



Selective mono-acylation of *meso*- and C_2 -symmetric 1,3- and 1,4-diols

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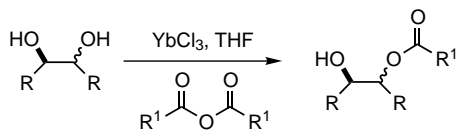
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Abstract—The direct one-pot mono-acylation of *meso* and C_2 -symmetric 1,3- and 1,4-diols has been achieved using carboxylic acid anhydrides and catalytic amounts of cerium trichloride. © 2002 Elsevier Science Ltd. All rights reserved.

The mono-functionalisation of symmetrical 1,*n*-diols is a non-trivial process. This is because the hydroxyl groups are in identical or similar chemical environments, and as such they react at a similar, if not the same, rate. The effect of this is that reactions run with a stoichiometric quantity of reagent tend to generate statistical mixtures of starting material, mono-functionalised and bis-functionalised products. Those reactions, however, which are run using an excess of reagent tend to favour the formation of bis-functionalised products. Several attempts have been made to obviate these problems.^{1–3} These include continual extraction of the mono-acylated product from the reaction medium,¹ heterogeneous or solid supported methods² and the formation/cleavage of cyclic ‘acetal-like’ systems.³ The problems inherent with these strategies are the laborious and/or the multi-step nature of the processes.

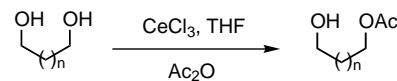
We have recently reported a novel and much simpler procedure for the one-step highly selective mono-acylation of *meso*- and C_2 -symmetric 1,2-diols.⁴ This procedure utilised an excess of carboxylic acid anhydride, as an acylating agent, and a catalytic amount of lanthanide trichloride as an acylation promoter (Scheme 1).^{5–7}



Scheme 1.

In this letter it is disclosed that these reaction conditions may be modified to enable the one-step mono-acylation of both *meso*- and C_2 -symmetric 1,3- and 1,4-diols in excellent yields (Scheme 2).

The optimal procedure for the mono-acylation of 1,2-diols involved the use of $YbCl_3$ (10 mol%) as a catalyst in the presence of acetic anhydride (10 equiv.). When 2-phenylpropane-1,3-diol was subjected to these conditions it was found that the diol was rapidly consumed (~ 2 h). However, 1H NMR (400 MHz) analysis of the crude reaction mixture indicated that the acylation was unselective, generating equal quantities of both the mono- and the bis-acylated product. This is in marked contrast to the rapid yet mono-selective reaction of 1,2-diols under these conditions. To rule out the possibility of an unusually rapid uncatalysed background reaction, 2-phenylpropane-1,3-diol was treated with acetic anhydride (10 equiv.) in the appropriate amount of THF. Even after 2 days only a trace amount of acylated product could be detected by 1H NMR (400 MHz). In an attempt to slow the catalysed reaction and increase mono selectivity $CeCl_3$ (10 mol%) was next used as a catalyst.⁸ In the case of 1,2-diols, $CeCl_3$ was as equally effective as $YbCl_3$ (10 mol%), but a longer reaction time was required. Indeed, the rate of the reaction was reduced, but after 23 h, 2-phenylpropane-1,3-diol had been consumed. Gratifyingly the 1H NMR



n = 1 or 2

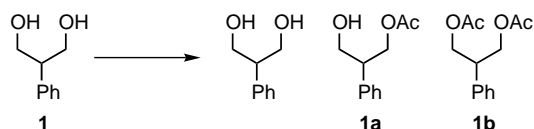
Scheme 2.

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(400 MHz) of the crude reaction mixture indicated that 85% of the material was the mono-acylated product. This was isolated via flash column chromatography in a 77% overall yield. These results are summarised in Table 1.

It was next sought to employ these conditions for the mono-acylation of other symmetrical 1,3-diols with a selection of anhydrides. As can be seen from Table 2, pro-chiral and C_2 -symmetric 1,3-diols can be treated with the appropriate anhydride to form the mono-acetate, mono-benzoate and even the mono-*tert*-butyloxy-carbonate, all in good to excellent yields. In the case of the benzylation of **3**, the $CeCl_3$ -promoted reaction was sluggish so $YbCl_3$ was employed.⁸

Table 1.



