

A facile one-pot synthesis of thioethers using heteropoly acids

Ajeet Kumar^a, Prashant Singh^b, Santosh Kumar^a, Ramesh Chandra^{a,b}, Subho Mozumdar^{a,*}

^a Department of Chemistry, University of Delhi, Delhi 110007, India

^b Dr. B.R. Ambedkar Center for Biomedical Research, University of Delhi, Delhi 110007, India

Received 23 February 2007; received in revised form 13 May 2007; accepted 15 May 2007

Available online 18 May 2007

Abstract

A convenient one-pot synthetic method for the formation of thioethers from various aryl/alkyl halides using heteropoly acid, is described. Heteropoly acid is a simple, cheap and robust catalyst that couples a broad range of electron-deficient as well as electron-rich substrates in excellent yields in short time.

© 2007 Elsevier B.V. All rights reserved.

Keywords: Heteropoly acid; Catalyst; Thioethers; Electron-deficient; Electron-rich

1. Introduction

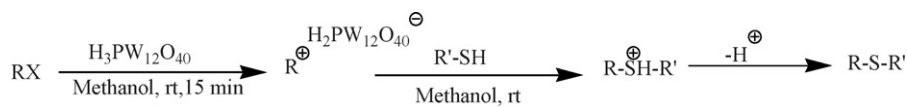
Heteropoly acids (HPAs) are promising material having strong acidity as well as oxidizing ability and used as catalyst for various kinds of organic transformation [1–4]. Catalysis by HPAs is an expanding field of active research being persuaded worldwide [5–8]. The HPAs are environmentally benign solid catalyst, which offers several advantages in terms of catalytic performance, strong acidic and redox site and selectivity to particular reaction product by selective stabilization of reaction intermediate. The HPAs by virtue of their strong acid site and redox characteristics have been used as catalyst under homogeneous as well as heterogeneous conditions. The advantage of using HPAs under homogeneous condition lies in their high solubility in polar solvent such as water, methanol acetonitrile, etc. After completion of the catalytic cycles, they can be easily isolated from the organic reaction media. These used catalysts can be subsequently recrystallized and reused for successive cycles. As far as catalysis is concerned, Keggin type HPAs have been widely investigated, because of their high structural and thermal stability with well defined acidic and redox properties. The acidic properties of Keggin type HPAs has been exploited for several important reactions such as hydration of olefins, esterification and condensation reactions of chemically diverse

organic substrates [9]. In recent years, there have been extensive efforts to utilize the potential of the HPAs in synthetic organic chemistry such as deprotection of *tert*-butyldimethylsilane [10], regioselective aerobic oxygenation of nitrobenzene to 2-nitrophenol [11] and oxidation of aliphatic, benzylic and allylic alcohols using dimethyl sulfoxides as oxygen transfer agent [12].

The preparation of various thioethers is one of the significant and widely used methods in organic [13–21] and medicinal chemistry [22–26]. Consequently, numerous synthetic methods for thioethers formation have been developed. One general method is the condensation of activated alkyl halides with alkali metal aryl thiolate that is prepared from aryl thiol in the presence of strong bases [27–30]. However, the synthetic scope of this classical reaction is limited by its long reaction time, high reaction temperature, and low yield. Methods for the introduction of a carbon–sulphur bond with use of a transition metal catalyst (Pd, Cu) have also been developed [31–38]. Although these cross-coupling methods successfully yield versatile sulfides, they require a long reaction time and vigorous conditions to achieve acceptable yields. Furthermore, some aryl thiols are unstable to oxidation; their disulfide compounds are easily formed. Therefore, there are many inconvenient aspects in handling unstable thiols, including storage under an atmosphere of inert gas and keeping them away from oxidants or substances that give free radicals. Recently, the Glaxo-Smith-Kline research group has demonstrated a one-pot synthesis of alkyl aryl sulfide via a direct reduction and coupling of aromatic sulfonyl chlorides to activated alcohols [39]. However, this method is only

* Corresponding author. Tel.: +91 9810728438; fax: +91 11276666235.

E-mail addresses: subhono@yahoo.co.in, subhomozumdar@yahoo.com (S. Mozumdar).



Scheme 1.

applicable to the synthesis of alkyl *p*-substituted aryl sulfides and the yields are moderately low.

