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Copper-catalyzed oxidative C–H, N–H coupling of azoles and thiophenes

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ABSTRACT

C–H, N–H coupling of azole and thiophene derivatives takes place in the presence of a catalytic amount of $Cu(OAc)_2$ and an additive. The reaction of azoles smoothly occurs with several amines and amides catalyzed by 20 mol% of $Cu(OAc)_2$-$2PPh_3$ and 4 equiv. of NaOAc under O_2 or in the presence of Ag_2CO_3 under N_2. The coupling reaction leads to a facile synthesis of a *N*-substituted analogue of 2,5-diarylthiazole, which shows photoluminescent properties with extended π-conjugation. Spectroscopic characteristics of the obtained thiazole derivatives are discussed by measurements of UV-vis absorption and photoluminescent spectra. Under the reaction conditions using Ag_2CO_3 as an additive and $Cu(OAc)_2$-$2PPh_3$ as a catalyst, thiophene derivatives also react with 2-pyrrolidone to undergo C–H, N–H amidation.

1. Introduction

Transition-metal-catalyzed C–H functionalization reactions are of great interest in organic synthesis because the reaction shows advantage in atom efficiency compared to related cross-coupling with organometallic compounds. A wide range of C–H coupling reaction has been shown to proceed in the presence of a metal catalyst.[1] Among those, the reaction of heteroaromatic compounds with organic halides is particularly important since a number of organic molecules bearing such heteroaromatic moieties are found in biologically important compounds as pharmaceutical products and agrochemicals[2] as well as advanced organic materials such as electronic and optical devices.[3] C–H functionalization of heteroaromatic compounds has thus been extensively studied and various reactions have been developed so far. We have also been engaged in the C–H coupling reaction of thiophene and thiazoles to reveal that several reactions with combination of catalyst system and additives are effective to form the carbon–carbon bond.[4]

By contrast to a wide range of examples forming the carbon–carbon bond with the reaction of heteroaromatics and aryl halides, the coupling reaction at the C–H bond with amines or amides leading to C–N bond formation has less been studied.[5] However, it is also important in organic synthesis to form the carbon–nitrogen bond since a variety of nitrogen-substituted heteroaromatic compounds are also found in a wide range of biologically active organic molecules.[6]

Although it is a method of choice to undergo coupling of heteroaromatic halides with amines, which is well-known as Buchwald-Hartwig amination,[7] it is intriguing to perform the reaction at the C–H bond of a heteroaromatic compound with amine, which is recognized as a class of C–H, N–H coupling. However, such a reaction has rarely been studied so far except several limited examples of the intramolecular case.[8] Herein, we report that C–H, N–H coupling of azoles that are five-membered heteroaromatic compounds takes place in the presence of a copper catalyst under oxidative conditions.[9,10] The related coupling with thiophene derivatives under similar conditions is also described.

2. Results and Discussion

C–H, N–H coupling of terminal alkynes and amides are shown to proceed by Stahl to form the corresponding alkynyl amides.[5a,11] The reaction occurs with a copper(II) catalyst in the presence of a metal carbonate or acetate as a base under an oxygen atmosphere. Accordingly, we started to find a suitable reaction conditions to undergo the amination reactions at the 2-position of azoles using related conditions to those for terminal alkynes. The reaction of benzothiazole (**1**) with *N*-methylaniline (**2a**) was carried out in the presence of 20 mol% of a copper salt under an oxygen atmosphere at 140 ºC (eq 1). Table 1 summarizes the results of the reaction of **1** and **2a** with several catalysts and additives. The reaction with a stoichiometric amount of copper(II) acetate afforded the corresponding aminated product **3a** in 49% yield. The reaction was found to proceed in 51% yield when the reaction was performed with 20

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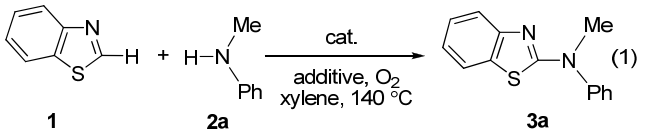
mol% of the catalyst. $NaHCO_3$ and NaF were also found to be effective additives. Although an organic base Et_3N was also an available additive, the yield was slightly decreased compared with the above inorganic bases. The highest yield was obtained when sodium acetate was employed as an additive. Stronger bases such as sodium hydroxide and sodium *t*-butoxide were not effective to afford the desired C–H, N–H coupling product. The reaction with other copper salt $CuCl_2$ was found to be less effective and other catalyst copper(I) iodide or palladium(II) acetate did not undergo the reaction. Among several ligands examined in place of PPh_3, XANTPHOS and DPPE also promoted the reaction. It seems to be essential to perform the reaction under an oxygen atmosphere, otherwise the reaction under air resulted in giving **3** in a lower yield (46%) and the reaction did not take place under nitrogen.



