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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 2683–2686

An efficient and chemoselective method for protection of thiols catalyzed by aluminumdodecatungstophosphate ($AlPW_{12}O_{40}$), as a highly water tolerant Lewis acid catalyst

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Received 1 November 2004; revised 2 February 2005; accepted 10 February 2005

Abstract—Protection of various thiols with diphenylmethanol was achieved in high yields at room temperature using catalytic amounts of $AlPW_{12}O_{40}$ in CH_2Cl_2. In the presence of this catalyst, protection of SH versus OH was achieved with high chemoselectivity and yields. The catalyst can be easily recovered and reused. Deprotection of DPM thioethers was also achieved using molecular iodine at reflux in CH_2Cl_2 in high yields.

1. Introduction

Protection of one functional group in the presence of other groups is an essential task for the synthesis of complex molecules. The protection of the SH functional group is important because of the reactivity of this functionality as a nucleophile and also its sensitivity to oxidation both by dimerization and *S*-oxide formation.[1,2] We have examined the selective protection of SH versus OH groups. The methods reported for the protection of SH groups are rather limited.[2]

The triphenylmethyl, diphenylmethyl, and benzyl groups are frequently used for the protection of alcohol, amine and carboxylic acid functional groups. Protection of alcohols as their diphenylmethyl ethers (DPM) is of value from different points of view.[3] DPM ethers are inexpensive and show high stability toward different reagents and conditions. DPM ethers are also found as parts of the structures of several pharmacologically active compounds.[4] Protection of OH groups as DPM ethers is usually achieved using diphenylmethyl chloride or bromide in the presence of a base,[5] diphenylmethyl diazomethane or diphenylmethyl phosphate–trifluoroacetic acid,[6] diphenylmethanol in the presence of concentrated sulfuric acid[7] or *p*-toluenesulfonic acid,[8] xenon difluoride,[9] ytterbium triflate–ferric chloride[3] or $Fe(NO_3)_3{\cdot}9H_2O$.[10] Most of these methods require a high catalyst to substrate ratio and also require long reaction times. Some of the above mentioned catalysts are not easily available and they require special precautions and some require harsh reaction conditions. However, to the best of our knowledge, a general method for protection of SH groups with diphenylmethanol has not been reported.

Heteropolyacids (HPAs) have been extensively studied as acid and oxidation catalysts for many reactions and have found industrial application in several processes.[11] HPAs are promising solid acids and can replace environmentally harmful liquid acid catalysts such as H_2SO_4.[11c–f] The Keggin type $H_3PW_{12}O_{40}$ is more active than conventional solid acids such as SiO_2–Al_2O_3, H_3PO_4–SiO_2, and zeolites.[11c–f] Solid acid catalysts are harmless to the environment with respect to corrosiveness, safety, quantity of waste, and separability. Aluminumdodecatungstophosphate ($AlPW_{12}O_{40}$) is prepared easily from commercially available $H_3PW_{12}O_{40}$ and $Al(NO_3)_3$ in water.[12a,13] This salt is water-stable and nonhygroscopic. In continuation of our interest on the catalytic activities of heteropolyacids,[12,13] we describe the use of $AlPW_{12}O_{40}$ as an effective catalyst for the protection of thiol groups as DPM thioethers. The catalyst used in this protocol was easily separated and reused in several runs without losing its catalytic activity. The results of this study are shown in Table 1. Various aliphatic and aromatic thiols and acid-sensitive substrates like furfurylmercaptan were converted efficiently into

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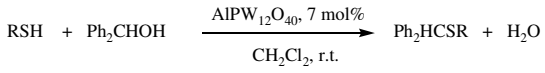
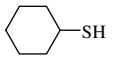
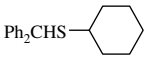
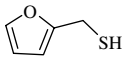
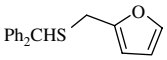
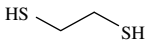
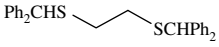
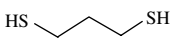
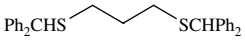
0040-4039/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2005.02.071

Table 1. Protection of thiols with DPM in the presence of catalytic amounts of $AlPW_{12}O_{40}$ (7 mol%) in CH_2Cl_2 at room temperature



Entry	Substrate	Product	Time (h)	Isolated yield (%)
1	PhSH	Ph_2CHSPh	2	92
2	*p*-MeC_6H_4SH	*p*-$MeC_6H_4SCHPh_2$	4	96
3	$PhCH_2SH$	Ph_2CHSCH_2Ph	4	90
4	$CH_3CH_2CH_2SH$	$Ph_2CHSCH_2CH_2CH_3$	24	81
5	$CH_3(CH_2)_6CH_2SH$	$Ph_2CHSCH_2\ (CH_2)_6CH_3$	16	86
6			5.5	95
7			9	92
8			6	92[a]
9			4	90[a]

