Pergamon

Tetrahedron Letters, Vol. 35, No. 33, pp. 6097-6100, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01258-X

Synthesis of 3-*gem*-Difluoro-2-Ethoxy allylic Alcohols from Ethyl Chlorodifluoroacetate

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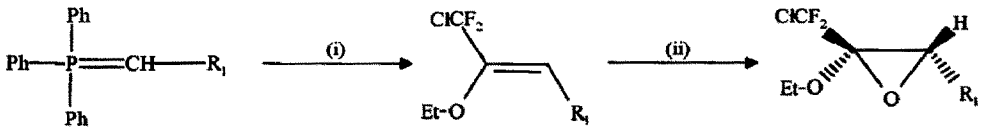
Key words: Ethylchlorodifluoroacetate, Wittig reaction, epoxidation, gem-difluoroallylic alcohols

Abstract: ***-The chlorine atom in chlorodifluoromethyl epoxy ethers is unusually reactive towards butyllithium. This reactivity has been used to develop a concise synthesis of gem-difluoro2-ethoxy allylic alcohols from the commercially available ethylchlorodifluoroacetate.***

There is considerable interest in the synthesis of *gem*-difluoroalkenes due to their incorporation into mechanism based inhibitors and other bioactive molecules.[1,2] In addition they are versatile building blocks for the introduction of the difluoromethyl unit through Diels-Alder reactions,[3] 1,3-dipolar cycloadditions,[4] 3,3-sigmatropic rearrangements,[5-7] 2,3-Wittig rearrangements,[8] and radical additions.[9] Furthermore *gem*-difluoroalkenes[10] and the difluoromethyl unit[4] can be readily hydrolysed to give the corresponding carbonyl compounds.

The synthesis of *gem*-difluoroallylic alcohols has been reported by a variety of methods, for example the trapping of stabilised difluorovinyl anions derived from 1,1,1-trifluoroethanol[5,11,12] and the non stabilised 2,2-difluorovinyl lithium[13] by aldehydes. An alternative approach from ethyl chlorodifluoroacetate utilises the Reformatsky reaction of 4-chloro-4,4-difluorocrotonate with carbonyl compounds using a zinc/copper couple [14] The transformation of an α–hydroxy ketone into the corresponding difluoroallylic alcohol has also been reported.[15]

We have previously reported an example of the Wittig reaction of a non stabilised phosphorane under salt free conditions with methyl chlorodifluoroacetate to form the corresponding *Z* enol ether in good yield.[16] This reaction has now been extended to a variety of non stabilised phosphoranes **1a-d** with ethyl chlorodifluoroacetate to form the enol ethers (Scheme 1).[17,18] Epoxidation of the thus synthesised chlorodifluoromethyl enol ethers **2a-d** under conditions previously employed for the corresponding trifluoromethyl compounds[19,20] gave the epoxy ethers **3a-d** in good yield[17,21] (Scheme 1).



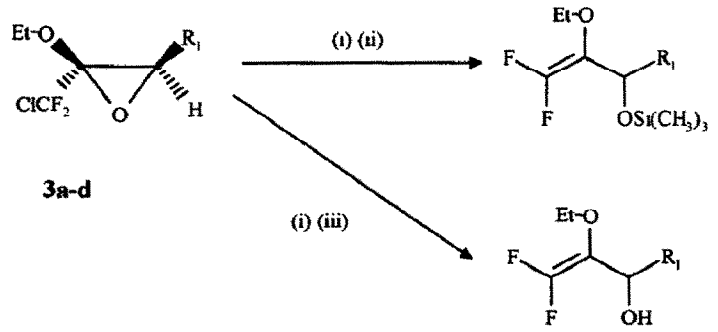
		Yield %[a]		Yield%[a]	
1a	R_1 = Ph	**2a**	58	**3a**	80
1b	R_1 = $(CH_2)_2Ph$	**2b**	55	**3b**	85
1c	R_1 = Cyclohexyl	**2c**	50	**3c**	82
1d	R_1 = $CH_2CH(OEt)_2$	**2d**	42	**3d**	60

(i) $ClCF_2CO_2Et$, THF, Reflux 3 h, (ii) MCPBA, CH_2Cl_2,R T 48 h.