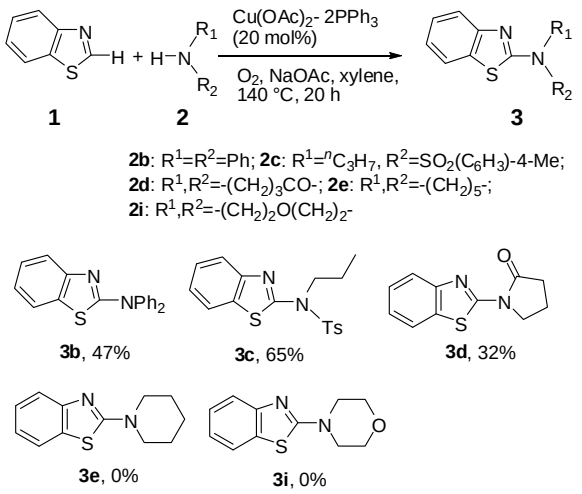
1 **2a** **3a**

Table 1. C–H, N–H coupling of benzothiazole **1** and *N*-methylaniline **2a**[a]

Entry	Catalyst (mol%)	Ligand	Additive (equiv)	Yield of **3a**[e]
1	$Cu(OAc)_2$ (100)	none	Na_2CO_3 (4)	49
2	$Cu(OAc)_2$ (20)	PPh_3 (40)	Na_2CO_3 (4)	51
3	$Cu(OAc)_2$ (20)	PPh_3 (40)	$NaHCO_3$ (4)	51
4	$Cu(OAc)_2$ (20)	PPh_3 (40)	NaF (4)	52
5	$Cu(OAc)_2$ (20)	PPh_3 (40)	Et_3N (4)	33
6	**$Cu(OAc)_2$ (20)**	**PPh_3 (40)**	**NaOAc (4)**	**82 (75)**
7	$Cu(OAc)_2$ (10)	PPh_3 (40)	NaOAc (4)	64
7	$Cu(OAc)_2$ (20)	PPh_3 (40)	NaOH (4)	0
8	$Cu(OAc)_2$ (20)	PPh_3 (40)	NaO^{t}Bu (4)	0
9	$Cu(OAc)_2$ (20)	PPh_3 (40)	Cs_2CO_3 (4)	0
10	$CuCl_2$ (20)	PPh_3 (40)	NaOAc (4)	23
11	CuI (20)	PPh_3 (40)	NaOAc (4)	0
12	$Pd(OAc)_2$ (20)	PPh_3 (40)	NaOAc (4)	0
13	$Cu(OAc)_2$ (20)	TMEDA (20)	NaOAc (4)	52
14	$Cu(OAc)_2$ (20)	XANTPHOS[b] (20)	NaOAc (4)	68
15	$Cu(OAc)_2$ (20)	DPPE (20)	NaOAc (4)	42
16[c]	$Cu(OAc)_2$ (20)	PPh_3 (40)	NaOAc (4)	46
17[d]	$Cu(OAc)_2$ (20)	PPh_3 (40)	NaOAc (4)	0

[a]The reaction was carried out with 0.2 mmol of **1** and 0.8 mmol of **2a** at 140 ºC for 20 h. [b]XANTPHOS: 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene. [c]The reaction under air [d]The reaction under N_2 atmosphere. [e]The yield based on ^{1}H NMR. In parenthesis, isolated yield was shown.

The reaction was examined with other nitrogen compounds such as secondary amines, sulfonamide, and carbamides. As summarized in Scheme 1, the reaction of benzothiazole **1** proceeded to afford the corresponding C–H, N–H coupling products. Diphenylamine (**2b**) also reacted with **1** in a slightly lower yield. The reaction with *N*-propyl-tosylamide (**2c**) also proceeded to afford the corresponding coupling product in 65% yield and a cyclic carbamide 2-pyrrolidinone (**2d**) reacted with **1** in a lower yield (32%), whereas no reaction took place with aliphatic amines piperidine (**2e**) and morpholine (**2i**) probably due to the high reaction temperature under oxygen atmosphere, which may prefer oxidation of amine to the desired C–H, N–H coupling.



1 **2** **3**

2b: R^1=R^2=Ph; **2c**: R^1=^{n}C_3H_7, R^2=$SO_2(C_6H_3)$-4-Me;
2d: R^1,R^2=-$(CH_2)_3CO$-; **2e**: R^1,R^2=-$(CH_2)_5$-;
2i: R^1,R^2=-$(CH_2)_2O(CH_2)_2$-

3b, 47% **3c**, 65% **3d**, 32%

3e, 0% **3i**, 0%

Scheme 1. C–H, N–H Coupling of **1** with several amines and amides.

Table 2. C–H, N–H coupling of azoles with a secondary amine.[a]

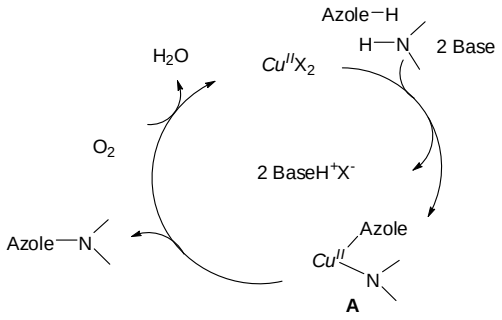
entry	Aryl−H	amine	product	yield (%)[b]
1	**4**	HNMePh **2a**	**5a**	71
2	**4**	$HNPh_2$ **2b**	**5b**	66
3	**4**	**2e**	**5e**	72
4	**4**	Et_2NH **2f**	**5f**	47
5	**6**	**2a**	**7a**	51
6	**8**	**2a**	--	0
7	**9**	**2a**	**10a**	73

[a]The reaction was carried out with 0.2 mmol of Aryl−H and 0.8 mmol of amine at 140 ºC for 20 h.[b] Isolated yield.

