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Investigation of the scope and mechanism of copper catalyzed regioselective methylthiolation of aryl halides

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ABSTRACT

Methylthiolation of structurally diverse aryl halides was accomplished under fluoride free conditions using catalytic amounts of CuI, and DMSO as the methylthiolation source. Optimization studies unveiled several varieties of promoters among which $Zn(OAc)_2$ was found ideal. The analogous reaction with DMSO-d_6 afforded corresponding deuterated aryl methyl thioether with 99% purity. Mechanistic studies revealed CuSMe as the active methylthiolation agent.

1. Introduction

Aryl methyl thioethers are ubiquitous structural constituents that are present in pharmaceuticals and various biologically active compounds.[1] In addition, they are versatile intermediates that can be converted into sulfoxides,[2] thiols and arenes,[3] and also finds application in C–C coupling reactions.[4] Straightforward methods for the synthesis of aryl methyl thioethers include reduction of sulfoxides,[5] reaction of aryl thiols with iodomethane[6] and aryl halides with dimethyl disulfide.[7] Multistep processes, such as lithiation of aryl halide or heteroatom-assisted lithiation of aromatic C–H bonds and subsequent electrophilic substitution with dimethyl disulfide were utilized for their synthesis.[8] A direct *ortho*-methylthiolation of 2-phenylpyridine with dimethyl disulfide promoted by copper(II) acetate under air atmosphere has also been realized.[9] Notably, Jiang et al. has reported an important catalytic process involving the coupling of aryl halide with sulfur in presence of copper(I)iodide followed by subsequent reduction and reaction with iodomethane.[10]

Recently, DMSO was used as a methylthiolation source for *ortho*-methylthiolation of the 2-arylpyridine and C–H thiolation of heteroarenes.[11] These protocols evade the direct usage of gaseous methanethiol or toxic dimethyl disulfide; however, their utility is confined to heteroarene substrates. An important advancement in this field is the report by Cheng et al. of CuI catalyzed methylthiolation of aryl iodides and aryl bromides with DMSO using ZnF_2 at 150 °C.[12] The procedure has the merit of starting from available or easy to prepare aryl halides. Importantly, their study demonstrated that the presence of fluoride as a promoter was essential for the process. Therefore, to ascertain the mechanistic aspects of methylthiolation and to evaluate the scope of the reaction under fluoride free conditions; herein, we report a convenient process for methylthiolation of aryl halides involving CuI and $Zn(OAc)_2$ using DMSO as the methylthiolation source under comparatively mild conditions.

2. Results and discussion

The preliminary studies for the methylthiolation of aryl halides were aimed to find the best promoter. For this, several reactions were carried out on a 0.5 mmol scale with different promoters using 4-iodoanisole as the model substrate and 10 mol % of CuI catalyst in 1.6 mL of DMSO. Selected results of the optimization studies are tabulated in Table 1, which clearly demonstrate that fluorides are not essential for accomplishing methylthiolation. Moreover, these studies prove that acetates, amines and ammonium salts are comparatively better promoters than fluorides.[13] Among the promoters screened, good results were obtained with

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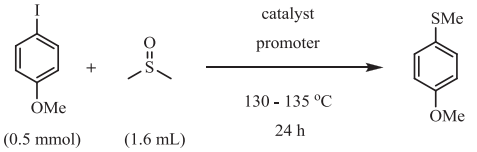
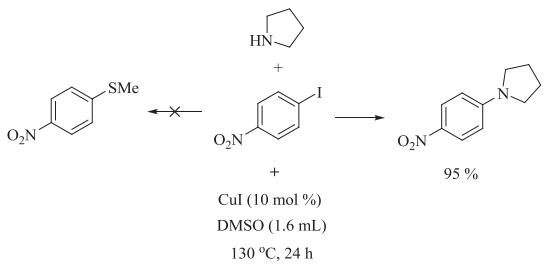
Table 1
Optimization of reaction parameters for methylthiolation of 4-iodoanisole[a]



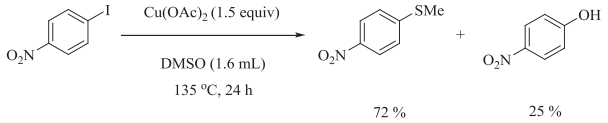
Entry	Catalyst	Promoter (equiv)	Yield[e]/%
1	CuI	NH_4F (4)	4
2	CuI	NH_5F_2 (4)	56
3	CuI	$Et_3N{\cdot}3HF$ (4)	35
4	CuI	Pyrrolidine (4)	80
5	CuI	Piperidine (4)	52
6	CuI	Morpholine (4)	32
7	CuI	*N*-Methylpyrrolidine (4)	10
8	CuI	2-Methylpiperidine (4)	8
9	CuI	ZnF_2 (2)	25
10	CuI	AgF (2)	27
11	—	Cu_2O (2)	0
12	—	CuI (2)	0
13	—	$Cu(OSO_2CF_3)$(2)	0
14	—	$Cu(acac)_2$(2)	27[b]
15	—	CuOAc (2)	93
16	—	$Cu(OAc)_2$ (1.5)	95
17	CuI	$Zn(OAc)_2$ (2)	85
18	CuI	$Ni(OAc)_2$ (2)	48[b]
19	CuI	$Mn(OAc)_2$ (2)	74[b]
20	CuI	$Zn(OAc)_2$ (2)	95[b]
21	CuI	K(OAc) (2)	5[b]
22	CuI	$Ni(OCOCF_3)$(2)	46[b]
23	CuBr	$Zn(OAc)_2$ (2)	93[b]
24	Cu_2O	$Zn(OAc)_2$ (2)	90[b]
25	Cu powder	$Zn(OAc)_2$ (2)	93[b]
26	$CuBr_2$	$Zn(OAc)_2$ (2)	83[b]
27	CuI	$Zn(OAc)_2$ (1)	80[b]
28	CuI	$Zn(OAc)_2$ (1.5)	94[b]
29	—	$Zn(OAc)_2$ (2)	14[b,d]
30	—	$Zn(OAc)_2$ (2)	48[c,d]

