Oxy-Cope rearrangements of fluorinated divinylcyclohexanols: a modular method for the construction of selectively fluorinated cyclic ketones

Gianluca Dimartino,[a] Thomas Gelbrich,[b] Michael B. Hursthouse,[b] Mark E. Light,[b] Jonathan M. Percy*[a] and Neil S. Spencer[a]

[a] *School of Chemistry, University of Birmingham, Edgbaston, Birmingham, UK B15 2TT.*
E-mail: jmpercy@chemistry.bham.ac.uk
[b] *EPSRC National X-Ray Crystallography Service, Department of Chemistry, University of Southampton, Highfield, Southampton, UK SO17 1BJ*

Received (in Liverpool, UK) 25th October 1999, Accepted 10th November 1999

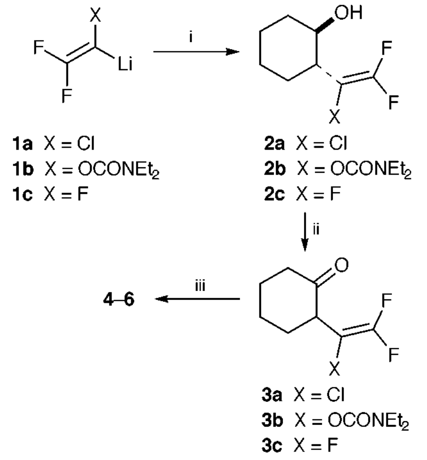
Oxy-Cope rearrangements of fluorinated divinylcyclohexanols afford access to cyclodecenones containing from two to five fluorine atoms.

The oxy-Cope rearrangement has become a tool of awesome transformative power;[1,2] ring systems can be constructed and interconverted with ease, opening routes to highly complex and densely functionalised polycyclic molecular architecture. However, oxy-Cope rearrangements of fluorinated substrates have remained uncharted territory.[3] The effect of fluorine atom substituents upon the thermodynamic parameters of simple Cope rearrangement systems is well known, thanks to the extensive and rigorous efforts of Dolbier.[4] Terminal fluorine atom substituents lower the enthalpy of activation, while the entropy of activation usually increases; overall, the rearrangement reaction in which the CF_2 centre rehybridises from sp^2 to sp^3 is favoured.

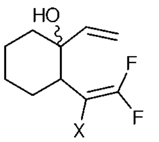
Cyclic (especially medium to large ring) difluoro ketones have a relatively unexplored chemistry because there are few rational routes for their synthesis. More highly fluorinated cyclic ketones show interesting keto/enol tautomerisation[5] behaviour that is quite different from that of acylic congeners,[6] an important class of compounds with well-defined and useful hydration behaviour.[7] Routes to conformationally-restricted difluoro ketones may therefore be of interest and there is also potential for novel transannular interactions and reactions.[8] We therefore decided to examine the oxy-Cope rearrangement as a possible novel strategy for the construction of medium to large rings with controllable patterns of selective fluorination.

We chose the divinyl cyclohexanol/cyclodecenone system, studied originally by Marvell and Whalley,[9] as our starting point and followed their synthetic strategy. Cyclohexene oxide was opened with metallated fluoroalkenes **1a**,[10a] **1b**[10b] and **1c**[10c] to afford alcohols **2a–c** in 69, 64 and 76% isolated yields. Swern oxidation of each followed to afford the corresponding ketones **3a** (83%), **3b** (52%) and **3c** (72%). We were happy to note that these β,γ-unsaturated species, which are presumably destabilised by the vinylic CF_2 centre, did not isomerise and could be purified by column chromatography (Scheme 1).

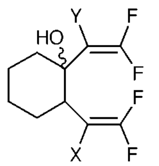
Next, we added vinylmetals, with the intention of demonstrating that a degree of flexibility was possible in precursor construction. Vinyllithium reacted smoothly with **3a** and **3c** to afford dienols **4a** and **4c** in 78 and 68% yields respectively. When the metallated fluoroalkene derived from HFC-134a **1c** was added to **3a**, a mixture of diastereoisomeric dienols **5a** with distinct ^{19}F NMR spectra were obtained (2.3 : 1 mixture, 57%). Finally lithiodihydropyran was added to **3a–c** to afford **6a–c**, completing a preliminary range of representative species. The three latter dienols in particular could not be purified because of decomposition during column chromatography, but crude material could be obtained directly from the addition reaction with satisfactory ^1H and ^{19}F NMR spectra. In general, we were not able to free any of the preceding dienols completely from trace amounts of hydrocarbon impurities so they were taken on without being characterised fully.



