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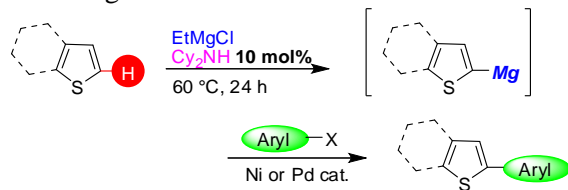


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ABSTRACT

The reaction of thiophene derivatives with Grignard reagent (EtMgCl) and a catalytic amount of amine (Cy₂NH) induced the metalation at the α-position. Following addition of several aryl halides in the presence of a nickel or palladium catalyst afforded C–H arylated products in good to excellent yields. The method was successfully applied to facile synthesis of differently-substituted 2,5-diarylthiophenes.

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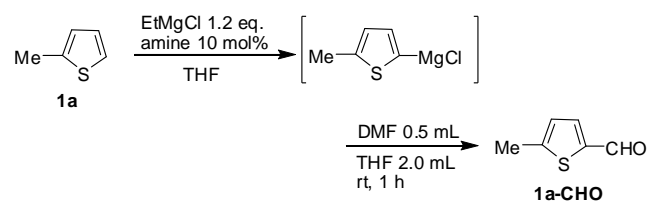
1. Introduction

C–H functionalization of heteroaromatic compounds with organic halides is of great interest in organic synthesis compared with those of the related cross-coupling reaction with metallic reagents.^{1, 2} Since a number of heteroaromatic components are found in biologically active molecules³ as well as advanced organic materials⁴; development of a practical synthetic strategy for such molecules is an important issue in organic synthesis. Therefore, the straightforward coupling with C–H functionalization is of considerable attention. We have recently shown head-to-tail-type oligothiophene and polythiophene syntheses with nickel-catalyzed cross coupling at the C–H bond of thiophene,^{5,6} in which magnesium amide TPMgCl·LiCl recognized as Knochel-Hauser base⁷ served as a deprotonating agent for in-situ formation of the metallic species. We also found that the metalation reaction of thiophene derivatives efficiently proceeded with a combination of a Grignard reagent and a catalytic amount of secondary amine and thus metalated thiophene reacted with halothiophene to form thiophene–thiophene bond.⁵ We envisaged that such a unique metalating system is also effective for the coupling reaction of various aryl halides as well as that of halothiophenes. Herein, we report that nickel or palladium-catalyzed cross coupling of aryl bromides and chlorides with thiophene derivatives using a metalating protocol by combination of catalytic amine and a Grignard reagent.

2. Results and discussion

We first examined the metalation of 2-methylthiophene (**1a**) with ethylmagnesium chloride (EtMgCl) and a catalytic amount of secondary amines to form the corresponding thienyl magnesium reagent as summarized in Table 1.

Table 1. Generation of thienyl magnesium species with EtMgCl and a catalytic amount of amine.^a



amine	temp./°C	time/h	yield ^b /%
Cy ₂ NH	60	1	23
	60	6	76
	60	12	97
	60	24	99
TMPH	60	5	71
	60	12	81
	60	24	94
CyMeNH	60	24	25
Et ₂ NH	60	24	24
Bu ₂ NH	60	24	26

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^a The reaction was performed with **1a** (0.5 mmol), EtMgCl (0.6 mmol) and amine (0.05 mmol) in 0.60 mL of THF. ^b Isolated yield.

