Heteropoly Acids as Heterogeneous Catalysts for Thioacetalization and Transthioacetalization Reactions

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Abstract: Heteropoly acids are effective solid catalysts for the thioacetalization of carbonyl compounds. Tungstophosphoric acid ($H_3PW_{12}O_{40}$), was found to be an effective and a highly selective catalyst for the thioacetalization of aldehydes, ketones and for the transthioacetalization of acetals, acylals and *O,S*-acetals which proceeded in excellent yields in the absence of solvent. The catalyst has also been successfully applied to the chemoselective conversion of α- or β-diketones and a β-keto ester into the corresponding dithioacetals. Sterically hindered carbonyl compounds such as camphor and benzophenone were also converted to their corresponding thioacetals in refluxing petroleum ether in 89–94% yields. Surprisingly, anthrone was reduced to anthracene in 91% yield.

Key words: carbonyl compounds, tungstophosphoric acid, heteropoly acids, thioacetalizations, transthioacetalizations

The protection of carbonyl groups as acetals or thioacetals is often necessary during the synthesis of multi-functional complex molecules[1] and natural products.[2] Generally, thioacetals have been prepared by the condensation of carbonyl compounds and thiols catalyzed with protic acids,[3,4] solid acids,[5,6] (such as HY or H-mordenite Zeolite, Nafion-H, Amberlyst-15), Lewis acids[7–9] or solid supports.[10,11] Transthioacetalization of acetals has also been conducted in the presence of $BF_3{\cdot}OEt_2$,[12] *i*-$Bu_2AlS(CH_2)_2SAl(i\text{-}Bu)_2$,[13] $CoCl_2{\cdot}Me_3SiCl$[14] and natural kaolinitic clay.[15] In recent years, catalytic properties of solid heteropoly compounds, in particular their acidic properties, have been the subjects of reviews.[16,17] Heteropoly acids (HPAs) in solution are stronger than the usual mineral acids such as H_2SO_4, HCl, HNO_3, etc.[18] Solid HPAs also are stronger than conventional solid acids such as SiO_2/Al_2O_3, H_3PO_4/SiO_2, and HX or HY zeolites.[19] HPAs with the Keggin structure constitute the most extensively studied and important class of polyoxometalates.[20–22]

In the past two decades, the broad utility of HPAs as acid and oxidation catalysts in solution as well as in the solid state for various industrial processes has been demonstrated for a wide variety of synthetically useful transformations of organic substrates.[23,24] Kinetic studies of liquid-phase acetal formation catalyzed by Keggin-type heteropoly acids are also reported.[25] Recently we have introduced new catalysts for thioacetalization and transthioacetalization reactions in the presence and absence of solvents[26–28] and we also have used tungstophosphoric acid as an efficient catalyst for the oxidation of anilines to their nitro compounds in aqueous micellar media with sodium perborate.[29] Solvent-free reactions have attracted the attention of chemists due to their environmental and economical advantages and due to their simplicity in process and handling.[30] Along this line, we now report that tungstophosphoric acid, in the solid state, could be used as an efficient catalyst for thioacetalization and transthioacetalization reactions in organic synthesis.

In this paper we describe the dithioacetalization of carbonyl compounds using HPAs or their salts as catalysts. The results of our studies show that $H_3PW_{12}O_{40}$, $(NH_4)_2HPW_{12}O_{40}$, $Cs_{2.5}H_{0.5}PW_{12}O_{40}$, and $H_4SiW_{12}O_{40}$ are very efficient catalysts for dithioacetalization reactions under solvent-free conditions. In Table 1, we have compared the catalytic activities of $H_3PW_{12}O_{40}$, $(NH_4)_2HPW_{12}O_{40}$, $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ and $H_4SiW_{12}O_{40}$ with TfOH, CH_3SO_3H and H_2SO_4 for a dithioacetalization reaction. As it is evident from the results summarized in Table 1, HPAs and their salts are very effective catalyst for this purpose.