[a] Yields refer to chromatographically pure compounds

Scheme 1

The chlorine atom in chlorodifluoroacetic acid derivatives has a low reactivity and has been reported only to react in the formation of difluorocarbene[22] or organo zinc compounds[7,15,23] which are nevertheless more easily formed from the corresponding bromo compounds. Despite this lack of encouraging precedents it was envisaged that the metallation of the chlorine atom in epoxy ethers **3a-d** could be favoured by the chelation of the adjacent oxygen atoms and by a possible concerted oxirane ring opening. Indeed the treatment of epoxides **3a-d** in THF at -78°C with 1.1 equivalent of t-butyl lithium for 45 minutes, followed by the addition of 1.1 equivalent of trimethylsilylchloride at -78°C resulted in the formation of the desired trimethylsilyl *gem*-difluoroallylic ethers **4a-d** in good yield (Scheme 2).[24] The corresponding difluoroallylic alcohols **5a-d** have been prepared by treatment of these trimethylsilyl compounds **4a-d** with fluoride ion or, more conveniently, by quenching with a methanolic ammonium chloride solution instead of trimethylsilyl chloride (Scheme 2).



3a-d

	Yield%[a]
4a	90
4b	91
4c	80
4d	72

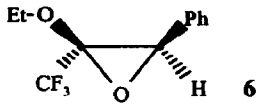
	Yield %[a]
5a	90
5b	90
5c	85
5d	70

(i) THF,1.1 equiv. t-butyl lithium, -78°C, 45min, (ii) 1 1 equiv. trimethylsilyl chloride, (iii).MeOH, NH_4Cl

[a] Yields refer to chromatographically pure compounds

Scheme 2

The same reactivity was observed when n-butyl lithium was used in place of t-butyl lithium with the desired compounds **4a-d** and **5a-d** being formed in slightly lower yields (for example, **4a**: 85%). The nature of the R_1 group has no effect on the outcome of this reaction even when sterically demanding **3c** or functionalised **3d** substituent is present.



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The postulated initial attack of the butyl lithium at the chlorine atom of the chlorodifluoromethyl group is supported by the fact that treatment of the corresponding trifluoromethyl epoxy ether **6** with t-butyl lithium under identical conditions to those employed for epoxy ethers **3** resulted in only a 10% conversion to a complex mixture of products. When the same reaction was carried out with n-butyl lithium no reaction was observed indicating that the other possible positions of attack in epoxy ethers **3** are inert under these conditions.

In conclusion we have shown that the chlorodifluoromethyl group is reactive towards butyl lithium when activated, for example when the loss of the chlorine is accompanied by an oxirane ring opening. Using this unusual reactivity we have developed a general synthetic route to 2-ethoxy 3,3-difluoro allylic alcohols in three steps from the commercially available ethyl chlorodifluoroacetate.

We are currently investigating the further reactivity of epoxy ethers of type **3** and of the *gem*-difluoroallylic alcohols of type **5**.

Acknowledgements: This work was supported by CNRS and European Community Network on Synthesis and Molecular Recognition of Selectively Fluorinated Bioactive Molecules (ERBCHRXCT930279)

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(17) New compounds were characterised by IR, ^{19}F NMR, ^{1}H NMR, ^{13}C NMR, and elemental analysis.