As part of our continuing interest in the development of new synthetic methodologies, herein we report an efficient method for the selective coupling of alkyl/aryl halide with thiols to synthesize corresponding thioethers using phosphotungstic acid as catalyst (Scheme 1). Our process is highly economic and eco-friendly as it does not require elevated temperature, any harsh acids or bases and produces high yield with excellent chemoselectivity. It further reduces the reaction time and is efficient for the synthesis of various thioethers with high yield and purity. Moreover, it is a one-pot synthesis, which does not require an inert atmosphere and has an easy work-up and product isolation from the catalyst.

2. Experimental

2.1. Reagents and analysis

All reactions were carried out at ambient temperature in oven-dried glassware. The materials were purchased from Sigma–Aldrich and Merck and were used without any additional purification. All reactions were monitored by thin layer chromatography (TLC) on gel F254 plates. The silica gel (250–400 meshes) for column chromatography was purchased from Spectrochem Pvt. Ltd., India. ^1H MR (300 MHz) and ^{13}C MR (300 MHz) spectra were recorded in CDCl_3 on a Bruker Spectrospin 300 MHz spectrometer (with TMS for ^1H and CDCl_3 for ^{13}C NMR as internal references). Mass Spectra were recorded on a TOF-Mass spectrometer model no. KC455. Melting points were recorded on Buchi melting point 540 instruments. The catalyst phosphotungstic acid was systematically characterized by using analytical and spectroscopic techniques such as thermogravimetric analysis on a DTA-60 Shimadzu TG/DTA system under static air at a heating rate of 5°C min^{-1} and the X-ray diffraction patterns were recorded using a Rigaku Rotaflex Rad-B diffractometer using Cu target $\text{Cu K}\alpha$ radiation with tube voltage 40 KV and 60 mA in 2θ ranging from 0 to 65° .

2.2. General procedure for the formation of thioethers

Thiol (5 mmol) and phosphotungstic acid (15 mol%) was added to a stirred solution of alkyl/aryl halide (5 mmol) in 5 ml solvent. The mixture was stirred for 10 min at 25°C , and the progress of the reaction was monitored using TLC. After completion of the reaction, the reaction mixture was poured into ice cold water which resulted in precipitation of the desired thioethers. The precipitated solid was filtered and washed with ethyl acetate (30 ml) and washed with water (3×10 ml) followed by aqueous sodium thiosulphate (2×10 ml, 10%). The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4) fol-

lowed by evaporation of solvent using a rotary evaporator under reduced pressure. The crude products were subjected to column chromatography using silica gel and eluent (95:5, hexane:ethyl acetate), which gives alkyl aryl sulfides in excellent yield. The catalyst could be recovered either by evaporation of solvent from the residue or by centrifuging the crude reaction mixture at 3000 rpm for 30 min. The residue was then washed with diethyl ether, dried at 100°C for 1 h and re-used in another run. The recycled catalyst was used for six reactions without observation of appreciable loss in its catalytic activities. Structural assignments of the products are based on their ^1H NMR, CHNSO, FT-IR and mass analyses. The analysis of complete spectral and compositional data revealed the formation of desired products.

3. Results and discussion

For the optimization of reaction conditions we studied the coupling of iodobenzene with thiophenol as a model reaction in the presence of various heteropoly acids viz. phosphotungstic acid, phosphomolybdic acid, tungstosilicic acid and molybdosilicic acid at room temperature using methanol as a solvent (Table 1). Out of all these HPAs phosphotungstic acid was screened out to be the best catalyst for optimum yield of thioethers. By using phosphotungstic acid as catalyst a sticky reaction mixture was obtained, with the formation of the corresponding thioether in around 80–90% yield. Increasing reaction time did not affect the yield of the product. A control experiment was conducted in the absence of a catalyst. The reaction did not proceed and the starting materials remain intact. Wide ranges of substituted halides were subjected to the optimized reaction conditions (Table 2, entries 7–10). Substituted halides carrying electron-withdrawing groups as well as electron-donating groups gave equally good yields. The substitution pattern in *ortho*-, *meta*-, and *para*-substituted halides did not greatly influence the yield (Table 2); however, *ortho*-substituted halides led to lower yields, probably due to the prevention of reductive elimination.