Table 2 summarizes the reaction of several azoles with a secondary amine. The reaction of benzoxazole (**4**) was found to proceed with *N*-methylaniline (**2a**) smoothly to afford the coupling product **5a** in 71% yield. In addition, **4** reacted also with diphenylamine **2b**, piperidine **2e**, and diethylamine **2f**. The corresponding C–H, N–H coupling products **5b**, **5e**, and **5f** were

obtained in 66%, 72%, and 47% yields, respectively. Benzoimidazole **6** also underwent the reaction of **2a** in 51% yield. Although the reaction of unsubstituted thiazole **8** with **2a** did not afford the amination product, 4,5-dimethylthiazole (**9**) reacted with **2a** in 73% yield. By contrast to the limited substrate scope in the reaction of benzothiazole (**1**), benzoxazole (**4**) allowed to react with a broad range of amines. Although it has not been clear for the understanding of the reaction mechanism, the reaction of **4** may proceed in a different manner.[10g]

We consider that the mechanism of the C–H, N–H coupling of azoles proceed in a similar manner to the case of the amination reaction of a terminal alkyne shown by Stahl[5a] as shown in Scheme 2. The C–H bond of azole at the 2-position and the N–H bond of amine (amide) react with a copper catalyst to form the intermediate **A**. Reductive coupling forming C–N bond leads to the coupling product accompanied by a reduced copper species, which is oxidized to copper(II) by oxygen. Thus, we considered that a basic oxidant may serve both as a base and the oxidizing agent. The related effect was previously revealed in the palladium-catalyzed homocoupling of thiophenes with a silver salt.[4b] Accordingly, the C–H, N–H coupling reaction was examined with several silver salts as an additive.



Scheme 2. Plausible Mechanism of CH, NH Coupling of Azole with a Copper Catalyst.

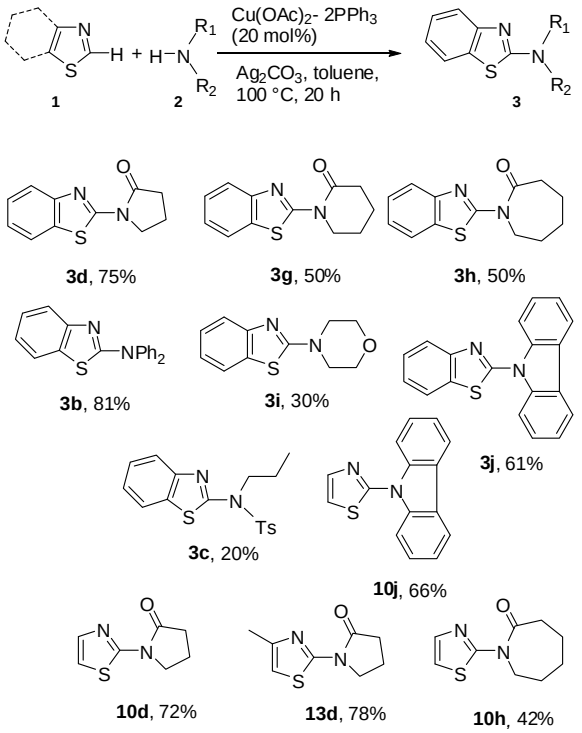
Table 3 summarizes the C–H, N–H coupling reaction of benzothiazole (**1**) and 2-pyrrolidinone (**2d**) with several additives. The reaction was carried out with 2 equiv. of **1** to **2d** in the presence of 20 mol% $Cu(OAc)_2$-$2PPh_3$ in xylene at 100 ºC. When the reaction was performed under similar conditions shown in Scheme 1, the lower temperature further decreased the yield to 7%. Among several silver salts examined, the use of silver(I) carbonate efficiently promoted the reaction to afford the corresponding C–H, N–H coupling product **3d** in 75% yield. Although it has recently been shown that C–H, N–H coupling of oxazole derivatives takes place, there is still few example for the reaction of thiazoles.[12] The reaction with silver(I) nitrate also afforded **3d** in 24% yield, however, other silver species resulted in much lower yields. Although the reaction with toluene as a solvent was found to be the optimum choice, 1,4-dioxane also effected the reaction to give **3d** in 60% yield. Other solvents such as acetonitrile, DMF, and 1,2-dichloroethane resulted in slightly lower yields, whereas the reaction in DMSO was ineffective. The role of silver would be a kind of base to facilitate activation of C–H and/or N–H bond as well as an oxidizing agent to regenerate the copper(II) species from the reduced copper.

