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Efficient preparation of 4-methoxy-5,6-dihydro-2*H*-pyran

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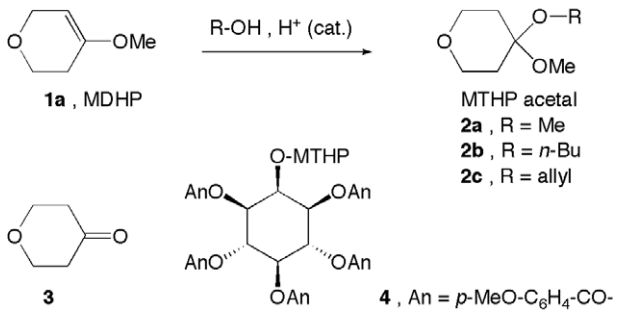
Abstract

We report the efficient synthesis of 4-methoxy-5,6-dihydro-2*H*-pyran (MDHP) via the $TiCl_4$ driven elimination of MeOH from 4,4-dimethoxytetrahydropyran. The previous difficulty of preparing MDHP restricted the wider use of 4-methoxytetrahydropyran-4-yl (MTHP) acyclic acetals, which have desirable protecting group properties when compared to more commonly used MOM- and THP-acetals. The behaviour of the elimination on related acetals is also examined.

The protection of hydroxyl groups during the synthesis of poly-oxygenated natural products is a ubiquitous synthetic process.[1] Acetals are one of the most common classes of –OH protective groups, especially for poly-ols where pairs of adjacent hydroxyls can be masked simultaneously as a cyclic acetal, for example, acetonide or benzylidene derivatives. However, there is a limited choice of reagents for the protection of isolated hydroxyls as acetals. This is because the corresponding acyclic acetals of simple carbonyl compounds, such as acetone and benzaldehyde, lack the entropic stabilisation of a ring.

The most prominent acyclic acetal protective groups are tetrahydropyran-2-yl (THP) and methoxymethyl (MOM) derivatives. The former, prepared by treating an alcohol with readily available 2,3-dihydro-4*H*-pyran in the presence of catalytic acid, have a convenient range of stability for many synthetic purposes, but contain a new stereogenic centre leading to the formation of diastereomers when protecting chiral substrates. The latter, prepared by the reaction of an alcohol with MOM–Cl under basic conditions, require relatively strongly acidic conditions to deprotect (due to the lack of alkyl groups to stabilise the intermediate cation), and MOM–Cl has a limited shelf-life.

4-Methoxytetrahydropyran-4-yl (MTHP) acetals have the synthetic advantages of both THP and MOM derivatives, in so far as they have a similar range of stability to THP acetals but, like MOM acetals, generate no new stereogenic centres.[1] MTHP-acetals are easily formed by the acid catalysed addition of an alcohol to 4-methoxy-5,6-dihydro-2*H*-pyran (MDHP, **1a**, Scheme 1). MDHP has itself been synthesised by the Brønsted acid catalysed extrusion of methanol from 4,4-dimethoxytetrahydropyran (**2a**), a compound that we have found is easily prepared on >100 g scale.[2] However, MTHP protection has not been widely used outside nucleotide chemistry, probably because the requisite MDHP is very expensive (Aldrich Chemical Co., £61.00 for 1 g, 95% purity). This may reflect the poor



Scheme 1. Protection of hydroxyl groups as MTHP-acetals.

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yield in the elimination of methanol from 4,4-dimethyl acetal **2a** and difficult purification of MDHP (**1a**) for which no improvement in the procedure has been reported for 32 years. We have repeated this procedure many times: typically in our hands, after quenching the acid catalyst, enol ether **1a** is distilled from the reaction mixture in a yield of around 55–60%. However, the MDHP is contaminated by acetal **2a** and tetrahydropyran-4-one (**3**), which are very difficult to separate due to the similarity of the boiling points of all three compounds (**1a** 60–62 °C/15 mmHg; **2a** 61–63 °C/11 mmHg; **3** 58 °C/12 mmHg). Furthermore, only about 75% of the starting acetal **2a** is returned from the extrusion as a distillable fraction, the remainder being a thick, presumably oligomeric, involatile residue.

Masking the axial 2-*O* of *myo*-inositol as its MTHP-acetal **4** has been reported[3] to provide a useful building block for phosphoinositide synthesis. We sought to repeat this protection of the axial 2-hydroxyl as part of our continued efforts in this field. However, the reaction did not proceed very far, except when using MDHP fractions having minimal contamination by acetal **2a** and ketone **5**. For this reason, we required a new method for preparing MDHP free of contamination.

