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Efficient and chemoselective acetalization and thioacetalization of carbonyls and subsequent deprotection using InF_3 as a reusable catalyst

Sridhar Madabhushi *, Kishore Kumar Reddy Mallu, Narsaiah Chinthala, China Ramanaiah Beeram, Venkata Sairam Vangipuram

Fluoroorganics Division, Indian Institute of Chemical Technology, Hyderabad 500607, India

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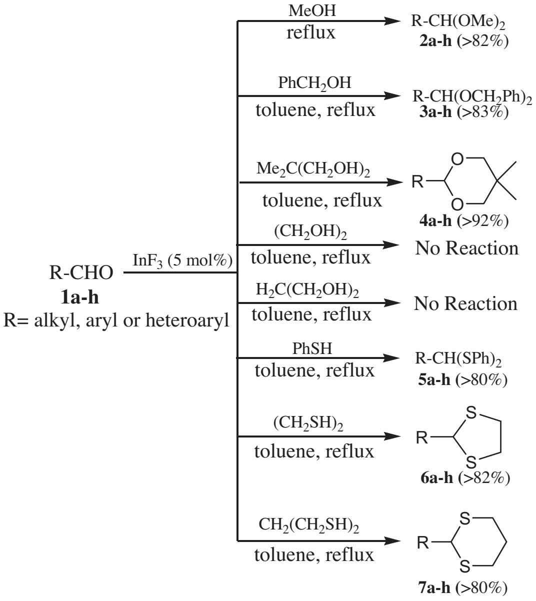
ABSTRACT

An efficient and chemoselective method for preparation of acetals and dithioacetals of aldehydes and their deprotection under catalysis of InF_3 is described.

Acetalization and thioacetalization are important transformations for the protection of a carbonyl group in multistep organic synthesis. Acetals and dithioacetals tolerate a wide range of nucleophilic, basic and organometallic reagents, reducing agents, and nonacidic oxidants. Dithioacetals or dithianes are also useful for the generation of masked carbonyl anions which are employed in a C–C bond formation reaction known as Corey-Seebach reaction.[1] Hence, studies on acetalization and thioacetalization of carbonyls continue to receive high attention and several methods were developed for acetalization and thioacetalization of carbonyls in the literature.[2] However, there is a dearth of methods for chemoselective acetalization and thioacetalization of carbonyls and the existing methods[3] suffer from one or more of the practical limitations such as long reaction times, high catalyst loading, limited substrate scope, use of toxic reagents and lack of commercial availability of the catalyst. In our recent study, we found an efficient method for selective acetalization and thioacetalization of a variety of aliphatic, aromatic, and heteroaromatic aldehydes using InF_3 as the catalyst as shown in Scheme 1 and under similar conditions, ketones remained unreactive.

In recent years, Indium (III) reagents, particularly $InCl_3$, $InBr_3$, InI_3, and $In(OTf)_3$, have emerged as promising catalysts for various organic transformations.[4] When compared to these indium reagents, InF_3 has, however, less significance as a catalyst and its applications in organic synthesis have remained scarce in the literature.



Scheme 1. Acetalization and thioacetalization of an aldehyde using InF_3 as a catalyst.

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* Corresponding author. Tel.: +91 040 27191772; fax: +91 040 27160387.
E-mail address: smiict@gmail.com (S. Madabhushi).

