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Mild and efficient methods for the conversion of benzylic bromides to benzylic thiols

Chien-Chung Han* and R. Balakumar

Department of Chemistry, National Tsing Hua University, Hsinchu, Taiwan, ROC

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Abstract—Very mild and efficient methods are established for the conversion of the benzylic bromides at room temperature to their corresponding benzylic thiols with high yields (94–99%) in 1 h under N_2.

A plethora of reports have appeared on the potential applications of thiol functionality in various scientific disciplines like medicinal chemistry,[1] self-assembled monolayers,[2] nanoparticles,[3] and conducting polymers.[4] In our own research on polyaniline (Pani), thiols have played a major role in increasing the utility of Pani which was hampered by its poor solubility. By functionalizing the polyaniline backbone with alkanethiols, its solution processibility can be greatly improved without suffering the adverse effect on conductivity. Thus we have synthesized and reported various alkylthio-substituted polyanilines which have good solution processibility and high conductivity.[5] As the conductivity of such functionalized polyanilines is encouraging, we decided to functionalize polyaniline with some benzylic thiols.

A survey of the existing literature indicated that thiols have been synthesized mainly from alkyl halides and sometimes from a variety of other starting materials like disulfides (via reduction),[6] alkenes (via anti-Markovnikov addition of thiolacetic acid, followed by deacetylation with strong base),[7] alcohols (via refluxing with HBr and thiourea, followed by refluxing with NaOH),[8] and less commonly from amines (via a rather complicated series of reactions to yield *N*-methylthiobenzothiazonium salts, followed by refluxing with hydrazine).[9]

Of all these methods, conversion of alkyl halides to thiols seems to be very attractive due to the ready availability of alkyl halides and the ease of the reaction. The most common reagent used for the conversion of alkyl halides to thiols is the potassium thioacetate. The reaction proceeds in two steps with the initial substitution of halide by thioacetate group to form the thioesters followed by the basic or acidic deacetylation of the thioesters. The yield of the thioester is generally in between 70% and 90%. The time required for the displacement of the halide by thioacetate varies vastly, ranging from 3 to 96 h.[10] Benzylic halides required overnight stirring at room temperature to yield the corresponding thioester.[11]

Regarding the deacetylation reaction, we were surprised to find that very harsh conditions were in general employed, like using rather strong bases (e.g., NaOH, KOH, NaOMe) at reflux temperatures and in some cases, the yield of the thiol was actually very low.[2,10,12,13] Alternatively, thiourea has been employed to convert alkyl and benzylic halides to the corresponding thiols in one pot reaction fashion via the basic hydrolysis of the isothiouronium salt with a reasonably good yield (ca. 60–80%). The main disadvantage of this method is the formation of an appreciable amount of disulfides byproduct and its need for long reaction times under strong basic conditions, and therefore is not suitable for base-sensitive compounds. There were only a few cases wherein the conversion from alkyl halide to alkanethiols can be carried out by a single step reaction, but they all required the use of special reagents. For example, 1-(2-hydroxyethyl)-4,6-diphenyl-pyridine-2-thione converted alkyl halides to thiols in a one-step reaction with fairly good yields (60–89%) in dry benzene at room temperature; it also converted benzylic halides

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* Corresponding author. Tel.: +886 3 5724998; fax: +886 3 5711082; e-mail: cchan@mx.nthu.edu.tw

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to their corresponding thiols in 80% yield over a period of 20 h.[14] Alternatively, bis(triaryl/trialkyl tin)sulfides in combination with 2 equiv tetrabutylammonium fluoride in a mixed solvent of acetonitrile/water converted alkyl halides to thiols at 20 °C with 59–82% yield (in 20–40 h).[15] Sulfurated sodium borohydride was also reported to produce 69% benzylic thiols from benzyl bromide under reflux for 16 h.[16] However, in these cases, special reagents have to be prepared and long reaction times are required.

