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PAPER

An odorless, one-pot synthesis of nitroaryl thioethers *via* S_NAr reactions through the *in situ* generation of *S*-alkylisothiouronium salts

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A newly developed C-S bond formation nucleophilic aromatic substitution (S_NAr) reaction in aqueous Triton X-100 (TX100) micelles has been disclosed. This chemistry, in which odorless, cheap and stable thiourea in place of thiols is used as the sulfur regeant, provides an efficient approach for the generation of nitroaryl thioethers, which are useful structural units of a great deal of bioactivity molecules rendering this methodology attractive to both synthetic and medicinal chemistry.

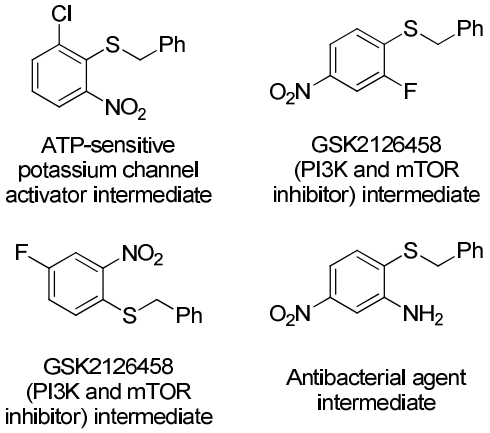
Introduction

The exploration of new protocols for C-S bond generation, which can lead to the discovery of eco-friendly, cheap and more efficient synthetic approaches for the preparation of biological, pharmaceutical, and material interesting organo-sulfur compounds has attracted a great deal of attention.[1] Typically, the formation of C-S bonds, especially C_{aryl}-S bonds can be majorly classified as three routes: (1) the electrophilic substitution reactions[2] of activated aryl halides with arenethiols; (2) the transition-metal-catalyzed coupling reactions;[3] (3) the nucleophilic aromatic substitution (S_NAr) reactions.[4]

Despite the great advancements achieved in transition-metal-catalyzed methods for C–S cross-couplings,[1d,5] S_NAr reactions are still attractive strategies[4,6] since they occurred under relatively milder conditions, more environmentally benign, and no expensive noble metal catalysts or capricious ligands for catalyst activation is required, all which make them more suitable for industrial production. Nevertheless, most of pioneering works in this field have the drawback of using malodorous and expensive thiols as starting materials. The human olfactory system is extremely sensitive to thiols. For example, *tert*-butyl thiol is added to natural gas to enable detection of leaks, which can be smelled at levels of <1 part per billion.[7] Thiols are also air sensitive, which can be readily oxidized to disulfides by atmospheric oxygen. Because of their potent stench and air sensitivity, the use of thiol as the starting materials, particularly on a large scale operation, is highly undesirable.

In order to eliminate the problems, Xu Q. et al have employed trialkylsilyl sulfur nucleophiles ($RSSiR_3$) instead of thiols as the substrates in S_NAr reactions for the generation of thioethers.[8] The sulfur nucleophiles ($RSSiR_3$) prove to be a useful reagent for the construction of C_{aryl}-S bonds due to their ready availability, stability, reactivity and high tolerance of various functionalities. However, the sulfur nucleophiles ($RSSiR_3$) pre-generated from thiols, are relatively high cost, and the use of (potentially toxic) organic solvents is the norm. Therefore, it will be interesting and significant to develop a new approach for the synthesis of thioethers *via* S_NAr reactions in "green" solvent using cheap and odorless sulfur sources.

Recently, attempts are also made for the formation of C-S bonds through the *in situ* generation of *S*-alkylisothiouronium salts in place of thiols, which are formed by organic halides and thiourea.[9] Guided by the 12 principles of green chemistry,[10] we herein describe an odorless and efficient protocol for the formation of nitroaryl thioethers, which constitute an important class of pharmaceutical intermediates (Scheme 1),[11] using cheap and stable thiourea as the sulfur source in water.

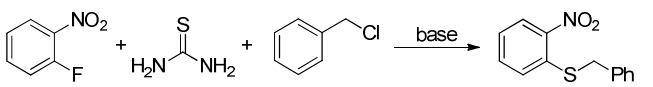


Scheme 1 Examples of nitroaryl thioether pharmaceutical intermediates

Results and Discussion

With our interest in the reaction in water,[12] a test experiment was performed for the synthesis of **3a** from **1a**, **2a** and thiourea in water at 80 °C for 48 h. To our delight, a moderate yield (79%) of **3a** was obtained (Table 1, entry 1), but the result was not satisfactory when the reaction was carried out at lower temperature (50 °C) (entry 2). To improve the poor yield, several surfactants were added in water to form micelles.