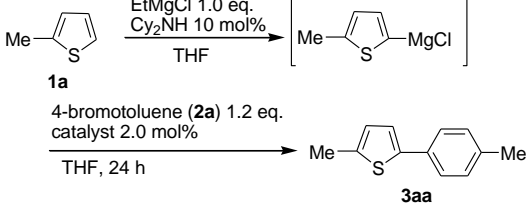
The progress of the reaction was confirmed by quenching with *N,N*-dimethylformamide (DMF) to afford 2-formyl-5-methylthiophene (**1a-CHO**)⁸. The reaction with 10 mol% of dicyclohexylamine (Cy₂NH) at 60 °C for 12 h afforded **1a-CHO** in 97% yield, while shorter reaction periods resulted in inferior yields. The use of 2,2,6,6-tetramethylpiperidine (TMPPH) required 24 h for the complete metalation. On the other hand, use of diethylamine (Et₂NH), cyclohexylmethylamine (CyMeNH) and dibutylamine (Bu₂NH) were found to be ineffective. We have already shown that metalation of 2-chloro-3-hexylthiophene with EtMgCl and 10 mol% of Cy₂NH under similar conditions proceeded efficiently within 1 h to result in the metalation in an excellent yield³. However, the reaction of 2-methylthiophene, whose C–H bond at the 5-position was less acidic, at 60 °C for 1 h underwent the metalation in a poor yield (23%).

With metalation conditions of **1a** at the 5-position using EtMgCl and 10 mol% of Cy₂NH at 60 °C for 24 h, we carried out a transition metal-catalyzed cross coupling reaction of 4-bromotoluene (**2a**). As shown in Table 2, the reaction with 2.0 mol% of nickel catalyst of bidentate diphosphine NiCl₂(dppe) at room temperature for 24 h proceeded smoothly to afford **3aa** in a quantitative yield.⁹ The reaction with NiCl₂(dppf) at 60 °C also gave **3aa** in a reasonable yield (68%), whereas the reaction with other nickel catalyst NiCl₂(PPh₃)₂ and NiCl₂(dppp) proceeded in poor yields. The reaction with palladium catalysts with phosphine ligands, PdCl₂(PPh₃)₂ and PdCl₂(dppf)·CH₂Cl₂, proceeded in moderate yields. Higher catalytic activity was achieved with 2.0 mol% of palladium catalyst bearing a *N*-heterocyclic carbene (NHC) ligand PEPPSI-SIPr¹⁰, to afford **3aa** in an excellent yield at room temperature.

The reaction of several thiophene derivatives was examined with a variety of aryl bromides. The results are shown in Table 3. Various aryl bromides bearing an electron-withdrawing or donating substituent reacted with 2-methylthiophene (**1a**) to afford the coupling products in good to excellent yields. Although the reaction with 4-bromo-*N,N*-dimethylaniline


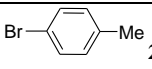
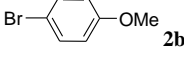
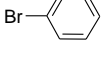
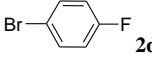
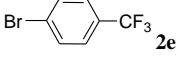
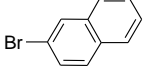
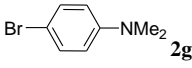
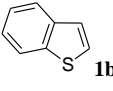
proceeded, the yield was slightly lower (38%, entry 7). In addition, the reaction with other thiophene derivatives benzo[*b*]thiophene (**1b**) and 2-alkynylthiophene **1c** took place similarly to afford the corresponding C–H arylation products with PEPPSI-SIPr¹⁰. Thiophene (**1d**) reacted with aryl bromides to afford 2-arylated thiophene (**3da**, **3db**, **3dg**) in good to excellent yields (entry 17–19). The reaction of benzo[*b*]furan was carried out with 4-bromobenzene to afford **3ec** in 58% yield (entry 20).

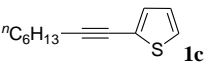

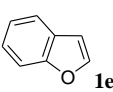
Table 2. Arylation of 2-methylthiophene (**1a**) with 4-bromotoluene (**2a**) with various catalysts^a

		
catalyst	temp./°C	yield ^b /%
NiCl ₂ (PPh ₃) ₂	60	31
NiCl ₂ (dppe)	rt	>99
NiCl ₂ (dppp)	60	23
NiCl ₂ (dppf)	60	68
PdCl ₂ (PPh ₃) ₂	60	82
PdCl ₂ (dppf)·CH ₂ Cl ₂	60	91
PdCl ₂ (dppf)·CH ₂ Cl ₂	rt	72
Pd-PEPPSI-SIPr	rt	87

^a The reaction was carried out with **1a** (0.5 mmol), EtMgCl (0.5 mmol) and Cy₂NH (0.05 mmol), **2a** (0.6 mmol) and catalyst (0.01 mmol) in 2.0 mL of THF. ^b Isolated yield.

