ELSEVIER

Journal of Fluorine Chemistry 78 (1996) 75–82

JOURNAL OF FLUORINE CHEMISTRY

The 'in situ' generation of fluorinated aldehydes and consecutive reactions with *P*- and *N*-nucleophiles

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Received 9 October 1995; accepted 6 February 1996

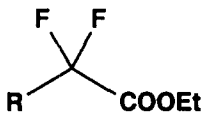
Abstract

An optimized method for the generation of fluorinated aldehydes starting from fluorinated carboxylic acid esters is described. The fluorinated aldehydes generated 'in situ' are used to synthesize hitherto unknown fluorinated hydroxyphosphonic acid esters as well as novel fluorinated *N*-(phenylamino)phosphonic acid esters. The method described here may be used as a 'one-pot synthesis'.

Keywords: DIBAL; Fluorinated aldehydes; Fluorinated hydroxyethane phosphonic acid esters; Fluorinated *N*-(phenylamino) ethane phosphonic acid esters; NMR spectroscopy

1. Introduction

In a previous communication [1], we reported on the synthesis of α,α-difluorinated carboxylic acid esters **1** and α,α-difluorinated aldehyde diethylacetals **2**.



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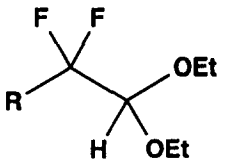

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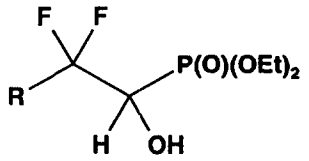
We are interested in the hitherto unknown β,β-difluorinated α-functionalized ethanephosphonic acids and esters, e.g.



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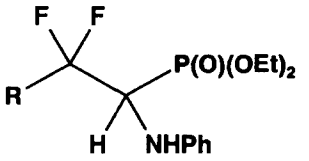

(5)

expecting potential biological activity for such systems, by analogy to Refs. [2,3]. Consequently, we were looking for a suitable method to efficiently synthesize precursors to these C-fluorinated organophosphorus compounds.

Classical pathways for the synthesis of α-amino- and α-hydroxy-phosphonic acids and esters using, for example, the amidoalkylation [4], imine [5], oxime [6] or the Abramov [7] methods fail for the following reasons: non-availability of precursors (e.g. fluorinated aldehydes) or the fluorinated compounds showing a different reaction behaviour in comparison to the non-fluorinated analogues. For example, it is assumed that the β,β-difluorinated α-oxophosphonates, which are required for the oxime method, represent the sole intermediates in the low-temperature reaction of difluorinated carboxylic acid chlorides with trialkylphosphites [8].

But this type of reaction depends strongly on the temperature, yielding 2-fluoroalk-1-ene-1-diethylphosphono-1-diethylphosphate or 2,2-difluoroalkane-1-diethylphosphono-1-diethylphosphate [9]. We verified these findings from [8] and [9] by re-investigating the reaction of 2-(4-fluorophenyl)-2,2-difluoroacetic acid chloride with triethylphosphite as shown in Fig. 1(a).

In addition, two well-established methods which were reported to yield α,β-functionalized phosphonates failed completely in our hands. The readily accessible trifluoroacetimidoyl chlorides [10] have been described to react with trialkylphosphites leading to trifluoroacetimidoyl phosphonates, which, after reduction with $NaBH_3CN$ as a mild reducing agent [11], should yield the desired 1-*N*-(aryl-

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[1] This study is part of the forthcoming dissertation, A.M. Haas, Heinrich-Heine-Universität Düsseldorf, 1996.

PII S0022-1139(96)03432-X

amino)-2,2,2-trifluoroethane-1-phosphonic acid esters as shown in Fig. 1(b). We varied the following parameters: (i) the reaction temperature from 80 °C to 130 °C; (ii) the reaction time from 8 h to 2 d; (iii) the starting trialkylphosphites, tris(trimethylsilyl)phosphite and dialkylphosphites; and (iv) the catalysts using Lewis acids ($BF_3 \cdot OEt_2$, $AlCl_3$, $TiCl_4$) or bases (NEt_3), but were not able to improve the yields: only traces of the products required were detected by means of ^{31}P NMR spectroscopy.

Aziridines and azines are used as versatile precursors in the synthesis of fluorinated amino acids [12]. These findings prompted us to investigate the ring-opening reaction of 2-phosphono- or 2-diethylphosphono-aziridines using pyridine·3HF. As far as we know there exists only one short report concerning this type of reaction in the open literature [13]. We found that 2-phosphonoaziridine and 2-diethylphosphonoaziridine were completely decomposed and no trace of the fluorinated phosphonic compounds expected, according to Fig. 1(c), was detected.

Encouraged by several communications on the generation of perfluorinated aldehydes and their application in Aldol- and Wittig–Horner reactions [14], we planned to use 'in situ'