Though the literature has reported some interesting schemes to obtain thiols, we felt that a simpler procedure in which thiols can be obtained by a single step under even milder conditions is still needed. As the two steps, viz., the formation of thioesters (from benzylic halides and thiolacetic acid) and their deacetylation, both require a base, we felt that the appropriate manipulation of base/solvent combinations may help us achieve the single step conversion of benzylic halides to thiols. Therefore, we carried out some systematic studies in achieving our target and the results are presented here. Initially we carried out our study with benzyl bromide in the presence of thiolacetic acid together with some mild bases and different solvents. We obtained some interesting results which are summarized in Table 1.

The results in Table 1 seem to indicate that the actual reaction outcomes depended highly on a delicate balance of base/solvent combination. For example, when 2.2 equiv of K_2CO_3 was used as the base in MeOH, the reaction (entry 1) yielded dibenzylsulfide as the major product (87%) and benzyl thiol as the minor product (13%). While the same base in THF and acetone (entries 2 and 3) gave only thioester even after heating at 50 °C for 15 h. On the other hand, the use of a weaker base, like $NaHCO_3$ (2.2 equiv) (entry 4), actually resulted in a slightly higher amount of the thiol (29%) plus the non-hydrolyzed thioester (66%) instead of the sulfide. Most interestingly, when a lesser amount of K_2CO_3 (1.2 equiv; entry 5) was used in combination with heating at 50 °C for 15 h, the reaction seemed to proceed very well, yielding 92% of thiol without the contamination of the sulfide. Because of these interesting preliminary findings, we decided to explore for the ideal solvent/base combination by studying the two reaction steps separately.

A wide variety of bases were tried in different solvents to study the formation of thioester and the results are presented in Table 2. The results (entries 1, 5, 6, and 8) indicate that, in MeOH at rt, a mild base (like K_2CO_3, $NaHCO_3$, and Et_3N; 1.2 equiv) was effective enough to promote the S_N2 displacement of the halide by thiolacetic acid within 0.5 h. Even a base as weak as pyridine can work fairly well at rt, if a higher amount of base (2.2 equiv) and a longer reaction time (4 h) was used (entry 8 vs 7). With K_2CO_3 as the base, the reaction proceeded much rapidly in relatively polar solvents like methanol, THF, and acetone (entries 1, 3, 4) than the less polar solvent like chloroform (entry 9). This may be due to the poor solubility of K_2CO_3 in chloroform, because an even weaker but better soluble base like Et_3N gives good yields of thioester both in methanol (entry 6) and in $CHCl_3$ (entry 10). The results in Table 2 suggest that a mild base in a polar solvent may be the ideal combination for the synthesis of thioester from benzyl bromide.

Having known the ideal conditions that are necessary for the formation of thioester, we then proceeded to

Table 2. Reaction conditions and products for the synthesis of benzyl thioacetate from benzyl bromide under nitrogen atmosphere

$$\text{BzBr} \xrightarrow[\text{Base, Solvent}]{\text{HSAc (1.2 equiv.)}} \text{BzSH}$$

Entry	Solvent	Base	Time (h)	Yield (%) BzBr/	BzSAc
1	MeOH	K_2CO_3	0.5	—	96
2	MeOH	—	0.5	100	—
3	THF	K_2CO_3	0.5	—	94
4	Acetone	K_2CO_3	0.5	—	98
5	MeOH	$NaHCO_3$	0.5	—	98
6	MeOH	Et_3N	0.5	—	97
7	MeOH	Pyridine	0.5	53	46
8	MeOH	Pyridine[a]	4	25	75
9	$CHCl_3$	K_2CO_3	24	76	23
10	$CHCl_3$	Et_3N	0.5	4	96

[a] 2.2 equiv of pyridine was used.

Table 1. Reaction conditions and products for the attempted synthesis of benzyl thiol directly from benzyl bromide under nitrogen atmosphere

$$\text{BzBr} \xrightarrow[\text{Base (1.2 equiv.), Solvent}]{\text{HSAc (1.2 equiv.)}} \text{BzSAc}$$
$$20\ ^\circ\text{C}$$

No.	Solvent/base (equiv)	T/t (°C/h)	Yield (%) RSAc/RSH/RSSR/RSR			
1	MeOH/K_2CO_3 (2.2)	20/0.5	—	13	—	87
2[a]	THF/K_2CO_3 (2.2)	50/15	98	—	—	—
3[a]	Acetone/K_2CO_3 (2.2)	50/15	97	—	—	—
4	MeOH/$NaHCO_3$ (2.2)	20/15	66	29	5	—
5[a]	MeOH/K_2CO_3 (1.2)	50/15	—	92	7	—

[a] After the base was added and stirred at rt for 0.5 h, the reaction mixture was then warmed up to 50 °C.

