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A surprising steric effect on a tandem cycloaddition/ring-opening reaction: rapid syntheses of difluorinated analogues of (hydroxymethyl)conduritols†

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Diffuorinated analogues of (hydroxymethyl)conduritols can be synthesised from selected furans and a difluorinated dienophile in two reaction steps.

The literature contains many examples of fluorinated building blocks.1 These are either commercially available compounds or readily prepared intermediates that can be manipulated using the important C–C bond-forming reactions of modern synthetic chemistry. Few, if any, of these building blocks allow the rapid synthesis of complex fluorine-containing molecules.

We identified cyclic carbonate 4 as a side product during the formation of endo and exo cycloadducts 2 and 3 via the furan Diels–Alder reaction of rare difluorinated dienophile4 in the presence of sub-stoichiometric amounts of stannic chloride (Scheme 1).1

We were interested in this product, as it complements species we could obtain by either hydrostannylation/stannate ring opening according to Lautens4 or via procedures in which sulfur electrophiles and reductive desulfonation/ring-opening chemistry are used.5 Furthermore, though the yield is modest, the product arises in a single reaction step from cycloaddition, followed by highly controlled ring-opening, so the sequence is particularly concise. We therefore decided to investigate further and found that 4 (26%) replaced exo-3 when the cycloaddition was carried out with stoichiometric Lewis acid.6 However, non-aqueous work-up of a reaction solution led to the exclusive presence of 2 and 3, as revealed by 19F NMR: we were only able to observe 4 after aqueous work-up. Substituted 2-methyl-, 2,3-dimethyl- and 2,5-dimethylfuran behaved quite differently, failing to afford cyclic carbonates. Instead, only exo cycloadducts were obtained and all attempts to force the reactions led to decomposition.

There is little in the literature that might help to predict how the Lewis acid would bind to 2/3. A search of the literature revealed only 5- and 6-membered chelates involving stannic chloride. Denmark and Fu have obtained structures for bis-phosphoramidate ligand–stannic chloride complexes,8 though these include much larger rings. We therefore attempted to grow crystals of a complex between the reactive exo-3 and stannic chloride. Diffusion of hexane into a DCM solution of 3 and stannic chloride at room temperature produced air-sensitive crystals of 7a (Fig. 1), which were transferred rapidly to the cold diffractometer stage.3 Clearly, this cannot be an intermediate on a direct pathway to 4. Scheme 2 presents our proposed mechanism for the formation of 4.

To trigger ring opening, stannic chloride must first bind to the bridging ether oxygen, which is a poor donor. To compensate for this, 6-membered chelate formation (in 5a) involving carbonyl and ether oxygen donors, which is impossible from the endo cycloadduct, is proposed. Bridge cleavage, which is strain relieving, may then occur reversibly. The proposed intermediate 6a is transformed into 4 when hydrolysis removes it from the equilibrium.7

We have used electronic structure calculations to investigate a number of aspects of this proposed mechanism.8 Minima and transition structures were calculated at the B3LYP/6-31G** level, including the effect of the solvent, DCM, using the polarisable continuum model (PCM). These calculations first showed that 5a and 7a differed in energy by only 21 kJ mol−1 in favour of 7a, thus confirming the proposed equilibrium between these structures. The proposed intermediate 6a was confirmed as an energy minimum and the transition structure linking it to reactant 5a was located, the barrier being 80 kJ mol−1. This transition structure showed a high degree of bond cleavage (C–O = 2.06 Å), suggesting that the effect of methylation at the bridgehead position is steric rather than electronic.† To investigate this further, the calculations were repeated for the methylated molecules. We now find 7b to be more stable than 5b by 42 kJ mol−1, with the barrier to the formation of

† Electronic supplementary information (ESI) available: calculations and Cartesian coordinates for 3–7 (Me substituted for Et throughout); data for 8–10. See http://www.rsc.org/suppdata/cc/b4/b401245c/

Scheme 1 Furan Diels–Alder reaction of difluorinated dienophile 1. (i) 25 mol% SnCl4, furan (2 equiv.), DCM, rt.

Scheme 2 Proposed mechanism for the formation of cyclic carbonate 4.

Fig. 1 Crystal structure of air-sensitive complex 7a formed between exo-3 and stannic chloride.
6b (from 5b) being increased to 95 kJ mol\(^{-1}\). Both these effects will contribute to the observed failure to yield the corresponding carbonate from the 2-methyl (or 2,3-dimethylfuran) cycloadduct.

Cyclic carbonate 9 and endo-cycloadduct 8a were obtained in moderate yield from the reaction between 1 and 3-bromofuran, a seldom-used diene\(^8\) (Scheme 3), as verified by X-ray diffraction analysis of single crystals. This result is in line with our previous conclusion that the steric hindrance at the bridgehead carbon where C–O scission occurs is more important for ring opening than electronic effects in the transition state.

The use of the vinyl bromide as a locus for the generation of diversity is an attractive possibility that we propose to explore more fully, since preliminary experiments have yielded encouraging results.

The potentiality of these reactions afford extremely rapid access to a very wide range of functionally rich difluorinated cyclohexene derivatives, though there is considerable scope for optimisation.

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Notes and references

\(^{1}\) Cycloaddition with stoichiometric tin(IV) chloride: preparation of 3. Tin(IV) chloride (2 mmol, 1.9 mL of a 1.03 M solution in DCM) was added slowly to a mixture of alkene 1 (2 mmol, 0.5 g) and furan (4 mmol, 0.3 mL) in DCM (3 mL); the mixture was stirred at room temperature for 36 h. The mixture was diluted with water (5 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were dried (MgSO\(_4\)) and concentrated in vacuo to leave an orange oil (0.61 g), which was purified by column chromatography (20% diethyl ether in light petroleum) to afford endo adduct 2a (0.22 g, 34%) and cyclic carbonate 3 (0.14 g, 26%) as cubic crystals; mp 61–62 °C; \(R_f\) (20% diethyl ether in light petroleum) 0.05; (Found: C, 45.66; H, 3.70; C\(_{12}\)H\(_{18}\)F\(_4\)O\(_2\); requires: C, 45.46; H, 3.82%.)

\(^{2}\) Reaction.

\(^{3}\) From the reaction between the 2-methyl (or 2,3-dimethylfuran) cycloadducts.

\(^{4}\) Fully, since preliminary experiments have yielded encouraging results.

\(^{5}\) Since electronic effects in the transition state.

\(^{6}\) For the only previous example of a difluorinated alkenoate dienophile, see: J. M. Percy, Top. Curr. Chem., 1997, 193, 131.

\(^{7}\) A referee suggested an alternative explanation in which water reacts strongly supported by the computational findings.