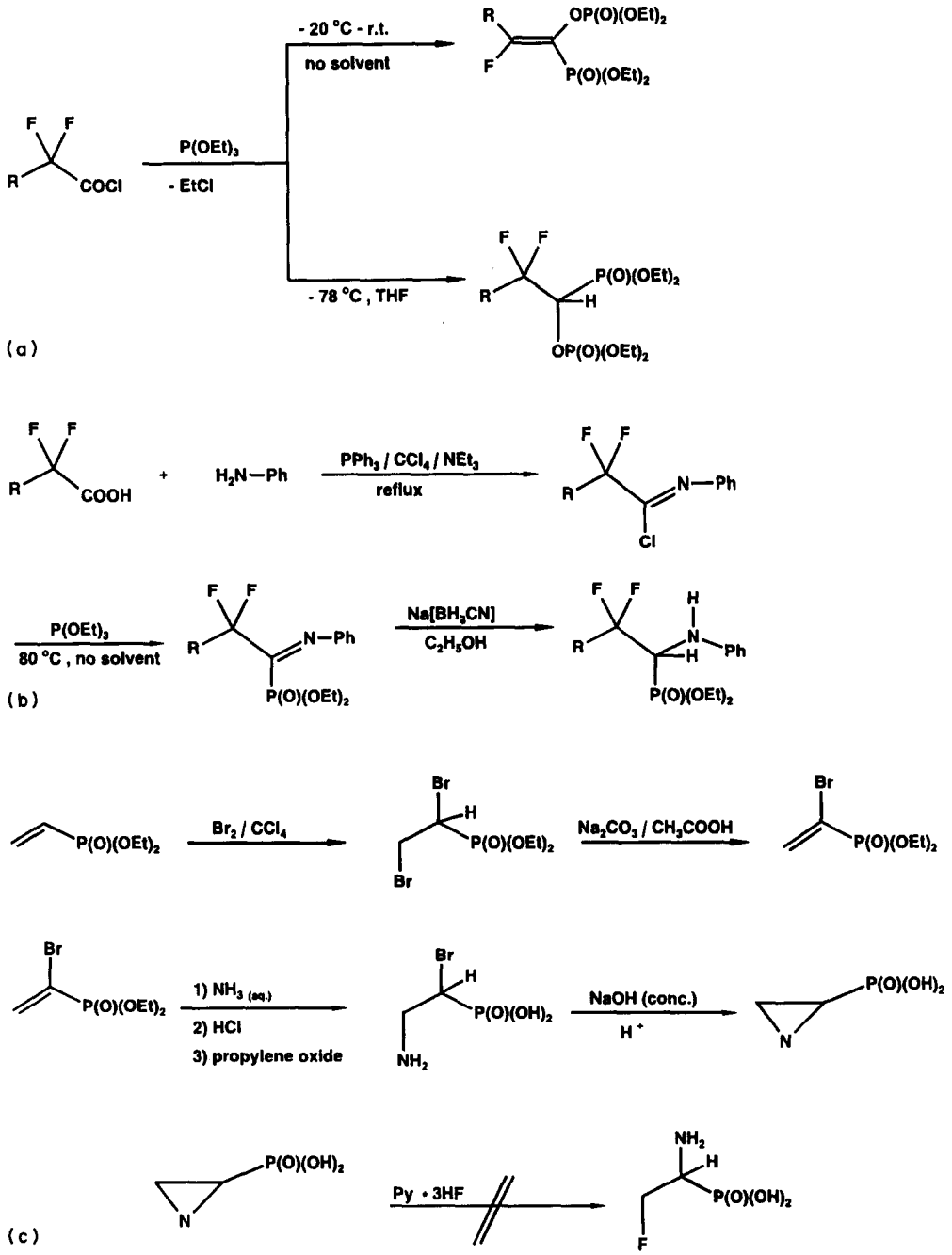


Fig. 1. (a) Reaction of 2-(4-fluorophenyl)-2,2-difluoroacetic acid chloride with triethylphosphite [8,9] (R = 4-F-Ph); (b) trifluoroacetimidoyl chlorides as intermediates in the aminophosphonic acid synthesis (R = F); and (c) aziridines as potential precursors to β-fluorinated α-aminophosphonic acids.

generated fluorinated aldehydes **3** in reactions with dialkylphosphites to produce the corresponding fluorinated hydroxyphosphonates **4** or to synthesize fluorinated 1-*N*-(phenylamino)phosphonic acids esters **5** via the imine procedure.

2. Results and discussion

2.1. 'In situ' generation of fluorinated aldehydes 3

The fluorinated carboxylic acid esters **1** were reduced with DIBAL (diisobutylaluminium hydride) **6** or LAH (lithium aluminium hydride) to yield 2-alkyl-2,2-difluoro- or 2-aryl-2,2-difluoro-acetaldehyde aluminoxy acetals **3** as shown in Scheme 1.

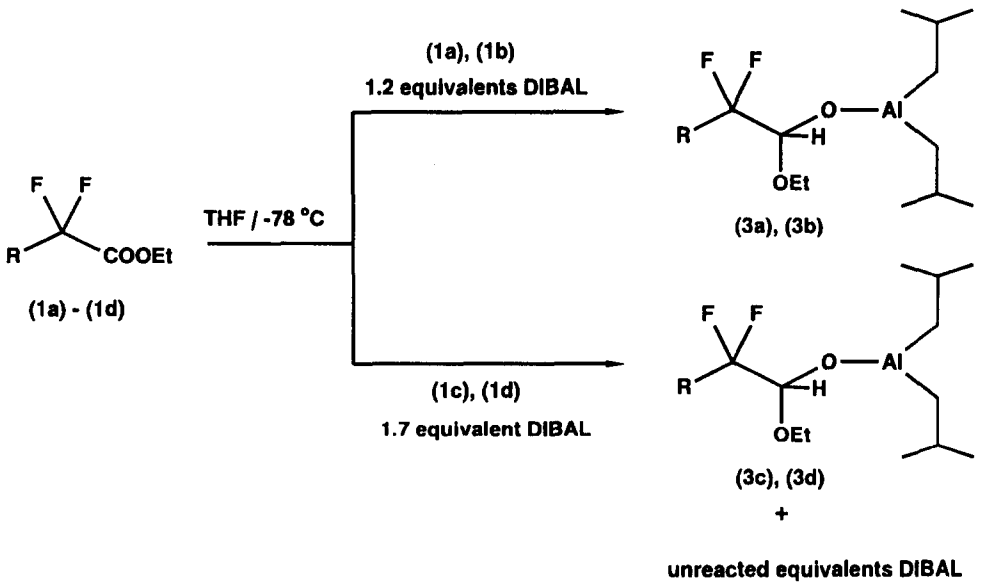
On optimizing the reduction step we found that a 1 M solution of DIBAL in hexane (Fluka) is convenient to use and produces less byproducts (difluorinated alcohols from over-reduction) than LAH powder or solutions of LAH in THF. In principle, LAH may be used in all the reactions described below, but yields will be lower (by 10%–20%) in the subsequent reactions of the 'in situ' generated aldehyde aluminoxyacetals with P- and N-nucleophiles. The procedure described under Experimental details for the reduction of trifluoroacetic acid methyl ester and 2,2-difluoro-2-phenylacetic acid ethyl ester using LAH was applied without modification for all reduction procedures described in this paper.