Table 1
Optimisation of the different HPAs for the formation of thioethers (Table 1, Entry 1)^a

Heteropoly acids	Time (h)	Yield (%) ^{b,c}
Phosphotungstic acid	1.0	91
Phosphomolybdic acid	1.0	69
Tungstosilicic acid	1.0	–
Molybdosilicic acid	1.0	–

^a Reaction condition: thiophenol (5 mmol), iodobenzene (5 mmol), HPAs (15 mol%), 25°C , solvent (10 ml), stirred under air atmosphere.

^b Isolated yield.

^c Determined by GC.

Table 2
 Synthesis of aryl sulfides using phosphotungstic acid as catalyst^a

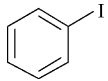
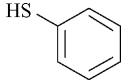
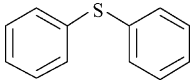
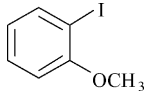
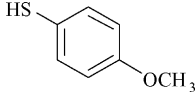
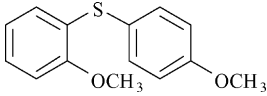
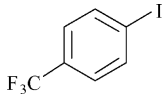
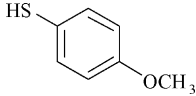
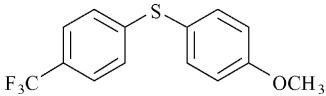
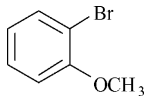
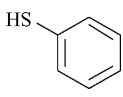
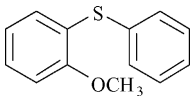
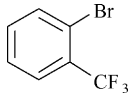
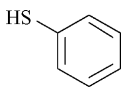
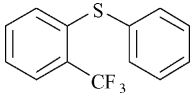
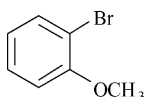
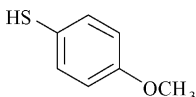
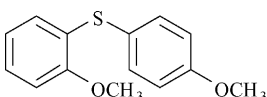
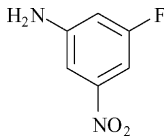
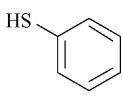
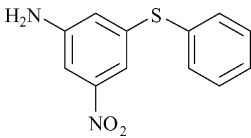
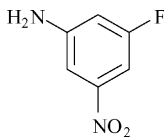
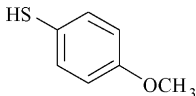
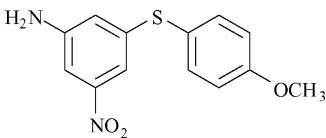
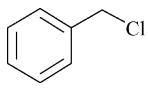
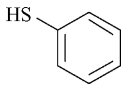
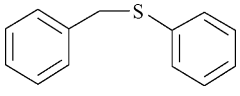
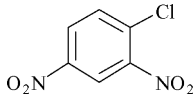
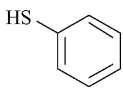
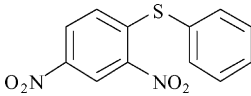
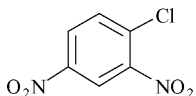
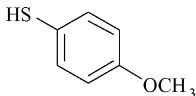
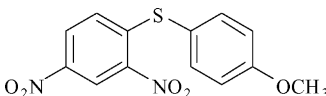
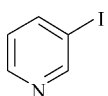
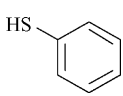
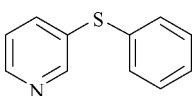
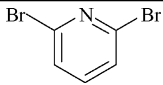
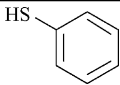
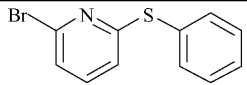
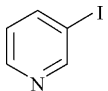
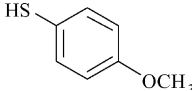
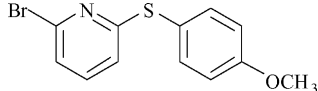
Entry	Halide ^b	Thiol	Product	Time (h)	Isolated Yield (%) ^c
1.				1.0	91
2.				1.3	90
3.				1.0	89
4.				1.2	81
5.				1.2	82
6.				1.5	79
7.				3.0	84
8.				2.5	86
9.				1.6	90
10.				2.0	82
11.				1.4	79
12.				2.5	74

Table 2 (Continued)

Entry	Halide ^b	Thiol	Product	Time (h)	Isolated Yield (%) ^c
13.				2.0	85
14.				2.3	83

^a Reaction condition: thiol (5 mmol), halide (5 mmol), phosphotungstic acid (15 mol%), 25 °C, methanol (10 ml), stirred under air atmosphere.

