



Nickel(II) chloride as an efficient and useful catalyst for chemoselective thioacetalization of aldehydes

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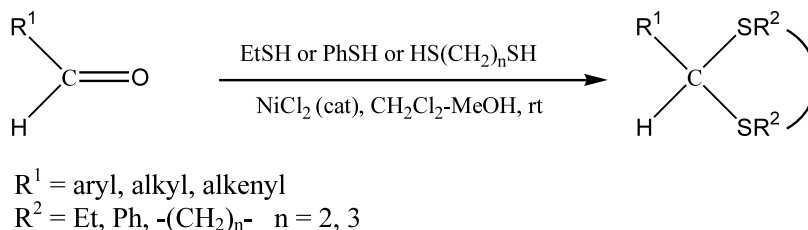
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This paper is dedicated to my teacher Professor Kamalendu Dey, Department of Chemistry, Kalyani University for his valuable guidance and constant encouragement

Abstract—A wide variety of acyclic and cyclic dithioacetals can be prepared chemoselectively from the corresponding aldehydes by employing a catalytic amount of nickel(II) chloride in dry CH_2Cl_2 –MeOH (5:1) at room temperature in good yields. Some of the major advantages of this procedure are high chemoselectivity, ease of operation, high yields and also compatibility with other protecting groups. © 2003 Elsevier Science Ltd. All rights reserved.

The protection of the carbonyl functionality as a dithioacetal¹ is a common practice in multistep synthesis of natural² and non-natural³ products due to the group's inherent stability under both acidic and basic conditions. In addition, thioacetals are also utilized as masked acyl anions⁴ or masked methylene functions⁵ in carbon–carbon bond forming reactions. They are usually prepared by the condensation of carbonyl compounds with thiols or dithiols using a strong protic acid such as HCl ⁶ or Lewis acids such as $\text{BF}_3 \cdot \text{OEt}_2$ ⁷ or ZnCl_2 ⁸ as catalysts. Unfortunately, these procedures have certain disadvantages such as a requirement for stoichiometric amounts of catalyst and also provide low yields. Other Lewis acids viz. AlCl_3 ,⁹ TiCl_4 ,¹⁰ LaCl_3 ,¹¹ SiCl_4 ,¹² WCl_6 ,¹³ $(\text{CH}_3)_3\text{SiCl}$,¹⁴ and 5 M LiClO_4 ¹⁵ have also been employed. All these methods have some drawbacks such as difficulties in work-up^{9,10} the requirement for an inert atmosphere,¹⁵ and the use of

relatively expensive reagents.^{10–15} Recently some solid supported reagents have been used for thioacetalization of various carbonyl compounds, e.g. SOCl_2 – SiO_2 ,¹⁶ $\text{Cu}(\text{OTf})_2$ – SiO_2 ,¹⁷ ZrCl_4 – SiO_2 ,¹⁸ TaCl_5 – SiO_2 ,¹⁹ and CoBr_2 – SiO_2 .²⁰ Very recently new methods for protection of carbonyl compounds as their dithioacetals employed LiBr ,^{21a} LiBF_4 ,^{22a} InCl_3 ,²³ molecular I_2 ,^{24a} NBS ,²⁵ and $\text{Sc}(\text{OTf})_3$.²⁶ Interestingly, only a few methods are known in the literature for the chemoselective protection of aldehydes^{15,16,21–26} in the presence of ketones. Some of the methods mentioned above involve relatively harsh conditions,¹⁶ access acyclic dithioacetals only with difficulty,¹⁶ require an inert atmosphere for the reaction^{15,23–25} and involve expensive reagents,^{17–20,23,26} are incompatible with other protecting groups such as TBS ethers^{7b,21b,22b,24b} and fail to protect deactivated aromatic substrates.²⁶ Consequently, what is needed is a methodology, which works





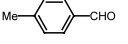
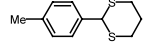
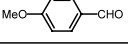
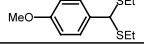
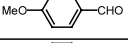
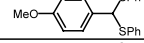
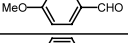
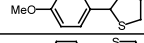
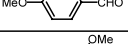
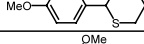
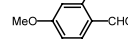
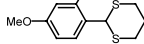
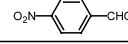
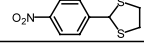
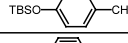
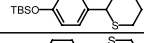
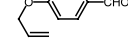
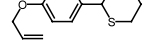
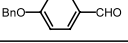
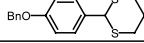
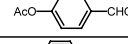
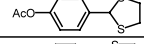
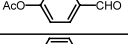
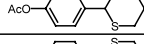
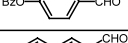
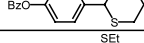

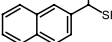

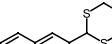

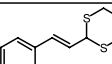

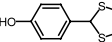

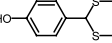

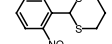

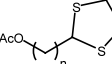

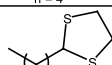

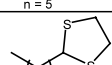

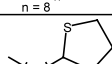

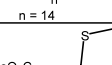


Scheme 1.

