ELSEVIER

Journal of Fluorine Chemistry 84 (1997) 149–153

JOURNAL OF FLUORINE CHEMISTRY

Synthesis of F-alkyl α-hydroxy acids and esters from F-alkyl epoxides and F-alkyl α-bromo acids and esters from F-alkyl bromohydrins

A. Ould Amanetoullah [a], M.M. Chaabouni [b], A. Baklouti [a,*]

[a] *Laboratoire de Chimie Structurale Organique, Faculté des Sciences de Tunis, Campus Universitaire, 1060 Tunis, Tunisia*

[b] *Ecole Supérieure des Industries Alimentaires, 58 Avenue Alain Savary, 1003 Tunis, Tunisia*

Received 18 December 1996; revised 8 May 1997; accepted 14 May 1997

Abstract

F-alkyl α-hydroxy acids and F-alkyl α-bromo acids were prepared respectively by the nitric acid ring-opening oxidative reaction of F-alkyl oxiranes, and oxidation by chromic acid of F-alkyl bromohydrins. The synthesized acids were converted to the corresponding methyl esters which may prove to be useful in the synthesis of F-alkylated heterocycles. © 1997 Elsevier Science S.A.

Keywords: Fluorine; Acid; Oxidation; Esterification

1. Introduction

α-Hydroxy and α-halo acids are largely described and presented in the literature as important intermediates, for example in asymmetric synthesis [1–6]. Some of these compounds have interesting biological and pharmacological properties [7].

However, very few methods of preparation of fluorinated α-hydroxy and α-halo acids are known. The two examples reported in the literature are related to the synthesis of monofluoro-α-hydroxy acids by action of Olah's reagent on glycidic esters [8] and the preparation of trifluorolactic acid by the ring-opening oxidative reaction of 1,2-epoxy-3,3,3-trifluoropropane [9].

In the first part of this work the second method mentioned above is adapted and extended to the F-alkyl and chlorine-containing oxiranes.

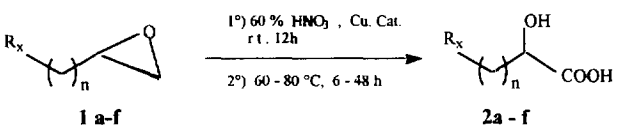
The oxidation of F-alkyl bromohydrins into F-alkylated α-bromo acids and the esterification of the different synthesized acids constitute the second and the third part of this work.

2. Results and discussion

2.1. α-Hydroxy acids

The poor reactivity of F-alkyl oxiranes in an acidic medium is well known. Neither the HF/pyridine ring-opening reaction [10], nor H_2SO_4 hydrolysis has been observed for these compounds [11]. On the contrary, we found that fluorinated and chlorinated α-hydroxy acids are obtained by a one pot tandem ring opening–oxidation reaction by action of concentrated nitric acid on F-alkyl and chlorine-containing oxiranes (Scheme 1). We found, as in the work of Katagari's group [9], that the addition of copper to the mixture accelerates this oxidation reaction. Under such conditions, only the McBee mechanism [12] and not previous protonation of the ring can be considered (Scheme 2).

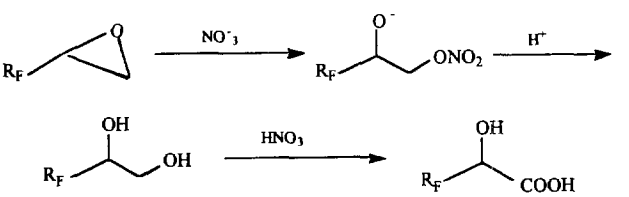
In the case of longer perfluorinated chains (C_6F_{13}, C_8F_{17}), only hydrolysis has been realized to give the corresponding fluorinated diols [13]. The use of more concentrated nitric



1 a-f **2a - f**

(n , R_X) : **a** (0, C_4F_9); **b** (1, C_4F_9); **c** (1, C_6F_{13}); **d** (0, CCl_3); **e** (1, CCl_3); **f** (0, CH_2Cl).

Scheme 1.

