TBAF-catalysed facile synthesis of unsymmetrical diaryl thioethers via mild S_NAr reactions

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By using tetrabutylammonium fluoride as the catalyst, the synthesis of unsymmetrical diaryl thioethers could be easily achieved in high yields via a mild nucleopilic aromatic substitution reaction of aryl fluorides and phenylthiotrimethylsilane.

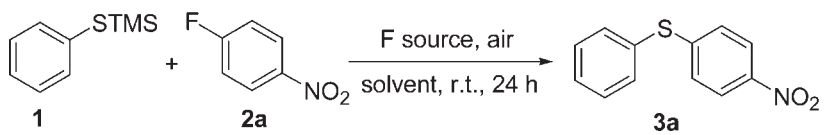
Keywords: tetrabutylammonium fluoride, phenylthiotrimethylsilane, nucleophilic aromatic substitution reaction, unsymmetrical diaryl thioethers

Unsymmetrical diaryl ether[1] and thioether[2,3] structures have attracted much interests due to their abundance in natural products and biologically and pharmaceutically active compounds. They can usually be obtained from aryl halides and phenols/thiols via (1) nucleophilic aromatic substitution (S_NAr) reactions,[4–6] (2) classic copper-assisted Ullmann reactions,[7–9] and (3) the more recently developed transition metal-catalysed arylations.[10–13] In comparison, Ullmann reactions usually require high temperatures and suffer from waste disposal problems due to the copper reagents used, and the transition metal catalysed arylations usually employ expensive metal catalysts and not readily available ligands. Thus, the S_NAr reactions are still attractive routes for these compounds. Besides, trialkylsilyl groups play an important role as effective protecting and nucleophile activation groups in organic synthesis.[14,15] Trialkylsilyl-protected ethers have been applied in unsymmetrical diaryl ether synthesis and several catalytic methods developed.[16–18] However, these methods are not as practical as expected, since high catalyst loadings,[17,18] critical reaction conditions,[18] or the use of not readily available catalysts[18] must be employed. Nevertheless, trialkylsilyl-pretected sulfur-centred nucleophiles have not yet attracted much interest in similar reactions.[15] We report here a TBAF-catalysed efficient synthesis of unsymmetrical diaryl thioethers from aryl fluorides and phenylthiotrimethylsilane (PhSTMS) via a mild S_NAr reaction.

The screening of conditions was carried out using PhSTMS (**1**) and *p*-nitrophenyl fluoride **2a** as the substrates and F anion source as the promotor at room temperature (Table 1). Solvent effects showed that acetonitrile was the best, giving an almost quantitative yield of the target product **3a** in the presence of TBAF (entries 1–4). Other fluoride salts were also examined but less effective (entries 5 and 6). It was found that the reaction could be conveniently carried out in air using commercial substrates and solvents directly without purification, which greatly simplified the operations. Catalytic reactions were also investigated, showing 1 mol% of TBAF was effective enough to ensure complete conversion (entries 8 and 9). Less TBAF (0.5 mol%) was less effective but could still afford a good product yield (entry 10).

As shown in Table 2, almost all *ortho*- and *para*-nitroaryl fluorides **2** could give high yields of the desired unsymmetrical diaryl thioethers under optimised reaction conditions. For difluorides **2h** and **2i** (entries 8 and 9), double sulfenylated products should be produced and **2h** gave **3h** as expected. However, **2i** gave only mono-sulfenylated **3i**. No double sulfenylated product could be detected and the reason is not yet clear. In addition, **2j** and **2k** are more sensitive toward air and TBAF catalysis failed with these subsatrates (entries 10 and 11). Only low to moderate product yields were obtained under air. Instead, high product yields could be obtained if the reactions were run under N_2 using degassed solvent. The sole product obtained from **2k** interestingly, proved to be fluorine-retained but nitro-replaced **3k** (entry 11). Though it has been noted that nitro is also a good leaving group,[19,20] it is usually the fluorine moiety that is more reactive and reacts first with nucleophiles.[15,21,22] Thus, **2k** is a rare case, whose reactivity and selectivity in the S_NAr reaction were reversed possibly by

Table 1 Condition optimisation for TBAF-mediated S_NAr reaction of PhSTMS and *p*-nitrophenyl fluoride