Catalyst (10 mol%)	Time (h)	Ratio 1/1a/1b	Yield 1a (%)
None	48	100/trace/0	0
$YbCl_3$	2	0/50/50	48
$CeCl_3$	23	0/85/15	77

Table 2.

Diol	Anhydride (10 eq.)	Product	Yield (%)
	Bz_2O		70
	Boc_2O		83
	Ac_2O		93
	Ac_2O		75
	Bz_2O		57 ^a

a) Bz_2O (5 eq.), $YbCl_3$ (10 mol%), 57% conversion at 22.5 h.

Having successfully extended the methodology to 1,3-diols, the next step was to investigate the possibility of the mono-acylation of 1,4-diols (Table 3). The first 1,4-diol to be investigated was *2R,5R*-hexanediol. Acylation in the presence of $CeCl_3$ (10 mol%) was slow (only 30% conversion after 23 h) but completely mono-selective. In an attempt to increase the rate of the acylation reaction, $YbCl_3$ (10 mol%) was used as a catalyst. In this case the acylation was rapid and generated 65% of the mono-acetate within 8 h (the remainder was the bis-acylated product). Diols **5** and **6** were formed by the $LiAlH_4$ reduction of the appropriate cyclic anhydrides. The anhydrides being generated by the Diels–Alder cyclisations of maleic anhydride and the appropriate diene. It was found that *meso*-diols **5** and **6** also underwent mono-acylation smoothly and in high yields, 80 and 83%, respectively. In the case of diol **5** the reaction was extended to the formation of the mono-benzoate, although the rate of benzylation (5 equiv. of Bz_2O was used) was such to warrant the use of $YbCl_3$ as a catalyst.

It is intriguing that the nature of the lanthanide trichloride catalyst is very influential on both the rate and the selectivity of these reactions. While the increased rate of reaction with lanthanides of greater atomic mass can be rationalised in terms of the increasing Lewis acidity of the lanthanide metal (i.e. the well known lanthanide contraction effect), it is more difficult to rationalise the mono- versus bis-selectivity differences. One possibility

Table 3.

Diol	Catalyst (10 mol%)	Product	Yield (%)
	$CeCl_3$		30 ^a
	$YbCl_3$		65
	$CeCl_3$		80
	$YbCl_3$		64 ^b
	$CeCl_3$		83

a) Ac_2O (10 eq.), 100% mono-acetate at 30% conversion after 23 h.

b) Bz_2O (5 eq.), 76% mono-benzoate at 84% conversion after 24 h.

is that the diol chelates to the lanthanide salt and the differences in the chelate ring size/stability and distances between the co-ordinating hydroxyl groups are more or less compatible with different sized lanthanides. The role of the lanthanide trichloride catalyst and its interaction with the diol is currently the subject of investigation and will be reported in due course.

In summary, however, it has been shown that it is now possible to mono-acylate *meso*- and C_2 -symmetric 1,3- and 1,4-diols directly in good to excellent yields. The methodology outlined will be of use to those in the synthetic chemistry community who seek to differentiate identical hydroxyl functionalities.

Representative experimental procedure

Acetic anhydride (0.8 ml, 8.6 mmol) was added to a stirred solution of diol (0.86 mmol) and $CeCl_3$ (21 mg, 0.086 mmol) in THF (2.4 ml) under a nitrogen atmosphere. When judged complete by TLC (EtOAc–hexane mixtures) the reaction was diluted with Et_2O and washed twice with a saturated $NaHCO_3$ solution and once with brine. The organics were dried ($MgSO_4$) and the solvent was evaporated to yield the crude product. The product was purified via flash column chromatography (EtOAc–hexane mixtures) to provide the mono-acetate in good to excellent yields (Tables 2 and 3).

Acknowledgements

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8. We have found that the rate of the acylation reaction increases as the atomic mass of the lanthanide used increases: $YbCl_3$ provides for the fastest reaction while $CeCl_3$ for the slowest.