[a] Unless otherwise stated, the reactions were performed on a 0.5 mmol scale with 4-iodoanisole (0.5 mmol), catalyst (10 mol %) and promoter (1–4 equiv) in 1.6 mL of DMSO at 130 °C for 24 h.
[b] Temperature=135 °C.
[c] Temperature=140 °C.
[d] Reaction performed in the absence of catalyst.
[e] Isolated yield.

pyrrolidine, $Cu(OAc)_2$, Cu(OAc) and $Zn(OAc)_2$. However, pyrrolidine, $Cu(OAc)_2$ and Cu(OAc) cannot be employed as promoters for methylthiolation of electron-deficient aryl halides like 4-iodonitrobenzene, since pyrrolidine exclusively undergoes N-arylation with 4-iodonitrobenzene instead of methylthiolation (Scheme 1), whereas significant amounts of 4-nitrophenol were formed when $Cu(OAc)_2$ and Cu(OAc) were used as promoters (Scheme 2). Thereafter, $Zn(OAc)_2$ was selected as the promoter and further screening studies were carried out to find the best catalyst. Notably, comparable results were obtained for most of the copper salts, although CuI, CuBr and copper powder showed slightly superior yields. Thus as illustrated in Table 1, the most promising



Scheme 1. N-Arylation versus methylthiolation.

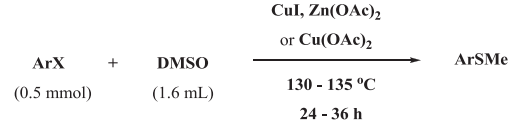


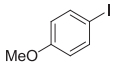
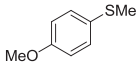
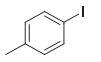
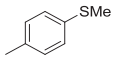
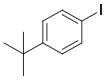
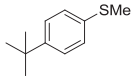
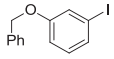
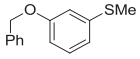
Scheme 2. Methylthiolation versus hydroxylation.

result was obtained by employing 10 mol % CuI, 1.5 equiv $Zn(OAc)_2$ and 1.6 mL DMSO at 135 °C for 24 h (Table 1, entry 28). In addition, we have also studied the effect of ligands and secondary additives in altering the reaction outcome. Contrarily, the ligand did not show any effect on the reactions using $Zn(OAc)_2$ and $Cu(OAc)_2$ as promoters. Nevertheless, some of the interesting combinations evaluated during the optimization studies are presented in Table S1 (see Supplementary data).

With the above optimized reaction conditions in hand (i.e., Table 1, entry 28), various structurally diverse aryl iodides were tested for methylthiolation. Electron-rich aryl iodides like 4-iodotoluene, 1-(*tert*-butyl)-4-iodobenzene, 1-(benzyloxy)-3-iodobenzene and 4-iodo-1,1′-biphenyl (Table 2, entries 2–4 and 6) underwent the reaction smoothly to afford the corresponding products in excellent

Table 2
Copper catalyzed methylthiolation of aryl halides



Entry	ArX	ArSMe	Yield[f]/%
			94,[a] 95[b]
2			82,[a] 84[b]
3			94,[a] 93[b]
4			75[a]
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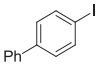
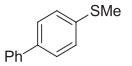
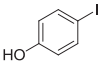
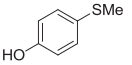
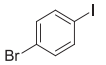
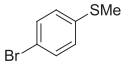
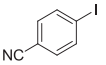
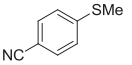
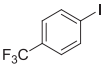
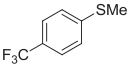
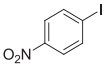
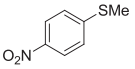
6			87[a]
7			78[a]
8			79[a,c]
9			78[a]
10			80[a]
11			96[a]

(*continued on next page*)

Table 2 (*continued*)

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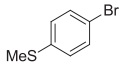
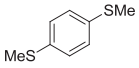
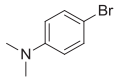
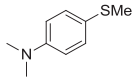
12			84,[d] 90[e]
13			74[d]
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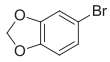
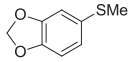
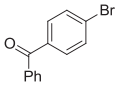
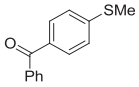
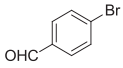
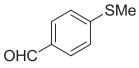
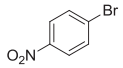
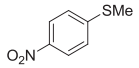
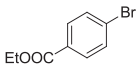
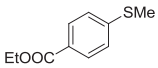
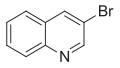
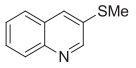
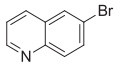
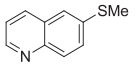
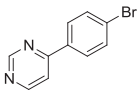
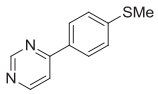
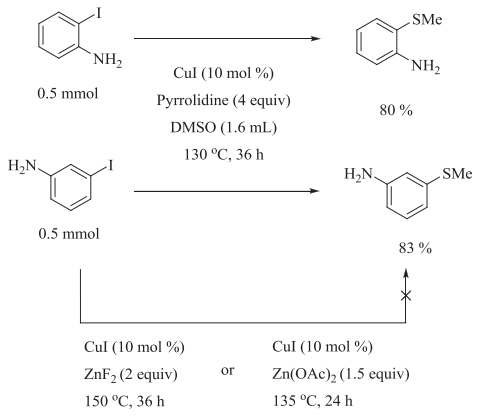
15			78[d]
16			83,[d] 53[e]
17			70[d]
18			84[d]
19			78[d]
20			83[d]
21			85[d]
22			80[d]
23			74[d]