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

Entry	F source/equiv.	Solvent	Yield/%[a]
1	TBAF (1.2)	THF	Trace
2	TBAF (1.2)	DMF	60
3	TBAF (1.2)	DMSO	54
4	TBAF (1.2)	CH_3CN	99
5	CsF (1.2)	CH_3CN	80
6	KF (1.2)	CH_3CN	18
7	NaF (1.2)	CH_3CN	Trace
8	TBAF (0.05)	CH_3CN	99
9	TBAF (0.01)	CH_3CN	96
10	TBAF (0.005)	CH_3CN	81

[a]Isolated yield based on **2a**.

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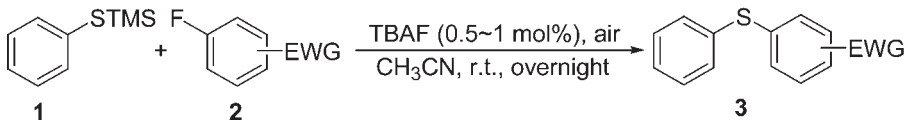
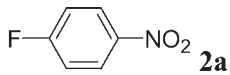
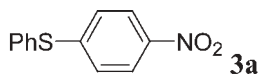
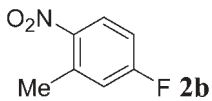
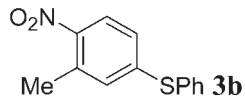
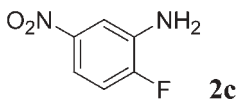
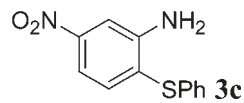
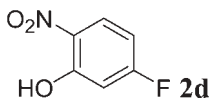
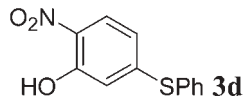
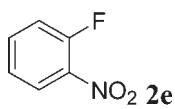
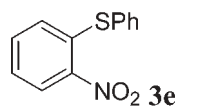
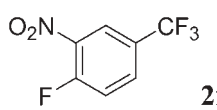
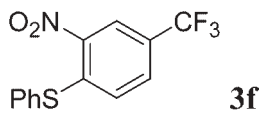
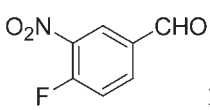
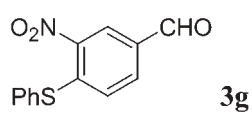
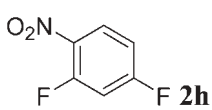
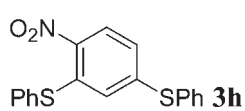
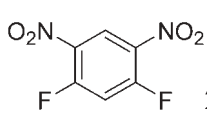
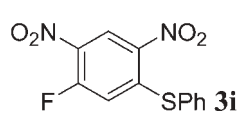
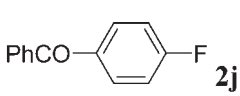
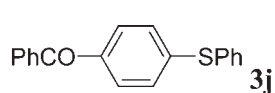
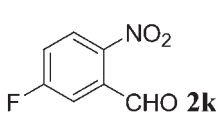
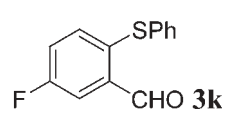
Table 2 TBAF-catalysed S_NAr reactions of PhSTMS and aryl fluorides for unsymmetrical diaryl thioether synthesis



1 2 3

entry	ArF	Product	Yield (%)[a]
1	 **2a**	 **3a**	96
2	 **2b**	 **3b**	93
3	 **2c**	 **3c**	92
4	 **2d**	 **3d**	90
5	 **2e**	 **3e**	94
6	 **2f**	 **3f**	94
7	 **2g**	 **3g**	95
8	 **2h**	 **3h**	90
9	 **2i**	 **3i**	89
10	 **2j**	 **3j**	47 (94)[b]
11	 **2k**	 **3k**	74 (98)[b]

[a] Isolated yield based on **2**.
[b] Reactions used both 1.2 equiv. of **1** and TBAF. Yields in parenthesis were obtained under N_2 in degassed CH_3CN.

the presence of the formyl group at the *ortho*-position to the nitro and *meta*- to the fluorine.

