methyl-thiazoles

SUMMARY

2,3-Dimethylthiazolium iodides (**1**) reacted easily with trifluoroacetic anhydride in the presence of pyridine to give 2-bis(trifluoroacetyl)methylene-2,3-dihydro-3-methylthiazoles (**2**) in excellent yields. Deacylation of **2** proceeded readily in moderate to high yields by acid catalyst such as silica gel and aqueous hydrochloric acid to afford the corresponding 2-trifluoroacetylmethylene-2,3-dihydro-3-methylthiazoles (**3**), which were smoothly reconverted into diacylated compounds (**2**) with trifluoroacetic anhydride. The highly poralized structure of **2** was also briefly discussed.

INTRODUCTION

Much attention in recent years has been focused on the development of new methodologies for the syntheses of many kinds of fluorine-containing heterocycles, since these compounds are now widely recognized as important organic materials showing specific functions as well as interesting biological activities.[1-4]

Besides, thiazole and thiazoline rings are important heterocyclic systems because of being applicable to the creation of useful biologically active substances as medicinal and agricultural chemicals. In medicinal scientific fields, some typical histamine H_2 receptor antagonists, which

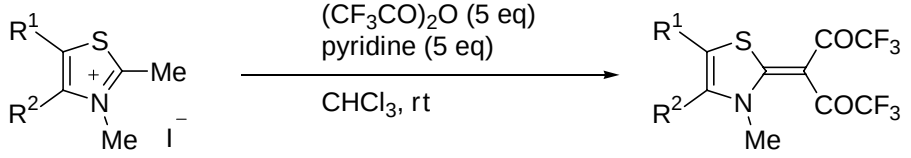
are well-known agents for peptic ulcer, are composed of a thiazole ring as an essential unit.[5-8] Third generation cephalosporins, which have a 2-(2-aminothiazol-4-yl)acetamido moiety as a 7β-side chain, have a broad spectrum of activity and further increased activity against gram-negative organisms.[9-12] In addition, most of fourth generation cephalosporins having a greater resistance to β-lactamases than the third generations also have a 7-(2-aminothiazol-4-yl)acetamido system.[11,12] Treatment with above medicines has been widely recommended as first-line treatment up to now in clinical practice. In common with these thiazole-containing medicines, chemical modification of thiazole ring has been attempted vigorously in agricultural scientific fields. For example, a fundamental approach to herbicides using new thiazolyliden-ketonitriles as suitable structure has been carried out since they have inhibitory activity of photosystem II.[13] In that study, it has been reported that 3-oxo-4-phenyl-2-[4-phenyl-3*H*-thiazol-(2*E*)-ylidene]butyronitrile possessed especially high activity of inhibition of photosystem II, and suggested that the thiazole-thiazoline tautomerism would contribute to the inhibition of photosynthetic electron flow.

In the course of our investigations on the synthesis of various trifluoroacetylated olefins by the electrophilic substitutions[14-18,23] of olefinic hydrogens and the nucleophilic substitutions[15,19-23] at olefinic carbons, it was found that ketene dithioacetals[14] and orthoacetates[15] reacted with trifluoroacetic anhydride quite easily to afford the corresponding β-trifluoroacetylated ketene *S*,*S*- and *O*,*O*-acetals, respectively, and that these acylated compounds cleanly underwent nucleophilic *O*-*N* and *S*-*N* exchange reactions[21,23] with various aliphatic and aromatic amines to give β-trifluoroacetylated ketene *S*,*N*-, *O*,*N*-, and *N*,*N*-acetals.

In continuation of our extensive studies on the synthesis of trifluoroacetylated ketene acetals and their analogues, we here report an efficient synthetic method for new cyclic β-trifluoroacetylated ketene *S*,*N*-acetals, 2-bis(trifluoroacetyl)methylene- and 2-trifluoroacetylmethylene-2,3-dihydro-3-methylthiazoles (**2** and **3**), from 2,3-dimethylthiazolium iodides (**1**) with trifluoroacetic anhydride by improving the previously reported method.[24] Moreover, the highly poralized structure of diacylated compounds (**2**) is also described.

RESULTS AND DISCUSSION

We examined the reaction of 3-methylthiazolium iodides (**1**) with trifluoroacetic anhydride (Scheme 1 and Table 1).



1a-f **2a-f**

Scheme 1

Table 1 Bis(trifluoroacetylation) of 2-methylthiazolium iodides (**1a-f**).

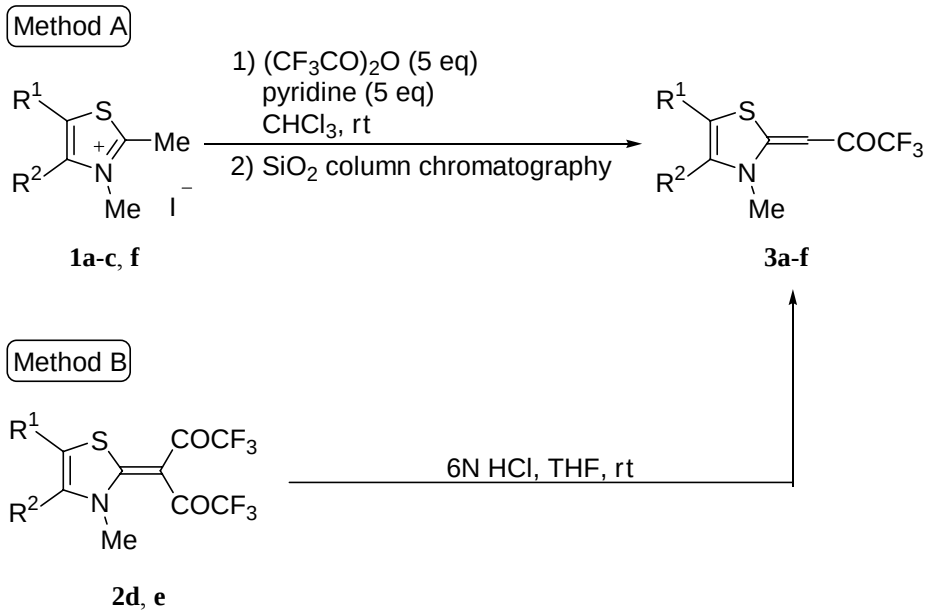
Entry	Substrate	R^1	R^2	Time (h)	Product	Yield (%)[a]
1	**1a**	H	H	4	**2a**	80
2	**1b**	H	Me	4	**2b**	84
3	**1c**	Me	H	4	**2c**	92
4[b]	**1d**	Me	Me	17	**2d**	89
5	**1e**	EtO	H	21	**2e**	70
6	**1f**	Cl	H	4	**2f**	91

[a] Isolated yields.

[b] Molar ratio, [**1d**] / [$(CF_3CO)_2O$] / [pyridine] = 1 / 10 / 10.

Reaction of 4,5-unsubstituted thiazolium iodides (**1a**) with 5 times molar amounts of trifluoroacetic anhydride in the presence of pyridine in chloroform easily proceeded at room temperature within 4 h to give 2-bis(trifluoroacetyl)methylene-2,3-dihydro-3-methylthiazole (**2a**) in 80% yield (entry 1). 4-Methyl-, 5-methyl-, and 5-chlorothiazolium iodides (**1b**,**c**,**f**) also exhibited the same reactivity with 4,5-unsubstituted thiazolium iodides (**1a**) to afford the

corresponding 2-bis(trifluoroacetyl)methylene-2,3-dihydro-3-methylthiazoles (**2b,c,f**) in high yields (entries 2, 3, and 6). However, in the cases of 4,5-dimethyl- and 5-ethoxythiazolium iodides (**1d,e**), prolongation of the reaction time or/and large excess (10 times molar) amounts of the reagents were necessary to complete the reaction (entries 4 and 5). Previously, Bailey et al. reported the reaction, as the sole example of thiazolium salts, of 2,3-dimethylbenzo[*d*]thiazolium iodide with trifluoroacetic anhydride (10 eq) in the presence of pyridine (9 eq) for 15 min at 0 °C without solvent to give 2-bis(trifluoroacetyl)methylene-2,3-dihydro-3-methylbenzo-[*d*]thiazole in a low yield (45%).[24] In contrast to this, the significant improvement of product yields would be achieved by the present method using chloroform as a solvent.



Scheme 2

Acid-catalyzed deacylation of **2a-f** proceeded quite easily at room temperature to afford the corresponding 2-trifluoroacetylmethylene-2,3-dihydro-3-methylthiazoles (**3a-f**) in moderate to high yields (Scheme 2 and Table 2). 4,5-Unsubstituted, 4-methyl, 5-methyl, and 5-chloro derivatives (**3a-c** and **3f**) could be quite easily synthesized merely by submitting the crude products (**2a-c** and **2f**), prepared by bis(trifluoroacetylation) of **1a-c** and **1f**, to column chromatography on silica gel (entries 1-3 and 6, Method A). Deacylation of 4,5-dimethyl and 5-ethoxy derivatives (**2d**, **e**) did not take place merely by passing them through silica gel column.

Treatment of **2d** and **2e** with 6N hydrochloric acid at room temperature for 4 h in tetrahydrofuran led to successful deacylation to give **3d** and **3e**, respectively (entries 4 and 5, Method B).
Next, we tried to synthesize 5-bromo-4-methyl derivative (**3g**) by bromination of 4-methyl one (**3b**) as depicted in Scheme 3. Regioselective bromination of **3b** with an equimolar amount of bromine proceeded quite easily and cleanly at room temperature for 4 h in chloroform to give the

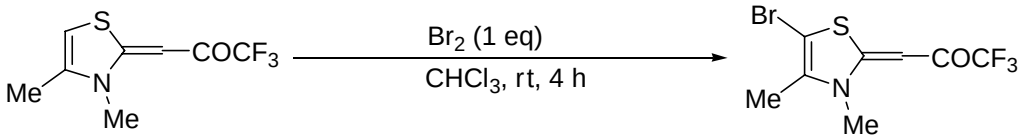
Table 2 Synthesis of monoacylated compounds (**3a-f**).

Entry	Substrate	R^1	R^2	Method[a]	Time (h)	Product	Yield (%)[b]
1	**1a**	H	H	A	4	**3a**	65
2	**1b**	H	Me	A	43	**3b**	87
3	**1c**	Me	H	A	4	**3c**	72
4	**2d**	Me	Me	B	4	**3d**	84
5	**2e**	EtO	H	B	4	**3e**	88
6	**1f**	Cl	H	A	23	**3f**	91

[a] Method A: SiO_2 column chromatography, Method B: 6N HCl.

[b] Isolated yields.

desired **3g** as a sole product in 79% yield without any formation of by-products brominated at other positions.

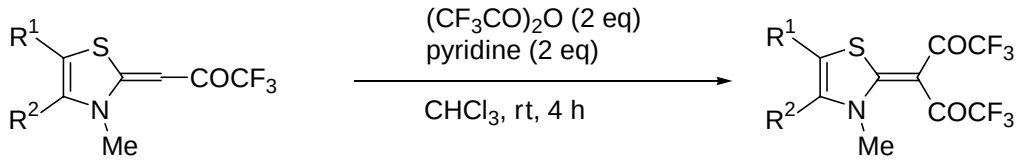


3b **3g** 79 %

Scheme 3

In addition we tried the transformation of monoacylated **3a-g** to diacylated **2a-g**, specially to prepare bis(trifluoroacetylated) 5-bromo-4-methyl derivative (**2g**). The desired diacylation was

successfully performed by treatment of **3a-g** with 2 times molar amounts of trifluoroacetic anhydride and pyridine in chloroform for 4 h to afford the corresponding **2a-g** in excellent yields (Scheme 4 and Table 3).



3a-g **2a-g**

Scheme 4

Table 3 Bis(trifluoroacetylation) of monoacylated compounds (**3a-g**).

Entry	Substrate	R^1	R^2	Product	Yield (%)[a]
1	**3a**	H	H	**2a**	97
2	**3b**	H	Me	**2b**	97
3	**3c**	Me	H	**2c**	91
4	**3d**	Me	Me	**2d**	96
5	**3e**	EtO	H	**2e**	91
6	**3f**	Cl	H	**2f**	97
7	**3g**	Br	Me	**2g**	98

[a] Isolated yields.

The selected ^{1}H NMR chemical shifts for thiazolium iodides (**1**), bis(trifluoroacetylated) derivatives (**2**), and mono(trifluoroacetylated) ones (**3**) are summarized in Table 4. Interestingly, the signals of H-4 (8.23 ppm) and H-5 (8.00 ppm) for **2a** (diacyl) appeared in much lower field than those (H-4: 7.28 ppm, H-5: 6.80 ppm) for **3a** (monoacyl) and were very close to those (H-4: 8.25 ppm, H-5: 7.98 ppm) for **1a** (thiazolium). The ^{1}H NMR spectra of other compounds (**1b**,**c**,**e**,**f**, **2b**,**c**,**e**,**f**, and **3b**,**c**,**e**,**f**) showed a marked tendency similar to those of **1a**, **2a**, and **3a**. IR spectra for diacylated derivatives (**2a-g**) showed an absorption in the range of 1641-1669 cm^{-1}

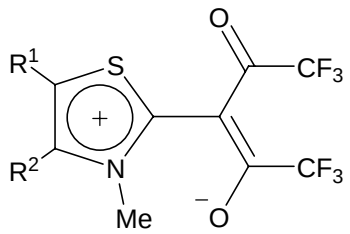
Table 4 The selected ^{1}H NMR chemical shifts of **1-3** in $CDCl_3$/DMSO-d_6 (2/1) [δ, ppm].

Compound	H-4	H-5	CH_3-3	CH_3-4	CH_3-5
1a	8.25[a]	7.98[a]	4.02[a]	-	-
2a	8.23	8.00	3.87	-	-
3a	7.28	6.80	3.66	-	-
1b	-	7.72	3.99	2.58	-
2b	-	7.75	3.68	2.59	-
3b	-	6.48	3.54	2.33	-
1c	8.12	-	4.10	-	2.52
2c	7.97	-	3.78	-	2.56
3c	6.95	-	3.59	-	2.29
1d	-	-	3.98	2.47	2.47
2d	-	-	3.67	2.49	2.49
3d	-	-	3.51	2.22	2.22
1e	8.03	-	4.20	-	-
2e	7.65	-	3.74	-	-
3e	6.70	-	3.54	-	-
1f	8.44	-	4.05	-	-
2f	8.27	-	3.71	-	-
3f	7.27	-	3.62	-	-
2g	-	-	3.76	2.57	-
3g	-	-	3.64	2.34	-

[a] Measured in DMSO-d_6.

(ν C=O). This band was absent for monoacylated derivatives (**3a-g**). These suggest that the aromatization of thiazoline to thiazolium takes place for diacylated derivatives (**2**) to form the inner thiazolium salts (**2'**) which have the highly polarized structure bearing an isolated

trifluoroacetyl group as depicted in Figure 1 (resonance contribution from a zwitter ionic structure).



2'

Figure 1

Finally we examined some reactions of **2b** with amines in order to prove the highly polarized structure of **2** from the standpoint of the reactivity. Reaction of **2b** with *N*,*N'*-diethylethylenediamine didn't take place in refluxing acetonitrile for 16 h and 80% of the substrate (**2b**) was recovered unchanged. Benzylamine reacted with **2b** in refluxing acetonitrile for 41 h to afford *N*-benzyl-2,2,2-trifluoroacetamide quantitatively with deacylated product (**3b**) in 94% yield. Thus, in both cases, neither nucleophilic *S*-*N* nor *N*-*N* exchange reaction occurred at the olefinic carbon atom in this new cyclic β-trifluoroacetylated ketene *S*,*N*-acetal system. This is undoubtedly due to the highly polarized thiazolium structure (**2'**) for **2b** in which there is a considerable *C*-*C* single-bond character on the exomethylene moiety.

In conclusion, the present method provides a simple and efficient access to various 2-bis(trifluoroacetyl)methylene- and 2-trifluoroacetylmethylene-2,3-dihydro-3-methylthiazoles which are not easily obtained by other methods. Evaluation of biological activities for **2a-g** and **3a-g** is now under way.

EXPERIMENTAL

General procedure for bis(trifluoroacetylation) of 2-methylthiazolium iodides (1).

To an ice-cooled mixture of **1**[25,26] (2 mmol) and pyridine (0.791 g, 10 mmol) was added dropwise a solution of trifluoroacetic anhydride (2.10 g, 10 mmol) in dry $CHCl_3$ (3 mL) with continuous stirring (in the case of **1d**, each 20 mmol of pyridine and trifluoroacetic anhydride was used). After stirring for 4 - 21 h at ambient temperature, the mixture was dissolved in CH_2Cl_2 (50 mL). The whole mixture was washed with aq. Na_2CO_3 and dried over Na_2SO_4. Removal of the solvent and pyridine under vacuum afforded 2-bis(trifluoroacetyl)methylene-2,3-dihydro-3-methylthiazoles (**2a-f**).

1,1,1,5,5,5-Hexafluoro-3-(3-methyl-3*H*-thiazol-2-ylidene)pentane-2,4-dione (2a): mp 98-99 °C (hexane-benzene) ; ^{1}H NMR ($CDCl_3$) δ 3.84 (s, 3H, CH_3), 7.72 (d, *J*= 4.0 Hz, 1H, SCH=C), 7.92 (d, *J*= 4.0 Hz, 1H, NCH=C); IR (KBr) 1641, 1597, 1547 cm^{-1}.

3-(3,4-Dimethyl-3*H*-thiazol-2-ylidene)-1,1,1,5,5,5-hexafluoropentane-2,4-dione (2b): mp 133-134 °C (hexane-benzene); ^{1}H NMR ($CDCl_3$) δ 2.57 (s, 3H, CCH_3), 3.70 (s, 3H, NCH_3), 7.45 (s, 1H, CH); IR (KBr) 1658, 1580 cm^{-1}. Anal. Calcd for $C_{10}H_7F_6NO_2S$: C, 37.62; H, 2.21; N, 4.39; F, 35.71. Found: C, 37.54; H, 2.04; N, 4.53; F, 35.75.