Table 1 Optimization of the reaction conditions[a]



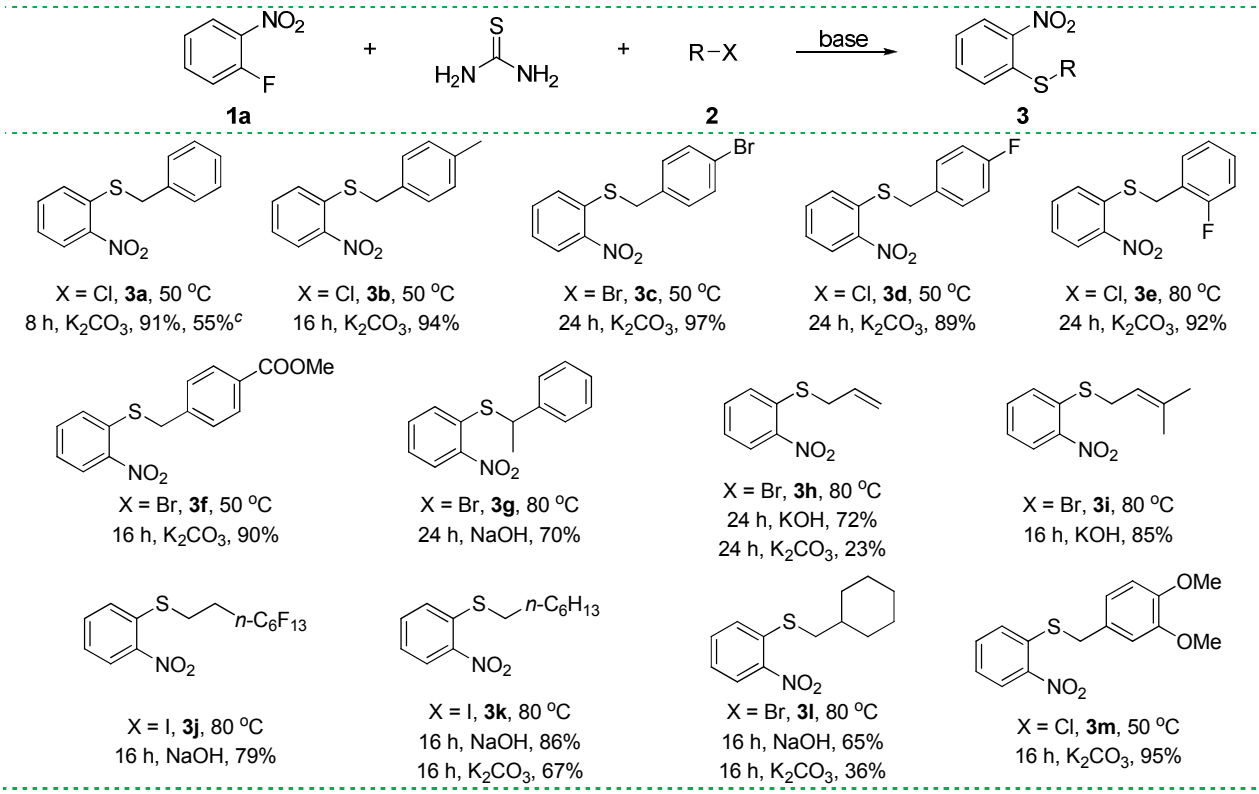
1a **2a** **3a**

entry	solvent	T (°C)	base	yield (%)[b]
1	H_2O	80	K_2CO_3	79[c]
2	H_2O	50	K_2CO_3	22
3	2 wt.% TX100[d]/H_2O	50	K_2CO_3	>99
4	2 wt.% SDS[e]/H_2O	50	K_2CO_3	54
5	2 wt.% CTAB[f]/H_2O	50	K_2CO_3	>99
6	2 wt.% TX100/H_2O	rt	K_2CO_3	72
7	2 wt.% CTAB/H_2O	rt	K_2CO_3	71
8	2 wt.% Brij35[g]/H_2O	rt	K_2CO_3	57
9	EtOH	rt	K_2CO_3	38
10	MeCN	rt	K_2CO_3	36
11	hexane	rt	K_2CO_3	0
13	DMF	rt	K_2CO_3	88
14	2 wt.% TX100/H_2O	rt	K_3PO_4	51
15	2 wt.% TX100/H_2O	rt	*t*-BuONa	49
16	2 wt.% TX100/H_2O	rt	NEt_3	66
17	2 wt.% TX100/H_2O	rt	NaOH	63

