Available online at www.sciencedirect.com

ScienceDirect

Tetrahedron Letters 47 (2006) 9317–9319

Tetrahedron Letters

Indium triflate mediated acetalization of aldehydes and ketones

Brendan M. Smith and Andrew E. Graham*

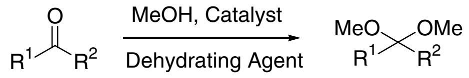
Department of Chemistry, University of Wales Swansea, Singleton Park, Swansea SA2 8PP, UK

Received 6 September 2006; revised 9 October 2006; accepted 19 October 2006
Available online 9 November 2006

Abstract—Aldehydes and ketones are rapidly transformed into either acyclic or cyclic acetals at room temperature in high yields and in very short reaction times using catalytic quantities of indium triflate, in contrast to previous reports.

Acetalization is a well-known synthetic procedure for the protection of carbonyl groups in multistage synthesis,[1] and is achieved by treatment of aldehydes or ketones with an alcohol or diol and a dehydrating agent in the presence of Brønsted or Lewis acids (Scheme 1).[2] The toxic nature of the acid employed or the requirement to utilize it in stoichiometric quantities has led to a number of reports detailing the use of Lewis acids active in catalytic quantities and which achieve this transformation under mild conditions.[3] While investigating the suitability of a number of Lewis acid catalysts to participate in tandem oxidation/acetalization sequences, we were surprised to observe that indium trichloride is a very much more active catalyst than was previously reported.

Indium salts have previously found widespread use as highly effective, water-tolerant Lewis acid catalysts in a variety of synthetic transformations,[4] including the conversion of aldehydes into acylals[5] and aldehydes and ketones into thioacetals.[6] Recently, Ranu reported that catalytic quantities of indium trichloride in cyclohexane/methanol mixtures catalyzed the formation of acetals in good yields, although the process required reaction times in the order of 6–14 h at elevated temperatures with the azeotropic removal of water.[7] The authors commented that the acetalization reaction was not effective in polar solvents such as THF, acetonitrile or dichloromethane. We noted, however, during our studies that treatment of benzaldehyde with catalytic quantities of either indium tribromide, indium trichloride[8] or indium triflate with a twofold excess of trimethyl orthoformate in dichloromethane at room temperature rapidly produced excellent yields of the desired dimethyl acetal. Indium triflate proved to be the most highly active catalyst, producing the acetal within 5 min of addition (Table 1), and was highly effective even at 0.1 mol % quantities in preparative scale reactions. Furthermore, these reactions did not require an aqueous work-up or chromatographic purification, with pure material being isolated by passing the reaction mixture through a short plug of neutral alumina to remove the catalyst.[9] We noted that reactions catalyzed by indium chloride or indium triflate in cyclohexane at room temperature led to very slow formation of the acetal, and the reactions in cyclohexane/methanol mixtures did not led to any acetal formation.



Scheme 1.

We next investigated the acetalization reactions of a range of carbonyl compounds using indium triflate (1 mol %) in dichloromethane at room temperature in the presence of trimethyl orthoformate, triethyl orthoformate or diols (Table 2). It was found that a range of carbonyl compounds were rapidly and efficiently transformed into their acetal counterparts in very high yields. In some cases, such as 2-furancarboxaldehyde and cyclopentanone, the transformation was found to be more efficient if the catalyst was added in two equal portions over the course of the reaction. The transformation of 2-furancarboxaldehyde is also noteworthy given the acid-sensitive nature of this compound.

Keywords: Indium triflate; Acetalization.

* Corresponding author. Tel.: +44 1792 295915; fax: +44 1792 295747; e-mail: A.E.Graham@swansea.ac.uk

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.10.111

Table 1. Indium catalyzed acetalization of benzaldehyde

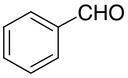
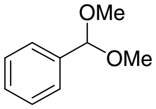
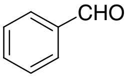
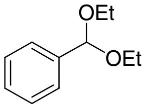
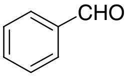
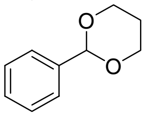
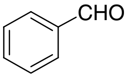
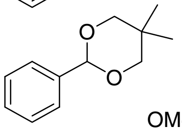
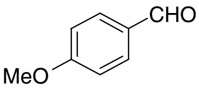
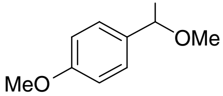
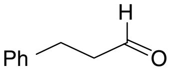
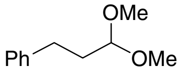
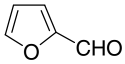
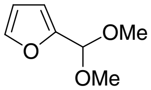
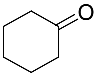
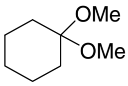
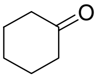
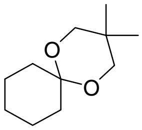
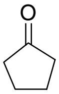
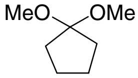
Entry	Conditions[a]	Time (min)	Conversion[b] (%)
1	$InCl_3$ (1 mol %), CH_2Cl_2, $(MeO)_3CH$ (2 equiv), rt	5	67
2	$InBr_3$ (1 mol %), CH_2Cl_2, $(MeO)_3CH$ (2 equiv), rt	5	93
3	$In(OTf)_3$ (1 mol %), CH_2Cl_2, $(MeO)_3CH$ (2 equiv), rt	5	100
4	$In(OTf)_3$ (0.1 mol %), CH_2Cl_2, $(MeO)_3CH$ (2 equiv), rt	5	100[c]

[a] Reactions with 1 equiv of $(MeO)_3CH$ gave similar conversions.

