TAPC-Catalyzed Synthesis of Thioethers from Thiols and Alcohols

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Abstract: A new synthesis of thioethers is described. The reaction of aryl alcohols with aryl, heteroaryl, and alkyl thiols in the presence of TAPC as an efficient catalyst affords good to excellent yields of thioethers. Furthermore, the reaction proceeds under metal-free and solvent-free conditions thus represents an interesting complement to known methods for thioether synthesis. A plausible mechanism for this reaction is delineated.

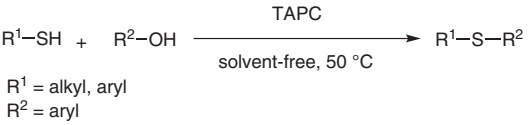
Key words: thioethers, S-alkylation, thiols, alcohols, solvent-free conditions

Thioethers are a useful class of organic compounds and find versatile applications as key reagents in organic synthesis, bioorganic, heterocyclic, and medicinal chemistry.[1] In recognition of their importance, a variety of methods is available for the preparation of thioethers, such as deoxygenation of sulfoxides,[2,3] addition of thiols to carbonyl compounds followed by in situ reduction of the generated intermediate thionium ion,[4] anti-Markovnikov addition of arene- and alkanethiols to alkenes,[5,6] Mitsunobu-type reactions,[7–11] metal-mediated cross-coupling processes,[12–14] metal-catalyzed hydrothiolation of alkynes,[15] thia-Michael addition reaction,[16] and S-alkylation of thiols with alcohols.[17] However, the classical method of choice is the condensation of a metal alkyl or aryl thiolate with an alkyl halide in the presence of a strong base.[18]

Although moderate to high yields can be obtained, often harsh reaction conditions or long reaction times are needed in these methods. In addition, thioalkylation is usually accomplished using alkyl halides which are toxic, dangerous, carcinogenic, and nonselective.[19,20]

1,3,5-Triazo-2,4,6-triphosphorine-2,2,4,4,6,6-chloride (TAPC) has been widely used in organic reactions;[21] however, it has not been studied as a catalyst in the synthesis of thioethers through S-alkylation of thiols with alcohols until now.

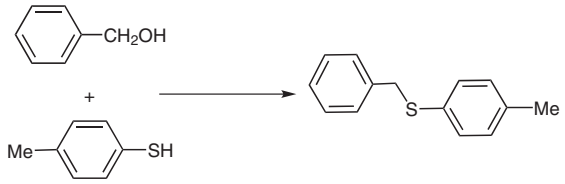
In continuation of our interest in exploring new methods in organic transformations,[22] we report that TAPC allows the efficient preparation of thioethers by the reaction of thiols with alcohols under solvent-free conditions at 50 °C (Scheme 1).



Scheme 1 Thioethers from alcohols and thiols

In order to optimize the reaction conditions, condensation of benzyl alcohol with 4-methylthiophenol was studied as a model reaction in the presence of TAPC. We found that, using benzyl alcohol (1 mmol), 4-methylthiophenol (1 mmol), and TAPC (0.1 mmol) in the absence of solvent, the reaction proceeded very cleanly at 50 °C, and the corresponding thioether was obtained in 93% yield (Table 1, entry 5). An increase in the reaction temperature and time did not improve the yields significantly.

Table 1 Effect of Increasing Amount of TAPC on S-Alkylation of 4-Methylthiophenol with Benzyl Alcohol[a]



Entry	TAPC (mmol)	Temp (°C)	Yield (%)[b]
1	0.05	50	50
2	0.07	50	70
3	0.09	50	85
4	0.1	25	60
5	0.1	50	93

[a] Reaction conditions: 4-methylthiophenol (1 mmol), benzyl alcohol (1 mmol), 2 min, solvent-free conditions, 50 °C.
[b] Isolated yield.

