

DRUG SYNTHESIS METHODS AND MANUFACTURING TECHNOLOGY

DECARBOETHOXYLATION OF ARYL-SUBSTITUTED α -CYANOESTERS BY THE METHOD OF PHASE TRANSFER CATALYSIS

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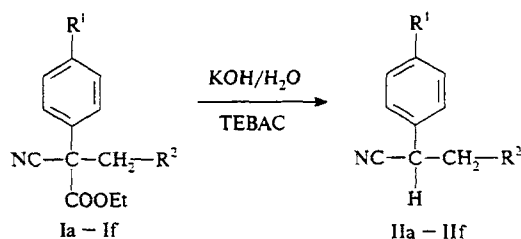
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Substituted arylacetonitriles appear as intermediate products in the synthesis of some drugs. For example, 1-phenyl-1-cyanopropane (II f) is involved in the synthesis of the broncholytic drug troventol, and 5-(*N,N*-diethylamino)-1-phenyl-1-cyanopentane (II a) is used in the production of the antiarrhythmic drug nibentan [1].

There are methods for obtaining the substituted acetonitriles from the corresponding α -cyanoesters by treatment with sodium ethylate [2], decarbalkoxylation in aqueous dimethyl sulfoxide in the presence of sodium chloride [3], or without the latter additive [4], and under the conditions of phase transfer catalysis using a crown-ether as the catalyst [5]. Another possibility consists in obtaining monoalkylphenylacetonitriles by alkylation of phenylacetonitrile with alkyl halides using a tetraalkylammonium salt as the phase transfer catalyst [6]. However, the latter method implies using a complicated system for isolation of the target products, involving a number of chemical conversions necessary to separate the monoalkyl derivative from a dialkylated product and the initial phenylacetonitrile.

We have developed a convenient method for the synthesis of substituted acetonitriles II a –II f from the corresponding α -cyanoesters (I a –I f) using triethylbenzylammonium chloride (TEBAC) as the phase transfer catalyst. This procedure allows the hydrolysis and decarboxylation of the ester to be performed "in a single pot" and the target product to be obtained in high yield without additional purification. The saponification and decarboxylation of I a –I f are performed in an aqueous potassium hydroxide solution in the presence of TEBAC, with or without aromatic hydrocarbons, in the tem-

perature interval from 45°C up to the boiling point of the reaction mixture.



I a , II a : R¹ = H, R² = (CH₂)₃NEt₂;
I b , II b : R¹ = H, R² = (CH₂)₃N(Me)CH₂CH₂C₆H₃(OMe)_{2-3,4};
I c , II c : R¹ = H, R² = (CH₂)₃N(Et)CH₂Ph;
I d , II d : R¹ = OMe, R² = (CH₂)₃NEt₂;
I e , II e : R¹ = F, R² = (CH₂)₃NEt₂;
I f , II f : R¹ = H, R² = Me.

EXPERIMENTAL PART

The data of elemental analyses agree with the results of analytical calculations using the proposed empirical formulas.

The mass spectra were obtained on an SSQ-710 chromatograph-mass spectrometer (Finnigan, USA) with a system of direct sample injection into the ionization source, operated at an ionizing electron energy of 70 eV and an ionization chamber temperature of 150°C.

The IR spectra were measured on a Perkin-Elmer Model 500 spectrophotometer (Sweden).

5-(*N,N*-Diethylamino)-1-phenyl-1-cyanopentane (II a). To a solution of 20 g (0.3564 mole) of potassium hydroxide in 30 ml of water was added with stirring 0.34 g (0.0015 mole) TEBAC and 31.65 g (0.1 mole) of 5-(*N,N*-diethylamino)-1-carboethoxy-1-phenyl-1-cyanopentane (I a)

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[1]. The reaction mass was heated with stirring to 45–50°C, kept at this temperature for 1 h, and cooled down to room temperature. On cooling, 50 ml of water and 67 ml of toluene were added and the mixture was extracted with toluene (2 × 30 ml). The toluene extracts were combined, washed with water (2 × 50 ml) to pH 7–8, and dried over anhydrous sodium sulfate. The dryer was separated by filtration and the solution washed with 50 ml toluene. Finally, toluene was distilled off and the residue distilled in vacuum to obtain 21.58 g (88.3%) of compound IIa in the form of an oily yellow liquid; b.p., 150–160°C/1 Torr.

IR spectrum, thin film (ν , cm^{-1}): 2260 ($\text{C}\equiv\text{N}$), 1610, 1510, 1480 ($\text{CH}=\text{CH}$ arom., CH_2); mass spectrum (m/z): $[\text{M}]^+$ 244, $[\text{M}-\text{Me}]^+$ 229, $\text{CH}_2=\text{N}^+\text{Et}_2$ 86.

