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Sequential and tandem oxidation/acetalization procedures for the direct generation of acetals from alcohols

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Abstract—Alcohols are transformed directly into either acyclic or cyclic acetals in both tandem and sequential oxidation/acetalization processes using manganese dioxide, trialkyl orthoformates and catalytic quantities of indium triflate.

1. Introduction

The development of preparative procedures, where a number of transformations are carried out in a one-pot process, offers significant advantages such as a reduction in the number of synthetic steps and a significant increase in efficiency.[1] A second beneficial feature is that it is not necessary to isolate intermediate compounds that are volatile, toxic or unstable, allowing them to be prepared in situ and thus avoiding problems associated with their isolation and handling. The introduction of tandem oxidation processes (TOP) by Taylor using manganese dioxide as a mild, heterogeneous oxidant has found application in a variety of tandem processes involving the oxidation of alcohols and their subsequent transformation by Wittig olefination, cyclopropanation, oxime formation and in the formation of heterocyclic nuclei.[2] We recently demonstrated that the acetalization of a variety of carbonyl compounds could be achieved in very short reaction times and in excellent yields using indium triflate ($In(OTf)_3$) as the Lewis acid catalyst in conjunction with trimethyl orthoformate, triethyl orthoformate or diols.[3] The success of this procedure encouraged us to adapt this technique for the direct conversion of alcohols to acetals without isolating the intermediate carbonyl compounds.[4]

Our initial studies considered the one-pot tandem oxidation/acetalization reaction of benzyl alcohol with manganese dioxide in the presence of an excess of trimethyl orthoformate and catalytic quantities of indium triflate. Disappointingly, while these reactions produced benzaldehyde, only small quantities of the desired acetal ($\sim$10%) were observed. We assumed that this may be due to hydrolysis of the orthoformate or of the acetal product under the reaction conditions and so pre-dried manganese dioxide was employed in subsequent reactions.[5] This approach, however, gave no discernable improvement in acetal yields. In an attempt to understand further the acetalization process we studied the corresponding sequential process, whereby the trimethyl or triethyl orthoformate and indium catalyst were added to the reaction once oxidation of the alcohol to the aldehyde was complete. In these cases, acetal formation proceeded to give excellent yields of products (Table 1). The use of alternative oxidants such as PCC supported on Celite or alumina in both tandem and sequential reactions gave only low yields of acetal products.

While this sequential process provides a potentially useful and more efficient route to acetals, our goal was to develop a methodology that could be applied to the generation and trapping of highly unstable aldehydes. We therefore next investigated a range of reagents for acetal formation and were gratified to observe that tandem oxidation/acetalization reactions of benzyl alcohol in the presence of an excess of triethyl orthoformate produced the desired diethyl acetals. These reactions proceeded efficiently at room temperature in dichloromethane although they required extended reaction times, or could be achieved in shorter reaction times in refluxing chloroform. The reaction appears to be general and is effective for a range of activated alcohols which

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Keywords: Indium triflate; Manganese dioxide; Tandem oxidation/acetalization.

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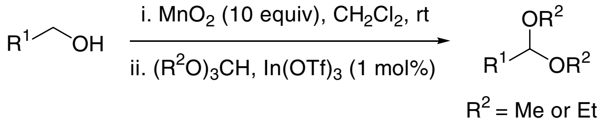
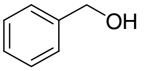
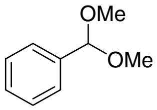
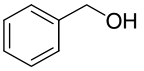
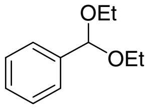
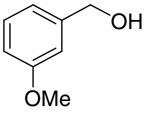
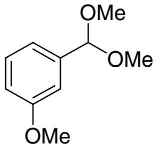
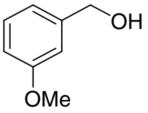
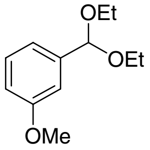
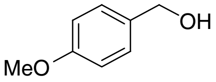
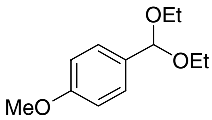
Table 1. Indium-mediated sequential acetalization reactions



Entry	Alcohol	Time (h)	Product	Conversion (%)[a]
1		24		100
2		24		95
3		24		85
4		24		99
5		24		77

[a] Estimated by ^1H NMR spectroscopy.

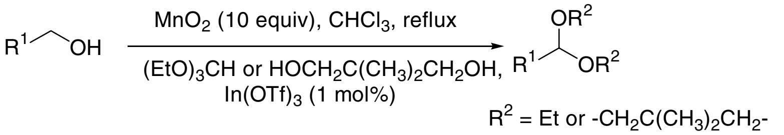
are efficiently transformed into their diethyl acetal counterparts in high yields (Table 2). Of particular note is the formation of acetals derived from propargyl alcohol and 2-butyne-1,4-diol given the instability of the corresponding aldehydes. Indeed, there appears to be no reports of acetals being generated directly from either propargyl aldehyde or from but-2-ynedial using traditional acetalization procedures. Previous approaches for the synthesis of these compounds have relied on either the addition of bromine to acrolein followed by a dehydrobromination step[6] or the addition of organometallic species produced from the reaction of acetylene with ethyl magnesium bromide to generate the bis-magnesium salt followed by reaction with triethyl orthoformate.[7] Recently, the preparation of acetylene dicarboxaldehyde dimethyl and tetramethyl acetals from 2,5-dimethoxy-2,5-dihydrofuran has been described, which is applicable for the large-scale preparation of these materials.[8] A major drawback of these approaches is the high price of the reagents, poor atom-economy or the requirement to utilize specialist techniques, which preclude their use in large-scale synthesis. We have found that our approach is effective on gram-scale reactions giving excellent yields of the desired acetals in a simple approach utilizing inexpensive materials. The transformation of 2-furancarboxaldehyde is also noteworthy given the acid-sensitive nature of this compound. We have also investigated the formation of cyclic acetals generated from diols, utilizing the greater susceptibility to oxidation of the activated alcohol substrates to ensure formation of the desired product. This proved successful and both benzyl alcohol and 4-methoxybenzyl alcohol underwent selective oxidation in the presence of 2,2-dimethyl-1,3-propanediol to produce high yields of the corresponding cyclic acetals.