Table 3. Reaction conditions and products for the conversion of benzyl thioacetate to thiol at 20 °C under nitrogen atmosphere

$$\mathrm{BzSAc} \xrightarrow[\text{20 °C}]{\text{Base (1.2 equiv.), Solvent}} \mathrm{BzSH}$$

Entry	Base	Solvent	Time (h)	Yield (%) BzSAc/BzSH/BzSSBz		
1	K_2CO_3	MeOH	0.5	—	96	—
2	$NaHCO_3$	MeOH	1	65	28	5
3	$NaHCO_3$	MeOH	15	—	83	16
4	Et_3N	MeOH	0.5	100	—	—
5	Et_3N	MeOH	15	23	69	8
6	Pyridine	MeOH	0.5	100	—	—
7	Pyridine	MeOH	15	21	59	11
8	K_2CO_3	THF	15	100	—	—
9	K_2CO_3	Acetone	15	100	—	—
10	K_2CO_3	CH_3NO_2	15	100	—	—
11	K_2CO_3	$CHCl_3$	15	100	—	—
12	K_2CO_3	CH_2Cl_2	15	100	—	—
13	K_2CO_3	Et_2O	15	100	—	—

search for the suitable base/solvent combination for the second step. Accordingly, with benzyl thioacetate as the substrate, the different combinations of bases and solvents were tried out. The results are presented in Table 3.

The results in Table 3 indicate that in MeOH, K_2CO_3 (1.2 equiv) can rapidly convert thioester to thiols with high yield (96%) in as short as 0.5 h (entry 1). Weaker bases such as $NaHCO_3$ (entry 3), Et_3N (entry 5), and pyridine (entry 7) can also give good or fair yields of thiol, but they require much longer reaction time (15 h). With regard to the solvent, it is interesting to note that the reaction is facilitated only in methanol; whereas in all other solvents (entries 8–13) only the starting material was recovered.

Based on our systematic studies, we felt that K_2CO_3/methanol is the most ideal combination of reaction condition to achieve a single step conversion of benzylic bromides to thiols. To avoid the formation of sulfide (as we have encountered in entry 1 of Table 1), we decided to add the base in a portionwise fashion as illustrated in method A of Table 4 (entries 1–4) for a variety of bromide substrates. Sure enough, we are able to synthesize thiols directly from benzylic bromides with very high yields (94–99%) at rt within 1 h.

In addition, we envisaged that method B may also work well for a single step conversion of the benzylic bromides to thiols (entries 5–8). We felt the fact that the solvents other than methanol do not interfere in the deacetylation process can be used to our advantage. For example, since polar solvent like THF works quite well for the first step, it can be used as the solvent for the formation of thioester by adding all the required base K_2CO_3 (2.2 equiv) in one portion at the very beginning. After the reaction mixture was stirred for a sufficient time (~0.5 h for entries 5–8), an equal volume of methanol can then be added as a cosolvent (or as a promoter) to initiate the deacetylation step. In this way, we felt we can avoid the formation of sulfide byproduct. The results in entries 5–8 of Table 4 show that similar high yields of thiols can also be obtained using this approach. When this reaction strategy (method B) was applied to other solvent like acetone, the reactions also worked well except that longer reaction times were required. The fact that the reaction proceeded slowly in acetone than in THF is probably due to polarity differences in their corresponding resultant co-solvent systems.