Apart from Brønsted acids, various Lewis acids have also been reported to mediate extrusion of methanol from dimethyl acetals to give the corresponding methyl enol ethers.[4a–d] These conditions were tested on dimethyl acetal **2a** (1 g scale) where the reactions were followed by TLC and the crude product mixture was analysed by ^{1}H NMR.

Boron trifluoride–diethyl ether complex has been used to eliminate cleanly the related dimethyl acetals of *N*-aryl piperidin-4-ones.[4a] Under these conditions [0 °C with a slight excess of *N*,*N*-diisopropylethylamine (DIPEA) in CH_2Cl_2] there was no reaction of **2a** with stoichiometric Lewis acid. However, on doubling the reagent equivalents, although enol ether **1a** started to form, significant ketone **5** (as well as starting acetal **2a**) was observed by TLC, and with time the reaction darkened—the latter is assumed to be related to decomposition. As our aim was to find a high-yielding route to MDHP (**1a**), darkening and the appearance of ketone **5** were taken as the signature of failure.

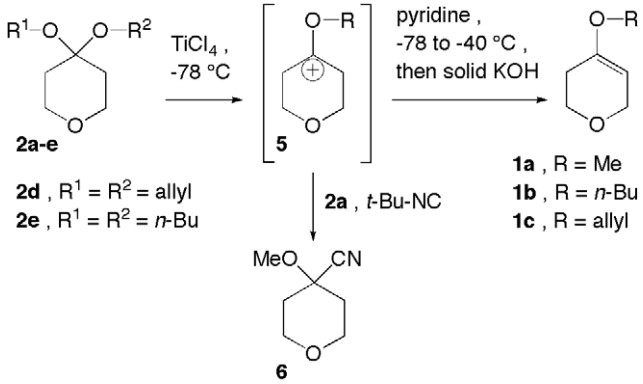
Although trimethylsilyl trifluoromethanesulfonate (TMSOTf) has been reported to be a general reagent for eliminating dimethyl and cyclic acetals,[4b] a similar result to that with $Et_2O{\cdot}BF_3$ was obtained with this reagent. There was no reaction, even at reflux, between dimethyl acetal **2a** and stoichiometric TMSOTf, in CH_2Cl_2 or MeCN, with a slight excess of DIPEA. However, doubling the amount of reagents led to rapid darkening and production of ketone **5**. Rapid decomposition was also observed using 2 equiv of aluminium trichloride and excess triethylamine in diethyl ether at 0 °C, conditions which have been reported to cleanly eliminate dimethyl acetals of *N*-sulfonyl piperidinones.[4c]

Having found with the above Lewis acids that >1 equiv of reagent was required to initiate significant methanol elimination from **2a**, but that this led to concomitant byproduct formation, we then explored whether 4-halo-4-methoxytetrahydropyrans could be eliminated under basic conditions. Despite possible stabilisation of such compounds by the electron withdrawing oxygen of the pyran ring, none have been reported. However, it was noted that the related 4-cyano-4-methoxytetrahydropyran (**6**) could be prepared in moderate yield by trapping the oxycarbenium cation **5** generated at low temperature from the reaction of dimethyl acetal **2a** and stoichiometric titanium tetrachloride with *tert*-butyl isocyanide[5] (Scheme 2).

We reasoned that the addition of a weak base to the initial mixture of 4,4-dimethoxytetrahydropyran (**2a**) and $TiCl_4$ should favour an E1 mechanism to provide the desired MDHP (**1a**) in a yield at least similar to **6**. Indeed, after the treatment of **2a** with $TiCl_4$ at −78 °C, the addition of DIPEA or pyridine, followed by aqueous work-up, gave mainly the desired enol ether **1a**. However, this was contaminated by ketone **5**, the product of hydrolysis, which we suspected had been generated during the aqueous work-up as a result of incomplete quenching of acid.

Using a fivefold excess of pyridine to initiate the elimination various anhydrous quenches for the $TiCl_4$ were tested: the addition of *tert*-BuOH, solid sodium hydrogen carbonate, or solid sodium carbonate to the reaction still led to the formation of tetrahydropyranone **3** after aqueous work-up. However, excess pyridine followed by solid potassium hydroxide gave exclusively the desired MDHP enol ether **1a**. Notably, if the pyridine was omitted and only solid KOH was added after the $TiCl_4$ then rapid degradation occurred with no identifiable products. On a 50 g scale using this quenching procedure an 86% yield of MDHP (**1a**) was achieved after distillation having almost no detectable contamination by either acetal **2a** or ketone **3**.[6] When the MDHP enol ether **1a** from this procedure was used to prepare 2-*O*-MTHP *myo*-inositol **4** from the corresponding alcohol, the reaction was faster (overnight vs 2 days) and required less reagent (5 vs 10 equiv) to reach completion compared to the published procedure.[3]