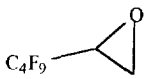
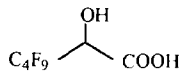
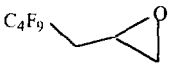
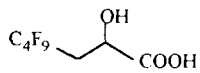
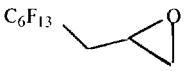
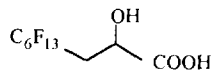
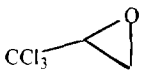
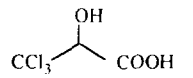
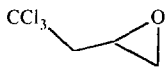
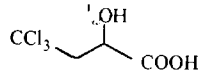
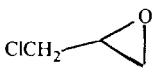
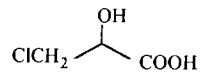
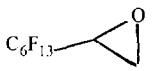
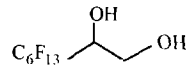
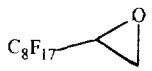
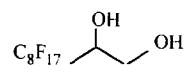
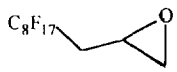
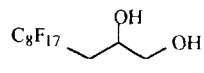


Scheme 2.

* Corresponding author.

PII S0022-1139(97)00051-1

Table 1
Products resulting from 60% nitric acid oxidation of epoxides **1a–1i**

Entry	Epoxide **1**	Temperature/time (°C/h)	Product **2** or **3**	Yield (%)	Melting point (°C)
a		80/24		80	61
b		80/48		75	92
c		80/48		71	115
d		80/12		80	123
e		80/48		58	51
f		80/6		50	80
g		25/12		86	76
h		25/12		85	141
i		25/12		80	59

acid, and/or a higher reaction temperature, leads to a mixture of complex degradation products.

The results of this opening-reaction are summarized in Table 1 and examination allows the following comments.

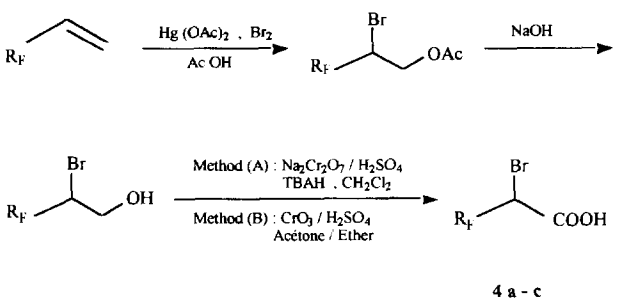
In the case of F-alkyl oxirane (**1a**, C_4F_9), the ring opening–oxidation reaction ends at hydroxy acid formation, whereas for longer F-alkyl chains (**1g**, C_6F_{13} and **1h**, C_8F_{17}) only the corresponding 1,2-diols are obtained. This result supports the mechanism proposed in Scheme 2.

The oxidation is easier when a methylene group bridge is present and leads to the hydroxy acids when the fluorinated chain part is C_4F_9 or C_6F_{13} (**1b, 1c**) and to the corresponding 1,2-diol when it is longer (C_8F_{17}, **1i**).

This reaction is extended to the chlorine containing oxiranes without the formation of secondary 1,2-diol products (**1d, 1e, 1f**).

2.2. α-Bromo acids

In order to synthesize α-brominated acid homologs of F-alkyl α-hydroxy acids we report two convenient oxidation methods allowing the transformation of 2-F-alkyl-2-bromoethanols into the corresponding F-alkyl α-bromoethanoic acids (Scheme 3). The F-alkyl alcohols are proved to be



4 a - c

R_F = C_4F_9 (**4a**); C_6F_{13} (**4b**); C_8F_{17} (**4c**)

Scheme 3.

exceedingly resistant to oxidation even under vigourous oxidation conditions [14,15]. However in our case we found that the mixture of chromate and sulfuric acid (Jones' reagent) reacts to give the expected acids. Two procedures have been adapted:

method A, a mixture of sulfuric acid, sodium dichromate and a catalytic amount of tetrabutyl ammonium hydrogenosulfate (TBAH) in dichloromethane;

method B, a mixture of sulfuric acid and chromium (VI) oxide in acetone-diethyl ether.

The latter method is more efficient (yield ~90%) as indicated in Table 2.

