



NCS with thiourea as highly efficient catalysts for acetalization of aldehydes

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ABSTRACT

NCS/thiourea-mediated acetalization of aldehydes and alcohols has rapidly provided acetals in almost quantitative yields.

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The selective protection of aldehydes is important for synthetic strategy and is commonly achieved by the formation of *O,O*-acetals.¹ This acetalization can be promoted with alcohols in the presence of protic acids,^{2–6} Lewis acids,^{7–16} transitional metal complexes as catalysts^{17,18}, and under basic conditions.^{19,20} Cheaper environmentally benign catalysts, such as clays,²¹ resins, zeolites,²² polymer-supported reagents²³, and functionalized silica,²⁴ have also been employed. However, these methods require high catalyst loading, stoichiometric amounts of acid, long reaction time or high temperature that may be incompatible with other sensitive functionality.

In recent years, NBS and I₂ have been used as catalysts to promote acetalization reactions under almost neutral conditions and with good chemoselectivity, but either needed to be handled under inert atmosphere condition or the substrates were toxic.^{25–29} We have recently focused upon thiourea catalysis of chlorohydrins,³⁰ β-chloroether³¹, and α-chloroketones³² with NCS and alcohols as optimal solvents. When ketones were replaced with aldehydes the product isolated was the acetal (not the α-chloroaldehyde). Acetal formation had previously been catalyzed by thiourea, yet catalysis of acetalization with both NCS and thiourea offered much faster reactions.

Without thiourea aldehyde (**1**) transformation was slow (Table 1, entry 1), yet the acetalization catalyzed by as little as 2 mol % thiourea rapidly occurred with good yield of the acetal (**2**) (Table 1, entry 2), half of this thiourea gave a slightly slower reaction with a higher yield (Table 1, entry 5). Alternatively less NCS demonstrated similar trends with duration and yield (Table 1, entry 3) that ended with 2 mol %, which caused a significant drop in yield (Table 1, entry 4). If both thiourea and NCS diminished simultaneously again the duration of the reaction increased, but high yields were retained (Table 1, entry 6).

Alternative acetal protection groups were then explored.³³ Suitably fast, high yielding and economic conditions (Table 1,

entry 3) were selected to study the variation of the alcohol. Methanol was replaced with ethanol (Table 2, entry 1) or benzyl alcohol (Table 2, entry 2) without significant change in reaction duration or yield. However, the use of the sterically more

Table 1

NCS- and thiourea-catalyzed acetalization of 3-phenylpropionaldehyde with methanol

Entry	Catalyst (mol %)	Time	Yield (%)
1	NCS (110)	9 h	92
2	NCS (110) + thiourea (2)	<5 min	85
3	NCS (5) + thiourea (2)	15 min	92
4	NCS (2) + thiourea (2)	1 h	76
5	NCS (110) + thiourea (1)	10 min	91
6	NCS (5) + thiourea (1)	45 min	94

Table 2

NCS/thiourea-catalyzed acetalization of 3-phenylpropionaldehyde with a variety of alcohols^a

Entry	ROH	Product	Time (min)	Yield (%)
1	EtOH	3 , R=Et	15 min	90
2	BnOH	3 , R=Bn	15 min	89
3	<i>i</i> PrOH	3 , R= ^{<i>i</i>} Pr	45 min	61
4 ^a	HOCH ₂ CH ₂ OH	4	168 h	92

^a Ethylene glycol (2 mmol) anhydrous THF (6 cm³).

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Table 3
NCS/thiourea-catalyzed acetalization of a variety of aldehydes with methanol^a

Entry	Product	Time	Yield (%)
1	R= <i>n</i> -C ₇ H ₁₅	45 min	92 ^a
2	R= <i>n</i> -C ₈ H ₁₇	45 min	95 ^a
3	R= <i>n</i> -C ₉ H ₁₉	45 min	94 ^a
4	R= <i>n</i> -C ₁₀ H ₂₁	45 min	97 ^a
5	R= <i>n</i> -C ₁₁ H ₂₃	45 min	99 ^a
6	R =	45 min	94 ^a
7	R =	45 min	97 ^a
8	R=Ph	2.5 h	50 ^b

^a Isolated yield of product (%).

^b Starting material converted to product (%), molar ratio determined by ¹H NMR.

hindered 2-propanol gave a slower reaction with a lower yield (Table 2, entry 3). Employment of ethan-1,2-diol for the provision of 1,3-dioxolane proffered a much slower reaction, yet with similar yield to those of **2** (Table 2, entry 4).

Alterations to the aldehyde were subsequently observed with initially a range of aliphatic aldehydes that were slower than **1** but in some cases with even higher yields (Table 3, entries 1–5). The effect of more sterically constrained aldehydes was then studied. The replacement of the α -protons of **1** with methyl groups caused a reduced reaction speed without significant alteration to the yield of the acetal (Table 3, entry 6). The acetalization of cyclohexanecarbaldehyde also had a retarded reaction duration when compared to **1**, but again an excellent yield was realized (Table 3, entry 7). Ultimately benzaldehyde was investigated to afford a much slower reaction. NCS may be converted to HCl that could function as an alternate catalyst.

In summary, a new catalytic acetalization of aldehydes promoted by NCS and thiourea has been demonstrated, when exposed to the air and under non-toxic conditions. These mild conditions offer a particularly efficient method for the preparation of acetals from a wide range of alkyl aldehydes and alcohols.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.006.

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