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Ferric chloride: A simple and an efficient catalyst for the chemoselective synthesis of 1,3-dithiolanes under solvent-free condition

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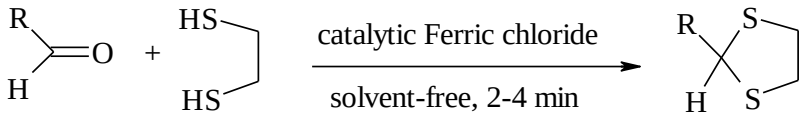
ABSTRACT

A simple and an efficient protocol for the conversion of aldehydes into 1,3-dithiolanes using 1,2-ethanedithiol in the presence of catalytic amount of ferric chloride ($FeCl_3$) at 80 °C under solvent-free condition is described. The protocol successfully tolerates a variety of functional groups, gives excellent product yield, and interestingly, is chemoselective in nature as aldehydes in the presence of ketones can selectively be converted into 1,3-dithiolanes under the present conditions.



R = Aryl

Key words: 1,3-Dithiolanes; aldehydes; 1,2-ethanedithiol; ferric chloride; solvent-free condition.

1. Introduction

1,3-Dithiolanes have long been used as carbonyl protective groups and as the most successful sulfur-stabilized acyl anion equivalents; also used widely as masked nucleophilic acylating agents, and play a key role in the synthon concepts.[1] In addition, 1,3-dithiolanes are versatile building blocks for the preparation of enantiomerically pure drugs,[2] natural products[3] and herbicidal antidotes.[4] Preparation of 1,3-dithiolanes involves the condensation of aldehydes and ketones with 1,2-dithiols in the presence of $BF_3.OEt_2$,[5] *p*-TSA,[6] Bu_4NBr_3,[7] TMSOTf,[8] $SOCl_2$-SiO_2,[9] $ZrCl_4$,[10] $RuCl_3$,[11] $LiClO_4$,[12] $Sc(OTf)_3$,[13] $In(OTf)_3$,[14] $Bi(NO_3)_3$,[15] CAN,[16] Ionic Liquid

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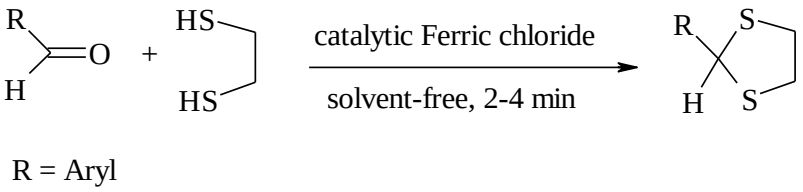
{[bmim]Br},[17] *p*-TsOH/SiO_2,[18] $H_3PW_{12}O_{40}$,[19] $TaCl_5$–SiO_2,[20] $Cu(OTf)_2$–SiO_2,[21] $InCl_3$,[22] LiBr,[23] $Co(BF_4)_3 \cdot xH_2O$,[24] $SnCl_2 \cdot 2H_2O$,[25] $Yb(OTf)_3$,[26] $InBr_3$,[27] $SnCl_2 \cdot 2H_2O$,[28] DMF at 0 °C,[29] and $Fe(CF_3CO_2)_3$/$Fe(CF_3SO_3)_3$.[30] Natural Kaolinitic clay[31] and resin-bound reagents[32] have also been used for the purpose. $HClO_4$-SiO_2[33], lanthanum(III) nitrate hexahydrate, [34] 30% H_2O_2/I_2 in aqueous micellar system,[35] Brønsted acidic ionic liquid with an alkane sulfonic acid,[36] glycerol,[37] tungstate-sulfuric acid,[38] PEG_{1000}-based dicationic acidic ionic liquid,[39] sulfonated polyanthracene,[40] graphene oxide,[41] sBa-15-ph-SO_3H[42,] ethyl lactate,[43] nitrated imidodiphosphoric acid[44] and alumina-sulfuric acid[45] also find application in the synthesis of 1,3-dithiolanes. Limitations associated with some of these methods include: use of excess 1,2-dithiol, involvement of anhydrous conditions, difficulties in work-up, difficulty in the isolation of the products, low yields, long reaction durations, requirement of inert atmosphere, harsh reaction conditions, complex and expensive catalysts; stoichiometric reagents and incompatibility with other groups. Therefore, there is still a need for the development of versatile, simple and environment friendly processes for the synthesis of 1,3-dithiolanes.