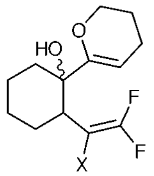
Scheme 1 *Reagents and conditions*: i, cyclohexene oxide, $BF_3 \cdot OEt_2$, THF, −78 °C; ii, DMSO, $(COCl)_2$, −78 °C, then Et_3N; iii, alkenylmetal, THF, −78 °C (see text).



4a X = Cl
4c X = F



5a X = Cl, Y = F



6a X = Cl
6b X = OCONEt2
6c X = F

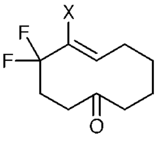
We chose to investigate the neutral oxy-Cope in anticipation of problems arising from the high nucleophilicity of potassium alkoxides and enolates, the potential for fluoride ion loss, and the known high electrophilicity of perhaloalkenes. The rearrangements were initiated by heating small samples of the dienols in dry xylene in sealed (Ace) tubes at progressively higher temperatures until appropriate ^{19}F NMR spectral changes were observed, or ^1H NMR changes in the case of **10**. No attempt was made at this stage to measure rate constants or determine activation parameters but we did run a number of substrates at 150 °C to allow some qualitative comparisons to be made (Table 1) with **10**.

Substrates **4a**, **5a** and **6a** all reacted smoothly at 150 °C in short reaction times; however, **10** failed to react at all in one week at that temperature and only underwent a slow conversion at 225 °C in xylene. Of the three series of compounds, the chlorinated congeners appeared to be more reactive than the fluorinated or oxygenated counterparts.[11] The relatively low temperatures of the rearrangements are most encouraging and suggest that a rather general method of fluoro ketone synthesis may be available.[12] Structural assignment was made by ^1H

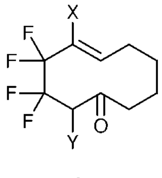
Table 1 Rearrangement conditions and outcomes for fluorinated dienols

Dienol	*T*[a]/°C	*t*[b]/*h*	Product	Yield[c] (%)
4a	125	8	**7a**	67
4a	150	3	**7a**	58
4c	125	46	**7c**	72
5a	150	1.75	**8a**	73
6a	150	3	**9a**	65
6b	155	9	**9b**	62
6c	140	17	**9c**	84
10	150	168	**11**	—
10	225	24	**11**	49

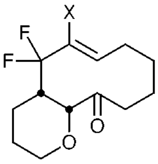
[a] Reactions in sealed tubes in xylene. [b] Time for complete consumption of starting dienol by NMR. [c] Isolated yield.



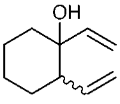
7a X = Cl
7c X = F



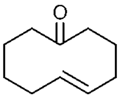
8a X = Cl, Y = F



9a X = Cl
9b X = OCONEt$_2$
9c X = F



10



11

NMR COSY and GOESY experiments.[13] By ^{19}F NMR, we were able to detect only products with a single double bond configuration, assumed *trans* with respect to the mutual location of the ring bonds. Unambiguous proof of alkene configuration was then obtained in the case of **9a** when single crystals[14] were grown and subjected to analysis by X-ray diffraction (Fig. 1). Also, the $^3J_{\text{H-F}}$ couplings across the alkene bond in **7c** (33.7 Hz) and **9c** (32.4 Hz) were entirely consistent with this arrangement.

We have therefore shown that oxy-Cope systems can be assembled rapidly, and that fluorinated cyclodecenones and more complex species can be developed from simple fluoroalkene building blocks. Work to define the scope and kinetic parameters of oxy-Cope rearrangement systems that contain fluorinated vinylic components is in progress.

Fig. 1 The molecular structure of **9a**. The *cis*-ring junction and *trans*-ring bonds can be seen clearly.

We thank the Engineering and Physical Sciences Research Council of Great Britain for a Project Studentship (to G. D.) under the ROPA Scheme.