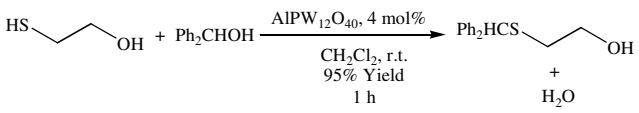
[a] Ratio of dithiol to diphenylmethanol was 1:2.

diphenylmethyl thioethers in high yields at room temperature in CH_2Cl_2. This catalyst effects protection of thiols very selectively and efficiently in the presence of hydroxyl groups. Thus, 2-thioethanol (1.1 mmol) and diphenylmethanol (1 mmol) in the presence of $AlPW_{12}O_{40}$ (4 mol%) produced 2-benzhydrylsulfanyl ethanol in 95% yield at room temperature (Scheme 1).

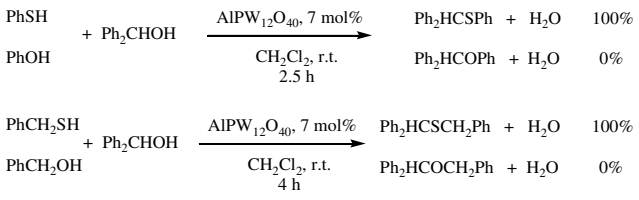
This selectivity was also demonstrated in competition experiments as shown in Scheme 2.

Protection of functional groups is only of value if a deprotection protocol is available. We present here a facile and simple procedure for deprotection of thioethers using molecular iodine in refluxing CH_2Cl_2. The reaction proceeded smoothly and the deprotected thiols were isolated as their disulfides in high yields. The isolated disulfides can be easily cleaved to their thiols by the traditional method using Zn powder/HOAc.[14]

In conclusion, we have developed a selective and efficient protocol for the protection of SH groups in the presence of OH groups catalyzed by $AlPW_{12}O_{40}$ as a water tolerant, heterogeneous, reusable, and environmentally benign catalyst. The operational simplicity, high yields of the products, high selectivity, and reusability of the catalyst are the advantages of the present protocol. Deprotection of the thioethers was achieved using molecular iodine in CH_3CN at room temperature in high yields.



Scheme 1.



Scheme 2.

2. Preparation of diphenylmethyl phenyl thioether as a typical procedure

A mixture of thiophenol (1.1 mmol, 0.121 g), diphenylmethanol (1 mmol, 0.184 g) and $AlPW_{12}O_{40}$ (0.07 mmol, 0.2 g) in CH_2Cl_2 (3 ml) was stirred at room temperature for 2 h. After completion of the reaction (monitored by TLC), CH_2Cl_2 (10 ml) was added in order to precipitate the catalyst which was removed by filtration. The excess thiol in the filtrate was neutralized by the addition of a solution of NaOH (5%, 10 ml). The organic phase was separated washed with water (10 ml) and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the pure product was isolated in 92% yield (0.25 g).

3. Deprotection of diphenylmethyl cyclohexyl thioether as a typical procedure

To a solution of diphenylmethyl cyclohexyl thioether (0.282 g, 1 mmol) in CH_2Cl_2 (5 ml), I_2 (0.152 g, 0.6 mmol) was added and the mixture stirred at reflux for 2 h. After completion of the reaction (monitored by TLC), a solution of 10% $Na_2S_2O_3$ (5 ml) was added to the mixture until the color of unreacted iodine disappeared. To the mixture, CH_2Cl_2 (10 ml) was added and the organic phase was separated, washed with water (10 ml) and dried over anhydrous $MgSO_4$. After evaporation of the solvent, further purification was achieved by column chromatography (eluent: petroleum ether/EtOAc (95/5)) to afford the corresponding disulfide in 89% yield.

3.1. Spectral data of DPM thioethers

3.1.1. Ph_2CHSPh. ^1H NMR (250 MHz, $CDCl_3$, TMS): δ (ppm) = 5.52 (s, 1H), 7.01–7.23 (m, 11H), 7.38 (d, 4H, J = 7.5); ^{13}C NMR (63 MHz, $CDCl_3$, TMS): δ (ppm) = 58.5, 128, 128.6, 129.3, 129.5, 129.8, 131.2, 137.3, 142.1; IR: ν (cm^{-1}) = 3060 (s), 3030 (s), 2935 (w), 1580 (s), 1475 (s), 1440 (s), 1170 (m), 1070 (s), 1015 (s), 920 (m), 850 (m), 750 (s) and 690 (s); MS (EI, 70 eV), *m/e*: M^+ = 276; Anal. Calcd for ($C_{19}H_{16}S$): C, 82.57; H, 5.83. Found: C, 82.43; H, 5.81.