^b Confirmed by comparison with authentic samples (FT-IR, TLC, M.P/B.P.).

^c Determined by GC.

Heteroaromatic halides as well as heterocyclic thiols were also efficiently converted into the corresponding sulfides. To the best of our knowledge, this has not been reported earlier.

3.1. Catalyst characterization

3.1.1. Thermal analysis

The catalyst was initially characterized by thermal analysis methods. The degree of hydration of the Phosphotungstic acid, was determined from TGA analysis and corresponded to the formula $H_3PW_{12}O_{40} \cdot xH_2O$. The TGA of the phosphotungstic acid (Fig. 1) shows first decomposition at 107 °C indicating loss of one molecule of water, which is water of crystallization (0.5% weight loss experimentally and 0.6% weight loss theoretically). At 364 °C there is a loss of 5.5 molecules of water that indicates 3.5% weight loss theoretically and 3.3% loss experimentally. Moreover, at 896 °C there was a loss of one-water molecules, which indicates 0.61% weight loss experimentally and 0.57% weight loss theoretically and we finally get mixture of oxide of phosphorous and tungsten. It has been already been reported that the degree of hydration in heteropoly acids depends on various factors such as relative humidity, solution acidity, degree of drying, temperature etc. DTA curve shows characteristics endothermic peaks at 250 and 500 °C, respectively.

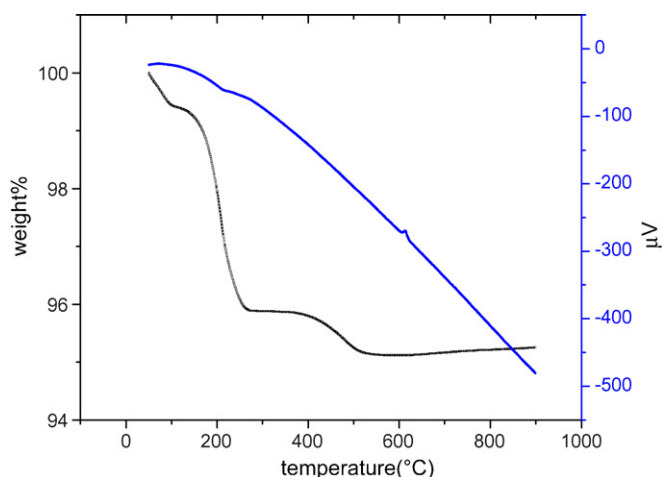


Fig. 1. TGA/DTA curve of phosphotungstic acid.

3.1.2. Infrared spectra

The Keggin primary structure presents the general formula $[8XM_{12}O_{40}]^{(8-n)-}$, where M are the addenda atoms, X the heteroatom and n is the X valence. The oxygen atoms in this structure fall into four classes of symmetric-equivalent oxygen: $X-O_a-(M)_3$, $M-O_b-M$, connecting two M_3O_{13} units by corner sharing; $M-O_c-M$, connecting two M_3O_{13} units by edge sharing and terminal $O_d=M$. The infrared spectra of phosphotungstic acid exhibit bands in the range of $3200-3400\text{ cm}^{-1}$ due to $\nu(O-H)$ and $\nu(H-O-H)$, respectively, for water of crystallization and constitutional water present in phosphotungstic acid (Fig. 2). Apart from these band the main characteristic features of bulk phosphotungstic acid in FT-IR are observed at 1081 cm^{-1} (P-O_a), 982 cm^{-1} (W-O_d), 891 cm^{-1} (W-O_b-W), 793 cm^{-1} (W-O_c-W), 595 and 524 cm^{-1} (O_a-P-O_a).