The reduction procedure using DIBAL described in Scheme 1 above was monitored in two cases by variable-temperature ^{19}F NMR spectroscopy, in order to find the optimum reduction conditions of temperature and the optimum stoichiometry. Best results were achieved using the following temperature profile. Addition of the DIBAL was started at −78 °C and after completion the temperature was increased slowly (2–4 h) to ambient value. The most effective solvent was tetrahydrofuran dried over sodium/benzophenone. Complete reduction of the aliphatic compounds trifluoroacetic acid methyl and ethyl esters and 2,2-difluoropropanoic acid ethyl ester was achieved by using 1.1–1.2 equiv. of DIBAL. Reduction at −78 °C was relatively fast and was complete within a few minutes, as verified by ^{19}F NMR spectroscopy. The aryl-substituted compounds, e.g. 2,2-difluoro-2-phenylacetic acid ethyl ester, required more DIBAL reducing agent (1.7 equiv.) under otherwise identical conditions. This special behaviour of the 2-aryl derivatives **1c** and **1d** may be due to the steric effects of the bulky phenyl and isobutyl groups in both educts, in accord with Scheme 1.

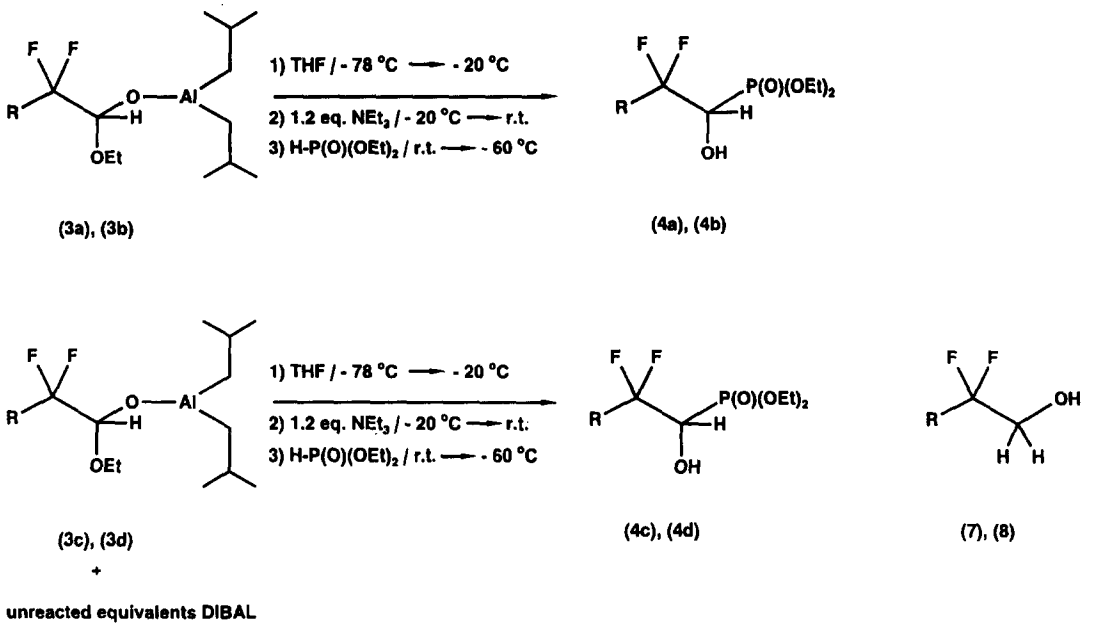
2.2. Reaction of 3 with P- and N-nucleophiles

As expected, the reaction of the aldehyde derivatives generated 'in situ' with *P*- and *N*-nucleophiles depends critically on the amount of unreacted DIBAL (see Scheme 1). We assume that *P*- and *N*-nucleophiles such as diethylphosphite, triethylamine and aniline first coordinate to the aluminium atom in the intermediate **3** or to the Lewis acid DIBAL. Consequently, in the case of intermediate **3a** and **3b**, which were allowed to react with triethylamine and diethylphosphite to yield the corresponding hydroxyphosphonates **4a** and **4b** [15], we observed good yields (63%–65%) when 1 equiv. of triethylamine was added in the first step at −20 °C, followed in the second step by the addition of 1 equiv. of diethylphosphite at room temperature. This is shown in Schemes 2 and 3 below.

In the case of the aldehyde derivatives **3c** and **3d**, which were generated with a large excess of DIBAL (see Scheme 1), we observed small amounts of hydroxyphosphonates and large amounts of the byproducts, the difluorinated ethanols **7** and **8** shown in Scheme 2. Further reduction of compounds



Scheme 1. Different reduction conditions for aliphatic compounds **1a–d**: **1a,3a**, R = F; **1b,3b**, R = CH_3; **1c,3c**, R = Ph; **1d,3d**, R = 3-CF_3–Ph.