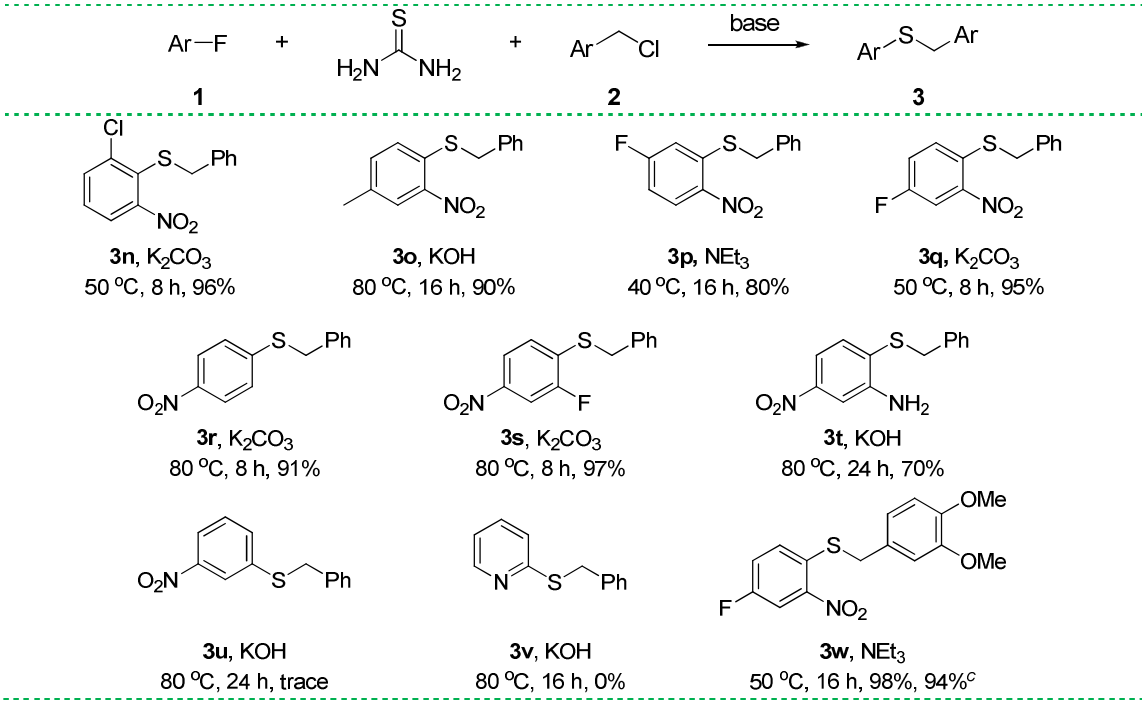
[a] Reaction conditions: **1a** 0.50 mmol, thiourea 1.50 mmol, **2a** 0.75 mmol, base 1.5 mmol, solvent 1 mL, 16 h. [b] GC yields. [c] The reaction time is 48 h. [d] *t*-Octylphenoxypolyethoxyethanol. [e] Sodium dodecyl sulphate. [f] Cetyltrimethylammonium bromide. [g] Polyoxyethyleneglycol dodecyl ether.

As expect, the use of surfactants promotes the reaction obviously (entries 3-8),[9a-f] and the transformation could occur even at room temperature (entries 6-9). Triton X-100 (TX100) aqueous solution provided higher yield than most organic solvents except DMF (entries 6, 9-13). Considering the potential toxicity and tedious work-up procedures of DMF, TX100 aqueous micelles proved to be the better choice for the process. We also screened different bases (entries 6, 14-17), and K_2CO_3 emerged as the best selection (entry 6).

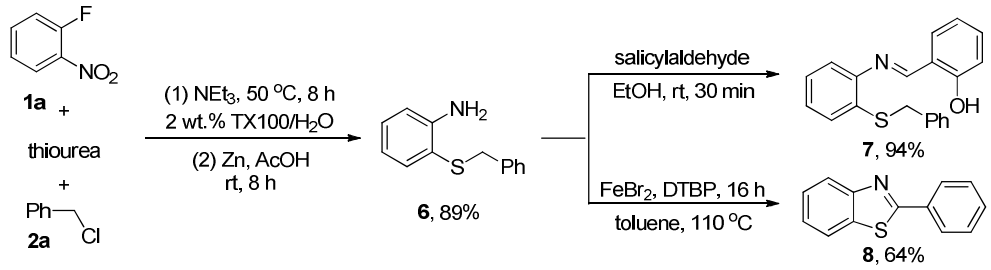
With the optimized conditions in hands, various organic halides were chosen to establish the scope and generality of the protocol (Scheme 2). Benzyl halides containing electron-withdrawing or electron-donating groups reacted well to yield the corresponding thioethers at 50 °C with excellent yields (**3a-f**, **3m**). 2-Nitrobenzene chloride was also applied in the reaction successfully, but only moderate yield (55%) of the product **3a** was gained even under harsher conditions. However, no reaction took place when 2-nitroaryl bromides and iodides were employed. Other aryl fluorides containing electron-withdraw groups (such as –CN, -COOEt) were also failed to apply in the protocol. Increasing of temperature and the use of strong base (NaOH) were required to achieve the S_NAr reaction using secondary benzyl halide ((1-bromoethyl)benzene) as the substrate (**3g**). Strong bases (such as NaOH, KOH) could afford better yields than K_2CO_3 when less active organic halides (such as allylic and alkyl halides) were employed (**3h-k**). It may be explained that *S*-allyl and *S*-alkyl isothiouronium salts have lower nucleophilicity than *S*-benzylisothiouronium salts, make them more easily to form by-products (diallyl or dialkyl thioethers) than react with nitrobenzene fluorides.