Table 2
Synthesised 2-F-alkyl α-bromoacids **4a–4c**

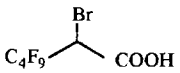
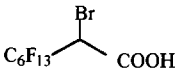
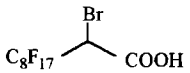
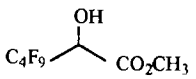
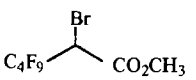
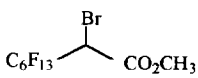
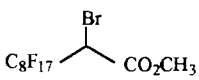
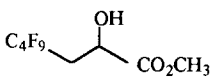
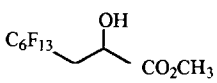
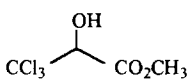
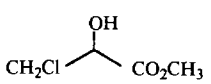
Entry	Compound	Melting point (°C)	Method A		Method B	
			Time (h)	Yield (%)	Time (h)	Yield (%)
4a		56	9	36	48	83
4b		96	24	54	24	95
4c		123	24	60	24	96

Table 3
Methyl esters **5a–5h** prepared using sulfuric acid in methanol

Entry	Compound **5**	Reaction time (h)	Yield (%)	Boiling point (°C/mm)
a		5	90	80/15
b		24	70	75/15
c		24	85	80/15
d		24	90	83/15
e		5	91	68/0,5
f		5	89	67/0,4
g		5	85	60/15
h		5	79	110/15

2.3. α-Hydroxy and α-brominated methyl esters

All synthesised acids have been converted into methyl esters **5** using the classical sulfuric acid/methanol reaction. The etherification of the hydroxy group is not observed in the case of F-alkyl α-hydroxy acids, so that the diazomethane esterification procedure used for simple α-hydroxy acids is not needed [16].

As can be seen in Table 3, the yields are good. The formation of these esters is described for the first time, and may prove to be useful in the synthesis of fluorinated heterocycles.

3. Experimental details

F-alkyl oxiranes **1a, 1g** and **1h** and F-alkyl bromohydrins were obtained from F-alkyl ethylenes [17,18]. 3-F-alkyl-1,2-epoxypropanes **1b, 1c** and **1i** and 4,4,4-trichloro-1,2-epoxybutane **1e** were respectively obtained by addition of R_FI and CCl_4 to allylic alcohol followed by dehalogenation [19,20]. 3,3,3-trichloro-1,2-epoxypropane **1d** and epichlorohydrin **1f** were purchased from Aldrich Chemical Co. Melting points were determined using an Electrothermal IA 9000 series II and are uncorrected. IR spectra were obtained using a Perkin–

Elmer FT-PARAGON 1000 PC. ^{1}H NMR spectra were recorded at 60 MHz on a Jeol-CHL spectrometer using TMS as internal standard. ^{19}F and ^{13}C NMR spectra were recorded on a Bruker AC 300 instrument. Chemical shifts were reported in ppm from external C_6F_6 for ^{19}F and from internal TMS for ^{13}C.

3.1. Synthesis of α-hydroxy acids 2a–2f

In a round-bottomed flask fitted with sealed stirrer unit, a reflux condenser and a dropping funnel, 30 mg of copper metal was dissolved in 5 ml of 1.38 d (60%) nitric acid, and then the solution was magnetically stirred. Epoxide **1** (11.4 mmol) was added dropwise to the blue colored solution at 0 °C and the reaction mixture was stirred until it became homogenous (about 12 h is needed at room temperature). Another 10 ml of nitric acid was added to the solution and the mixture was slowly warmed to 60–80 °C (as soon as the first vigorous evolution of NO_2 was observed). The reaction mixture was kept warm for 12 h to complete the reaction, then cooled to room temperature. Saturated aqueous Na_2CO_3 solution was added to the solution to make it basic and it was stirred for at least 2 h. The solution was again acidified by an appropriate amount of concentrated hydrochloric acid. The acidified solution was repeatedly extracted with ether (4×50 ml). The organic layer was combined and dried over anhydrous Na_2SO_4. After the evaporation of the solvent under reduced pressure the solid obtained was recrystallized from $CHCl_3$.

2-*Nonafluorobutyl-2-hydroxy ethanoic acid* **2a**. IR KBr ν (cm^{-1}): 3400–2800 (OH); 1724 (C=O). ^{1}H NMR [$(CD_3)_2CO$] δ: 4.91 (m, 1H, CH); 7.75 (b, 2 H, OH, COOH). ^{13}C NMR [$(CD_3)_2CO$] δ: 168.36 (COOH); 125–105 (ma, C_4F_9); 79.19 (t, CH–OH). ^{19}F NMR [$(CD_3)_2CO$] δ: 82.48 (t, 3F, CF_3, $^3J_{FF}$=12.76 Hz); 43.81 (AB, 2F, $CF_{2(\alpha)}$, $^2J_{FF}$=282.88 Hz); 38.61 (AB, 2F, $CF_{2(\beta)}$, $^2J_{FF}$=289.83 Hz); 41.75 (AB, 2F, $CF_{2(\omega)}$, $^2J_{FF}$=302.75 Hz).

