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Simple synthesis of mono- and difluoroalanines

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Abstract

Highly basic tris(diethylamino)-*N*-methylphosphazene was used for mono- and difluoromethylation of diethyl *N*-acetylaminomalonate by CH_2BrF or $CHClF_2$ in dichloromethane at −40°C. Acidic hydrolysis of fluoromethylated products afforded fluoro- and difluoroalanine, respectively.

Keywords: Fluorinated amino acids; Difluoromethylation; Fluoromethylation; Tris(diethylamino)-*N*-methylphosphazene

1. Introduction

During the past years, fluorinated amino acids have attracted remarkable interest due to their potent biological activity [1,2]. One of the most broadly used procedures for the synthesis of α-fluoromethylated amino acids includes difluoromethylation of carbanions generated by various bases from the Schiff base of amino acids [3] (Scheme 1).

The Schiff base or *N*-trichloroethoxycarbonyl derivative of diethyl aminomalonate was shown to react with $CHClF_2$ in THF as a solvent by treatment with three equivalents of sodium bis(trimethylsilyl)amide or sodium hydride at −30°C to give the difluoromethylated derivatives in 50% and 41% yields, respectively [4].

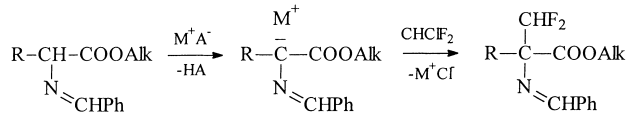
In connection with our studies on the synthesis of fluorinated amino acids via difluoromethylation [5,6] and the application of aminophosphorus derivatives in synthesis of fluoroorganics [7], we wish to report here that the strongly basic non-nucleophile, tris(diethylamino)-*N*-methylphosphazene [8], can be used for mono- and difluoromethylation of diethyl *N*-acetylaminomalonate under mild and simple reaction conditions.

2. Results and discussion

Diethyl α-difluoromethyl-*N*-acetylaminomalonate **2a** has been obtained in 69% yield upon passing $CHClF_2$ through a solution of commercially available diethyl *N*-acetylaminomalonate **1** and three equivalents of tris(diethylamino)-*N*-methylphosphazene in methylene chloride at −40°C (Scheme 2). The reaction demands no special protection from moisture which causes many problems under usually used bases, such as LDA, $NaN(SiMe_3)_2$ and NaH [3]. The yield of malonate **2a** was much higher than the yield of difluoromethylation products obtained under conditions previously described [4]. A similar reaction with fluorobromomethane resulted in a yield of 51% of diethyl α-fluoromethyl-*N*-acetylaminomalonate **2b**.

The reaction presumably proceeds via formation of fluoro- and difluorocarbenes, but no special investigation of the reaction mechanism was carried out. Attempted difluoromethylation of the methyl esters of *N*-Boc-phenylalanine and *N*-Boc-phenylglycine in the presence of tris(-diethylamino)-*N*-methylphosphazene did not give the desired products. This failure may be due to the reduced CH-acidity of the starting amino acid derivatives, which bear only one ester group in the α-position.

The acidic hydrolysis of fluoro- and difluoromethyl acetylaminomalonates **2a,b** was performed by refluxing with a mixture of 98% formic and 36% hydrochloric acids to afford hydrochlorides of 3,3-difluoroalanine **3a** and



Scheme 1

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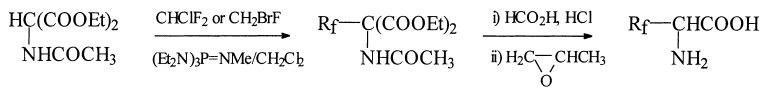

1 **2a,b** **3a,b**

R_f	CHF_2	CH_2F
2,3	**a**	**b**

Scheme 2

3-fluoroalanine **3b**. The titled amino acids were obtained in free state by propylene oxide treatment in about 30–40% overall yield, based on starting diethyl *N*-acetylaminomalonate.