In summary, we have developed an efficient and practical TBAF-catalysed method for unsymmetrical diaryl thioether synthesis via unusually mild S_NAr reactions of PhSTMS and aryl fluorides. Further extension of substrate scope and applications of this novel TBAF-catalysis are underway in our laboratory.

Experimental

Substrates, catalyst, and solvents were purchased and used without further purification. ^1H NMR (300 MHz) spectra were measured on a Bruker Avance (300 MHz) spectrometer using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard. GC–MS and Mass spectra were measured on a Shimadzu GC–MS-QP2010 Plus spectrometer (EI). IR spectra were recorded on a Bruker Vector-55 instrument.

Preparation of **3a–k**; *general procedure*

The mixture of PhSTMS **1** (0.218 g, 1.2 mmol, 1.2 equiv.), aryl fluorides **2** (1.0 mmol), and TBAF (2.61 mg, 1 mol%) in acetonitrile (2 mL) was stirred at room temperature (15–20 °C) in air for 24 h and the reaction was monitored by TLC and/or GC–MS. Solvent was then evaporated under reduced pressure and the residue purified by flash column chromatography on silica gel using petroleum ether and ethyl acetate as eluent.

(4-Nitrophenyl)phenylthioether **(3a)**[23]: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.05 (d, *J* = 7.0 Hz, 2H), 7.56–7.53 (m, 2H), 7.48–7.45 (m, 3H), 7.17 (d, *J* = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 148.5, 145.4, 134.7, 130.4, 130.0, 129.7, 126.7, 124.0.

(3-Methyl-4-nitrophenyl)phenylthioether **(3b)**[24]: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.88 (d, *J* = 8.6 Hz, 1H), 7.53–7.42 (m, 5H), 7.04 (d, *J* = 1.8 Hz, 1H), 6.98 (dd, *J* = 8.6 Hz, *J* = 1.8 Hz, 1H), 2.53 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 146.4, 146.0, 134.8, 134.2, 131.0, 130.5, 130.1, 129.5, 125.6, 125.0, 21.0. IR (KBr, cm^{-1}): 1701, 1597, 1332, 891, 748. MS (EI): 245 (M^+), 228, 184, 165, 109, 77, 51. HRMS Calcd for $C_{13}H_{11}NO_2S$: 245.0511. Found: 245.0515.

(3-Amino-4-nitrophenyl)phenylthioether **(3c)**[25]: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.57 (d, *J* = 2.4 Hz, 1H), 7.51 (dd, *J* = 8.3 Hz, *J* = 2.4 Hz, 1H), 7.41 (d, *J* = 8.3 Hz, 1H), 7.33-7.19 (m, 5H), 4.54 (s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 149.0, 147.8, 135.5, 133.6, 129.5, 129.1, 127.2, 124.2, 112.8, 109.2. IR (KBr, cm^{-1}): 3494, 3398, 1615, 11507, 1343, 737. MS (EI) 246 (M^+), 231, 199, 167, 139, 100, 77, 52. HRMS Calcd for $C_{12}H_{10}N_2O_2S$: 246.0463. Found: 246.0464.

(3-Hydoxy-4-nitrophenyl)phenylthioether **(3d)**[26]: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.76 (s, 1H), 7.93 (d, *J* = 9.5 Hz, 1H), 7.58–7.46 (m, 5H), 6.69–6.66 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 155.4, 152.9, 135.3, 130.9, 130.1, 129.3, 125.3, 118.0, 115.3. IR (KBr, cm^{-1}): 3235, 3014, 1606, 1315, 920, 749. MS (EI) 247 (M^+), 200, 171, 139, 109, 77, 51. HRMS Calcd for $C_{12}H_9NO_3S$: 247.0303. Found: 247.0307.

(2-Nitrophenyl)phenylthioether **(3e)**[27]: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.22 (d, *J* = 8.2 Hz, 1H), 7.60–7.57 (m, 2H), 7.49–7.48 (m, 3H), 7.34–7.21 (m, 2H), 6.86 (d, *J* = 8.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 145.0, 139.4, 135.9, 133.4, 130.9, 130.1, 130.0, 128.3, 125.7, 124.9.