Table 3. C–H coupling of thiophene derivatives with aryl bromide^a

entry	Substrate	Aryl–Br	catalyst	temp./°C, time/h	yield ^b /%
1			NiCl ₂ (dppe)	rt, 24	>99 (3aa)
2	1a			rt, 24	79 (3ab)
3	1a			rt, 24	97 (3ac)
4	1a			rt, 24	98 (3ad)
5	1a			rt, 23	76 (3ae)
6	1a			rt, 23	75 (3af)
7	1a			rt, 23	38 ^c (3ag)
8		2a	PEPPSI-SIPr	rt, 4	94 (3ba)
9	1b	2b		rt, 5	90 (3bb)

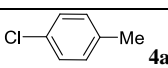
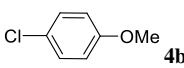
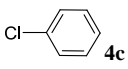
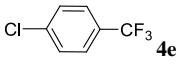
10	1b	2c		rt, 20	62 (3bc)
11	1b	2d	PEPPSI-SIPr	rt, 22	95 (3bd)
12	1b	2e		rt, 5	96 (3be)
13	1b	2f		rt, 18	66 (3bf)
14	1b	2g		rt, 19	71 (3bg)
15		2a		rt, 22	75 (3ca)
16	1c	2b		rt, 24	86 (3cb)
17 ^d		2a		rt, 24	95 (3da)
18 ^d	1d	2b		rt, 24	75 (3db)
19 ^d	1d	2g		rt, 24	70 ^c (3dg)
20		2c		rt, 22	58 (3ec)

^a Unless noted, the reaction was performed with substrate (0.5 mmol), EtMgCl (0.5 mmol), amine (0.05 mmol), aryl bromide (0.60 mmol) and catalyst (2.0 mol%) in 2.0 mL of THF. ^b Unless specified, isolated yield. ^c The yield was estimated by ¹H NMR analysis. ^d The reaction was carried out with thiophene (0.6 mmol), EtMgCl (0.6 mmol), amine (0.06 mmol), aryl bromide (0.50 mmol) and catalyst (2.0 mol%) in 2.0 mL of THF.

It is also remarkable that the reaction with aryl chlorides **4** proceeded under similar conditions. The reaction of 2-methylthiophene with 4-chlorotoluene (**4a**) was found to take place at 60 °C for 24 h with PEPPSI-SIPr to afford **3aa** in a quantitative yield, whereas the use of NiCl₂(dppe), which showed

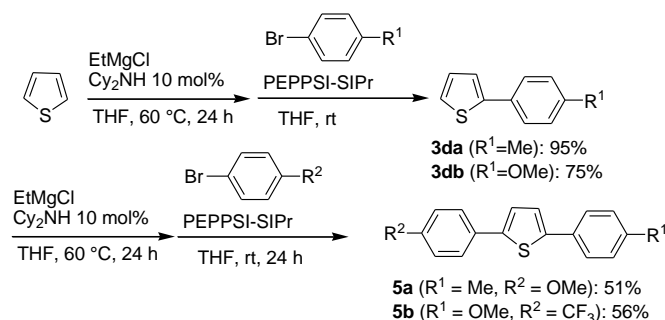
excellent performance in the reaction with aryl bromide, resulted in a lower yield. As shown in Table 4, several unactivated and activated aryl chlorides such as **4a-e** reacted smoothly with thiophene derivatives **1a** and **1b** to afford the corresponding coupling products in good to excellent yields.