To explore the scope of the reaction of tetrahydropyran-4-yl acetals with $TiCl_4$, the elimination conditions were



Scheme 2. $TiCl_4$ mediated elimination of acetals.

tested on some other 4,4-dialkyloxy acetals (**2b**–**e**). 4-*n*-Butyloxy- and 4-allyloxy-4-methoxytetrahydropyrans (**2b** and **2c**, respectively) were prepared by reaction of MDHP (**1a**) with an excess of each of the corresponding alcohols in the presence of catalytic triphenylphosphonium hydrobromide.[7] We found that diallyl acetal **2d** was cleanly prepared from triallyl orthoformate generated in situ and ketone **5** in the presence of catalytic *para*-toluenesulfonic acid. However, the reported[8] conversion of ketones to diallyl acetals with trimethylsilyl allyl ether and catalytic TMSOTf failed. Dibutyl acetal **2e** was separated chromatographically from the preparation of **2b**.

Treatment of diallyl acetal **2d** with $TiCl_4$ at both −78 and −60 °C, followed by pyridine, failed to give any reaction. When the reaction was allowed to warm to −40 °C before the pyridine was added decomposition occurred with no identifiable products being isolated. In contrast, when dibutyl acetal **2d** was treated similarly with $TiCl_4$ at −40 °C, ^{1}H NMR of the crude showed the desired butyl enol ether **1b** in the presence of the starting acetal **2d** in a ratio of ca. 4:1. The need for a significant rise in temperature before elimination occurred, led us to consider the possibility that steric hindrance might permit selective elimination of mixed acetals to occur. However, when the mixed 4-methyl-4-butyl acetal **2b** was treated with $TiCl_4$ at −60 °C, ^{1}H NMR of the crude product showed no significant selectivity. Notably, applying the same procedure to allylmethoxy acetal **2c**, again with elimination at −40 °C, did give some allyl enol ether **1c** selectively (**1c**:**1a** was ca. 9:1).

In summary, we have developed a clean and efficient synthesis of the reagent MDHP (**1a**), which had previously been difficult to prepare and prohibitively expensive to use on a large scale. This allows ready protection of isolated hydroxyl groups as their MTHP-acetals which have a similar stability to, but do not introduce the undesirable stereogenic centre of, popular THP-ethers.

Acknowledgements

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Supplementary data

Experimental procedures and ^{1}H NMR data for compounds **1b**, **1c** and **2b**–**e**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.01.039.

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6. *Preparation of 4-methoxy-5,6-dihydro-2H-pyran* (**1a**): To a stirred solution of 4,4-dimethoxytetrahydropyran (**2a**, 50.2 g, 0.34 mol) in CH_2Cl_2 (500 mL) at −78 °C was added $TiCl_4$ (41.4 mL, 0.38 mol) over 2 min. After 1 h, pyridine (137.5 mL, 1.7 mol) was added followed by ground KOH (108 g, dried at 100 °C). After 20 min the reaction was brought to room temperature and stirred for further 1 h; if TLC analysis (hexane–EtOAc 1:1 v/v, R_f (**1a**) = 0.76, R_f (**2a**) = 0.47, R_f (**3**) = 0.29) still shows the presence of tetrahydropyranone (**3**), then further KOH should be added and stirring continued until a single product spot is observed. The reaction mixture was poured into Et_2O (1 L), then filtered through Celite® and the filter bed washed with further Et_2O (0.25 L). The combined filtrates were washed with water (0.25 L), then saturated brine (0.25 L) and dried ($MgSO_4$). This solution was concentrated under reduced pressure (water bath <30 °C, ⩾1 cm/Hg). To the residue was added triethylamine (5 mL) and this was distilled under reduced pressure, with ice cooling of the receiver flask, using a helix packed fractionation column to give MDHP (**1a**, 33.6 g, 86%), bp 60–62 °C/15 mmHg. A Vigreux column may be used to obtain equally pure MDHP, but the yield will be reduced by pyridine contaminated fractions. Alternatively, particularly for smaller scales, after the pyridine has distilled over, the orange/yellow residue may be flushed through a pad of silica (slurried from Et_2O–Et_3N 99:1 v/v) in a large glass sinter, washed with further Et_2O–Et_3N until no MDHP remains in the eluent; on an identical scale to the above, 35.3 g MDHP (91%) was obtained using this procedure.
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