3.1.2. $Ph_2CHSC_6H_4$–Me-*p*. ^1H NMR (250 MHz, $CDCl_3$, TMS): δ 2.19 (s, 3H), 5.45 (s, 1H), 6.92 (d, 2H, J = 7.75), 7.11–7.26 (m, 8H), 7.38 (d, 4H, J = 7.5) ppm; ^{13}C NMR (63 MHz, $CDCl_3$, TMS): 21.8, 58.8, 128.0, 129.3, 130.3, 132.2, 137.6, 142.0 ppm; IR (neat): ν 3060 (s), 3030 (s), 2935 (m), 1580 (s), 1475 (s), 1440 (s), 1170 (m), 1070 (s), 1015 (s), 920 (m), 850 (m), 750 (s), 690 (s) cm^{-1}. MS (EI, 70 eV), *m/e*: M^+ = 290; Anal. Calcd for ($C_{20}H_{18}S$): C, 82.71; H, 6.25. Found: C, 82.60; H, 6.23.

3.1.3. Ph_2CHSCH_2Ph. ^1H NMR (250 MHz, $CDCl_3$, TMS): δ 3.49 (s, 2H), 5.01 (s, 1H), 7.14–7.25 (m, 11H), 7.34 (d, 4H, J = 7.5) ppm; ^{13}C NMR (63 MHz, $CDCl_3$, TMS): 37.2, 53.9, 127.6, 127.8, 129.0, 129.6, 138.6, 141.7 ppm; IR: ν (cm^{-1}) = 3060 (s), 3030 (s), 2935 (m), 1580 (s), 1475 (s), 1440 (s), 1170 (m), 1070 (s), 1015 (s), 920 (m), 850 (m), 750 (s), 690 (s). MS (EI, 70 ev), *m/e*: M^+ = 290; Anal. Calcd for ($C_{20}H_{18}S$): C, 82.71; H, 6.25. Found: C, 82.61; H, 6.24.

3.1.4. $Ph_2CHSCH_2CH_2CH_3$. ^1H NMR (250 MHz, $CDCl_3$, TMS): δ 0.86 (t, 3H, J = 5), 1.52 (m, 2H), 2.34 (t, 2H, J = 7.3), 5.12 (s, 1H), 7.11–7.26 (m, 6H), 7.39 (d, 4H, J =7.5) ppm; ^{13}C NMR (63 MHz, $CDCl_3$, TMS): 14.7, 23.2, 34.6, 54.8, 127.6, 128.4, 128.8, 142.2 ppm; IR: ν (cm^{-1}) = 3040 (m), 3020 (m), 2925 (m), 2860 (m), 1610 (m), 1490 (s), 1450 (s), 1090 (m), 1030 (m), 740 (s), 700 (s). MS (EI, 70 ev), *m/e*: M^+ = 242; Anal. Calcd for ($C_{16}H_{18}S$): C, 79.29; H, 7.49. Found: C, 79.30; H, 7.48.

3.1.5. $Ph_2CHSCH_2(CH_2)_6CH_3$. ^1H NMR (250 MHz, $CDCl_3$, TMS): δ 0.86 (t, 3H, J = 5), 1.22–1.26 (m, 10H), 1.50 (m, 2H), 2.34 (t, 2H, J = 7.27), 5.12 (s, 1H), 7.11–7.26 (m, 6H), 7.39 (d, 4H, J = 7.5) ppm; ^{13}C NMR (63 MHz, $CDCl_3$, TMS): 14.7, 23.2, 29.0, 29.6, 32.4, 33.0, 34.6, 54.8, 127.6, 128.4, 128.8, 142.2 ppm; IR (neat): ν (cm^{-1}) = 3040 (m), 3020 (m), 2925 (s), 2860 (s), 1610 (m), 1490 (s), 1450 (s), 1090 (m), 1030 (m), 740 (s), 700 (s). MS (EI, 70 eV), *m/e*: M^+ = 312; Anal. Calcd for ($C_{21}H_{28}S$): C, 80.71; H, 9.03. Found: C, 80.68; H, 9.00.

3.1.6. $Ph_2CHSC_6H_{11}$. ^1H NMR (250 MHz, $CDCl_3$, TMS): δ 1.09–1.18 (m, 3H), 1.29–1.37 (m, 2H),1.42–1.46 (m, 1H), 1.65–1.67 (m, 2H), 1.84–1.89 (m, 2H), 2.45 (m, 1H), 5.22 (s, 1H), 7.10–7.26 (m, 6H), 7.40 (d, 4H, J = 7.5) ppm; ^{13}C NMR (63 MHz, $CDCl_3$, TMS): 26.6, 33.8, 44.0, 58.6, 127.6, 128.4, 128.8, 142.6 ppm; IR: ν (cm^{-1}) = 3060 (m), 3030 (m), 2940 (s), 2860 (s), 1610 (m), 1490 (s), 1450 (s), 1330 (w), 1260 (m), 1200 (m), 1070 (m), 1030 (m), 740 (s), 700 (s). MS (EI, 70 ev), *m/e*: M^+ = 282; Anal. Calcd for ($C_{19}H_{22}S$): C, 80.80; H, 7.85. Found: C, 80.79; H, 7.83.

