Facile Syntheses of *gem*-Difluoroalkenes from Chlorodifluoromethylketones

Jean-Pierre Bégué,^a Danièle Bonnet-Delpon,^a Jonathan M. Percy,^{*b} Michael H. Rock^a and Robin D. Wilkes^b

^a CNRS-BIOCIS, Réactiviteé des Molecules Fluorées, Faculté de Pharmacie de Châtenay-Malabry, 5 Rue J. B. Clement, 92296 Châtenay-Malabry, France

^b School of Chemistry, University of Birmingham, Edgbaston, Birmingham, UK B15 2TT

Chlorodifluoromethyl ketones reacted with diazomethane to afford epoxides in high yield; upon treatment with butyllithium, the epoxides underwent efficient ring opening to afford 3,3-difluoro-2-alkyl-alken-1-ols, suitable substrates for sigmatropic rearrangement leading to compounds containing a CF₂ group in mid-chain.

Consistent with our general interest in the chemistry of functionalised difluoroalkenes,1 we have developed a new method for the preparaton of geminally dialkylated difluoroalkenes. We,1 and others,2 have shown that difluoroenol derivatives can be made from trifluoroethanol by dehydrofluorination-metallation sequences. However, few general approaches to geminal or 1,1-difluoro-2,2-dialkylalkenes have appeared in the literature. Ishihara and coworkers³ transformed aryl chlorodifluoromethyl ketones to gem-dialkyl difluoroalkenes via the corresponding difluoroenol phosphates. These underwent an addition-elimination reaction with Gilman reagents, thus introducing an alkyl substituent. An alternative ylide-based approach starting from dibromodifluoromethane was described by Burton and coworkers.⁴ However, applications to functionalised systems are limited and low yields of products are often obtained.5

Recently, the dechlorinative ring opening of chlorodifluoromethyl epoxides was shown to lead to the formation of difluoroallylic alcohols in high yield.⁶ We anticipated that a modification of the published route would lead to the less accessible title compounds. Readily available chlorodifluoromethyl ketones⁷ reacted efficiently with diazomethane in diethyl ether at ambient temperature (Scheme 1),⁸ allowing the isolation of a range of epoxides 1 (Table 1), setting the stage for the ring opening reaction. We found that the reagent of choice



Scheme 1 Reagents and conditions: i, CH_2N_2 , diethyl ether, 25 °C; ii, 1.1 equiv. BuLi, THF, -78 °C, 5 min; iii, NH_4Cl , MeOH, -78 °C

Table 1

R		Yield ^a 1 (%)	Yield ^a 2 (%)
a	$Ph(CH_2)_3$	90	80
b	$Ph(CH_2)_2$	88	82
с	PhCH ₂	85	75
d	Ph	65 ^b	70
e	$Me(CH_2)_6$	80	80
f	cyclohexyl(CH ₂) ₂	85	78

^a Yields refer to chromatographically pure compounds. ^b The ketone reacted very slowly with diazomethane. Three sequential treatments were required to obtain the quoted yield.



Scheme 2 Reagents and conditions: i, allyl bromide, 50% NaOH_(aq), Bu₄NHSO₄ (cat.), 25 °C, 18 h; ii, 2.0 equiv. LDA, THF, -78 °C, 2 h then -30 °C, 18 h

for initiating the ring opening reaction was butyllithium (1.1 equiv.).[†] The allylic alcohol products **2** are attractive because of their potential for further transformation by way of sigmatropic rearrangement.⁹ For example, **2a** [R=(CH₂)₃Ph] was converted to allyl ether **3** (60%, unoptimised) which underwent [2,3]-Wittig rearrangement¹⁰ following treatment with LDA (Scheme 2) resulting in the formation of **4** in high (81%) yield.

This research was supported by CNRS, European Community HCM Network on Synthesis and Molecular Recognition of Selectively Fluorinated Bioactive Molecules ERBCHRXCT930279 (Fellowship to M. H. R.) and the EPSRC (UK, Fellowship to R. D. W.).