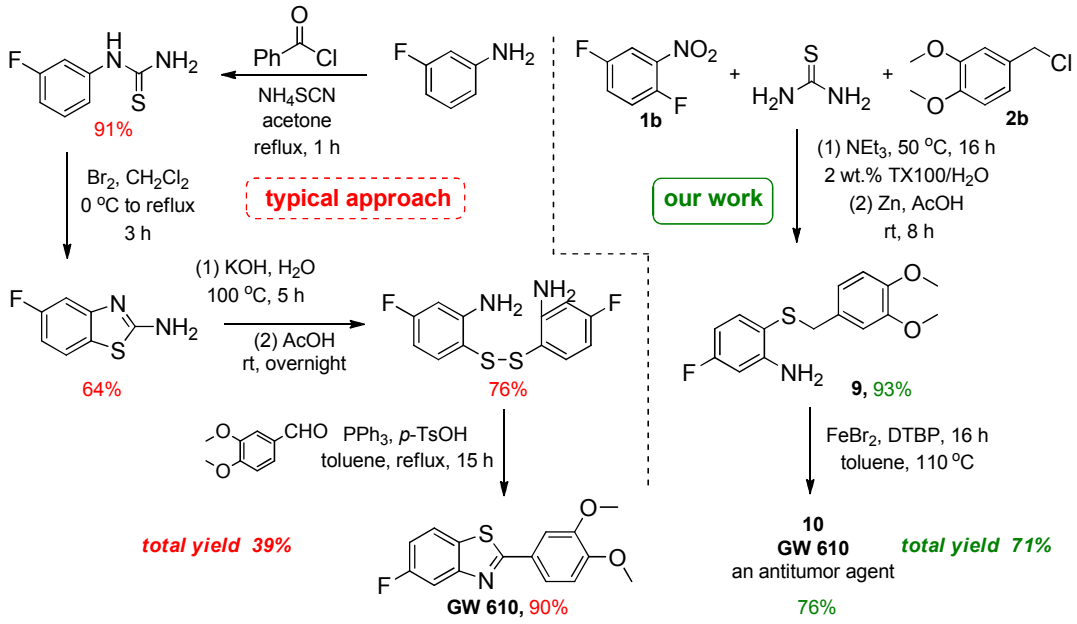
Scheme 2 The S_NAr reactions of 2-nitrobenzene fluoride **1a**, thiourea and organic haildes **2**.[a,b] [a] Reaction conditions: **1a** 0.50 mmol, thiourea 1.50 mmol, **2** 0.75 mmol, base 1.5 mmol, 2 wt.% TX100/H_2O 1 mL. [b] Isolated yields. [c] Reaction conditions: 2-nitrobenzene chloride 0.50 mmol, thiourea 1.50 mmol, **2a** 0.75 mmol, KOH 1.5 mmol, 2 wt.% TX100/H_2O 1 mL, 80 °C, 24 h.



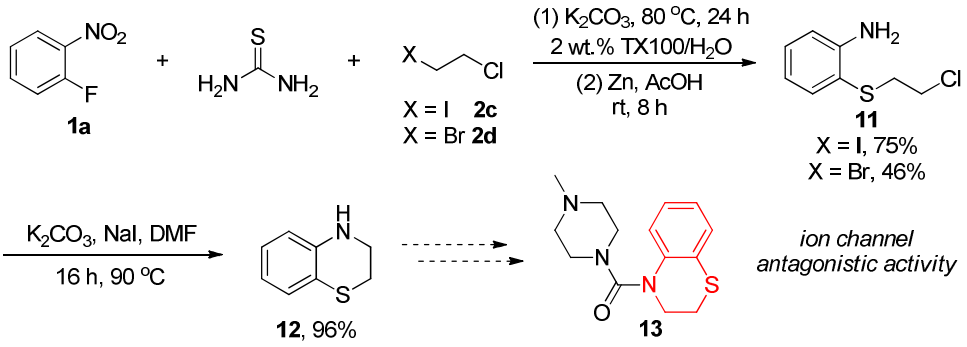
Scheme 3 The S_NAr reactions of nitrobenzene fluorides **1**, thiourea and benzyl chlorides **2**.[a,b] [a] Reaction conditions: **1a** 0.50 mmol, thiourea 1.50 mmol, **2** 0.75 mmol, base 1.5 mmol, 2 wt.% TX100/H_2O 1 mL. [b] Isolated yields. [c] The scale of the reaction is 20 mmol.