[a] Reaction performed with aryl halides (0.5 mmol), CuI (10 mol %) and $Zn(OAc)_2$ (1.5 equiv) in 1.6 mL DMSO at 135 °C for 24 h.
[b] Reaction performed with $Cu(OAc)_2$ (1.5 equiv) instead of $Zn(OAc)_2$ and CuI at 130 °C.
[c] Reaction performed at 130 °C for 36 h.
[d] Reaction performed with CuI (25 mol %) and $Zn(OAc)_2$ (2 equiv) for 36 h.
[e] Reaction performed with $Cu(OAc)_2$ (2 equiv) instead of $Zn(OAc)_2$ at 135 °C for 36 h.
[f] Isolated yield.

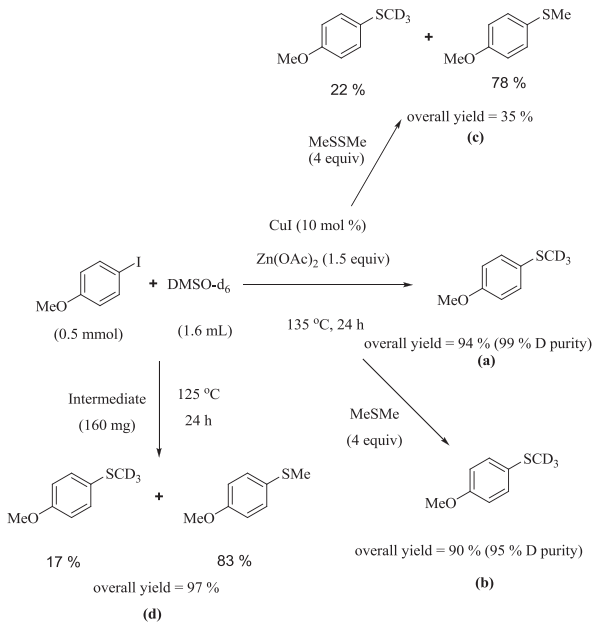
yields. On the other hand the reactions of electron-deficient substrates like 4-iodobenzonitrile, 1-iodo-4-(trifluoromethyl)benzene and 4-iodonitrobenzene, were rather sluggish at 130 °C. However, excellent yields were obtained with these substrates albeit at 135 °C (Table 2, entries 9–11). Thereafter, the utility of this protocol was explored for commercially more attractive aryl bromides as substrates. Unlike electron-rich aryl iodides, the reactions of their corresponding bromo-counterparts were rather sluggish at 130 °C. Notably, several electron-rich and electron-deficient aryl bromides reacted smoothly at a slightly higher temperature (135 °C) in presence of 25 mol % CuI catalyst to afford the corresponding methylthiolation products in good yields (Table 2, entries 12–19). It is noteworthy that the reaction of 4-bromoiodobenzene proceeded chemoselectively to afford 4-bromothioanisole in good yields (Table 2, entry 8). The reaction of sterically hindered 2-iodo-1,3-dimethoxybenzene also furnished a good yield of product (Table 2, entry 5). The reaction scope was expanded successfully to heterocycles like bromo-quinolines, pyridines and pyrimidines (Table 2, entries 20–23). It is significant to note that aryl halides with sensitive functional groups like CN, COOEt, NMe_2, SMe, OMe, OCH_2Ph, OH, CHO, COPh, acetal, CF_3 and NO_2 tolerated the reaction conditions to furnish the respective products in good yields. In contrast, free amino groups did not survive under this protocol as the reaction of 3-iodoaniline failed to yield the desired product. On the other hand, the methylthiolation of iodoanilines was accomplished in good yields using pyrrolidine as promoter instead of $Zn(OAc)_2$ (Scheme 3). However, the protocol failed for aryl triflates, aryl mesylates and both electron-rich and electron-deficient aryl chlorides.



Scheme 3. Chemoselective methylthiolation of iodoaniline promoted by pyrrolidine.