3-(3,5-Dimethyl-3*H*-thiazol-2-ylidene)-1,1,1,5,5,5-hexafluoropentane-2,4-dione (2c): mp 128-129 °C (hexane-benzene); ^{1}H NMR ($CDCl_3$) δ 2.59 (s, 3H, CCH_3), 3.81 (s, 3H, NCH_3), 7.75 (s, 1H, CH); IR (KBr) 1654, 1580 cm^{-1}.

1,1,1,5,5,5-Hexafluoro-3-(3,4,5-trimethyl-3*H*-thiazol-2-ylidene)pentane-2,4-dione (2d): mp 173- 174 °C (hexane-benzene); ^{1}H NMR ($CDCl_3$/DMSO-d_6= 2/1) δ 2.49 (s, 6H, CCH_3), 3.67 (s, 3H, NCH_3); IR (KBr) 1664, 1591 cm^{-1}. Anal. Calcd for $C_{11}H_9F_6NO_2S$: C, 39.65; H, 2.72; N, 4.20; F, 34.21. Found: C, 39.93; H, 2.61; N, 4.04; F, 34.06.

3-(5-Ethoxy-3-methyl-3*H*-thiazol-2-ylidene)-1,1,1,5,5,5-hexafluoropentane-2,4-dione (2e): mp 96- 97 °C (crude product); ^{1}H NMR ($CDCl_3$) δ 1.49 (t, *J*= 6.8 Hz, 3H, $CH_2C\underline{H}_3$), 3.76 (s, 3H, NCH_3), 4.23 (q, *J*= 6.8 Hz, 2H, CH_2), 7.40 (s, 1H, CH); IR (KBr) 1659, 1600, 1576 cm^{-1}.

3-(5-Chloro-3-methyl-3*H*-thiazol-2-ylidene)-1,1,1,5,5,5-hexafluoropentane-2,4-dione (2f): mp (decomp) 91-93 °C (crude product); ^{1}H NMR ($CDCl_3$) δ 3.72 (s, 3H, CH_3), 7.54 (s, 1H, CH); IR (KBr) 1669, 1589, 1554 cm^{-1}.

Synthesis of 2-trifluoroacetylmethylene-2,3-dihydro-3-methylthiazoles (3a-c,f): Method A.
To an ice-cooled mixture of **1** (2 mmol) and pyridine (0.791 g, 10 mmol) was added dropwise a solution of trifluoroacetic anhydride (2.10 g, 10 mmol) in dry $CHCl_3$ (3 mL) with continuous stirring. After stirring for 4 - 43 h at ambient temperature, the mixture was dissolved in CH_2Cl_2 (50 mL). The whole mixture was washed with aq. Na_2CO_3 and then with dil. HCl, and dried over Na_2SO_4. Evaporation of the solvent and fractionation of a residue by silica gel column chromatography (CH_2Cl_2) afforded 2-trifluoroacetylmethylene-2,3-dihydro-3-methylthiazoles (**3a-c**,**f**).

Synthesis of 2-trifluoroacetylmethylene-2,3-dihydro-3-methylthiazoles (3d,e): Method B.
To a solution of **2** (0.710 mmol) dissolved in THF (4 mL) was added 6 N HCl (8 mL). After stirring for 4 h at ambient temperature, the mixture was extracted with CH_2Cl_2 (50 mL). The organic layer was washed with water and dried over Na_2SO_4, and the solvent was evaporated to give 2-trifluoroacetylmethylene-2,3-dihydro-3-methylthiazoles (**3d**,**e**).

1,1,1-Trifluoro-3-(3-methyl-3*H*-thiazol-2-ylidene)propan-2-one (3a): mp 175-176 °C (hexane-benzene); ^{1}H NMR ($CDCl_3$) δ 3.62 (s, 3H, CH_3), 5.95 (s, 1H, $CHCOCF_3$), 6.66 (d, *J*= 4.2 Hz, 1H, SCH=C), 6.84 (d, *J*= 4.2 Hz, 1H, NCH=C); IR (KBr) 1581, 1527 cm^{-1}. Anal. Calcd for $C_7H_6F_3NOS$: C, 40.19; H, 2.89; N, 6.70; F, 27.25. Found: C, 40.46; H, 2.88; N, 6.90; F, 27.05.

3-(3,4-Dimethyl-3*H*-thiazol-2-ylidene)-1,1,1-trifluoropropan-2-one (3b): mp 175-176 °C (hexane-benzene); ^{1}H NMR ($CDCl_3$) δ 2.29 (s, 3H, CCH_3), 3.48 (s, 3H, NCH_3), 5.87 (s, 1H,

$CHCOCF_3$), 6.28 (s, 1H, SCH=C); IR (KBr) 1582, 1522 cm^{-1}. Anal. Calcd for $C_8H_8F_3NOS$: C, 43.05; H, 3.61. Found: C, 43.33; H, 3.46.

3-(3,5-Dimethyl-3*H*-thiazol-2-ylidene)-1,1,1-trifluoropropan-2-one (3c): mp 173-174 °C (hexane-benzene); ^1H NMR ($CDCl_3$) δ 2.27 (s, 3H, CCH_3), 3.53 (s, 3H, NCH_3), 5.82 (s, 1H, $CHCOCF_3$), 6.67 (s, 1H, NCH=C); IR (KBr) 1580, 1520 cm^{-1}. Anal. Calcd for $C_8H_8F_3NOS$: C, 43.05; H, 3.61; N, 6.27; F, 25.53. Found: C, 42.91; H, 3.48; N, 6.30; F, 25.32.

1,1,1-Trifluoro-3-(3,4,5-trimethyl-3*H*-thiazol-2-ylidene)propan-2-one (3d): mp 155-156 °C (hexane-benzene); ^1H NMR ($CDCl_3$) δ 2.16 (s, 6H, CCH_3), 3.42 (s, 3H, NCH_3), 5.75 (s, 1H, CH); IR (KBr) 1580, 1511 cm^{-1}.

3-(5-Ethoxy-3-methyl-3*H*-thiazol-2-ylidene)-1,1,1-trifluoropropan-2-one (3e): mp 145-146 °C (hexane-benzene); ^1H NMR ($CDCl_3$) δ 1.40 (t, *J*= 6.0 Hz, 3H, $CH_2C\underline{H}_3$), 3.48 (s, 3H, NCH_3), 4.00 (q, *J*= 6.0 Hz, 2H, CH_2), 5.77 (s, 1H, $CHCOCF_3$), 6.33 (s, 1H, NCH=C); IR (KBr) 1609, 1563, 1534 cm^{-1}. Anal. Calcd for $C_9H_{10}F_3NO_2S$: C, 42.69; H, 3.98; N, 5.53; F, 22.51. Found: C, 42.40; H, 3.73; N, 5.41; F, 22.21.

3-(5-Chloro-3-methyl-3*H*-thiazol-2-ylidene)-1,1,1-trifluoropropan-2-one (3f): mp 154-155 °C (hexane-benzene); ^1H NMR ($CDCl_3$) δ 3.56 (s, 3H, NCH_3), 5.95 (s, 1H, $CHCOCF_3$), 6.83 (s, 1H, NCH=C); IR (KBr) 1581, 1567, 1528, 1511 cm^{-1}. Anal. Calcd for $C_7H_5ClF_3NOS$: C, 34.51; H, 2.07; N, 5.75; F, 23.39; Cl, 14.55. Found: C, 34.92; H, 1.99; N, 5.78; F, 23.12; Cl, 14.20.

Synthesis of 3-(5-bromo-3,4-dimethyl-3*H*-thiazol-2-ylidene)-1,1,1-trifluoropropan-2-one (3g).

To a stirred solution of **3b** (304 mg, 1.36 mmol) in $CHCl_3$ (10 mL) was added dropwise Br_2 (227 mg, 1.42 mmol) and the mixture was stirred for 4 h at ambient temperature. After evaporation of the solvent, purification of a residue by silica gel column chromatography (benzene) afforded **3g** (325 mg, 79%).

3g: mp (decomp) 154-155 °C (hexane-benzene); ^{1}H NMR ($CDCl_3$) δ 2.29 (s, 3H, CCH_3), 3.49 (s, 3H, NCH_3), 5.95 (s, 1H, CH); IR (KBr) 1600, 1581, 1527, 1518 cm^{-1}. Anal. Calcd for $C_8H_7BrF_3NOS$: C, 31.80; H, 2.34; N, 4.64; F, 18.87; Br, 26.45. Found: C, 31.94; H, 2.46; N, 4.59; F, 18.75; Br, 26.14.

General procedure for bis(trifluoroacetylation) of 2-trifluoroacetylmethylene-2,3-dihydro-3-methylthiazoles (3).

To an ice-cooled mixture of **3** (1 mmol) and pyridine (158 mg, 2 mmol) was added dropwise a solution of trifluoroacetic anhydride (420 mg, 2 mmol) in dry $CHCl_3$ (4 mL) with continuous stirring. After stirring for 4 h at ambient temperature, the mixture was dissolved in CH_2Cl_2 (50 mL). The whole mixture was washed with aq. Na_2CO_3 and dried over Na_2SO_4. Removal of the solvent and pyridine under vacuum gave 2-bis(trifluoroacetyl)methylene-2,3-dihydro-3-methylthiazole (**2a**-**g**).

3-(5-Bromo-3,4-dimethyl-3*H*-thiazol-2-ylidene)-1,1,1,5,5,5-hexafluoropentane-2,4-dione (2g): mp (decomp) 178-179 °C (hexane-benzene); ^{1}H NMR ($CDCl_3$) δ 2.51 (s, 3H, CCH_3), 3.67 (s, 3H, NCH_3); IR (KBr) 1668, 1588, 1550 cm^{-1}. Anal. Calcd for $C_{10}H_6BrF_6NO_2S$: C, 30.17; H, 1.52; N, 3.52; F, 28.63; Br, 20.07. Found: C, 30.17; H, 1.49; N, 3.52; F, 28.25; Br, 19.93.

Reaction of 2b with *N*,*N*′-diethylethylenediamine.

To a stirred solution of **2b** (180 mg, 0.56 mmol) in MeCN (4 mL) was added *N*,*N*′-diethylethylenediamine (67 mg, 0.58 mmol) and the mixture was refluxed for 16 h. Evaporation of the solvent gave **2b** (144 mg, 80% recovery).

Reaction of 2b with benzylamine.

To a stirred solution of **2b** (101 mg, 0.32 mmol) in MeCN (4 mL) was added benzylamine (119 mg, 1.11 mmol) and the mixture was refluxed for 41 h. After evaporation of the solvent, a residue was fractionated by silica gel column chromatography. Elution with benzene afforded slightly contaminated benzyltrifluoroacetamide (69 mg) and that with CH_2Cl_2 gave **3b** (67 mg, 94%).

REFERENCES

1. G. I. Gregory, 'Recent Advances in the Chemistry of β-Lactam Antibiotics,' The Royal Society of Chemistry, London, 1981.
2. S. Mitsuhashi, 'Beta-lactam Antibiotics,' Japan Scientific Societies Press, Tokyo, 1981.
3. B. Aracil, J. L. Gomez-Garces, and J. I. Alos, *J. Antimicrob. Chemother.*, 1999, **43**, 399.
4. R. F. Grossman, D. A. Campbell, S. J. Landis, G. E. Garber, G. Murray, H. G. Stiver, R. Saginur, R. A. McIvor, J. Laforge, C. Rotstein, J. Dubois, M. Rivard, and F. Boulerice, *J. Antimicrob. Chemother.*, 1999, **43**, 549.
5. U. Buehmann, E. C. Herrmann, C. Z. Koetter, and C. Naturforsch, *J. Biosci.*, 1987, **42**, 704.
6. R. Filler and Y. Kobayashi, 'Biomedicinal Aspects of Fluorine Chemistry,' Kodansha & Elsevier Biomedical, Tokyo, 1982.
7. R. Filler, 'Organofluorine Chemicals and Their Industrial Applications,' Ellis Horwood, London, 1979.
8. J. T. Welch, *Tetrahedron*, 1987, **43**, 3123.
9. R. Filler, Y. Kobayashi, and L. M. Yagupolskii, 'Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications,' Elsevier, Amsterdam, 1993.
10. D. L. Bourdet, K. Lee, and D. R. Thakker, *J. Med. Chem.*, 2004, **47**, 2935.
11. I. Yanagisawa, Y. Hirata, and Y. Ishii, *J. Med. Chem.*, 1987, **30**, 1787.
12. T. H. Brown, R. C. Blakemore, G. J. Durant, C. R. Ganellin, M. E. Parsons, A. C. Rasmussen, and D. A. Rawlings, *Eur. J. Med. Chem.,* 1993, **28**, 601
13. S. Vladimirov, J. Brboric, M. Svonja, and D. Zivanov-Stakic, *J. Pharm. Biomed. Anal.*, 1995, **13**, 933.
14. M. Hojo, R. Masuda, and Y. Kamitori, *Tetrahedron Lett.*, 1976, 1009.
15. M. Hojo, R. Masuda, and E. Okada, *Synthesis*, 1986, 1013.
16. M. Hojo, R. Masuda, Y. Kokuryo, H. Shioda, and S. Matsuo, *Chem. Lett.*, 1976, 499.
17. M. Hojo, R. Masuda, and E. Okada, *Tetrahedron Lett.*, 1986, **27**, 353.
18. M. Hojo, R. Masuda, and E. Okada, *Synthesis*, 1990, 347.
19. Y. Kamitori, M. Hojo, R. Masuda, T. Fujitani, T. Kobuchi, and T. Nishigaki, *Synthesis*, 1986, 340.

20. M. Hojo, R. Masuda, E. Okada, S. Sakaguchi, H. Narumiya, and K. Moriomoto, *Tetrahedron Lett.*, 1989, **30**, 6173.
21. M. Hojo, R. Masuda, E. Okada, H. Yamamoto, K. Moriomoto, and K. Okada, *Synthesis*, 1990, 195.
22. M. Hojo, R. Masuda, and E. Okada, *Chem. Lett.*, 1990, 2095.
23. M. Hojo, R. Masuda, E. Okada, and Y. Mochizuki, *Synthesis*, 1992, 455.
24. A. S. Baily, J. H. Ellis, J. M. Harvey, A. N. Hilton, and J. M. Peach, *J. Chem. Soc., Perkin Trans. 1*, 1983, 795.
25. M. Hojo, R. Masuda, S. Kosaka, and K. Nagase, *Synthesis*, 1979, 272.
26. M. Hojo, T. Ichi, R. Masuda, M. Kobayashi, and H. Shibano, *J. Org. Chem*., 1988, **53**, 2209.

PART II

Molecular Orbital Calculation Studies Related to the Syntheses of Novel Fluorine-Containing Benzo[*b*][1,4]diazepines and Dihydropyrans

CHAPTER 5

Reaction of β,β-Bis(trifluoroacetyl)vinyl Ethers and β-Trifluoroacetylvinyl Ethers with 1,2-Phenylenediamines Accessing Fluorine-Containing Benzo[*b*][1,4]diazepine Derivatives - A Study about the Reaction Based on Molecular Orbital Calculations

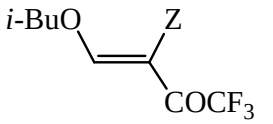
SUMMARY

β,β-Bis(trifluoroacetyl)vinyl ether (**1**) reacted with 1,2-phenylenediamine to give dihydrobenzodiazepinol (**4a**) selectively, whereas β-trifluoroacetylvinyl ether (**2**) and β-trifluoroacetyl-α-phenylvinyl ether (**3**) gave the corresponding *O-N* exchange products (**6b**, **c**) when reacted with 1,2-phenylenediamine. The factors determining the reaction products of the reaction of three substrates **1**-**3** having similar structures with 1,2-phenylenediamine were elucidated on the basis of molecular orbital calculations. The dehydration processes from dihydrobenzodiazepinols (**4** and **8**) to benzodiazepines (**5** and **7**) are also discussed.

INTRODUCTION

In recent years, much attention has been focused on the development of new methodologies for the syntheses of many kinds of fluorine-containing heterocycles, since these compounds are now widely recognized as important organic materials showing specific functions as well as interesting biological activities.[1-4] In our previous paper,[5] we reported an efficient and convenient synthetic method accessing fluorine-containing dihydrobenzo[*b*][1,4]diazepinols which have remarkable anti-tumor activities[6] from β,β-bis(perfluoroalkanoyl)vinyl ethers. During the investigations, we found that the reaction of β,β-bis(trifluoroacetyl)vinyl *iso*-butyl

ether (**1**) with 1,2-phenylenediamine gave 2,5-dihydro-3-trifluoroacetyl-2-trifluoromethyl-1*H*-benzo[*b*][1,4]diazepin-2-ol (**4a**) selectively under very mild conditions without microwave irradiation. Our results showed clear contrast with Reddy's reports of obtaining 1*H*-benzo[*b*][1,4]diazepine (**5a**) by the reaction of **1** with 1,2-phenylenediamine carried out under microwave irradiation.[7,8] We also found that the reaction of β-trifluoroacetylvinyl *iso*-butyl ether (**2**) with 1,2-phenylenediamine produced only *O*-*N* exchange product (**6b**). A similar *O*-*N* exchange product was seen in Bonacorso's work in which **6c** was obtained as the sole product of the reaction of β-trifluoroacetyl-α-phenylvinyl methyl ether (**3**) with 1,2-phenylenediamine.[9] Moreover, it has been reported that **6c** was converted to the corresponding 3*H*-benzo[*b*][1,4]diazepine (**7c**) by heating **6c** in the presence of acetic acid.[9] In contrast, **6b** did not give any benzodiazepines or dihydrobenzodiazepinols, even in the presence of acid catalyst.