In conclusion, we have realized a simple procedure for fluoro- and difluoromethylation of diethyl *N*-acetylaminomalonate under mild conditions. Application of this method for fluoro- and difluoroalanine synthesis starting from commercially available diethyl *N*-acetylaminomalonates gives results superior to utilization of sodium hydride or bis(trimethylsilyl)amide.

3. Experimental details

^1H and ^{19}F NMR spectra were recorded on Variant Gemini-200 instrument (200 and 188.28 MHz) using TMS and CCl_3F as internal standards, respectively. The starting materials tris(diethylamino)-*N*-methylphosphazene [8], fluorobromomethane [9] were prepared according to literature procedures.

Compounds **3a,b** were identified by HPLC and comparison of ^1H NMR data with data obtained for authentic samples [4,10,11].

*3.1. Diethyl 2-(acetylamino)-2-(difluoromethyl)malonate (**2a**)*

A mixture of 4.0 g (18.5 mmol) of **1** and 20 g (72.4 mmol) of tris(diethylamino)-*N*-methylphosphazene in 25 ml of CH_2Cl_2 was cooled to $-40^\circ C$, and 43.3 g (501 mmol) of difluorochloromethane was passed through the stirred solution at such a rate to keep the mixture at $-35^\circ C$. The reaction mixture was warmed to room temperature, and thoroughly washed with diluted HCl (10%, 3×25 ml) and water (3×50 ml). The organic layer was dried over $MgSO_4$ and the solvent was evaporated in vacuo. Purification by column chromatography on silica gel 60 ($CHCl_3$/hexane, 3:1) afforded **2a** as a colorless oil: 3.4 g (69%); ^1H NMR ($CDCl_3$) δ: 6.74 (bs, 1H, NH), 6.47 (t, 1H, CHF_2, $^2J_{H-F}$ 54.8 Hz), 4.34 (q, 4H, OCH_2, $^3J_{H-H}$ 7.0 Hz), 2.1 (s, 3H, $COCH_3$), 1.3 (t, 6H, CH_3, $^3J_{H-H}$ 7.0 Hz); ^{19}F NMR ($CDCl_3$) δ_F: −128.5 (d, $^2J_{H-F}$ 54.8 Hz).

*3.2. Diethyl 2-(acetylamino)-2-(difluoromethyl)malonate (**2b**)*

Diethyl 2-(acetylamino)-2-(difluoromethyl)malonate (**2b**) was prepared from 1.92 g (8.9 mmol) of **1**, 9.7 g (35.1 mmol) of tris(diethylamino)-*N*-methylphosphazene and 1 g (8.9 mmol) of fluorobromomethane under the same reaction conditions as **2a** and purified by column chromatography on silica gel 60 ($CHCl_3$/hexane, 3:2). Colorless oil crystallizing on cooling to 5°C; 1.1 g (49.9%); ^1H NMR ($CDCl_3$) δ: 6.9 (br.s, 1H, NH), 5.08 (d, 2H, CH_2F, $^2J_{H-F}$ 47.0 Hz), 4.3 (q, 4H, OCH_2, $^3J_{H-H}$ 7.2 Hz), 2.09 (s, 3H, $COCH_3$), 1.28 (t, 6H, CH_3, $^3J_{H-H}$ 7.2 Hz).

*3.3. 3,3-Difluoroalanine (**3a**)*

A mixture of 3 g (11.3 mmol) of **2a**, 7.5 ml of 97% HCOOH and 7.5 ml of 36% aq. HCl was refluxed for 5 h. The solvent was evaporated under reduced pressure. The residue was dissolved in 15 ml of ethanol and 5 ml of propene oxide [10] were added at 0°C to precipitate 0.9 g (64%) of difluoroalanine **3a**.

*3.4. 3-Fluoroalanine (**3b**)*

3-Fluoroalanine (**3b**) was prepared from 0.75 g (3 mmol) of **2b** under the same reaction conditions as **3a**. Yield of **3b** was 0.2 g (61%).

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