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Indium triflate mediated tandem acetalisation-acetal exchange reactions under solvent-free conditions

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ABSTRACT

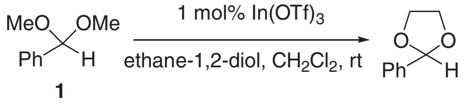
Acyclic acetals and ketals undergo exchange reactions in the presence of catalytic quantities of indium(III) triflate and diols to generate the corresponding cyclic acetals and ketals in excellent yield. The protocol is rapid, employs mild conditions and can be adapted to employ solvent-free reaction conditions. We have further developed this methodology to encompass a tandem acetalisation-acetal exchange protocol which provides facile access to cyclic ketals from unreactive ketones also under very mild, solvent-free reaction conditions.

The protection of carbonyl compounds as both cyclic or acyclic acetals in multistage synthetic sequences is a very well established strategy,[1] and is usually achieved by treatment of aldehydes or ketones with an alcohol or diol and a dehydrating agent in the presence of Brønsted or Lewis acids.[2] The toxic nature of the acid employed or the requirement to utilise 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 reaction conditions.[3] Despite this considerable body of work, substrate scope continues to be a major limiting factor, in particular, for the protection of unreactive ketones especially in the presence of thermally labile or acid sensitive functionality. As part of an ongoing programme to develop highly efficient and environmentally benign reaction processes,[4] we disclose that indium(III) triflate [In(OTf)$_3$] is a highly efficient catalyst in acetal exchange reactions, giving excellent yields of cyclic acetals and ketals directly from acyclic acetals and ketals in the presence of near stoichiometric quantities of diols under solvent-free conditions.

We recently disclosed that In(OTf)$_3$ was a highly efficient Lewis acid catalyst for the formation of both cyclic and acyclic acetals and ketals from a range of aldehydes and ketones, without the requirement for prolonged reaction times, high temperatures, azeotropic removal of water or a large excess of reagents.[5] Disappointingly, deactivated aromatic ketones provided only moderate conversions, and it occurred to us that this problem might be addressed by considering the reactions of more accessible acyclic substrates in acetal exchange reactions. Such exchange processes are well established in carbohydrate chemistry,[6] but have attracted significantly less attention in carbonyl protection strategies.[7] With this goal in mind, we initially considered the reaction of benzaldehyde dimethyl acetal (**1**) in the presence of catalytic quantities of In(OTf)$_3$ and ethane-1,2-diol, and were gratified to observe that the exchange reaction proceeded rapidly to give quantitative conversions to the desired cyclic product (Scheme 1).[8]

The generality of the reaction was next investigated using a range of acylic acetals and ketals in the presence of a small excess of diols (Table 1). Reaction of dimethyl or diethyl acetals proceeded rapidly at room temperature in the presence of 1 mol % of the catalyst to provide the corresponding cyclic acetals in excellent isolated yields (Table 1 entries 1–6). Most gratifying was the observation that dimethyl and diethyl ketals also underwent rapid exchange reactions under these conditions to provide cyclic ketals, again in excellent isolated yields (entries 7 and 8).

With our initial target achieved, we sought to further improve the efficiency of this transformation by considering reaction protocols under solvent-free conditions. There has been considerable recent interest in the development of such reaction processes,



Scheme 1. Indium triflate mediated acetal exchange reaction.

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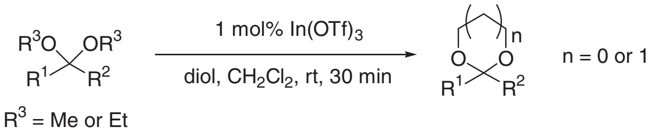
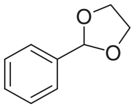
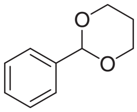
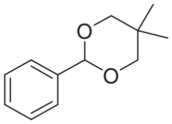
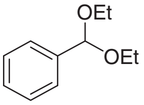
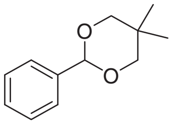
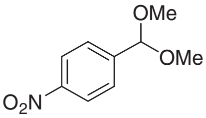
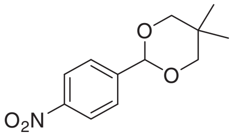
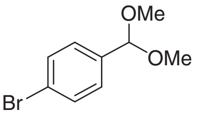
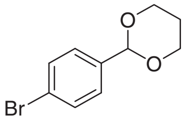
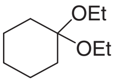
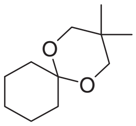
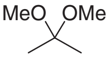
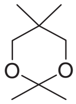
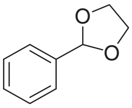
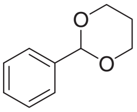
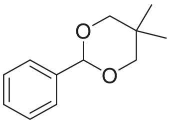
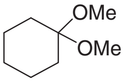
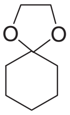
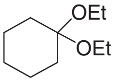
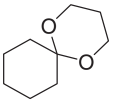
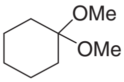
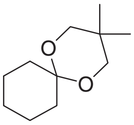
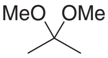
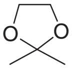
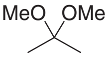
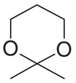
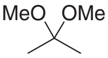
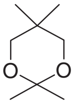
Table 1
Acetal exchange reactions catalysed by In(OTf)$_3$