3.1.3. X-ray diffraction

X-ray powder analysis is widely used to study the structure of heteropoly complexes. The X-ray diffraction pattern of phosphotungstic acid is shown in Fig. 3. The low intensity peaks count justifies the amorphous nature of the catalyst. The characteristics 2θ value comes at 6.915, 8.635, 17.125 and 44.755.

3.2. Concentration of catalyst

Catalyst concentration plays a major role in optimization of the product yield. On increasing the molar concentration of the HPA from 2 to 20 mol%, it was observed that increased loading of the catalyst from 10 to 20 mol%

Table 3

Optimization of the amount of Phosphotungstic acid for the formation of thioethers (Table 1, Entry 1)^a

Catalysts (mol%)	Time	Yield (%) ^b
2	30	58
5	30	61
10	30	73
15	30	83
20	30	72

^a Reaction condition: thiophenol (5 mmol), iodobenzene (5 mmol), phosphotungstic acid (15 mol%), 25 °C, solvent (10 ml), stirred under air atmosphere.

^b Determined by GC.

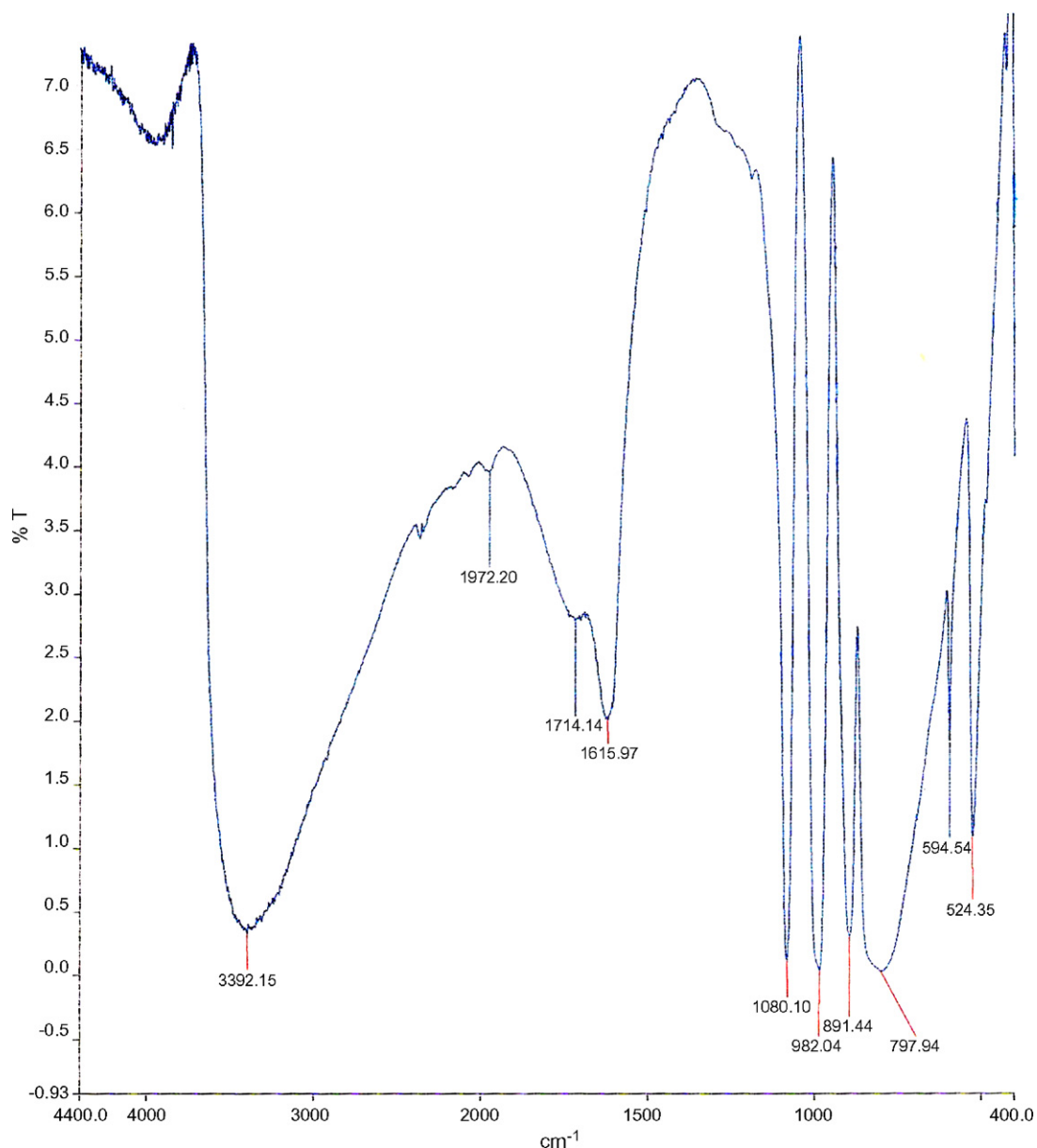


Fig. 2. FT-IR spectra of phosphotungstic acid.

gave almost same yield of product (Table 3). However, it appears that a concentration of 15 mol% of phosphotungstic acid is the suitable choice for the optimum yield of thioethers.

3.3. Solvent effect

