Amberlyst® 15 as a Mild, Chemoselective and Reusable Heterogeneous Catalyst for the Conversion of Carbonyl Compounds to 1,3-Oxathiolanes

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Abstract: The synthesis of 1,3-oxathiolanes from carbonyl compounds has been performed in good yields using Amberlyst®15 as a convenient, reusable, heterogeneous catalyst. The procedure can be applied for the chemoselective protection of aldeydes in the presence of a ketone function. In addition, Amberlyst®15 can be recycled without loss of activity and can be even employed in the regeneration of carbonyl group.

Key words: aldehydes, ketones, protecting groups, catalysis, heterocycles

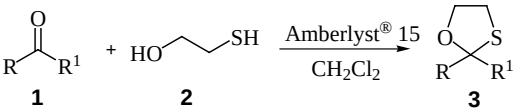
The electrophilic nature of the carbonyl group is a dominant feature of their extensive chemistry. One of the major challenging problems during many multistep syntheses is how to protect a carbonyl from nucleophilic attack until its electrophilic properties can be exploited. For this reason, the protection and deprotection of the carbonyl groups remain crucial challenges to organic chemists. Among the carbonyl protecting groups, 1,3-oxathiolanes have a special place. They are considerably more stable than the corresponding *O,O*-acetals under acidic conditions and compared with *S,S*-acetals are more easily deprotected.[1] Moreover, 1,3-oxathiolanes constitute an important class of compounds as acyl anion equivalents in C–C bond formation, although a new stereogenic center can be formed which may complicate the spectral interpretation.[2] As with most protecting groups, therefore, a variety of methods should be available for the formation and deprotection of the title compounds. However, in contrast to many methods available for the well-known *O,O*- and *S,S*-acetals,[1] only a few are reported for the oxathioacetals formation employing HCl,[3] *p*-toluenesulfonic acid,[4] TMSCl/NaI,[5] $BF_3{\cdot}OEt_2$,[6] SO_2,[7] $ZrCl_4$[8] and TMSOTf,[9] as homogeneous solutions.

In recent years, there has been a tremendous upsurge of interest in various chemical transformations mediated by heterogeneous catalysts. Environmental and economical considerations prompt an urgent need to redesign commercially important processes and, in this context, heterogeneous catalysis plays a dramatic role.[10]

Polystyryl diphenylphosphine/iodine complex[11] and natural Kaolinitic Clay have been employed as heterogeneous catalysts[12] for the title conversion. Nevertheless, the above methods present important drawbacks such as the pre-preparation of the catalyst, the demand of inert atmosphere,[11] the need for benzene (highly toxic) as solvent[12c,d] and the help of microwave irradiation in a complex apparatus.[12a,b] Moreover with multifunctional compounds the reaction does not show good selectivity, i.e. with keto esters both transesterification and ketone protection are observed.[12b] Additionally, the possibility of recycling the catalyst has not been reported.

In connection with our studies on reactions carried out with heterogeneous catalysts for the preparation of fine chemicals following environmentally acceptable methodologies[13] we have found that commercial Amberlyst® 15, a macroreticular ion-exchange resin which contains sulfonic groups,[14] can be utilised as an excellent catalyst for the conversion of carbonyl compounds to 1,3-oxathiolanes.

Our procedure (Scheme 1) is performed by stirring an equimolecular mixture of the carbonyl compound **1**, the mercaptoethanol **2** in dichloromethane in the presence of Amberlyst® 15 (activated at 130 °C for 2 h) for the selected reaction time (Table).



1 **2** **3**

Scheme 1

As shown in the Table, different types of carbonyl compounds can be efficiently transformed into their corresponding 1,3-oxathiolanes **3** and, because the conversion of aldehydes is faster than ketones, the chemoselective protection of aldehyde in the presence of ketone function can be performed in high yield and with excellent chemoselectivity (97%) [Scheme 2, **4** to **5**].