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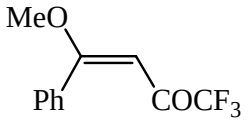
2 Z= H



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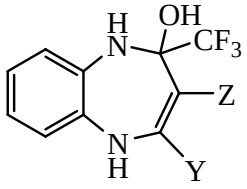

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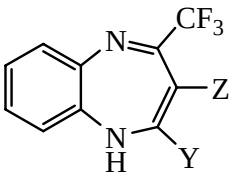

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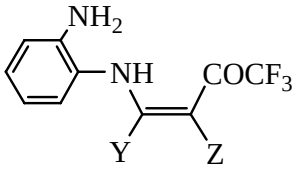

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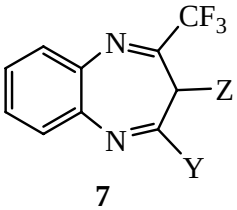

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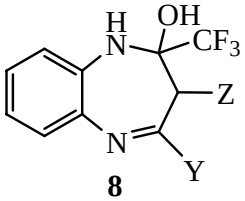

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4 - 8	**a**	**b**	**c**
Y	H	H	Ph
Z	$COCF_3$	H	H

Scheme 1

The finding that the conversion of *O*-*N* exchange product **6c** to benzodiazepine **7c** occurred in the presence of acid catalyst suggests that dehydration on dihydrobenzodiazepinol **4c** or **8c**, which is

thought to be the precursor of **7c**, proceeded smoothly by acid catalysis. However, acid-catalyzed dehydration of dihydrobenzodiazepionol **4a** was not successful and the corresponding benzodiazepine **5a** was not obtained at all.[5]

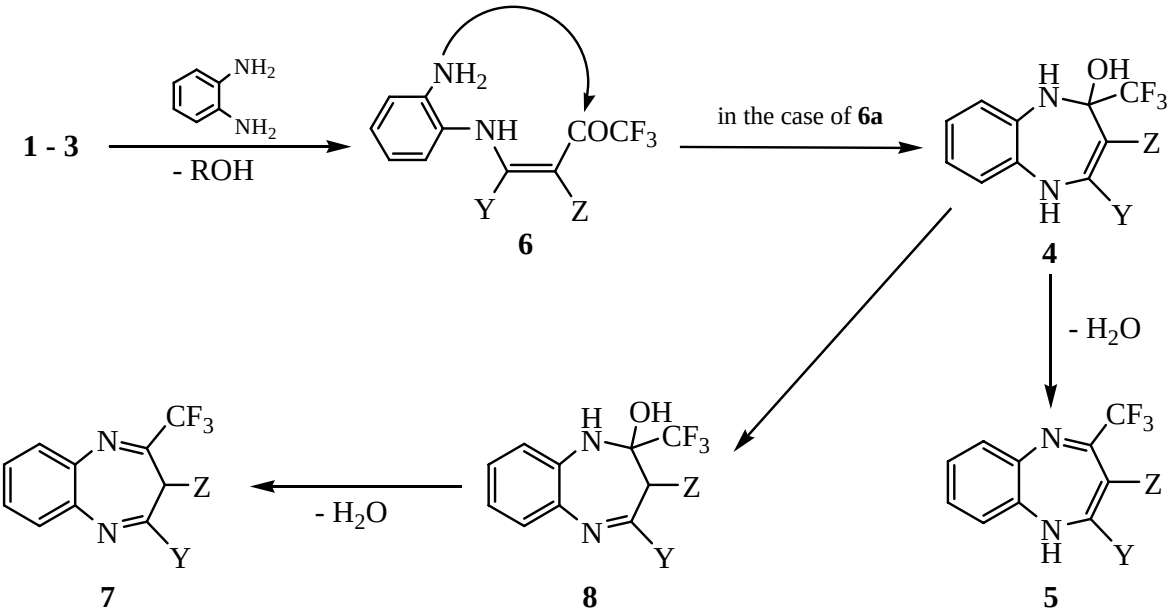
We here present the most reasonable interpretation on the basis of molecular orbital calculations for these interesting differences in reactivity among three substrates **1**-**3** in the reaction with 1,2-phenylendiamine. Moreover, dehydration processes of dihydrobenzodiazepinols **4** and **8** to benzodiazepines **5** and **7** are also discussed.

RESULTS AND DISCUSSION

Derivatives of β-trifluoroacetylated vinyl ethers such as β-trifluoroacetylketene acetals,[10] β,β-bis(trifluoroacetyl)vinyl ethers,[11] β-trifluoroacetyl-α-phenylvinyl ethers,[12] and β-trifluoroacetylvinyl ethers[13] readily undergo nucleophilic *O*-*N* exchange reactions at olefinic carbons with various aliphatic and aromatic amines to give the corresponding β-trifluoroacetylated ketene *O*,*N*-acetals, β,β-bis(trifluoroacetyl)enamines, β-trifluoroacetyl-α-phenylenamines, and β-trifluoroacetylenamines. Consequently, *O*-*N* exchange products **6a**-**c** were supposed to be the initial intermediates in the reaction of three substrates **1**-**3** with 1,2-phenylenediamine (Scheme 1). In the cases of β-trifluoroacetylvinyl *iso*-butyl ether (**2**) and β-trifluoroacetyl-α-phenylvinyl methyl ether (**3**), the reaction stops at this stage. In contrast, the subsequent intramolecular nucleophilic addition of the remaining aromatic NH_2 group to trifluoroacetyl carbonyl group in **6** (**6a**) proceeds to give dihydrobenzodiazepinol **4** (**4a**) in the case of bis(trifluoroacetyl)vinyl *iso*-butyl ether (**1**) as illustrated in Scheme 2.

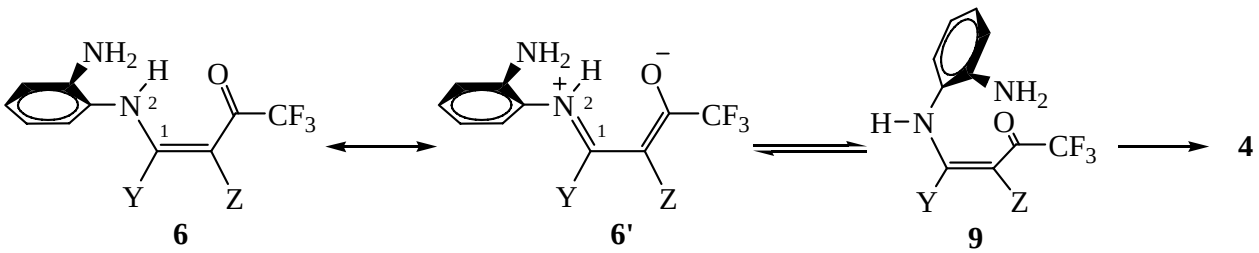
If dehydration of dihydrobenzodiazepinols **4** is possible, 1*H*-benzo[*b*][1,4]diazepines (**5**) is obtained. If isomeric 2,3-dihydro-1*H*-benzo[*b*][1,4]diazepin-2-ols (**8**) are thermodynamically more stable than 2,5-dihydro-1*H*-benzo[*b*][1,4]diazepin-2-ols (**4**), 3*H*-benzo[*b*][1,4]diazepines (**7**) are produced from **4** via **8**.

As an initial step to clarify the reason why cyclization of *O-N* exchange products **6** to dihydrobenzodiazepinols **4** did not occur in the cases of **6b** and **6c** whereas it proceeded smoothly in the case of **6a**, we computed the most stable structures of **6a-c** and their energies (E_6) using



Scheme 2

RB3LYP/6-31G*//RB3LYP/6-31G*. As depicted in Scheme 3, the transformation from the most stable conformers **6** to **9** suitable for subsequent cyclization would be necessary to convert **6** to dihydrobenzodiazepinols (**4**). We presumed that the facility of the transformation from **6** to **9** would be correlated with multiple bonding characters on C(1)-N(2) bond of **6** owing to the push-pull type canonical contribution of **6'**. Thus, we calculated Mulliken bond orders[14] on C(1)-



Scheme 3

Table 1 The values of Mulliken bond order P_{CN} for **6** and the energies E_6, E_9 (au) for **6** and **9**.

6, **6'**, **9**, **4**	Y	Z	P_{CN}	E_6	E_9
a	H	$COCF_3$	1.303	-1321.07586	-1321.05816
b	H	H	1.267	-870.72864	-870.70436
c	Ph	H	1.233	-1101.78062	-1101.76393

N(2) bond of **6a-c** and performed structural optimization for conformers (**9a-c**). In Table 1, the values of bond order P_{CN} for **6a-c** are listed together with the energies of **6a-c** (E_6) and **9a-c** (E_9). P_{CN} of **6a** is apparently larger than those of **6b** and **6c** indicating enhanced multiple bonding character on C(1)-N(2) bond of **6a** compared to those of **6b** and **6c**. Enhanced multiple bonding character would prevent the rotation around C(1)-N(2) bond on conformer (**6a**) and, consequently, the transformation from **6a** to conformer (**9a**). Therefore, the above results are incompatible with the experimental results in which cyclization of intermediate (**6a**) occurred easily to give dihydrobenzodiazepinol (**4a**),[5] while **6b** and **6c** did not cyclize to **4b** and **4c**, respectively. Therefore, the conformation change process from **6** to **9** is not important for the overall cyclization process from **6** to **4**, showing that the cyclization process from conformers (**9**) to dihydrobenzodiazepinols (**4**) is a key step in determining whether *O-N* exchange products (**6**) are converted to **4**.

We focused on intramolecular frontier orbital interactions, i.e. the interactions between nitrogen in aromatic NH_2 group (HOMO) and carbonyl carbon in $COCF_3$ group (LUMO) on conformers (**9a-c**). Thus, frontier electron densities, fr^{HOMO} at $\underline{\mathbf{N}}H_2$ and fr^{LUMO} at $\underline{\mathbf{C}}OCF_3$ on **9a-c** were calculated and the results are shown together with C-N distances between $\underline{\mathbf{N}}H_2$ and $\underline{\mathbf{C}}OCF_3$ in Table 2. In the case of **9a** bearing two trifluoroacetyl groups, frontier electron density on LUMO is concentrated at carbonyl carbon of the other trifluoroacetyl group, which is not a reaction center of the present cyclization reaction. Therefore, we used the electron density on the 2nd LUMO, which has a slightly higher energy level (ca. 0.65 eV) than LUMO on **9a**.

Both values of fr^{HOMO} and fr^{LUMO} on **9a** are apparently larger than those on **9b** and **9c**. These values of frontier electron density indicate that the intramolecular frontier orbital interaction on

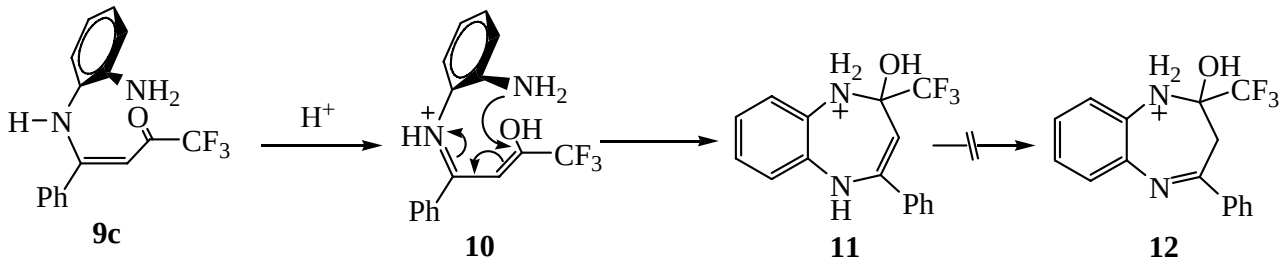
Table 2 Frontier electron densities, fr^{HOMO} at $\underline{N}H_2$ and fr^{LUMO} at $\underline{C}OCF_3$, and C-N distances (Å) between $\underline{N}H_2$ and $\underline{C}OCF_3$ on **9a-c**.

	9a	**9b**	**9c**
fr^{HOMO}	0.393	0.386	0.371
fr^{LUMO}	0.597[a]	0.391	0.215
C-N distance	2.756	3.041	3.025

[a] Electron density on 2nd LUMO.

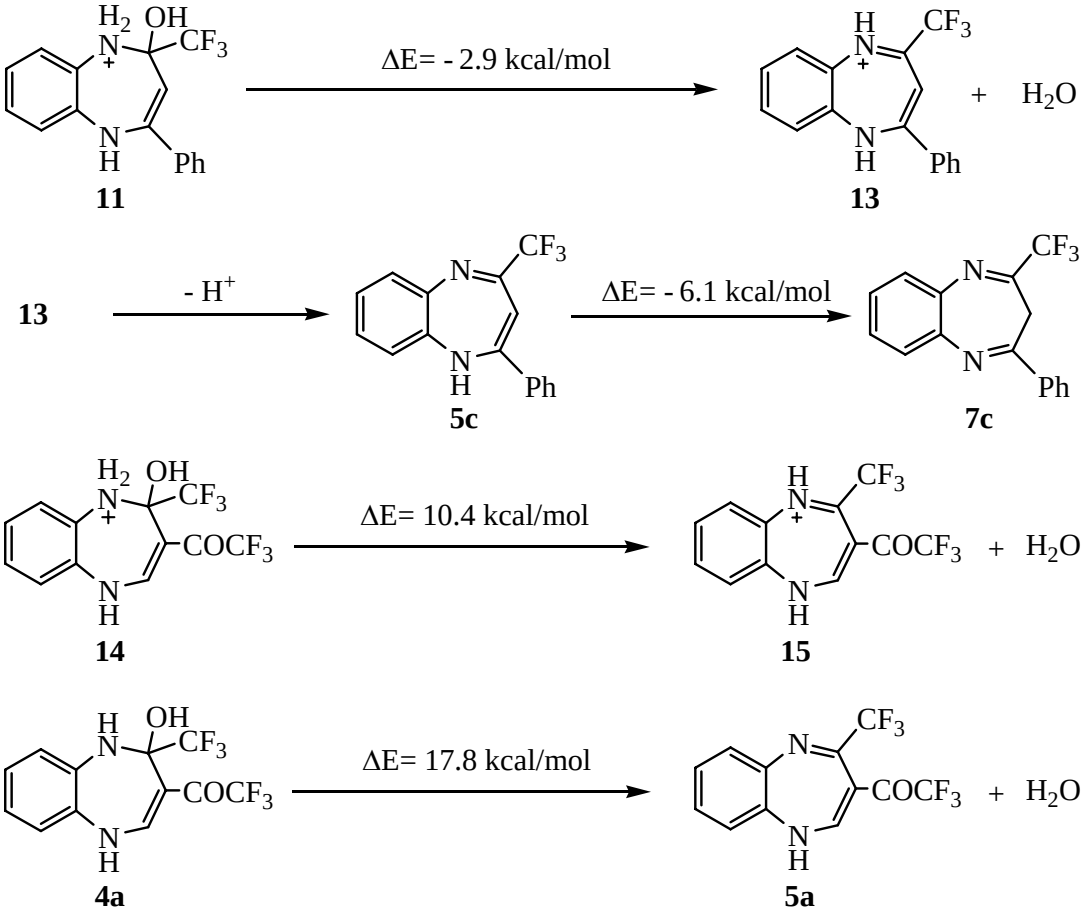
9a would be considerably greater than those on **9b** and **9c**. In addition, the C-N distance on **9a** being ca. 0.3 Å shorter than those on **9b** and **9c** would also assist the intramolecular frontier orbital interaction on **9a** to a greater extent. The strong intramolecular frontier orbital interaction would promote the cyclization of **9a** to dihydrobenzodiazepinol (**4a**) under very mild reaction conditions. In contrast, the intramolecular HOMO-LUMO interaction on **9b** and **9c** would not be strong enough to mediate cyclization of **9b** and **9c** to the corresponding dihydrobenzodiazepinols (**4b** and **4c**), respectively, under similar reaction conditions.

To clarify the relative stability of dihydrobenzodiazepinols (**4** and **8**) depicted in Scheme 2, we computed the optimized structures of **4a**,**c** and **8a**,**c** together with their energies. Our results indicate that **8a** is ca. 4.5 kcal/mol less stable than **4a**, whereas **8c** is ca. 10 kcal/mol more stable than **4c**. Therefore, the isomerization process from **4a** to **8a** is thought to be inhibited. This would be a reason why the reaction of β-bis(trifluoroacetyl)vinyl *iso*-butyl ether (**1**) with 1,2-phenylendiamine produced dihydrobenzodiazepinol (**4a**) (not **8a**) as a sole product. On the other hand, **4c** is thought to isomerize immediately to more stable **8c** when **4c** is able to form by cyclization of **6c**. However, it is necessary to take in account that acid catalyst was necessary for cyclization of **6c**.[9] As illustrated in Scheme 4, cyclization of **6c** would proceed via cation (**10**) produced by protonation on carbonyl oxygen of conformer (**9c**) in the presence of acid catalyst to produce 2-hydroxy-2,5-dihydro-1*H*-benzo[*b*][1,4]diazepin-1-ium cation (**11**). Cation (**11**) was estimated to be 0.52 kcal/mol more stable than isomeric 2-hydroxy-2,3-dihydro-1*H*-



Scheme 4

benzo[*b*][1,4]diazepin-1-ium cation (**12**). Thus, isomerization from **11** to **12** would not be an energetically favorable process and, therefore, subsequent dehydration is thought to proceed predominantly from **11**.