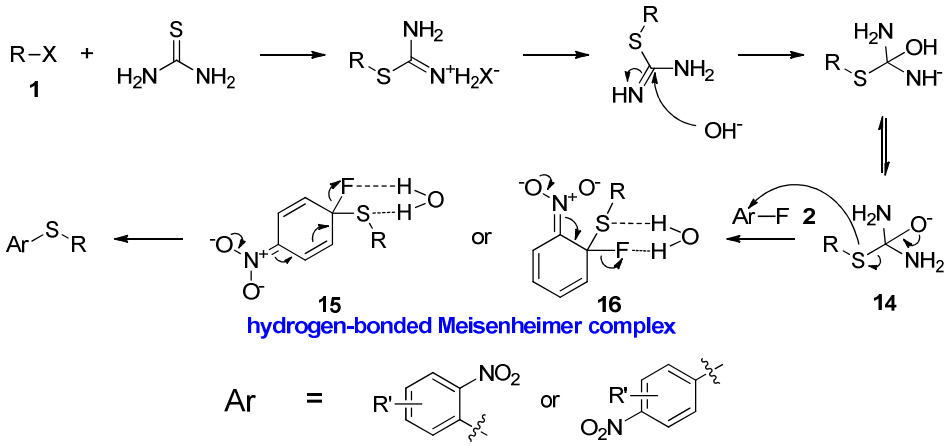
Scheme 4 Transformation of **6** prepared by a one-pot two-step process in water.



Scheme 5 The synthesis of an antitumor agent GW610 **10**



Scheme 6 The synthesis of 1,4-benzothiazine **12** by this protocol



Scheme 7 A proposed mechanism for the S_NAr reactions by the *in situ* generation of *S*-alkylisothiouronium salts in water

Likewise, a variety of nitrobenzene fluorides could also be reacted with thiourea and benzyl chlorides to generate the nitroaryl thioethers in water (Scheme 3). Because only benzene fluorides containing nitro group in *orth* or *para* position can form the Meisenheimer complex,[13] 3-nitrobenezne fluorides and 2-fluoropryrine failed to produce the desire thioethers (**3u**, **3v**). The electronic effects play a crucial role on the transformation. Normally, electron-donating group on nitrobenzene fluorides would inhibit the S_NAr reaction. In order to show the possibility for large-scale operation, we also scaled up the reaction to 20 mmol, and the reaction proceeded well with 94% yield of the desired product **3w**.

The nitro group on benzene ring serves as an intermediate for a common multitude of transformations into other important functional groups (such as $-NH_2$, -OH, -F, -H). Therefore, this methodology was applied to a two-step synthesis of the aminoaryl thioether **6** (Scheme 4). It can react with salicylaldehyde to produce Schiff base **7**, which is a potential antibacterial agent.[14] In addition, we can construct 2-phenyl benzothiazoles from 2-(benzylthio)aniline **6** *via* an iron-catalyzed oxidative process using di-*tert*-butyl peroxide (DTBP) as the oxidant, which may be a robust method for the synthesis of substituted benzothiazoles.

To further demonstrate the potential of this methodology, aniline **9** was synthesized by a tandem reaction in water, following through the iron-catalyzed oxidative procedure to afford GW610 **10** (an antitumor agent) with 71% total yield (Scheme 5).[15] Compared with the typical approach,[16] our work provided higher yield (71% *vs* 39%) in fewer steps (2 *vs* 4) under more environmental friendly conditions. Moreover, some hazard and toxic reagents (such as Br_2 and NH_4SCN) were avoided in this protocol.

1,4-Benzothiazine derivatives are well-known to display diverse biological activities in *vivo* and in *vitro*. For an example, **13** prepared from **12**, is a pharmaceutically active compound exhibiting ion channel antagonistic activity (Scheme 6).[17] Thus, the attempts for this protocol to be used for the synthesis of **11**, which could be transform to 1,4-benzothiazine **12** *via* a cyclization reaction was also realized to explore the applications of this chemistry in organic synthesis.

