

ANCHIMERICALLY ASSISTED LEWIS ACID CLEAVAGE OF TETRAHYDROFURANS TO FURNISH 1,4-DIOLS

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Treatment of 3-aryloxy- and 2-(aryloxymethyl)tetrahydrofurans with TiCl_4 results in cleavage of the heterocyclic ring with intervention by the appropriately situated ester group to form intermediates which, on work-up and hydrolysis, furnish 1,4-diols.

The Lewis acid mediated cleavage of tetrahydrofurans to furnish appropriately 1,4-functionalised acyclic materials is a highly useful conversion having many variants.¹ However, the majority of procedures result in the introduction of the Lewis acid counterion and, with some notable exceptions,² show little regiochemical differentiation with unsymmetrically substituted substrates (Figure 1).

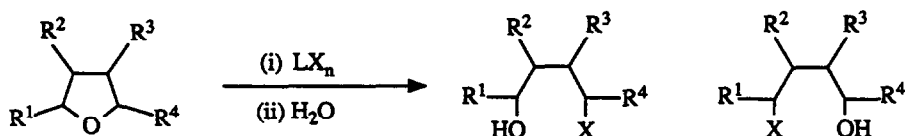


Figure 1

In seeking a means of obtaining 1,4-diols *via* Lewis acid catalysed cleavage of tetrahydrofurans, we reasoned that substrates possessing a suitably placed oxygen nucleophile might undergo anchimerically assisted cleavage of the heterocyclic ring to give a cationic intermediate which could resist nucleophilic attack by the external counterion present.³ Hydrolysis of the reaction mixture would then furnish acyclic products possessing a 1,4-dioxygenation pattern (Figure 2).

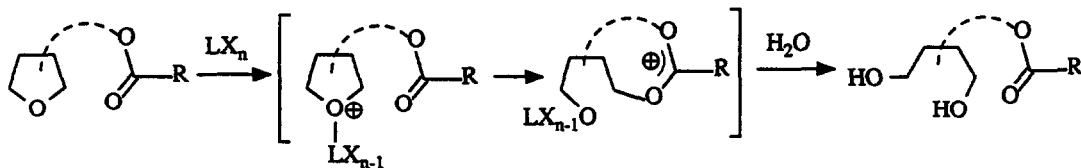


Figure 2

Our initial studies concentrated upon the use of 3-benzoyloxytetrahydrofuran (1b) as a standard substrate. After testing a range of Lewis acids and reaction conditions, we found that excess TiCl_4 in dichloromethane for 72 h at reflux resulted in the formation of an inseparable *ca.* 1 : 1 mixture of two isomeric acyclic diol benzoates

(2b) and (3b) after aqueous work - up in 47% isolated yield (Figure 3), with 43% recovered starting material. Exhaustive benzylation of the isolated product mixture with excess benzoyl chloride / triethylamine furnished tribenzoate (4) as the sole product in 85% yield.⁴ The formation of two isomeric products after the cleavage step provides evidence for the intramolecular nucleophilic participation of the ester group in this process. In keeping with such a mechanism, the more electron rich 4-methoxybenzoate ester (1c) was cleaved more cleanly and efficiently to furnish (2c) and (3c) in 71% combined yield, permitting the isolation of butane-1,2,4-triol (5) in 61% overall yield on subsequent saponification of the crude product mixture (MeOH, K₂CO₃, r.t. 10h).

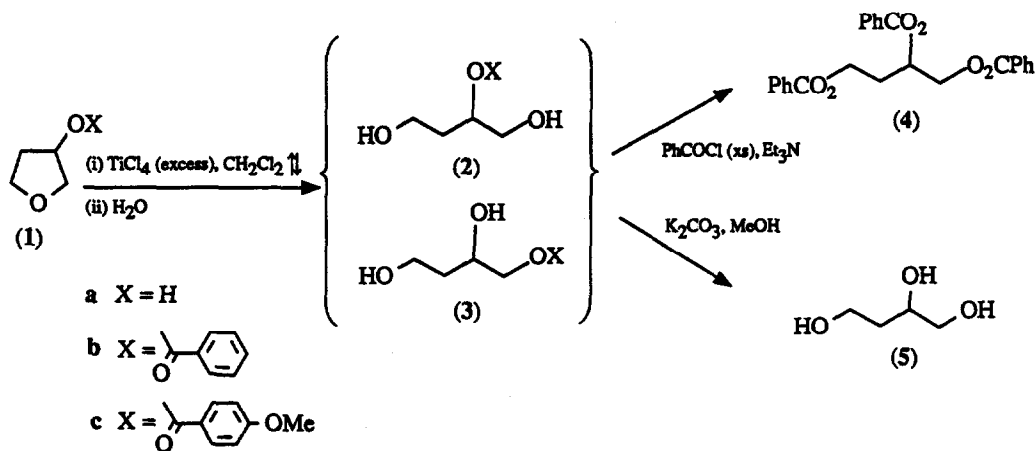


Figure 3

Attempted cleavages of ester derivatives of 2-hydroxymethyltetrahydrofuran (6a) were less successful as the substrates proved more resistant to opening of the heterocyclic ring. Thus, the benzoate derivative (6b) furnished a mixture of acyclic esters (7b) and (8b) in 6% yield, together with 41% recovered starting material, on refluxing with 5 equivalents of TiCl₄ in dichloromethane for 96 h followed by aqueous work - up (Figure 4). Attempts to accelerate this reaction by heating to reflux in chloroform led to complex mixtures of chlorinated materials. This situation was scarcely improved with the 4-methoxybenzoate substrate (6c) which led to the formation of the cleavage products in 9% yield with 88% recovered starting material under the same conditions.