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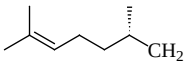
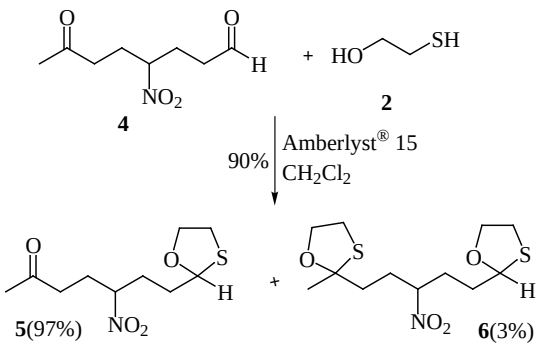
Table 1,3-Oxathiolanes **3** Prepared

Product	R	R^1	Reaction Time (h)	Yield (%)[a]
3a	H	Ph	1	84[b]
3b	H	*p*-$NO_2C_6H_4$	1	88[b]
3c	H	*p*-ClC_6H_4	1	84[b]
3d	H	(*E*)-PhCH=CH	1	78[b]
3e	H	*i*-Pr	1	81[b]
3f	H	$Ph(CH_2)_2$	1	95[b]
3g	H	Et_2CH	1	85[b]
3h	H		1	88[b]
3i	H	$PhCH_2$	1	91[b]
3j	H	*c*-C_6H_{11}	1	85[b]
3k	H	$CH_3(CH_2)12$	1	75
3l	$(CH_2)_2CH(CH_2)_2$ $CH(CH_3)_3$		5	95[b]
3m	Me	$PhCH_2$	15	84[b]
3n	Me	$MeO_2C(CH_2)_2$	8 + 2[c]	88
3o	Pr	Pr	8 + 2[c]	84
3p	Me	$(CH_3)_2C(CH_2)_2$ NO_2	2 + 2[c]	90
3q	$(CH_2)_2CH(CH_2)_2$ C_6H_5		15	92

[a] Isolated yield.
[b] These products were characterised by comparison of their IR, ^1H NMR and Mass spectra with those of the authentic samples.[7,8,12b,15–18]
[c] The reaction mixture was further heated at 45 °C for the indicate time.

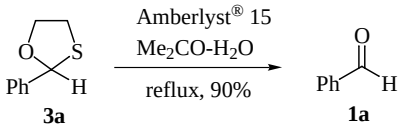


Scheme 2

It is important to point out that in the protection of the keto ester **1n** no transesterification process was observed.

In addition, we found that Amberlyst® 15 could be recycled without loss of the activity simply by filtering the catalyst, washing with dichloromethane and heating at 130 °C for 1 hour. In fact, the conversion of benzaldehyde (**1a**) into its 1,3-oxathiolane **3a** has been repeated three times, through the same catalyst, with the following yields: 84%, 82% and 83%.

Finally, we tried the regeneration of the carbonyl group from 1,3-oxathiolane **3a**, by the same catalyst (Scheme 3), simply by refluxing (8 h) a solution of **3a** in acetone–water (99:1) in the presence of Amberlyst®15; the aldehyde **1a** was isolated in 90% yield.



Scheme 3

In conclusion, we have described a new, mild, efficient heterogeneous catalysis for the conversion of carbonyl compounds to 1,3-oxathiolanes. Furthermore, we have found that Amberlyst® 15 (i) shows high chemoselectivity, (ii) can be efficiently recycled, and (iii) can even be employed in the regeneration of carbonyl function from 1,3-oxathiolanes.

^{1}H NMR spectra were recorded in $CDCl_3$ at 200 MHZ on a Varian Gemini instrument; *J* values are given in Hz. IR spectra were recorded with a Perkin Elmer 257 spectrophotometer. Mass spectra were determined on a capillary GC/MS operating in the split mode with He carrier gas and fitted with a mass-selective detector (MDS). The reactions were monitored by TLC or GC performed on a Carlo Erba Fractovap 4160 using a capillary column of Duran Glass, stationary phase OV1. Microanalyses were performed using a Fisons model EA 1108. The products were purified by flash chromatography on Merck silica gel with EtOAc–cyclohexane as eluent.

