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Scandium triflate as a recyclable catalyst for chemoselective thioacetalization

Ahmed Kamal* and Gagan Chouhan

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500007, India

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Abstract—Scandium triflate [Sc(OTf)$_3$] has been found to be an extremely efficient and recyclable catalyst for the addition of ethanethiol, 1,2-ethanedithiol and 1,3-propanedithiol to both aromatic and aliphatic aldehydes. In addition, by employing this catalyst, high chemoselective thioacetalization of carbonyl compounds has been achieved. © 2002 Elsevier Science Ltd. All rights reserved.

Thioacetalization of carbonyl compounds plays an important role in organic synthesis. Since the introduction of 1,3-dithianes as nucleophilic acylating reagents by Corey and Seebach,[1] dithioacetals have become widely used tools for C–C bond formation. Furthermore, the stability exhibited by 1,3-dithiolanes under acidic and basic conditions has led to their synthetic utility as carbonyl protecting groups and as intermediates for the conversion of carbonyl compounds to their parent hydrocarbons.[2] In the literature there are numerous methods reported for the preparation of thioacetals from carbonyl compounds employing acid catalysts such as Zn or Mg(OTf)$_2$,[3] BF$_3$·Et$_2$O,[4] AlCl$_3$,[5] TiCl$_4$[6] and LaCl$_3$.[7] A large number of these methods require long reaction times and reflux temperatures and result in unwanted side reactions whilst offering poor selectivity when applied to mixtures of aldehydes and ketones. Although some recent methods employing LiBr,[8] InCl$_3$[9] and LiBF$_4$[10] have been reported to show chemoselectivity, these Lewis acids are destroyed in the work-up procedure and cannot be recovered and reused. However, the developments in this area demand further searches for better catalysts that could be superior to the existing ones with regard to toxicity, handling, selectivity and recyclability. Recently, scandium triflate has been identified as a mild and selective reagent for various transformations in organic synthesis.[11] In particular, scandium(III) trifluoromethanesulfonate (triflate) has been used extensively as a Lewis acid in aldol,[12] Diels–Alder,[13] Friedel–Crafts[14] and Fries rearrangement reactions.[15] Scandium triflate has several advantages over other Lewis acids, it is stable in water and therefore does not decompose under aqueous work-up conditions, unlike other conventional Lewis acids. Thus, recyclization of the scandium triflate is often possible and renders the procedure relatively environmentally acceptable by utilizing these properties; this catalyst has been successfully applied to several synthetic reactions.[16]

We here in report an efficient method for the thioacetalization of carbonyl compounds in good to high yields, as well as the chemoselective protection of various carbonyl compounds by employing scandium triflate. This methodology provides selective protection of the aldehyde functionality of β- and γ-ketoaldehydes. Moreover, this catalyst has been recovered almost quantitatively from the aqueous layers and has been reused for second thioacetalization processes and the yields of the second runs were comparable to those of the first run (Table 1, products **2b**, **2d**, **3g**).

Interestingly, the experimental procedure for thioacetalization is remarkably simple and does not require the use of dry solvents or inert atmospheres. A catalytic quantity of scandium triflate (4 mol%) was added to a stirred solution of the carbonyl compound in dichloromethane and to this was added the required thiol (1.2 equiv.) and the mixture stirred at room temperature. The generality of this process has been proved with a wide range of aromatic, aliphatic and heterocyclic aldehydes. Accordingly, dithioacetals, 1,3-dithiolanes and 1,3-dithianes have been obtained by the reaction of ethanethiol, 1,2-ethanedithiol and 1,3-propanedithiol, respectively, in the presence of catalytic amounts of Sc(OTf)$_3$ (Scheme 1); the results are illustrated in Table 1.[17]

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* Corresponding author. Tel.: +91-40-7193157; fax: 91-40-7160757; e-mail: ahmedkamal@iict.ap.nic.in