Research and developmental studies on the use of readily available, environmentally benign, simple and inexpensive reagent- $FeCl_3$ has expanded greatly in synthetic organic chemistry. A few examples include the use of $FeCl_3$ in the synthesis of dihydropyrimidinones,[46] *bis*-indoline[47] and 4(3*H*)-quinazolinones;[48] oxidation of Hantzsch 1,4-dihydropyridines,[49] Beckmann rearrangement of ketoximes,[50] alkylation of active methylene compounds,[51] preparation and characterization of poly(*o*-phenylenediamine) microrods[52] and in regiospecific nucleophilic ring opening of epoxides.[53]

2. Results and Discussion

In continuation of work from our laboratory on the development of environment friendly methods for the of synthesis of sulfur containing heterocycles,[54] herein, we report an efficient and solvent-free method for the synthesis of 1,3-dithiolanes, which does not rely on the use of complex catalysts or complex reagents. Our procedure involves heating a solvent-free mixture of an aldehyde, 1,2-ethanedithiol and catalytic amount of $FeCl_3$ to get the desired products within 5 min as shown in the **Scheme 1**.



R = Aryl

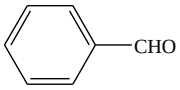
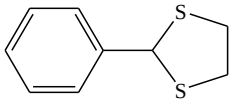
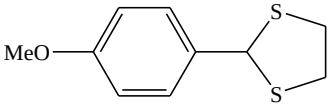
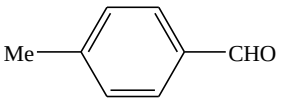
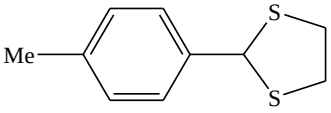
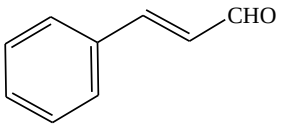
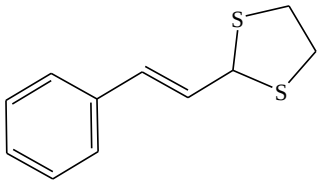
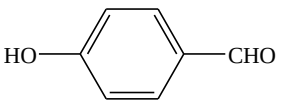
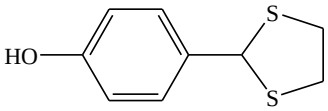
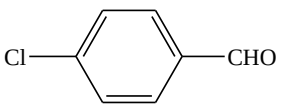
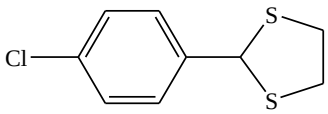
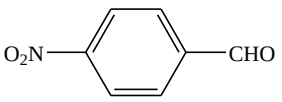
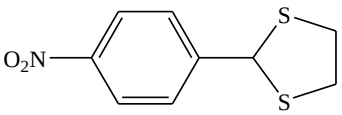
Scheme 1: $FeCl_3$ catalyzed synthesis of 1,3-dithiolanes under solvent-free condition

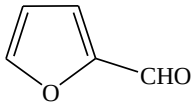
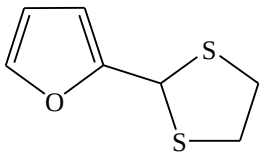
The use of $FeCl_3$ as a catalyst plays a key role in the success of the present reaction in terms of the rate and the yield of the products. It was observed that, by heating a mixture of 5 mmol of furfural with 5 mmol 1,2-ethanedithiol at 80 °C in the presence of 5 mmol of $FeCl_3$, gave the respective 1,3-dithiolane in the modest yield of 75 % in 10 min. Decreasing the amount of the catalyst and time to 2.5 mmol/ 8 min, 1.0 mmol/ 5 min and 0.5 mmol/ 2 min resulted in increase in the product yield from 80, 88 to 92 % respectively. Therefore, the use of just 0.5 mmol of $FeCl_3$ at 80 °C in less than 2 min under solvent-free condition is sufficient to drive the reaction towards getting the product in excellent yield, therefore, 0.5 mmol of $FeCl_3$ was chosen for further studies.

By using 0.5 mmol of $FeCl_3$ in a solvent-free condition at 80 °C, a systematic study was undertaken to investigate the thioacetalization of a variety of aldehydes bearing electron

withdrawing and electron donating groups and the results of this study are presented in the **Table 1**. To our delight, in all the cases respective products were obtained in excellent yield within 4 min.