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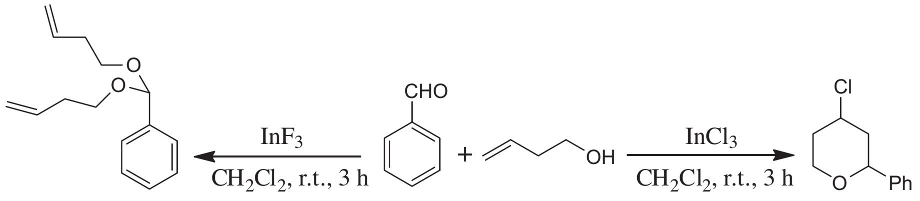
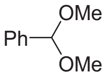
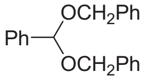
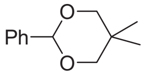
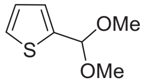
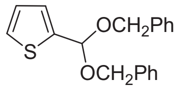
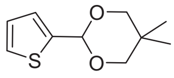
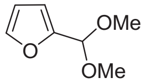
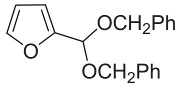
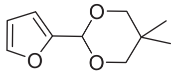
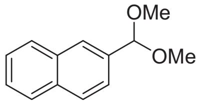
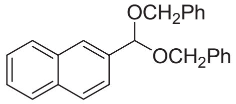
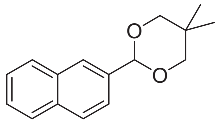
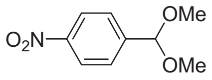
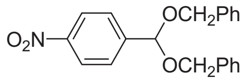
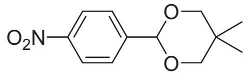
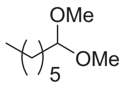
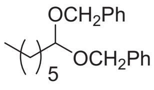
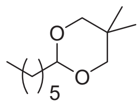
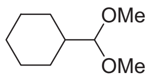
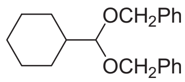
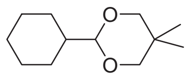
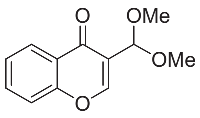
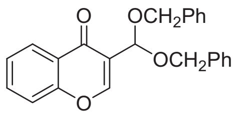
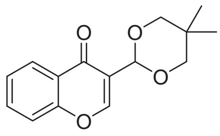


Scheme 2. Reactions of benzaldehyde and homoallyl alcohol in the presence of InF_3 and $InCl_3$.

Table 1
InF_3 catalyzed synthesis of acetals and dioxanes

Entry	Acetal **2** % yield[a] (reaction time)	Acetal **3** % yield[a] (reaction time)	Dioxane **4** % yield[a] (reaction time)
a	 87 (5h)	 86 (4h)	 94 (4.5h)
b	 87 (4.5h)	 87 (4h)	 95 (4h)
c	 85 (4.5h)	 85 (4h)	 96 (4h)
d	 85 (5h)	 85 (4.5h)	 98 (4.5h)
e	 82 (4h)	 83 (5h)	 92 (5h)
f	 86 (4h)	 87 (4h)	 95 (3.5h)
g	 86 (4h)	 90 (4h)	 97 (3.5h)
h	 84 (4h)	 86 (5h)	 (95 (5h)

[a] Isolated yields and all products gave satisfactory ^1H, ^{13}C NMR, IR, and Mass spectral data.

Recently, we were interested in the preparation of 4-fluoropyrans by Prins reaction of a homoallylic alcohol and benzaldehyde and we envisioned that InF_3 could possibly promote this reaction as Lee et al.,[5] reported earlier formation of 4-chloropyrons using $InCl_3$. In our study, the expected Prins reaction, however, did not proceed with InF_3 but it was found to catalyze formation of acetal of benzaldehyde with homoallyl alcohol in good yield (86%) as shown in Scheme 2, which is hitherto not known in the literature.

The above observation prompted us to study the scope of acetalization of carbonyl groups with other alcohols under catalysis of InF_3. In our preliminary study, we found a variety of aldehydes such as benzaldehyde **1a**, thiophene-2-carboxaldehyde **1b**, furfural **1c**, 2-napthaldehyde **1d**, 4-nitrobenzaldehyde **1e**, heptanal **1f**, cyclohexanecarboxaldehyde **1g,** and chromone-3-carboxaldehyde **1h** to undergo efficient acetalization with methanol and InF_3 as a catalyst under reflux condition producing corresponding acetals **2a–h** in 82–87% yields. In a similar study, we observed efficient acetalization of aldehydes **1a-h** with benzylalcohol, which gave corresponding dibenzylacetals **3a–h** in 83–90% yields and also with 2,2-dimethyl-1,3-propanediol giving corresponding dioxanes