A novel one pot synthesis of benzyl sulfides: samarium-induced, benzyl bromide mediated reduction of alkyl thiocyanates and diaryl disulfides in methanol

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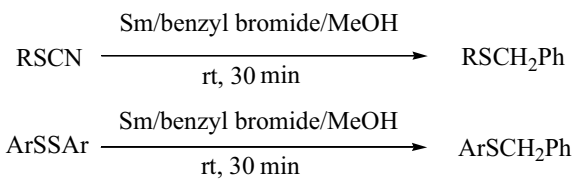
A convenient synthesis of benzyl sulfides by the treatment of alkyl thiocyanates or diaryl disulfides with metallic samarium and benzyl bromide in methanol has been developed.

Keywords: metallic samarium, benzyl bromide, benzyl sulfides, alkyl thiocyanates, diaryl disulfides

Recently, direct use of metallic samarium as a reducing agent in organic functional group interconversions has received much attention.[1] Although the application of SmI_2 in organic synthesis has been well documented,[2] its usage is limited because SmI_2 is expensive, sensitive to air and difficult to store. On the other hand, metallic samarium is stable in air and commercially available. Attractively, it is much cheaper than SmI_2 and many other catalysts, such as $Ru_3(CO)_{12}$, Yb and $LaNI_5H_6$. Furthermore, it exhibits strong reducing power (Sm^{3+}/Sm = –2.41V) and every samarium atom can donate three electrons in the reaction so that it is very economical. Such advantages prompted us to use the more convenient and cheaper metallic samarium as a reducing agent in organic functional group interconversions.

Usually, in order to be an effective reducing agent, samarium metal has to be activated. Many reagents such as I_2, HCl, NH_4Cl, TMSCl, *etc*. have been used as activators.[3] Recently, allyl bromide has also been reported as a samarium activator by Banik's group.[4] They demonstrated that in the Sm/Allyl bromide/MeOH system, reductive coupling of aromatic ketones was achieved in good yield. To the best of our knowledge the use of benzyl bromide to activate metallic samarium has not been reported. We therefore decided to investigate the reducing power of the Sm/benzyl bromide/MeOH system. Choosing alkyl thiocyanates and diaryl disulfides as the substrates, we found that this system also showed a good reducing power. We now report that in a one-pot protocol, we have successfully obtained benzyl sulfides in high yields by reducing alkyl thiocyanates and diaryl disulfides using a Sm/benzyl bromide/MeOH system (Scheme 1).

After a series of experiments, we found that treated with 3 equiv. of metallic samarium metal and 3 equiv. of benzyl bromide, alkyl thiocyanates were quickly converted into benzyl sulfides in good yields (Table 1, entries 1–4). When diaryl disulfides were treated with 5 equiv. of samarium metal and 5 equiv. of benzyl bromide or *p*-bromobenzyl bromide, corresponding benzyl sulfides were also obtained in high yields (entries 5–10). Surprisingly, when we made an attempt to treat alkyl thiocyanates with *p*-bromobenzyl bromide by this method, no benzylated products were detected (entry 11).



Scheme 1

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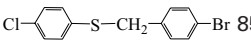
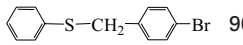
Table 1 Synthesis of benzyl sulfides

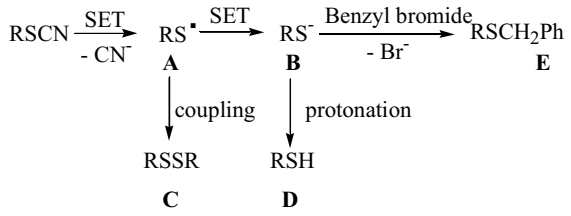
Entry	Substrate	Molar ratio (substrate: Sm: benzyl bromide)	Product	Yield/%[a]
1	$HO(CH_2)_6SCN$	1:3:3	$HO(CH_2)_6SCH_2Ph$	81%
2	$PhCH_2SCN$	1:3:3	$PhCH_2SCH_2Ph$	85%
3	*n*-$C_{12}H_{25}SCN$	1:3:3	*n*-$C_{12}H_{25}SCH_2Ph$	86%[b]
4	*n*-$C_{16}H_{33}SCN$	1:3:3	*n*-$C_{16}H_{33}SCH_2Ph$	88%
5	$(PhS)_2$	1:5:5	$PhSCH_2Ph$	90%
6	$(p\text{-}MePhS)_2$	1:5:5	*p*-$MePhSCH_2Ph$	90%
7	$(p\text{-}ClPhS)_2$	1:5:5	*p*-$ClPhSCH_2Ph$	93%
8	$(p\text{-}BrPhS)_2$	1:5:5	*p*-$BrPhSCH_2Ph$	95%
9	$(p\text{-}ClPhS)_2$	1:5:5[c]		85%
10	$(PhS)_2$	1:5:5[c]		90%
11	*n*-$C_{12}H_{25}SCN$	1:3:3[c]	–	–[d]
12	*n*-$C_{12}H_{25}SCN$	1:1:1	*n*-$C_{12}H_{25}SCH_2Ph$	5%[e]