3-*Nonafluorobutyl-2-hydroxy propanoic acid* **2b**. IR KBr ν (cm^{-1}): 3400 (OH); 1731 (C=O). ^{1}H NMR [$(CD_3)_2CO$] δ: 2.0–3.05 (ma, 2H, CH_2); 4.44 (m, 1H, CH); 7.75 (b, 2H, OH, COOH). ^{13}C NMR [$(CD_3)_2CO$] δ: 174.32 (COOH); 125–105 (ma, C_4F_9); 65.38 (CH–OH); 35.75 (t, CH_2). ^{19}F NMR [$(CD_3)_2CO$] δ: 82.40 (t, 3F, CF_3, $^3J_{FF}$=9.46 Hz); 50.6 (AB, 2F, $CF_{2(\alpha)}$, $^2J_{FF}$=286.42 Hz); 39.19 (ma, 2F, CF_2); 37.76 (ma, 2F, CF_2).

3-*Tridecafluorohexyl-2-hydroxy propanoic acid* **2c**. IR KBr ν (cm^{-1}): 3400 (OH); 1732 (C=O). ^{1}H NMR [$(CD_3)_2CO$] δ: 2.49–2.89 (ma, 2H, CH_2); 4.64 (m, 1H, CH); 7.75 (b, 2H, OH, COOH). ^{13}C NMR [$(CD_3)_2CO$] δ: 173.9 (COOH); 125–105 (ma, C_6F_{13}); 65.30 (CH–OH); 35.35 (t, CH_2). ^{19}F NMR [$(CD_3)_2CO$] δ: 82.99 (t, 3F, CF_3, $^3J_{FF}$=9.63 Hz); 51.19 (AB, 2F, $CF_{2(\alpha)}$, $^2J_{FF}$=262.61 Hz); 42.34 (ma, 2F, CF_2); 41.26 (ma, 2F, CF_2), 40.48 (ma, 2F, CF_2), 37.89 (ma, 2F, CF_2).

3,3,3-*Trichloro-2-hydroxy propanoic acid* **2d**. IR KBr ν (cm^{-1}): 3400 (OH); 1725 (C=O). ^{1}H NMR [$(CD_3)_2CO$] δ: 4.78 (s, 1H, CH); 8.21 (b, 2H, OH, COOH). ^{13}C NMR [$(CD_3)_2CO$] δ: 168.53 (COOH); 99.63 (CCl_3); 82.06 (CH–OH).

4,4,4-*Trichloro-2-hydroxy butanoic acid* **2e**. IR KBr ν (cm^{-1}): 3400 (OH); 1725 (C=O). ^{1}H NMR [$(CD_3)_2CO$] δ: 3.04 (m, 2H, CH_2); 4.58 (m, 1H, CH); 6.21 (b, 2H, OH, COOH). ^{13}C NMR [$(CD_3)_2CO$] δ: 173.96 (COOH); 98.39 (CCl_3); 69.33 (CH–OH); 58.97 (CH_2).

3-*Chloro-2-hydroxy propanoic acid* **2f**. IR KBr ν (cm^{-1}): 3540.72 (OH); 1746.14 (C=O). ^{1}H NMR [$(CD_3)_2CO$] δ: 3.80 (m, 2H, CH_2); 4.48 (m, 1H, CH); 7.89 (b, 2H, OH, COOH). ^{13}C NMR [$(CD_3)_2CO$] δ: 172.73 (COOH); 70.93 (CH–OH); 47.39 (CH_2Cl).

3.2. Synthesis of F-alkyl ethane-1,2-diols 3g–3i

In a round-bottomed flask fitted with sealed stirrer unit, a reflux condenser and a dropping funnel, 30 mg of copper metal was dissolved in 5 ml of 1.38 d (60%) nitric acid, and the solution was then magnetically stirred. Epoxide **1** (20 mmol) was added dropwise, with stirring, to the blue colored solution at 0 °C. The mixture was allowed to stand at room temperature for 12 h. Saturated aqueous Na_2CO_3 solution was added to the solution to make it basic and stirred for at least 2 h. The solution was again acidified by an appropriate amount of concentrated hydrochloric acid. The acidified solution was repeatedly extracted with ether (4×50 ml). The organic layer was combined and dried over anhydrous Na_2SO_4. After the evaporation of solvent under reduced pressure the solid obtained was recrystallized from $CHCl_3$. The ^{1}H and ^{19}F NMR spectra of **3g** and **3h** are in accord with the assigned structures [16].