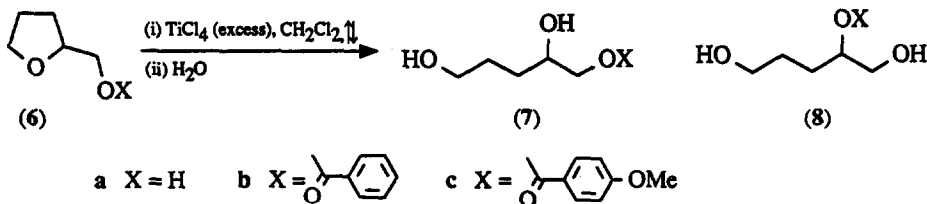


Figure 4

We next turned our attention to the reactivity of ester derivatives of 2-*exo*- and 2-*endo*-7-oxabicyclo[2.2.1]-heptan-2-ol (9a)⁵ and (10a)⁶ which embody both of the structural relationships contained in substrates (1) and (6) together with the higher strain associated with the bicyclic system. The 2-*exo*-benzoate (9b) and 2-*exo*-4-methoxybenzoate (9c) proved to be resistant to ring cleavage under the conditions but the 2-*endo*-benzoate (10b) showed much greater reactivity than its monocyclic counterparts. Treatment of (10b) with 5 equiv. TiCl₄ in CH₂Cl₂ at room temperature for 12h, followed by aqueous work - up smoothly furnished a

1 : 1 mixture of diol benzoates (11b) and (12b) in 72% yield, whose structures were inferred from a consideration of n.m.r. data. Whilst the components of the mixture could be separated by careful chromatography, exposure to traces of base caused their rapid interconversion (Figure 5).

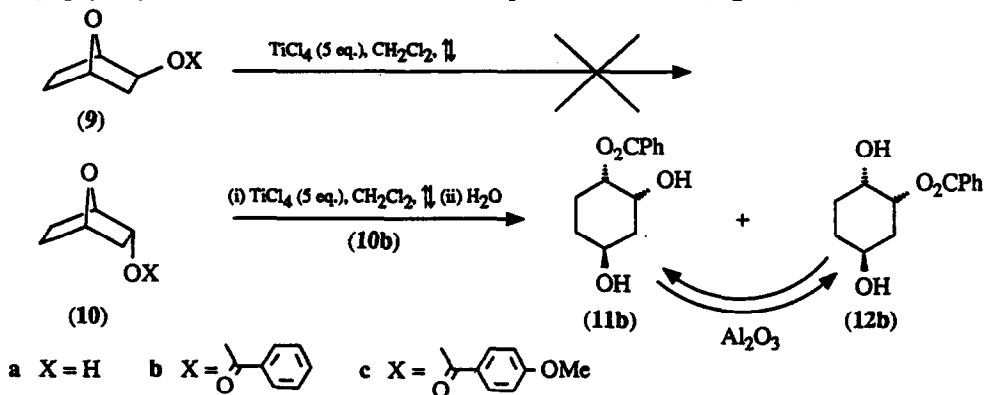


Figure 5

In order to corroborate the proposed structures, the mixture was saponified (K_2CO_3 , MeOH , r.t.) to furnish a single triol (quant.)⁷ which was shown by X-ray crystallographic analysis to be 1,2-*syn*-4-*anti*-cyclohexanetriol (13) (Figure 6).⁸ The ready interconversion of the two benzoates (11b) and (12b) is in keeping with the substitution pattern and stereochemistry proposed.

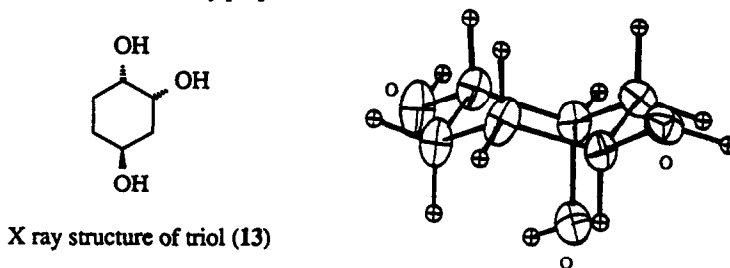


Figure 6

The marked difference in reactivity of the *exo*- and *endo*- substrates (9b) and (10b) is presumably due to the steric requirement for *anti*- approach of the ester group to the developing carbocation as cleavage of the oxygen bridge proceeds (Figure 7),⁹ and also explains the relative stereochemistry of the oxygen substituents in the cleavage products.

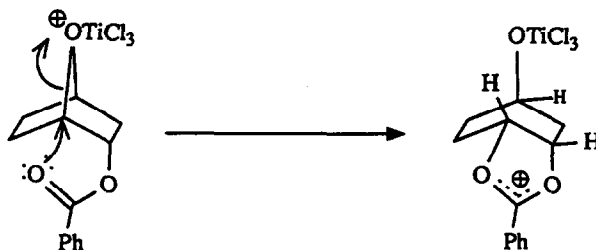


Figure 7

In conclusion, we have demonstrated the potential of a mild means of cleaving tetrahydrofurans to furnish

products having 1,4-dioxygenation, profiting from internal assistance of an appropriately placed aromatic ester moiety to trap the intermediate cationic species. In the bicyclic substrates (9b) and (10b), this procedure has been shown to have a high steric requirement.

Acknowledgements: We thank the SERC for financial support (to F. J. W.)

References

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(Received in UK 6 February 1990)