We therefore chose the most effective catalyst $H_3PW_{12}O_{40}$, for the protection of other carbonyl com-

Table 1 Thioacetalization of Benzaldehyde with Propane-1,3-dithiol in the Presence of Heteropoly Acids (HPAs), Some of Their Salts and Other Strong Protic Acids in Solventless Systems

Entry	Catalyst	Substrate/ Thiol/Cat.	Time (min)	GC Yield (%)
1	$H_3PW_{12}O_{40}$	1:1.2:0.005	<1	≥98
2	$H_3PW_{12}O_{40}$	1:1.2:0.002	2	≥98
3	$H_3PW_{12}O_{40}$	1:1.2:0.001	2.5	≥98
4	$H_3PW_{12}O_{40}{\cdot}nH_2O$	1:1.2:0.001	3.5	>98
5	$(NH_4)_2HPW_{12}O_{40}$	1:1.2:0.001	18	98
6	$Cs_{2.5}H_{0.5}PW_{12}O_{40}$	1:1.2:0.001	50	97
7	$H_4SiW_{12}O_{40}{\cdot}nH_2O$	1:1.2:0.001	120	96
8	TfOH	1:1.2:0.003	60	30
9	CH_3SO_3H	1:1.2:0.003	60	24
10	H_2SO_4	1:1.2:0.0015	120	20

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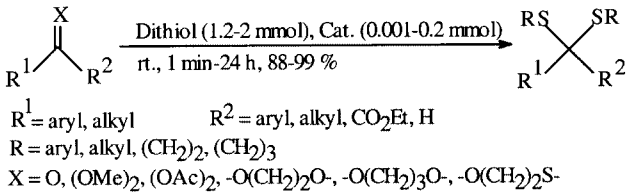
pounds. Various types of aromatic and aliphatic aldehydes were cleanly and rapidly converted to their corresponding dithioacetals in excellent yields in the presence of a 1.2 fold molar excess of thiol or dithiol and 0.001 mmol (0.003 equiv) of tungstophosphoric acid at room temperature (Scheme 1, Table 2, entries 1–8).



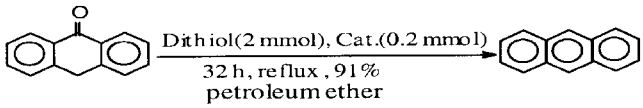
Scheme 1

Aliphatic ketones were also converted to the corresponding dithioketals in excellent isolated yields (Table 2, entries 9,10). However, aromatic ketones required prolonged reaction times even in the presence of 0.02–0.05 mmol of the catalyst (Table 2, entries 11,12). The presented results show that aliphatic and aromatic aldehydes were protected more quickly than aromatic or hindered ketones. It was also observed that transthioacetalization of acetals, ketals, *O,S*-acetals and acylals was achieved efficiently with catalytic amounts of tungstophosphoric acid to afford the corresponding *S,S*-acetals in excellent yields under solvent–free conditions (Table 2, entries 14−20). Protection of carbonyl groups of hindered ketones such as (+)-camphor and benzophenone is a very difficult process and is usually accompanied with low yields of the products and requires long reaction times. In the absence of solvent, thioacetalization of these sterically hindered ketones proceeded in 30% and 50% yields, respectively after 24 hours at room temperature. However, this reaction in refluxing petroleum ether (bp 60–80 °C) proceeded efficiently and gave the desired products in 89% and 94% yields, respectively. Thioacetalization of anthrone with propane-1,3-dithiol in boiling petroleum ether (bp 60–80 °C) gave anthracene in 91% yield instead of producing the 1,3-dithiane (Scheme 2).

Table 2 Thioacetalization of Carbonyl Compounds, Acetals, Ketals, *O,S*-Acetals and Acylals with Tungstophosphoric Acid ($H_3PW_{12}O_{40}$)