3-*Heptadecafluorooctyl propane-1,2-diol* **3i**. IR KBr ν (cm^{-1}): 3320 (OH). ^{1}H NMR [$(CD_3)_2$ CO] δ: 2.0–3.0 (ma, 2H, CH_2); 3.63 (m, 4H, CH_2–OH, OH); 4.54 (m, 1H, CH).

3.3. Synthesis of 2-F-alkyl 2-bromo ethanoic acids 4a–4c

Method A. A solution of 3 g (0.01 mmol) of $Na_2Cr_2O_7 \cdot 2H_2O$ in 10 ml of water, 0.17 g (50 mmol) of TBAH, 10 ml of CH_2Cl_2 and 1.6 g (3 mmol) of 2-F-octyl-2-bromo ethanol were placed in a round bottomed-flask, equipped with an addition funnel and a condenser. To the stirred solution, an aqueous 9 M H_2SO_4 solution (5.5 ml) was added dropwise at room temperature. Stirring was continued at 50 °C for 24 h. After cooling, the mixture was diluted with water and extracted by diethyl ether (3×50 ml). The organic layer was washed with water (2×50 ml) and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure the residue **4c** was recrystallized from $CHCl_3$–Et_2O.

Method B. The Jones reagent was prepared by careful addition of sulfuric acid (25 ml) to a solution of chromium (VI) oxide (25 g, 0.25 mol) in water (75 ml). 2-F-hexyl-2-bromo

ethanol (5 g, 11.2 mmol), acetone (4 ml) and ether (2 ml) were placed in a round-bottomed flask equipped with an addition funnel and a condenser. Jones' reagent was added dropwise until a persistent red–brown solution was obtained. The reaction mixture was stirred at room temperature for 24 h. The solution was extracted with ether (3×50 ml) and the ether extracts were washed with water (2×50 ml). The organic phase was dried over Na_2SO_4, the drying agent was filtered off. After the evaporation of solvents under reduced pressure solid product **4b** was isolated. Recrystallization from $CHCl_3$ gives product **4b** in its pure form. Using this procedure compounds **4a** and **4c** were recrystallized respectively from petroleum ether and $CHCl_3$.

2-Nonafluorobutyl-2-bromo ethanoic acid **4a**. IR ($CHCl_3$) ν (cm^{-1}): 3485; 3169.17 (OH); 1746.9 (C=O). ^1H NMR ($CDCl_3$) δ: 4.79 (m, 1H, CH); 10.1 (b, 1H, COOH). ^{13}C NMR ($CDCl_3$) δ: 168.89 (COOH); 120–105 (ma, C_4F_9); 38.90 (t, CH–Br). ^{19}F NMR ($CDCl_3$) δ: 80.61 (t, 3F, CF_3, $^3J_{FF}=8.50$ Hz); 49.28 (AB, 2F, $CF_{2(\alpha)}$, $^2J_{FF}=278.60$ Hz); 41.11 (AB, 2F, $CF_{2(\beta)}$, $^2J_{FF}=297.08$ Hz); 35.75 (ma, 2F, $CF_{2(\omega)}$).

2-Tridecafluorohexyl-2-bromo ethanoic acid **4b**. IR KBr ν (cm^{-1}): 3480.1 (OH); 1754.6 (C=O). ^1H NMR [$(CD_3)_2CO$] δ: 5.20 (m, 1H, CH); 9.70 (b, 1H, COOH). ^{13}C NMR [$(CD_3)_2CO$] δ: 164.58 (COOH); 120–105 (ma, C_6F_{13}); 40.63 (t, CH–Br). ^{19}F NMR [$(CD_3)_2CO$] δ: 83.47 (t, 3F, CF_3, $^3J_{FF}=10.39$ Hz); 52.68 (AB, 2F, $CF_{2(\alpha)}$, $^2J_{FF}=276.78$ Hz); 45.02 (AB, 2F, $CF_{2(\beta)}$, $^2J_{FF}=291.15$ Hz); 42.70 (ma, 2F, CF_2); 41.75 (ma, 2F, CF_2); 38.29 (ma, 2F, $CF_{2(\omega)}$).

