Perchloric Acid Adsorbed on Silica Gel ($HClO_4$-SiO_2) as an Extremely Efficient and Reusable Catalyst for 1,3-Dithiolane/Dithiane Formation

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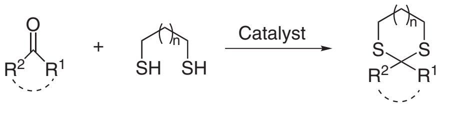
Received 28 March 2006; revised 10 April 2006

Abstract: Perchloric acid adsorbed on silica gel ($HClO_4$-SiO_2) has been found to be an extremely efficient and reusable catalyst for 1,3-dithiolane and 1,3-dithiane formation under solvent-free conditions at room temperature.

Keywords: $HClO_4$–SiO_2, catalyst, dithiolanes, dithianes, solvent-free

1,3-Dithiolane and 1,3-dithiane formation are important organic transformations due to their versatile applications in the protection of carbonyl groups,[1] generation of umpoled carbonyls,[2] conversion of carbonyl groups to methylene derivatives,[3] and titanium alkylidene mediated carbonyl olefination.[4] Dithiolane/dithiane containing compounds possess a broad spectrum of biological activity such as leishmanicidal,[5] anti-HIV,[6] interferon-gamma and lipopolysaccharide-induced nitric oxide production inhibitor,[7] anti-convulsant,[8] radioprotective,[8,9] anti-tumor,[10] radical scavenging, and hepatoprotective properties.[11] Other uses are found in the synthesis of new antibacterial penem compounds[12] and process stabilizers for polyolefins.[13] Thus, there has been unbound interest in 1,3-dithiolane/dithiane synthesis, which has led to the development of various methodologies. These include, condensation of a carbonyl compound with 1,2-ethanedithiol/ 1,3-propanedithiol in the presence of various acid catalysts that can be classified as: (i) metal salts/complex,[1,14] (ii) solid acids,[1,15] and (iii) protic/Lewis acids on solid support[1,16] (Scheme 1). However, various drawbacks such as moderate yields, long reaction times, harsh reaction conditions, tedious work-up, use of expensive reagents, use of solvents and toxic agents, special efforts required to prepare the catalyst, requirement for special apparatus, etc. associated with many of these methods make the development of a more efficient catalyst necessary.



Scheme 1 Lewis acid catalyzed formation of 1,3-dithiolane/dithiane from carbonyl compounds and dithiols

The tight legislation on the maintenance of 'green' synthetic pathways and processes that requires the prevention of waste formation (e.g. metallic impurities from catalysts), avoiding the use of auxiliary substances (e.g. halogenated and high boiling solvents), and minimizing the energy requirement[17] influenced us to design a new method, which operated under metal- and solvent-free conditions, at room temperature, in short reaction times to afford high yields so as to overcome the existing disadvantages and fulfill the triple bottom-line philosophy of green chemistry.[18]

The leading contenders for environmentally acceptable processes are supported reagents.[19] Since the activity and selectivity of a reagent dispersed on the surface of a support is improved as the effective surface area of the reagent can be increased manifold, the reaction is expected to be complete in short reaction times. Good thermal and mechanical stabilities, ease of handling due to invariably low toxicity and non-corrosive free flowing nature, ease of separation from the reaction mixture through filtration, and scope of reuse make supported reagents suitable for industrial applications. Herein we report that perchloric acid adsorbed on silica gel ($HClO_4$-SiO_2)[19e] is an extremely efficient and reusable catalyst for 1,3-dithiolane and 1,3-dithiane formation.

Various aromatic, heteroaromatic, and alicyclic aldehydes and ketones upon treatment with 1,2-ethanedithiol (**1**) and 1,3-propanedithiol (**2**) in the presence of $HClO_4$-SiO_2 (1 mol%) afforded the corresponding dithiolane/dithiane in 75–100% yields after 1–30 min (TLC, IR) under solvent-free conditions at room temperature (Table 1). The reaction was compatible with a wide range of functional groups such as hydroxyl, alkoxy, halogen, cyano, nitro etc. that are likely to compete for coordination with the catalyst and for substrates (Table 1, entries 22 and 24)[20] that are sensitive to acid. Excellent chemoselectivity was observed for α,β-unsaturated substrates (Table 1, entries 19 and 20) without any competitive conjugate addition.[21] No aqueous work-up was needed, the products were easily isolated from the reaction mixture by dilution with EtOAc followed by filtration, and the catalyst was recovered and reused without significant loss of activity (see experimental procedure).