5-{N-Methyl-N-[2-(3,4-dimethoxyphenyl)ethyl]amino}-1-phenyl-1-cyanopentane (IIb). To a solution of 4 g (0.1 mole) of sodium hydroxide in 4 ml of water was added with stirring 0.1 g (0.0004 mole) TEBAC, and a solution of 4.4 g (0.01 mole) of 1-carboethoxy-5-{N-methyl-N-[2-(3,4-dimethoxyphenyl)ethyl]amino}-1-phenyl-1-cyanopentane (Ib) in 7 ml of dry toluene. The reaction mass was heated to 50°C, kept at this temperature for 1.5 h, and cooled down to room temperature. On cooling, 15 ml of water and 15 ml of toluene were added and the mixture was extracted with toluene (2 × 15 ml). The toluene extracts were combined, washed with water (15 ml) to pH 7–8, and dried over anhydrous sodium sulfate. The drying agent was separated by filtration and the solution was washed with 10 ml toluene. Finally, toluene was distilled off to yield 3.43 g (93.2%) of compound IIb in the form of an oily yellow liquid.

IR spectrum, thin film (ν , cm^{-1}): 2240 ($\text{C}\equiv\text{N}$), 1605, 1590, 1510 ($\text{CH}=\text{CH}$ arom., CH_2); mass spectrum (m/z): $[\text{M}^+]$ 366, $[\text{M}-\text{CH}_2\text{C}_6\text{H}_3(\text{OMe})_2]^+$ 215, $[\text{CH}_2=\text{CHC}_6\text{H}_3(\text{OMe})_2]^+$ 164, $[\text{CH}_2\text{C}_6\text{H}_3(\text{OMe})_2]^+$ 151, $[\text{PhCHCN}]^+$ 116.

5-(N-Benzyl-N-ethylamino)-1-phenyl-1-cyanopentane (IIc) was obtained similarly to compound IIa from 29.24 g (0.0772 mole) 5-(N-benzyl-N-ethylamino)-1-carboethoxy-1-phenyl-1-cyanopentane (Ic) in 33 ml toluene, 0.27 g (0.0012 mole) TEBAC, and a solution of 12.2 g (0.2174 mole) potassium hydroxide in 10 ml of water treated for 3 h at 80°C. Yield of compound IIc, 21.76 g (91.6%); b.p., 210–215°C (1–1.5 Torr).

IR spectrum, thin film (ν , cm^{-1}): 2240 ($\text{C}\equiv\text{N}$), 1600, 1490, 1450 ($\text{CH}=\text{CH}$ arom., CH_2); mass spectrum (m/z): $[\text{M}]^+$ 306, $[\text{M}-\text{Me}]^+$ 291, $\text{CH}_2=\text{N}^+(\text{Et})\text{CH}_2\text{Ph}$ 148, $[\text{CH}_2\text{Ph}]^+$ 91.

5-(N,N-Diethylamino)-1-(4-methoxyphenyl)-1-cyanopentane (IIId) was obtained similarly to compound IIa from 45.15 g (0.1303 mole) 5-(N,N-diethylamino)-1-carboethoxy-1-(4-methoxyphenyl)-1-cyanopentane (Id) in 46 ml benzene, 0.27 g (0.0012 mole) TEBAC, and a solution of 25.74 g (0.4587 mole) potassium hydroxide in 22 ml of water treated with stirring for 1 h at 79°C. On cooling, 55 ml of water was added and the mixture was extracted with benzene (2 ×

40 ml), the extract being treated as described for compound IIa. Compound IIId in the form of an oily liquid was obtained at a yield of 28.43 g (79.5%); b.p., 178–190°C (1 Torr).

IR spectrum, thin film (ν , cm^{-1}): 2220 ($\text{C}\equiv\text{N}$), 1610, 1585, 1510 ($\text{CH}=\text{CH}$ arom., CH_2); mass spectrum (m/z): $[\text{M}]^+$ 274, $[\text{M}-\text{Me}]^+$ 259, $[\text{MeOC}_6\text{H}_4\text{CHCN}]^+$ 146, $\text{CH}_2=\text{N}^+\text{Et}_2$ 86.

5-(N,N-Diethylamino)-1-(4-fluorophenyl)-1-cyanopentane (IIe) was obtained similarly to compound IIa from 8.98 g (0.0268 mole) 5-(N,N-diethylamino)-1-carboethoxy-(4-fluorophenyl)-1-cyanopentane (Ie), 0.1 g (0.0004 mole) TEBAC, and a solution of 5.4 g (0.0963 mole) potassium hydroxide in 12 ml of water. Compound IIId in the form of a colorless oily liquid was obtained at a yield of 6.5 g (92.2%); b.p., 110–120°C (5 ± 2 Torr).

IR spectrum, thin film (ν , cm^{-1}): 2230 ($\text{C}\equiv\text{N}$), 1600, 1510, 1470 ($\text{CH}=\text{CH}$ arom., CH_2); mass spectrum (m/z): $[\text{M}]^+$ 262, $[\text{M}-\text{Me}]^+$ 247, $[\text{FC}_6\text{H}_4\text{C}(\text{CN})=\text{CH}_2]^+$ 147, $[\text{FC}_6\text{H}_4\text{CHCN}]^+$ 134, $\text{CH}_2=\text{N}^+\text{Et}_2$ 86.