In order to elucidate the role of the solvents, various solvents were used in order to evaluate the scope and limitations of the

Table 4
Effect of solvents on Phosphotungstic acid catalysed synthesis of thioethers^{a,b}

Solvent	Entry-a (Table 1)		Entry-b (Table 1)		Entry-d (Table 1)	
	Time	Conversion (%) ^c	Time	Conversion (%) ^c	Time	Conversion (%) ^c
Dichloromethane	30	70	30	72	30	52
Methanol	30	58	30	62	30	50
Ethanol	30	65	30	71	30	55
Tetrahydrofuran	30	80	30	79	30	72

^a Reaction condition: thiol (5 mmol), halide (5 mmol), phosphotungstic acid (15 mol%), 25 °C, solvent (10 ml), stirred under air atmosphere.

^b Confirmed by comparison with authentic samples (FT-IR, TLC, M.P/B.P.).

^c Determined by GC.

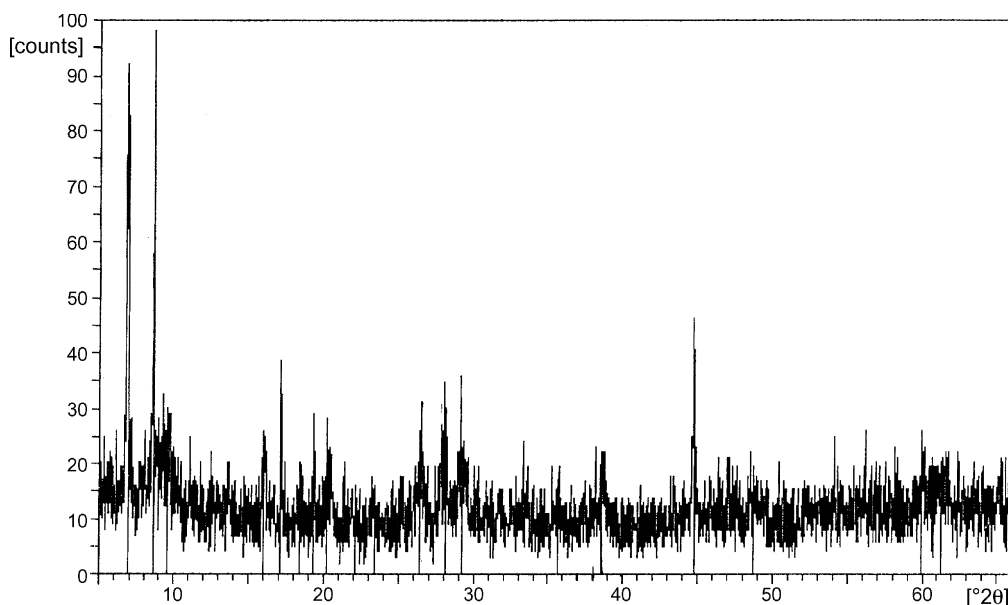


Fig. 3. X-ray diffraction pattern of phosphotungstic acid.

reaction. After screening different solvents, it was found that phosphotungstic acid catalyzed synthesis of thioethers was not only faster but also resulted in higher yields in methanol than in other solvents (Table 4). Clearly, methanol stands out as the solvent of choice, with its fast conversion and quantitative yield. Interestingly, the reaction was extremely slow in THF. In general, the reaction rate was high in polar solvents, whereas it was low in non-polar solvents (Table 4).