R^1	R^2	X	R	Substrate/Thiols/Cat.	Time (min)	Yield[a] (%)	Ref.
Ph	H	O	$(CH_2)_3$	1:1.2:0.001	2.5	98	3,5,9,15
Ph	H	O	Ph	1:1.2:0.01	10	97	28
Ph	H	O	Bu	1:1.2:0.01	25	97	3
p-$MeOC_6H_4$	H	O	$(CH_2)_3$	1:1.2:0.001	1	99	10,15
p-ClC_6H_4	H	O	$(CH_2)_3$	1:1.2:0.001	30	95	10,15
o-ClC_6H_4	H	O	$(CH_2)_3$	1:1.2:0.001	50	97	28
C_5H_{11}	H	O	$(CH_2)_3$	1:1.2:0.001	3	89	31
PhCH=CH	H	O	$(CH_2)_3$	1:1.2:0.001	2	91	32
$PhCH_2$	Me	O	$(CH_2)_3$	1:1.5:0.001	10	96	28
$-(CH_2)_5-$		O	$(CH_2)_3$	1:1.2:0.001	4	98	9,15
Ph	Me	O	$(CH_2)_2$	1:1.5:0.02	70	98	5,9,15
Ph	Ph	O	$(CH_2)_3$	1:1.7:0.05	40	94[b]	5,9,15
(+)-camphor		O	$(CH_2)_3$	1:2:0.2	24[c]	89[b]	3,15
Ph	H	$(OMe)_2$	$(CH_2)_3$	1:1.2:0.004	5	98	3,5,9,15
Ph	H	$O(CH_2)_3O$	$(CH_2)_3$	1:1.2:0.004	5	94	3,5,9,15
o-ClC_6H_4	H	$O(CH_2)_3O$	$(CH_2)_3$	1:1.2:0.01	50	94	28
p-MeC_6H_4	H	$O(CH_2)_3S$	$(CH_2)_3$	1:1.2:0.01	8	96	28
$-(CH_2)_5-$		$O(CH_2)_3O$	$(CH_2)_3$	1:2:0.01	10	89	9,15
Ph	Me	$O(CH_2)_3O$	$(CH_2)_3$	1:1.2:0.02	2[c]	94	5,9,15
p-MeC_6H_4	H	$(OAc)_2$	$(CH_2)_3$	1:1.2:0.01	4	98	28

[a] In refluxing petrolrum ether (bp 60-80 °C).
[b] The products were purified by column chromatography on silica gel (60–230 Mesh, EtOAc–petroleum ether 9:1).
[c] Reaction time in hours.



Scheme 2

In order to show the chemoselectivity of the method for the protection of different carbonyl groups we performed a number of competitive reactions that demonstrate the high selectivity of the method (Scheme 3).[33]

In conclusion, a wide range of aldehydes, ketones, α- or β-diketones and a β-keto ester could be transferred to the corresponding 1,3-dithiolane and 1,3-dithianes in good to excellent yields by the described method. Selectivity of the method is very promising and discriminates between different CO functionalities. The catalytic activities of the heteropoly acids were much higher than those of conventional acid catalysts such as sulfuric acid, methanesulfonic acid and triflic acid.

Tungstophosphoric acid ($H_3PW_{12}O_{40}{\cdot}nH_2O$) was purchased from Merck and was purified by extraction with Et_2O from an aqueous solution of the acid. After evacuating at 150–300 °C for 1–2 h under reduced pressure pure $H_3PW_{12}O_{40}$ was obtained.[19] Tungstosilicic acid ($H_4SiW_{12}O_{40}{\cdot}nH_2O$) was purchased from Merck and dehydrated by evacuating at 150–300 °C. The acidic salts of heteropoly acids were prepared according to the known procedures.[34] The products were purified by column chromatography and the purity determination of the products was accomplished by GC on a Shimadzu model GC-14A instrument or by TLC on silica gel polygram SIL G/UV 254 plates. Mass spectra were run on a Shimadzu GC-Mass-QP 1000 EX at 20 ev. The IR spectra were recorded on a Perkin Elmer 781 spectrophotometer. The NMR spectra were recorded on a Bruker avance DPX 250 MHz spectrometer.

Solvent-Free Thioacetalization and Transdithioacetalization of Carbonyl Compounds; General Procedure

Aldehydes or ketones (5 mmol), dithiol (6–7.5 mmol) and tungstophosphoric acid (0.015–0.288 g, 0.005–0.1 mmol) were mixed and the resulting mixture was magnetically stirred at r.t. After completion of the reaction (controlled by TLC or GC) the reaction was quenched with 20% aq solution of Na_2CO_3 (5 mL), and the mixture was continuously extracted with CH_2Cl_2 (10 mL) in a micro continuos extractor (in order to minimize the amount of the required solvent). The organic layer was isolated, and washed with H_2O (2 × 10 mL) and dried (Na_2SO_4). Evaporation of the solvent gave almost pure products. Further purification was performed by column chromatography on silica gel (60–230 mesh) using petroleum ether–EtOAc (9:1) as eluent to afford the desired pure products in good to excellent yields (Table 2). Crystalline unknown compounds **2**,**8** (Scheme 3) were recrystallized from hexane for further purification.

Thioacetalization of Sterically Hindered Ketones in Petroleum Ether; General Procedure

Ketones (5 mmol), dithiol (8.5–10 mmol) and tungstophosphoric acid (0.6–2.88 g, 0.2–1 mmol) and petroleum ether (bp 60–80 °C, 10 mL) were mixed together and refluxed for the appropriate time (Table 2, entries 12,13 and anthrone). After completion of the reaction (controlled by TLC), the volume of the mixture was reduced to 3 mL and subsequently quenched with 20% aq solution of Na_2CO_3 (5 mL). The workup of the mixture was performed as mentioned in the preceding experimental section. The desired products were isolated in high purities and no further purification was necessary.