Scheme 2. Reaction of fluorinated aluminoxy acetals 3 with diethylphosphite: **3a,4a**, R = F; **3b,4b**, R = CH_3; **3c,4c,7**, R = Ph; **3d,4d,8**, R = 3-CF_3-Ph.

1c and **1d** was caused by the addition of triethylamine to the reaction mixture. The base which coordinates to the aluminium atom of unreacted DIBAL (and to the aluminium atom of compounds **3c** and **3d** enhances the reducing power of the agent and therefore leads to large amounts of further reduced products, according to Scheme 3 [16].

The reduction procedure was modified as follows. All fluorinated carboxylic acid esters were allowed to react with 1.2 equiv. of DIBAL at −78 °C. Subsequently, 1.2 equiv. of triethylamine were added in order to enhance the reductive power of DIBAL and to facilitate the reaction of the aldehyde derivative **3** (generated 'in situ') with diethylphosphite. Coordination of a Lewis base to the aluminium atom of intermediates **3** is required to weaken the strong O–Al bond and to enable the quasi-acetals to react like aldehydes with dialkylphosphites [14].

The products **4a–d** were isolated after washing the reaction mixture with a 2 M aqueous solution of tartaric acid (removal of Al^{3+}), followed by extraction with ethyl acetate. Compound **4a** is a white solid of low melting point. All other products (**4b–d**) were yellowish oils. The compounds were purified via column chromatography. The yields of this 'one-pot synthesis' ranged from 60% to 72%.

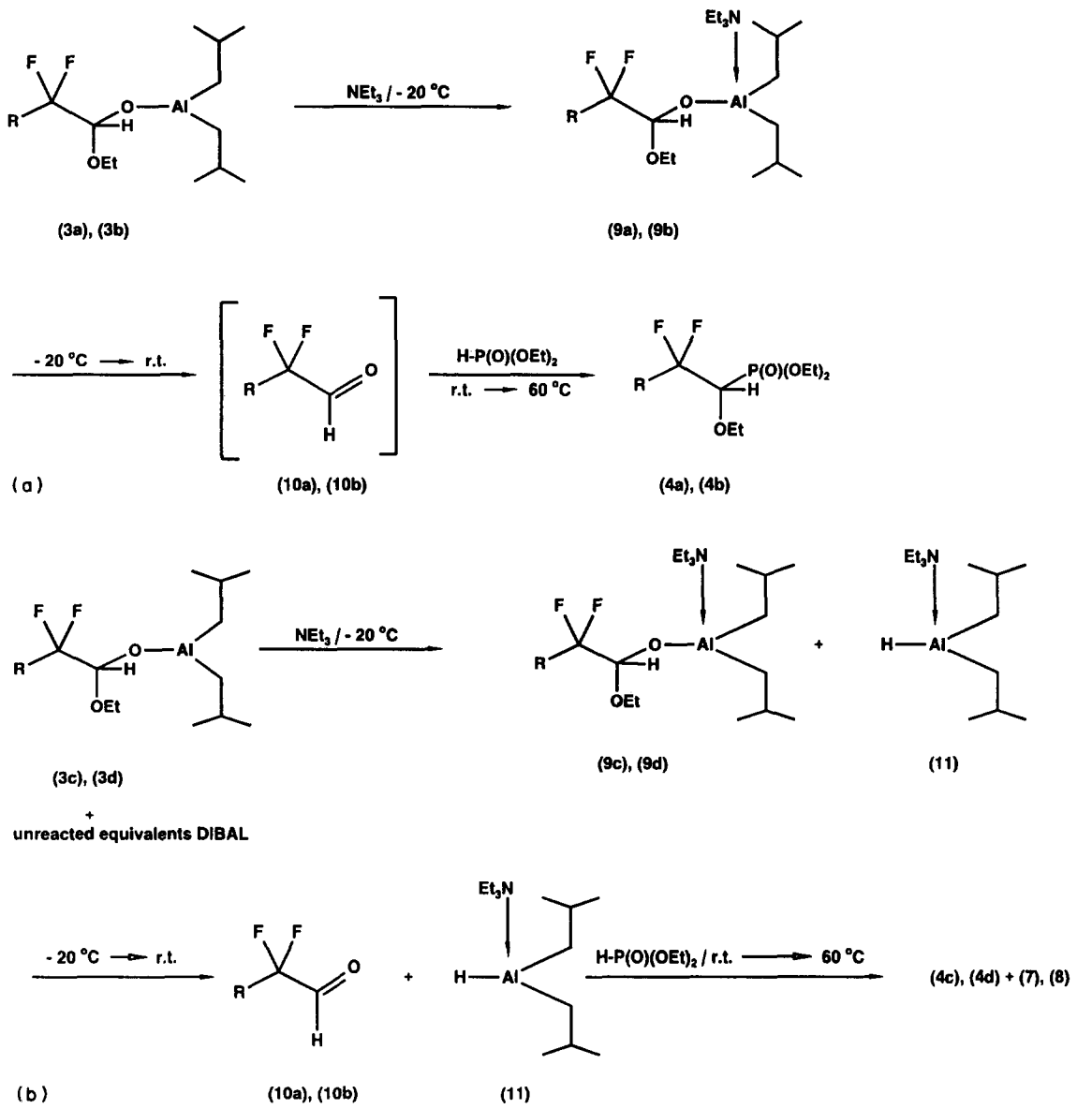
Encouraged by the successful synthesis of the new fluorinated hydroxyphosphonic acid esters **4**, we tried to synthesize fluorinated imines to obtain useful building blocks for new α-amino-β,β-difluorinated ethane phosphonic acid esters. Aniline was used as the amine component, as shown in Scheme 4. During the initial attempts the aliphatic aluminoxy acetal triethylamine adducts **9a** and **9b** were used and prepared as described above. To the aldehyde derivatives (generated 'in situ') in THF was added 1.2 equiv. of aniline at ambient temperature. The mixture was heated to 60 °C until the slow formation of the imines **12a** and **12b** (see Scheme 4) was complete (about 24 h). Applying shorter reaction times led to lower yields of the isolated *N*-(phenylamino)-2,2-difluoro ethane-1-phosphonic acid ethyl ester **5**. This effect is due to the side-reaction of the intermediate imines (not isolated) with diethylphosphite at 60 °C. During addition of the diethylphosphite to the 2,2,2-trifluoroethane-1-*N*-phenylimine **12a**, a strong exothermic effect was observed. 2,2-Difluoropropane-1-*N*-phenylimine **12b** does not react exothermically. The reaction of imines **12a** and **12b** with diethylphosphite was complete after 8 h at 60 °C to yield the corresponding 1-*N*-(phenylamino)-2,2,2-trifluorethane-1-phosphonic acid diethyl ester **5a** and 1-*N*-(phenylamino)-2,2-difluoropropane-1-phosphonic acid diethyl ester **5b**. The work-up procedures for compounds **4** and **5** were identical. Compound **5a** may be crystallized overnight from a mixture of ethyl acetate and hexane. Crude **5b** is a yellowish oil which crystallizes after several weeks. 1-*N*-(Phenylamino)-2-aryl-2,2-difluoroethane-1-phosphonic acid diethyl esters are not accessible by simple analogy. The reaction of aniline with the aldehyde derivative (**9c**, R = Ph) is strongly exothermic leading to a complex reaction mixture. Probably, one of the components formed was **5c** (R = Ph), but all attempts to separate the mixture have been unsuccessful to date.

