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Copper-Catalyzed Thiolation Annulations of 1,4-Dihalides with Sulfides Leading to 2-Trifluoromethyl Benzothiophenes and Benzothiazoles

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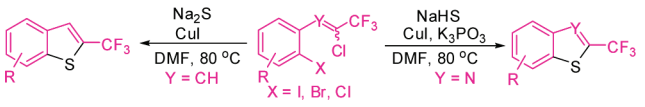

Copper-catalyzed double thiolation reaction of 1,4-dihalides with sulfides has been developed for selectively synthesizing 2-trifluoromethyl benzothiophenes and benzothiazoles. In the presence of CuI, a variety of 2-halo-1-(2-haloaryl)-3,3,3-trifluoropropylenes smoothly underwent the thiolation annulation with Na_2S to afford 2-trifluoromethyl benzothiophenes in moderate to good yields. Moreover, the conditions are compatible with *N*-(2-haloaryl)trifluoroacetimidoyl chlorides in the presence of NaHS and K_3PO_4, leading to 2-trifluoromethyl benzothiazoles.

Benzothiophene and benzothiazole derivatives represent an important class of heterocyclic compounds due to their wide range of applications in the pharmaceutical and agrochemical industries;[1] these heterocycles are the core of numerous medicinal molecules, such as clinically used raloxifene,[2] zileuton,[3] and zopolrestat.[4] For this reason, many attractive and efficient methods have been developed for synthesizing benzothiophene and benzothiazole derivatives. In particular, the synthesis of trifluoromethyl-containing heterocycle molecules is the subject of intense investigation because the trifluoromethyl group has a significant effect on the biological activity and often manifests changes in chemical and physical properties.[5−8] However, only a few effective approaches are available to synthesize trifluoromethyl-containing benzothiophenes[6] or benzothiazoles.[7,8] Generally, trifluoromethyl benzothiophenes are prepared through the direct trifluoromethylation of the preexisting benzothiophene skelecton.[6] However, these methods suffer from poor regioselectivity and low yields. For trifluoromethyl benzothiazoles, there are two synthetic transformations: one involves the condensation of 2-aminothiophenols with trifluoroacetic acid or trifluoroacetic anhydride,[7] and the other transformation is palladium-catalyzed C−H bond functionalization of trifluoromethylimidoyl chlorides with sodium hydrosulfide hydrate.[8]

Recently, transition metal-catalyzed Ullmann reactions for the formation of a carbon−sulfur bond have been extensively studied.[9] However, this Ullmann reaction strategy for the one-pot formation of double carbon−sulfur bonds remains as an unexplored area. As a continuing interest in the synthesis of trifluoromethyl-containing heterocyclic compounds,[10] we report here a novel protocol for the synthesis of 2-trifluoromethyl benzothiophenes and benzothiazoles by

(1) (a) Guo, H. F.; Shao, H. Y.; Yang, Z. Y.; Xue, S. T.; Li, X.; Liu, Z. Y.; He, X. B.; Jiang, J. D.; Zhang, Y. Q.; Si, S. Y.; Li, Z. R. *J. Med. Chem.* **2010**, *53*, 1819. (b) Raga, M.; Palacin, C.; Castello, J. M.; Ortiz, J. A.; Cuberes, M. R.; Moreno-Manas, M. *Eur. J. Med. Chem.* **1986**, *21*, 329. (c) Wang, X.; Sarris, K.; Kage, K.; Zhang, D.; Brown, S. P.; Kolasa, T.; Surowy, C.; Kouhen, O. F. E.; Muchmore, S. W.; Brioni, J. D.; Stewart, A. O. *J. Med. Chem.* **2009**, *52*, 170. (d) Van Zandt, M. C.; Jones, M. L.; Gunn, D. E.; Geraci, L. S.; Jones, J. H.; Sawicki, D. R.; Sredy, J.; Jacot, J. L.; DiCioccio, A. T.; Petrove, T.; Mitschler, A.; Podjarny, A. D. *J. Med. Chem.* **2005**, *48*, 3141. (e) Mortimer, C. G.; Wells, G.; Crochard, J. P.; Stone, E. L.; Bradshaw, T. D.; Stevens, M. F. G.; Westwell, A. D. *J. Med. Chem.* **2006**, *49*, 179. (f) Aiello, S.; Wells, G.; Stone, E. L.; Kadri, H.; Bazzi, R.; Bell, D. R.; Stevens, M. F. G.; Matthews, C. S.; Bradshaw, T. D.; Westwell, A. D. *J. Med. Chem.* **2008**, *51*, 5135.