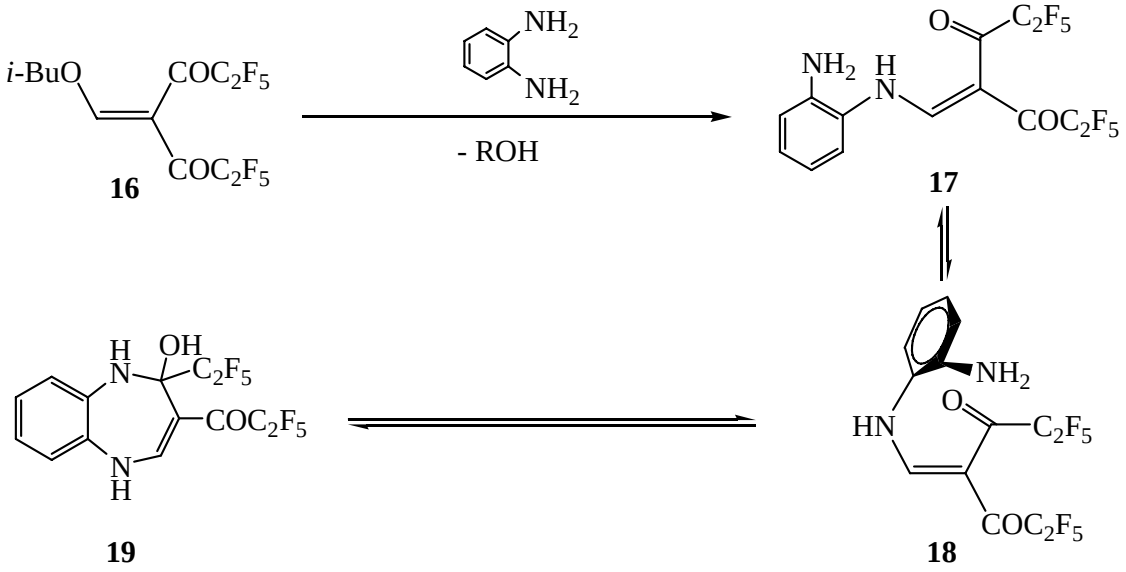
Scheme 5

As for the dehydration processes from dihydrobenzodiazepinol (**4a**) to benzodiazepine (**5a**) in the presence of acid catalyst, we can postulate the most reasonable model reactions, as shown in Scheme 5. Cation (**14**) was employed as the most suitable precursor for acid-catalyzed dehydration of **4a**. Dehydration of **14** gives 5H-benzo[*b*][1,4]diazepin-1-ium cation (**15**). On the other hand, cation (**13**) would be formed by dehydration of cation (**11**). Deprotonation of **13** gives 1*H*-benzo[*b*][1,4]diazepine (**5c**) which would isomerize to 3*H*-benzo[*b*][1,4]diazepine (**7c**) because **7c** was estimated to be 6.1 kcal/mol more stable than **5c**.

We compared the energies of cations (**11** and **14**) with the total energies of cations (**13** and **15**), respectively, and water. The process from **11** to **13** was predicted to be an exothermic reaction with a heat of reaction of -2.9 kcal/mol, while that from **14** to **15** was predicted to be endothermic with 10.4 kcal/mol. These results suggest that dehydration of cation (**11**) readily occurs to give **13**, whereas that of cation (**14**) producing **15** in an energetically unfavorable process. Since cation (**11**) is produced by acid-catalyzed cyclization of **6c** (Scheme 4) and deprotonation of cation (**13**), benzodiazepine (**7c**) is easily produced via **5c** (Scheme 5), and the overall reaction from **6c** to **7c** is predicted to proceed smoothly by acid catalysis. However, acid-catalyzed dehydration of **4a** to **5a** via **14** is estimated to be difficult. These predictions are quite compatible with the experimental results[5,9] where the *O-N* exchange product (**6c**) could be converted to the corresponding benzodiazepine (**7c**) by heating **6c** in the presence of acetic acid, while acid-catalyzed dehydration of dihydrobenzodiazepionol (**4a**) to the corresponding benzodiazepine (**5a**) was unsuccessful.

We also carried out calculations about the dehydration process from dihydrobenzodiazepinol (**4a**) to benzodiazepine (**5a**) in the absence of an acid catalyst. The process from **4a** to **5a** and water was estimated to be an endothermic reaction with 17.8 kcal/mol (Scheme 5), suggesting that dehydration of **4a** to **5a** requires high external energy. It is likely that microwaves merely assisted the endothermic dehydration of dihydrobenzodiazepinols (**4**) to benzodiazepines (**5**) as an effective external energy in Reddy's work[7,8] because we found **4** could be readily obtained by the reaction of β,β-bis(trifluoroacetyl)vinyl *iso*-butyl ether (**1**) with 1,2-phenylenediamines without microwave irradiation under very mild conditions.[5] In contrast with the case of **5c**, **5a** was estimated to be 3.6 kcal/mol more stable than **7a**, which explains why the isomerization from **5a** to **7a** was not observed.[7,8]

Finally, we made calculations about the reaction of β,β-bis(pentafluoropropionyl)vinyl *iso*-butyl ether (**16**) with 1,2-phenylenediamine. This reaction was found to give a mixture of *O*-*N* exchange product (**17**) and dihydrobenzodiazepinol (**19**), and the complete conversion from **17** to **19** could not be achieved by prolonging reaction time (in Scheme 6).[5]



Scheme 6

The cyclization process from conformer (**18**) to dihydrobenzodiazepinol (**19**) was estimated to be an endothermic reaction with a heat of reaction of 1.7 kcal/mol whereas that from conformer (**9a**) to dihydrobenzodiazepinol (**4a**) was predicted to be exothermic with -1.5 kcal/mol. In the case of the reaction of **16** with 1,2-phenylenediamine, the relative instability of **19** compared to **18** and possible equilibrium between **18** and **19** are thought to prevent the complete conversion from *O*-*N* exchange product (**17**) to dihydrobenzodiazepinol (**19**).

CONCLUSION

Based on molecular orbital calculations, we can rationalize the difference of products resulting from the reactions of β,β-bis(trifluoroacetyl)vinyl *iso*-butyl ether (**1**), β-trifluoroacetylvinyl *iso*-

butyl ether (**2**), and β-trifluoroacetyl-α-phenylvinyl methyl ether (**3**) with 1,2-phenylenediamine. Intramolecular frontier orbital interaction on *O-N* exchange products (**6**) (conformers **9**) as intermediates of the above reactions would be a key factor in determining whether the subsequent cyclization reactions yielding dihydrobenzodiazepinols (**4**) take place. Unsuccessful dehydration of dihydrobenzodiazepinol (**4a**) to benzodiazepine (**5a**) in the presence of acid catalyst is attributed to the endothermic dehydration process from protonated dihydrobenzodiazepinol (**14**) to protonated benzodiazepinol (**15**) requiring high energy.

COMPUTATIONAL METHODS

All calculations employed in this paper were accomplished using the computer programs packages SPARTAN and PC SPARTAN 04.[15] All calculations for geometrical optimizations were performed with the 6-31G* basis set at B3LYP [16] level. The starting geometries employed for all optimizations were resulted from molecular mechanics using SYBYL[17] force field and subsequent semi-empirical PM3[18] optimizations. The calculations for energy of intermediates were also taken with the 6-31G* basis set at B3LYP level.

REFERENCES

1. R. Filler and Y. Kobayashi, 'Biomedicinal Aspects of Fluorine Chemistry,' Kodansha & Elsevier Biomedical, Tokyo, 1982.
2. R. Filler, 'Organofluorine Chemicals and Their Industrial Applications,' Ellis Horwood, London, 1979.
3. J. T. Welch, *Tetrahedron*, 1987, **43**, 3123.
4. R. Filler, Y. Kobayashi, and L. M. Yagupolskii, 'Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications,' Elsevier, Amsterdam, 1993.
5. N Ota, T. Tomoda, N. Terai, Y. Kamitori, D. Shibata, M. Médebielle, and E. Okada, *Heterocycles*, in press.
6. E. Okada, N. Ota, T. Tomoda, M. Fujimoto, and H. Takenaka, Jpn. Kokai Tokkyo Koho 2006-
   273844, 2006.
7. A. C. S. Reddy, P. S. Rao, and R. V. Venkataratnam, *Tetrahedron Lett*., 1996, **37**, 2845.
8. A. C. S. Reddy, P. S. Rao, and R. V. Venkataratnam, *Tetrahedron*, 1997, **53**, 5847.
9. H. B. Bonacorso, L. M. L. Marques, N. Zanatta, and M. A. P. Martins, *Synth. Commun*., 2002, **32**, 3225.
10. M. Hojo, R. Masuda, E. Okada, H. Yamamoto, K. Morimoto, and K. Okada, *Synthesis*, 1990, 195.
11. M. Hojo, R. Masuda, E. Okada, and Y. Mochizuki, *Synthesis*, 1992, 455.
12. M. Hojo, R. Masuda, and E. Okada, *Synthesis*, 1986, 1013.
13. M. Hojo, R. Masuda, E. Okada, S. Sakaguchi, H. Narumiya, and K. Morimoto, *Tetrahedron Lett*., 1989, **30**, 6173.
14. R. S. Mulliken, *J. Chem. Phys*., 1955, **23**, 1833, 1841, 2338, 2343.
15. Wavefunction, Inc.
16. A. D. Becke, *J. Chem. Phys*., 1993, **98**, 5648.
17. M. Clark, R. D. Cramer III, and N. van Opdensch, *J. Computational Chem*., 1989, **10**, 982.
18. J. J. P. Stewart, J. Computer Aided Molecular Design, 1992, **6**, 69.

CHAPTER 6

Reaction of β-Trifluoroacetylketene Acetals and β-Trifluoroacetyl-vinyl Ethers with 1,2-Phenylenediamines Accessing Fluorine-Containing Benzo[*b*][1,4]diazepine Derivatives: A Molecular Orbital Calculation Study

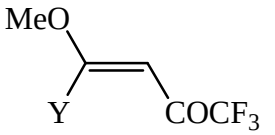
SUMMARY

β-Trifluoroacetylketene acetals (**1**) were found to react easily with 1,2-phenylene-diamines to give dihydrobenzodiazepinols (**5a**) together with benzodiazepines (**6a**) under very mild conditions. In contrast, β-trifluoroacetyl-α-phenylvinyl ethers (**2**) and β-trifluoroacetylvinyl ethers (**3**) exclusively yielded *O*-*N* exchanged products (**9**) when they were reacted with 1,2-phenylenediamines. The factors determining product formation by the reaction of each of three similar substrates (**1**-**3**) with 1,2-phenylenediamine were elucidated on the basis of molecular orbital calculations. The dehydration processes converting dihydrobenzodiazepinols (**5** and **7**) to the corresponding benzodiazepines (**6** and **8**) are also discussed.

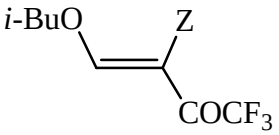
INTRODUCTION

Recently much attention has focused on developing new methodologies for the syntheses of many kinds of fluorine-containing heterocycles, as these compounds are now widely recognized as important organic materials showing specific functions and interesting biological activities.[1-4] In our preceding papers, we reported facile and convenient methods for synthesizing fluorine-containing dihydrobenzo[*b*][1,4]diazepinols and benzo[*b*][1,4]diazepines, which have remarkable anti-tumor activities,[5] from β-trifluoroacetylketene acetals[6] and β,β-bis(trifluoroacetyl)vinyl

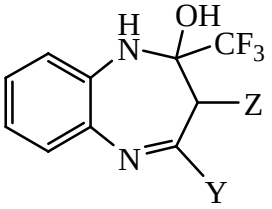
ethers.[7] In these investigations, we found that β-trifluoroacetylketene dimethyl acetal (**1**) readily reacts with 1,2-phenylenediamine under very mild conditions to give 2,3-dihydro-1*H*-benzo[*b*][1,4]diazepin-2-ol (**5a**) as the major product and 3*H*-benzo[*b*][1,4]diazepine (**6a**) as the minor product. In contrast, only *O*-*N* exchanged products (**9**) were obtained by the reaction of β-trifluoroacetylvinyl *iso*-butyl ether (**3**) with 1,2-phenylenediamine. Bonacorso *et al*. reported



1 Y= MeO
2 Y= Ph



3 Z= H
4 Z= $COCF_3$



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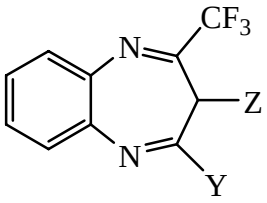

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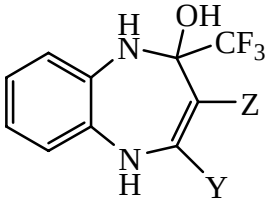

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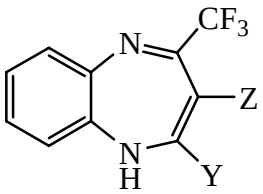

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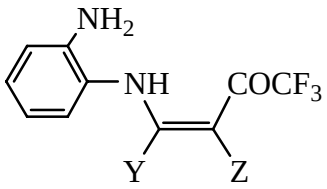


9

5-9	a	b	c	d
Y	MeO	Ph	H	H
Z	H	H	H	$COCF_3$

Scheme 1

that **9b** was the sole product of the reaction of β-trifluoroacetyl-α-phenylvinyl methyl ether (**2**) with 1,2-phenylenediamine.[8] In addition, it has been reported that 3*H*-benzo[*b*][1,4]diazepine (**6b**) is obtained by heating **2** with 1,2-phenylenediamine in the presence of acetic acid.[8] In

contrast, neither heating nor acid catalysis is necessary for the reaction of **1** with 1,2-phenylenediamine to produce benzodiazepinol (**5a**) and benzodiazepine (**6a**).[6] However, no benzodiazepine derivatives were obtained even when **3** was heated with 1,2-phenylenediamine in the presence of an acid catalyst.

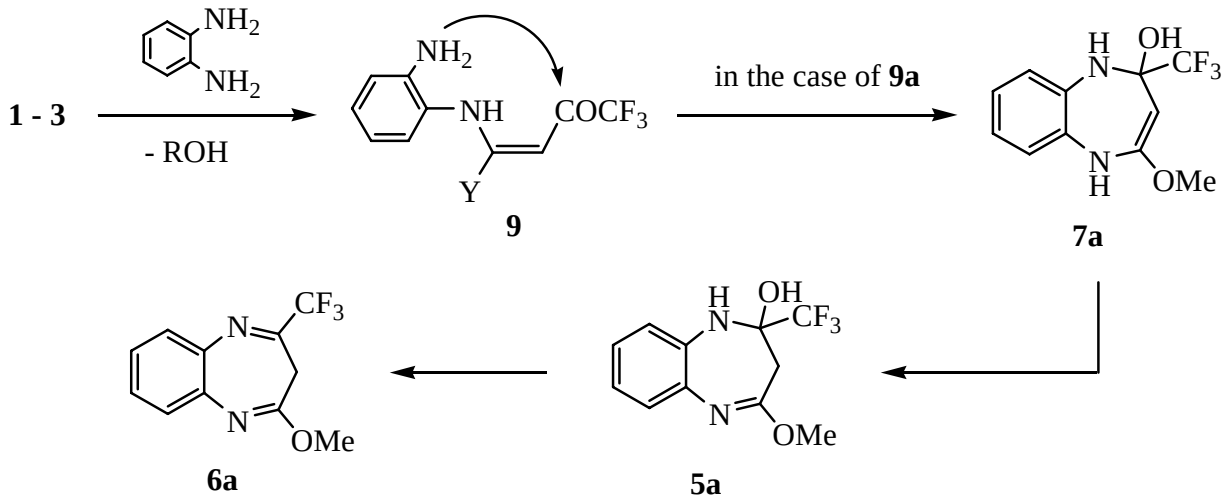
We also found that β,β-bis(trifluoroacetyl)vinyl ether (**4**) reacts with 1,2-phenylenediamine under very mild conditions to give 2,5-dihydro-1*H*-benzo[*b*][1,4]diazepin-2-ol (**7d**).[7] Moreover, it was reported that the reaction of **4** with 1,2-phenylenediamine under microwave irradiation afforded 1*H*-benzo[*b*][1,4]diazepine (**8d**).[9] When **1** was reacted with 1,2-phenylenediamine, only **5a** and **6a** were obtained, with no formation of benzodiazepinol (**7a**) or benzodiazepine (**8a**). Using molecular orbital calculations, we previously elucidated the reaction of β,β-bis(trifluoroacetyl)vinyl ether (**4**) with 1,2-phenylenediamine, affording benzodiazepinol (**7a**).[10] In the present chapter, the factors determining the products obtained by the reaction of each of three similar substrates (**1**-**3**) with 1,2-phenylenediamine are clarified using molecular orbital calculations. Also, the dehydration of dihydrobenzodiazepinols (**5** and **7**) to benzodiazepines (**6** and **8**) is discussed.