Table 4. Reaction conditions and products for a single step conversion of benzylic bromides to thiols in 1 h at 20 °C using K_2CO_3 as base under nitrogen atmosphere

$$\mathrm{BzSH} \overset{\text{Method A}}{\xleftarrow[\substack{\text{(ii) } K_2CO_3 \text{ (1.2 equiv.)} \\ \text{0.5 h / } N_2}]{\substack{\text{(i) HSAc (1.2 equiv.)} \\ K_2CO_3 \text{ (1.2 equiv.)} \\ \text{MeOH / 0.5 h / } N_2}}} \mathrm{BzBr} \overset{\text{Method B}}{\xrightarrow[\text{(ii) MeOH / 0.5 h / } N_2]{\substack{\text{(i) HSAc (1.2 equiv.)} \\ K_2CO_3 \text{ (2.2 equiv.)} \\ \text{THF / 0.5 h / } N_2}}} \mathrm{BzSH}$$

Entry[a,b]	Substrate	Solvent	Yield (%) BzSH
1	Benzyl bromide	MeOH	96
2	2-(Bromomethyl)biphenyl	MeOH	98
3	4-Bromobenzyl bromide	MeOH	99
4	1,4-Bis(bromomethyl)benzene	MeOH	97
5	Benzyl bromide	THF	94
6	2-(Bromomethyl)biphenyl	THF	99
7	4-Bromobenzyl bromide	THF	97
8	1,4-Bis(bromomethyl)benzene	THF	94

[a] Entries 1–4 used method A and entries 5–8 used method B. In method A, the base was added in two portions within the first 0.5 h; while in method B, after the base was added as one portion and stirred for 0.5 h, an equal volume of MeOH was added to the reaction solution.

[b] In entries 4 and 8, the base equiv is proportional to the number of bromo groups and the product is a dithiol.

In conclusion, efficient and very mild reaction methods, for the synthesis of benzylic thiols directly from benzylic bromide using rather mild bases at rt within 1 h with very high yields, have been successfully established. Our results indicate that a polar solvent like methanol and THF, and a milder base like K_2CO_3 have been proved to be the ideal solvent/base combination to achieve a high yield of thiols from benzylic bromides in a single step. The two proposed methods can be used, depending on the reactivity natures of the employed substrates. For example, if the first step (i.e., formation of thioester) is fast enough than the second step (i.e., deacetylation), then method A (K_2CO_3/methanol) can be used. Alternatively, when the first step is relatively slower, then method B should be used. In method B, the use of an organic solvent other than MeOH is served as an effective strategy to suppress the deacetylation at the initial stage to prevent the premature formation of the thiols, which would otherwise be converted into the corresponding sulfides in the presence of a large excess amount of base and unreacted benzylic bromides. Certainly, method B is particularly suitable for those benzylic halides having relatively poorer solubility in MeOH. A detailed study is under progress to apply these reaction methods to other alkyl halides.

All the products are unambiguously characterized using ^{1}H and ^{13}C NMR and HRMS. The typical experimental methods are described as follows. *Method A*: 4-bromobenzyl bromide (5 mmol) is dissolved in 15 mL of methanol in a two neck RB flask fitted with a solid addition flask containing 6 mmol of K_2CO_3. Another 6 mmol of K_2CO_3 is first added to the reaction mixture and stirred for 0.5 h under a steady stream of nitrogen. Then, the second portion of K_2CO_3 from the solid additional flask was added to the reaction mixture. After another 0.5 h, ~1–2 mL of dil HCl solution was added to neutralize the reaction solution (to pH ~ 6), which was then extracted with 2 × 20 mL of $CHCl_3$. The chloroform layer was washed with water, dried over anhydrous $MgSO_4$, and the solvent removed under reduced pressure to yield 99% of (4-bromophenyl)methanethiol. *Method B*: 4-bromobenzyl bromide (5 mmol) is dissolved in 15 mL of THF in a two neck RB flask. To this solution was added 12 mmol of K_2CO_3 and stirred for 0.5 h under a steady stream of nitrogen. Then 15 mL of methanol was injected. After stirring for another 0.5 h, the reaction mixture was then neutralized by adding ~1–2 mL of dil HCl. After removing the solvent under reduced pressure, the residue is then dissolved in 20 mL of $CHCl_3$ and washed with water. The $CHCl_3$ layer was dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure to yield 99% of (4-bromophenyl)methanethiol.

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