(2) (a) Qin, Z.; Kasrati, I.; Chandrasena, R. E. P.; Liu, H.; Yao, P.; Petukhov, P. A.; Bolton, J. L.; Thatcher, G. R. J. *J. Med. Chem.* **2007**, *50*, 2682. (b) Jones, C. D.; Jevnikar, M. G.; Pike, A. J.; Peters, M. K.; Black, L. J.; Thompson, A. R.; Falcone, J. F.; Clemens, J. A. *J. Med. Chem.* **1984**, *27*, 1057.

(3) (a) Guinchard, X.; Denis, J. N. *J. Org. Chem.* **2008**, *73*, 2028. (b) Hsiao, C. N.; Kolasa, T. *Tetrahedron Lett.* **1992**, *33*, 2629.

(4) Mylari, B. L.; Larson, E. R.; Beyer, T. A.; Zembrowski, W. J.; Aldinger, C. E.; Dee, M. F.; Siegel, T. W.; Singleton, D. H. *J. Med. Chem.* **1991**, *34*, 108.

(5) For reviews, see: (a) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3. (b) Maienfisch, P.; Hall, R. G. *Chimia* **2004**, *58*, 93. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (d) *Organofluorine Chemistry*; Uneyama, K., Ed.; Blackwell Publishing: Oxford, UK, 2006. (e) *Organofluorine Compounds: Chemistry and Application*; Hiyama, T., Ed.; Springer: New York, 2000. (f) *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Kirsch, P., Ed.; Wiley-VCH: Weinheim, Germany, 2004. (g) Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 214.

(6) (a) Sawada, H.; Nasaharu, M.; Yoshida, M.; Yoshida, T.; Kamigata, N. *J. Fluorine Chem.* **1990**, *46*, 423. (b) Akiyama, T.; Kato, K.; Kajitani, M.; Sakaguchi, Y.; Nakamura, J.; Hayashi, H.; Sugimori, A. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3531. (c) Matthews, D. P.; Whitten, J. P.; McCartthy, J. R. *Tetrahedron Lett.* **1986**, *27*, 4861.

(7) (a) Ge, F.; Wang, Z.; Wan, W.; Lu, W.; Hao, J. *Tetrahedron Lett.* **2007**, *48*, 325. (b) Li, Z.; Yang, Q.; Qian, X. *Bioorg. Med. Chem.* **2005**, *13*, 4864.

(8) (a) Zhu, J.; Chen, Z.; Xie, H.; Li, S.; Wu, Y. *Org. Lett.* **2010**, *12*, 2434. (b) You, W.; Yan, X.; Liao, Q.; Xi, C. *Org. Lett.* **2010**, *12*, 3930.

(9) (a) Fanta, P. E. *Chem. Rev.* **1946**, *38*, 139. (b) Fanta, P. E. *Chem. Rev.* **1964**, *64*, 613. (c) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (d) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428. (e) Liang, Y.; Li, J.-H. *Chin. J. Org. Chem.* **2005**, *25*, 147. (f) Frlan, R.; Kikelj, D. *Synthesis* **2006**, 2271. (g) Chemler, S. R.; Fuller, P. H. *Chem. Soc. Rev.* **2007**, *36*, 1153. (h) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3096. (i) Yin, L.; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133. (j) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954. (k) Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450. (l) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (m) Ma, D.; Xie, S.; Xue, P.; Zhang, X.; Dong, J.; Jiang, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 4222.

(10) (a) Chen, M.-W.; Zhang, X.-G.; Zhong, P.; Hu, M.-L. *Synthesis* **2009**, 1431. (b) Dong, S.-X.; Zhang, X.-G.; Liu, Q.; Tang, R.-Y.; Zhong, P.; Li, J.-H. *Synthesis* **2010**, 1521.