Table 3. C–H, N–H coupling of benzothiazole **1** with **2d** with a silver salt as an additive.[a]

entry	additive	solvent	yield of **3d** (%)
1	NaOAc (O_2)	toluene	7
2	$AgNO_3$	toluene	24
3	AgOAc	toluene	trace
4	AgF	toluene	3
5	Ag_2O	toluene	7
6	Ag_2CO_3	toluene	75
7	Ag_2CO_3	1,4-dioxane	60
8	Ag_2CO_3	DMSO	trace
9	Ag_2CO_3	CH_3CN	38
10	Ag_2CO_3	DMF	42
11[b]	Ag_2CO_3	1,2-dichloroethane	20
12[c]	Ag_2CO_3	toluene	0

[a]Unless otherwise specified, the reaction was carried out with 0.2 mmol of **3d** and 0.4 mmol of **1** at 100 ºC for 15 h under N_2. The yield was estimated by ^{1}H NMR. [b]The reaction at 80 ºC. [c] The reaction without copper catalyst.

With the optimized reaction conditions in hand, we then examined the reaction of several thiazole derivatives with amines and amides. As shown in Scheme 3, the reaction of benzothiazole (**1**) with six and seven-membered cyclic amides with less steric congestion than acyclic ones afforded the corresponding C–H, N–H coupling products, while primary and acyclic secondary amides did not afford the coupling products under similar conditions. The reaction of secondary amines also took place in a comparable yield to the case with NaOAc under O_2. On the other hand, the reaction with sulfonamide **2c** proceeded less efficiently probably due to the poisoning of silver by the interaction with the sulfonamide group. It should be pointed out that unsubstituted thiazole **8** reacted with **3d** in 72% yield. The result markedly contrasts to that with NaOAc/O_2 (0% yield). The C–H, N–H coupling with **8** and 4-methylthiazole (**11**) also proceeded with several amines and amides to afford the corresponding products **10** and **13** in a reasonable yield. The improved substrate scope in the reaction of **1** with variety of amines and amides compared with our initial conditions would be the lower reaction temperature and inferior solubility of Ag_2CO_3 in a less polar organic solvent. In addition, superior basicity of silver to NaOAc may improved the efficiency in the reaction with amides **3d**, **3g**, and **3h**.

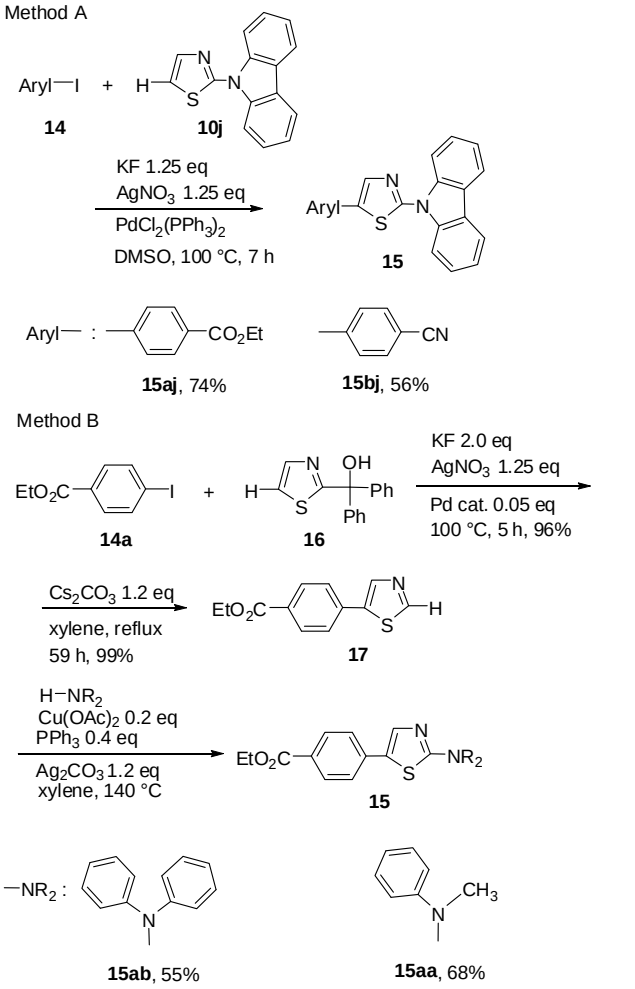


Scheme 3. C–H, N–H Coupling of Thiazole Derivatives with Several Amines and Amides with Ag_2CO_3 as an additive.

The C–H, N–H coupling of thiazole was applied to the synthesis of *N*-substituted analogue of 2,5-diarylthiazole, which was shown to exhibit photoluminescent properties by the donor-acceptor-type substituent effect.[4a,4i] It is intriguing to study electro-optical properties of thiazole derivatives if the donor substituent at the 2-position of thiazole is replaced with diarylamino group, which can be introduced by the C–H, N–H coupling.