To explore the mechanism of the methylthiolation reaction, various studies were carried out using GC–MS and NMR. The vapour phase analysis (using GC–MS Headspace) of the reaction performed under standard conditions using 4-iodoanisole revealed the presence of significant amount of MeSMe along with comparatively smaller amounts of MeSSMe, MeSSSMe, $MeSCH_2SMe$ and $MeSCH_2CH_2OH$.[14] In a similar way, the corresponding reaction with DMSO-d_6 provided the respective deuterated intermediates and products. It is noted that for this reaction, no kinetic isotope effect was observed. To verify whether MeSMe and MeSSMe are the precursors for methylthiolation of aryl halides, three sets of reactions were performed, one with added MeSMe (4 equiv), another with added MeSSMe (4 equiv) and another blank under standard conditions using 4-iodoanisole and DMSO-d_6 at 135 °C. It is to be noted that if MeSMe or MeSSMe are the active methylthiolation agents, good yields and low deuterium incorporation in product should be obtained. Notably, the yields and the amount of deuterium incorporated in the products were of the order, blank (94, 99% D)>MeSMe (90, 95% D)>MeSSMe (35, 22% D) (Scheme 4 and Fig. 1).[15] Additionally, to check any involvement of the above mentioned intermediates in their copper coordinated forms, two more experiments were performed using stoichiometric amounts of preformed $CuI(SMe_2)_{0.75}$ and $CuI[(SMe)_2]$, respectively, in absence of both catalyst and additive using 4-iodoanisole and DMSO-d_6.[16] However, the reaction failed in the former case, whereas poor yield of product was obtained with the latter. All these results clearly show that MeSMe, MeSSMe and the aforementioned copper coordinated species are less likely to be the active methylthiolation agents in the reaction performed under the standard conditions.

Interestingly, when CuI is heated with $Zn(OAc)_2$ in DMSO at 135 °C for 12 h, a yellow precipitate (intermediate 1) was obtained, which was practically insoluble in all solvents except in mineral acids where it decomposes, liberating gas having a sulfurous odour. This intermediate was characterized using powder XRD, TGA–MS,



Scheme 4. Isotopic substitution studies for methylthiolation.

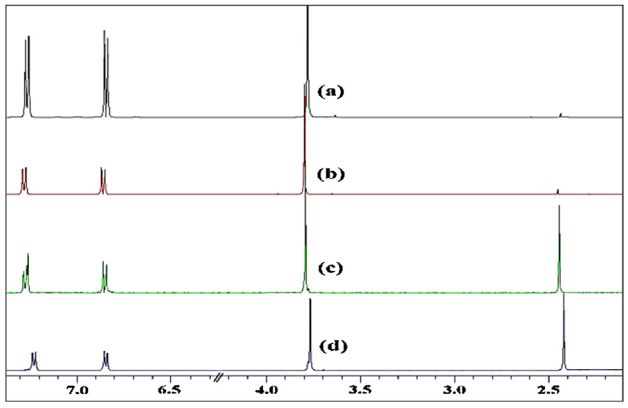


Fig. 1. ^{1}H NMR spectra of (4-methoxyphenyl)(methyl)-sulfane. Reactions performed with (a) DMSO-d_6; (b) DMSO-d_6 and MeSMe; (c) DMSO-d_6 and MeSSMe; (d) DMSO-d_6 and intermediate 2.

XPS, IR and elemental analysis (see Supplementary data). The XRD pattern of this compound was identical to that of polymeric $\{Cu(CH_3S^-)\}_x$ reported by Bumgartner et al. (Fig. 2).[17] ICP OES and CHNS analysis of this compound revealed the presence of 54.20% of copper, 11.05% of carbon, 25.88% of sulfur and 2.52% of hydrogen, respectively. The remaining content of the sample was assumed to be oxygen originating from the polymeric residue. TGA–MS analysis of this compound revealed ~25% weight loss between 230 and 320 °C, which can be attributed due to the formation of Cu_2S by the decomposition of CuSMe (Fig. 3), and is in consonance with the m/z values of 15, 47 and 48 obtained in the mass spectrum corresponding to CH_3^+, CH_3^+, CH_3S^+ and CH_3SH^+ ion fragments, respectively (Fig. 3). In agreement with the above results, the IR spectrum of this compound also showed characteristic absorption peaks at 2958, 2913, 1411, 1299, 934, 682 cm^{-1} corresponding to ν_a(C–H), ν_s(C–H), $\delta_a(CH_3)$, $\delta_s(CH_3)$, $\rho(CH_3)$ and ν(S–C), respectively (see ESD).[16c] Notably, the binding energy peaks at 933.0 and 952.9 eV found in the XPS spectra correspond to the Cu $2p_{3/2}$ and Cu $2p_{1/2}$ lines, exemplifying the +1 oxidation state of copper (Fig. 4).

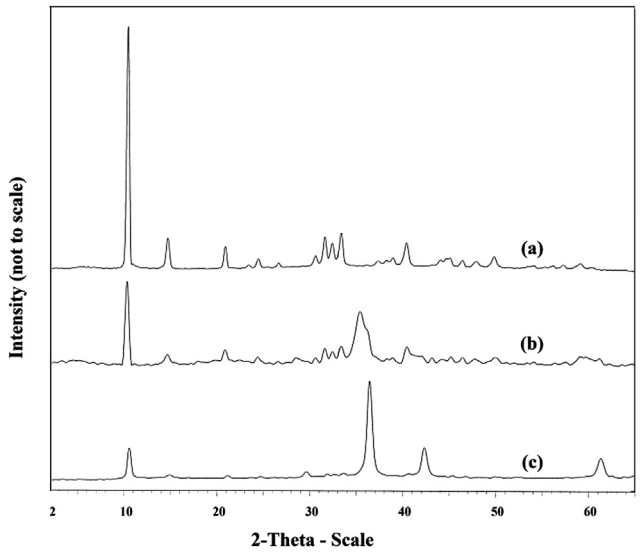


Fig. 2. XRD pattern: (a) intermediate 1 (identical for intermediate 4 and CuSMe), (b) intermediate 3 and (c) intermediate 3 isolated after 24 h.

