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

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Difluorinated 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 dienophile1 in the presence of sub-stoichiometric amounts of stannic chloride (Scheme 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 readily prepared intermediates that can be manipulated using the Lewis acid would bind to attempts to force the reactions led to decomposition.

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 this cannot be an intermediate on a direct pathway to 4. Scheme 2 presents our proposed mechanism for the formation of 4.

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† 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/ccc/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.

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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-(2,3-dimethyl) furoxan.

Cyclocarbonate 9 and endo-cycloadduct 8b were obtained in moderate yield from the reaction between 1 and 3-bromofuran, a seldom-used diene (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. Cycloadduct 8 reacted with phenylboronic acid under Leadbetter’s aqueous microwave-mediated conditions and afforded 10. Exposure of 9 to excess DIBAI-H provided tetrol 11 in moderate yield; a styryl group was then introduced via the coupling reaction.

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

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Notes and references
† 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 alkeneolate I (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 (MgSO4) 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; Rf (20% diethyl ether in light petroleum) 0.05; (Found: C, 45.66; H, 3.70; C9H6Br2F2O4 requires: C, 45.6; H, 3.82%); Vmax (film/cm⁻¹): 1980 br (OH), 1846 (C=O), 1750 (C=O), 1743 (C=O), 1427 (C=O), 1220 (C=O), 11875 (C=O); 3/4p (150 MHz, CDCl3): 6.15–6.09 (1H, m), 5.85–5.91 (1H, m), 5.48 (1H, d, J = 4.0), 4.64–6.06 (1H, m), 4.32–3.32 (2H, m), 3.84 (1H, 3J, J = 7.7 Hz); δ (75 MHz, CDCl3): 164.2 (d, 2J = 17.1), 153.1, 153.5 (2J = 5.9, 14.1), 122.0 (d, 2J = 11.1), 116.6 (d, 2J = 256, 250.9), 80.6 (d, 2J = 33.1, 25.3), 76.8 (d, 3J = 2.3), 65.2 (d, 2J = 27.1, 20.9 Hz). 64.2, 13.7: δ (282 MHz, CDCl3): –115.3 (1F, d, 2J = 261.5, 1JF = 13.4 Hz); m/e (CI): 283 (100%, [M + Na]+).

§ Crystal data for 6 (mp not measured): C9H6Br2F2NO3, M = 579.8; monoclinic, a = 10.4879(11), b = 18.0701(19), c = 10.7203(11) Å, β = 102.90(2)°; V = 2023.4(8) Å³; T = 150(2) K; space group P2₁/n, Z = 4, μ(Mo-Kα) = 1.802 mm⁻¹; 10 971 reflections measured, 4033 unique (Rint = 0.0261), which were used in all calculations; R1 = 0.0278, wR2 = 0.0651; the final wR(F2) was 0.0369 (all data). For 8 (mp 71–72 °C): C19H15BrF3NO6, M = 398.2; monoclinic, a = 11.6660(9), b = 8.035(6), c = 18.3629(14) Å, β = 102.7150(10)°, U = 1682.9(2) Å³; T = 150(2) K; space group P21/n, Z = 4, μ(Mo-Kα) = 2.488 mm⁻¹; 12 743 reflections measured, 3310 unique (Rint = 0.0269), which were used in all calculations; R1 = 0.0417, wR2 = 0.0994; the final wR(F2) was 0.0888 (all data). For 9 (mp 123–125 °C): C9Br2H4F3NO6, M = 343.1; monoclinic, a = 7.0099(8), b = 11.5134(13), c = 14.9905(17) Å, β = 94.40(2)°; U = 1199.62 Å³; T = 150(2) K; space group P21/n, Z = 4, μ(Mo-Kα) = 3.474 mm⁻¹; 8057 reflections measured, 4055 unique (Rint = 0.0326), which were used in all calculations; R1 = 0.0328, wR2 = 0.0768; the final wR(F2) was 0.0768 (all data). CCDC 229969–229971. See: J. Leroy, H. Molines and C. Wakselman, Org. Lett., 2002, 1062–1063.


2 P. J. Crowley, A. C. Moralee, J. M. Percy and N. S. Spencer, Synlett, 2000, 1737.


6 A referee suggested an alternative explanation in which water reacts with 5a, which then progresses irreversibly. We cannot disprove this suggestion, but must point out that our hypothesis does appear to be strongly supported by the computational findings.