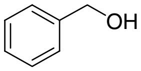
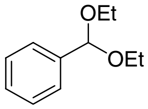
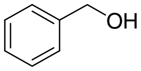
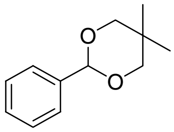
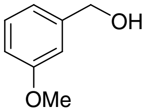
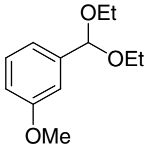
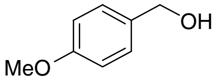
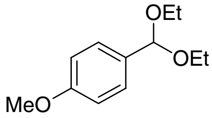
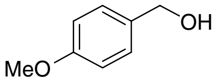
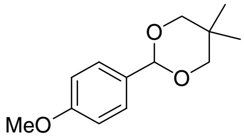
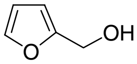
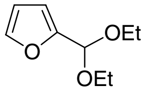
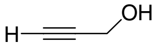
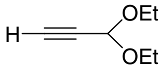
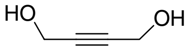
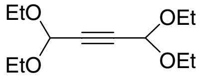
In conclusion, we have demonstrated that the oxidation of activated alcohols using manganese dioxide proceeds efficiently in the presence of triethyl orthoformate to generate acetals in good to excellent yields. These tandem processes are particularly useful for the formation of acetals derived from highly unstable aldehydes, such as but-2-ynedial, providing a direct and efficient route for the generation of both cyclic and acyclic acetals.

2. Experimental procedure

Indium triflate (7.1 mg, 1 mol %) was added to a mixture of 2-butyne-1,4-diol (108 mg, 1.25 mmol), manganese dioxide (1.09 g, 12.5 mmol) and triethyl orthoformate (372 mg, 2.51 mmol) in chloroform (20 mL) and the mixture was heated to reflux and stirred for 6 h. Further portions of manganese dioxide (545.3 mg, 6.27 mmol), triethyl orthoformate (372 mg, 2.51 mmol) and indium catalyst (7.1 mg, 1 mol %) were added at this time and the reaction mixture was heated at reflux for a further 24 h. The mixture was cooled to room temperature

Table 2. Tandem oxidation/acetalization reactions catalyzed by indium triflate



Entry	Alcohol	Time (h)	Product	Yield[a] (%)
1		8		78
2		24		72[b]
3		8		77
4		8		71
5		24		94[b]
6		8		82
7		42		78[c]
8		30		66

[a] All compounds gave satisfactory spectroscopic data.

[b] At room temperature in CH_2Cl_2.

[c] Percentage conversion from ^1H NMR spectroscopy.

and the manganese dioxide was removed by filtration through a short plug of Celite, which was washed with chloroform (2 × 5 mL), and the solvent was removed under reduced pressure to give the crude product, which was purified by distillation to give the product *1,1,4,4-tetraethoxybut-2-yne* (190 mg, 66%) as a clear oil; ^1H NMR ($CDCl_3$; 400 MHz) δ 1.16 (t, 12H, $J = 7$ Hz), 3.53 (m, 4H), 3.67 (m, 4H), 5.26 (s, 2H); ^{13}C NMR ($CDCl_3$; 100 MHz) δ 91.6, 80.9, 61.4, 15.5; ν_{max} (film)/cm^{-1} (neat) 2979, 2897, 1671, 1446, 1375, 1339, 1050, 914 and 732; MS (EI) *m*/*z* 230; HRMS (EI) calculated for $C_{12}H_{21}O_4$ ($[M–H]^+$) 229.1434; found, ($[M–H]^+$) 229.1433.

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4. The synthesis of acetals by tandem process has been described in a limited number of cases; for the synthesis of unstable *o*-benzoquinone monodimethylacetals by oxidation of 2-methoxyphenols in methanol with (diacetoxy)iodobenzene (DAIB) or [bis-(trifluoroacetoxy)]iodobenzene (BTIB), see: (a) Chu, C.-S.; Lee, T.-H.; Rao, P. D.; Song, L.-D.; Liao, C.-C. *J. Org. Chem* **1999**, *64*, 4111–4118; (b) Lin, K.-C.; Shen, Y.-L.; Kameswara Rao, N. S.; Liao, C.-C. *J. Org. Chem.* **2002**, *67*, 8157–8165; For rhodium-catalyzed tandem hydroformylation/acetalization reactions, see: Roggenbuck, R.; Schmidt, A.; Eilbracht, P. *Org. Lett.* **2002**, *4*, 289–291.
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