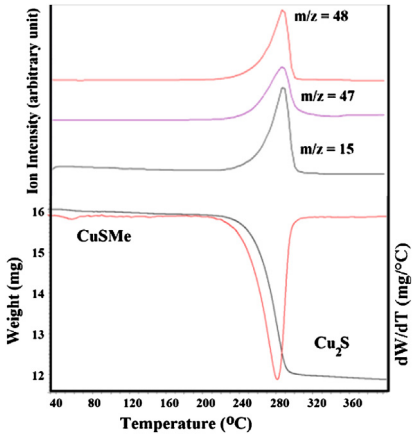


Fig. 3. TGA and MS spectra of intermediate 1 (CuSMe).

All these characterization data strongly emphasize the intermediate 1 to be CuSMe containing trace amounts of polymeric residue. In a similar way, we have isolated and characterized the intermediates obtained in the reaction of $Cu(OAc)_2$, Cu(OAc) and

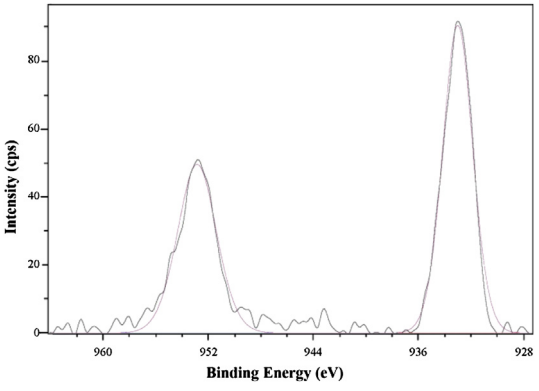
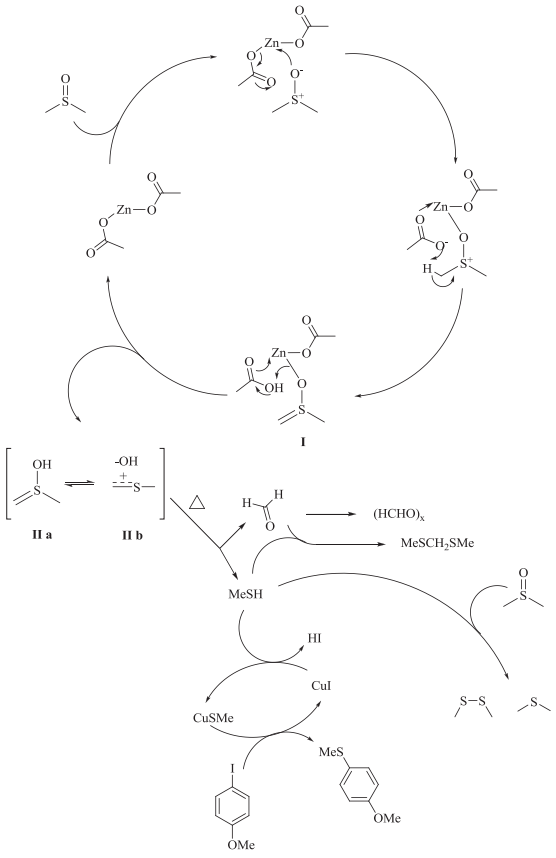


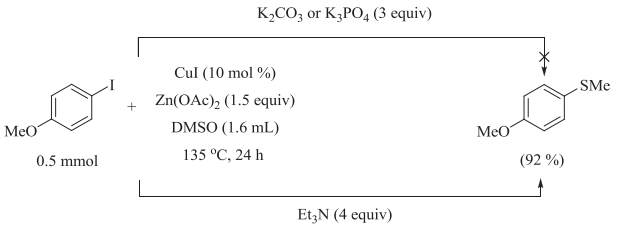
Fig. 4. XPS spectra of intermediate 1 (CuSMe).

pyrrolidine (namely, intermediate 2, intermediate 3 and intermediate 4, respectively) with DMSO at 135 °C for 12 h. Remarkably, these intermediates resembled the intermediate 1; however, the presence of small amounts of Cu_2O was also confirmed in intermediate 2 and intermediate 3 by XRD analysis. The amount of the Cu_2O formed was found to increase with increase in reaction time and temperature as demonstrated by XRD studies (Fig. 2). The diffraction peaks at 2θ values of 29.60°, 36.52°, 42.44°, 61.54° correspond to (110), (111), (200) and (220) crystal planes of crystalline Cu_2O, respectively (JCPDS file no. 05-0667). When methylthiolation of 4-iodoanisole was carried out with intermediate 2 in the absence of catalyst and promoter in DMSO-d_6 at 130 °C, excellent yield was obtained for the corresponding methylthiolation product (97, 17% D, Scheme 4). Remarkably, only very small amount of deuterium was incorporated into the methyl thioether moiety, specifying the presence of SMe group in the intermediate.[18]