[a]Isolated yield.
[b]^{1}H NMR analysis of the crude product was performed, the ratio of *n*-$C_{12}H_{25}SCH_2Ph$: *n*-$C_{12}H_{25}SH$: $(n\text{-}C_{12}H_{25}S)_2$ was 91: 2: 7.
[c]*p*-Bromobenzyl bromide was used to replace benzyl bromide.
[d]No benzylated product was found.
[e]Only part of *n*-$C_{12}H_{25}SCN$ was consumed, ^{1}H NMR analysis of the crude product was performed and the ratio of *n*-$C_{12}H_{25}SCH_2Ph$: *n*-$C_{12}H_{25}SH$: $(n\text{-}C_{12}H_{25}S)_2$ was 20: 5: 75, determined by ^{1}H NMR.

In these reactions, several functionalities such as OH, Cl, and Br remained intact (entries 1, 7–9).

In the process of exploring the role of benzyl bromide, we found that in the absence of benzyl bromide no reactions proceeded. When 1 equiv of benzyl bromide and 1 equiv of metallic samarium were used to mediate the reaction of *n*-$C_{12}H_{25}SCN$, only part of *n*-$C_{12}H_{25}SCN$ and metallic samarium was consumed. The yield of benzylated product was only 5%. ^{1}H NMR analysis of the crude product showed the ratio of *n*-$C_{12}H_{25}SCH_2Ph$: *n*-$C_{12}H_{25}SH$: $(n\text{-}C_{12}H_{25}S)_2$ to be 20: 5: 75 (entry 12). When 3 equiv. of benzyl bromide and 3 equiv. of metallic samarium were used in the reaction, the ratio of *n*-$C_{12}H_{25}SCH_2Ph$: *n*-$C_{12}H_{25}SH$: $(n\text{-}C_{12}H_{25}S)_2$ was 91: 2: 7 (entry 3) the proportion of the benzylated product being increased greatly and the yield of the wanted product was 86%. Based on these results, we considered that benzyl bromide might act as an activator of metallic samarium to mediate the reduction of alkyl thiocyanates to alkyl thiolates and alkyl disulfides.[5] In this process, benzyl bromide was partially consumed to activate the metallic samarium; the remaining benzyl bromide was captured by alkyl thiolate and hence gave benzylated product. Similarly, diaryl disulfides can also be reduced by activated samarium to aryl thiolates and benzylated by benzyl bromide.

The possible mechanism of the reaction is proposed in Scheme 2. It may involve a single-electron transfer (SET) process.



Scheme 2

A single-electron transfer to alkyl thiocyanate firstly gives radical A. The following, either self-coupling of radical A or further a single-electron transfer to radical A is feasible. As a result, a little of the disulfide C and a large amount of the alkyl thiolate B are formed. Meanwhile, alkyl thiolate B can be protonated to generate the alkyl thiol D or smoothly benzylated by benzyl bromide to provide product E.

We also tried several other protic solvents as reaction media in place of MeOH. We found that using EtOH or *i*-PrOH as reaction medium, even if the mixture was stirred overnight, no reaction occurred and only starting material was recovered (Table 2, entries 2, 3). In a previous report, water as a protic solvent efficaciously promoted the reductivity of SmI_2.[6] However, Sm/benzyl bromide in the medium containing water was inert (Table 2, entries 4, 5). Though the reason has not been clarified, our experiments indicate that only MeOH is an effective protic solvent in this system.

In summary, a one-pot synthetic method for benzyl sulfides by the treatment of alkyl thiocyanates or diaryl disulfides with metallic samarium and benzyl bromide in methanol has been developed. The notable advantages of this method are good yields, simple operation and neutral reaction conditions.

Experimental

IR spectra were measured with a Nicolet Avatar 360 FT-IR spectrometer. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian unity + 500 spectrometer with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. Melting points were measured using Yanaco MP-500 melting point apparatus and are uncorrected.