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SCHEME 1

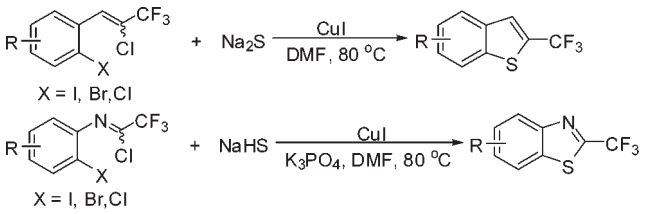
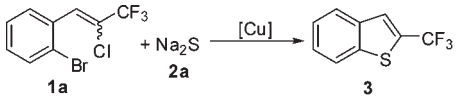


TABLE 1. Screening Conditions[a]



entry	[Cu]	base	solvent	ligand	*T* (°C)	yield (%)
1			DMF		80	0
2	CuI		DMF		80	77
3	CuBr		DMF		80	54
4	CuCl		DMF		80	56
5	$Cu(OAc)_2$		DMF		80	30
6	$Cu(OTf)_2$		DMF		80	43
7	CuI		DMF	TMEDA	80	75
8	CuI		DMF	L-proline	80	72
9	CuI		DMF	bipyridine	80	74
10	CuI	NaOH	DMF		80	58
11	CuI	Cs_2CO_3	DMF		80	67
12	CuI	K_3PO_4	DMF		80	33
13	CuI		toluene		80	trace
14	CuI		THF		80	trace
15	CuI		DMSO		80	47
16	CuI		DMF		100	78
17	CuI		DMF		60	65
18[b]	CuI		DMF		80	21

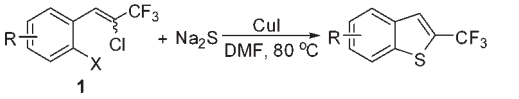
[a]Reaction conditions: **1** (0.2 mmol), $Na_2S \cdot 9H_2O$ (2 equiv), [Cu] (10 mol %), ligand (20 mol %), and base (2 equiv) in solvent (3 mL) for 10 h. [b]$NaHS \cdot xH_2O$ (2 equiv) instead of $Na_2S \cdot 9H_2O$.

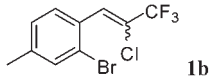
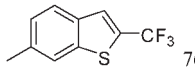
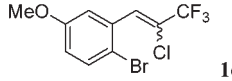
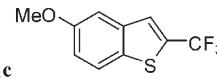
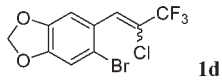
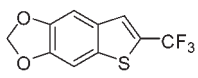
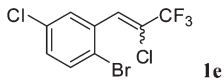
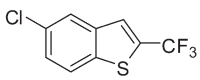
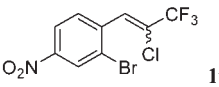
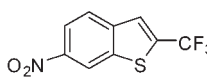
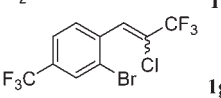
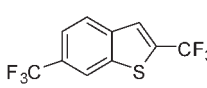
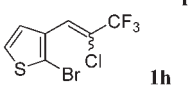
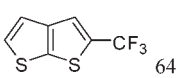
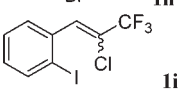
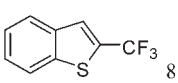
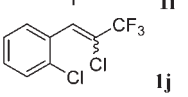
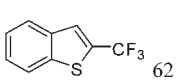
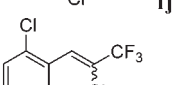
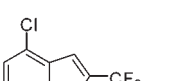
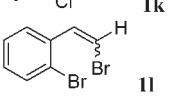
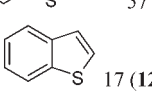
copper-catalyzed thiolation annulations of 1,4-dihalides with sodium sulfide or sodium hydrosulfide (Scheme 1).