(18) Typical procedure: To a solution of the phosphorane **1a** prepared from the corresponding phosphonium salt (R_1 = C_6H_5) (13.0 g, 30 mmol) and sodium hydride (1.2 g, 30 mmol) in THF (100 mL) with a catalytical amount of hexamethyldisilazane[16], ethyl chlorodifluoroacetate (4.8 g, 30 mmol, 1 mol. equiv.) was added dropwise at 0°C. Once the addition was completed the reaction mixture was heated at reflux for 3h, then concentrated under reduced pressure and the triphenylphosphine oxide was precipitated by the addition of pentane (150 mL). Filtration through a silica gel column to eliminate triphenylphosphine oxide followed by concentration under reduced pressure gave the crude product which was purified by flash chromatography (pentane-Et_2O 95.5) to give the pure chlorodifluoromethyl enol ether **2a** (4.1 g, 58%). I.R. neat 1661cm^{-1}(ν C=C). ^{19}F NMR ($CDCl_3$ $CFCl_3$) δ -55.6; ^{1}H NMR ($CDCl_3$) δ 1.3 (t, J= 7Hz, 3H), 3.85 (q, J= 7Hz, 2H), 6.35 (1H), 7.3 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.7, 69.5, 115.0, 124.4 (t, J_{CF} = 282Hz), 128.9, 129.75, 132.8, 147.0 (t, J_{CF}= 25.5Hz). Anal. Calc. for $C_{11}H_{11}F_2ClO$: C 56.75, H 4 75, Found C 56.6, H 4.8.

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(21) Typical procedure: Enol ether **2a** (2.3 g, 10 mmol) was dissolved in CH_2Cl_2 (25 mL) in a one neck flask and a solution of MCPBA 70% (2 95 g 1.2 equiv.) in CH_2Cl_2 (25 mL) was added dropwise with stirring Once the addition was complete the reaction was stirred at room temperature for a further 48h (reaction monitored by GC), then washed with an aqueous saturated $NaHCO_3$ solution (25 mL); the aqueous fraction was extracted with CH_2Cl_2 (3 x 25 mL), the combined organic fractions were dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (eluent: pentane-Et_2O: 95.5) to give the pure chlorodifluoromethyl epoxy ether 3a (1.95 g, 80%). ^{19}F NMR ($CDCl_3$) δ -65.0; ^{1}H NMR ($CDCl_3$) δ 1.1 (t, J= 7 2Hz, 3H), 3.7 (m, 2H), 4.4 (s, 1H), 7.4 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.1, 63.4, 65 2, 86.1 (t, J_{CF} = 33Hz), 125 7 (t J_{CF} = 297Hz), 127 5, 128.4, 129.2, 131.7, Anal. Calc. for $C_{11}H_{11}F_2ClO_2$: C 53.1, H 4.4; Found C 53.2, H 4.55.

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(24) Typical procedure: To a solution of the epoxide **3a** (0 61 g, 2.5 mmol) in THF (25 mL) at -78°C was added t-Buli (1.62 mL of a 1.7M solution in hexanes) The pale pink solution was stirred for 45 min then treated with trimethylsilyl chloride (0.38 mL, 3 mmol) and stirred for a further 1h at -78°C, and then allowed to warm to room temperature over 1h. The reaction mixture was then poured into saturated ammonium chloride solution (25 mL) and extracted with diethyl ether (3 x 70 mL) The combined organic extracts were dried ($MgSO_4$) and evaporated to give a colourless oil which was purified by chromatography on silica gel (eluent: pentane-Et_2O: 95:5) to give the pure *gem*-difluoroallylic trimethylsilyl ether **4a** (0 71 g, 90%) I.R. neat 1720cm^{-1}(νC=C). ^{19}F NMR ($CDCl_3$) δ 101.1 (d, 69 Hz) 111.9 (d, 69.3 Hz); ^{1}H NMR ($CDCl_3$) δ 0 1 (s, 9H), 0.95 (t, J= 7.Hz, 3H), 3 48 (m, 1H), 3.6 (m, 1H), 5.3 (t, J_{HF}= 3.2Hz, 1H) 7 1 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 15 1, 69 9, 114 1, 119 0 (dd J_{CF} = 52 Hz, 17 Hz), 120 8, 126.2, 127.3, 127.5, 128.1, 140.9, 151 5 (d, J_{CF} =280 5Hz), 156 7 (d, J_{CF} =280 75Hz) Anal. Calc. for $C_{14}H_{20}F_2O_2Si$. C 58.7, H 7.0 ; Found C 58.5, H 6.8.

(*Received in France* 31 *May* 1994; *accepted* 28 *June* 1994)