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Highly diastereoselective synthesis of β-trifluoromethyl-*N*-acetyltryptophan

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Abstract

Diethyl 2-[2,2,2-trifluoro-1-(indol-3-yl)ethyl]malonates **1**, prepared by the reaction of 2,2,2-trifluoro-1-(indol-3-yl)ethanol **2** with sodium salts of diethyl 2-substituted malonates, were readily hydrolyzed in an aqueous NaOH solution to form the corresponding disodium salts. Subsequent acidification of the salt resulted in the decarboxylation forming *syn*-isomers of the title compound in high yield.

Preparation of slightly fluorine-substituted compounds is important[1,2] because of the significant effects of selective fluorine substitution in the bioactive molecules on their bioactivities.[3] It is of interest to introduce fluorine selectively to the side chain of well-known bioactive indole derivatives, e.g. tryptophan[4] and indolmycin.[5] An available intermediate, 2,2,2-trifluoro-1-(indol-3-yl)ethanol **2**,[6] was considered suitable for this purpose. One excellent character of compound **2** is that the hydroxy group is readily replaced by certain nucleophiles, e.g. thiol[7] and carbanion.[8]

To prepare the title tryptophan **3a**, compound **2** was made to react with ethyl acetamidomalonate and replacement product **1a** was obtained in moderate yield. Unexpectedly, decarboxylation product **3a** was formed highly stereoselectively when **1a** was hydrolyzed in aqueous NaOH solution followed by acidifying with concentrated hydrochloric acid. The details of this reaction are described below.

The diester compounds **1a–1c** were prepared by the reaction of 2,2,2-trifluoro-1-(indol-3-yl)ethanol (1 equiv.) with the corresponding sodium salts (1.1 equiv.) formed in situ by mixing diethyl 2-substituted malonates (R′: NHAc, OAc and Me) with sodium ethoxide in toluene at 90–100°C (Scheme 1). The predominant product was **1b** (R=OH) rather than **1b′** (R′=OAc), the acyl group of **1b′** being easily removed during the reaction. Products **1a**, **1b** and **1c** were isolated in 55, 95 and 41% yields, respectively, by silica gel column chromatography. The lower yield for **1a** is due to the formation of bis[2,2,2-trifluoro-1-(indol-3-yl)ethyl] ether (33%), of which only a trace amount was detected in the reaction of ethyl 2-acetoxymalonate under the same conditions.

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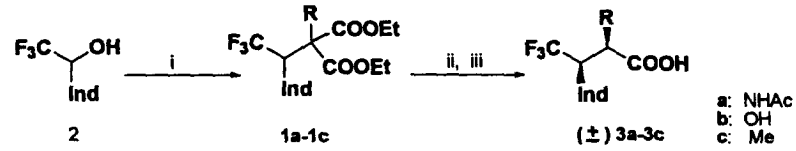

Scheme 1. Ind=indol-3-yl. Reagents and conditions: (i) diethyl 2-substituted malonate, EtONa, Toluene; (ii) 2N NaOH, dioxane; (iii) conc. HCl, pH=3–4

The diesters **1a–1c** were completely hydrolyzed in a 1:1 (v/v) mixture of 2N NaOH and dioxane at 40°C for 24 h. Hydrolysis was followed by TLC with 1:1 (v/v) ethyl acetate and hexane. The hydrolysis mixture was acidified with concentrated hydrochloric acid at room temperature. Almost all the products were monocarboxylic acids **3a–3c** rather than the expected dicarboxylic acids. Monocarboxylic acids **3a**, **3b** and **3c** were isolated in 91, 89 and 75% yields, respectively, by column chromatography.

A notable stereochemistry problem arises because of the presence of two chiral carbon atoms in the products **3a–3c**. In fact, no stereoselectivity was observed during hydrolysis and decarboxylation of ethyl 2-acetoxy-2-carbethoxy-3-(indol-3-yl)butyrate, a non-fluorinated analogue of **1b**.[5a] Product analysis, however, showed clearly that one pair of enantiomers was formed in preference to the other during the reaction. The diastereomeric ratio for **3a** was 97:3 as determined by HPLC. The corresponding diastereomers of **3b** were formed in the same ratio. However, two diastereomers of **3c** were formed in the ratio of 58:42, indicating that decarboxylation was low stereoselective in this case. The configurations of the predominant **3a** were proved to be (2*R*,3*R*) and (2*S*,3*S*) by X-ray crystal structure analysis.

In conclusion, the title β-trifluoromethylated tryptophan can be conveniently prepared by the method described. The effect of α-substituent groups of the compounds **3** on the diastereoselective decarboxylation is still under investigation.

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