The scope of the procedure was assessed with a panel of representative thiols, and the results are summarized in Table 2. The present procedure is quite general as a wide range of thiols such as aromatic, aliphatic, cyclic, and heterocyclic thiols can be reacted easily with cinnamyl alcohol and electronically diverse benzyl alcohols under mild conditions. We noted that electronic factors play a role in these reactions. Aromatic alcohols substituted with electron-donating groups (Table 2, entry 10) reacted faster than those substituted with electron-withdrawing groups

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(Table 2, entry 12) whereas in aromatic thiols moderate electron-donating and electron-withdrawing groups, represented by 4-methoxythiophenol (Table 2, entry 3) and 4-fluorothiophenol (Table 2, entry 4), respectively, had relatively minor influence on the outcome of the condensation and gave rise to the corresponding thioethers in excellent yields.

Table 2 Synthesis of Thioethers from Thiols and Alcohols Using TAPC[a]

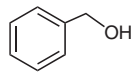
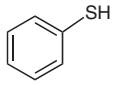
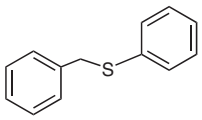
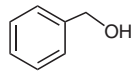
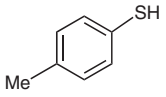
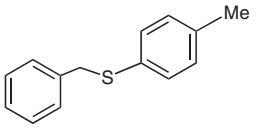
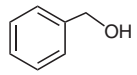
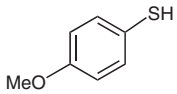
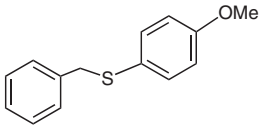
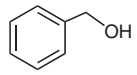
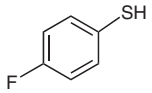
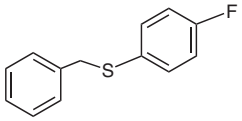
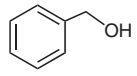
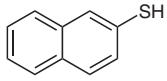
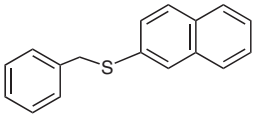
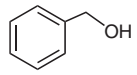
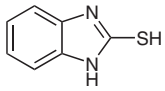
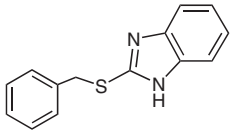
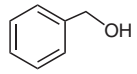
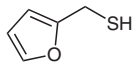
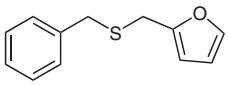
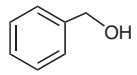
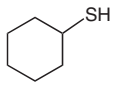
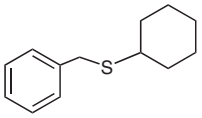
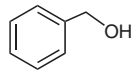
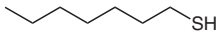
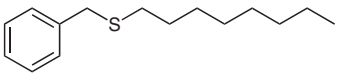
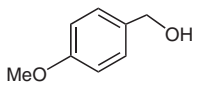
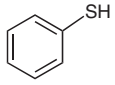
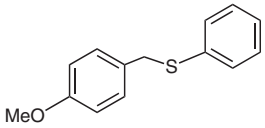
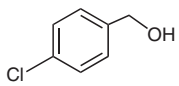
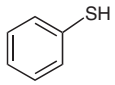
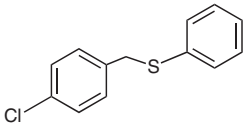
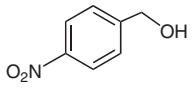
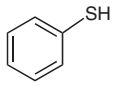
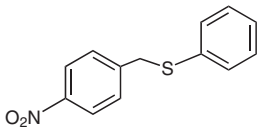
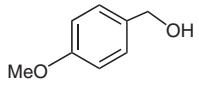
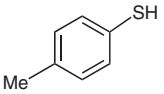
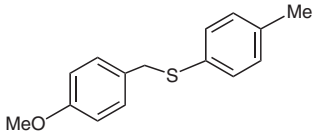
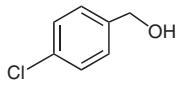
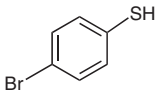
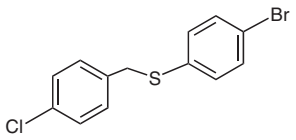
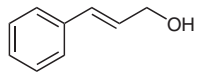
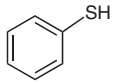
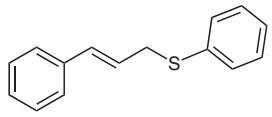
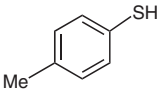
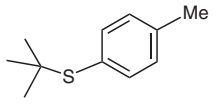
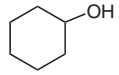
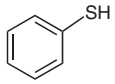
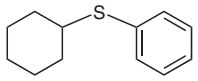
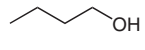
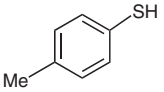
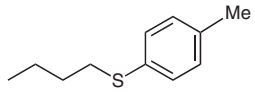
Entry	Alcohol	Thiol	Thioether	Time (min)	Yield (%)[b]	Mp (°C)
1				2	92	46[22r]
2				2	93	44–45[23]
3				3	97	47–49[23]
4				5	95	32–33[24]
5				3	91	89–90[25]
6				4	96	184–185[22r]
7				6	93	oil[22r]
8				8	98	oil[26]
9				10	95	oil[17]
10				4	98	86[23]
11				3	91	77–78[24]

