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Bi(III) Catalysed *O*-acylative cleavage of 2,5-dimethyltetrahydrofuran: a substrate dependent borderline mechanism

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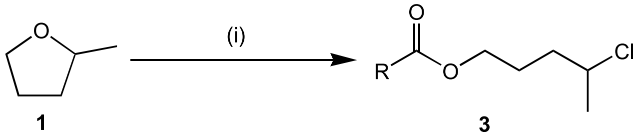
Abstract—The Bi(III) catalysed *O*-acylative cleavage of *cis*- and *trans*-2,5-dimethyltetrahydrofuran **4** with AcCl, BzCl or *i*-PrCOCl is stereochemically consistent with the operation of a concerted process (A_ND_N), which proceeds via a stabilised carbocation or 'loose' S_N2 transition state. However, the *O*-acylative cleavage of *cis*-2,5-dimethyltetrahydrofuran **4** with sterically demanding electrophiles such as *t*-BuCOCl, appears to be stereochemically consistent with the alternative S_N1 (D_N+A_N) pathway. The apparent merging of mechanistic pathways is rationalised by the participation of a strained acyloxy cation.

1. Introduction

It has been known for some time that the cleavage of cyclic ethers to afford 4-halobutanes may be achieved using Lewis acids.[1] This procedure has failed to attain any prominence in organic synthesis, possibly because both stoichiometric amounts of Lewis acid and extended periods of heating are often required for cleavage to occur (i.e., $ZnCl_2$,[2] $FeCl_3$,[3] $MgBr_2$,[4a] $AlCl_3$[5]). In addition, the majority of procedures reported to date fail to afford regioselective cleavage (i.e., 1° vs 2°). Our interest in the unique stereoelectronic and mechanistic characteristics associated with main group organometallic complexes[6] encouraged us to investigate Bi(III) salts as versatile, cheap non-toxic catalysts for organic synthesis.[7] We recently reported a mild (DCM/20 °C), high yielding Bi(III) catalysed (5%) *O*-acylative cleavage procedure using a variety of acid chlorides RCOCl **2**, which in the case of 2-methyltetrahydorfuran **1**, affords haloesters **3** with excellent regioselectivity (Scheme 1).[8]



Scheme 1. (i) RCOCl **2**, $BiCl_3$ (5%), DCM, r/t.[8]

As the Bi(III) catalysed *O*-acylative cleavage of tetrahydrofuran fails to afford products consistent with the operation of a unimolecular process, that is, 3-chlorobutylbenzoate, we assumed that this reaction must proceed via a concerted mechanism. The regioselectivity observed for the Bi(III) catalysed *O*-acylative cleavage of **1** is however, inconsistent with the classical perception of a bimolecular process. Insight into the mechanism of such reactions may be gained by examining the stereochemical outcome accompanying the *O*-acylative cleavage of enantiomerically pure 2-alkyltetrahydrofurans. However, we have chosen an alternative approach which examines the *O*-acylative cleavage of *cis*- and *trans*-2,5-dimethyltetrahydrofuran **4**; the loss of configurational integrity during *O*-acylative cleavage will afford mixtures of diastereoisomers as opposed to enantiomers. We describe here studies which reveal the possible origin of the regioselectivity accompanying the Bi(III) catalysed *O*-acylative cleavage of 2-methyltetrahydrofuran **1**. In addition, we describe how the *cis* and *trans* isomers of 2,5-dimethyltetrahydrofuran **4** appear to undergo *O*-acylative cleavage via alternative mechanisms, depending upon the structure of the electrophile.

2. Results and discussion

2.1. *O*-Acylative cleavage using acid chlorides 2a–c

2,5-Dimethyltetrahydrofuran **4**, used here as the commercially available mixture of *cis* and *trans*-isomers,[9a]

Keywords: Bi(III) Catalysis; Cyclic ethers; *O*-Acylative cleavage; Borderline mechanism.

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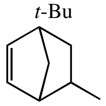
undergoes smooth $BiCl_3$ (5%) catalysed *O*-acylative cleavage with acid chlorides RCOCl **2a–c** to afford the corresponding 1-methyl-4-chloropentyl esters **5a–c** in isolated yields of >95% (Table 1). As anticipated, both the *syn*- (i.e., 1*SR*,4*SR*) and *anti*- (i.e., 1*SR*,5*RS*) diastereoisomers of **5a–c** are formed in approximately equal amounts, as established by $^1H/^{13}C$ NMR, GC and GC–MS analyses.

Table 1. Chloroesters **5a–e**

4

5a-e, > 95%

	R	Isomeric ratio
5a	Me	1:1
5b	Ph	1:1
5c	*i*-Pr	1:1
5d	*t*-Bu	5:3 (*anti*:*syn*)
5e		1:1 (*exo*- *anti*:*syn*) 4:2 (*endo*- *anti* and *syn*)

The *cis* isomer of **4** employed for these studies was obtained by the stereospecific catalytic hydrogenation of 2,5-dimethylfuran using Raney nickel.[9] ^1H NMR spectroscopy was used to establish that the hydrogenation of 2,5-dimethylfuran is accompanied by a small quantity (ca. 5%) of the epimeric *trans* isomer. The Bi(III) catalysed *O*-acylative cleavage of *cis*-**4** with acid chlorides **2a–c** affords a single diastereoisomer (GC ca. 95%) of the corresponding 1-methyl-4-chloropentyl esters **5a–c** (see Section 4).