This communication presents the synthesis of compounds related to 2-aryl- and 2-alkyl-2,2-difluoroethane-1-hydroxy-1-phosphonic acid esters **4**, and of the corresponding 1-*N*-(phenylamino)ethane phosphonic acid esters **5**, as summarized in Table 1.

3. Experimental details

3.1. General

NMR spectra were recorded on a Bruker AM 200 spectrometer using 10% solutions in $CDCl_3$. References: internal



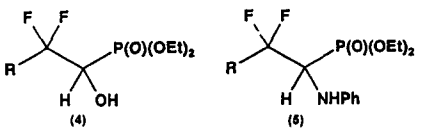
Scheme 3. The influence of triethylamine on the reduction process and on the reaction of compounds **3** with diethylphosphite. (a) **3a,4a,9a,10a**, R = F; **3b,4b,9b,10b**, R = CH_3. (b) **3c,4c,7,9c,10c**, R = Ph; **3d,4d,8,9d,10d**, R = 3-CF_3–Ph.

tetramethylsilane (^1H, ^{13}C), external 85% phosphoric acid (^{31}P) and internal hexafluorobenzene as a secondary standard which is characterized by a sharp singlet (^{19}F). The chemical shift δ_F of C_6F_6 versus $CFCl_3$ is 162.28 ppm. DIBAL was purchased from Fluka as a 1 M solution in hexane. LAH powder was purchased from Merck. THF (p.a.) was dried over Na/benzophenone and distilled. It was stored under N_2 in a pressure bottle for a maximum of 2 d. Triethylamine was stored over potassium hydroxide and distilled before use. All other educts and solvents were distilled before use.

3.2. *'In situ' generation of the fluorinated aldehyde derivatives* **9**; *general procedure*

A 100 ml three-necked flask, fitted with magnetic stirrer, dropping funnel, reflux condenser and a septum, was care-

Table 1
Physical data and yields of compounds **4** and **5**



Compound No.	R	Yield (%)	M.p. (°C)
4a	F	72	59
4b	CH_3	69	liquid
4c	Ph	70	liquid
4d	3-CF_3–Ph	71	liquid
5a	F	65	<220 (decomp.)
5b	CH_3	64	159–160

fully evacuated and dried. The apparatus was flushed with dry nitrogen. In this flask were placed (via a syringe and septum) 25 mmol of the freshly distilled fluorinated carboxylic acid ester **1** and 30 ml of THF. The flask was cooled to −78 °C and 30 ml (30 mmol, 1.2 equiv.) of a 1 M solution of DIBAL in hexane was added during 1 h via a syringe and septum. After stirring the reaction mixture for 30 min at −78 °C, 3.0 g (30 mmol, 1.2 equiv., 4.2 ml) of triethylamine was added dropwise (dropping funnel) at −78 °C during 30 min. This reaction mixture was allowed to warm up to ambient temperature within 2 h. Without further treatment, the aldehyde derivatives generated 'in situ' were used to synthesize compounds **4** and **5**.

3.3. 2-Aryl- and 2-alkyl-2,2-difluoroethane-1-hydroxy-1-phosphonic acid esters 4 from reactions of compounds 9 with diethylphosphite