Entry	Acetal	Product[a]	Yield[b] (%)
1	**1**		90
2	**1**		92
3	**1**		95
4			93
5			85
6			89
7			87
8			85

[a] All reactions were carried out at room temperature in CH$_2$Cl$_2$ using 1 mol % In(OTf)$_3$ and 1.1 equiv of diol.
[b] All compounds gave satisfactory spectroscopic data.

Table 2
Acetal exchange reactions under solvent-free reaction conditions

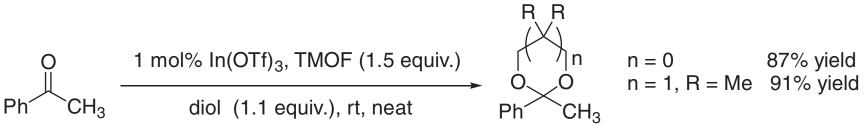
Entry	Acetal	Product[a]	Yield[b] (%)
1	**1**		92
2	**1**		89
3	**1**		96
4			88
5			90
6			92
7			87
8			91
9			95

[a] All reactions were carried out at room temperature using 1 mol % of In(OTf)$_3$ and 1.1 equiv of diol.
[b] All compounds gave satisfactory spectroscopic data.

not only due to their improved environmental profile, but also because of the potential for improved chemoselectivity and improved reaction rates and yields.[9] With this goal in mind we investigated the reactions of **1** with a series of diols, and were delighted to observe complete conversion into the corresponding cyclic acetals under reaction conditions similar to those in dichloromethane (Table 2, entries 1–3).[10] Significantly, both dimethyl and diethyl ketals readily underwent rapid and complete exchange to provide the corresponding cyclic ketals in excellent isolated yields (entries 4–9). All products required minimal purification, typically only involving removal of the catalyst and unreacted diol.

Finally, we considered the development of a tandem acetalisation-acetal exchange reaction sequence. It was envisaged in this protocol that the carbonyl compound would initially react with trimethyl orthoformate (TMOF) under In(OTf)$_3$ catalysis to generate the dimethyl acetal in the presence of a diol. Once formed, this dimethyl acetal would undergo rapid exchange, again under In(OTf)$_3$ catalysis, to generate the corresponding cyclic acetal or ketal. Such tandem reaction protocols have attracted considerable recent interest due to the improvements in efficiency, and the benefits of producing reactive or unstable species in situ.[11] We previously reported that unreactive ketones, such as acetophenone, provided poor isolated yields of the corresponding dimethyl acetals in In(OTf)$_3$-catalysed reactions due to the establishment of an equilibrium which favours the carbonyl compound. In order to achieve acceptable yields, it was necessary to employ extended reaction times in solvents such as benzene and toluene with azeotropic removal of water.[3g] We reasoned that a tandem protocol, if successful, would provide a potentially very attractive, highly flexible and efficient alternative to current methodologies. Furthermore, the ability to generate the dimethyl acetal in situ provides additional savings in efficiency, given that no isolation and purification is required. Gratifyingly, reaction of acetophenone with one equivalent of TMOF under solvent-free conditions proceeded readily to give high conversions to the corresponding ketal products. These conversions could be improved to near quantitative on increasing the quantity of TMOF to 1.5 equiv providing a facile and high yielding route to these materials (Scheme 2).[12]

In conclusion, we have demonstrated that In(OTf)$_3$ efficiently catalyses acetal and ketal exchange reactions under extremely mild reaction conditions employing low catalyst loadings to give



Scheme 2. Indium triflate mediated tandem acetalisation-acetal exchange reactions.

excellent isolated yields of cyclic acetal and ketal products. The process is highly efficient, employing near-stoichiometric quantities of the diol and proceeds rapidly at room temperature. Furthermore, the reaction can be adapted to employ solvent-free conditions, further improving the efficiency. We have extended our studies in this area to develop a tandem acetalisation-acetal exchange protocol, again employing solvent-free conditions, which is applicable to the synthesis of cyclic ketals from unreactive ketones. The reaction of acetophenone in the presence of TMOF and a diol proceeds under In(OTf)$_3$ catalysis to produce the dimethyl acetal in situ which then undergoes rapid exchange to give the corresponding cyclic ketal. The ketals are produced in high yields under very mild reaction conditions without the requirement for high temperatures or extended reaction times. We are currently investigating the scope and application of this novel tandem process.