Table 2 Synthesis of Thioethers from Thiols and Alcohols Using TAPC[a] (continued)

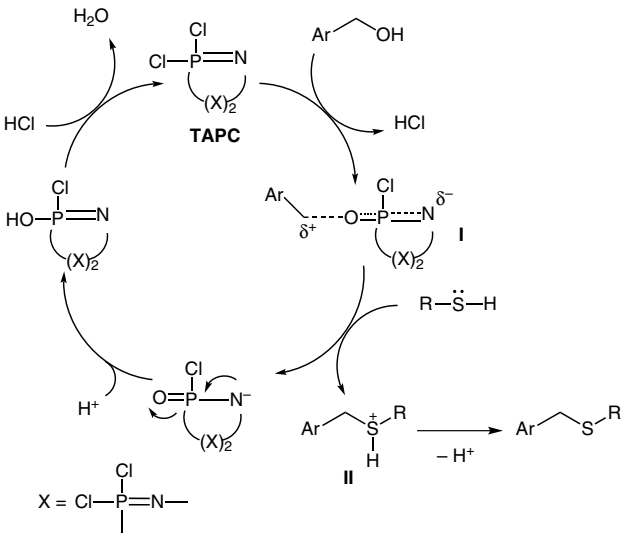
R^1–SH + R^2–OH ⟶ R^1–S–R^2

Entry	Alcohol	Thiol	Thioether	Time (min)	Yield (%)[b]	Mp (°C)
12				60	50	72–74[23]
13				3	96	66[23]
14				3	97	87–89[24]
15				4	92	oil[27]
16				70	0	–
17				60	0	–
18				60	0	–

[a] The purified products were characterized by mp and ^{1}H NMR spectroscopy.
[b] Yields refer to pure isolated products.

Heterocyclic thiols such as 2-mercaptobenzimidazole (Table 2, entry 6) and (furan-2-yl)methanethiol (Table 2, entry 7) worked well without the formation of any side products. Furthermore, cyclohexanethiol (Table 2, entry 8) and 1-octanethiol (Table 2, entry 9), aliphatic thiols, afforded the thioethers in excellent yields. Nevertheless, this protocol has its limitations. Aliphatic alcohols do not react with thiols in the presence of this catalyst and remain intact after the typical reaction times (Table 2, entries 16–18).