We began our study with the reaction between 2-chloro-1-(2-bromophenyl)-3,3,3-trifluoropropylene (**1a**) and Na_2S (**2a**) to explore the optimal reaction conditions (Table 1). Initially, the effect of Cu catalysts, including CuI, CuBr, CuCl, $Cu(OAc)_2$, and $Cu(OTf)_2$, was investigated, and CuI displayed the highest efficiency (entries 1−6). While no desired product **3** was observed from the reaction of substrate **1a** with Na_2S without Cu catalysts (entry 1), 77% yield of the target product **3** was isolated in the presence of 10 mol % CuI (entry 2). The other Cu catalysts, such as CuBr, CuCl, $Cu(OAc)_2$, or $Cu(OTf)_2$, were inferior to CuI; however, they can catalyzed the reaction (entries 3−6). We found that the previously reported effective ligands,[9] including TMEDA, L-proline, and bipyridine, have no influence on the reaction in terms of yields (entries 7−9). According to the earlier reports,[9] bases could improve the Ullmann reactions by trapping the halide atoms. However, the activity of substrate **1a** was lowered in the presence of bases (entries 10−12). Examination of the effects of solvents and reaction temperatures showed that the reaction proceeded optimally in DMF at 80 °C (entries 13−17). It is noteworthy that NaHS (**2b**) is less active for the thiolation annulation reaction of substrate **1a** (entry 18).

With the optimal reaction conditions determined, the 1,4-dihalides scope for the thiolation annulation reaction was examined (Table 2). We initially investigated the reaction of a variety of 1-bromo-2-(2-chloro-3,3,3-trifluoroprop-1-enyl)-benzenes **1b**−**h** with Na_2S and CuI (entries 1−7). Several functional groups, such as Me, MeO, methylendioxy, Cl, NO_2, and CF_3 groups, on the aromatic ring were tolerated in these reactions (entries 1−6). Me-substituted substrate **1b**, for instance, smoothly underwent the reaction with Na_2S and CuI in 76% yield (entry 1). Notably, product **7** was selectively obtained by reacting with vinyl chloride in 62% yield (entry 4). Substrates **1f** and **1g**, with an electron-withdrawing group, were also suitable under optimal conditions (entries 5 and 6), whereas annulation of thiophene **1h** with Na_2S and CuI afforded an interesting thieno[2,3-*b*]thiophene **10** in 64% yield (entry 7). As expected, iodide **1i** displayed greater activity, thereby leading to a good yield (entry 8). For less active 1-chloro-2-(2-chloro-3,3,3-trifluoroprop-1-enyl)benzenes **1j** and **1k**, satisfactory yields were still achieved at higher temperature (entries 9 and 10). We found that the trifluoromethyl group played an important role in this annulation

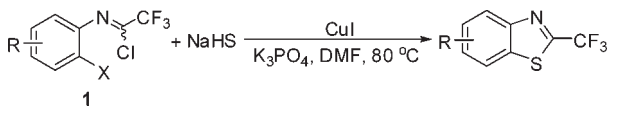
TABLE 2. Thiolation Annulation Reactions of 2-Halo-1-(2-halophenyl)-3,3,3-trifluoropropylenes (1) with Na_2S[a]



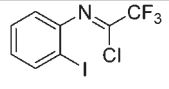
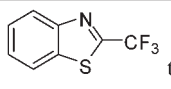
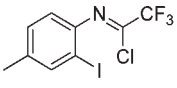
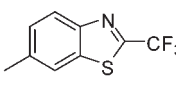
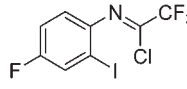
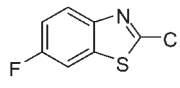
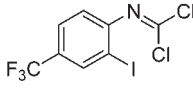
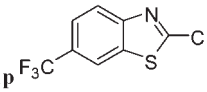
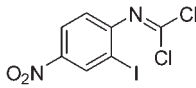
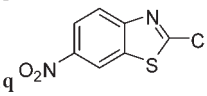
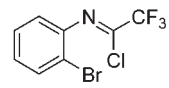
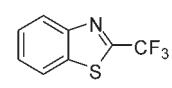
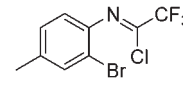
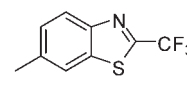
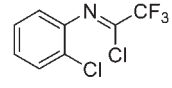
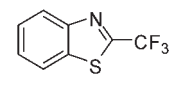
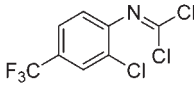
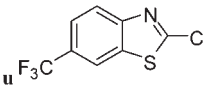
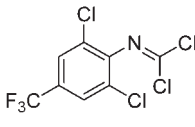
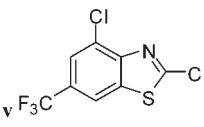
Entry	Substrate **1**	Product/Yield (%)
1	 **1b**	 76 (**4**)
2	 **1c**	 52 (**5**)
3	 **1d**	 56 (**6**)
4	 **1e**	 62 (**7**)
5	 **1f**	 57 (**8**)
6	 **1g**	 74 (**9**)
7	 **1h**	 64 (**10**)
8	 **1i**	 81 (**3**)
9[b]	 **1j**	 62 (**3**)
10[b]	 **1k**	 57 (**11**)
11[b]	 **1l**	 17 (**12**)