RESULTS AND DISCUSSION

Similar to β,β-bis(trifluoroacetyl)vinyl ethers,[11] β-trifluoroacetyl-α-phenylvinyl ethers,[12] and β-trifluoroacetylvinyl ethers,[13] β-trifluoroacetylketene acetals readily undergo nucleophilic *O*-*N* exchange reactions at olefinic carbons with various aliphatic and aromatic amines to give the corresponding β-trifluoroacetylated ketene *O*,*N*-acetals.[14] Consequently, the *O*-*N* exchanged product (**9a**) depicted in Scheme 1 was thought to be the initial intermediate in the reaction of β-trifluoroacetylketene dimethyl acetal (**1**) with 1,2-phenylenediamine. The theory was similar to the cases of **9b**-**d** which were supposed to be the initial intermediates in the reaction of β-trifluoroacetyl-α-phenylvinyl methyl ether (**2**), β-trifluoroacetylvinyl *iso*-butyl ethers (**3**), and β,β-bis(trifluoroacetyl)vinyl *iso*-butyl ether (**4**), respectively, with 1,2-phenylenediamine.[10]

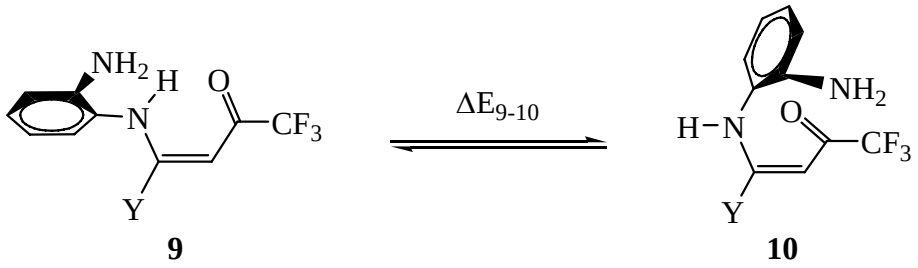
The subsequent intramolecular nucleophilic addition of the aromatic NH_2 group to the trifluoroacetyl carbonyl group in **9a** would proceed to give dihydrobenzodiazepinol **7a**, whereas a

similar cyclization reaction would not take place in **9b** and **9c**. Dehydrobenzodiazepinol (**5a**) and benzodiazepine (**6a**) are thought to derive from **7a**, if the isomerization of **7a** to **5a** and the dehydration of **5a** to **6a** are possible, as shown in Scheme 2.



Scheme 2

As an initial step to elucidate the difference in reactivity of **9a-c**, we computed the most stable structures of **9a-c** and their energies (E_9) using RB3LYP/6-31G*//RB3LYP/6-31G*. As illustrated in Scheme 3, transformation from the most stable conformers (**9**) to **10**, which are



Scheme 3

suitable for subsequent cyclization, would be required for the conversion of **9** to the corresponding dihydrobenzodiazepinols (**7**). We presumed that the ease of cyclization of **9** to **7** would be correlated with the energy difference between **9** and **10**. Structural optimization was

performed for conformers (**10a-c**), and $\Delta E_{9\text{-}10}$ (E_{10}-E_9) values were calculated. Table 1 summarizes the values of $\Delta E_{9\text{-}10,}$ together with the energies of **9a-c** (E_9) and **10a-c** (E_{10}).

Table 1 The values of $E_{9,}$ E_{10} (au) and $\Delta E_{9\text{-}10}$ (kcal/mol) for **9** and **10**.

9, **10**	Y	E_9	E_{10}	$\Delta E_{9\text{-}10}$
a	MeO	-985.25765	-985.23508	14.2
b	Ph	-1101.78062	-1101.76393	10.5
c	H	-870.72864	-870.70436	15.2

The largest $\Delta E_{9\text{-}10}$ was estimated for the transformation of **9c** to **10c**. This result seems to explain the extremely slow cyclization of *O-N* exchanged product **9c** to dihydrobenzodiazepinol **7c**, resulting in the reaction of β-trifluoroacetylvinyl *iso*-butyl ether (**3**) with 1,2-phenylenediamine to afford **9c** as the sole product. However, the difference in $\Delta E_{9\text{-}10}$ between **9a** and **9c** was estimated to be no more than 1 kcal/mol. Moreover, $\Delta E_{9\text{-}10}$ for **9b** is smaller than that for **9a**. These results are incompatible with the experimental results, where **9a** cyclized easily to give dihydrobenzodiazepinol (**5a**) and benzodiazepine (**6a**) *via* **7a**,[6] while **9b** and **9c** did not cyclize to any benzodiazepine derivative under similar conditions. Therefore, the conformational change required to convert **9** to **10** is not so important energetically for the overall cyclization process from **9** to **7**. This means that the cyclization process from conformers (**10**) to dihydrobenzodiazepinols (**7**) is a key step determining whether *O-N* exchanged products **9** are converted to **7** or not.

As a second step, we tried to elucidate the transition state for the cyclization reaction from **10** to **7**. Our attempts to compute the transition state structures for the cyclization reactions of **10a-c** resulted in failure. Therefore, we focused on intramolecular frontier orbital interactions, i.e., the interactions between the nitrogen in the NH_2 group (HOMO) and the carbonyl carbon in the $COCF_3$ group (LUMO) for conformers (**10a-c**). Frontier electron densities, fr^{HOMO} at $\underline{\mathbf{N}}H_2$ and fr^{LUMO} at $\underline{\mathbf{C}}OCF_3$ for **10a-c** are shown in Table 2.

Both fr^{HOMO} and fr^{LUMO} in **10a** are larger than those in **10b**. These results suggest that the

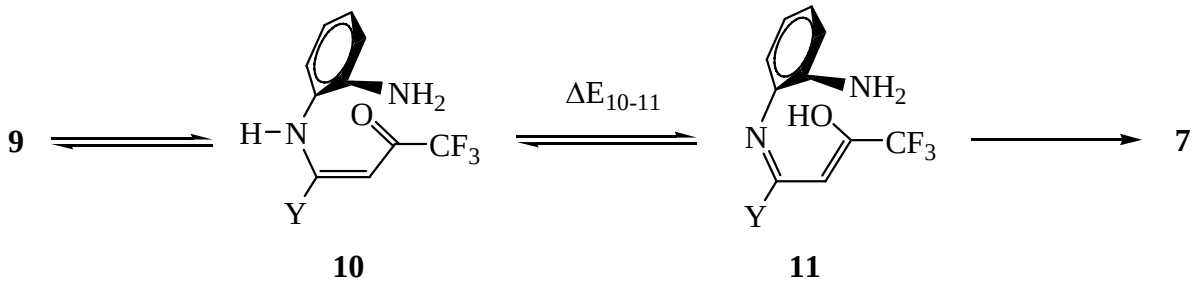
intramolecular HOMO-LUMO interaction in **10a** is considerably greater than that in **10b**. Strong intramolecular frontier orbital interaction is expected to promote the cyclization of **10a** to

Table 2 Frontier electron densities, fr^{HOMO} at $\underline{\mathbf{N}}H_2$ and fr^{LUMO} at $\underline{\mathbf{C}}OCF_3$ on **10a-c**.

	10a	**10b**	**10c**
fr^{HOMO}	0.427	0.371	0.386
fr^{LUMO}	0.341	0.215	0.391

7a under very mild reaction conditions. In contrast, intramolecular HOMO-LUMO interaction in **10b** would not be large enough to mediate the cyclization to **7b**. On the other hand, the values of fr^{HOMO} and fr^{LUMO} in **10c** are considerably larger than those in **10b**, indicating that the intramolecular HOMO-LUMO interaction in **10c** would be comparable with that in **10a**. Therefore, these data are in conflict with our experimental results where *O-N* exchanged product (**9c**) did not cyclize to dihydrobenzodiazepinol (**7c**).

It is necessary to take into account steric factors in enamine (**9**) to explain the lack of cyclization of **9c**. Steric repulsion between the methoxy group and the 2-aminophenylamino group in **9a** would assist the transformation from **9a** to **10a**. In contrast, steric repulsion promoting the conformational change from **9c**, which bears no α-substituent, to **10c** is unlikely. Difficulty in forming **10c** from **9c** is a likely reason why **9c** could not be converted to dihydrobenzodiazepinol (**7c**).



10 **11**

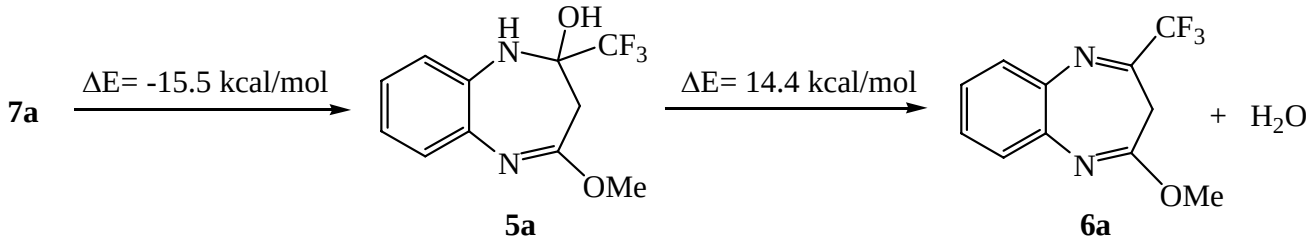
Scheme 4

As shown in Scheme 4, an alternative reaction to go from **9** to **7** *via* enol type intermediates (**11**) is also possible. In order to estimate the relative stability of **11** compared to **10**, we computed the optimized structures of **11a-c**, and calculated the energy difference ($\Delta E_{10\text{-}11}$) between **10a-c** and the corresponding **11a-c**. The results are summarized in Table 3. In all cases, enol type intermediates (**11**) are ca. 13 - 15 kcal/mol more unstable compared with **10**. These results indicate that the cyclization of *O-N* exchanged products (**9**) to dihydrobenzodiazepinols (**7**) proceeds predominantly along the direct reaction pathway (Scheme 2).

Table 3 The values of $\Delta E_{10\text{-}11}$ (kcal/mol) and frontier electron densities, fr^{HOMO} at $\underline{\mathbf{N}}H_2$ and fr^{LUMO} at $\underline{\mathbf{C}}(OH)CF_3$ for **11a-c**.

11	Y	Z	$\Delta E_{10\text{-}11}$ (E_{11}-E_{10})	fr^{HOMO}	fr^{LUMO}
a	MeO	H	14.4	0.408	0.725
b	Ph	H	13.4	0.407	0.320
c	H	H	14.9	0.359	0.527

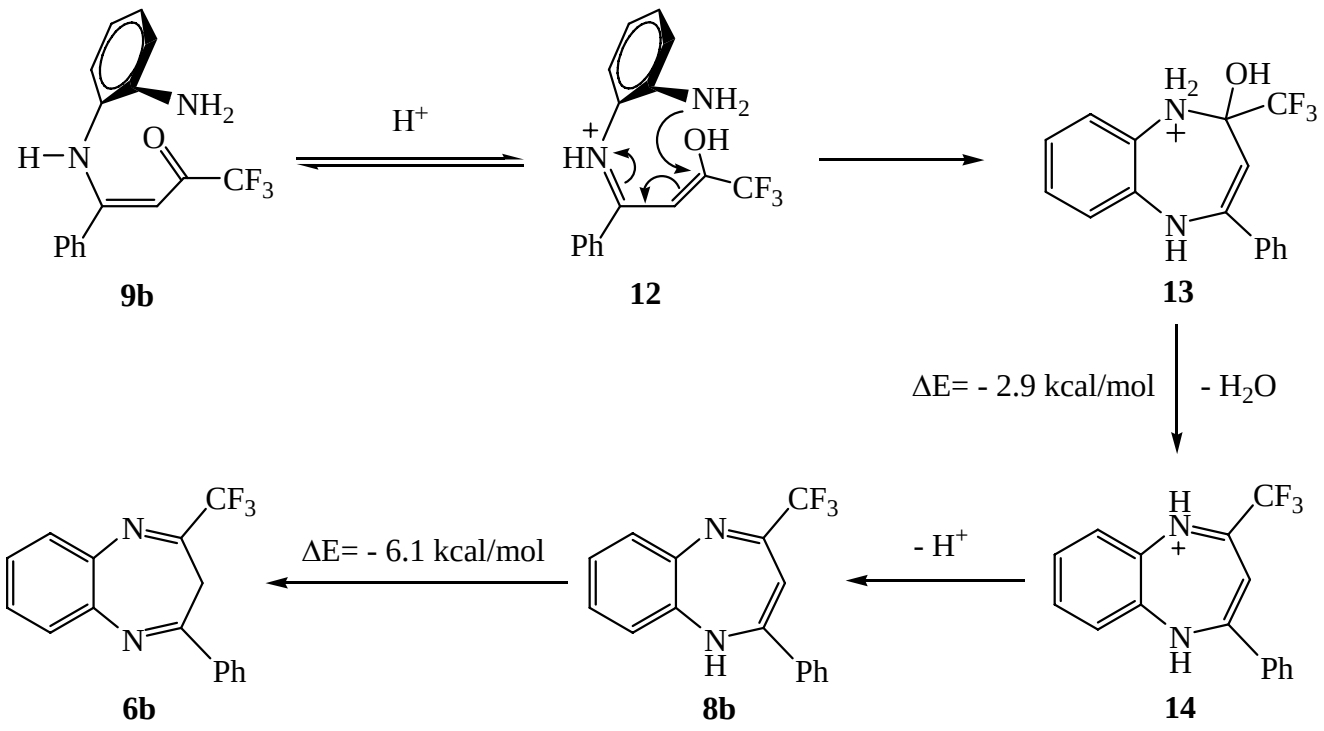
Frontier electron densities, fr^{HOMO} at $\underline{\mathbf{N}}H_2$ and fr^{LUMO} at $\underline{\mathbf{C}}(OH)CF_3$ for **11a-c** are listed in Table 3. It appears that intramolecular HOMO-LUMO interaction in **11a** is rather larger than that in **11b**. Thus, the trend in the intramolecular frontier orbital interaction for **11a-c** is similar to that for **10a-c**, and is compatible with the experimental results described above, even if the reaction from *O-N* exchanged products (**9**) to dihydrobenzodiazepinols (**7**) occurs partially along the reaction pathway *via* **11** (Scheme 4).



Scheme 5

To clarify the relative stability of dihydrobenzodiazepinols **5** and **7**, we computed optimized structures of **5a**,**b** and **7a**,**b** together with their energies. Our results indicate that **5a** is ca. 16 kcal/mol more stable than **7a** and, therefore, **7a** generated by cyclization of **9a** would immediately isomerize to the more stable **5a** (Scheme 5). This could explain why the reaction of β-trifluoroacetylketene dimethyl acetal (**1**) with 1,2-phenylenediamine gives dihydrobenzodiazepinol (**5a**).

Similar to the case of **5a**, **5b** was estimated to be ca. 10 kcal/mol more stable than **7b**. Therefore, isomerization from **7b** to **5b** is thought to occur easily, and subsequent dehydration of **5b** would give **6b**, if cyclization of **9b** to **7b** is possible. However the cyclization reaction of **9b** to afford **6b** requires acid catalysis.[8] As discussed previously,[10] benzodiazepine (**6b**) would be formed from **9b** along the reaction pathway illustrated in Scheme 6.

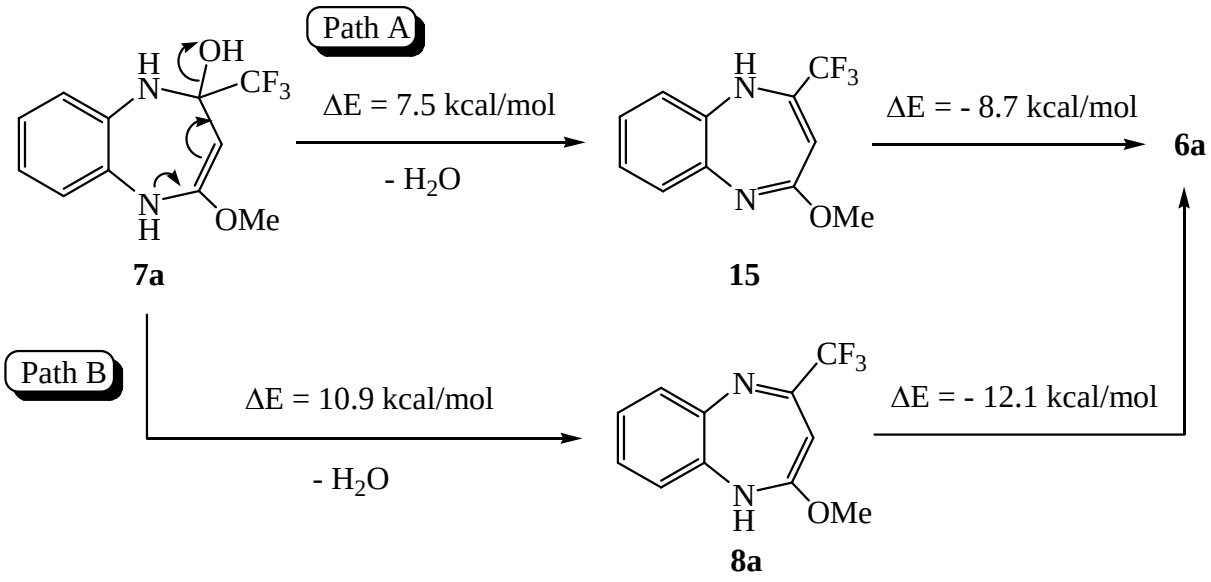


Scheme 6

Two exothermic processes, i.e., the dehydration from cation (**13**) to **14** and the isomerization from **8b** to **6b,** are thought to be key steps in the reaction of β-trifluoroacetylvinyl ether (**2**) with

1,2-phenylenediamine affording benzodiazepine (**6b**).[8]

Dehydration of dihydrobenzodiazepinol (**5a**) to benzodiazepine (**6a**) was estimated to be an endothermic reaction (14.4 kcal/mol; Scheme 5). This result is compatible with our experimental result where dehydration of **5a** to **6a** required heating (ca. 120 °C) under reduced pressure (ca. 2.5 mmHg).[6] Obviously, **6a** obtained by the reaction of β-trifluoroacetylketene dimethyl acetal (**1**) with 1,2-phenylenediamine did not derive from **5a** as shown in Scheme 2, because the reaction of **1** with 1,2-phenylenediamine proceeded at ambient temperature to give **6a** together with **5a**.