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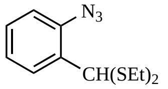
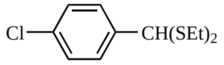
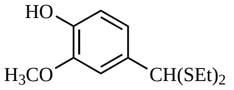
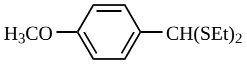
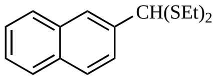
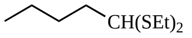
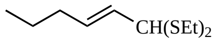
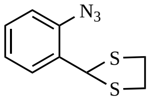
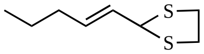
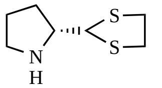
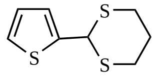
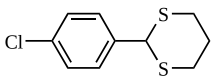
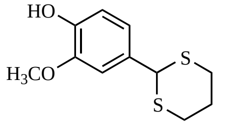
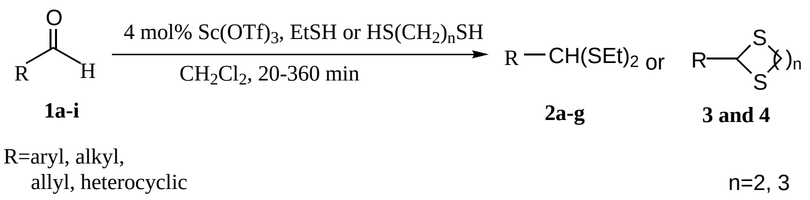
Table 1. Preparation of dithioacetals 1,3-dithiolanes and 1,3-dithianes using scandium triflate

Entry (1)	Products (**2-4**)[a]		Time (min)	Yield (%)[b]
a		(**2a**)	20	94
b		(**2b**)	20	93/88[c]
c		(**2c**)	360	59
d		(**2d**)	35	80/80[c]
e		(**2e**)	360	57
f		(**2f**)	50	90
g		(**2g**)	50	87
a		(**3a**)	20	92
g		(**3g**)	50	88/85[c]
h		(**3h**)	240	76
i		(**4i**)	50	80
b		(**4b**)	30	90
c		(**4c**)	360	55

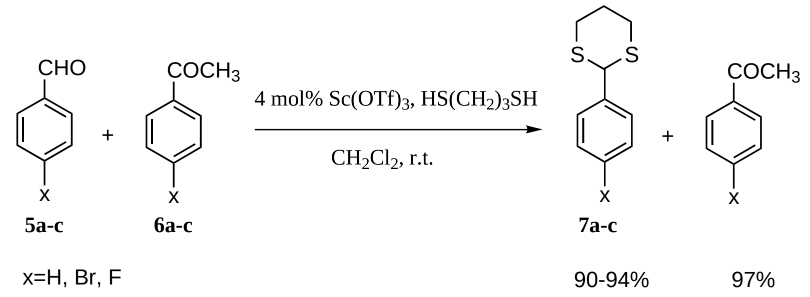
[a] All products were characterised by ^{1}H NMR, IR and mass spectroscopy.[b] Isolated yields after column chromatography on silica gel.[c] Isolated yields with reused catalyst (recovered catalyst 92%)



Scheme 1.

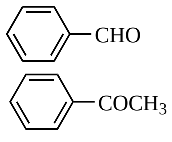
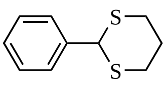
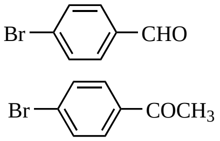
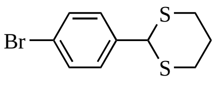
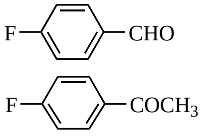
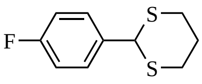
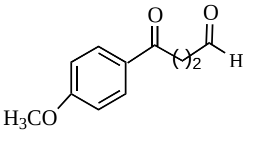
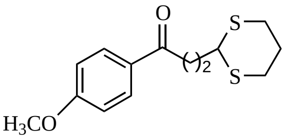
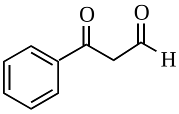
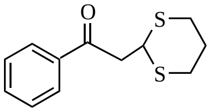
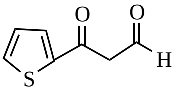
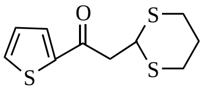
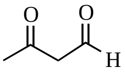
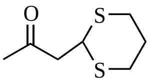
It has been observed that both activated and weakly activated aromatic aldehydes form thioacetals in near quantitative yields, whereas in the cases of entries **1c** and **1e** the yields are only moderate even after prolonged reaction times. Aliphatic aldehydes (entries **1f** and **1g**) also react efficiently to produce the corresponding thioacetals. Similarly, 1,3-dithiolanes (**3a**, **3g**, **3h**) and 1,3-dithianes (**4b**, **4c**, **4i**) have been obtained by the reaction of 1,2-ethanedithiol and 1,3-propanedithiol, respectively, in good yields.