[a]Reaction conditions: **1** (0.2 mmol), $Na_2S \cdot 9H_2O$ (2 equiv), and CuI (10 mol %) in DMF (3 mL) at 80 °C for 10 h. [b]At 120 °C for 10 h.

TABLE 3. Thiolation Reactions of *N*-(2-Haloaryl)trifluoroacetimidoyl Chlorides (1) with NaSH and K_3PO_4[a]



1

Entry	Substrate 1	Product/Yield (%)
1[b]	 1m	 trace (**13**)
2[c]	1m	62 (**13**)
3[d]	1m	66 (**13**)
4	1m	72 (**13**)
5	 1n	 71 (**14**)
6	 1o	 68 (**15**)
7	 1p	 67 (**16**)
8	 1q	 61 (**17**)
9	 1r	 58 (**13**)
10	 1s	 65 (**14**)
11[e]	 1t	 31 (**13**)
12[e]	 1u	 43 (**16**)
13[e]	 1v	 35 (**18**)

[a]Reaction conditions: **1** (0.2 mmol), CuI (10 mol %), $NaSH \cdot xH_2O$ (2 equiv), and K_3PO_4 (2 equiv) in DMF (3 mL) at 80 °C for 10 h. [b]Na_2S (2 equiv) without bases. [c]Without bases. [d]K_2CO_3 (2 equiv) instead of K_3PO_4. [e]At 120 °C for 10 h.

reaction, and a low yield was isolated from substrate **1m** without the trifluoromethyl group (entry 11).

Subsequently, Cu-catalyzed annulation reactions of numerous 2,2,2-trifluoro-*N*-(2-haloaryl)acetimidoyl chlorides **1m**−**v** were carried out (Table 3). However, a trace amount of the desired product **13** was observed from the reaction of 2,2,2-trifluoro-*N*-(2-iodophenyl)acetimidoyl chloride (**1m**) with Na_2S under the optimal conditions (entry 1). After a series of trials, we found that the treatment of substrate **1m** with NaHS (**2a**) could furnish product **13** in 62% yield (entry 2). Interestingly, both K_2CO_3 and K_3PO_4 improved the reaction, and the latter was more effective; the yield was enhanced to 72% by using the K_3PO_4 base (entries 3 and 4). Thus, a number of 2,2,2-trifluoro-*N*-(2-iodoaryl)acetimidoyl chlorides **1n**−**q** were first examined in the presence of NaHS, CuI, and K_3PO_4, and the conditions were compatible with various functional groups, including Me, F, CF_3, and NO_2 groups, on the aryl ring (entries 5−8). For example, Me-substituted substrate **1n** gave the desired product **14** in 71% yield (entry 5). Although the activities of the electron-deficient substrates **1p** and **1q** were lower, moderate yields were still obtained (entries 7 and 8). Two *N*-(2-bromophenyl)-2,2,2-trifluoroacetimidoyl chlorides **1r** and **1s** were also suitable for the reaction with NaHS and K_3PO_4 (entries 9 and 10). Less active *N*-(2-chlorophenyl)-2,2,2-trifluoroacetimidoyl chlorides **1t**−**v** could undergo the annulation reaction; however, the yields were not satisfactory (entries 11−13).