2-Heptadecafluorooctyl-2-bromo ethanoic acid **4c**. IR KBr ν (cm^{-1}): 3482.1 (OH); 1763.3 (C=O). ^1H NMR [$(CD_3)_2CO$] δ: 5.21 (m, 1H, CH); 8.2 (b, 1H, COOH). ^{13}C NMR [$(CD_3)_2CO$] δ: 164.56 (COOH); 120–105 (ma, C_8F_{17}); 40.65 (t, CH–Br). ^{19}F NMR [$(CD_3)_2CO$] δ: 83.34 (t, 3F, CF_3, $^3J_{FF}=10.59$ Hz); 52.82 (AB, 2F, $CF_{2(\alpha)}$, $^2J_{FF}=275.12$ Hz); 45.12 (AB, 2F, $CF_{2(\beta)}$, $^2J_{FF}=298.41$ Hz); 42.62 (ma, 6F, 3×CF_2); 41.74 (ma, 2F, CF_2); 38.24 (ma, 2F, $CF_{2(\omega)}$).

*3.4. Synthesis of methyl esters (**5a–5i**), general procedure*

A solution of 0.01 mmol of acid in 4 ml of dried methanol was placed in a round-bottomed flask equipped with a magnetic stirrer bar and a condenser. The reaction mixture was heated under reflux with 0.1 ml of concentrated H_2SO_4. The mixture was cooled to room temperature and then diluted with 10 ml of water. The product was extracted with ether (3×60 ml). The combined extracts were dried over $MgSO_4$. The solvent was stripped off, then by distillation the residue gives ester **5**. Yields and boiling points are given in Table 3.

Acknowledgements

We thank Atochem Company for the gift of perfluoroalkyl ethylenes.

References

[1] R.S. Ward, A. Pelter, D. Goubet, M.C. Pritchard, Tetrahedron Asymmetry 6 (1995) 469.
[2] F. Cavelier, S. Gomez, R. Jaquier, M. Llinares, J.-L. Mercadier, C. Petrus, J. Verducci, Tetrahedron Asymmetry 4 (1993) 2495.
[3] D. Seebach, R. Naef, G. Calderari, Tetrahedron 40 (1984) 1313.
[4] E.J. Corey, J.O. Link, Tetrahedron Lett. 33 (1992) 3431.
[5] D. Dubé, D. Dechênes, J. Tweddell, H. Gagnon, R. Carlini, Tetrahedron Lett. 36 (1995) 1827.
[6] V.S. Martin, M.T. Nunez, C.E. Tonn, Tetrahedron Lett. 29 (1988) 2701.
[7] M. Larchevêque, Y. Petit, Bull. Soc. Chim. Fr. (1981) 130.
[8] A.I. Ayi, M. Remli, R. Condom, R. Guedj, J. Fluorine Chem. 17 (1981) 565.
[9] T. Katagiri, F. Obara, S. Toda, K. Furuhashi, Syn. Lett. (1994) 507
[10] M.M. Chaabouni, A. Baklouti, Bull. Soc. Chim. Fr. (1989) 549.
[11] C. Coudures, R. Pastor, S. Szonyi, A. Cambon, J. Fluorine Chem. 24 (1984) 105.
[12] E.T. Mac Bee, C.E. Hathaway, R.W. Roberts, J. Am. Chem. Soc. 78 (1956) 3851.
[13] A. Ayari, S. Szonyi, E. Rouvier, A. Cambon, J. Fluorine Chem. 50 (1990) 67.
[14] M.M. Chaabouni, A. Baklouti, J. Fluorine Chem. 47 (1990) 227.
[15] S. Achilefu, L. Mansuy, C. Selve, S. Thiebaut, J. Fluorine Chem. 70 (1995) 19.
[16] E. Haslam, Tetrahedron 36 (1981) 2409.
[17] M.M. Chaabouni, A. Baklouti, S. Szonyi, A. Cambon, J. Fluorine Chem. 46 (1990) 307.
[18] C. Coudures, R. Pastor, A. Cambon, J. Fluorine Chem. 24 (1984) 93.
[19] P. Laurent, H. Blancou, A. Commeyras, J. Fluorine Chem. 64 (1993) 125
[20] E. Levas, A. Lecoq, Ann. Chim. 3 (1968) 529.