The present method is convincingly superior to the reported procedures with respect to reaction time and temperature, yield, amount of catalyst, and solvent-free conditions employed. This claim is justified through a few represen-

SYNTHESIS 2006, No. 16, pp 2767–2771
Advanced online publication: 04.07.2006
DOI: 10.1055/s-2006-942474; Art ID: Z05806SS

tative examples in which the efficiency of $HClO_4$-SiO_2 has been compared with those of recently reported (i) Lewis acid, (ii) solid acid, and (iii) supported Lewis/protic acid catalysts. The 1,3-dithiolane of benzaldehyde was obtained in 90%, 96%, 78%, 95%, and 89% yields in MeCN, CH_2Cl_2–MeOH, THF, MeCN, and MeCN after 60, 165, 300, 90, and 90 minutes in the presence of $LiBF_4$ (10 mol%),[14a] $NiCl_2$ (10 mol%),[14b] $Bi(NO_3)_3$ (0.1 mol%),[14c] $MoO_2(acac)_2$ (10 mol%),[14d] and $Y(OTf)_3$ (5 mol%),[14e] respectively. The dithiolane was formed in 95% yield by Amberlyst® 15 -catalyzed (10%) transthioacetalization of benzaldehyde with 2,2-dimethyl-1,3-dithiolane under microwave irradiation at 190 °C for 15 minutes.[15] SiO_2-$AlCl_3$ (33 mol%)[16a] in DCE under reflux afforded a 95% yield after 72 minutes and a 97% yield was obtained in CH_2Cl_2 at room temperature after 30 minutes when the reaction was catalyzed by PPA-SiO_2 (0.25 g/mmol).[16b] Compared to these results, the 96% yield obtained after one minute under solvent-free conditions in the presence of $HClO_4$-SiO_2 (1 mol%) is superior. The dithiolane formation of 1-naphthaldehyde demonstrated the superiority of the present methodology over $Cu(BF_4)_2{\cdot}xH_2O$ which provided an 86% yield after 30 minutes[14f] compared to the 99% yield afforded by the $HClO_4$-SiO_2-catalyzed reaction. During the present investigation, $Cu(BF_4)_2{\cdot}xH_2O$-catalyzed reaction of 2-acetylfuran and 2-acetylthiophene with 1,2-ethanedithiol afforded 71% and 50% yields, respectively, after a reaction time of 30 minutes at room temperature, compared to 83% and 75% yields, respectively, obtained after ten minutes in the presence of $HClO_4$-SiO_2. The reaction of acetophenone with 1,2-ethanedithiol afforded a 45% yield (GCMS) of the dithiolane after five hours at room temperature, whereas quantitative formation of dithiolane took place when the reaction was catalyzed by $HClO_4$-SiO_2.

Table 1 $HClO_4$–SiO_2-Catalyzed Dithiolane/Dithiane Formation[a]

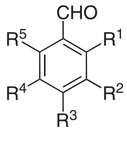
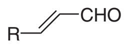
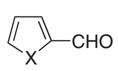
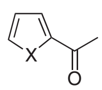
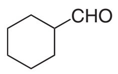
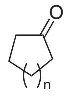
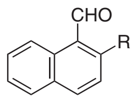
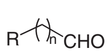
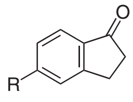
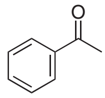
Entry	Substrate	Dithiol	Time (min)	Yield (%)[b,c]
1	 $R^1 = R^2 = R^3 = R^4 = R^5 = H$	**1**	1	96
2	$R^1 = R^2 = R^3 = R^4 = R^5 = H$	**2**	1	99
3	$R^1 = R^2 = R^4 = R^5 = H; R^3 = Me$	**1**	1	93
4	$R^1 = R^2 = R^4 = R^5 = H; R^3 = OMe$	**1**	3	88
5	$R^1 = R^2 = R^4 = R^5 = H; R^3 = OMe$	**2**	1	98
6	$R^1 = R^3 = R^5 = OMe; R^2 = R^4 = H$	**1**	1	93
7	$R^1 = R^2 = R^4 = R^5 = H; R^3 = OH$	**1**	1	96
8	$R^1 = R^2 = R^4 = R^5 = H; R^3 = Cl$	**1**	1	99
9	$R^1 = R^2 = R^4 = R^5 = H; R^3 = Cl$	**2**	1	100
10	$R^1 = R^2 = R^4 = R^5 = H; R^3 = F$	**1**	1	98
11	$R^1 = R^2 = R^4 = R^5 = H; R^3 = NO_2$	**1**	10	80
12	$R^1 = R^2 = R^4 = R^5 = H; R^3 = NO_2$	**2**	5	85
13	$R^1 = R^2 = R^4 = R^5 = H; R^3 = CN$	**1**	10	88
14	$R^1 = R^2 = R^4 = R^5 = H; R^3 = CF_3$	**1**	2	98
15	$R^1 = R^2 = R^4 = R^5 = H; R^3 = OBn$	**1**	5	99
16	$R^1 = R^5 = H; R^2 = R^4 = OMe; R^3 = OH$	**1**	1	97
17	$R^1 = R^2 = OMe; R^3 = R^4 = R^5 = H$	**1**	3	96
18	$R^1 = R^4 = R^5 = H; R^2 = OEt; R^3 = OH$	**1**	1	94
19	 R = Me	**1**	10	82