The relative configuration of the product chloroesters **5a–c** was established unambiguously by an in situ hydrolysis and re-cyclisation procedure to afford the corresponding 2,5-dimethyltetrahydrofuran **4**.[4b] Thus, a single diastereoisomer of **5a–c** was gently heated in the presence of potassium hydroxide and ethylene glycol for 6 h to afford **4**, which was distilled (bp = 91–92 °C) directly from the crude reaction mixture (yield = 50%). ^1H NMR spectroscopy was used to establish that in each case, re-cyclised **4** was in fact the *cis* isomer.[10] Heating the 1:1 diastereoisomeric mixtures of **5a–c** in potassium hydroxide/ethylene glycol afforded the corresponding 1:1 mixtures of *cis*/*trans* **4**. It may be concluded then, that the re-cyclisation of esters **5** to ether **4** (step **B**) proceeds via a concerted S_N2 (A_ND_N)[11] mechanism (Fig. 1). From this, it follows that the original $BiCl_3$ catalysed *O*-acylative cleavage of *cis*-**4** with **2a–c** must afford *syn*-**5a–c** (Fig. 1).

If *cis*-**4** had undergone a stepwise Bi(III) catalysed *O*-acylative cleavage process to afford a liberated intermediate, appreciable amounts of both diastereoisomers of **5a–c** should have been observed, and as a consequence, a mixture of *cis*- and *trans*-**4** would be obtained upon re-cyclisation. This is not the case. Furthermore, if *O*-acylative cleavage with retention of configuration had occurred, *trans*-**4** would be the ultimate product of the ring opening and subsequent re-cyclisation of *cis*-**4**. It would appear then, that the ethereal C–O bond of the intermediate acyloxy:$BiCl_4^-$ ion pair becomes significantly polarised without actual cleavage prior to attack by the chloride anion (step **A**; Fig. 1). The result may be viewed as either an unusually 'loose' transition-state for an S_N2 reaction, or a carbocation that is stabilised by the interaction of both attacking and leaving groups.[12] This would appear to account for the observed regioselectivity attending the Bi(III) catalysed *O*-acylative cleavage of **1**. A search of the literature reveals just one other example of a 'loose' S_N2 transition-state being invoked to rationalise the unexpected regioselectivity attending ring cleavage.[13] Here also, an acylated heteroatom serves to stabilise a developing carbocation during the cleavage of a 2,2-dimethyl *N*-acylaziridine with thiolate as nucleophile.

2.2. *O*-Acylative cleavage using acid chlorides 2d–e

Surprisingly, the Bi(III) catalysed *O*-acylative cleavage of **4** with *t*-BuCOCl **2d** affords **5d**, not as a 1:1 mixture but as a 3:5 mixture of diastereoisomers (retention times = 17.4 and 17.9 min, respectively; Scheme 2). The relative configuration of the major diastereoisomer in this mixture was deduced by the in situ hydrolysis/re-cyclisation procedure described earlier. Thus, heating a 5:3 mixture of **5d** in potassium hydroxide/ethylene glycol affords a 5:3 mixture of *trans*-**4** and *cis*-**4**, respectively. As the re-cyclisation procedure proceeds via a concerted mechanism, the initial $BiCl_3$ *O*-acylative cleavage of **4** with **2d** must generate *anti*-**5d** (retention time = 17.9 min) as the major diastereoisomer.

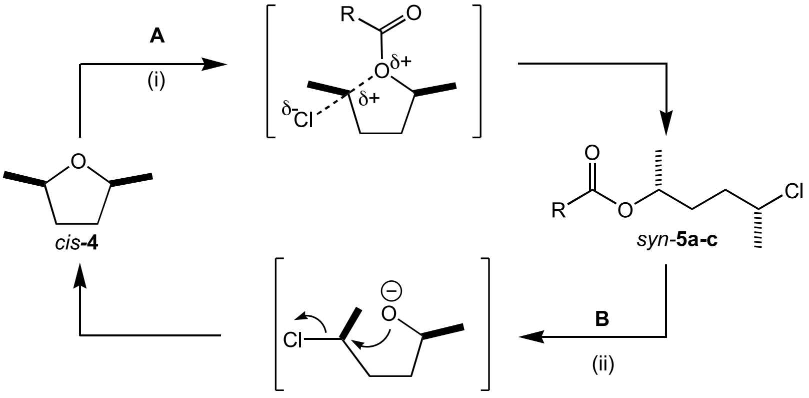


Figure 1. (i) RCOCl 2a–c, $BiCl_3$ (5%), DCM, r/t, 4 h; (ii) KOH, $HO(CH_2)_2OH$, 60 °C, 6 h.