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Tetrahedron Letters

Tetrahedron Letters 47 (2006) 5155–5157

A rapid and efficient method for 1,3-dithiolane synthesis

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Received 25 February 2006; revised 5 May 2006; accepted 11 May 2006
Available online 6 June 2006

Abstract—A mild, efficient and solvent-free protocol for conversion of aldehydes and ketones into their corresponding 1,3-dithiolanes using 1,2-ethanedithiol in the presence of a catalytic amount of $SnCl_2{\cdot}2H_2O$ is reported.

Protection and deprotection of reactive functional groups in organic compounds is very important in multistep organic synthesis.[1] Besides choosing the right protecting group with optimum stability, the selection of a mild and efficient catalyst to affect these protection and deprotection processes also play a pivotal role in dictating the efficiency.

Protection of carbonyl compounds as 1,3-dithiolanes[1] is an important protocol in organic synthesis because of their easy introduction, stability towards acidic media and a wide range of homogeneous and heterogeneous reagents are available to deprotect thioacetals.[2] Thioacetals and oxathioacetals find applications as important starting materials for stereoselective synthesis, where they can act as acyl anion equivalents in carbon–carbon bond forming reactions.[3] The protection of carbonyls as 1,3-dithiolanes can be accomplished using $BF_3{\cdot}Et_2O$,[4] $InCl_3$,[5] $TiCl_4$,[6] $Sc(OTf)_3$,[7] Mg and Zn triflates,[8] and $Ni(BO_3)_3$[9] in homogeneous reaction conditions, silica gel treated with $SOCl_2$,[10] Amberlyst-15,[11] zeolites,[12] Nafion-H,[13] Fe^{3+}-montmorillonite,[14] $CoBr_2$ on silica gel,[15] $ZrCl_4$,[16] Envirocat EPZG,[17] $Cu(OTf)_2$-silica gel[18] and heteropoly acids[19] in heterogeneous reaction conditions.

Organic reactions under solvent-free conditions[20] have become increasingly popular because of their operational simplicity. Moreover, recent years have witnessed a phenomenal growth in the application of microwave (MW) irradiation[21] in organic transformations.

We set out to explore the possibility of using a catalytic amount of $SnCl_2{\cdot}2H_2O$, an extremely mild Lewis acid for protection of aldehydes and ketones as 1,3-dithiolanes, by reaction with 1,2-ethanedithiol. To establish the catalytic activity, $SnCl_2{\cdot}2H_2O$ (0.05 mmol) was ground with *p*-methylbenzaldehyde (1 mmol) and then stirred with 2 equiv of 1,2-ethanedithiol at room temperature. Monitoring the progress of the reaction by TLC, we found that the reaction did indeed take place under these conditions and the rate of conversion was very good (75% yield, after 2.5 h). The use of 1 mL of diethyl ether in the reaction mixture resulted in complete conversion within 45 min. Next, the rate of conversion for the same reaction was studied in various solvents (Table 1, entry 1), at rt and at reflux temperature ultimately. Diethyl ether was the best solvent affecting this conversion within 11 min. However, the fact that the reaction took place under solvent-free conditions prompted us to investigate the effect of microwave (MW) irradiation. When *p*-methylbenzaldehyde and 1,2-ethanedithiol were irradiated with microwaves at 100 W in the presence of 5 mol % $SnCl_2{\cdot}2H_2O$, the reaction went to completion within three minutes giving the corresponding protected aldehyde in 89% yield. The reaction[22] was then generalised as shown in Table 1 (Scheme 1).

The substrate catalyst ratio was then optimised (Table 2). An increase of reaction time from 3 to 5 min did not change the yield considerably, when 2 mol % catalyst was used (Table 2, entry 1). Increase in the catalyst ratio from 5 to 7 mol % and 10 mol % did not change the yield and the reactions (Table 2, entries 3–5) went to completion in only 3 min. Therefore, 5 mol % $SnCl_2{\cdot}2H_2O$ was the optimum catalyst ratio for this conversion.

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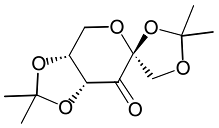
doi:10.1016/j.tetlet.2006.05.057

Table 1. $SnCl_2{\cdot}2H_2O$ catalysed formation of 1,3-dithiolanes via Scheme 1[a]