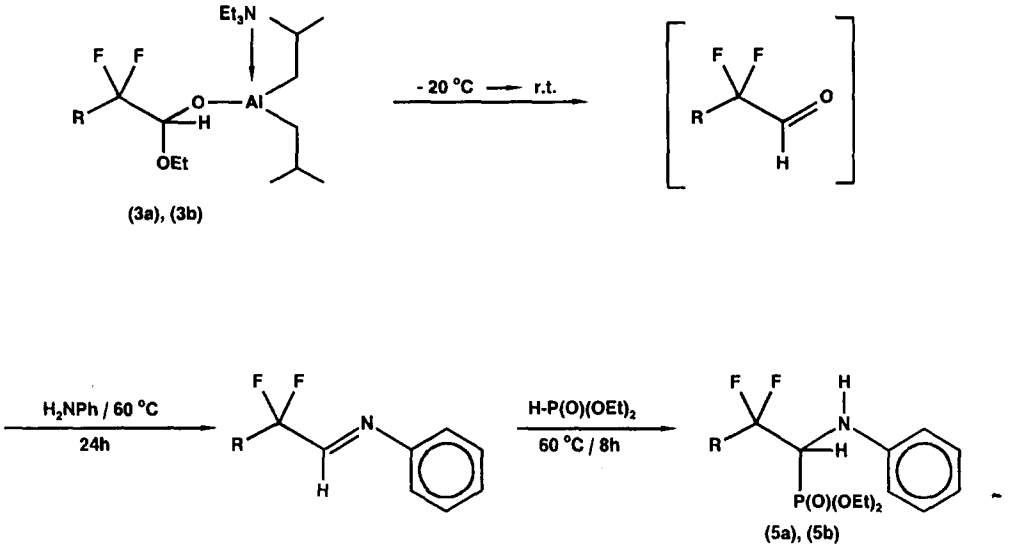
The THF solution of compounds **9** was cooled to −20 °C and 4.1 g (30 mmol, 1.2 equiv., 3.9 ml) of freshly distilled diethylphosphite was added. After warming up the reaction mixture to ambient temperature, it was slowly heated to 60 °C and kept at this temperature for 8 h. The cooled product was poured into 200 ml of a 2 M aqueous solution of tartaric acid and extracted three times with 100 ml of ethyl acetate. The organic phases were combined, washed with brine (200 ml) and dried over anhydrous sodium sulphate. Evaporation of the solvents afforded compounds **4a–d** in all cases as yellow oils which were purified by column chromatography on silica gel 60 (200 g, column length 30 cm, column diameter 3.7 cm) using ethyl acetate as the eluent.

2,2,2-Trifluoroethane-1-hydroxy-1-phosphonic acid diethyl ester (**4a**): Yield, 62%; m.p. 59 °C. ^{1}H NMR (10% $CDCl_3$/TMS) δ: 5.60 (s, br., 1H, O*H*); 4.34 (dq., 1H, C–*H*, $^3J_{FH}$ = 8.2 Hz, $^2J_{PH}$ = −12.6 Hz); 4.27 (m, 4H, POCH_2, $^3J_{HH}$ = 7.2 Hz, $^2J_{HH}$ = −7.4 Hz); 1.38 (t, 6H, $^3J_{HH}$ = 7.2 Hz, $^4J_{PH}$ = 0.4 Hz) ppm. ^{31}P{^{1}H} NMR (10% $CDCl_3$/85% H_3PO_4) δ: 14.86 (q, $^3J_{PF}$ = 8.0 Hz) ppm. ^{19}F NMR (10% $CDCl_3/C_6F_6$) δ: 89.28 (dd, $^3J_{FH}$ = 8.2 Hz, $^3J_{PF}$ = 8.0 Hz) ppm. Analysis: Calc. for $C_6H_{12}F_3O_4P$ (236.13): C, 30.52; H, 5.12%. Found: C, 30.29; H, 5.03%.

2,2-Difluoropropane-1-hydroxy-1-phosphonic acid diethyl ester (**4b**): Yield, 69%. ^{1}H NMR (10% $CDCl_3$/TMS) δ: 4.22–4.09 (m, 4H, $POCH_2$, $^2J_{HH}$ = −10.0 Hz, $^3J_{HH}$ = 7.0, 7.1 Hz, $^3J_{PH}$ = 7.8, 8.0 Hz); 4.07–4.05 (m, 1H, C*H*, $^2J_{PH}$ = −11.3 Hz, $^3J_{FH}$ = 12.67, 11.2 Hz); 1.69 (t, 3H, CF_2CH_3, $^3J_{FH}$ = 19.2, 19.2 Hz); 1.27 (t, 6H, OCH_2CH_3, $^3J_{HH}$ = 7.0, 7.1 Hz, $^4J_{PH}$ = 0.5 Hz) ppm. ^{31}P{^{1}H} NMR (10% $CDCl_3$/85% H_3PO_4) δ: 18.59 (m, $^3J_{PF}$ = 6.3, 20.5 Hz) ppm. ^{19}F NMR (10% $CDCl_3/C_6F_6$) δ: 66.10 (m, $^3J_{PF}$ = 6.2, 20.0 Hz, $^3J_{FH}$ = 12.6, 11.2 Hz, $^3J_{FH}$ = 19.1, 19.5 Hz) ppm. Analysis: Calc. for $C_7H_{15}F_2O_4P$ (232.16): C, 35.20; H, 6.51%. Found: C, 35.11; H, 6.50%.

2-Phenyl-2,2-difluoroethane-1-hydroxy-1-phosphonic acid diethyl ester (**4c**): Yield, 70%. ^{1}H NMR (10% $CDCl_3$/TMS) δ: 7.48–7.23 (m, 5H); 5.47 (s, br, 1H, O*H*); 4.25 (m, 1H, C*H*, $^2J_{PH}$ = −17.0 Hz, $^3J_{FH}$ = 9.2, 16.5 Hz); 4.09–3.98 (m, 4H, POCH_2, $^3J_{HH}$ = 7.4 Hz); 1.19 (t, 3H, $^3J_{HH}$ = 7.4 Hz); 1.15 (t, 3H); 1.15 (t, 3H, $^3J_{HH}$ = 7.4 Hz) ppm. ^{31}P{^{1}H} NMR (10% $CDCl_3$/85% H_3PO_4) δ: 17.94 (m, $^3J_{PF}$ = 6.8, 8.9 Hz) ppm. ^{19}F NMR (10% $CDCl_3/C_6F_6$) δ: 59.72 (m, $^2J_{FF}$ = −254.4 Hz, $^3J_{PF}$ = 6.8, 8.9 Hz, $^3J_{FH}$ = 9.5, 16.5 Hz) ppm. Analysis: Calc. for $C_{12}H_{17}F_2O_4P$ (294.24): C, 48.97; H, 5.83%. Found: C, 48.64; H, 5.86%.