Received, 10th July 1995; Com. 5/04471E

Footnote

† In a typical procedure, butyllithium (0.45 ml of a 2.45 mol dm⁻³ solution in hexanes) was added to a cold (-78 °C) solution of epoxide **1a** (0.25 g, 1 mmol) in anhydrous THF (15 ml). The orange solution was stirred for 5 min then quenched with saturated methanolic ammonium chloride solution at -78 °C. The reaction mixture was poured into saturated ammonium chloride solution (25 ml) and extracted with diethyl ether (3 × 70 ml). The combined organic extracts were dried (MgSO₄) and evaporated *in vacuo* to afford a pale yellow oil. Flash chromatography (silica gel, 5% v/v diethyl ether in pentane) afforded alcohol **2a** (0.19 g, 90%), v_{max} (film) 1720 cm⁻¹ (C=C); $\delta_{\rm H}$ (CDCl₃, 200 MHz) 7.40–7.20 (5 H, m, Ar–H), 4.15 (2 H, s, CH₂OH), 2.70 [2 H, t, *J* = 7.8 Hz, CH₂(CH₂)₂], 2.50 (1 H, s, OH), 2.20–2.06 (2 H, m, CH₂Ph) and 1.90–1.75 (2 H, m, CH₂CH₂CH₂)₂ $\delta_{\rm C}$ (CDCl₃, 200 MHz) 154.5 (t, ¹J_{CF} 286.2 Hz), 142.1, 128.6, 126.2, 90.1 (t, ²J_{CF} 14.7 Hz), 57.5 (t, ³J_{CF} 5.0 Hz), 35.6, 29.4 (¹J_{CF} 2.3 Hz) and 24.5; $\delta_{\rm F}$ (CDCl₃, 400 MHz) –91.05 (d, ²J_{FF} 47 Hz) and -92.05 (d, ²J_{FF} 47 Hz).

References

- J. Percy, *Tetrahedron Lett.*, 1990, **31**, 3931; J. M. Percy and M. H. Rock, *Tetrahedron Lett.*, 1992, **33**, 6177; A. J. Bennett, J. M. Percy and M. H. Rock, *Synlett*, 1992, 483; S. T. Patel, J. M. Percy and R. D. Wilkes, *Tetrahedron*, 1995, **51**, 9201.
- 2 J. Ichikawa, T. Sonoda and H. Kobayashi, Tetrahedron Lett., 1989, 30, 1641; T. Nakai, K. Tanaka and N. Ishihawa, Chem. Lett., 1976, 1263.
- 3 T. Ishihara, M. Yamano and T. Ando, *Tetrahedron Lett.*, 1983, 24, 5657.
- 4 S. Hayashi, T. Nakai, N. Ishikawa, D. J. Burton, D. G. Naae and H. S. Kesling, *Chem. Lett.*, 1979, 983.
- 5 T. F. Heron, W. B. Motherwell and M. J. Tozer, *Tetrahedron Asymmetry*, 1994, 5, 2269; J. S. Holton, W. B. Motherwell, B. C. Ross, M. J. Tozer, D. J. Williams and A. M. Z. Slawin, *Tetrahedron*, 1993, 49, 8087.
- 6 J.-P. Bégué, D. Bonnet-Delpon and M. H. Rock, *Tetrahedron Lett.*, 1994, 35, 6097.
- 7 K. M. Neder, S. A. French and S. P. F. Miller, *Tetrahedron*, 1994, **50**, 9847; J. P. Bégué, D.Bonnet-Delpon, D. Mesureur, G. Née and S. W. Wu, *J. Org. Chem.*, 1992, **57**, 3807.
- 8 P. Bravo, A. Farina, M. Frigiero, S. V. Meille, V. Soloshonok and F. Viani, *Tetrahedron Asymmetry*, 1994, 5, 987.
- 9 An example of a [3,3]-Claisen rearrangement of an alcohol of this type has been reported; T. Taguchi, T. Morikawa, O. Kitagawa, T. Mishima and Y. Kobayashi, *Chem. Pharm. Bull.*, 1985, 33, 5137.
- 10 J. M. Percy and S. T. Patel, J. Chem. Soc., Chem. Commun., 1992, 1477;
 - S. T. Patel, J. M. Percy and R. D. Wilkes, J. Org. Chem., submitted.