The exact mechanism of the reaction is not clear; generation of a classical carbocation is unlikely in these reactions because the S-alkylation of thiophenol with 4-methoxybenzyl alcohol in the presence of mesitylene was not accompanied by a byproduct. The low yield and the rather slow rate of the reaction including 4-nitrobenzyl alcohol (Table 2, entry 12) is an indication of the generation of an unstable partially positively charged intermediate. By considering these facts, the probable mechanism of the reaction is shown in Scheme 2. The nucleophilic attack of aromatic alcohol on TAPC leads to the intermediate **I** in which benzylic carbon is more electrophilic. Subsequently, the nucleophilic attack of thiol derivative on this intermediate produces the intermediate **II** followed by the exit of hydrogen ion to yield the corresponding thioether. Fur-



Scheme 2 Plausible mechanistic pathway

ther studies to establish the mechanistic pathway for the present reaction are currently in progress.

In conclusion, we have described a new application of TAPC for the easy and efficient synthesis of different thioethers by the reaction of aliphatic and aromatic thiols with cinnamyl alcohol and electronically diverse benzyl alcohols under solvent-free conditions. The method is not suitable for the preparation of thioethers from aliphatic alcohols. We believe that the use of TAPC as a catalyst for the present reaction is advantageous in many ways and will open up several new possibilities for its further use in developing many metal-free environmentally friendly and cost-effective methodologies in organic synthesis.

Alcohols and thiols are commercial products (Merck chemical company) and were used without further purification. TAPC was prepared according to reported procedure.[28]

Melting points were determined in a capillary tube and are not corrected. ^{1}H NMR spectra were recorded on a Bruker-200 spectrometer using TMS as internal standard.

General Procedure for the Preparation of Thioethers

To the mixture of alcohol (1 mmol) and TAPC (0.1 mmol, 0.035 g), thiol (1 mmol) was added at 50 °C with continuous stirring for the appropriate reaction time as indicated in Table 2. The progress of the reaction was monitored by TLC. After the completion of the reaction, H_2O (10 mL) was added to the reaction mixture. The residue was then extracted with EtOAc (4 × 5 mL), and the combined extracts were dried ($MgSO_4$). The filtrate was evaporated, and the corresponding thioether was obtained as the only product. The identity of the products was confirmed by comparing their physical and spectral data with the known compounds. Spectral and physical data for selected compounds follow.

Benzyl(4-methoxyphenyl)sulfane (Table 2, Entry 3)

Mp 47–49 °C (lit.[23] mp 48–49 °C).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.83 (s, 3 H), 4.12 (s, 2 H), 6.84–6.88 (m, 2 H), 7.21–7.36 (m, 6 H).

2-[(Phenylmethyl)thio]naphthalene (Table 2, Entry 5)

Mp 89–90 °C (lit.[25] mp 90–90.5 °C).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.31 (s, 2 H), 7.24–7.56 (m, 7 H), 7.79–8.08 (m, 5 H).

2-[(Benzylthio)-1*H*-benzo[*d*]imidazole (Table 2, Entry 6)

Mp 184–185 °C (lit.[22r] mp 184–185 °C).

^{1}H NMR (200 MHz, DMSO): δ = 4.59 (s, 2 H), 7.10–7.16 (m, 2 H), 7.25–7.36 (m, 3 H), 7.45–7.49 (m, 4 H).

2-[(Benzylthio)methyl]furan (Table 2, Entry 7)

Oil (lit.[22r] oil).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.70 (s, 2 H), 3.80 (s, 2 H), 6.27 (d, *J* = 3.2 Hz, 1 H), 6.43 (d, *J* = 3.2 Hz, 1 H), 7.37–7.50 (m, 6 H).