3.1.7. $Ph_2CHSC_5H_5O$. ^1H NMR (250 MHz, $CDCl_3$, TMS): δ 3.52 (s, 2H), 5.09 (s, 1H), 6.02 (s, 1H), 6.18 (s, 1H), 7.17–7.31 (m, 7H), 7.69 (d, 4H, J = 7.5) ppm; ^{13}C NMR (63 MHz, $CDCl_3$, TMS): 29.2, 54.2, 109.7, 111, 127.8, 129, 129.1, 141.4, 142.7, 151.9 ppm; IR: ν (cm^{-1}) = 3060 (s), 3040 (s), 2950 (m), 1610 (s), 1500 (s), 1450 (s), 1415 (w), 1250 (m), 1200 (s), 1160 (s), 1080 (s), 1015 (s), 920 (s), 730 (s), 700 (s). MS (EI, 70 ev), *m/e*: M^+ = 280; Anal. Calcd for ($C_{18}H_{16}OS$): C, 77.11; H, 5.75. Found: C, 77.30; H, 5.75.

3.1.8. $Ph_2CHSCH_2CH_2SCHPh_2$. ^1H NMR (250 MHz, $CDCl_3$, TMS): δ 2.51 (s, 4H), 5.05 (s, 2H), 7.09–7.24 (m, 12H), 7.32 (d, 8H, J = 7.5) ppm; ^{13}C NMR (63 MHz, $CDCl_3$, TMS): 32.6, 54.7, 127.2, 128.1, 128.3, 141.7 ppm; IR: ν (cm^{-1}) = 3060 (s), 3010 (s), 2900 (s), 1610 (m), 1500 (s), 1450 (s), 1415 (w), 1250 (m), 1200 (s), 1160 (s), 1080 (s), 1015 (s), 920 (s), 730 (s), 700 (s). MS (EI, 70 ev), *m/e*: M^+ = 426; Anal. Calcd for ($C_{28}H_{26}S_2$): C, 78.83; H, 6.14. Found: C, 78.85; H, 6.16.

3.1.9. $Ph_2CHSCH_2CH_2CH_2SCHPh_2$. ^1H NMR (250 MHz, $CDCl_3$, TMS): δ 1.71 (t, 2H, J = 7), 2.34 (t, 4H, J = 7), 5.03 (s, 2H), 7.09–7.23 (m, 12H), 7.32 (d, 8H, J = 7.5) ppm; ^{13}C NMR (63 MHz, $CDCl_3$, TMS): 29.2, 31.86, 54.7, 127.2, 128.1, 128.3, 141.7 ppm; IR: ν (cm^{-1}) = 3060 (s), 3010 (s), 2900 (s), 1610 (m), 1500 (s), 1450 (s), 1415 (w), 1250 (m), 1200 (s), 1160 (s), 1080 (s), 1015 (s), 920 (s), 730 (s), 700 (s). MS (EI, 70 ev), *m/e*: M^+ = 440; Anal. Calcd for ($C_{29}H_{28}S_2$): C, 79.04; H, 6.40. Found: C, 78.99; H, 6.41.

3.1.10. $Ph_2CHSCH_2CH_2OH$. ^1H NMR (250 MHz, $CDCl_3$, TMS): δ 2.45 (t, 2H, J = 6.15), 2.88 (s, 1H), 3.51 (t, 2H, J = 6.15), 5.14 (s, 1H), 7.10–7.24 (m, 6H), 7.36 (d, 4H, J = 7.5) ppm; ^{13}C NMR (63 MHz, $CDCl_3$, TMS): 34.8, 53.5, 60.3, 127.2, 128.1, 128.3, 141.7 ppm; IR: ν (cm^{-1}) = 3200–3600 (b), 3060 (s), 3010 (s), 2900 (s), 1610 (m), 1500 (s), 1450 (s), 1415 (w), 1250 (m), 1200 (s), 1160 (s), 1080 (s), 1015 (s), 920 (s), 730 (s), 700 (s). MS (EI, 70 ev), *m/e*: M^+ = 244; Anal. Calcd for ($C_{15}H_{16}OS$): C, 73.73; H, 6.60. Found: C, 73.70; H, 6.58.

Acknowledgements

Financial support from Iran Chapter of TWAS based at ISMO and Shiraz University Research Council are highly appreciated.

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