In addition, we also focused on investigating the ratio of nitrobenzene fluoride **1**, thiourea and organic haildes **2** to further optimize the reaction conditions, making the protocol more environmentally friendly. Take the reaction of **1a**, **2a** and thiourea as an example, different ratios of **1a** : **2**a : thiourea (1/1/1.5, 1/1.2/1.5, 1/1.2/2, 1/1.5/2) were used in the reaction respectively. The reactions were performed at 50 °C for 8 h, and the corresponding yields were 74%, 85%, 91% and 90%, indicating that the ratio of **1a**, **2a** and thiourea could be reduced to 1/1.2/2 without significant change in yield.

Finally, a proposed mechanism for the reaction was also illustrated in Scheme 7. This reaction proceeds by the *in situ* generation of a *S*-alkylisothiouronium salt which is hydrolyzed in the reaction mixture to produce a thiolate moiety **14** and urea.[8a-f] Because 3-nitrobenzene fluorides and aryl fluorides containing other electron-withdraw groups (such as –CN, -COOEt) failed to provide the desired products in the protocol and no regioisomeric products was found during the reaction, we believe the S_NAr reactions in water is an addition-elimination mechanism.[13] The generated **14** which is a synthetic equivalent of thiol and an odorless moiety react with **2** to form hydrogen-bonded meisenheimer complex at first, following by elimination and rearrangement processes to yield the final thioethers. It should be noted that hydrogen bonding between one H_2O molecule and the Meisenheimer complex may generate a six-membered ring structure like **15** and **16**, which may enhance the leaving ability of F group to increase the reaction rate.[13]

The catalytic effects of TX100 micelles in the reaction could be explained from two points. In TX100 aqueous micelles, according to substrates polarity, they were buried in hydrophobic cores. On one hand, due to the huge interfacial area in micelles, the base could contact with substrates sufficiently. On the other hand, micelle droplets formed by TX100 with substrates were hydrophobic enough to exclude F^- and urea,[18] making it easy to form the product. Thus, the reaction occurred more easily in a micelle special with respect to its functioning as a micro- or nanoreactor.[19]

Conclusions

In summary, we have developed a one-pot, odorless method for the synthesis of nitroaryl thioethers by S_NAr reaction using thiourea as the sulfur source. The nonionic surfactant Triton X-100 that self-assembles in water to form micelles proves to enhance the reaction remarkably. The novel procedure is free of organic solvents and foul-smelling thiols during these reactions, and workup entails only an in-flask extraction with a minimal amount of a single, recoverable organic solvent, making it more environmentally friendly and suitable for large-scale operations. Additionally, 2-nitroaryl thioethers can be also transformed to corresponding 2-aminoaryl thioethers by a one-pot tandem process in water, which are versatile precursors to convert benzothiazoles and 1,4-benzothiazine derivatives.

Experimental Section

General procedures for the synthesis of nitroaryl thioethers from organic halides, thiourea and aryl fluorides in water: A mixture of organic halide **1** 0.75 mmol, nitroaryl fluoride **2** 0.50 mmol, thiourea 1.50 mmol and base 1.50 mmol in 2 wt.% aqueous Triton X-100 solution (1.0 mL) is stirred at 40-80 ^oC for 8-24 h. Upon completion, the reaction mixture is diluted with EtOAc (4.0 mL), filtered through a bed of silica gel layered over Celite, The volatiles are removed in *vacuo* to afford the crude product. The extent of conversions is determined by GC. Sometimes, further column chromatography on silica gel affords the pure desired product **3**.

General procedure for the synthesis of anilines 6, 9 and 11 *via* a two-step one-pot process: A mixture of organic halide 0.75 mmol, aryl fluoride 0.5 mmol, thiourea 1.5 mmol and NEt_3 (K_2CO_3 for **11**) 1.5 mmol in 2 wt.% aqueous Triton X-100 solution (1.0 mL) is stirred at 50 ^oC (80 ^oC for **11**) for 8-24 h. Upon completion, zinc power 2.5 mmol and AcOH 2.5 mmol are employed in aqueous medium, and the mixture is allowed to stir at room temperature for another 8 h. Then, the reaction mixture is diluted with EtOAc (4.0 mL), filtered through a bed of silica gel layered over Celite, The volatiles are removed in vacuo to afford the crude product. The extent of conversions is determined by GC. Further column chromatography on silica gel affords the pure desired product.

The procedure for the synthesis of 7: A mixture of **6** 0.50 mmol and salicylaldehyde 0.50 mmol in ethanol (1.0 mL) is stirred at room temperature for 30 min. The solution is then kept undisturbed for **6** hours at room temperature. The yellow crystalline product **7** that formed was filtered off washed several times with ethanol and dried in a vacuum.