Table 1 HClO$_4$–SiO$_2$-Catalyzed Dithiolane/Dithiane Formation[a]

Entry	Substrate	Dithiol	Time (min)	Yield (%)[b,c]
20	R = Ph	**1**	3	98
21	 X = S	**1**	5	90
22	X = O	**1**	5	97
23	 X = S	**1**	10	83
24	X = O	**1**	10	75
25		**1**	10	83
26	 n = 1	**1**	5	94
27	n = 2	**1**	5	96
28	n = 2	**2**	1	95
29	n = 3	**1**	3	97
30	 R = H	**1**	3	99
31	R = OMe	**1**	5	95
32	R = OMe	**2**	1	93
33	 R = Me; n = 1	**1**	1	85
34	R = Ph; n = 1	**1**	1	94
35	R = Ph; n = 2	**1**	2	95
36	 R = H	**1**	30	95
37	R = OMe	**1**	25	85
38		**1**	5 h	100

[a] The carbonyl compound (2.5 mmol) was treated with dithiol (1.2 equiv) in the presence of HClO$_4$–SiO$_2$ (1 mol% in HClO$_4$) at r.t. (ca. 25–30 °C) under solvent-free conditions.

[b] Yield of the corresponding isolated and purified dithiolane/dithiane.

[c] All compounds were characterized by IR, NMR, and mass spectroscopy.

In conclusion, HClO$_4$-SiO$_2$ is an extremely efficient and reusable catalyst for 1,3-dithiolane/dithiane formation. The advantages are high chemoselectivity, high yields, extremely fast reaction, low cost, and operation at room temperature. With increasingly tight legislation on the release of waste and use of toxic substance, as a measure to control environmental pollution,[17] the solvent free conditions employed in the present method make it 'environmentally friendly' and a practical approach for the synthesis of 1,3-dithiolanes/dithianes.[22]

Perchloric acid ($HClO_4$) aqueous solution (70%) was purchased from Loba Chemie, India and silica gel (230–400 mesh) from Spectrochem Pvt. Ltd. India. All commercial reagents and solvents were used without further purification unless otherwise specified. The $HClO_4$-SiO_2 was prepared as reported in the literature.[19e] NMR spectra were recorded on a Bruker Avance DPX 300 MHz NMR spectrometer using TMS as an internal standard. Mass spectra were obtained using a GCMS-QP 5000 (Schimadzu) [for EI] and LCMS-Finnigan MAT LCQ [for APCI] mass spectrometers. The IR spectra were recorder on a Nicolet Impact 410 FTIR spectrometer. Elemental analysis was carried out on an Elementar Vario EL.

The spectral data (IR, NMR, and MS) of all known compounds prepared were in full agreement with authentic samples.

Dithiolane/Dithiane Formation from Carbonyl Compounds; Typical Procedure

To a magnetically stirred mixture of 4-chlorobenzaldehyde (0.35 g, 2.5 mmol) and 1,2-ethanedithiol (0.28 g, 3 mmol) was added $HClO_4$-SiO_2 (50 mg, 0.025 mmol of $HClO_4$, 1 mol%) and the mixture was stirred at r.t. under a nitrogen atmosphere for 1 min (TLC). The reaction mixture was diluted with EtOAc (10 mL) and filtered through a cotton plug. The residue was washed with EtOAc (2 × 5 mL) and the combined filtrates were concentrated under vacuum to afford the product (530 mg, 99%).

IR (KBr): 3446, 2903, 1904, 1671, 1589, 1486, 1403, 1277, 1168, 1084, 1012, 971, 750, 724, 688, 511 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.31$–3.40 (m, 2 H), 3.44–3.52 (m, 2 H), 5.59 (s, 1 H), 7.25–7.28 (d, $J = 8.8$ Hz, 2 H), 7.44–7.46 (d, $J = 8.2$ Hz).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 40.27$, 55.47, 128.59, 129.31, 133.66, 139.04.