Table 4. C–H coupling of several thiophene derivatives with aryl chloride^a

entry	Substrate	Aryl–Cl	catalyst	temp./°C, time/h	yield ^b /%
1	1a		PEPPSI-SIPr	60, 24	>99 (3aa)
2	1a	4a	NiCl ₂ (dppe)	rt, 24	32 (3aa)
3	1a		PEPPSI-SIPr	rt, 24	82 (3ab)
4	1a			rt, 24	83 (3ac)
5	1a			rt, 24	52 (3ae)
6	1b	4a		60, 21	74 (3ba)
7	1b	4b		rt, 19	63 (3bb)
8	1b	4c		rt, 24	77 (3bc)
9	1b	4e		rt, 19	82 (3be)

^a Unless noted, the reaction was performed with substrate (0.5 mmol), EtMgCl (0.5 mmol), amine (0.05 mmol), aryl chloride (0.60 mmol) and catalyst (2.0 mol%) in 2.0 mL of THF. ^b Isolated yield.

Our further concern is focused on the synthesis of differently-substituted 2,5-diarylthiophenes. As we have previously reported that 2,5-diarylthiophene derivatives showed relatively stronger photoluminescence than those of thiazoles,²ⁱ it is intriguing to investigate a facile preparation method of the thiophene derivative. Synthesis of 2,5-diarylthiophene was performed as shown in Scheme 1. The reaction of 2-arylatedthiophene, which was prepared in a manner shown in Table 3, at the 5-position was carried out with EtMgCl and 10 mol% of Cy₂NH for metalation to afford the corresponding 2,5-diarylated thiophene **5a-5b** in good yields.¹¹



Scheme 1. Synthesis of differently substituted 2,5-diarylthiophene by C–H arylation.

In conclusion, we have shown that metalation with a combination of an alkyl Grignard reagent and a catalytic amount of secondary amine is widely effective for heteroaromatic compounds such as thiophenes and furans and thus metalated species are shown to be employed not only for halothiophenes but a variety of aryl bromides and chlorides. Accordingly, the protocol involving metalation and the following cross coupling is effective for general arylation of thiophene derivatives. Differently substituted 2,5-diarylthiophene was also obtained in a facile manner with iterative arylation reactions.