The procedure for the synthesis of 8 and 10: A mixture of **6** or **9** 0.50 mmol, $FeBr_2$ 0.05 mmol and DTBP 2.00 mmol in toluene is stirred at 110 ^oC for 16 h. Upon completion, the reaction mixture is diluted with EtOAc (4.0 mL), filtered through a bed of silica gel layered over Celite, The volatiles are removed in *vacuo* to afford the crude product. The extent of conversions is determined by GC. Further column chromatography on silica gel affords the pure desired product **8** or **10**.

The procedure for the synthesis of 12: A mixture of **11** 0.50 mmol, NaI 0.60 mmol and K_2CO_3 1.00 mmol in DMF (1 mL) is stirred at 90 ^oC for 16 h. Upon completion, the reaction mixture is diluted with EtOAc (10.0 mL), and washed by water (10×3 mL). The collected organic phase is filtered through a bed of silica gel layered over Celite, and removed in *vacuo* to afford the product **12**.

Characterization data for unknown compounds

(4-Fluorobenzyl)(2-nitrophenyl)sulfane **3d,** light yellow solid, mp: 78-80 ^oC. ^1H NMR ($CDCl_3$, 500 MHz) δ 4.17 (s, 2H), 7.01-7.04 (t, J = 8.5 Hz, 2H), 7.25-7.28 (m, 1H), 7.36-7.43 (m, 3H), 7.51-7.54 (m, 1H), 8.20 (d, J = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 35.9, 114.8 (d, J = 21 Hz, 1C), 124.0, 125.1, 126.1, 129.6, 129.7, 132.5, 136.3, 145.1, 160.3-162.3 (d, J = 245 Hz, 1C). MS (ESI) *m/z*: 263 [M^+]. Anal. Calcd for $C_{13}H_{10}FNO_2S$: C, 59.30; H, 3.83%, N, 5.32%. Found: C, 59.51; H, 4.21%; N, 5.12%.

(2-Fluorobenzyl)(2-nitrophenyl)sulfane **3e,** light yellow solid, mp: 71-73 ^oC. ^1H NMR ($CDCl_3$, 500 MHz) δ 4.24 (s, 2H), 7.06-7.13 (m, 2H), 7.26-7.30 (m, 2H), 7.42-7.47 (m, 2H), 7.53-7.56 (t, J = 7.5 Hz, 1H), 8.20 (d, J = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 29.3, 114.6 (d, J = 22 Hz, 1C), 121.3 (d, J = 14 Hz, 1C), 123.5, 124.0, 125.1, 126.1, 128.6, 128.7, 130.0, 132.6, 136.2, 145.1, 159.0-160.9 (d, J = 246 Hz, 1C). MS (ESI) *m/z*: 263 [M^+]. Anal. Calcd for $C_{13}H_{10}FNO_2S$: C, 59.30; H, 3.83%, N, 5.32%. Found: C, 59.28; H, 3.60%; N, 5.44%.

.

(2-Nitrophenyl)(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)-sulfane **3j,** light yellow oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 2.46

(m, 2H), 3.22-3.25 (m, 2H), 7.34-7.37 (m, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.63-7.66 (m, 1H), 8.24-8.26 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.1, 29.2-29.5 (m), 49.9, 124.4, 125.2, 125.4, 132.9, 134.4, 145.6. ^{19}F NMR ($CDCl_3$, 470 MHz) δ -126.1, -123.3, -122.8, -121.8, -114.2, -80.8. MS (ESI) *m/z*: 501 [M^+]. Anal. Calcd for $C_{14}H_8F_{13}NO_2S$: C, 33.55; H, 1.61%, N, 2.79%. Found: C, 33.19; H, 1.94%; N, 3.13%.

Heptyl(2-nitrophenyl)sulfane **3k,** light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.87-0.90 (t, J = 7.0 Hz, 3H), 1.28-1.37 (m, 6H), 1.45-1.50 (m, 2H), 1.71-1.77 (m, 2H), 2.94-2.97 (t, J = 7.5 Hz, 2H), 7.23-7.26 (m, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.53-7.55 (m, 1H), 8.19-8.21 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.0, 21.6, 26.9, 27.9, 28.1, 30.7, 31.4, 123.3, 125.1, 125.6, 132.3, 137.3, 145.1. MS (ESI) *m/z*: 253 [M^+]. Anal. Calcd for $C_{13}H_{19}NO_2S$: C, 61.63; H, 7.56%, N, 5.53%. Found: C, 61.59; H, 7.87%; N, 5.14%.