3.4. Effect of reaction time on the yield

Reaction time is also an important factor for the reaction. Table 5 shows the effect of the reaction time on the yield. We can see from Table 5 (Table 2, entry 1) that the yield increased with an increase in of time. After 1 h the yield was the highest so we chose 1 h as the optimum reaction time.

3.5. Recyclability

Phosphotungstic acid can be separated easily from the reaction mixture by mild centrifugation. It was used as a catalyst for the same reaction again and the change in their catalytic activity

Table 5
Effect of reaction time on the yield^a

Reaction time (min)	Yield (%) ^{b,c}
5	0
10	0
20	63
40	87
60	95
80	95
100	91

^a Reaction condition: thiophenol (5 mmol), iodobenzene (5 mmol), phosphotungstic acid (15 mol%), 25 °C, methanol (10 ml), stirred under air atmosphere.

^b Confirmed by comparison with authentic samples (FT-IR, TLC, M.P/B.P.).

^c Determined by GC.

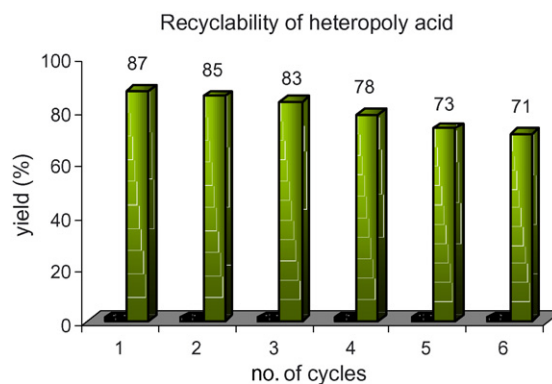


Fig. 4. Recyclability of phosphotungstic acid for the formation of thioethers (Table 1, Entry a).

was checked. The relation between the number of cycles of the reaction and the catalytic activity in terms of yield is presented in Fig. 4. It was observed that with increasing number of cycles of the reaction, the catalytic activity of the HPA slightly decreased. This can probably be due to the slow oxidation of the catalyst (Table 2, entry 1).

4. Conclusion

The present procedure represents a clean, environmentally friendly, practical and simple method with easy workup. It is applicable to a wide scope of structural types, and produced corresponding sulfides in excellent yields in very short reaction times using low mole percent of the catalyst; moreover, phosphotungstic acid is a non-toxic, inexpensive and reusable catalyst.

Acknowledgments

S. Mozumdar gratefully acknowledges financial support from the Department of Science and Technology, Government of India (SR/S1/PC-03/02, SR/S5/NM-63/2002).