Scheme 7

Two reaction pathways from dihydrobenzodiazepinol (**7a**) to benzodiazepine (**6a**) are possible (Scheme 7). Path A requires dehydration of **7a** to benzodiazepine (**15**) and subsequent isomerization of **15** to **6a**. Path B requires conversion of **7a** to **6a** *via* benzodiazepine (**8a**). The first dehydration process in both Path A and Path B is endothermic. However, ΔE (7.5 kcal/mol) between **7a** and **15** is about 3 kcal/mol less than that between **7a** and **8a** (10.9 kcal/mol), and about 7 kcal/mol smaller than that between **5a** and **6a** (14.4 kcal/mol; Scheme 5). Dehydration of dihydrobenzodiazepinol (**7a**) arising from cyclization of **9a** to **15** would proceed partially before the isomerization of **7a** to **5a** occurs. This is a possible reason why the reaction

of **1** with 1,2-phenylenediamine gives **6a** as a minor product together with **5a** under very mild conditions.

CONCLUSION

On the basis of molecular orbital calculations, we can explain reasonably the preferred products formed by the individual reaction of β-trifluoroacetylketene dimethyl acetal (**1**), β-trifluoroacetyl-α-phenylvinyl methyl ether (**2**), and β-bis(trifluoroacetyl)vinyl *iso*-butyl ether (**3**) with 1,2-phenylenediamine. Intramolecular frontier orbital interaction in *O*-*N* exchanged products (**10**) formed as intermediates in the above reactions would be a key factor determining whether the subsequent cyclization yielding dihydrobenzodiazepinols (**7**) proceeds or not. Major formation of product (**5a**) as a result of the reaction of **1** with 1,2-phenylenediamine could be rationalized by isomerization of **7a** to **5a** because of the relative thermodynamic stability of 2,3-dihydro-1*H*-benzo[*b*][1,4]diazepin-2-ol (**5a**) compared to 2,5-dihydro-1*H*-benzo[*b*][1,4]diazepin-2-ol (**7a**). The minor product (**6a**) would not derive from **5a** but would be produced from **7a** *via* 1*H*-benzo[*b*][1,4]diazepine (**15**).

COMPUTATIONAL METHODS

All calculations employed in this paper were accomplished using the computer programs packages SPARTAN and PC SPARTAN 04.[15] All calculations for geometrical optimizations were performed with the 6-31G* basis set at B3LYP [16] level. The starting geometries employed for all optimizations were resulted from molecular mechanics using SYBYL[17] force field and subsequent semi-empirical PM3[18] optimizations. The calculations for energy of intermediates were also taken with the 6-31G* basis set at B3LYP level.

REFERENCES

1. R. Filler and Y. Kobayashi, 'Biomedicinal Aspects of Fluorine Chemistry,' Kodansha & Elsevier Biomedical, Tokyo, 1982.
2. R. Filler, 'Organofluorine Chemicals and Their Industrial Applications,' Ellis Horwood, London, 1979.
3. J. T. Welch, *Tetrahedron*, 1987, **43**, 3123.
4. R. Filler, Y. Kobayashi, and L. M. Yagupolskii, 'Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications,' Elsevier, Amsterdam, 1993.
5. E. Okada, N. Ota, T. Tomoda, M. Fujimoto, and H. Takenaka, Jpn. Kokai Tokkyo Koho, 2006-273844, 2006.
6. N. Ota, E. Okada, N. Terai, T. Miyamura, D. Shibata, and T. Sakata, *Heterocycles*, in press.
7. N. Ota, T. Tomoda, N. Terai, Y. Kamitori, D. Shibata, M. Médebielle, and E. Okada, *Heterocycles*, in press.
8. H. B. Bonacorso, L. M. L. Marques, N. Zanatta, and M. A. P. Martins, *Synth. Commun*., 2002, **32**, 3225.
9. A. C. S. Reddy, P. S. Rao, and R. V. Venkataratnam, *Tetrahedron Lett*., 1996, **37**, 2845; A. C. S. Reddy, P. S. Rao, and R. V. Venkataratnam, *Tetrahedron*, 1997, **53**, 5847.
10. N. Ota, Y. Kamitori, T. Tomoda, N. Terai, and E. Okada, *Heterocycles*, in press.
11. M. Hojo, R. Masuda, E. Okada, and Y. Mochizuki, *Synthesis*, 1992, 455.
12. M. Hojo, R. Masuda, and E. Okada, *Synthesis*, 1986, 1013.
13. M. Hojo, R. Masuda, E. Okada, S. Sakaguchi, H. Narumiya, and K. Morimoto, *Tetrahedron Lett*., 1989, **30**, 6173.
14. M. Hojo, R. Masuda, E. Okada, H. Yamamoto, K. Morimoto, and K. Okada, *Synthesis*, 1990, 195.
15. Wavefunction, Inc.
16. A. D. Becke, *J. Chem. Phys*., 1993, **98**, 5648.
17. M. Clark, R. D. Cramer III, and N. van Opdensch, *J. Computational Chem*., 1989, **10**, 982.
18. J. J. P. Stewart, J. Computer Aided Molecular Design, 1992, **6**, 69.

CHAPTER 7

Hetero Diels-Alder Reaction of β-Trifluoroacetylated Vinyl Ethers with Vinyl Ethers to Access Fluorine-Containing Dihydropyran Derivatives - A Molecular Orbital Calculation Study

SUMMARY

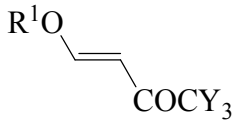
The reactivity differences between β-trifluoroacetylvinyl ethers (**1**), β,β-bis(trifluoroacetyl)vinyl ethers (**2**), β-acetylvinyl ethers (**3**), and β,β-diacetylvinyl ethers (**4**) in the hetero Diels-Alder reaction with vinyl ethers giving dihydropyrans (**5**, **6**, **7**, and **8**, respectively) are discussed on the basis of molecular orbital calculations. Frontier orbital interactions and activation energies of these reactions were estimated using DFT calculations.

INTRODUCTION

In recent years, research efforts have focused on developing new methodologies for the syntheses of fluorine-containing heterocycles. These compounds are widely recognized as important organic materials, showing specific functions as well as biological activities that are of interest.[1-4] Previously, we reported efficient and convenient synthetic methods to obtain fluorine-containing dihydropyrans (**5**, **6**) from β-trifluoroacetylvinyl ethers (**1**)[5] and β,β-bis(trifluoroacetyl)vinyl ethers (**2**).[6] We found that the hetero Diels-Alder reaction of **1** with vinyl ethers readily occurred at 80 °C and that of **2** with vinyl ethers proceeded smoothly below 40 °C.[5,6] On the other hand, the hetero Diels-Alder reaction of β-acetylvinyl ethers (**3**) bearing no fluorine atoms with vinyl ethers required high reaction temperatures (190-210 °C) to access the corresponding dihydropyrans (**7**).[7] Even in the case of β,β-diacetylvinyl ethers (**4**) with two electron-withdrawing acetyl groups, elevation of the reaction temperature (over 100 °C) was necessary for the corresponding

cycloaddition to afford dihydropyrans (**8**).[8]

In general, Lewis acid catalysis is necessary for inverse-electron-demand Diels-Alder reaction of heterodienes with electron-rich alkenes under mild conditions.[9] Therefore, it is worth noting that the reaction of **2** with vinyl ethers proceeded, even at ambient temperatures, in the absence of a catalyst.[6] We were thus very interested in the effect of trifluoromethyl and trifluoroacetyl groups on the present hetero Diels-Alder reaction.



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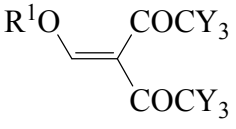
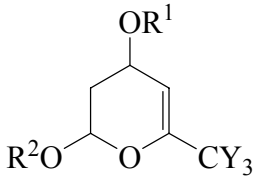
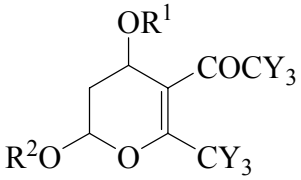


2: Y= F
4: Y= H



5: Y= F
7: Y= H



6: Y= F
8: Y= H

R^1, R^2: **a** = Me, **b** = Et, **c** = *i*-Bu, **d** = Ph

The hetero Diels-Alder reaction to afford **5** and **6** is a potential route to prepare carbohydrates and related compounds bearing a CF_3 component. Furthermore, dihydropyrans (**5**, **6**) are potentially useful intermediates to access a variety of fluorine-containing organic compounds including heterocycles. We found the specific ring-opening reactions of **5** and **6** with nucleophiles, such as thiols,[10,11] amines,[12] and aromatic compounds[13] afford novel fluorine-containing dienone derivatives, which are expected to be versatile building blocks for various CF_3-containing heterocycles. Despite its importance for the synthesis of various dihydropyran derivatives including **5** and **6**, there have been no reports of molecular orbital calculations elucidating the hetero Diels-Alder reaction of electron-deficient heterodienes (**1**-**4**) with electron-rich alkenes, such as vinyl ethers.

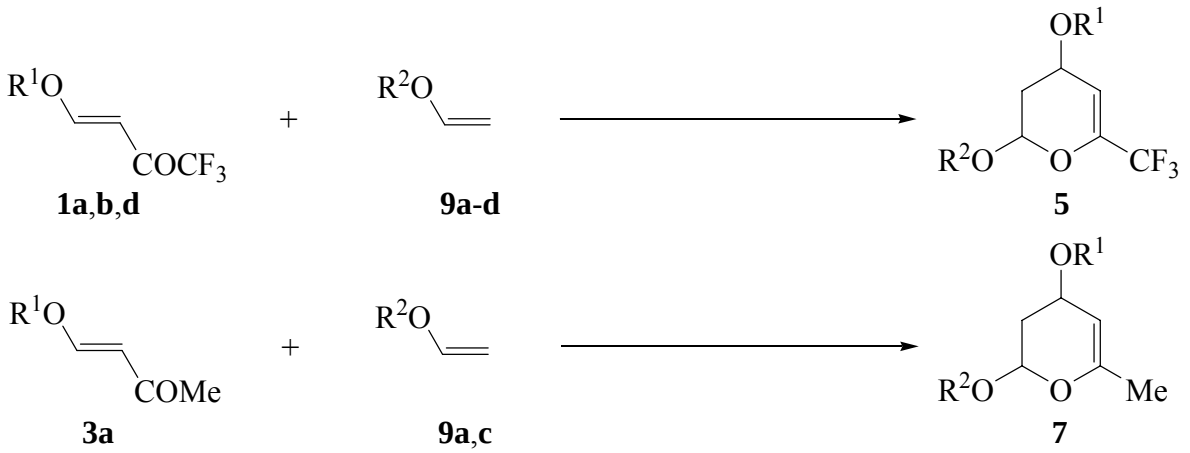
Here, we present hetero Diels-Alder reaction of these systems along with the results of molecular orbital calculations. The reactivity differences between compounds **1**-**4** in the hetero Diels-Alder reaction with electron-rich alkenes are elucidated on the basis of DFT calculations.

RESULTS AND DISCUSSION

Previously, we reported that the hetero Diels-Alder reaction of β-trifluoroacetylvinyl ethers (**1b**,**d**) with vinyl ethers (**9b-d**) readily occurred at 80 °C to give the corresponding 3,4-dihydro-2*H*-pyrans (**5bb**,**bc**,**db**,**dd**) in excellent yields (Scheme 1, Table 2, Entries 2,3,5 and 6).[5] In contrast, the corresponding reaction of 4-methoxy-3-buten-2-one (**3a**) with isobutyl vinyl ether (**9c**), affording 2-isobutoxy-6-methyl-3,4-dihydro-2*H*-pyran (**7ac**), proceeded much slower, even at 190-210 °C, and the conversion did not exceed 45% (Scheme 1, Table 2, Entry 8).[7] In order to understand the reactivity difference between **1** and **3** for the hetero Diels-Alder reaction with vinyl ethers (**9**), we carried out 6-31G* level DFT calculations (RB3LYP/6-31G*) on the reactions shown in Scheme 1.

The optimized structures and their energy values were computed for β-trifluoroacetylvinyl ethers (**1a**,**b**,**d**), 4-methoxy-3-buten-2-one (**3a**), and vinyl ethers (**9a-d**). The values of total energy and frontier orbital energy of these substrate molecules are summarized in Table 1.

The energy level gaps (ΔE_f^1) between the HOMO of **9a-d** and the LUMO of **1a**,**b**,**d** and **3a**, and those (ΔE_f^2) between the HOMO of **1a**,**b**,**d** and **3a** and the LUMO of **9a-d** were calculated for all hetero Diels-Alder reactions depicted in Scheme 1 (Table 2). In all the cases, the values of ΔE_f^1 were much smaller than those of ΔE_f^2, clearly indicating that the cycloaddition reactions in Scheme 1 are tentative inverse electron-demand Diels-Alder reaction of electron-deficient heterodienes (**1** and **3**) with electron-rich alkenes (**9**).



Scheme 1

Table 1 The total energy (E), and the energy levels of HOMO (E_{HOMO}) and LUMO (E_{LUMO}) on **1a**,**b**,**d**, **3a** and **9a-d**

1, **3**	R^1	E (au)	E_{HOMO} (eV)	E_{LUMO} (eV)	**9**	R^2	E (au)	E_{HOMO} (eV)	E_{LUMO} (eV)
1a	Me	-643.47522	-6.957	-1.824	**9a**	Me	-193.11042	-5.919	1.057
1b	Et	-682.79517	-6.888	-1.775	**9b**	Et	-234.42986	-5.874	1.101
1d	Ph	-835.21747	-6.702	-1.977	**9c**	*i*-Bu	-311.05832	-5.89	1.085
3a	Me	-345.76472	-6.360	-0.928	**9d**	Ph	-384.85540	-5.943	-0.114

The calculated ΔE_f^1 for the hetero Diels-Alder reactions of β-trifluoroacetylvinyl ethers (**1a**,**b**,**d**) with vinyl ethers (**9a-d**) were 3.896 - 4.123 eV (Entries 1-6) and the difference between each ΔE_f^1 did not exceed 0.23 eV. On the other hand, ΔE_f^1 for the reactions of 4-methoxy-3-buten-2-one (**3a**) with vinyl ethers (**9a**,**c**) were 4.970 - 4.991 eV (Entries 7, 8). The ΔE_f^1 values for the reaction of **1a**, **1b**, and **1d** were ca. 1 eV smaller than those for the reaction of **3a**.

The smaller ΔE_f^1 causes a stronger frontier orbital interaction between the heterodienes and alkenes, thus promoting the hetero Diels-Alder reaction more effectively. The results are compatible with the experimental results showing that cycloaddition of β-trifluoroacetylvinyl ethers (**1b**,**d**) with vinyl ethers (**9b-d**) occurs more readily than that of β-acetylvinyl ether (**3a**) with isobutyl vinyl ether (**9c**).[5,7] The strong electron-withdrawing fluorine substituents effectively lower the LUMO level of **1** (Table 1), thereby decreasing ΔE_f^1 (Table 2) and making the hetero Diels-Alder reaction of **1** with **9** more facile than that of non-fluorinated **3** with **9**.

The hetero Diels-Alder reaction of β,β-bis(trifluoroacetyl)vinyl ether (**2**) with vinyl ether (**9**) occurs more readily than that of β-trifluoroacetylvinyl ether (**1**) with **9**.[6] The reaction of alkyl β,β-bis(trifluoroacetyl)vinyl ethers (**2b**,**c**) with **9b** and **9d** and that of aryl β,β-bis(trifluoroacetyl)vinyl ether (**2d**) with **9d** proceeded successfully at ambient temperature and 40 °C, respectively, to afford the corresponding dihydropyrans (**6bb**,**cb**,**bd**,**dd**) in moderate to high yields (Scheme 2, Table 4).[6] Furthermore, cycloaddition of **2b** with 1,1-diphenoxyethylene (**10d**) and that of **2b** and **2c** with ethyl vinyl sulfide (**11b**) also proceeded successfully under similar conditions to afford the

Table 2 The energy level gaps between HOMO and LUMO (ΔE_f^1 and ΔE_f^2) for hetero Diels-Alder reaction of β-acylvinyl ethers (**1a**,**b**,**d** and **3a**) with vinyl ethers (**9a-d**)

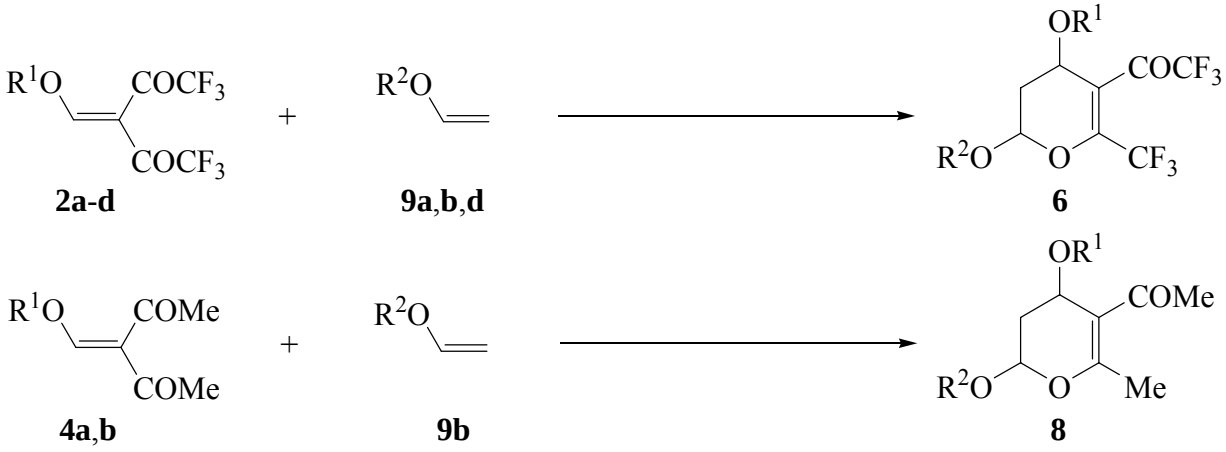
Entry	**1**, **3**	R^1	**9**	R^2	Product (Yield, %)	ΔE_f^1 (eV)[a]	ΔE_f^2 (eV)[b]
1	**1a**	Me	**9a**	Me	**5aa**	4.095	8.014
2	**1b**	Et	**9b**	Et	**5bb** (93)[5]	4.099	7.989
3	**1b**	Et	**9c**	*i*-Bu	**5bc** (100)[5]	4.123	7.973
4	**1d**	Ph	**9a**	Me	**5da**	3.942	7.759
5	**1d**	Ph	**9b**	Et	**5db** (72)[5]	3.896	7.803
6	**1d**	Ph	**9d**	Ph	**5dd** (77)[5]	3.965	6.588
7	**3a**	Me	**9a**	Me	**7aa**	4.991	7.417
8	**3a**	Me	**9c**	*i*-Bu	**7ac** (<45)[7]	4.970	7.445

[a] $\Delta E_f^1 = (E_{LUMO}$ of **1**, **3**$) - (E_{HOMO}$ of **9**$)$. [b] $\Delta E_f^2 = (E_{LUMO}$ of **9**$) - (E_{HOMO}$ of **1**, **3**$)$.

corresponding **12bd**, **13bb**, and **13cb**, respectively (Figure 1, Table 4).[6] In contrast, the hetero Diels-Alder reaction of β,β-diacetylvinyl ethers (**4a**,**b**) with ethyl vinyl ethers (**9b**) in Scheme 2 required a much higher reaction temperature (140 °C).[8]

The energy values and the frontier orbital energy levels of the most stable structures of β,β-bis(trifluoroacetyl)vinyl ethers (**2a-d**) and β,β-diacetylvinyl ethers (**4a**,**b**) are summarized in Table 3. As expected, the LUMO energies of **2a-d**, **4a**, and **4b** (Table 3) were lower than those of **1a-d** and **3a** (Table 1). These results clearly indicate that the hetero Diels-Alder reaction of **2a-d**, **4a**, and **4b** with electron-rich alkenes, such as **9a-d**, is also of the inverse electron-demand type reaction.