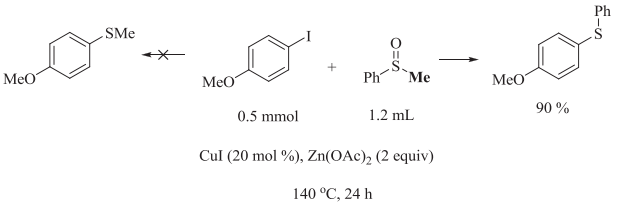
A plausible mechanism for methylthiolation is illustrated in Scheme 5. Initially, DMSO will be O-activated by $Zn(OAc)_2$ (or any Lewis Acid), and an α-H of DMSO is abstracted by acetate anion to form I and acetic acid within the reaction sphere.[19–21] This hypothesis is supported by the fact that the methylthiolation of 4-iodoanisole failed under the standard conditions in presence of added base (e.g., K_2CO_3 or K_3PO_4); see Scheme 6. In addition, the same reaction using diphenyl sulfoxide (which does not have α-H), failed, whereas with methyl phenyl sulfoxide proceeded chemoselectively to furnish the respective phenylthiolation product exclusively in good yield (Scheme 7).[22] In succession, formation of **II a** occurs through the reaction of acetic acid with **I** thereby regenerating $Zn(OAc)_2$; concentration of the latter was in turn found to be rather unchanged throughout the course of the reaction as inferred from NMR analysis (see Supplementary data).[23]



Scheme 5. Proposed mechanism for methylthiolation.



Scheme 6. Effect of added base on methylthiolation.



Scheme 7. Chemoselective phenylthiolation of 4-iodoanisole with methyl phenyl sulfoxide.

Subsequently, MeSH and HCHO are formed by the isomerization of **II a**, followed by the decomposition of **II b** as depicted in Scheme 5.[24–31] It is to be noted that the $MeSCH_2SMe$ peak detected in GC–MS analysis of the reaction mixture (Fig. 5) can be attributed to the reaction of MeSH with HCHO, which is an indirect evidence for the formation of the same. Thus, CuSMe is formed by the reaction of CuI with MeSH,[32a] and finally aryl halides will react with CuSMe forming the methylthiolation product.[32,33] In addition, the formation of phenol in the reaction of activated aryl halides (e.g., 4-iodonitrobenzene) with $Cu(OAc)_2$ or Cu(OAc) can be accounted considering the mechanistic pathway mentioned in Scheme 8.[32c,d,34] The formation of Cu_2O and the intermediate (methylthio)methyl acetate was confirmed by XRD and GC–MS analysis, respectively (Figs. 2 and 6).[24] In a similar manner, the role of pyrrolidine as a promoter can be explained considering the hydrogen bonding between oxygen of DMSO and *N*-hydrogen of pyrrolidine. The hydrogen bonding increases the acidity of methyl protons of DMSO,[35] thus promoting the proton abstraction step by base (Scheme 9). Accordingly, the reaction will be more efficient for strong and sterically less hindered bases like pyrrolidine, which is in consistent with the data presented in Table 1 (entries 4–8).[13,36]

In an analogous way, we have probed S_NAr mechanistic aspect of methylthiolation, the results of which are tabulated in Table S2 (see

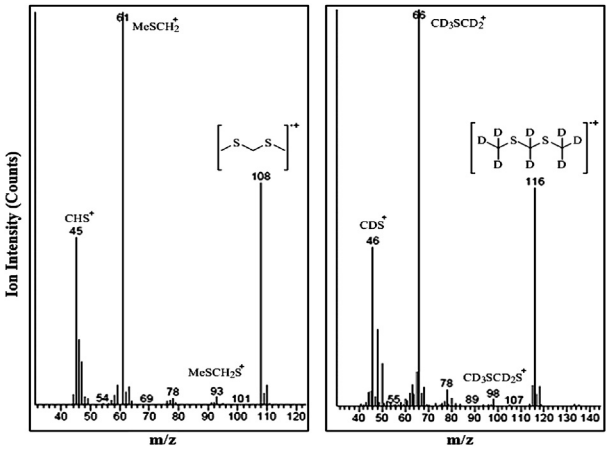
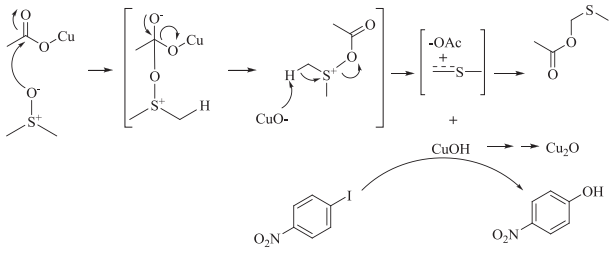


Fig. 5. EIMS spectra of bis(methylthio)methane (left) and deuterated bis(methylthio) methane (right).



Scheme 8. Proposed mechanism for hydroxylation.

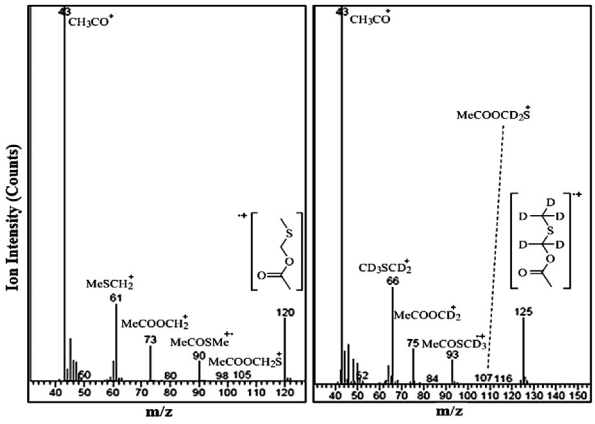
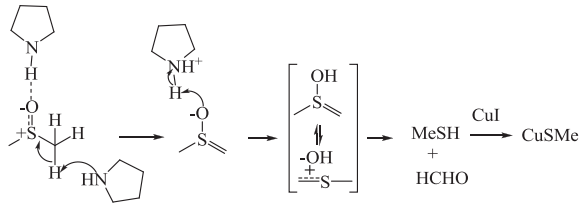


Fig. 6. EIMS spectra of (methylthio)methyl acetate (left) and deuterated (methylthio) methyl acetate (right).



