SYNTHESIS OF 2,4-DIPHENYL-5-ETHOXYCARBONYL-1-HEPTADEUTERATED ISOPROPYL-2-IMIDAZOLINE

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Summary

The synthesis of the title compound is described from heptadeuterated isopropyl alcohol in six steps. Overall yield obtained was 6%.

Key words: Deuterium, Isopropylamine, Isopropylbenzamidine, Imidazoline.

Introduction

In order to elucidate mass fragmentation of 2,4-diphenyl-5-ethoxycarbonyl-1-isopropyl-2-imidazoline (1, 2), deuterium labelled imidazoline was synthesised in six steps. The starting material was the deuterated isopropanol which was transformed into isopropylamine according to the Gabriel synthesis of amino acid procedure (3). Alkaline isopropylamine was achieved from the hydrochloride salt using calcium oxide (4). Ethyl 2-bromo cinnamate **2** was obtained by a classical procedure (Scheme 1) and condensed with benzamidine **7** to give the expected imidazoline **8** (Scheme 2)

Experimental

Solvents were redistilled just before utilization. Infrared spectra (IR) were recorded on thin film using Beckman Spectrometer model Acculab IV. NMR spectra were obtained as $CDCl_3$ solution using a Hitachi Perkin Elmer R.24A spectrometer. Circular centrifugal thin layer chromatography (CCTLC) was

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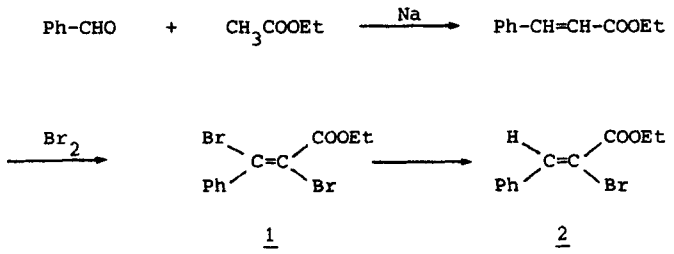


Scheme 1

performed on a Chromatotron apparatus equipped with Merck Kieselgel 60 PF_{254} circular plate containing gypsum for preparative layer chromatography. Deuterated isopropanol d_8 was purchased from C.E.A. (Saclay).

Ethyl 2,3-bromo cinnamate 1

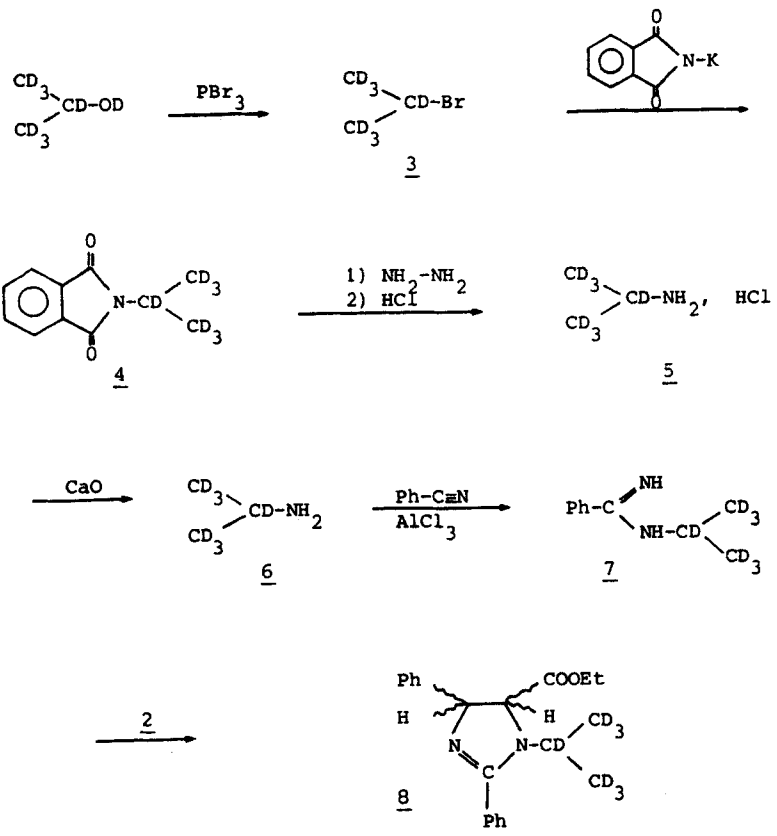
In a dry 500 ml flask equipped with a condenser, a magnetic stirrer and a thermometer, a solution of bromine (49.6 g, 0.31 mol) in benzene (50 ml) was added dropwise to ethyl cinnamate (52.8 g, 0.3 mol) in chloroform (150 ml) at 0°C. The resulting mixture was stirred at 0°C for 2 h. After removal of solvent under partial vacuum, the residue was washed with chloroform until the whole disappearance of the red colour of the mixture. The colourless oil was allowed at 4°C to solidify overnight.