(Cyclohexylmethyl)(2-nitrophenyl)sulfane **3l,** light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.97-1.05 (m, 2H), 1.10-1.23 (m, 3H), 1.57-1.69 (m, 4H), 1.87-1.90 (m, 2H), 2.76 (d, J = 8.5 Hz, 2H), 7.14-7.17 (t, J = 7.5 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.45-7.48 (t, J = 8.0 Hz, 1H), 8.11 (d, J = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.0, 25.2, 32.2, 35.8, 38.7, 123.2, 125.1, 125.7, 132.3, 137.6, 145.2. MS (ESI) *m/z*: 251 [M^+]. Anal. Calcd for $C_{13}H_{17}NO_2S$: C, 62.12%; H, 6.82%, N, 5.57%. Found: C, 61.91; H, 6.56%; N, 5.38%.

(3,4-Dimethoxybenzyl)(2-nitrophenyl)sulfane **3m,** light yellow solid, mp: 96-98 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.87 (s, 6H), 4.16 (s, 2H), 6.79-6.84 (d, J = 8.0 Hz, 1H), 6.93-6.96 (m, 2H), 7.24-7.27 (m, 1H), 7.45-7.54 (m, 2H), 8.19 (d, J = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 37.7, 56.0 (2C), 111.4, 112.2, 121.5, 124.9, 126.1, 127.2, 127.3, 133.6, 137.9, 146.1, 148.8, 149.3. MS(ESI) *m/z*: 305 [M^+]. Anal. Calcd for $C_{15}H_{15}NO_4S$: C, 59.00%; H, 4.95%, N, 4.59%. Found: C, 59.32; H, 4.56%; N, 4.97%.

Benzyl(5-fluoro-2-nitrophenyl)sulfane **3p,** light yellow solid, mp: 74-76 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.17 (s, 2H), 6.91-6.94 (m, 1H), 7.14-7.16 (dd, J = 9.5, 2.0 Hz, 1H), 7.30-7.44 (m, 5H), 8.28-8.31 (dd, J = 9.0, 5.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 36.7, 110.9-111.1 (d, J = 24 Hz, 1C), 112.2-112.5 (d, J = 28 Hz, 1C), 127.0, 128.0, 128.1, 133.2, 140.6, 141.1, 163.2-165.2 (d, J = 258 Hz, 1C). MS(ESI) *m/z*: 263 [M^+]. Anal. Calcd for $C_{13}H_{10}NO_2S$: C, 59.30%; H, 3.83%, N, 5.32%. Found: C, 59.08; H, 4.12%; N, 5.26%.

(3,4-Dimethoxybenzyl)(5-fluoro-2-nitrophenyl)sulfane **3w,** light yellow solid, mp: 92-94 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.97 (s, 6H), 4.25 (s, 2H), 6.91 (d, J = 8.0 Hz, 1H), 7.02-7.03 (m, 2H), 7.36-7.40 (m, 1H), 7.52-7.55 (dd, J = 9.0, 5.0 Hz, 1H), 7.98-8.01 (dd, J = 8.5, 3.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 37.0, 54.9 (2C), 110.3, 111.0, 112.0-112.2 (d, J = 26 Hz, 1C), 120.1, 120.2-120.4 (d, J = 25 Hz, 1C), 126.1, 128.3, 131.7, 145.7, 147.8, 148.3, 157.4-159.4 (d, J = 248 Hz, 1C). MS(ESI) *m/z*: 323 [M^+]. Anal. Calcd for $C_{15}H_{14}FNO_4S$: C, 55.72%; H, 4.36%, N, 4.33%. Found: C, 56.01; H, 3.97%; N, 4.14%.

2-(3,4-Dimethoxybenzylthio)-4-fluoroaniline **9,** light yellow oil.. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.69 (s, 3H), 3.72 (s, 2H), 3.76 (s, 3H), 4.42 (s, 2H), 6.23-6.27 (m, 1H), 6.31-6.33 (dd, J = 10.5, 2.5 Hz, 1H), 6.51 (d, J = 1.5 Hz, 1H), 6.58-6.60 (dd, J = 8.0, 1.0 Hz, 1H), 6.67 (d, J = 8.0 Hz, 1H), 7.04-7.07 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 39.6, 55.7, 55.9, 101.1-101.3 (d, J = 25 Hz, 1C), 105.1-105.2 (d, J = 21 Hz, 1C), 111.2, 112.2-112.3 (d, J = 23 Hz, 1C), 121.1, 130.9, 138.7, 138.8, 150.6-150.7 (d, J = 10 Hz, 1C), 163.4-165.4 (d, J = 244 Hz, 1C). MS(ESI) *m/z*: 293 [M^+]. Anal. Calcd for $C_{15}H_{16}FNO_2S$: C, 61.41%; H, 5.50%, N, 4.77%. Found: C, 61.13; H, 5.22%; N, 4.38%.

Notes and references

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† Electronic Supplementary Information (ESI) available: More experimental entails, characterization data and copies of ^{1}H NMR, ^{13}C NMR spectra of all products. See DOI: 10.1039/b000000x/

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