Scheme 9. Proposed mechanism for formation of CuSMe using pyrrolidine.

Supplementary data). It is important to note that for an S_NAr reaction to proceed, the intermediacy of a thiolate anion is essential.[37] In a standard reaction, MeSSMe and MeSH are two plausible precursors for the thiolate anion.[38] However, the concentration of these intermediates formed in a standard reaction is low thereby ruling out the likely involvement of S_NAr mechanism in the major mechanistic pathway of methylthiolation.[25] Notably, a reaction performed with $Zn(OAc)_2$ and 4-iodoanisole in DMSO at 140 °C furnished the methylthiolation product in moderate yield (Table 1, entry 30), whereas the analogous reaction of 4-bromoanisole and 4-chloronitrobenzene failed at 140 °C.[39,40] These results suggest a II-bond metathesis type mechanism for the reaction mentioned in Table 1, entry 30.[32,34]

3. Conclusions

In conclusion, a convenient and efficient protocol for the regioselective methylthiolation of various structurally diverse aryl halides, such as aryl iodides, aryl bromides and heterocyclic aryl bromides is demonstrated under fluoride free conditions. Several sensitive functional groups like NH_2, NMe_2, OH, CHO, CN, COOEt, acetal, OCH_2Ph, COPh, NO_2 etc. were tolerated to afford the respective aryl methyl thioethers in excellent yields. Extensive optimization studies unveiled different promoters that include amines, ammonium salts and metal acetates besides metal fluorides. Isotopic studies showed that the protocol can be successfully employed for the synthesis of deuterated aryl methyl thioethers in high purity. The mechanistic studies revealed that irrespective of the nature of promoters, the active catalyst in this process was found to be CuSMe, which was isolated and characterized by employing various techniques.

4. Experimental section

4.1. General remarks

All the chemicals were purchased from either Sigma–Aldrich or Alfa Aesar Company and are used as received. The Thin Layer Chromatography (TLC) was performed on Merck silica gel 60 F_{254} plates using diethyl ether and hexane as eluting agents. Purification of products was carried out by column chromatography using silica gel (200–400 mesh) and a mixture of ethyl acetate and hexane (or diethyl ether and *n*-pentane) as eluting agent. All products were characterized by ^1H and ^{13}C NMR, and mass spectrometry. The NMR spectra of samples were acquired on a Bruker Avance 300 MHz or Varian Unity Inova 500 MHz spectrometer using TMS as an internal standard in $CDCl_3$ or DMSO-d_6 as solvent. EIMS and ESI MS spectra were acquired on a Shimadzu QP 2010+GC–MS and Thermo LCQ fleet ion trap mass spectrometer (ESI MS), respectively. High resolution mass spectra were acquired using Exactive Orbitrap LC–MS, Thermo Scientific. Elemental analysis was carried out on an Elementar Vario-EL CHNS analyzer. Static Headspace GC–MS analysis was performed using 6890 NGC with 5973 inert MSD, Agilent Technologies. Infrared (IR) absorption data were acquired on a Thermo Nicolet Nexus 670 FT-IR spectrometer with DTGS KBr detector. XPS spectra were recorded on a Kratos AXIS 165 equipped with Mg Kα radiation (1253.6 eV) at 75 W apparatus using Mg Kα anode and a hemi spherical analyzer. The C 1s line at 284.6 eV was used as an internal standard for the correction of binding energies. The X-ray diffraction (XRD) patterns of intermediates were obtained on a Rigaku Miniflex X-ray diffractometer using Ni filtered Cu Kα radiation (λ=0.15406 nm), at a scan rate of 2° min^{-1}, with the beam voltage and beam current of 30 kV and 15 mA, respectively. ICP OES analysis was performed on a Thermo Intrepid XSP DUO instrument. TGA–MS was performed using 851e Mettler Toledo. Scanning electron micrograph (SEM EDAX) was acquired on an SEM Hitachi S520.

4.2. General procedure for methylthiolation of aryl iodides and aryl bromides listed in Table 2

An oven dried pressure tube was charged with aryl halide (0.5 mmol), CuI (10–25 mol %), anhydrous $Zn(OAc)_2$ (1.5–2 equiv) and anhydrous DMSO (1.6 mL). The tube was sealed with a Teflon screw cap and stirred at 135 °C for 24–36 h. The reaction mixture was then cooled to room temperature and stirred in 10 mL of diethyl ether for 5 min. It is filtered through a sintered funnel and the filtrate is washed with excess ice cold water and further extracted with diethyl ether (3×10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product, which was purified by column chromatography using 200–400 mesh silica gel and a mixture of diethyl ether and hexane (or pentane, for Table 2, entries 2, 8, 10, 14, 16 and 24) as eluents to afford the desired products in good yields.