Ethyl 2-bromo cinnamate 2 :

To a solution of the above crude dibromide ester 1 (100.8 g, 0.3 mol) in chloroform (150 ml), triethylamin (33.3 g, 0.33 mol) in chloroform (50 ml) were added dropwise. After stirring for 3 h. at room temperature, filtration and evaporation of the solvent gave a oily residue which was distilled under vacuum. Yield: 59 % of the theoretical amount.
I.R.: 1740, 1630, 1230 cm^{-1}; ^1H NMR (δ ppm): 1.30 (t, 3H, Me); 4.15 (q, 2H, CH_2); 7.10-7-85 (m, 5H, arom.); 8.1 (s, 1H).

Heptadeuterated isopropyl bromide 3:

In a 25 ml flask cooled at -10°C in a salt and ice bath mixture were placed heptadeuterated isopropanol (5g, 73 mmol). Phosphorous tribromide (6.6 g, 24 mmol) were added by small portions. The temperature was kept always lower than 0°C. The reaction was allowed under stirring for 4 h. at this temperature.



Scheme 2

After distillation under atmospheric pressure (B.p: 55-57°C), the bromide was purified as below: previously cooled to -10°C, the crude bromide was washed twice with a solution of concentrated sulphuric acid previously cooled at -10°C, neutralized with potassium carbonate (0.4 g) to yield 2.8 g (90 %) of a colourless liquid.

Heptadeuterated isopropylamine 6:

To 2,8 g (22 mmol) of deuterated isopropyl bromide, potassium phthalimide (4.2 g, 22 mmol) and N,N-dimethylformamide (12.5 ml) (DMF) were added. The resulting mixture was refluxed with stirring, for 4 h. After cooling at 0°C, and filtration, DMF was removed under partial vacuum. To the above crude imide 4 was added hydrazine hydrate (1 g, 22 mmol) in methanol (2 ml). The mixture was heated on a steam-bath for 1 h. and during this time a white solid separated. After addition of water (6.6 ml), the methanol was removed under

partial vacuum. Then, concentrated hydrochloride acid (10 ml) was added, and the mixture was heated for 1 h. on a steam-bath. The mixture was cooled, phthalhydrazide was removed by filtration and the filtrate evaporated to dryness. The yield of isopropylamine hydrochloride **5** was 1.35 g (60%).

After admission of dry air into the reaction vessel an excess of freshly ignited calcium oxide (0.97 g, 13 mmol) was introduced and the mixture of lime and isopropylamine hydrochloride **5** was stirred for 4 h. at the room temperature, then distilled under atmospheric pressure. The evolved heptadeuterated isopropylamine **6** (0.6 g, 75%) was collected in a test tube cooled with liquid nitrogen.

Heptadeuterated N-isopropyl benzamidine 7:

To isopropylamine (0.6 g, 9 mmol) **6**, benzonitrile (9.9 g, 10.8 mmol) and aluminium trichloride (1.37 g, 12 mmol) were added. The mixture was left for 3 h. at the room temperature then heated for 1 h at 120°C. Benzonitrile in excess was extracted by ether (3 x 10 ml). The crude product was basified by a solution of 70% sodium hydroxide. The crude benzamidine was extracted by ether (3 x 5 ml). Ether was dried and discarded to give 0.56 g (38 %) of benzamidine as an yellowish oil.
I.R.: 3200; 1680 cm^{-1}.

2,4-Diphenyl-5-ethoxycarbonyl-1-heptadeuterated isopropyl-2-imidazoline 8:

In a 15 ml flask equipped with a water condenser, a magnetic stirrer and a thermometer, was placed ethyl 2-bromocinnamate (0.78 g, 3 mmol) **2** in benzene (5ml). Isopropylbenzamidine (0.56 g, 3.3 mmol) **7** in triethylmine (0.54 g) was added dropwise at 0°C. After stirring at the room temperature overnight, the mixture was heated under reflux for a further 2h. Evaporation of the solvent gave 0.33 g (33 %) of a pale yellow oil which was chromatographed on silica gel using a gradient of chloroform-ethyl acetate. The separation of stereoisomers was carried out by CCTLC using a gradient of chloroform-hexane.

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