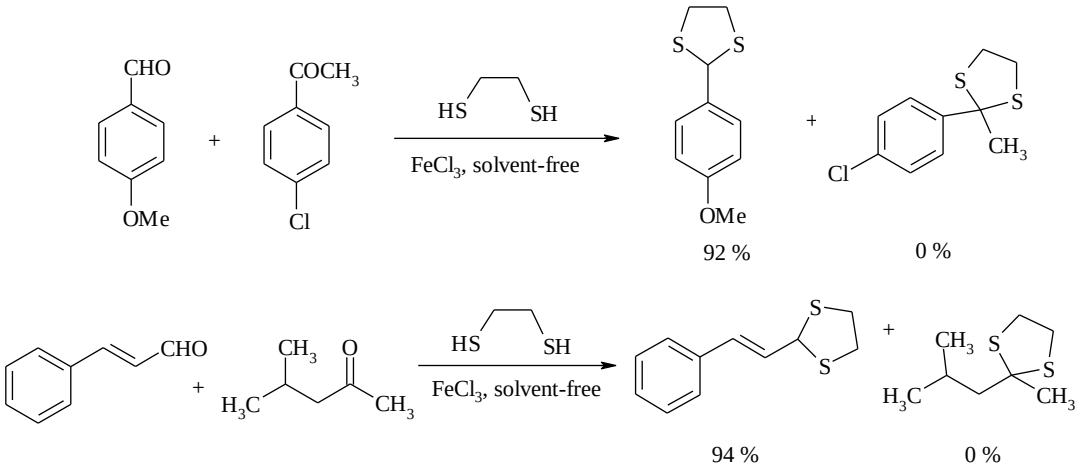
Table 1: $FeCl_3$ catalyzed chemoselective synthesis 1,3-dithiolanes under solvent-free condition at 80 °C[a]

Entry	Substrate	Time (Min)	Product (**3**)	Yield (%)[b]
a		3		92
b		2		92
c		3		89
d		2		94
e		4		86
f		2		88
g		4		83

h		2		92

[a]Substrates:-1,2-Ethanedithiol: Ferric chloride::5:5:0.5 mmol; [b]Isolated yield.

It was observed that, aromatic or acyclic ketones did not undergo the reaction at 80 °C. This prompted us to extend the reaction for the chemoselective protection of an aldehyde in the presence of a ketone, and in a typical experiment, a mixture of 4-methoxybenzaldehyde (5 mmol) and 4-chloroacetophenone (5 mmol) was treated with 1,2-ethanedithiol (5 mmol) in the presence of $FeCl_3$ (0.5 mmol) at 80 °C for 5 min; and observed that, only the 1,3-dithiolane of 4-methoxybenzaldehyde formed in 94% yield and the unreacted 4-chloroacetophenone was recovered back (**Scheme 2**). A similar result was obtained when the experiment was performed on a mixture of cinnamaldehyde and 4-methyl-2-pentanone.



Scheme 2: Chemoselective conversion of an aldehyde into1,3-dithiolane

3. Experimental Section

3.1. *General Information:*

Aldehydes, 1,2-ethanedithiol and $FeCl_3$ are commercially available and were used as received. Progress of the reaction was monitored on TLC (Merck60 silica gel F-254 plates), and the spots were visualized under UV light (254 or 365 nm) by comparison with the authentic samples. Melting points were determined on a Buchi melting point apparatus. IR, ^{1}H NMR and the Mass spectra were recorded on Nicolet 400D FT-IR spectrophotometer, 400 MHz Brucker spectrometer and Shimadzu GC-MS QP 5050A/ Agilent Technologies LC-MS 1200 series instruments respectively.

3.2. *General procedure for the preparation of 1,3-dithiolanes*:

A mixture of aldehyde (5 mmol), 1,2-ethanedithiol (5 mmol) and $FeCl_3$ (0.5 mmol) taken in a flat-bottomed glass tube was heated for 1–4 min at 80 °C in an oil bath. The progress of the reaction was monitored by TLC using 20% EtOAc in petroleum ether as an eluent. After completion of the reaction, the mixture was dissolved in ethyl acetate and filtered. The residual $FeCl_3$ was recycled for three more runs without losing its activity. The filtrate was concentrated

in *vacuo* and the resulting product was directly charged on a silica gel column and eluted with a mixture of EtOAc-petroleum ether (1.5:8.5) to get the pure 1,3-dithiolane.

Spectral data of 1,3- Dithiolanes

2-Phenyl-1,3-dithiolane
M.p: semi-solid;
IR (KBr): υ 3058, 2921, 1494, 1450, 1276, 1072, 1027, 838, 696 cm^{-1};
^1H NMR (400 MHz, $CDCl_3$): δ 3.30–3.38 (m, 2H), 3.47–3.55 (m, 2H), 5.73 (s, 1H), 7.25–7.52 (m, 3H), 7.51–7.52 (d, *J* = 7.6 Hz, 2H);
MS: m/z = 182.7 (M^+).