Synthesis of the *N*-substituted analogue of 2,5-diarylthiazole **15** was performed as outlined in Scheme 4. The reaction of 2-aminated thiazole **10j** was treated with an aryl iodide bearing a electron-withdrawing substituent in the presence of $PdCl_2(PPh_3)_2$ and $AgNO_3$/KF to afford the corresponding coupling product **15aj, 15bj** (Method A).[13] Alternatively, **17** was prepared by the reaction of 5-arylthiazole, which was obtained by palladium-catalyzed C–H arylation of masked thiazole and following removal of the masking group, with several secondary amines.[14]

Table 4 summarizes UV-vis absorption and photoluminescent properties of thus obtained *N*-substituted analogue of 2,5-diarylthiazole **15** along with 2,5-diarylthiazole **18** and 5-arylthiazole **17**. Remarkable shifts of both absorption and emission maxima to longer wavelength were observed by the introduction of amino groups into the 2-position of thiazole comparing with that of **17**. These values were similar to the case of the donor-acceptor-type 2,5-diarylthiazole **18**. However, it was found that much stronger photoluminescence was observed in the *N*-substituted analogue particularly in diarylaminated ones **15aj** and **15ab**, whereas **15aa** derived from *N*-methylaniline indicated a smaller quantum yield. Worthy of note is the strongest photoluminescence in **15aj** bearing carbazole group showing the Φ value of 0.71. Photoluminescent behaviors of thiazole derivatives by the irradiation of long-wave UV light (366 nm) was shown in Figure 1.



Scheme 4. C–H, N–H Coupling of Thiazole Derivatives with Several Amines and Amides.

Table 4. UV-vis absorption and photoluminescent properties of thiazole derivatives.[a]

Compound	Substituents 5-position, 2-position	λ_{max}, nm absorption	λ_{max}, nm emission	Φ^b
15aj	4-C_6H_4COOEt, carbazole	355	415	0.71
15ab	4-C_6H_4COOEt, NPh_2	361	447	0.51
15aa	4-C_6H_4COOEt, NMePh	366	434	0.26
15bj	4-C_6H_4CN, carbazole	369	451	0.64
17	4-C_6H_4COOEt, H	292	348	0.17
18	4-C_6H_4COOEt, 4-C_6H_4OMe	347	424	0.24

[a]Measurements of the spectra were carried out as a chloroform solution (2.5×10^{-6} M). [b]The quantum yield Φ was estimated based on 7-diethylamino-4-methylcoumarin as 0.01 mM solution of ethyl acetate (Φ=0.99) .

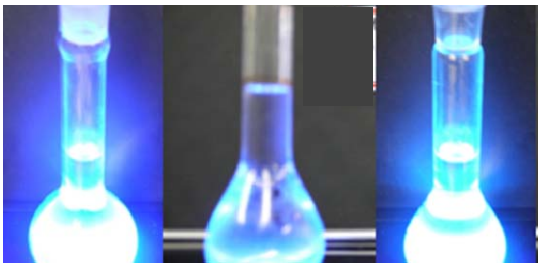
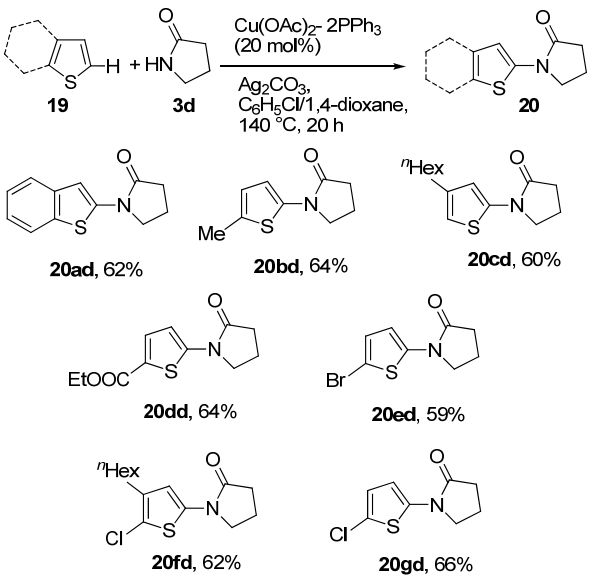


Figure 1. Photoluminescence of *N*-substituted analogue of 2,5-diarylthiazole by the irradiation of 366 nm UV light to 1 mM solution of chloroform: **15aj** (left); **15aa** (center); **15ab** (right).

It was also found that the reaction conditions of C–H, N–H coupling of azoles with silver(I) carbonate was applicable to the reaction of thiophene derivatives. Although several examples of the amination reaction at an electron-deficient C–H bond like azoles has been shown to proceed,[9,10] it is unrevealed, to the best of our knowledge, that the related reaction at the C–H bond of an electron-enriched carbon atom takes place. When the reaction of benzothiophene (**19a**) and 2-pyrollidinone (**3d**) was carried out with silver(I) carbonate and a catalytic amount of $Cu(OAc)_2$-$2PPh_3$ in a mixed solvent system of chlorobenzene and 1,4-dioxane, 62% of the corresponding C–H, N–H coupling product was obtained (Scheme 5).[15] Several thiophene derivatives were found to react with **3d** as summarized in Scheme 5. Thiophene derivatives bearing an alkyl substituent at the 4- and 5-positions reacted smoothly to afford the corresponding coupling products. Thiophene bearing an ester functionality was found to be tolerable for the reaction conditions. In addition, halothiophenes such as bromo and chlorothiophenes also tolerated to afford the corresponding C–H, N–H coupling products bearing a halogen atom.[16,17]



Scheme 5. C–H, N–H Coupling of Thiophene Derivatives with **3d**.