Keywords: protection; dithioacetals; ethanethiol; thiophenol; 1,2-ethanedithiol; 1,3-propanedithiol; nickel(II) chloride.

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Table 1. Protection of various aldehydes as the corresponding dithioacetals using nickel(II) chloride (NiCl_2) as catalyst

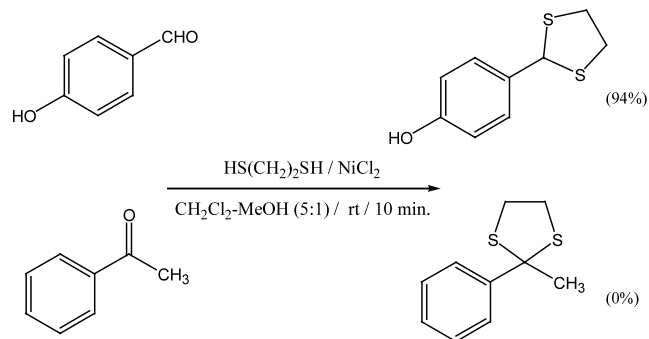
Run	Substrate	Thiol used	Time min/[h]	Product ^a	Yield ^b %
1		1,2-ethanedithiol	[2.75]		96
2		1,3-propanedithiol	[2.50]		94
3		1,3-propanedithiol	[2.25]		92
4		ethanethiol	[5.00]		87
5		thiophenol	[13]		90
6		1,2-ethanedithiol	[0.75]		90
7		1,3-propanedithiol	[1.15]		89
8		1,3-propanedithiol	12		96
9		1,2-ethanedithiol	[20]		82
10		1,3-propanedithiol	[1]		87
11		1,3-propanedithiol	[2.50]		79
12		1,3-propanedithiol	[0.45]		90
13		1,2-ethanedithiol	[3.50]		76
14		1,3-propanedithiol	[4.00]		77
15		1,3-propanedithiol	[5.50]		79
16		ethanethiol	[3.0]		85
17		1,3-propanedithiol	[1.75]		97
18		1,3-propanedithiol	40		83
19		1,2-ethanedithiol	8		96
20		1,3-propanedithiol	30		93
21		1,3-propanedithiol	[18]		84
22		1,2-ethanedithiol	[8]		84
23		1,2-ethanedithiol	[7.0]		80
24		1,2-ethanedithiol	[1.5]		89
25		1,2-ethanedithiol	[7.5]		85
26		1,2-ethanedithiol	10		75

^a All products were characterized by IR, ¹H-NMR, ¹³C-NMR and elemental analysis. ^b Isolated yields after purification

under mild conditions, using inexpensive reagents. Within our ongoing research programme to develop new synthetic methodologies,^{27,28} we proposed that nickel(II) chloride, which acts as a mild Lewis acid might be a useful catalyst for thioacetalization of carbonyl compounds. In this communication, we wish to report a simple and easy method for chemoselective thioacetalization of various aromatic and aliphatic aldehydic compounds using nickel(II) chloride as a new catalyst, depicted in Scheme 1.

According to expectations, the reaction of benzaldehyde (1 mmol) with 1,2-ethanedithiol (1.1 mmol) in the presence of nickel(II) chloride (0.1 mmol) at room temperature in CH_2Cl_2 –MeOH (5:1, 3 mL) afforded the desired 1,3-dithiolane derivative in 96% yield (run 1). Similarly, the 1,3-dithiane derivative of benzaldehyde was obtained from benzaldehyde (run 2), on treatment with 1,3-propanedithiol following an identical procedure. By following this reaction procedure,²⁹ both aromatic as well as aliphatic aldehydes (runs 3–26) were converted smoothly to the corresponding acyclic dithioacetals or cyclic dithioacetals in good yields, on reaction with either thiols or dithiols in the presence of a catalytic amount of nickel(II) chloride at room temperature. The results are summarized in Table 1 with products fully characterized by IR, ^1H NMR, ^{13}C NMR and elemental analysis.³⁰ The results shown in Table 1 clearly indicate the scope and generality of the reaction with respect to different aromatic, aliphatic and unsaturated aldehydes. It is noteworthy that the conversion can be achieved in the presence of other protecting groups such as acetyl, benzyl, benzoyl, allyl, esters and TBS ethers. We have also noticed that highly deactivated aromatic aldehydes can be protected as dithioacetals in good yields (runs 9 and 21) with longer reaction times. It is important to mention that the diethyldithioacetal of naphthaldehyde was obtained from naphthaldehyde (run 16) by using nickel(II) chloride catalyst in 85% yield in 3 h, which provides a much better yield than the procedure reported recently.²⁶ We have also observed that nickel(II) chloride hexahydrate can be used but requires longer reaction times than anhydrous nickel(II) chloride.