2-(4′-Methoxyphenyl)-1,3- dithiolane
M.p: 58–60 °C;
IR (KBr): υ 2918, 2831, 1606, 1490, 1465, 1305, 1228, 1174, 1029, 837, 754, 624, 557 cm^{-1};
^1H NMR (400 MHz, $CDCl_3$): δ 3.27–3.33 (m, 2H), 3.44–3.50 (m, 2H), 3.71(s, 3H), 5.68 (s, 1H), 6.85 (d, *J* = 16 Hz, 2H), 7.41 (d, *J* = 16 Hz, 2H);
MS: m/z = 212.6 (M^+).

2-(4′-Methylphenyl)-1,3- dithiolane
M.p: 55–57 °C;
IR (KBr): υ 3062, 2975, 2930, 1605, 1507, 1456, 1292, 1060, 845, 707 cm^{-1};
^1H NMR (400 MHz, $CDCl_3$): δ 2.33 (s, 3H), 3.30–3.32 (m, 2H), 3.33–3.50 (m, 2H), 5.60 (s, 1H), 7.15 (d, *J* = 7.54 Hz, 2H), 7.44 (d, *J* = 7.54 Hz, 2H);
MS: m/z = 197.0 (M^+).

2-(2′-Phenylethenyl)-1,3- dithiolane
M.p. 65–66 °C;
IR (KBr): υ 3029, 3930, 1600, 1450, 1419, 1345, 1279, 1070, 970, 740 cm^{-1};
^1H NMR (400 MHz, $CDCl_3$): δ 3.24–3.59 (m, 4H), 5.25 (d, *J* = 8.8 Hz, 1H), 6.15 (dd, J_1 = 15.5 Hz, J_2 = 8.8 Hz, 1H), 6.50 (d, *J* = 15.5 Hz, 1H), 7.25–7.53 (m, 5H);
MS: m/z = 208.0 (M^+).

2-(4′-Hydroxyphenyl)-1,3-dithiolane
M.p: 115–117 °C;
IR (KBr): υ 3380, 2961, 1595, 1495, 1462, 1352, 1271, 1230, 1090, 1045, 845, 755 cm^{-1};
^1H NMR (400 MHz, $CDCl_3$): δ 3.39–3.46 (m, 2H), 3.57–3.63 (m, 2H), 5.90 (s, 1H), 6.80 (d, *J* = 8.4Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.54(s, 1H);
MS: m/z = 199.0 (M^+).

2-(4′-Chlorophenyl)-1,3-dithiolane
M.p. 117–118 °C;
IR (KBr): υ 3081, 2922, 1630, 1469, 1442, 1380, 1061, 851, 750 cm^{-1};
^1H NMR (400 MHz, $CDCl_3$): δ 3.30–3.37 (m, 2H), 3.42–3.52 (m, 2H), 5.61 (s, 1H), 7.27 (d, *J* = 6.55 Hz, 2H), 7.73 (d, *J* = 6.55 Hz, 2H);
MS: m/z = 217.0 (M^+).

2-(4′-Nitrophenyl)-1,3-dithiolane
M.p: 74–76 °C;
IR (KBr): υ 3085, 2922, 1580, 1535, 1345, 1275, 1076, 822, 730 cm^{-1};
^1H NMR (400 MHz, $CDCl_3$): δ 3.35 (s, 2H), 3.47–3.57 (m, 2H), 5.70 (s, 1H), 7.70 (d, *J* = 8.5 Hz, 2H), 8.17 (d, *J* = 8.5 Hz, 2H);
MS: m/z = 228.0 (M^+).

2-(1′,3′- Dithiolan-2′-yl) furan
B.p: 110–111 °C/5 torr;
IR (KBr): υ 3100, 2920, 1580, 1505, 1415, 1365, 1250, 1010, 930, 849 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.19–3.41 (m, 4H), 5.62 (s, 1H), 6.29 (d, *J* = 4.0 Hz, 2H), 7.32 (t, *J* = 4.0 Hz, 1H);
MS: m/z = 173.0 (M^+).

4. Conclusions

In conclusion, we have disclosed herein, an efficient, solvent-free chemoselective protocol for the synthesis of a series of 1,3-dithiolanes using catalytic $FeCl_3$. The attractive features of this procedure are: excellent product yield, milder reaction condition, high reproducibility, use of inexpensive starting materials, shorter reaction duration, simple reaction set-up, and use of an inexpensive recyclable catalyst. The protocol, therefore, is potentially useful for the industrial applications.

5. Acknowledgements

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6. Conflict of interest

There is no conflict of between the authors for publishing this work.

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