Notes and references

1 C. J. Roxburgh, *Tetrahedron*, 1995, **51**, 9767.
2 L. A. Paquette, *Tetrahedron*, 1997, **53**, 13971.
3 For reviews of [3,3]-rearrangements of fluorinated substrates, see: S. T. Purrington and S. C. Weeks, *J. Fluorine Chem.*, 1992, **56**, 165; V. G. Andreev and A. F. Kolomiets, A. F. *Usp. Khim.*, 1993, **62**, 594. Rearrangements in the context of fluorinated building block chemistry are discussed in: J. M. Percy, *Top. Curr. Chem*., 1997, **193**, 131; J. M. Percy and M. E. Prime, *J. Fluorine Chem*., 1999, in the press.
4 W. R. Dolbier and K. W. Palmer, *J. Am. Chem. Soc.*, 1993, **115**, 9349.
5 P. E. Lindner and D. M. Lemal, *J. Org. Chem.*, 1996, **61**, 5109; P. E. Lindner, R. A. Correa, J. Gino and D. M. Lemal, *J. Am. Chem. Soc.*, 1996, **118**, 2556.
6 P. E. Lindner and D. M. Lemal, *J. Am. Chem. Soc.*, 1997, **119**, 3259.
7 D. Schirlin, J. M. Rondeau, B. Podlogar, C. Tardif, C. Tarnus, V. Vandorsselaer and R. Farr, *ACS Symp. Ser.*, 1996, **639**, 169; H. L. Sham, *ACS Symp. Ser.*, 1996, **639**, 184.
8 D. Colclough, J. B. White, W. B. Smith and Y. L. Chu, *J. Org. Chem.*, 1993, **58**, 6303; Y. L. Chu, D. Colclough, D. Hotchkin, M. Tuazon and J. B. White, *Tetrahedron*, 1997, **53**, 14235.
9 E. N. Marvell and W. Whalley, *Tetrahedron Lett.*, 1970, 509.
10 (*a*) J. M. Bainbridge, S. J. Brown, P. N. Ewing, R. R. Gibson and J. M. Percy, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2541; (*b*) J. A. Howarth, W. M. Owton, J. M. Percy and M. H. Rock, *Tetrahedron*, 1995, **51**, 10289; (*c*) J. Burdon, P. L. Coe, I. B. Haslock and R. L. Powell, *Chem. Commun.*, 1996, 49.
11 N. Y. Jing and D. M. Lemal, *J. Am. Chem. Soc.*, 1993, **115**, 8481. In a study of a Cope rearrangement of a perfluorinated hexadiene, the substitution of a chlorine atom for a fluorine atom was reported to exert only a minimal effect upon rearrangement rate and outcome. Products of biradical pathways reported by these authors were not detected in our study.
12 *Selected data* for **9c:** colourless rhombi, mp 94 °C; (Found: C, 59.68; H, 6.61. Calc. for $C_{13}H_{17}F_3O_2$: C, 59.54; H, 6.49%); δ_H(300 MHz, $CDCl_3$) 5.32 (dddd, ^3J 32.4, J 11.4, J 6.3, J 3.0, 1H), 4.16 (dd, ^2J 11.4, J 5.5, 1H), 3.72 (t, J 3.4, 1H), 3.48 (ddt, ^2J 11.4, J 13.0, J 3.1, 1H), 3.10 (dd, J 19.1, J 10.5, 1H), 2.88 (dddd, ^3J 31.6, J 10.8, ^3J 5.5, J 2.9, 1H), 2.38–2.30 (m, 2H), 2.19–2.05 (m, 3H), 2.04–1.95 (m, 1H), 1.86 (dtd, J 16.8, 10.9, 5.5, 1H), 1.73 (ddt, J 19.8, ^2J 14.3, J 5.5, 1H), 1.63–1.55 (m, 1H), 1.40 (d, ^2J 14.3, 1H), 1.31 (q, J 14.0, 1H); δ_F (282 MHz, $CDCl_3$) −101.9 (dd, ^2J 255.6, ^3J 26.7, 1F), −109.5 (dd, ^2J 255.6, ^3J 31.7, 1F), −124.8 (t, ^3J 31.2, 1F); $^{13}\delta_C$ (75 MHz, $CDCl_3$) 207.5, 150.5 (ddd, ^2J 260.5, ^2J 38.4, ^2J 27.7), 117.6 (ddd, ^1J 244.7, ^1J 252.1, ^2J 37.9), 113.0, 83.2, 69.5, 40.9 (dd, ^2J 27.1, ^2J 21.5), 38.5, 29.1, 28.5, 23.1, 22.0, 20.5; ν_{max}/cm^{-1} 1711.9; *m*/*z* (CI) 280 ($M+NH_4^+$).
13 J. Stonehouse, P. Adell, J. Keeler and A. J. Shaka, *J. Am. Chem. Soc.*, 1994, **116**, 6037.
14 *Crystal data* for **9a**: $C_{13}H_{17}ClF_2O_2$, M = 278.7, triclinic, a = 8.0670(2), b = 8.3194(3), c = 10.5779(3) Å, U = 633.65(3) Å^3, T = 150(2) K, space group $P\bar{1}$, Z = 2, μ(Mo-K$_\alpha$) 0.318 mm^{-1}, 10852 reflections measured, 2555 unique (R_{int} = 0.0441) which were used in all calculations. The final $wR(F^2)$ was 0.0718 (all data). CCDC 182/1482. See http://www.rsc.org/suppdata/cc/1999/2535/ for crystallographic data in .cif format.

Communication 9/08450I