2-(3-Trifluoromethylphenyl)-2,2-difluoroethane-1-hydroxy-1-phosphonic acid diethyl ester (**4d**): Yield, 71%. ^{1}H NMR (10% $CDCl_3$/TMS) δ: 7.87–7.54 (m, 4H, arom); 5.42 (s, br, 1H, OH); 4.40 (m, 1H, C*H*, $^2J_{PH}$ = −16.3 Hz, $^3J_{FH}$ = 11.1, 8.9 Hz); 4.17 (m, 4H, POCH_2, $^3J_{HH}$ = 7.6 Hz); 1.31 (dt, 3H, CH_2CH_3, $^3J_{HH}$ = 7.6 Hz, $^4J_{PH}$ = 0.5 Hz) ppm. ^{31}P{^{1}H} NMR (10% $CDCl_3$/85% H_3PO_4) δ: 17.62 (m, $^3J_{PF}$ = 6.7, 10.1 Hz) ppm. ^{19}F NMR (10% $CDCl_3/C_6F_6$) δ:



Scheme 4. Synthesis of 1-*N*-(phenylamino)-2,2,2-trifluoroethane- and 1-*N*-(phenylamino)-2,2-difluoropropane-1-phosphonic acid diethyl ester: **5a,9a,10a,12a**, R = F; **5b,9b,10b,12b**, R = CH_3.

99.14 (s, CF_3); 63.50–56.35 ($^3J_{FH}$ = 11.1, 8.9 Hz, $^3J_{PF}$ = 6.7, 10.1 Hz) ppm. Analysis: Calc. for $C_{13}H_{16}F_5O_4P$ (362.23): C, 43.09; H, 4.45%. Found: C, 43.28; H, 4.45%.

3.4. 1-N-(Phenylamino)ethane phosphonic acid esters **5** *obtained from the reactions of compounds* **9a** *and* **9b** *with aniline and diethylphosphite*

The THF solution of compounds **9a** and **9b** was cooled to −20 °C and 2.8 g (30 mmol, 1.2 equiv. 2.73 ml) of aniline were added via dropping funnel. The reaction mixture was allowed to warm up to ambient temperature and was then slowly heated to 60 °C. After 24 h at 60 °C, the reaction mixture was cooled to ambient temperature, poured into 200 ml of a 2 M solution of tartaric acid and extracted three times with 100 ml of ethyl acetate. The combined organic phases were washed with brine (200 ml) and dried over anhydrous sodium sulphate. Evaporation of the solvent afforded yellow oils which were purified by recrystallization from hexane/chloroform or by column chromatography on silica gel 60 (column length 30 cm, diameter 3.7 cm, eluent: hexane/ethyl acetate, 1:1).

1-*N*-(Phenylamino)-2,2,2-trifluoroethane-1-phosphonic acid diethyl ester (**5a**): Yield, 65%. ^{1}H NMR (10% $CDCl_3$/TMS) δ: 7.29–7.20 (m, 2H, arom); 6.89–6.74 (m, 3H, arom); 4.48–4.37 (1H, m, NH, $^3J_{NH-CH}$ = 12.5 Hz); 4.37–4.29 (1H, m, CH, $^3J_{HH}$ = 12.5 Hz, $^3J_{FH}$ = 7.9 Hz, $^3J_{PF}$ = 8.3 Hz, $^2J_{PH}$ = −12.0 Hz); 4.28–4.09 (m, 4H, OCH_2, $^3J_{HH}$ = 7.61 Hz); 1.36 (t, 3H, $^3J_{HH}$ = 7.1 Hz, $^4J_{PH}$ = 0.5 Hz); 1.27 (t, 3H, $^3J_{HH}$ = 7.1 Hz, $^4J_{PH}$ = 0.5 Hz) ppm. ^{31}P{^{1}H} NMR (10% $CDCl_3$/85% H_3PO_4) δ: 15.24 (q, $^3J_{PF}$ = 8.3 Hz) ppm. ^{19}F NMR (10% $CDCl_3/C_6F_6$) δ: 92.64 (m, $^3J_{FH}$ = 7.9 Hz, $^3J_{PF}$ = 8.3 Hz) ppm. Analysis: Calc. for $C_{12}H_{17}F_3NO_3P$ (311.24): C, 46.29; H, 5.51%. Found: C, 46.35; H, 5.54%.

1-*N*-(Phenylamino)-2,2-difluoropropane-1-phosphonic acid diethyl ester (**5b**): Yield, 64%. ^{1}H NMR (10% $CDCl_3$/TMS) δ: 7.23–7.07 (2H, arom); 6.74–6.61 (3H, arom); 4.20–3.86 (m, OCH_2, CH); 1.72 (t, 3H, CH_3, $^3J_{FH}$ = 19.0 Hz); 1.21 (t, 3H, $^3J_{HH}$ = 7.1 Hz); 1.13 (t, 3H, $^3J_{HH}$ = 7.1 Hz) ppm. ^{31}P{^{1}H} NMR (10% $CDCl_3$/85% H_3PO_4) δ: 18.8 (m, $^3J_{PF}$ = 12.4, 13.7 Hz) ppm. ^{19}F NMR (10% $CDCl_3/C_6F_6$) δ: 70.63–67.62 ($^2J_{FF}$ = −247.9 Hz, $^3J_{PF}$ = 14.7, 10.88 Hz, $^3J_{FH}$ = 19.0, 11.3, 13.0 Hz) ppm. Analysis: Calc. for $C_{13}H_{20}F_2NO_3P$ (307.28): C, 50.80; H, 6.56%. Found: C, 50.98; H, 6.55%.