General procedure for the synthesis of benzyl sulfides

The general procedure is as follows: At room temperature benzyl bromide (1.5 mmol for alkyl thiocyanate or 2.5 mmol for diaryl disulfide) or *p*-bromobenzyl bromide (2.5 mmol for diaryl disulfide) was added to a mixture of samarium metal (1.5 mmol for alkyl thiocyanate or 2.5 mmol for diaryl disulfide) and substrate (0.5 mmol) under nitrogen. Subsequently, MeOH (8 ml) was added quickly from a syringe. An exothermic reaction occurred when MeOH was added. After 30 min, monitoring by TLC indicated that the starting material had been completely consumed. The reaction mixture was diluted with 10 ml ethyl acetate, and was filtered through a small plug of silica gel. The filtered solution was concentrated. In some cases, the ^{1}H NMR analysis of the crude products was performed. All crude products were purified by flash chromatography to yield the desired products. All products (see Table 1) were known compounds and their ^{1}H NMR and IR spectroscopic data are given below:

Table 2 Reactions of $C_{12}H_{25}SCN$ with samarium metal and benzyl bromide in various protic solvents

Entry	Reaction medium	Reaction time	Yield of n-$C_{12}H_{25}SCH_2Ph$
1	MeOH	30 min	86%[a]
2	EtOH	24 h	—[b]
3	*i*-PrOH	24 h	—[b]
4	THF/H_2O (10/1)	24 h	—[b]
5	MeOH/H_2O (10/1)	24 h	—[b]

[a]Isolated yield.
[b]No reaction, only starting material was recovered.

Entry 1. 6-(benzylthio)hexan-1-ol: Colourless oil (lit.[7]). Isolated yield: 81%. IR(film) υ: 3364, 3026, 1598, 1500 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.23–1.63 (m, 8H), 2.42 (t, *J* = 7.5 Hz,2H), 3.63 (t, *J* = 7.0 Hz, 2H), 3.67 (s, 2H), 7.23–7.38 (m, 5H).

Entry 2. dibenzylsulfane: White solid. Isolated yield: 85%. m.p. 50–51°C (lit.[8] 50–51°C); IR (film) υ: 3030, 1600, 1485 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.60 (s, 4H), 7.20–7.38 (m, 10H).

Entry 3 and 12. benzyl(dodecyl)sulfane: Colourless oil (lit.[9]). Isolated yield: 86%. IR (film)υ: 3022, 1600, 1494 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.5 Hz, 3H), 1.10–1.42 (m, 18H), 1.50–1.60 (m, 2H), 2.40 (t, *J* = 7.5, 2H), 3.72 (s, 2H), 7.16–7.40 (m, 5H).

Entry 4. benzyl(hexadecyl)sulfane: White solid. Isolated yield: 88%. m.p. 30–31°C (lit.[10] 31–32°C); IR (film)υ: 3030, 1602, 1496 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.5 Hz, 3H), 1.19–1.38 (m, 26H), 1.52–1.60 (m, 2H), 2.41 (t, *J* = 7.0 Hz, 2H), 3.71 (s, 2H), 7.19–7.33 (m, 5H).

Entry 5. benzyl(phenyl)sulfane: White solid. Isolated yield: 90%. m.p. 43–44°C (lit.[11] 44–45°C); IR (film)υ: 3026, 1598, 1489 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.14 (s, 2H), 7.17–7.45 (m, 10H).

Entry 6. benzyl(p-tolyl)sulfane: White solid. Isolated yield: 90%. m.p. 44–45°C (lit.[12] 43–46°C); IR (film)υ: 3030, 1600, 1496 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.38 (s, 3H), 4.10 (s, 2H), 7.00–7.49 (m, 9H).

Entry 7. benzyl(4-chlorophenyl)sulfane: White solid. Isolated yield: 93%. m.p. 51–53°C (lit.[13] 52–53°C); IR (film)υ: 3028, 1602, 1493 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.09 (s, 2H), 7.00–7.50 (m, 9H).

Entry 8. benzyl(4-bromophenyl)sulfane: White solid. Isolated yield: 95%. m.p. 63–65°C (lit.[14] 63–65°C); IR (film)υ: 3024, 1586, 1496 cm^{-1}; ^{1}H NMR (500 MHz,$CDCl_3$): δ = 4.09 (s, 2H), 7.00–7.60 (m, 9H).

Entry 9. (4-bromobenzyl)(4-chlorophenyl)sulfane: White solid. Isolated yield: 85%. m.p. 82–84°C (lit.[15] 83–85°C); IR(film)υ: 3034, 1594, 1485 cm^{-1}; ^{1}H NMR (500 MHz,$CDCl_3$): δ = 4.00 (s, 2H), 7.00–7.60 (m, 8H).

Entry 10. (4-bromobenzyl)(phenyl)sulfane: White solid. Isolated yield: 90%. m.p. 78–79°C (lit.[16] 78–79°C); IR (film)υ: 3030, 586, 1486 cm^{-1}; ^{1}H NMR (500 MHz,$CDCl_3$): δ = 4.04 (s, 2H), 7.05–7.44 (m, 9H).

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