We calculated the energy level gaps (ΔE_f^1) between the HOMO of **9a**, **9b**, and **9d** and the LUMO of **2a-d**, **4a**, and **4b** for all cases of cycloaddition in Scheme 2 (Table 4). Moreover, for the cycloaddition of **2a** and **2b** with 1,1-diphenoxyethylene (**10d**) and vinyl sulfides (**11a**,**b**), which afforded the dihydropyrans (**12ad**,**bd** and **13aa-cb**; Figure 1), we evaluated the ΔE_f^1 values (Table 4).



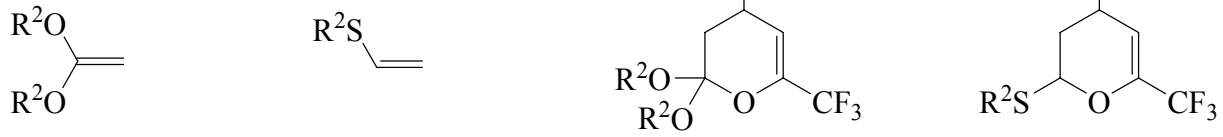
Scheme 2

Table 3 The total energy (E), and the energy levels of HOMO (E_{HOMO}) and LUMO (E_{LUMO}) on **2a-d** and **4a**,**b**

2	R^1	E (au)	E_{HOMO} (eV)	E_{LUMO} (eV)	**2**, **4**	R^2	E (au)	E_{HOMO} (eV)	E_{LUMO} (eV)
2a	Me	-1093.81611	-7.556	-2.532	**2d**	Ph	-1285.55773	-7.159	-2.623
2b	Et	-1133.13671	-7.477	-2.457	**4a**	Me	-498.40763	-6.473	-1.578
2c	*i*-Bu	-1211.76615	-7.467	-2.454	**4b**	Et	-537.72748	-6.431	-1.519

The values of ΔE_f^1 for the hetero Diels-Alder reaction of β,β-bis(trifluoroacetyl)vinyl ethers (**2a-d**) with vinyl ethers (**9a-d**) were in the range of 3.319 - 3.486 eV (Entries 1-6). These ΔE_f^1 values were ca. 0.8 eV smaller than those for the reaction of β,β-diacetylvinyl ethers (**4a**,**b**) with **9b** (Entries 7, 8), and ca. 0.6 eV smaller than those for the reaction of β-trifluoroacetylvinyl ethers (**1a**,**b**,**d**) with **9a-d** (Entries 1-6 in Table 2). These results are consistent with the experimental results, showing that the cycloaddition of β,β-diacetylvinyl ethers (**4a**,**b**) with ethyl vinyl ether (**9b**) requires elevated reaction temperature up to 140 °C[8] and that of β-trifluoroacetylvinyl ethers (**1b**,**d**) with vinyl ethers (**9b-d**) occurs at 80 °C,[5] whereas the corresponding cycloaddition of β,β-bis(trifluoroacetyl)vinyl ethers (**2b-d**) with **9b-d** readily occurs below 40 °C.[6]

The values of ΔE_f^1 for the cycloaddition of **2a** and **2b** with 1,1-diphenoxyethylene (**10d**; Entries 9, 10) were slightly (ca. 0.2 eV) larger than those for the corresponding cycloaddition of **2a** and **2b**



10 **11** **12** **13**

Figure 1

with phenyl vinyl ether (**9d**; Entries 4,5). In contrast, ΔE_f^1 for the cycloaddition of **2a-c** with vinyl sulfides (**11a**,**b**; Entries 11-13) were slightly (ca. 0.2 eV) smaller than those for the corresponding cycloaddition of **2a-c** with vinyl ether (**9a**,**b**; Entries 1-3). However, differences in the ΔE_f^1 smaller than 0.3 eV would show no significant effect on the reaction. These results are also in good agreement with experimental results, showing that the cycloaddition of β,β-bis(trifluoroacetyl)vinyl ether (**2**) with ketene acetals (**10d**) and vinyl sulfides (**11a**,**b**) occurs as readily as that of **2** with vinyl ethers (**9**).[6]

In order to confirm these findings on the hetero Diels-Alder reactions of heterodienes (**1-4**) with electron-rich alkenes (**9-11**), we computed transition state structures for representative cases of these reactions and estimated their energies. Two pairs of optimized transition state structures (***endo*-TS5bb** and ***exo*-TS5bb**; ***endo*-TS6bb** and ***exo*-TS6bb**) corresponding to the *endo*- and *exo*-[4+2]cycloaddition of **1b** with **9b** and those of **2b** with **9b** are depicted in Figure 2 together with their energy values. The transition state structure, ***endo*-TS5bb**, was estimated to be 0.8 kcal/mol more stable than ***exo*-TS5bb**, and ***endo*-TS6bb** was estimated to be 2.1 kcal/mol more stable than ***exo*-TS6bb**. These findings are in good agreement with our experimental results, in which *endo*-[4+2]cycloaddition occurs preferentially in both cases of the reaction of **1b** with **9b** and **2b** with **9b** to give dihydropyrans (***cis*-5bb** and ***cis*-6bb**, respectively) as the major products together with ***trans*-5bb** and ***trans*-6bb** as the minor products, respectively.[5,6]

Some interatomic distances in ***endo*-TS5bb** and ***endo*-TS6bb** are also indicated in Figure 2. In both cases, the C(1')–O(4) bond was longer (0.398 Å and 0.542 Å, respectively) than the C(2')–C(1) bond.

Table 4 The energy level gaps between HOMO and LUMO, ΔE_f^1 for hetero Diels-Alder reaction of β,β-diacylvinyl ethers (**2a-d** and **4a**,**b**) with electron-rich alkenes (**9a**,**b**,**d**, **10d** and **11a**,**b**)

Entry	**2**, **4**	R^1	**9-11**	R^2	Product (Yield, %)	ΔE_f^1(eV)[a]
1	**2a**	Me	**9a**	Me	**6aa**	3.387
2	**2b**	Et	**9b**	Et	**6bb** (95)[6]	3.417
3	**2c**	*i*-Bu	**9b**	Et	**6cb** (98)[6]	3.420
4	**2a**	Me	**9d**	Ph	**6ad**	3.410
5	**2b**	Et	**9d**	Ph	**6bd** (85)[6]	3.486
6	**2d**	Ph	**9d**	Ph	**6dd** (50)[6]	3.319
7	**4a**	Me	**9b**	Et	**8ab**	4.296
8	**4b**	Et	**9b**	Et	**8bb** (87)[8]	4.355
9	**2a**	Me	**10d**	Ph	**12ad**	3.592
10	**2b**	Et	**10d**	Ph	**12bd** (77)[6]	3.667
11	**2a**	Me	**11a**	Me	**13aa**	3.148
12	**2b**	Et	**11b**	Et	**13bb** (100)[6]	3.169
13	**2c**	*i*-Bu	**11b**	Et	**13cb** (100)[6]	3.172

[a] $\Delta E_f^1 = (E_{LUMO}$ of **2**, **4**$) - (E_{HOMO}$ of **9-11**$)$.

From the energy values of the *endo* type transition state structures, we estimated the activation energies ($\Delta E^{\neq}$)[14] of hetero Diels-Alder reactions of β-acylvinyl ethers (**1a**,**b**,**d** and **3a**) and β,β-diacylvinyl ethers (**2a**,**b** and **4a**,**b**) with electron-rich alkenes (**9a-d**, **10a**, and **11a**,**b**) (Table 5). The estimated $\Delta E^{\neq}$ values of the cycloaddition of β-trifluoroacetylvinyl ethers (**1a**,**b**,**d**) with vinyl ethers (**9a-c**; Entries 1-5) were 12-14 kcal/mol, which was over 6 kcal/mol lower than that of the reactions of β-acetylvinyl ethers (**3a**) with **9a** and **9c** (Entries 6, 7). The $\Delta E^{\neq}$ for the cycloaddition of β,β-bis(trifluoroacetyl)vinyl ethers (**2a**,**b**) with **9a** and **9b** (Entries 8, 9) was 7-8 kcal/mol, which was over 7 kcal/mol lower than that of the corresponding reaction of β,β-diacetylvinyl ethers (**4a**,**b**; Entries 11,12), and at least 4 kcal/mol lower than the corresponding reaction of

β-trifluoroacetylvinyl ethers (**1a**,**b**,**d**; Entries 1-5). The $\Delta E^{\neq}$ for the cycloaddition of **2b** with phenyl vinyl ether (**9d**; Entry 10) was estimated to be 12.2 kcal/mol, which was ca. 5 kcal higher

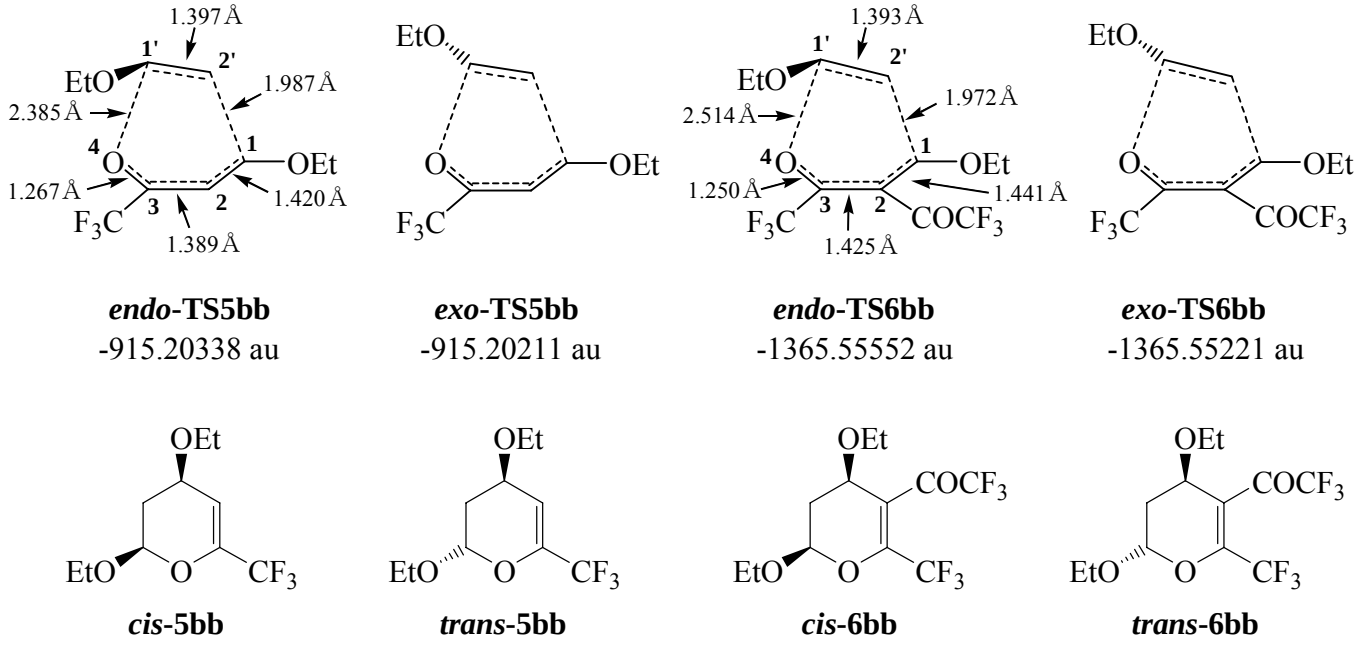


Figure 2

than that of the corresponding reaction with ethyl vinyl ether (**9b**; Entry 9). This relatively high activation energy corresponds to the fact that the cycloaddition of **2b** with phenyl vinyl ether **9d** required a prolonged reaction time (24 h) compared to that of **2b** with **9b** (15 min).[6]

The $\Delta E^{\neq}$ values were in decreasing order: β-acetylvinyl ethers (**3**; Entries 6, 7), β,β-diacetylvinyl ether (**4**; Entries 11, 12), β-trifluoroacetylvinyl ethers (**1**; Entries 1-5), and β,β-bis(trifluoroacetyl)vinyl ethers (**2**; Entries 8-10). This order is consistent with the decreasing order of the reaction temperature required for the hetero Diels-Alder reactions of **1**-**4** with vinyl ethers (**9**); **3**: 190-210 °C,[7] **4**: 140 °C,[8] **1**: 80 °C,[5] and **2**: rt-40 °C.[6]

We also estimated the $\Delta E^{\neq}$ for the hetero Diels-Alder reactions of β,β-bis(trifluoroacetyl)vinyl ethers (**2a**,**b**) with ketene acetals and vinyl sulfides instead of vinyl ethers. 1,1-Dimethoxyethylene (**10a**) was selected as a model compound for the ketene acetals. In the case of the cycloaddition of **2b** with **10a** (Entry 13), an $\Delta E^{\neq}$ of less than 4 kcal/mol was estimated. In contrast, the predicted

$\Delta E^{\neq}$ of the reaction of **2a** and **2b** with vinyl sulfides (**11a**,**b**; Entries 14, 15) was relatively high in

Table 5 Estimated activation energy ($\Delta E^{\neq}$) for hetero Diels-Alder reactions of β-acylvinyl ethers (**1a**,**b**,**d** and **3a**) and β,β-diacylvinyl ethers (**2a**,**b** and **4a**,**b**) with electron-rich alkenes (**9a-d**, **10a**, and **11a**,**b**)

Entry	**1-4**	R^1	**9-11**	R^2	Product	$\Delta E^{\neq}$ (kcal/mol)
1	**1a**	Me	**9a**	Me	**5aa**	13.9
2	**1b**	Et	**9b**	Et	**5bb**	13.6
3	**1b**	Et	**9c**	*i*-Bu	**5bc**	13.4
4	**1d**	Ph	**9a**	Me	**5da**	13.0
5	**1d**	Ph	**9b**	Et	**5db**	12.4
6	**3a**	Me	**9a**	Me	**7aa**	20.0
7	**3a**	Me	**9c**	*i*-Bu	**7ac**	20.0
8	**2a**	Me	**9a**	Me	**6aa**	8.0
9	**2b**	Et	**9b**	Et	**6bb**	6.9
10	**2b**	Et	**9d**	Ph	**6bd**	12.2
11	**4a**	Me	**9b**	Et	**8ab**	15.4
12	**4b**	Et	**9b**	Et	**8bb**	15.6
13	**2b**	Et	**10a**	Me	**12ba**	3.3
14	**2a**	Me	**11a**	Me	**13aa**	10.7
15	**2b**	Et	**11b**	Et	**13bb**	9.8

comparison with that of the corresponding reaction with vinyl ethers (**9a**,**b**; Entries 8, 9). These results explain why the reaction of **2b** with ethyl vinyl sulfide (**11b**) proceeds more slowly than that of **2b** with ethyl vinyl ether (**9b**),[6] even when the HOMO-LUMO gap (ΔE_f^1) between **2b** and **11b** (Table 4, Entry 12) is narrower than that between **2b** and **9b** (Table 4, Entry 2).

The difference in $\Delta E^{\neq}$ on the reactions of **9**, **10**, and **11** would be attributed to stronger electron-donating ability of oxygen compared to sulfur. The terminal olefin carbon of the

ketene acetal (**10a**) bearing two methoxy groups has more negative charge than that of vinyl ether (**9a**). On the other hand, the terminal olefin carbon of vinyl sulfide (**11a**) has less negative charge than **9a**. A stronger electrostatic interaction between **10a** and electron deficient **2b** would assist the molecular orbital interaction, in particular, that of C(2')-C(1) on the transition state (Figure 2), thus further decreasing $\Delta E^{\neq}$. In contrast, the reverse would be true on the transition state of the reaction of **2b** with **11a**.