Acknowledgments

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References and notes

- Diederich, F.; Stang, P. J., Eds. *Metal-Catalyzed Cross-Coupling Reaction*, Wiley-VCH: Weinheim, 1998.
- Reviews on C–H functionalization of heteroaromatic compounds: (a) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253. (b) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792. (c) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447. (d) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (e) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.*, **2007**, *36*, 1173. (f) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (g) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (h) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. (i) Sugie, A.; Mori, A. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 548.
- For reviews: (a) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885. (b) Nicolaou, K. C.; Chen, J. S.; Edmonds, D. J.; Estrada, A. A. *Angew. Chem. Int. Ed.* **2009**, *48*, 660. (c) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442.
- For reviews: (a) Osaka, I.; McCullough, R. D. *Acc. Chem. Res.* **2008**, *41*, 1202. (b) Takimiya, K.; Shinamura, S.; Osaka, I.; Miyazaki, E. *Adv. Mater.* **2011**, *23*, 4347. (c) Pron, A.; Gawrys, P.; Zagorska, M.; Djurado, D.; Demadrille, R. *Chem. Soc. Rev.* **2010**, *39*, 2577.
- (a) Tanaka, S.; Tamba, S.; Tanaka, D.; Sugie, A.; Mori, A. *J. Am. Chem. Soc.* **2011**, *133*, 16734. (b) Tamba, S.; Shono, K.; Sugie, A.; Mori, A. *J. Am. Chem. Soc.* **2011**, *133*, 9700. (c) *J. Synth. Org. Chem. Jpn.* in press. (d) Tamba, S.; Tanaka, S.; Okubo, Y.; Okamoto, S.; Meguro, H.; Mori, A. *Chem. Lett.* **2011**, *40*, 398.
- See also: Asselin, S. M.; Bio, M. M.; Langille, N. F.; Ngai, K. Y. *Org. Process Res. Dev.* **2010**, *14*, 1427.
- (a) Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 2958. (b) Lin, W.; Baron, O.; Knochel, P. *Org. Lett.* **2006**, *8*, 5673. (c) Mosrin, M.; Knochel, P. *Org. Lett.* **2008**, *10*, 2497. (d) Clososki, G. C.; Rohbogner, C. J.; Knochel, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7681. (e) Rohbogner, C. J.; Clososki, G. C.; Knochel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 1503. (f) Piller, F. M.; Knochel, P. *Org. Lett.* **2009**, *11*, 445. (g) Hauser, C. R.; Walker, H. G. *J. Am. Chem. Soc.* **1947**, *69*, 295. (h) Hauser, C. R.; Frostick, F. C. *J. Am. Chem. Soc.* **1949**, *71*, 1350.
- General procedure: To a solution of 0.99 M EtMgCl (0.61 mL, 0.6 mmol) in THF were added dicyclohexylamine (0.01 mL, 0.05 mmol), and 2-methylthiophene (**1a**, 0.048 mL, 0.50 mmol) dropwise under a nitrogen atmosphere. After stirring at 60 °C for 24 h, 1.4 mL of THF and *N,N*-dimethylformamide (0.5 mL, 6.46 mmol) were successively added and stirring was continued for further 1 h. The mixture was quenched by saturated aqueous solution of ammonium chloride (1.0 mL) and the solution was poured into the mixture of diethyl ether/water to result in separation into two phases. Aqueous was extracted with diethyl ether twice and the combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to leave a crude oil, which was purified by column chromatography on silica gel (hexane/EtOAc = 20/1) to afford 62.3 mg of 2-formyl-5-methylthiophene (**1a-CHO**, colorless oil, 99%).