3. Conclusion

In conclusion, we have shown that azoles and thiophenes reacts with several organic molecules bearing a N–H bond at the 2-position of azoles or the C–H bond adjacent to the sulfur atom of thiophene. Since a number of aminated derivatives of five-membered heteroaromatic compounds are found in biologically active molecules and advanced organic materials, the method would be a potentially effective tool for the introduction of nitrogen functionality to such heteroaromatic compounds.

4. Experimental Section

General: ^{1}H NMR (500 or 300 MHz) and ^{13}C NMR (125 or 75 MHz) spectra were measured on a Brucker Avance 500 spectrometer or Varian Gemini 300. Unless noted, $CDCl_3$ was used as a solvent. The chemical shifts were expressed in ppm with $CHCl_3$ (7.26 ppm for ^{1}H) or $CDCl_3$ (77.0 ppm for ^{13}C) as internal standards. IR spectra were recorded on Bruker Alpha with an ATR attachment (Ge). High resolution mass spectra (HRMS) were measured by JEOL JMS-T100LP AccuTOF LC-Plus (ESI) with a JEOL MS-5414DART attachment at Kobe University or JEOL JMS-700 MStation (EI) at the Graduate School of Material Science, Nara Institute of Science and Technology. For thin layer chromatography (TLC) analyses throughout this work, Merck precoated TLC plates (silica gel 60 F254) were used. UV-vis spectra were measured by ALS SEC-2000 UV/VIS spectrometer with SEC-2000 DH as a light source. Photoluminescent spectra were measured with HITACHI F-7000.

***N*-Benzothiazole-2-yl-*N*-methlyaniline (3a):**[18] A solution of copper(II) acetate (7.3 mg, 0.04 mmol), triphenylphosphine (21 mg, 0.08 mmol), benzothiazole (**1**, 22 μL, 0.2 mmol), *N*-methylaniline **2a** (0.088 mL, 0.8 mmol) and NaOAc (66 mg, 0.8 mmol) in 1.0 mL of xylene was stirred at 140 ºC for 20 h under O_2. After cooling to room temperature, the mixture was passed through a Celite pad, which was washed with chloroform repeatedly. The filtrate was washed with water three times. The organic layer was concentrated under reduced pressure to leave a crude oil, which was purified by column chromatography on silica gel to afford 39 mg of **3a** as a colorless oil (75%).

***N*-Benzothiazole-2-yl-δ-valerolactam (3g)**: Mp. 128.6-129.1 °C; ^{1}H NMR (500 MHz) δ 1.87-1.95 (m, 4H), 1.98-2.05 (m, 2H), 4.26 (t, *J* = 6.1 Hz, 2H), 7.29 (dd, *J* = 7.6 Hz, 1H), 7.42 (dd, *J* = 7.6, 1H), 7.80 (d, *J* = 7.9 Hz, 1H), 7.82 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (125 MHz) δ 20.0, 22.6, 33.0, 48.5, 121.0, 121.2, 123.8, 125.8, 133.3, 148.0, 159.2, 170.3; IR (ATR) 2946, 2910, 2881, 1655, 1502, 1442, 1399, 1253, 1174, 956, 759, 724 cm^{-1}; HRMS (EI+) Calcd for $C_{12}H_{12}N_2OS$ $[M]^+$ 232.0670; found: m/z 232.0670.

***N*-Benzothiazole-2-yl-ε-caprolactam (3h)**: ^{1}H NMR (500 MHz) δ 1.75-1.95 (m, 6H), 2.80-2.89 (m, 2H), 4.58 (t, *J* = 4.4 Hz, 2H), 7.39 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.41 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.76-7.83 (m, 2H); ^{13}C NMR (125 MHz) δ 23.4, 28.0, 29.3, 37.8, 47.7, 121.0, 121.1, 123.6, 125.8, 133.5, 147.8, 159.7, 175.4; IR (ATR) 839, 964, 1156, 1189, 1217, 1247, 1267, 1397, 1441, 1459, 1497, 1671 cm^{-1}; HRMS (EI+) Calcd for $C_{13}H_{14}N_2OS$ $[M]^+$: 246.0827; found: m/z 246.0826.

***N*-Benzothiazole-2-yl-carbazole (3j)**: Mp. 128.4-129.2 °C; ^{1}H NMR (500 MHz) δ 7.25-7.30 (m, 4H), 7.39-7.45 (m, 4H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.93-7.97 (m, 3H), 8.37 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (125 MHz) δ 113.2, 120.1, 121.1, 122.2, 122.7, 124.5, 125.2, 126.5, 127.0, 132.0, 139.2, 150.2, 157.7; IR (ATR) 1596, 1510, 1442, 1335, 1274, 1210, 954 cm^{-1}; HRMS (EI+) Calcd for $C_{19}H_{12}N_2S$ $[M]^+$: 300.0712; found: m/z300.0721.