[b] Estimated by ^1H NMR spectroscopy.

[c] 0.1 mol % quantities of catalyst are also effective on preparative scale reactions.

Table 2. Acetalization of carbonyl compounds catalyzed by indium triflate

Entry	Carbonyl[a]	Time (min)	Product[b]	Yield[c] (%)
1		5		99[d]
2		5		98
3		10		89
4		5		89
5		5		98
6		5		98[e]
7		5		99[f]
8		5		94
9		5		92
10		10		93[f]

[a] All carbonyl compounds were used as supplied.

[b] All reactions were carried out at room temperature in CH_2Cl_2 using 1 mol % of catalyst.

[c] All compounds gave satisfactory spectroscopic data.

[d] 98% yield obtained with 0.1 mol % catalyst in 5 min.

[e] 98% yield obtained with 0.1 mol % catalyst in 5 min.

[f] Catalyst added in two equal portions.

The reaction of acetophenone produced only low yields (∼30%) of the corresponding acetal under these conditions.

In conclusion, indium salts are more highly efficient catalysts for the synthesis of dimethyl acetals than previously thought and produce acetals under very mild conditions from a range of carbonyl compounds in high yields and in very short reaction times. The reactions are extremely simple and do not generally require chromatographic purification and proceed without the requirement for inert or anhydrous reaction conditions or elevated temperatures.

Typical experimental procedure: To a mixture of 2-furancarboxaldehyde (113 mg, 1.17 mmol) and trimethyl orthoformate (250 mg, 2.35 mmol) in dichloromethane (15 mL) at room temperature was added indium triflate (3.3 mg, 0.5 mol %) and the reaction mixture stirred at room temperature for 3 min. A further portion of the catalyst (3.3 mg, 0.5 mol %) was added at this time and the reaction mixture stirred for a further 2 min. Next, the mixture was passed through a short plug of neutral alumina which was then washed with additional dichloromethane (2 × 5 mL) and the solvent was removed under reduced pressure to give the product *2-furancarboxaldehyde dimethyl acetal* (165 mg, 99%); ^{1}H NMR ($CDCl_3$; 400 MHz) $\delta = 3.28$ (s, 6H), 5.37 (s, 1H), 6.29 (m, 1H), 6.35 (m, 1H), 7.34 (m, 1H); ^{13}C NMR ($CDCl_3$; 100 MHz) $\delta = 151.3$, 142.9, 110.5, 108.9, 98.4, 53.2; ν_{max} (film)/cm^{-1} (neat) 2942, 2896, 2833, 1346, 1190, 1053, 976 and 738; MS (EI) m/z 142; HRMS (EI) calcd for $C_9H_{10}O_3$ (M^+) 142.0624, found (M^+) 142.0624.

Acknowledgements

The authors thank the Engineering and Physical Sciences Research Council for financial support (BMS) and the EPSRC National Mass Spectrometry Service, University of Wales Swansea, UK.

References and notes

1. Kocienski, P. J. *Protecting Groups*; Thieme: New York, 2003.
2. (a) Wenkert, E.; Goodwin, T. E. *Synth. Commun.* **1977**, *7*, 409–415; (b) Torok, D. S.; Figueroa, J. J.; Scott, W. J. *J. Org. Chem.* **1993**, *58*, 7274–7276; (c) Lu, T.-J.; Yang, J.-F.; Sheu, L.-J. *J. Org. Chem.* **1995**, *60*, 2931–2934; (d) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2003**, *59*, 2765–2771.
3. (a) Gemal, A. L.; Luche, J. H. *J. Org. Chem.* **1979**, *44*, 4187–4189; (b) Ishihara, K.; Karumi, Y.; Kubota, M.; Yamamoto, H. *Synlett* **1996**, 839–841; (c) Clerici, A.; Pastori, N.; Porta, O. *Tetrahedron* **1998**, *54*, 15679–15690; (d) Firouzabadi, H.; Iranpoor, N.; Karimi, B. *Synlett* **1999**, 321–323; (e) Leonard, N. M.; Oswald, M. C.; Freiberg, D. A.; Nattier, B. A.; Smith, R. C.; Mohan, R. S. *J. Org. Chem.* **2002**, *67*, 5202–5207; (f) Kumar, R.; Chakraborti, A. K. *Tetrahedron Lett.* **2005**, *46*, 8319–8323.
4. Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *Curr. Org. Chem.* **2003**, *7*, 1661–1689.
5. Yin, L. A.; Zhang, Z. H.; Wang, Y. M.; Pang, M. L. *Synlett* **2004**, 1727–1730.
6. Ceschi, M. A.; de Araujo Felix, L.; Peppe, C. *Tetrahedron Lett.* **2000**, *41*, 9695–9699.
7. Ranu, B. C.; Jana, R.; Samanta, S. *Adv. Synth. Catal.* **2004**, *346*, 446–450.
8. Indium trichloride has been reported to be a poor catalyst for acetal formation in the absence of trimethyl orthoformate; Kim, Y.-J.; Varma, R. S. *Tetrahedron Lett.* **2005**, *46*, 7447–7449.
9. An aqueous work-up of the reaction mixture led to a rapid and complete hydrolysis of the acetal back to the corresponding carbonyl compound.