1,3-Oxathiolanes 3; General Procedure

Amberlyst® 15 (220 mg, activated at 130 °C for 2 h) was added to a stirred solution of carbonyl compound **1** (5 mmol) in CH_2Cl_2 (6 mL), then 2-mercaptoethanol **2** (5 mmol), in CH_2Cl_2 (6 mL) was added dropwise over a few minutes. The obtained solution was stirred at r.t. (for some ketones heating at 45 °C was needed) for the appropriate time (see Table). After completion of the reaction (TLC and GC), the solution was washed with aq 2 N NaOH (2 × 5 mL), dried ($MgSO_4$), evaporated and the crude product was purified by flash chromatography (EtOAc–cyclohexane) to afford the pure compound **3**.

Spectral data of some of the representative purified compounds are given below.

3g

^{1}H NMR ($CDCl_3$): δ = 0.91 (t, 3 H, *J* = 7.4 Hz), 0.92 (t, 3 H, *J* = 7.4 Hz), 1.30–1.70 (m, 5 H), 2.80 (ddd, 1 H, *J* = 13.7, 6.3, 6.0 Hz), 2.89 (ddd, 1 H, *J* = 13.7, 5.5, 5.7 Hz), 3.74 (td, 1 H, *J* = 6.0, 9.0Hz), 4.36 (ddd, 1 H, *J* = 2.7, 6.3, 9.0 Hz), 5.07 (d, 1 H, *J* = 6.31 Hz).

^{13}C NMR ($CDCl_3$): δ = 10.96, 11.08, 22.60, 22.66, 32.09, 45.96, 71.26, 90.41.

MS (EI, 70 eV): *m/z* (%) = 160 (M^+), 115, 101, 83, 55, 41 (100).

Anal. Calcd for $C_8H_{16}OS$: C, 59.95; H, 10.06; S, 20.00. Found: C, 59.86; H, 10.19; S, 20.12.

3h (as a 50:50 diastereomeric mixture)

^{1}H NMR ($CDCl_3$): δ = 0.75 (s, 3 H), 0.78 (s, 3 H), 1.42 (s, 3 H), 1.50 (s, 3 H), 1.53 (s, 3 H), 1.61 (s, 3 H), 0.7–1.8 (m, 7 H), 2.85–3.10 (m, 2 H), 3.9–4.1 (m, 2 H), 4.89 (m, 1 H), 5.01 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 17.25, 19.3, 19.8, 22.18, 24.0, 25.1, 25.26, 25.32, 26.03, 30.77, 34.01, 36.0, 37.1, 37.36, 40.45, 44.1, 71.80, 74.4, 85.23, 87.2, 124.6, 125.8, 130.3, 133.2.

MS (EI, 70 eV): *m/z* (%) = 214 (M^+), 154, 137, 81 (100), 69, 59.

Anal. Calcd for $C_{12}H_{22}OS$: C, 67.24; H, 10.34; S, 14.95. Found: C, 67.30; H, 10.29; S, 14.52.

3k

^{1}H NMR ($CDCl_3$): δ = 0.88 (t, 3 H, *J* = 6.2 Hz), 1.7–1.2 (m, 24 H), 3.0 (m, 2 H), 3.9 (m, 2 H), 5.05 (t, 1 H, *J* = 5.1 Hz);

^{13}C NMR ($CDCl_3$): δ = 14.11, 22.7, 23.5, 26.4, 27.5, 29.1, 32.6, 33.7, 36.4, 71.18, 87.12.

MS (EI, 70 eV): *m/z* (%) = 272 (M^+), 194, 89 (100), 61, 60, 55, 43, 41.

Anal. Calcd for $C_{16}H_{32}OS$: C, 70.53; H, 11.84; S, 11.76. Found: C, 70.48; H, 11.88; S, 11.65.