3.5. 'In situ' generation of the aldehyde derivatives **9a** *and* **9c** *with lithium aluminium hydride [17]*

A solution consisting of 25 mmol of the corresponding fluorinated carboxylic acid ester in 30 ml of dry THF was cooled to −78 °C. A suspension of 0.24 g (6.25 mmol) of LAH in 10 ml of THF was added dropwise over a period of 1 h at −78 °C. The reaction mixture was stirred at that temperature for 3 h. Subsequently, 3.0 g (30 mmol, 1.2 equiv., 4.2 ml) of triethylamine was added dropwise at −78 °C and the reaction mixture allowed to warm up to ambient temperature.

4. Conclusions

Reduction of fluorinated carboxylic acid esters **1** may be carried out with 1.2 mol of DIBAL (or less expediently with LAH) to yield the aluminoxy acetals of fluorinated aldehydes **3**. The best conditions involve reaction temperatures from −78 °C to −20 °C in the reduction and from −20 °C to 60 °C in the phosphite addition step. Triethylamine is essential as a base to enhance the reducing power of DIBAL (reduction of compounds **1c** and **1d**) and to facilitate the reaction of the aldehyde aluminoxy acetal **3** with P- and N-nucleophiles. We have found that this method provides general access to 2-aryl- and 2-alkyl-2,2-difluoroethane-1-hydroxy-1-phosphonic acid esters **4**. In the reaction of aluminoxy acetals of aldehydes **9** with aniline and diethylphosphite, only the aliphatic compounds **9a** and **9b** furnished the fluorinated 1-*N*-(phenylamino)ethane phosphonic acid esters **5** in good yield. The aromatic aldehyde aluminoxy acetal **9c** seems to be unstable at ambient temperature in the presence of bases such as triethylamine and aniline. Indeed, very recently the instability of 2,2-difluoro-2-phenylacetaldehyde was reported [16]. We assume that under the influence of bases and light the decomposition of compound **9** is accelerated (possibly via elimination of HF and photochemical conversion of the intermediate fluoroketene).

Acknowledgements

This work was supported by the Fonds der Chemischen Industrie. Thanks are due to the Ministerium für Wissenschaft und Forschung NRW for supporting the Arbeitsgemeinschaft Fluorchemie, Nordrhein-Westfalen.

References

[1] G. Hägele and A.M. Haas, *J. Fluorine Chem., 76*(1995) 15–19.
[2] G. Resnati, *Tetrahedron, 49* (1993) 9385.
[3] (a) J.T. Welch, *Tetrahedron, 43* (1987) 3123; (b) J. Mann, *Chem. Soc. Rev., 16* (1987) 381; (c) A. Haas and M.R.C. Gerstenberger, *Angew. Chem., 93* (1981) 659.
[4] (a) J. Oleksyszyn and L. Subotkowska, *Synthesis,* (1980) 906; (b) J. Oleksyszyn, R. Tyka and P. Mastalerz, *Synthesis,* (1978) 479.
[5] (a) U. Gruß and G. Hägele, *Phosphorus, Sulphur, Silicon, 97* (1994) 209; (b) K. Issleib, K.P. Döpfer and A. Balszuweit, *Phosphorus, Sulfur, 14* (1983) 171.
[6] (a) J. Oleksyszyn, E. Gruszecka, P. Kafarski and P. Mastalerz, *Monatsh. Chem., 113* (1982) 59; (b) K.D. Berlin, R.T. Claunch and E.T. Gaudy, *J. Org. Chem., 33* (1968) 3090.
[7] (a) V.S. Abramov, *Zh. Obshch. Khim., 22* (1952) 647; (b) T. Gajda, *Synthesis,* (1990) 717; (c) T. Gajda, *Phosphorus, Sulfur, Silicon, 53* (1990) 327.

[8] (a) T. Ishihara, T. Maekawa and T. Ando, *Tetrahedron Lett., 25* (1984) 1377; (b) T. Ishhara, T. Maekawa and T. Ando, *Tetrahedron Lett., 24* (1983) 4229.
[9] (a) T. Ishihara, T. Maekawa, Y. Yamasaki and T. Ando, *J. Fluorine Chem., 34* (1986) 271; (b) T. Ishihara, T. Maekawa, Y. Yamasaki and T. Ando, *J. Fluorine Chem., 34* (1986) 323; (c) P. Mastalerz, in R. Engel (ed.), *Handbook of Organophosphorus Chemistry,* Marcel Dekker Inc., New York, 1992, Chap. 7, p. 3.3.
[10] K. Tamura, H. Mizukami, K. Maeda, H. Watanabe and K. Uneyama, *J. Org. Chem., 58* (1993) 32.
[11] G.A. Flynn, D.W. Beight, E.H.W. Bohme and B.W. Metcalf, *Tetrahedron Lett., 26* (1985) 285.
[12] A. Ayi and R. Guedj, *J. Chem. Soc., Perkin Trans. 1,* (1983) 2045.
[13] J. Zygmunt, *Tetrahedron, 41* (1985) 4979.
[14] S. Kiyooka and M. Shirouchi, *J. Org. Chem., 57* (1992) 1.
[15] P.G. Baraldi, M. Guarneri, F. Moroder, G.P. Pollini and D. Simoni, *Synthesis,* (1986) 653.
[16] H. Suga and M. Schlosser, *Tetrahedron, 46* (1990) 4261.
[17] S. Kaneko, T. Yamazaki and T. Kitazume, *J. Org. Chem., 58* (1993) 2302.