***N*-thiazole-2-yl-ε-caprolactam (10h)**: Mp. 88.4-89.4 °C; ^{1}H NMR (500 MHz) δ 1.75-1.95 (m, 6H), 2.80-2.89 (m, 2H), 4.40-

4.53 (m, 2H), 6.97 (d, *J* = 3.6, Hz, 1H), 7.46 (dd, *J* = 3.6 Hz, 1H) ^{13}C NMR (75 MHz) δ 23.2, 27.6, 29.3, 37.4, 47.5, 114.7, 136.3, 159.9, 174.3; IR (ATR) 2927, 2867, 1653, 1499, 1442, 1265, 1220, 1171, 732, 624 cm^{-1}; HRMS (DART-ESI+) Calcd for $C_9H_{12}N_2OS$ [M+H]$^+$: 197.0749; found: m/z 197.0749.

2-(Carbazole-9-yl)-5-(4-ethoxycarbonylphenyl)thiazole (15aj): Mp. 124.1-124.9 °C; ^{1}H NMR (500 MHz) δ 1.43 (t, *J* = 6.9, 3H), 4.11 (q, *J* = 7.7 Hz, 2H), 7.41 (dd, *J* = 7.4 Hz, 2H), 7.55 (dd, *J* = 7.8, 1.1 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 2H), 8.03 (s, 1H) , 8.11 (m, 4H), 8.34 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (125 MHz) δ14.2, 60.9, 112.8, 119.9, 122.3, 124.8, 125.5, 126.7, 129.5, 130.2, 132.5, 135.2, 136.0, 138.8, 158.3, 165.8; IR (ATR) 3061, 2974, 2928, 2909, 1703, 1606, 1495, 1466, 1452, 1334, 1276, 1213, 1190, 1108, 846, 767, 743, 712 cm^{-1}; HRMS (EI+) Calcd for $C_{24}H_{18}N_2O_2S$ [M]$^+$: 398.1089; found: m/z 398.1086.

2-(Carbazole-9-yl)-5-(4-cyanophenyl)thiazole (15bj): Mp. 188.2-188.7 °C; ^{1}H NMR (300 MHz) δ 7.41 (m, 2H), 7.55 (m, 2H), 7.73 (m, 4H), 8.02 (s, 1H), 8.10 (d, *J* = 7.6Hz, 2H), 8.35 (d, *J* = 8.3Hz, 2H); ^{13}C NMR (75MHz) δ 111.3, 112.9, 118.5, 120.2, 122.8, 125.1, 126.4, 127.0, 127.9, 132.8, 132.9, 137.0, 139.0, 159.1; IR (ATR) 2227, 1496, 1465, 1450, 1338, 1214, 1160, 824, 751, 720 cm^{-1}; HRMS (DART-ESI+) Calcd for $C_{22}H_{13}N_3S$ [M+H]$^+$: 352.0908; found: m/z 352.0900.

2-Diphenylamino-5-(4-ethoxycarbonylphenyl)thiazole (15ab): Mp. 141.3-142.0 °C; ^{1}H NMR (300 MHz) δ 1.39(t, *J* = 7.1, 3H), 4.37 (q, *J* = 7.1 Hz, 2H), 7.28 (m, 2H), 7.41 (m, 10H), 7.61 (s, 1H), 7.97(d, *J* = 8.4, 2H); ^{13}C NMR (75 MHz) δ 14.3, 61.0, 125.0, 126.1, 126.7, 128.5, 128.9, 129.9, 130.2, 135.7, 136.1, 144.6, 166.1, 169.3; IR (ATR) 2968, 2926, 1703, 1490, 1472, 1447, 1279, 1185, 1105, 695 cm^{-1}; HRMS (DART-ESI+) Calcd for $C_{24}H_{20}N_2O_2S$ [M+H]$^+$: 401.1324; found: m/z 401.1303.

2-(*N*-Methyl-*N*-phenylamino)-5-(4-ethoxycarbonylphenyl)thiazole (15aa): Mp. 71.2-72.0 °C; ^{1}H NMR (300 MHz) δ 1.38 (t, *J* = 7.1 Hz, 3H), 3.59 (s, 3H), 4.36 (q, *J* = 7.1 Hz, 2H), 7.40 (m, 7H), 7.58 (s, 1H), 7.96 (d, *J* = 7.7Hz, 2H); ^{13}C NMR (75 MHz) δ 14.3, 40.3, 60.9, 124.7, 125.2, 126.2, 127.1, 128.3, 130.0, 130.1, 136.3, 136.6, 145.9, 166.2, 170.2; IR (ATR) 2982, 2929, 1710, 1519, 1290, 1272, 1189, 1107, 771, 761, 697 cm^{-1}; HRMS (DART-ESI+) Calcd for $C_{19}H_{18}N_2O_2S$ [M+H]$^+$: 339.1167; found: m/z 339.1165.

General procedure for the oxidative copper-catalyzed amination of heteroaromatic compounds.

A solution of $Cu(OAc)_2$ (18.2 mg, 0.1 mmol), PPh_3 (52.4 mg, 0.2 mmol), benzothiophene (134.2 mg, 1.0 mmol), 2-pyrrolidinone (38 μL, 0.5 mmol) and Ag_2CO_3 (165.4 mg, 0.6 mmol) in 5 mL of C_6H_5Cl/dioxane (4:1) were stirred at 140 ºC for 20 h under O_2. After cooling to room temperature, the mixture was passed through a Celite pad, which was washed with chloroform or dichloromethane repeatedly. The filtrate was concentrated under reduced pressure to leave a crude oil, which was purified by column chromatography on silica gel to afford 66.7 mg of **20ad** as a pale yellow solid (62%).