References

- [1] J.H. Clarke, A.P. Kyben, D.J. Macquarrie, S.J. Barlow, P. Landon, *Chem. Commun.* (1989) 1353.
- [2] B.M. Chaudary, M.L. Kantam, M. Sateesh, K.K. Rao, P.L. Santhi, *Appl. Catal. A* (1997) 257.
- [3] Y. LZumi, M. Ogawa, K. Urabe, *Appl. Catal. A* 132 (1995) 127.
- [4] A. Molnar, C. Keresszegi, B. Torok, *Appl. Catal. A* 189 (1999) 217.
- [5] I.V. Kozhevnikov, *Chem. Rev.* 98 (1998) 171.
- [6] N. Mizuno, M. Misono, *Chem. Rev.* 98 (1998) 199.
- [7] T. Okuhara, *Chem. Rev.* 102 (2002) 3641.
- [8] P. Gouzerh, A. Proust, *Chem. Rev.* 98 (1998) 3641.
- [9] R. Fazaeli, S. Tangestaninejad, H. Aliyan, *Appl. Catal. A* 318 (2007) 218.
- [10] G.D. Kishore Kumar, S. Bhaskaran, *J. Org. Chem.* 70 (2005) 4520.
- [11] A.M. Khenkin, L. Weiner, R. Neumann, *J. Am. Chem. Soc.* 127 (2005) 9988.
- [12] A.M. Khenkin, R. Neumann, *J. Org. Chem.* 67 (2002) 7075.
- [13] A. Saxena, A. Kumar, S. Mozumdar, *Appl. Catal. A* 317 (2007) 210.
- [14] L. Field, *Synthesis* (1972) 101.
- [15] B.T. Grobel, D. Seebach, *Synthesis* (1977) 357.
- [16] C.P. Baird, C.M. Rayner, *J. Chem. Soc., Perkin Trans. 1* (1998) 1973.
- [17] D.J. Procter, *J. Chem. Soc., Perkin Trans. 1* (2000) 835.
- [18] P. Emond, J. Vercouillie, R. Innis, S. Chalon, S. Mavel, Y. Frangin, C. Halldin, J.C. Besnard, D. Guilloteau, *J. Med. Chem.* 45 (2002) 1253.
- [19] M. Winn, E.B. Reilly, G. Liu, J.R. Huth, H.S. Jae, J. Freeman, Z. Pei, Z. Xin, J. Lynch, J. Kester, T.W.V. Geldern, S. Leitz, P. Devries, R. Dickinson, D. Mussatto, G.F. Okasinski, *J. Med. Chem.* 44 (2001) 4393.
- [20] P.J. Brown, D.A. Winegar, K.D. Plunket, L.B. Moore, M.C. Lewis, J.G. Wilson, S.S. Sundseth, C.S. Koble, Z. Wu, J.M. Chapman, J.M. Lehmann, S.A. Kliewer, T.M. Wilson, *J. Med. Chem.* 42 (1999) 3785.
- [21] K.G. Liu, M.H. Lambert, L.M. Leesnitzer, W.R. Oliver, R.J. Ott, K.D. Plunket, L.W. Stuart, P.J. Brown, T.M. Willson, D.D. Sternbach, *Bioorg. Med. Chem. Lett.* 11 (2001) 2959.
- [22] M.M. Pollard, J.C. Vederas, *Tetrahedron* 62 (2006) 11908.
- [23] Y. Guindon, R. Frenette, R. Fortin, J. Rokach, *J. Org. Chem.* 48 (1983) 1357.
- [24] F.J.A. Hundscheld, V.K. Tandon, P.H.F.M. Rouwette, A.M.V. Leusen, *Tetrahedron* 43 (1987) 5073.
- [25] M. Ouertani, J. Collin, H. Kagan, *Tetrahedron* 41 (1985) 3689.
- [26] S. Tsay, L. Lin, P. Furth, C. Shum, D. King, S. Yu, B. Chen, J. Hwu, *Synthesis* 3 (1993) 329.
- [27] X. Cao, T. Chen, H. Chow, J. Tu, *Chem. Commun.* (1995) 1297.
- [28] H.J. Cristau, B. Chabaud, A. Chene, H. Christol, *Synth. Commun.* (1981) 892.
- [29] J.S. Bradshaw, J.A. South, R.H. Hales, *J. Org. Chem.* 37 (1972) 2381.
- [30] A.W. Herriott, *Synth. Commun.* (1975) 447.
- [31] N. Zheng, J.C. McWilliams, F.J. Fleitz, J.D. Armstrong, R.P. Volante, *J. Org. Chem. Soc.* 63 (1998) 9606.
- [32] J. Louie, J.F. Hartwig, *J. Am. Chem. Soc.* 117 (1995) 11598.
- [33] A.G. Martinez, J.O. Barcina, A.F. Cerezo, L.R. Subramanian, *Synlett* (1994) 561.
- [34] T. Migita, T. ShiMizu, J. Shiobara, Y. Kato, M. Kosugi, *Bull. Chem. Soc. Jpn.* 53 (1980) 1385.
- [35] G.Y. Li, G. Zheng, A.F. Noonan, *J. Org. Chem.* 66 (2001) 8677.
- [36] C.G. Bates, R.K. Gujadhur, D. Venkataraman, *Org. Lett.* 4 (2002) 2803.
- [37] R.J.S. Hickman, B.J. Christie, R.W. Guy, T.J. White, *J. Chem.* 38 (1985) 899.
- [38] P.S. Herradura, K.A. Pendola, R.K. Guy, *Org. Lett.* 2 (2000) 2019.
- [39] M.T. Martain, A.M. Thomas, D.G. York, *Tetrahedron Lett.* 43 (2002) 2145.