Acknowledgments

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8. *Typical experimental procedure*: In(OTf)$_3$ (5.6 mg, 1 mol %) was added to a mixture of benzaldehyde dimethylacetal (152 mg, 1.00 mmol) and 2,2-dimethyl-1,3-propanediol (111 mg, 1.10 mmol) in CH_2Cl_2 (2 ml) and the reaction mixture stirred at room temperature for 30 min. At this time, the solvent was removed and the reaction mixture was passed through a short plug of silica which was then washed with hexane (2 × 2 ml) and the solvent was removed under reduced pressure to give the product, 5,5-dimethyl-2-phenyl-[1,3]-dioxane[3g] as a colourless oil (183 mg, 95%); ^{1}H NMR (CDCl$_3$; 400 MHz) δ = 0.75 (3H, s), 1.25 (3H, s), 3.60 (2H, d, J = 11 Hz), 3.80 (2H, d, J = 11 Hz), 5.45 (1H, s), 7.25–7.35 (3H, m), 7.45–7.55 (2H, m); ^{13}C NMR (CDCl$_3$; 100 MHz) δ = 138.4, 128.8, 128.2, 126.1, 101.7, 77.6, 30.2, 22.9, 21.8; ν_{max} (film)/cm^{-1} (neat) 2954, 2846, 1388, 1101, 1017, 745 and 696; MS (EI) m/z 192; HRMS (ES) calcd for $C_{12}H_{17}O_2$ (M+H)$^+$ 193.1223. Found (M+H)$^+$ 193.1224.
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10. *Typical experimental procedure under solvent-free conditions.* In(OTf)$_3$ (5.6 mg, 1 mol %) was added to a mixture of cyclohexanone dimethyl acetal (144 mg, 1.00 mmol) and finely ground 2,2-dimethyl-1,3-propanediol (111 mg, 1.10 mmol) and the reaction mixture stirred at room temperature for 30 min. At this time, residual MeOH was removed under reduced pressure and the crude residue was passed through a short plug of silica which was washed with hexane (2 × 2 ml). The solvent was removed under reduced pressure to give the product, 3,3-dimethyl-1,5-dioxa-spiro[5.5]undecane[3f] as a colourless oil (170 mg, 92%); ^{1}H NMR (CDCl$_3$; 400 MHz) δ = 0.90 (6H, s), 1.30–1.75 (10H, m), 3.45 (4H, s); ^{13}C NMR (CDCl$_3$; 100 MHz) δ = 97.7, 69.8, 32.6, 30.2, 25.8, 22.8, 22.6; ν_{max} (film)/cm^{-1} (neat) 2936, 2858, 1104, 914, and 733; MS (EI) m/z 184; HRMS (ES) calcd for $C_{11}H_{21}O_2$ (M+H)$^+$ 185.1536. Found (M+H)$^+$ 185.1537.
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12. *Typical experimental procedure for tandem acetalisation-acetal exchange under solvent-free conditions*: In(OTf)$_3$ (5.6 mg, 1 mol %) was added to a mixture of acetophenone (120 mg, 1.00 mmol), trimethyl orthoformate (159 mg, 1.50 mmol) and ethane-1,2-diol (68 mg, 1.10 mmol) and the reaction mixture stirred at room temperature for 1 h. At this time, residual MeOH was removed under reduced pressure and the crude product was passed through a short plug of silica which was washed with hexane (2 × 2 ml). The solvent was removed under reduced pressure to give the product 2-methyl-2-phenyl-1,3-dioxolane[3g] as a light yellow oil (143 mg, 87%); ^{1}H NMR (CDCl$_3$; 400 MHz) δ = 1.65 (3H, s), 3.70–3.85 (2H, m), 3.95–4.05 (2H, m), 7.25–7.40 (3H, m), 7.45–7.55 (2H, m); ^{13}C NMR (CDCl$_3$; 100 MHz) δ = 143.5, 128.3, 127.9, 125.3, 108.8, 64.2, 27.5; ν_{max} (film)/cm^{-1} (neat) 2892, 1375, 1201, 1069, 733 and 650; MS (EI) m/z 164.