CONCLUSION

Molecular orbital calculations suggest that the efficiency of heterodienes (**1**-**4**) on hetero Diels-Alder reaction with electron-rich alkenes (**9**-**11**) can be attributed to energy level gaps (ΔE_f[1]) between the LUMO of **1**-**4** and the HOMO of **9**-**11**. We confirmed these results by estimating the activation energies ($\Delta E^{\neq}$) of these hetero Diels-Alder reactions. It is worth noting that one trifluoroacetyl group in the heterodienes (**1**) lowers the activation energy of the hetero Diels-Alder reaction more effectively than the two acetyl groups in **4**. A more stable *endo* type transition state in the hetero Diels-Alder reaction of β-trifluoroacetylvinyl ethers (**1**) and β,β-bis(trifluoroacetyl)vinyl ethers (**2**) with ethyl vinyl ether (**9**) explains the formation of the major product, the *cis*-isomers of dihydropyrans (**5**, **6**).

COMPUTATIONAL METHODS

All calculations employed in this paper were accomplished using the computer programs packages SPARTAN and PC SPARTAN 04.[15] All calculations for geometrical optimizations were performed with the 6-31G* basis set at B3LYP [16] level. The starting geometries employed for all optimizations were resulted from molecular mechanics using SYBYL[17] force field and subsequent semi-empirical PM3[18] optimizations. The calculations for transition state geometries and their energies were also taken with the 6-31G* basis set at B3LYP level.

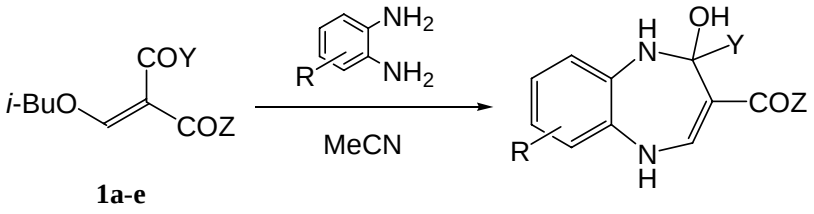
REFERENCES AND NOTES

1. R. Filler and Y. Kobayashi, 'Biomedicinal Aspects of Fluorine Chemistry,' Kodansha & Elsevier Biomedical, Tokyo, 1982.
2. R. Filler, 'Organofluorine Chemicals and Their Industrial Applications,' Ellis Horwood, London, 1979.
3. J. T. Welch, *Tetrahedron*, 1987, **43**, 3123.
4. R. Filler, Y. Kobayashi, and L. M. Yagupolskii, 'Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications,' Elsevier, Amsterdam, 1993.
5. M. Hojo, R. Masuda, and E. Okada, *Synthesis*, 1989, 215.
6. M. Hojo, R. Masuda, and E. Okada, *Synthesis*, 1990, 347.
7. G. Berti, G. Catelani, F. Colonna, and L. Monti, *Tetrahedron*, 1982, **38**, 3067.
8. R. R. Schmidt and M. Maier, *Tetrahedron Lett*., 1982, **23**, 1789.
9. For instance, see; L. F. Tietze and G. Kettschau, *Topics in Current Chemistry*, 1997, **189**, 1; J. Esquivias, R. G. Arrayas, and J. C. Carretero, *J. Am. Chem. Soc.*, 2007, **129**, 1480.
10. M. Hojo, R. Masuda, and E. Okada, *Chem. Lett*., 1990, **19**, 113.
11. M. Hojo, R. Masuda, and E. Okada, *Synthesis*, 1991, 46.
12. M. Hojo, R. Masuda, and E. Okada, *Synthesis*, 1990, 425.
13. N. Ota, E. Okada, A. Sonoda, N. Muro, D. Shibata, and M. Médebielle, *Heterocycles*, 2008, **76**, 215.
14. Correction for zero-point vibrational energy was not carried out.
15. Wavefunction, Inc.
16. A. D. Becke, *J. Chem. Phys*., 1993, **98**, 5648.
17. M. Clark, R. D. Cramer III, and N. van Opdensch, *J. Computational Chem*., 1989, **10**, 982.
18. J. J. P. Stewart, *J. Computer Aided Molecular Design*, 1992, **6**, 69.

GENERAL CONCLUSION

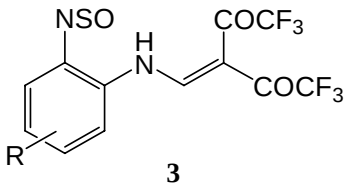
In this doctoral dissertation were presented novel methodologies for the syntheses of fluorine-containing heterocyclic compounds using trifluoroacetylated alkenes such as β,β-bis(trifluoroacetyl)vinyl ethers and β-trifluoroacetylketene acetals as indispensable key intermediates. Moreover, novel synthetic methods of versatile building blocks, fluorinated 3-allylidenepentane-2,4-diones, for the construction of CF_3-containing heterocyclic compounds, have been also investigated.

Chapter 1 describes convenient syntheses of 1*H*-benzo[*b*][1,4]diazepinols (**2a**) by the reaction of β,β-bis(trifluoroacetyl)vinyl ether (**1a**) with various 1,2-phenylenediamines under mild conditions.



1a-e **2a-e**

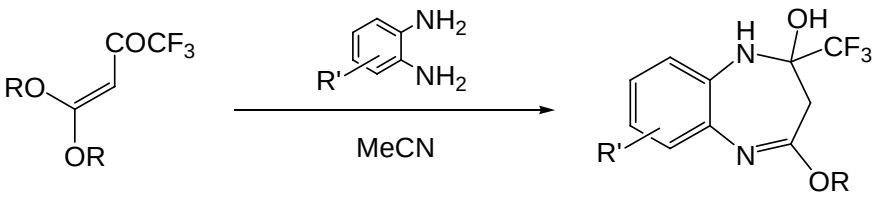
1,2	Y	Z
a	CF_3	CF_3
b	CF_2Cl	CF_2Cl
c	CF_2CF_3	CF_2CF_3
d	CF_3 / CF_2CF_3	CF_2CF_3 / CF_3
e	CF_3 / CCl_3	CCl_3 / CF_3



3

The results of our approaches on the reaction of **1a** with 1,2-phenylenediamines show sharp contrast with those carried out under microwave irradiation. This method was applicable to the synthesis of the diazepinols (**2b**-**e**) from several β,β-bis(perhaloalkanoy)lvinyl ethers (**1b**-**e**). Moreover, it was found that **2a** reacted with thionyl chloride under mild conditions to afford the unexpected *N*-sulfinylanilines (**3**) in high yields.

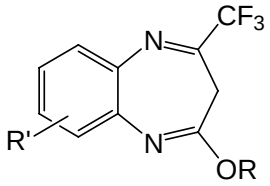
Chapter 2 describes the reaction of β-trifluoroacetylketene acetals (**3a**,**b**) with various 1,2-phenylenediamines under very mild conditions without microwave irradiation to give the desired fluorine-containing 2,3-dihydro-1*H*-benzo[*b*][1,4]diazepinols (**4a**,**b**) having an alkoxy group at the C-4 position.



3
a: R = Me
b: R = Et

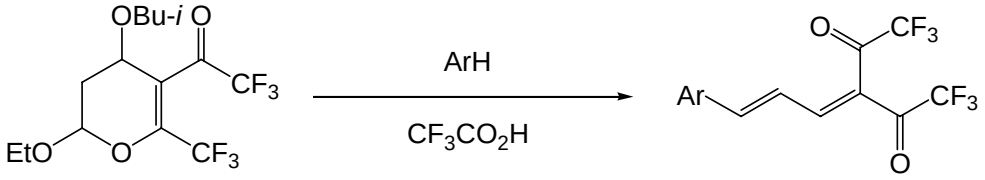
4
a: R = Me
b: R = Et

It was also found that the thermal dehydration of **4** is easily carried out under reduced pressure to yield the corresponding 3*H*-benzo[*b*][1,4]diazepines (**5a**,**b**).



5
a: R = Me
b: R = Et

Chapter 3 demonstrates a facile and convenient C_8-unit introduction method for various aromatic compounds by utilizing a fluorine-containing dihydropyran derivative (**6**), which was accessible by the hetero Diels-Alder reaction of β,β-bis(trifluoroacetyl)vinyl ether (**1a**) with ethyl vinyl ether.



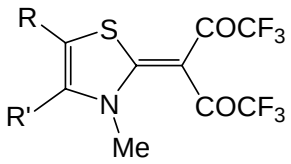
6

7

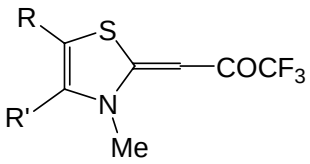
ArH: aromatic compound

The novel fluorinated 3-allylidenepentane-2,4-diones (**7**) were synthesized by the ring-opening reaction of **1a** with aromatic compounds in refluxing trifluoroacetic acid. These 3-allylidenepentane-2,4-diones (**7**) will serve as versatile building blocks for the construction of CF_3-containing heterocyclic compounds, which may be expected to become useful tools for the exploration of novel pharmacophore.

Chapter 4 describes an efficient synthetic method for novel cyclic β-trifluoroacetylated ketene *S*,*N*-acetals, 2-bis(trifluoroacetyl)methylene- and 2-trifluoroacetylmethylene-2,3-dihydro-3-

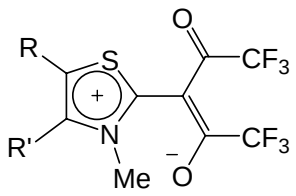


8a



8b

methylthiazoles (**8a**,**b**) from the corresponding 2,3-dimethylthiazolium iodides with trifluoroacetic anhydride. This novel heterocyclic system **8a**, which are not easily accessible by other methods, has interesting highly polarized structure (**8a'**).

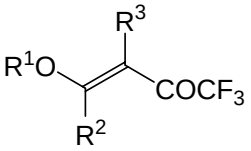


8a'

In chapters 5 and 6, the difference between the two types of benzo[*b*][1,4]diazepine derivatives (**2** and **4**) is discussed on the basis of molecular orbital calculations.

Chapter 5 describes the molecular orbital calculation study on the difference of products resulting from the reactions of β,β-bis(trifluoroacetyl)vinyl *iso*-butyl ether (**1a**), β-trifluoroacetylvinyl *iso*-butyl ether (**9**), and β-trifluoroacetyl-α-phenylvinyl methyl ether (**9'**) with 1,2-phenylenediamine. Moreover, chapter 6 shows the molecular orbital calculation study on

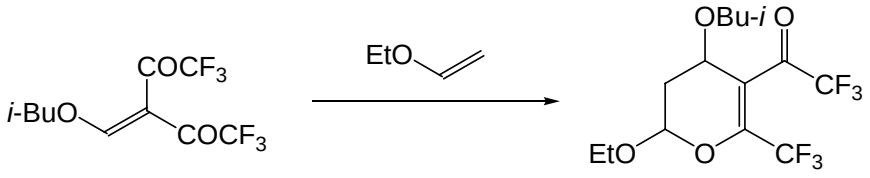
the difference of the benzo[*b*][1,4]diazepine formation between β-trifluoroacetylketene dimethyl acetal (**3a**), β-trifluoroacetyl-α-phenylvinyl methyl ether (**9'**), and β-bis(trifluoroacetyl)vinyl *iso*-butyl ether (**1a**) by the reactions with 1,2-phenylenediamine respectively.



1a, **3a**, **9**, **9'**

	R^1	R^2	R^3
1a	*i*-Bu	H	$COCF_3$
3a	Me	MeO	H
9	*i*-Bu	H	H
9'	Me	Ph	H

Chapter 7 demonstrates the rationalized explanation about the hetero Diels-Alder reaction of **1a** and the other β,β-bis(trifluoroacetyl)vinyl ethers with various vinyl ethers from the viewpoint of the molecular orbital calculation. The fluorine-containing dihydropyran (**6**) derived from our important key intermediate (**1a)** is the essential compound for one step introduction of 4,4-bis(trifluoroacetyl)-1,3-butadiene system to aromatics described in chapter 3.



1a **6**

PUBLICATION LIST

CHAPTER 1

A Convenient Synthesis of Fluorine-Containing Dihydrobenzo[*b*][1,4]diazepinols and its Application to a Synthesis of Novel *N*-Sulfinylanilines

N. Ota, T. Tomoda, N. Terai, Y. Kamitori, D. Shibata, M. Médebielle, and E. Okada, *Heterocycles*, 2008, **76**, 1205.

CHAPTER 2

A Convenient Synthetic Method for Fluorine-Containing 4-Alkoxy-dihydrobenzo[*b*][1,4]-diazepinols and 3*H*-Benzo[*b*][1,4]diazepines by the Reaction of β-Trifluoroacetylketene Acetals with 1,2-Phenylenediamines

N. Ota, E. Okada, N. Terai, T. Miyamura, D. Shibata, and T. Sakata, *Heterocycles*, 2009, **77**, 983.

CHAPTER 3

One Step Introduction of 4,4-Bis(trifluoroacetyl)-1,3-butadiene System to Aromatic Rings Using Fluorine-Containing 3,4-Dihydro-2*H*-pyrans. A Facile Synthetic Method for 1,1,1,5,5,5-Hexafluoro-3-[(*E*)-3-arylallylidene]pentane-2,4-diones

N. Ota, E. Okada, A. Sonoda, N. Muro, D. Shibata, and M. Médebielle, *Heterocycles*, 2008, **76**, 215.

CHAPTER 4

A Facile and Convenient Synthetic Method for 2-Bis(trifluoroacetyl)methylene- and 2-Trifluoroacetylmethylene-2,3-dihydro-3-methylthiazoles

N. Ota, E. Okada, Y. Kamitori, D. Shibata, and M. Médebielle, *Heterocycles*, 2007, **74**, 721.

CHAPTER 5

Reaction of β,β-Bis(trifluoroacetyl)vinyl Ethers and β-Trifluoroacetylvinyl Ethers with 1,2-Phenylenediamines Accessing Fluorine-Containing Benzo[*b*][1,4]diazepine Derivatives - A Study about the Reaction Based on Molecular Orbital Calculations

N. Ota, Y. Kamitori, T. Tomoda, N. Terai, and E. Okada, *Heterocycles*, 2009, **77**, 461.

CHAPTER 6

Reaction of β-Trifluoroacetylketene Acetals and β-Trifluoroacetylvinyl Ethers with 1,2-Phenylenediamines Accessing Fluorine-Containing Benzo[*b*][1,4]diazepine Derivatives: A Molecular Orbital Calculation Study

N. Ota, Y. Kamitori, N. Terai, T. Sakata, and E. Okada, *Heterocycles*, 2009, **79**, 599.

CHAPTER 7

Hetero Diels-Alder Reaction of β-Trifluoroacetylated Vinyl Ethers with Vinyl Ethers to Access Fluorine-Containing Dihydropyran Derivatives - A Molecular Orbital Calculation Study

N. Ota, Y. Kamitori, D. Shibata, and E. Okada, *Heterocycles*, in press.

ORAL AND POSTER PRESENTATIONS LIST (in Japanese)

1. A Convenient Synthetic Method for New Fluorine-Containing Naphthalene-Fused Heterocycles Using Aromatic Nucleophilic Substitutions of *N*,*N*-Dimethyl-2-trifluoroacetyl-1-naphthylamine.
   The 33rd Congress of Heterocyclic Chemistry, Sapporo, November 2003.

2. A New Fluorine-Containing Building Block, 1-Amino-2-trifluoroacetylnaphthalene. A Convenient Synthetic Method for Benzoquinazolines and Benzoquinolines Having a Single Trifluoromethyl Group.
   The 17th French - Japanese Symposium on Medicinal and Fine Chemistry, Sendai, May 2004.

3. Trifluoroacetylvinylation of Aromatics Using Fluorine-Containing 3,4-Dihydro-2*H*-pyrans.
   The 34th Congress of Heterocyclic Chemistry, Ishikawa, November 2004.

4. A Convenient Synthetic Method for Fluorine-Containing Dihydrobenzo[*b*][1,4]diazepines by the Reaction of β,β-Bis(trifluoroacetyl)vinyl Ethers with 1,2-Phenylenediamines.
   The 85th National Meeting of the Chemical Society of Japan, Kanagawa, March 2005.

5. A Convenient Synthesis of Novel Fluorine-Containing Dihydrobenzo[*b*][1,4]diazepines by the Reaction of β,β-Bis(trifluoroacetyl)vinyl Ethers with 1,2-Phenylenediamines.
   The 35th Congress of Heterocyclic Chemistry, Osaka, October 2005.

6. Modification of Fluorine-Containing Dihydrobenzo[*b*][1,4]diazepines Having Antitumor Activities - A Convenient Synthesis of Novel Fluorine-Containing *N*-Sulfinylanilines.
The 86th National Meeting of the Chemical Society of Japan, Chiba, March 2006.

7. Synthesis of Novel Fluorine-Containing *N*-Sulfinylanilines Having Antitumor Activities by the Reaction of Dihydrobenzodiazepines with Thionyl Chloride.
The 36th Congress of Heterocyclic Chemistry, Nagasaki, October 2006.

8. Annulation of Trifluoroacetylketene Acetals and Trifluoroacetylvinyl Ethers with 1,2-Phenylenediamines.
The 87th National Meeting of the Chemical Society of Japan, Osaka, March 2007.

9. A Facile Synthetic Method for Fluorine-Containing Dihydrobenzodiazepinols and Benzodiazepines by the Reaction of β-Trifluoroacetylketene Dimethyl Acetals with 1,2-Phenylenediamines.
The 87th National Meeting of the Chemical Society of Japan, Osaka, March 2007.

10. Reaction of Trifluoroacetylketene Acetals and Trifluoroacetylvinyl Ethers with 1,2-Phenylenediamines Accessing Fluorine-containing Benzodiazepine Derivatives - Analysis of the Reaction on the Basis of Molecular Orbital Calculations.
The 37th Congress of Heterocyclic Chemistry, Nagano, October 2007.

11. Annulation of Trifluoroacetyl- and Bis(trifluoroacetyl)vinyl Ethers with 1,2-Phenylenediamines.
The 88th National Meeting of the Chemical Society of Japan, Tokyo, March 2008.