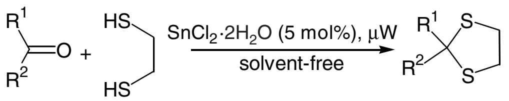
Entry	Substrate	Conditions[b]	Time (min)	Yield[c] (%)
1	p-$CH_3C_6H_4CHO$	Solvent free, rt	150	75
		Diethyl ether, rt	45	80
		Diethyl ether, reflux	11	90
		Methylene chloride, reflux	75	75
		Chloroform, reflux	30	83
		Tetrahydrofuran, reflux	25	85
		Acetonitrile, reflux	145	80
		Solvent free, μW, 100 W	3	89
2	p-ClC_6H_4CHO	Solvent free, μW, 100 W	3	92
3	C_6H_5CHO	Solvent free, μW, 100 W	3	75
4	p-$NO_2C_6H_4CHO$	Solvent free, μW, 100 W	3	86
5	p-OH C_6H_4CHO	Solvent free, μW, 100 W	4	81
6	p-$OMeC_6H_4CHO$	Solvent free, μW, 100 W	3	82
7	Citral	Solvent free, μW, 100 W	5	68[d]
8	*n*-Octanal	Solvent free, μW, 100 W	3	86
9	m-$(CO_2Me)C_6H_4CHO$	Solvent free, μW, 100 W	4	91
10	*p*-Bromo acetophenone	Solvent free, μW, 100 W	4	90
11	Acetophenone	Solvent free, μW, 100 W	5	89
12	Cyclohexanone	Solvent free, μW, 100 W	4	93
13	Cyclopentanone	Solvent free, μW, 100 W	4	92
14	Menthone	Solvent free, μW, 100 W	4	85
15	Carvone	Solvent free, μW, 100 W	3	75
16	Benzophenone	Solvent free, μW, 100 W	15	75
17	Benzophenone	Solvent free, μW, 180 W	12	96
18	Methyl acetoacetate	Solvent free, μW, 100 W	4	83
19	Cholestanone	Solvent free, μW, 100 W	5	84
20		Solvent free, μW, 100 W	30	No reaction
21	Vanillin	Solvent free, μW, 100 W	5	81

[a] Substrate–1,2-ethanedithiol–$SnCl_2{\cdot}2H_2O$ = 1:1:0.05.

[b] Microwave irradiation using a Samsung microwave oven, Model-1630N.

[c] Yield of the isolated pure product which was characterised by ^1H NMR, IR and mass spectroscopy.

[d] Another unidentified by-product was observed.



Scheme 1.

Table 2. Optimisation of the amount of $SnCl_2{\cdot}2H_2O$ in the formation of 1,3-dithiolanes of *p*-methylbenzaldehyde

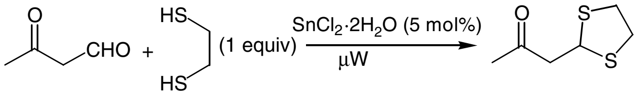
Entry	Substrate	Mol % catalyst	Time[a] (min)	Yield[b] (%)
1	p-$CH_3C_6H_4CHO$	2	3	52
2		2	5	55
3		5	3	89
4		7	3	88
5		10	3	89

[a] Microwave irradiation using a Samsung microwave oven, Model-1630N.

[b] Yield of the purified product.

Both aliphatic and aromatic aldehydes (Table 1, entries 1–9 and 21) gave reasonably good yields of 1,3-dithiolanes, except citral (Table 1, entry 7), in which case, an unidentified by-products was formed besides the desired product. Interestingly, citral (entry 7) gave a 68% yield as against a 55% yield (13% increase in % of yield) when the amount of 1,2-ethanedithiol was reduced to 1 equiv from 2 equiv. Both cyclic and acyclic ketones (Table 1, entries 10–19) gave very good yields of the desired 1,3-dithiolanes. Even benzophenone (entry 16) also gave 75% of its 1,3-dithiolane derivative when treated with 1 equiv of 1,2-ethanedithiol for 15 min. Changing the power to 180 W (entry 17) gave an even better result. The reaction went to completion within 12 min giving a 96% yield. Shi's Ketone (entry 20) was recovered intact even after microwave irradiation for 30 min.

In order to study the chemoselectivity of our method, 3-oxo-butyraldehyde was treated with 1,2-ethanedithiol (1 equiv). The aldehyde group was protected as its 1,3-



Scheme 2.

dithiolane in preference to the ketone functionality (Scheme 2).

In conclusion, we have reported an efficient and chemoselective and yet simple, straightforward, environmentally benign protocol for the synthesis of 1,3-dithiolanes from carbonyl compounds using $SnCl_2 \cdot 2H_2O$. No aqueous work-up, no solvent, dehydrating agent, anhydrous atmosphere or tedious removal of water during the reaction were required. The compatibility of the catalyst with acid sensitive functional groups such as nitro, methoxy, carbomethoxy, 1,3-dioxolane, etc. were the main advantages of the method.

Acknowledgements

The authors are grateful to the Vice-Chancellor, Dibrugarh University for providing the facilities for our work. Help from Dr. Nabin C. Barua, Sc F and Deputy Director, RRL, Jorhat, India is gratefully acknowledged.

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22. Typical procedure: A mixture of *p*-methylbenzaldehyde (0.240 g, 2 mmol), 1,2-ethanedithiol (0.188 g, 2 mmol) and $SnCl_2 \cdot 2H_2O$ (0.023 g, 0.1 mmol) was taken in an Erlenmeyer flask and irradiated with microwaves. After a few seconds, the $SnCl_2 \cdot 2H_2O$ dissolved in the reaction mixture. By monitoring with TLC, the conversion was found to be complete in 3 min. After cooling, the homogeneous mixture was passed through a small silica gel (60–120 mesh) pad and the product was eluted using 1% ethyl acetate in hexane as eluent. Yield = 89% (0.349 g, 1.78 mmol). IR (KBr): 740, 820, 840, 1025, 1080, 1290, 1400, 1480, 2870 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 3H), 3.25–3.45 (m, 4H), 5.55 (s, 1H), 7.09 (d, 2H), 7.40 (d, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): 21.01, 40.08, 56.05, 127.75, 129.10, 137.07, 137.75 ppm; MS: *m*/*z* 196, 168, 153, 135, 91, 45.