- Representative procedure: To 25 mL Schlenk tube equipped with a magnetic stirring bar were added 0.99 M EtMgCl (0.5 mL, 0.5 mmol) in THF and dicyclohexylamine (0.01 mL, 0.05 mmol). To the solution were added 2-methylthiophene (**1a**, 0.048 mL, 0.50 mmol) and stirring was continued at 60 °C for 24 h. Then, 1.5 mL of THF, 4-bromotoluene (**2a**, 0.074 mL, 0.6 mmol) and NiCl₂(dppe) (6.79 mg, 0.01 mmol) were added successively. The mixture was allowed to stir at room temperature for 24 h. The mixture was quenched by saturated aqueous solution of ammonium chloride (1.0 mL). The solution was poured into the mixture of diethyl ether/water and two phases were separated. Aqueous was extracted with diethyl ether twice and the combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to leave a crude oil, which was purified by column chromatography on silica gel using hexanes as an eluent to afford 94.7 mg of 5-(4-methylphenyl)-2-methylthiophene (**3aa**, colorless solid, >99%). 2-methyl-5-(2-naphthyl)thiophene (**3af**): ¹H NMR (CDCl₃, 300 MHz) δ 2.54 (s, 3H), 6.78 (d, *J* = 3.6 Hz, 1H), 7.24 (d, *J* = 3.6 Hz, 1H), 7.40–7.5 (m, 2H), 7.69 (d, *J* = 8.5 Hz, 1H), 7.77–7.87 (m, 3H), 7.97 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 15.4, 123.2, 123.5, 124.0, 125.6, 126.3, 126.4, 127.6, 127.8, 128.3, 132.0, 132.4, 133.6, 139.7, 141.9; IR (ATR) 1596, 1503, 1228, 860, 820, 799, 750 cm⁻¹; HRMS (DART-ESI+) Calcd for C₁₅H₁₃S [M+H]⁺: 225.0738; found: *m/z* 225.0735. 2-(4-methylphenyl)-5-(1-octen-1-yl)thiophene (**3ca**): ¹H NMR (CDCl₃, 300 MHz) δ 0.91 (t, *J* = 6.9 Hz, 3H), 1.22–1.40 (m, 4H), 1.38–1.52 (m, 2H), 1.55–1.67 (m, 2H), 2.36 (s, 3H), 2.44 (t, *J* = 7.0 Hz, 2H), 7.06 (d, *J* = 3.6 Hz, 1H), 7.09 (d, *J* = 3.6 Hz, 1H), 7.17 (d, *J* = 8.2 Hz 2H), 7.45 (d, *J* = 8.2 Hz, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 14.0, 19.7, 21.1, 22.5, 28.5, 28.6, 31.3, 73.9, 95.1, 122.1, 122.9, 125.6 (×2), 129.5 (×2), 131.1, 131.8, 137.5, 144.5; IR (ATR) 2954, 2928, 2856, 1507, 1456, 1428, 1377, 1262, 1185, 1121, 817, 796 cm⁻¹; HRMS (DART-ESI+) Calcd for C₁₉H₂₃S [M+H]⁺: 283.1520; found: *m/z* 283.1513.
- PEPPSI stands for pyridine-enhanced precatalyst preparation stabilization and initiation. See: (a) O'Brien, C. J.; Kantchev, E. A. B.; Valente, C.; Hadei, N.; Chass, G. A.; Lough, A.; Hopkinson, A. C.; Organ, M. G. *Chem.-Eur. J.* **2006**, *12*, 4743. (b) Organ, M. G.; Calimsiz, S.; Sayah, M.; Hoi, K. H.; Lough, A. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2383.
- 2-(4-Methoxyphenyl)-5-(4-methylphenyl)thiophene (**5a**): ¹H NMR (CDCl₃, 300 MHz) δ 2.37 (s, 3H), 3.84 (s, 3H), 6.92 (d, *J* = 8.8 Hz, 2H), 7.16 (d, *J* = 3.8 Hz, 1H), 7.19 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 3.8 Hz, 1H), 7.51 (d, *J* = 8.2 Hz, 2H), 7.55 (d, *J* = 8.8 Hz, 2H); ¹³C NMR (CDCl₃, 75 MHz) δ 21.1, 55.3, 114.3 (×2), 122.8, 123.4, 125.4 (×2), 126.8 (×2), 127.3, 129.5 (×2), 131.6, 137.1, 142.8, 143.0, 159.1; IR (ATR) 2916, 1606, 1543, 1518, 1499, 1468, 1454, 1440, 1309, 1291, 1273, 1247, 1180, 1123, 1112, 1032, 830, 795 cm⁻¹; HRMS (DART-ESI+) Calcd for C₁₈H₁₇OS [M+H]⁺: 281.1000; found: *m/z* 281.1010. 2-(4-Methoxyphenyl)-5-(4-trifluoromethylphenyl)thiophene (**5b**): ¹H NMR (CDCl₃, 300 MHz) δ 3.85 (s, 3H), 6.94 (d, *J* = 8.8 Hz, 2H), 7.20 (d, *J* = 3.8 Hz, 1H), 7.35 (d, *J* = 3.8 Hz, 1H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.70 (d, *J* = 8.5 Hz, 2H); ¹³C NMR (CDCl₃, 75 MHz) δ 55.3, 114.4 (×2), 123.1, 125.3, 125.4, 125.8 (q, *J*_{C-F} = 4.0 Hz, ×2), 126.7 (×2), 127.0 (×2), 128.9 (q, *J*_{C-F} = 32 Hz), 137.7, 140.5, 145.2, 159.5; IR (ATR) 1605, 1502, 1454, 1321, 1296, 1278, 1257, 1191, 1176, 1115, 1074, 1064, 1029, 1014, 831, 799 cm⁻¹; HRMS (DART-ESI+) Calcd for C₁₈H₁₄F₃OS [M+H]⁺: 335.0717; found: *m/z* 335.0705.