It is interesting to note that ketones did not produce the corresponding thioacetals under the same reaction conditions. This reactivity of $Sc(OTf)_3$ led us to explore the chemoselective protection of aldehydes in the presence of ketones. With this objective, as a representative example we carried out some experiments with equimolar mixtures of an aldehyde and a ketone (Scheme 2, Table 2). It was observed that in this mixture, the corresponding aldehyde formed the dithiolane whilst the ketone was almost completely recovered.

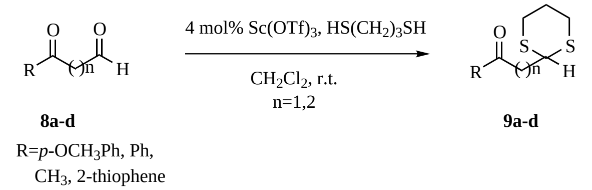


Scheme 2.

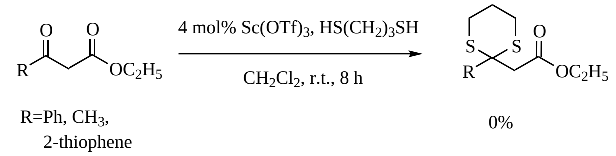
Table 2. Chemoselective protection of aldehyde functionalities using scandium triflate

Entry	Substrate	Product[a]		Time (min)	Yield (%)[b]
5a **6a**			(**7a**)	30	94
5b **6b**			(**7b**)	30	92
5c **6c**			(**7c**)	30	90
8a			(**9a**)	90	60
8b			(**9b**)	120	57
8c			(**9c**)	80	63
8d			(**9d**)	90	60

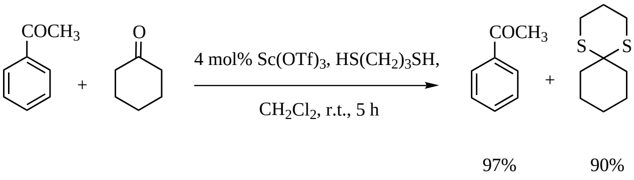
[a]All products were characterised by ^1H NMR, IR and mass spectroscopy. [b]Isolated yields after column chromatography on silica gel.



Scheme 3.



Scheme 4.



Scheme 5.

This method has also been extended for the intramolecular chemoselectivity between keto and aldehyde functionalities (Scheme 3). However, enolizable ketones under the same conditions with scandium triflate did not produce the corresponding dithioacetals, even after prolonged reaction times (Scheme 4).

Furthermore, it was also observed that the aliphatic ketone, cyclohexanone, could be selectively protected in the presence of the aromatic ketone, acetophenone, by employing the present methodology (Scheme 5).

In conclusion, we have demonstrated the use of scandium triflate for the thioacetalization of aromatic, aliphatic and heterocyclic aldehydes under extremely mild conditions where the catalyst could be readily recovered and reused thus making this procedure environmentally acceptable. Moreover, the demonstration of the high chemoselectivity between the two keto functionalities as well as the keto and aldehyde groups, in good to high yields and in short reaction times makes the present method a practical protocol for thioacetalization.

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17. **Typical experimental procedure**: To a stirred solution of scandium triflate (4 mol%) and *p*-chlorobenzaldehyde (4 mmol) in dichloromethane (50 ml) at room temperature was added ethanethiol (4.8 mmol). The mixture was stirred at room temperature for 20 min. After completion of the reaction, as indicated by TLC, water (25 ml) was added to the reaction mixture, which was then extracted with dichloromethane. The crude product was purified by silica gel column chromatography to furnish the thioacetal in 93% yield. The aqueous layer containing the catalyst could be evaporated under reduced pressure to give a white solid. The FT-IR spectrum of the recovered material was identical to that of the commercially available salt, which could be reused for the next thioacetalization reaction (Table 1, product **2b**).