(2-Nitro-4-(trifluoromethyl)phenyl)phenylthioether **(3f)**[28]: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.50 (s, 1H), 7.61–7.51 (m, 6H), 6.96 (d, *J* = 8.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 144.6, 144.2, 135.9, 130.7, 130.4, 129.7, 129.4 (d, $J_{C\text{-}F}$ = 2.5 Hz), 128.9, 127.3 (q, $J_{C\text{-}F}$ = 33.8 Hz), 123.1 (q, $J_{C\text{-}F}$ = 3.8 Hz), 122.9 (q, $J_{C\text{-}F}$ = 271.3 Hz).

3-Nitro-4-(phenylthio)benzaldehyde **(3g)**[29]: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.97 (s, 1H), 8.70 (d, *J* = 1.8 Hz, 1H), 7.80 (dd, *J* = 8.5 Hz, *J* = 1.8 Hz, 1H), 7.61–7.53 (m, 5H), 6.98 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 189.0, 147.3, 144.7, 135.9, 133.1, 131.8, 130.7, 130.5, 129.7, 128.8, 127.7. IR (KBr, cm^{-1}): 3722, 3062, 22840, 1698, 1333, 727. MS (EI) 259 (M^+), 214, 194, 167, 139, 97, 77, 51. HRMS Calcd for $C_{13}H_9NO_3S$: 259.0303. Found: 259.0306.

2,4-Bis(phenylthio)nitrobenzene **(3h)**[30]: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.07 (d, *J* = 8.8 Hz, 1H), 7.37–7.22 (m, 10H), 6.87 (dd, *J* = 8.8 Hz, *J* = 2.0 Hz, 1H), 6.31 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 147.9, 141.8, 141.0, 135.8, 134.9, 130.1, 130.0, 126.0, 124.3, 122.3. IR (KBr, cm^{-1}): 1575, 1506, 1326, 860, 747. MS (EI) 339 (M^+), 309, 274, 243, 200, 166, 139, 77, 51. HRMS Calcd for $C_{18}H_{13}NO_2S_2$: 339.0388. Found: 339.0387.

(5-Fluoro-2,4-dinitrophenyl)phenylthioether **(3i)**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.08 (d, *J* = 7.1 Hz, 1H), 7.63–7.59 (m, 5H), 6.66 (d, *J* = 7.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 157.1 (d, $J_{C\text{-}F}$ = 272.5 Hz), 151.0 (d, $J_{C\text{-}F}$ = 10.0 Hz), 139.3, 135.9, 133.0, 131.6, 131.0, 128.9, 128.4, 125.0, 117.1 (d, $J_{C\text{-}F}$ = 27.5 Hz). IR (KBr, cm^{-1}): 1608, 1522, 1338, 976, 832, 715. MS (EI) 294 (M^+), 184, 157, 125, 97, 77, 51. HRMS Calcd for $C_{12}H_7FN_2O_4S$: 294.0111. Found: 294.0110.

Phenyl(4-(phenylthio)phenyl)methanone **(3j)**[31]: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.68 (d, *J* = 8.5 Hz, 2H), 7.66–7.30 (m, 10H), 7.15 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 195.8, 144.2, 137.6, 134.8, 133.8, 132.3, 130.8, 129.9, 129.7, 128.8, 128.3, 127.3.

5-Fluoro-2-(phenylthio)benzaldehyde **(3k)**[32]**:** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.30 (s, 1H), 7.79 (d, *J* = 2.2 Hz, 1H), 7.44–7.32 (m, 5H), 7.27 (dd, *J* = 8.3 Hz, *J* = 2.2 Hz, 1H), 7.00 (d, *J* = 8.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 190.9, 137.7 (d, $J_{C\text{-}F}$ = 308.0 Hz), 135.2, 134.0 (d, $J_{C\text{-}F}$ = 29.6 Hz), 133.1, 132.8, 132.1, 131.1, 129.7, 129.6, 128.3 (d, $J_{C\text{-}F}$ = 37.3 Hz). IR (KBr, cm^{-1}): 3724, 2928, 1871, 1694, 1456, 1188, 750, 690. MS (EI) 232 (M^+), 203, 149, 109, 69, 57. HRMS Calcd for $C_{13}H_9FOS$: 232.0358. Found: 232.0362.

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