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References and Notes

(1) Cremlyn, R. J. *An Introduction to Organosulfur Chemistry*; Wiley: Chichester, **1996**.
(2) (a) Madesclaire, M. *Tetrahedron* **1988**, *44*, 6537. (b) Firouzabadi, H.; Iranpoor, N.; Jafarpour, M. *J. Sulfur Chem.* **2005**, *26*, 313.
(3) Nicolaou, K. C.; Koumbis, A. E.; Snyder, S. A.; Simonsen, K. B. *Angew. Chem. Int. Ed.* **2000**, *39*, 2529.
(4) Procter, D. J.; Archer, N. J.; Needham, R. A.; Bell, D.; Marchington, A. P.; Rayner, C. M. *Tetrahedron* **1999**, *55*, 9611.
(5) Kumar, P.; Pandey, P. K.; Hegde, V. R. *Synlett* **1999**, 1921.
(6) Chelucci, G.; Culeddu, N.; Saba, A.; Valenti, R. *Tetrahedron: Asymmetry* **1999**, *10*, 3537.
(7) Falck, J. R.; Lai, J.-Y.; Cho, S.-D.; Yu, J. *Tetrahedron Lett.* **1999**, *40*, 2903.
(8) Garofalo, A.; Campiani, G.; Fiorini, I.; Nacci, V. *Tetrahedron* **1999**, *55*, 1479.
(9) Shibata, K.; Yamaga, H.; Mitsunobu, O. *Heterocycles* **1999**, *50*, 947.
(10) Palomo, C.; Oiarbide, M.; Lopez, R.; Gomez-Bengoa, E. *Tetrahedron Lett.* **2000**, *41*, 1283.
(11) Zaragoza, F. *Tetrahedron* **2001**, *57*, 5451.
(12) (a) Herradura, P. S.; Pendola, K. A.; Guy, R. K. *Org. Lett.* **2000**, *2*, 2019. (b) Firouzabadi, H.; Iranpoor Gholinejad, M. *Adv. Synth. Catal.* **2010**, *352*, 119.
(13) Wendeborn, S.; De Mesmaeker, A.; Brill, W. K.-D.; Berteina, S. *Acc. Chem. Res.* **2000**, *33*, 215.
(14) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2002**, *4*, 4309.
(15) Ogawa, A.; Ikeda, T.; Kimura, K.; Hirao, T. *J. Am. Chem. Soc.* **1999**, *121*, 5108.
(16) (a) Firouzabadi, H.; Iranpoor, N.; Abbasi, M. *Adv. Synth. Catal.* **2009**, *351*, 755. (b) Firouzabadi, H.; Iranpoor, N.; Jafarpour, M.; Ghaderi, A. *J. Mol. Catal. A: Chem.* **2006**, *249*, 98.
(17) Firouzabadi, H.; Iranpoor, N.; Jafarpour, M. *Tetrahedron Lett.* **2006**, *47*, 93.
(18) (a) Patai, S. *The Chemistry of the Functional Groups – The Chemistry of the Thiol Group*; Wiley: London, **1974**, 669. (b) Parham, W. E.; Wynberg, H. *Org. Synth., Coll. Vol. IV* **1963**, 295. (c) Boscato, J. F.; Catala, J. M.; Franta, E.; Brossas, J. *Tetrahedron Lett.* **1980**, *21*, 1519. (d) Hundscheid, F. J. A.; Tandon, V. K.; Rouwette, P. H. A. M.; van Leusen, A. M. *Tetrahedron* **1987**, *43*, 5073. (e) Malmstrom, J.; Gupta, V.; Engman, L. *J. Org. Chem.* **1998**, *63*, 3318. (f) Blanchard, P.; Jousselme, B.; Frere, P.; Roncali, J. *J. Org. Chem.* **2002**, *67*, 3961.
(19) Tundo, P.; Selva, M. *Acc. Chem. Res.* **2002**, *35*, 706.
(20) Ono, Y. *Pure Appl. Chem.* **1996**, *68*, 367.
(21) (a) Schenk, R.; Römer, G. *Ber. Dtsch. Chem. Ges. B* **1924**, *57*, 1343. (b) Allcock, H. R. *J. Am. Chem. Soc.* **1964**, *86*, 2591. (c) Graham, J. C.; Marr, D. H. *Can. J. Chem.* **1972**, *50*, 3857. (d) Hashimoto, M.; Obora, Y.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2008**, *73*, 2894. (e) Voznicova, R. K.; Taraba, J.; Prihoda, J.; Alberti, M. *Polyhedron* **2008**, *27*, 2077. (f) Allcock, H. R.; Desorcie, J. L.; Harris, P. J. *J. Am. Chem. Soc.* **1983**, *105*, 2814. (g) Rolland, O.; Griffe, L.; Poupot, M.; Maraval, A.; Ouali, A.; Coppel, Y.; Fournie, J. J.; Bacquet, G.; Turrin, C. O.; Caminade, A. M.; Majoral, J. P.; Poupot, R. *Chem. Eur. J.* **2008**, *14*, 4836.
(22) (a) Bahrami, K.; Khodaei, M. M.; Kavianinia, I. *Synthesis* **2007**, 547. (b) Bahrami, K.; Khodaei, M. M.; Naali, F. *J. Org. Chem.* **2008**, *73*, 6835. (c) Bahrami, K.; Khodaei, M. M.; Tirandaz, Y. *Synthesis* **2009**, 369. (d) Khodaei, M. M.; Bahrami, K.; Tirandaz, Y. *J. Sulfur Chem.* **2009**, *30*, 581. (e) Bahrami, K.; Khodaei, M. M.; Farrokhi, A. *Tetrahedron*