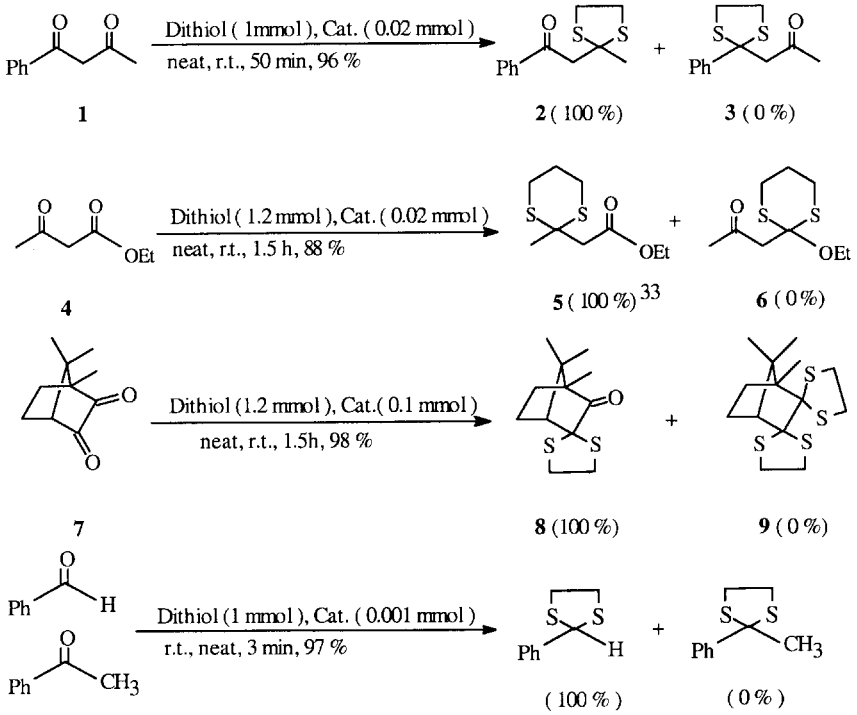
2

White crystals; mp 69–70 °C (uncorrected).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.95 (s, 3 H, CH_3), 3.22–3.39 (m, 4 H, SCH_2CH_2S), 3.76 (s, 2 H, CH_2), 7.41–7.96 (m, 5 H, C_6H_5).

^{13}C NMR (63.9 MHz, $CDCl_3$): δ = 197.09, 137.19, 133.66, 128.99, 128.40, 62.78, 54.03, 39.82, 32.73.

IR (KBr): 1677 cm^{-1} (C=O).



Scheme 3

MS (20 eV): *m*/*z* (%) = 238 (M^+, 14.6), 179 (9.5), 133 (8.7), 119 (54.1), 105 (100), 77 (54.7), 59 (16.6), 51 (22.6).

Anal. Calcd for $C_{12}H_{14}OS_2$: C, 60.47; H, 5.92. Found: C, 60.41;H, 5.9.

8

White crystals; mp 68–70 °C (uncorrected).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.86 (s, 3 H, CH_3), 0.93 (s, 3 H, CH_3), 0.98 (s, 3 H, CH_3), 1.55–1.67 (m, 2 H, 6-H), 1.76–1.87 (m, 1 H, 7-H_{endo}), 1.90–2.04(m, 1 H, 7-H_{exo}), 2.28–2.30 (m, 1 H, 3-H), 3.19–3.49 (m, 4 H, SCH_2CH_2S).

^{13}C NMR (63.9 MHz, $CDCl_3$): δ = 218.03, 69.88, 60.60, 56.06, 46.75, 41.47, 37.73, 30.95, 28.25, 22.62, 20.37, 10.47.

IR (KBr): 1738 cm^{-1} (C=O).

MS (20 eV): *m*/*z* (%) = 242 (M^+, 10.8), 214 (20.7), 186 (24.6), 131 (100), 83 (11.5), 71 (26.4), 57 (44.6), 41 (49.2).

Anal. Calcd $C_{12}H_{18}OS_2$: C, 59.46; H, 7.48. Found: C, 59.42; H, 7.47.

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