4.2.1. (3-(Benzyloxy)phenyl)(methyl)sulfane(Table 2, entry 4). R_f=0.72 (1:9 ethyl acetate/hexane); Colourless liquid; IR (KBr): ν=2921, 1585, 1475, 1428, 1379, 1283, 1229, 1165, 1100, 1078, 1024, 855, 768, 738, 692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.54–7.28 (m, 5H), 7.24–7.15 (m, 1H), 6.96–6.81 (m, 2H), 6.79–6.70 (m, 1H), 5.03 (s, 2H), 2.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=159.04, 139.84, 136.74, 129.58, 128.53, 127.95, 127.44, 118.95, 112.94, 111.25, 69.93, 15.57. EIMS: *m/z* 230 $[M]^+$. Anal. Calcd for $C_{14}H_{14}OS$: C, 73.01; H, 6.13; S, 13.92. Found: C, 73.09; H, 6.17; S, 13.87.

4.2.2. 4-(4-(Methylthio)phenyl)pyrimidine (Table 2, entry 23). R_f=0.27 (3:7 ethyl acetate/hexane); Colourless solid; mp 124 °C; IR (KBr): ν=2917, 1576, 1532, 1490, 1460, 1388, 1313, 1260, 1172, 1091, 818, 769, 654, 467 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=9.24 (s, 1H), 8.74 (d, *J*=5.3 Hz, 1H), 8.03 (d, *J*=8.3 Hz, 2H), 7.71–7.65 (m, 1H), 7.35 (d, *J*=8.3 Hz, 2H), 2.54 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=163.15, 159.03, 157.32, 143.05, 132.69, 127.29, 125.96, 116.32, 15.05. ESI MS: *m/z* 203 $[M+H]^+$. HRMS (ESI): *m/z* calcd for $C_{11}H_{11}N_2S$ (M+H): 203.06375; found 203.06364.

Acknowledgements

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Supplementary data

Characterization data, ^1H and ^{13}C NMR spectra of all the compounds; GC–MS Headspace analysis, TGA, XPS, XRD, HRMS and FT-IR spectra are provided in the Supplementary data. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.07.039.

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14. These intermediates are formed in absence of 4-iodoanisole as well as in absence of CuI or both.
15. Low amount of deuterium incorporation in methylthiolation product for the reaction employing MeSSMe and DMSO-d_6 (Scheme 4) is assumed due to the thiolate–dimethyl disulfide interchange reaction (see Scheme S1 and S2 in Supplementary data for details). Similarly, the low yield obtained in this reaction is probably due to saturation of the coordination site of Zn (in $Zn(OAc)_2$) by excess MeSSMe. For thiolate–dimethyl disulfide interchange reaction, see reference: (a) Bach, R. D.; Dmitrenko, O.; Thorpe, C. *J. Org. Chem.* **2008**, *73*, 12–21; (b) Singh, R.; Whitesides, G. M. In *Supplement S: the Chemistry of Sulphur-containing Functional Groups*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: Chichester, UK, 1993; pp 633–658.
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18. The intermediate **2** (same case with intermediates **1**, **3** & **4**) remains initially as a precipitate in the reaction medium. This precipitate slowly disappears with the progress of reaction (if taken stoichiometrically), indicating the formation of a soluble copper salt (likely CuI). In addition, methylthiolation of 4-iodoanisole proceeded in toluene as well as in DMF with these intermediates in the absence of catalyst, additive and DMSO, albeit in poor yield.
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20. The reactions of O-activated DMSO are well known, such as in Moffatt oxidation and Swern oxidation. The final fate of DMSO in these reactions is reduction to MeSMe.
21. Zn^{2+} and Cu^{2+} are good Lewis acids. $Zn(OAc)_2$ is highly soluble in DMSO, whereas ZnF_2 is only slightly soluble in DMSO. The order of solubilities of acetates in DMSO is $Zn(OAc)_2$>$Cu(OAc)_2$~$Mn(OAc)_2$>$Ni(OAc)_2$>K(OAc). However; when compared to acetates, fluorides are more basic and nucleophilic.
22. The GC–MS and NMR analysis of the reaction mixture disclosed the formation of PhSPh, PhSSPh and PhSMe, and also the absence of methylthiolation product.
23. This study reveals that the role of promoter is indeed catalytic in nature. However, stoichiometric quantities of $Zn(OAc)_2$ were used to speed up the reaction process as well as to improve the product yields. For similar observations using acid promoters, see reference: Smythe, J. A. *J. Chem. Soc., Trans.* **1909**, 349–370.
24. This is analogous to Pummerer rearrangements. An important condition for this reaction is that, nucleophile addend and electrophilic initiator should not combine together before the initiation of reaction process. For reference; see: (a) Smith, L. H. S.; Coote, S. C.; Sneddon, H. F.; Procter, D. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 5832–5844; (b) Feldman, K. S. *Tetrahedron* **2006**, *62*, 5003–5034.
25. MeSH and formaldehyde were not detected in GC–MS analysis, partly due to their gaseous and highly reactive nature. CHNS analysis of intermediates **1**–**4** revealed the presence of slightly more amount of carbon and hydrogen than that was required for the exact composition of CuSMe, indicating the presence of small amount of residual matter like paraformaldehyde. Similarly, SEM EDAX and XPS analysis of these intermediates revealed the presence of oxygen (see Supplementary data).
26. The non-tolerance of iodoaniline substrate to methylthiolation under standard conditions may be either due to the reaction of aniline with formaldehyde or with HI (both are speculated to be intermediates, Scheme 5). However; in case of pyrrolidine, which is a comparatively stronger base than the anilines, and being abundant (4 equiv) in the reaction medium may suppress the reactive acidic intermediates resulting in the success of methylthiolation.
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