2009, *65*, 7658. (f) Bahrami, K.; Khodaei, M. M.; Soheilizad, M. *Synlett* **2009**, 2773. (g) Bahrami, K.; Khodaei, M. M.; Soheilizad, M. *J. Org. Chem.* **2009**, *74*, 9287. (h) Bahrami, K. *Tetrahedron Lett.* **2006**, *47*, 2009. (i) Khodaei, M. M.; Bahrami, K.; Khedri, M. *Can. J. Chem.* **2007**, *85*, 7. (j) Khodaei, M. M.; Bahrami, K.; Karimi, A. *Synthesis* **2008**, 1682. (k) Bahrami, K.; Khodaei, M. M.; Karimi, A. *Synthesis* **2008**, 2543. (l) Bahrami, K.; Khodaei, M. M.; Naali, F. *Synlett* **2009**, 569. (m) Khodaei, M. M.; Bahrami, K.; Sheikh Arabi, M. *J. Sulfur Chem.* **2010**, *31*, 83. (n) Bahrami, K.; Khodaei, M. M.; Sheikh Arabi, M. *Tetrahedron Lett.* **2010**, *51*, 6939. (o) Bahrami, K.; Khodaei, M. M.; Soheilizad, M. *Tetrahedron Lett.* **2010**, *51*, 4843. (p) Bahrami, K.; Khodaei, M. M.; Tajik, M. *Synthesis* **2010**, 4282. (q) Bahrami, K.; Khodaei, M. M.; Fattahpour, P. *Catal. Sci. Technol.* **2011**, *1*, 389. (r) Bahrami, K.; Khodaei, M. M.; Sheikh Arabi, M. *J. Org. Chem.* **2010**, *75*, 6208.

(23) Brookes, R. F.; Cranham, J. E.; Greenwood, D.; Stevenson, H. A. *J. Sci. Food Agric.* **1958**, *9*, 141.

(24) Clark, N. G.; Cranham, J. E.; Greenwood, D.; Marshall, J. R.; Stevenson, H. A. *J. Sci. Food Agric.* **1957**, *8*, 566.

(25) Weinstein, A. H.; Pierson, R. M. *J. Org. Chem.* **1958**, *23*, 554.

(26) Takido, T.; Itabashi, K. *Synthesis* **1987**, 817.

(27) Peppe, C.; de Castro, L. B. *Can. J. Chem.* **2009**, *87*, 678.

(28) Steinman, R.; Schirmer, F. B. Jr.; Audrieth, L. F. *J. Am. Chem. Soc.* **1942**, *64*, 2377.