3n

IR (neat): 1710 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.61 (s, 3 H), 2.1–2.2 (m, 2 H), 2.4–2.6 (m, 2 H), 3.0–3.1 (m, 2 H), 3.68 (s, 3 H), 4.0–4.3 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 28.90, 29.35, 33.99, 35.00, 51.44, 70.24, 95.71, 174.13.

MS (EI, 70 eV): *m/z* (%) = 190 (M^+), 175, 159, 131, 115, 103, 99, 60 (100), 43.

Anal. Calcd for $C_8H_{14}O_3S$: C, 50.50; H, 7.41; S, 16.85. Found: C, 50.61; 7.34; S, 16.94.

3o

^{1}H NMR ($CDCl_3$): δ = 0.9 (t, 6 H, *J* = 7.3 Hz), 1.3–1.5 (m, 4 H), 1.65–1.85 (m, 4 H), 2.98 (t, 2 H, *J* = 5.8 Hz), 4.1 (t, 2 H, *J* = 5.8 Hz).

^{13}C NMR ($CDCl_3$): δ = 14.33, 18.38, 33.66, 43.18, 70.52, 98.71.

MS (EI, 70 eV): *m/z* (%) = 174 (M^+), 131(100), 71, 60, 43.

Anal. Calcd for $C_9H_{18}OS$: C, 62.02; H, 10.41; S, 18.39. Found: C, 62.26; H, 10.29; S, 18.52.

3p

IR (neat): 1537 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.58 (br s, 9 H), 1.72–1.84 (m, 2 H), 1.9–2.23 (m, 2 H), 2.95–3.18 (m, 2 H), 4.01–4.26 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 25.96, 26.26, 29.51, 34.41, 36.47, 37.51, 70.65, 88.07, 94.36.

MS (EI, 70 eV): *m/z* (%) = 219 (M^+), 173, 113, 103, 95, 60, 43 (100).

Anal. Calcd for $C_9H_{17}NO_3S$: C, 49.29; H, 7.81; N, 6.39; S, 14.62. Found: C, 49.16; H, 7.89; N, 6.25; S, 14.92.

3q (as a 57:43 diastereomeric mixture of E/Z)

^{1}H NMR ($CDCl_3$): δ = 1.56–2.28 (m, 8 H), 2.46–2.6 (m, 1 H), 3.0–3.1 (m, 2 H), 4.18 (dt, 2 H, *J* = 5.9, 5.8 Hz), 7.1–7.3 (m, 6 H).

^{13}C NMR ($CDCl_3$): δ = 31.63, 33.05, 33.45, 39.85, 40.24, 43.02, 43.45, 69.82, 70.09, 93.59, 97.32, 126.20, 126.33, 127.00, 128.51, 128.56, 146.34, 146.85.

MS (EI, 70 eV): *m/z* (%) = 234 (M^+), 174, 115 (100), 104, 91, 60.

Anal. Calcd for $C_{14}H_{18}OS$: C, 71.75; H, 7.74; S, 13.68. Found: C, 71.69; H, 7.82; S, 13.60.

5

IR (neat): 1719, 1543 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.7–2.3 (m, 6 H), 2.13 (s, 3 H), 2.47 (t, 2 H, *J* = 7.1 Hz), 2.9–3.1 (m, 2 H), 3.7–3.8 (m, 1 H), 4.2–4.4 (m, 1 H), 4.4–4.6 (m, 1 H), 5.0–5.2 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 28.67, 28.85, 29.13, 31.45, 34.01, 39.15, 71.80, 85.97, 89.01, 205.33.

MS (EI, 70 eV): *m/z* (%) = 246 (M^+ – 1), 199, 139, 102, 89 (100), 60, 43.

Anal. Calcd for $C_{10}H_{17}NO_4S$: C, 48.57; H, 6.93; N, 5.66; S, 12.96. Found: C, 48.66; H, 6.89; N, 5.72; S, 13.01.

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