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A facile one-pot synthesis of thioethers using heteropoly acids

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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.

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

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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 homogenous as well as heterogeneous conditions. The advantage of using HPAs under homogenous 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

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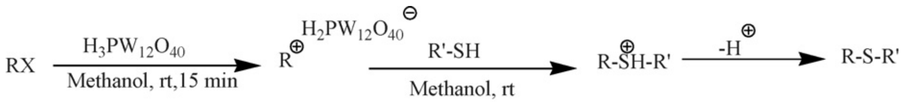

Scheme 1.

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. ^{1}H 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 ^{1}H 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 $5\,^{\circ}C\,min^{-1}$ and the X-ray diffraction patterns were recorded using a Rigaku Rotaflex Rad-B diffractometer using Cu target Cu Kα 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) followed 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 ^{1}H 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, tungustosilicic 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
Tungustosilicic 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.