***N*-Benzothiophene-2-yl-2-pyrrolidinone (20ad)**: Mp. 191.2-192.1 °C; ^{1}H NMR (300 MHz) δ 2.18-2.33 (m, 2H), 2.66 (t, *J* = 7.7 Hz, 2H), 3.94 (t, *J* = 7.3 Hz, 2H), 6.67 (s, 1H), 7.25 (dd, *J* = 7.3, 1.2 Hz, 1H), 7.32 (dd, *J* = 7.3, 1.2 Hz, 1H), 7.63 (d, *J* = 7.5 Hz, 1H), 7.76 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (75 MHz) δ 17.7, 31.3, 48.7, 106.0, 121.9, 122.1, 123.1, 124.4, 135.5, 136.9, 140.3, 172.7; IR (ATR) 3055, 2973, 2939, 2898, 1687, 1536, 1442, 1400, 1270, 806, 750 cm^{-1}; HRMS (DART-ESI+) Calcd for $C_{12}H_{11}NOS$ [M+H]$^+$: 218.0640; found: m/z 218.06401.

***N*-(4-Hexylthiophene-2-yl)-2-pyrrolidinone (20cd)**: Mp. 74.1-75.0 °C; ^{1}H NMR (300 MHz) δ 0.87 (t, *J* = 6.6 Hz, 3H), 1.22-1.38 (m, 6H), 1.51-1.66 (m, 2H), 2.13-2.28 (m, 2H), 2.53 (t, *J* = 7.6 Hz, 2H), 2.60(t, *J* = 8.0 Hz, 2H), 3.85(t, *J* = 7.0 Hz, 2H), 6.37 (d, *J* = 1.7 Hz, 1H), 6.48-6.53 (m, 1H); ^{13}C NMR (75 MHz) δ14.1, 17.8, 22.6, 28.9, 30.2, 30.7, 31.2, 31.6, 48.7, 11.1, 112.4, 139.9, 140.1, 171.9; IR (ATR) 2954, 2925, 2851, 1683, 1554, 1494, 1294, 801, 730 cm^{-1}; HRMS (DART-ESI+) Calcd for $C_{14}H_{21}NOS$ [M+H]$^+$: 252.1422; found: m/z 252.1423.

***N*-(5-Ethoxycarbonylthiophene-2-yl)-2-pyrrolidinone (20dd)**: Mp. 117.9-118.5 °C; ^{1}H NMR (300 MHz) δ 1.35 (t, *J* = 7.1 Hz, 3H), 2.18-2.33 (m, 2H), 2.64 (t, *J* = 8.0 Hz, 2H), 3. 89 (t, *J* = 7.3 Hz, 2H), 4.30 (q, *J* = 7.1 Hz, 2H), 6.76 (d, *J* = 4.1 Hz, 1H), 7.62 (d, *J* = 4.1 Hz, 1H) ^{13}C NMR (75 MHz) δ 14.3, 17.7, 30.9, 48.2, 60.8, 110.9, 124.8, 131.2, 145.9, 162.8, 172.5; IR (ATR) 2969, 2925, 1696, 1686, 1454, 1269, 1238, 1093, 811, 751 cm^{-1}; HRMS (DART-ESI+) Calcd for $C_{11}H_{13}NO_3S$ [M+H]$^+$: 240.0694; found: m/z 240.0695.

***N*-(5-Chloro-4-hexylthiophene-2-yl)-2-pyrrolidinone (20fd)**: Mp. 99.7-100.4 °C; ^{1}H NMR (300 MHz) δ 0.87 (t, *J* = 6.3 Hz, 3H), 1.21-1.38 (m, 6H), 1.46-1.62 (m, 2H), 2.14-2.32 (m, 2H), 2.50 (t, *J* = 7.6 Hz, 2H), 2.59 (t, *J* = 8.0 Hz, 2H), 3.80 (t, *J* = 7.0 Hz, 2H), 6.13 (s, 1H) ; ^{13}C NMR (75 MHz) δ 14.0, 17.7, 22.5, 27.9, 28.8, 29.5, 30.8, 31.5, 47.7, 110.1, 117.3, 135.4, 136.2, 171.9; IR (ATR) 2953, 2924, 2858, 1678, 1565, 1499, 1411, 1295, 1035, 797, 723, 699 cm^{-1}; HRMS (DART-ESI+) Calcd for $C_{14}H_{20}ClNOS$ [M+H]$^+$: 286.1032; found: m/z. 286.1031.

Other coupling products **3a**[18], **3b**[19], **3c**[9], **3d**[10a], **5a**[9], **5b**[9], **5e**[20], **5f**[21], **7a**[18], **10a**[9], **3i**[22], **10d**[23], **13d**[24] **10j**[25], **17**[14], **18**[26], **20bd**[23], **20ed**[27] and **20gd**[28] are known in the literatures.

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Copper-catalyzed oxidative C–H, N–H coupling of azoles and thiophenes

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