In summary, we have disclosed a practical protocol for selectively synthesizing 2-trifluoromethyl benzothiophenes and benzothiazoles by copper-catalyzed thiolation annulation reactions of 1,4-dihalides with Na_2S or NaHS. This protocol allows the formation of two C−S bonds in a one-pot reaction through the thiolation annulation of various 1,4-dihalides, including less active dichlorides, with CuI and Na_2S (or NaHS). Most importantly, these products with a CF_3 functional group may make this class of compounds with some new biological activities as well as new chemical and physical properties for further elaboration.

Experimental Section

Typical Experimental Procedure for the Synthesis of 2-Trifluoromethyl Benzothiophenes in the Presence of Na_2S. Substrate **1a**−***l*** (0.2 mmol), $Na_2S \cdot 9H_2O$ (96.0 mg, 0.4 mmol), CuI (3.8 mg, 0.02 mmol), and DMF (3 mL) were added to a two-necked flask in turn. Then the solution was stirred at 80 °C for 10 h until complete consumption of starting material as monitored by TLC and GC-MS analysis. After the reaction was finished, the mixture was washed with brine, extracted with EtOAc, dried over anhydrous Na_2SO_4, and evaporated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc/petroleum ether) to afford the desired product.

6-Methyl-2-(trifluoromethyl)benzo[*b*]thiophene (4): white solid; mp 89.3−91.2 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 9.0 Hz, 1H),7.64 (d, J = 9.0 Hz, 1H), 7.26−7.23 (m, 1H), 2.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.5, 136.9, 135.5, 130.0 (q, J_{C-F} = 27.5 Hz, 1C), 127.1, 125.4 (q, J_{C-F} = 3.8 Hz, 1C), 124.6, 122.6 (J_{C-F} = 267.5 Hz, 1C), 122.3, 21.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ −56.2 (s, 3F); LRMS (EI, 70 eV) m/z (%) 216 (M^+, 77), 215 (40), 197 (6), 147 (100), 69 (12); HRMS (EI) calcd for $C_{10}H_7F_3S^+$ (M^+) 216.0215, found 216.0219.

Typical Experimental Procedure for the Synthesis of 2-Trifluoromethyl Benzothiazoles in the Presence of NaSH. Dihalides **1m**−**v** (0.2 mmol), $NaSH \cdot xH_2O$ (24.4 mg, 0.4 mmol), $K_3PO_4 \cdot 3H_2O$ (106.4 mg, 0.4 mmol), CuI (3.8 mg, 0.02 mmol), and DMF (3 mL) were added to a two-necked flask in turn. Then the solution was stirred at 80 °C for 10 h until complete consumption of starting material as monitored by TLC and GC-MS analysis. After the reaction was finished, the mixture was washed with brine, extracted with EtOAc, dried over anhydrous Na_2SO_4, and evaporated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc/petroleum ether) to afford the desired product.

2-(Trifluoromethyl)benzo[*d*]thiazole (13):[6c] yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J = 7.9 Hz, 1H), 7.94 (d, J = 7.9 Hz, 1H), 7.60−7.49 (m, 2H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 155.8 (q, J_{C-F} = 40.0 Hz, 1C), 152.0, 134.9, 127.4, 127.3, 124.9, 121.9, 124.3 (q, J_{C-F} = 271.2 Hz, 1C); ^{19}F NMR (282 MHz, $CDCl_3$) δ −61.5 (s, 3F); LRMS (EI, 70 eV) *m*/*z* (%) 203 (M^+, 100), 153 (24), 108 (33), 69 (20).

Acknowledgment. We thank the Natural Science Foundation of China (Nos. 20872112 and 20972114) and Zhejiang Provincial Natural Science Foundation of China (No. Y407116) for financial support.

Supporting Information Available: Analytical data and spectra (^1H and ^{13}C NMR) for all the products **3**−**11** and **13**−**18** and the typical procedure. This material is available free of charge via the Internet at http://pubs.acs.org.