Interestingly, this procedure can also be extended for chemoselective protection of an aldehyde in the presence of a ketone. For instance, when an equimolar mixture of *p*-hydroxybenzaldehyde and acetophenone was allowed to react with 1,2-ethanedithiol in presence of a catalytic amount of NiCl_2 only the 1,3-



Scheme 2.

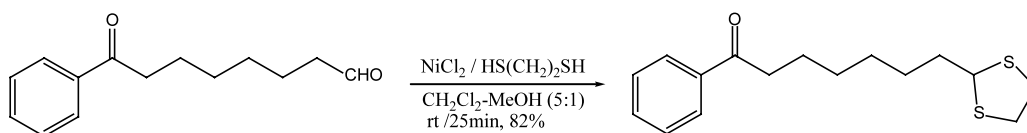
dithiolane derivative of the *p*-hydroxybenzaldehyde was obtained, see Scheme 2.

Furthermore, the aldehyde functionality of a keto-aldehyde, was protected chemoselectively in good yield under identical reaction conditions, see Scheme 3.

In conclusion, we have demonstrated a very simple and convenient protocol for the protection of various aldehydes as dithioacetals in the presence of a wide range of other protecting groups using a catalytic amount of NiCl_2 . An aldehyde group can be protected chemoselectively in the presence of a keto group under these conditions. Moreover, highly deactivated aromatic aldehydes can be converted to the corresponding dithioacetals without any difficulty. Other nickel salts can be used for similar transformations and will be reported in due course.

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Scheme 3.

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- A typical experimental procedure is as follows: To a stirred solution of an aldehyde (1 mmol) in CH_2Cl_2 –MeOH (5:1, 3 mL) was added the thiol (2.2 mmol) or dithiol (1.1 mmol) at room temperature. Nickel(II) chloride (0.1 mmol, 13 mg), prepared from $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ by heating in an oven at 150°C and cooling in a desiccator at rt, was added. After adding the catalyst the reaction mixture turned into black in the case of 1,2-ethanedithiol or dark brown for 1,3-propanedithiol. The reaction mixture was stirred at room temperature and monitored by TLC until the starting material had disappeared. After completing the reaction, it was concentrated in vacuo and the residue was passed through a silica gel column.
- Spectroscopic data of 2-(*p*-methoxyphenyl)-1,3-dithiolane:** IR (KBr): 1608, 1520, 1256, 1180, 1028 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 3.30–3.35 (m, 2H, $2\times\text{-SCH-}$), 3.47–3.51 (m, 2H, $2\times\text{-SCH-}$), 3.78 (s, 3H, OCH_3), 5.63 (s, 1H, ArCH), 6.83 (d, 2H, $J=8.7$ Hz, ArH), 7.44 (d, 2H, $J=8.7$ Hz, ArH). Anal. calcd for $\text{C}_{10}\text{H}_{12}\text{OS}_2$: C, 56.57; H, 5.70; S, 30.20. Found: C, 56.38; H, 5.63; S, 30.01%.
For 2-(4-*tert*-butyldimethylsilyloxyphenyl)-1,3-dithiane: IR (Neat) 1608, 1511, 1270, 1173 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 0.19 (s, 6H, $2\times\text{SiCH}_3$), 0.97 (s, 9H, $\text{Si}(\text{CH}_3)_3$), 1.83–1.98 (m, 1H, $\text{SCH}_2\text{CHCH}_2\text{S}$), 2.10–2.19 (m, 1H, $\text{SCH}_2\text{CHCH}_2\text{S}$), 2.85–2.92 (m, 2H, $2\times\text{-SCH-}$), 2.99–3.10 (m, 2H, $2\times\text{-SCH-}$), 5.12 (s, 1H, ArCH), 6.78 (d, 2H, $J=8.4$ Hz, ArH), 7.30 (d, 2H, $J=8.4$ Hz, ArH); ^{13}C NMR (75 MHz, CDCl_3): δ –4.5 (2C), 18.1, 25.0, 25.6 (3C), 32.1 (2C), 50.8, 120.1 (2C), 128.8 (2C), 131.8, 155.7. Anal. calcd for $\text{C}_{16}\text{H}_{26}\text{OS}_2\text{Si}$: C, 58.84; H, 8.02; S, 19.63. Found: C, 58.60; H, 7.95; S, 19.70%.