MS (ESI): $m/z = 216$ (M^+); identical with an authentic sample.

Catalyst Recovery

The cotton plug was dipped into EtOAc (10 mL) in a 25 mL beaker to allow the catalyst to settle. The cotton was removed and the EtOAc decanted off. The recovered catalyst was dried under vacuum (5 mmHg) at 100 °C for 2 h and used for two further reactions with 4-chlorobenzaldehyde (2.5 mmol) to afford the desired product in 95% and 90% yields.

2-(2-Methyl[1,3]dithiolan-2-yl)furan

Colorless liquid.

IR (neat): 2965, 2924, 2855, 1497, 1447, 1422, 1375, 1278, 1226, 1154, 1072, 1009, 922, 739 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.12$ (s, 3 H), 3.43 (s, 4 H), 6.24–6.29 (m, 2 H), 7.35 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 30.19$, 41.06, 61.69, 106.72, 110.65, 142.86, 158.65.

MS (APCI): $m/z = 187$ $(M + 1)^+$.

Anal. Calcd for $C_8H_{10}OS_2$: C, 51.58; H, 5.41. Found: C, 51.56; H, 5.42.

2-Methyl-2-thiophen-2-yl[1,3]dithiolane

Colorless liquid.

IR (neat): 2962, 2922, 2854, 1663, 1423, 1372, 1275, 1234, 1202, 1073, 852 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.22$ (s, 3 H), 3.48 (s, 4 H), 6.87–6.89 (dd, $J = 3.92$, 3.49 Hz, 1 H), 7.10 (d, $J = 2.66$ Hz, 1 H), 7.17 (d, $J = 4.34$ Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 34.68$, 41.57, 64.95, 125.42, 125.83, 127.32, 154.16.

MS (APCI): $m/z = 203$ $(M + 1)^+$.

Anal. Calcd for $C_8H_{10}OS_3$: C, 47.48; H, 4.98. Found: C, 47.50; H, 4.97.

2-(2-Methoxy-1-naphthyl)-1,3-dithiolane

White solid; mp 122–124 °C.

IR (KBr): 3014, 2971, 2932, 2840, 1595, 1502, 1441, 1291, 1248, 1176, 1149, 1074, 1049, 1025, 798, 744, 582, 539 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.42$–3.50 (m, 2 H), 3.61–3.70 (m, 2 H), 3.94 (s, 3 H), 6.94 (s, 1 H), 7.19 (d, $J = 9.1$ Hz, 1 H), 7.31–7.36 (dd, $J = 7.5$, 7.2 Hz, 1 H), 7.46–7.51 (dd, $J = 8.0$, 7.3 Hz, 1 H), 7.73–7.79 (dd, $J = 8.9$, 7.9 Hz, 2 H), 8.79 (d, $J = 8.6$ Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 40.22$, 47.52, 56.95, 113.20, 115.74, 123.62, 125.45, 128.59, 129.73, 130.86, 132.34, 155.65.

MS (ESI): $m/z = 262$ (M^+).

Anal. Calcd for $C_{14}H_{14}OS_2$: C, 64.08; H, 5.38. Found: C, 64.10; H, 5.37.

2-(5-Methoxyindan-1-yl)-1,3-dithiolane

White solid; mp 46–48 °C.

IR (KBr): 2965, 2941, 2339, 1604, 1488, 1466, 1423, 1301, 1263, 1170, 1139, 1082, 1023, 924, 911, 840, 822, 764, 675 cm^{-1}.

^1H NMR (300 MHz; $CDCl_3$): $\delta = 2.66$–2.71 (m, 2 H), 2.90–2.95 (m, 2 H), 3.38–3.52 (m, 4 H), 3.77 (s, 3 H), 6.71 (s, 1 H), 6.77–6.80 (dd, $J = 2.1$, 8.4 Hz, 1 H), 7.45 (d, $J = 8.4$ Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 31.50$, 41.35, 49.03, 56.00, 73.26, 109.84, 114.18, 125.95, 137.47, 144.58, 160.59.

MS (APCI): $m/z = 239$ $(M + 1)^+$.

Anal. Calcd for $C_{12}H_{14}OS_2$: C, 60.46; H, 5.92. Found: C, 60.44; H, 5.93.

Acknowledgment

The authors thank the Department of Science and Technology, New Delhi, India for financial support (Grant No. 93143).

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