1-Carboethoxy-5-{N-methyl-N-[2-(3,4-dimethoxyphenyl)ethyl]amino}-1-phenyl-1-cyanopentane (Ib). To a solution of 20.47 g (0.0631 mole) of 5-bromo-carboethoxy-1-phenyl-1-cyanopentane [1] in 40 ml of freshly distilled acetonitrile was added with stirring at room temperature 21.74 g (0.1114 mole) N-methylhomoveratrylamine. The reaction mass was boiled for 20 h and acetonitrile distilled off in vacuum. The residue was mixed with 80 ml of water and heated. The oily bottom layer was separated and dried in vacuum to obtain 14.26 g of compound Ib. The aqueous layer was extracted with toluene (2 × 50 ml). The toluene extracts were combined, washed with 2 N hydrochloric acid (2 × 40 ml), and dried over anhydrous sodium sulfate. The dryer was separated by filtration and the solution was washed with 15 ml toluene. Finally, toluene was distilled off to obtain 2.77 g of compound Ib in the form of a transparent light-brown liquid. On standing, the aqueous acid washing solutions yielded an oily liquid. The oily liquids were combined, alkalinized with a NaOH solution to pH 11–12, and extracted with toluene (3 × 70 ml). The extracts were washed with water (2 × 40 ml) and dried over anhydrous sodium sulfate. The dryer was separated by filtration and the solution was washed with 50 ml toluene. Finally, toluene was distilled off to yield 7.27 g of compound Ib in the form of a transparent light-brown liquid. The total yield of compound Ib was 24.3 g (87.7%).

IR spectrum, thin film (ν , cm^{-1}): 2240 ($\text{C}\equiv\text{N}$), 1745 ($\text{C}=\text{O}$), 1590, 1510 ($\text{CH}=\text{CH}$ arom., CH_2); mass spectrum (m/z): $[\text{M}^+]$ 438, $[\text{M}-\text{COOC}_3\text{H}_4]^+$ 366, $[\text{M}-\text{CH}_2\text{C}_6\text{H}_3(\text{OMe})_2]^+$ 287, $[\text{M}-(\text{CH}_2)_2\text{C}_6\text{H}_3(\text{OMe})_2]^+$ 273, $[\text{M}-\text{CH}_2\text{C}_6\text{H}_3(\text{OMe})_2-\text{COOC}_3\text{H}_4]^+$ 215, $[\text{M}-(\text{CH}_2)_2\text{C}_6\text{H}_3(\text{OMe})_2-\text{COOC}_2\text{H}_4]^+$ 201, $[(\text{CH}_2)_2\text{C}_6\text{H}_3(\text{OMe})_2]^+$ 165, $[\text{CH}_2\text{C}_6\text{H}_3(\text{OMe})_2]^+$ 151, $[\text{PhCHCN}]^+$ 116.

5-(N-Benzyl-N-ethylamino)-1-carboethoxy-1-phenyl-1-cyanopentane (Ic). To 12.65 g (0.0390 mole) of 5-bromo-carboethoxy-1-phenyl-1-cyanopentane [1] was added 11.1 g

(0.0821 mole) of benzylethylamine and 40 ml of benzene, and the mixture was boiled for 14 h and cooled. The precipitate was separated by filtration and washed with 15 ml of absolute ether. Then the volume of the solution was reduced by evaporation, the unreacted benzylethylamine being distilled off at 2 Torr. To the residue was added 75 ml of ether and 50 ml of water. The ether extract was washed with water (2 \times 50 ml) and dried over magnesium sulfate. The drying agent was separated by filtration and the solution was washed with 50 ml ether. Finally, the ether was distilled off to yield 14.03 g (95%) of compound Ic.

IR spectrum, thin film (ν , cm^{-1}): 2240 ($\text{C}\equiv\text{N}$), 1740 ($\text{C}=\text{O}$), 1600, 1490, 1450 ($\text{CH}=\text{CH}$ arom., CH_2); mass spectrum (m/z): $[\text{M}^+]$ 378, $[\text{M}-\text{Me}]^+$ 363, $[\text{M}-\text{COOEt}]^+$ 305, $\text{CH}_2=\text{N}^+(\text{Et})\text{CH}_2\text{Ph}$ 148, $[\text{CH}_2\text{Ph}]^+$ 91.

5-(N,N-diethylamino)-1-carboethoxy-1-(4-methoxyphenyl)-1-cyanopentane (Id) was obtained by a process similar to that described in [1], proceeding from (4-methoxyphenyl)acetonitrile [7] and diethylcarbonate in the presence of sodium ethylate, followed by treatment of the sodium salt of the ethyl ether of (4-methoxyphenyl)cianoacetic acid with 1,4-dibromobutane and the interaction of 5-bromo-1-carboethoxy-1-(4-methylphenyl)-1-cyanopentane with diethylamine.

IR spectrum, thin film (ν , cm^{-1}): 2240 ($\text{C}\equiv\text{N}$), 1740 ($\text{C}=\text{O}$), 1610, 1585, 1510 ($\text{CH}=\text{CH}$ arom., CH_2); mass spectrum (m/z): $[\text{M}^+]$ 346, $[\text{M}-\text{Me}]^+$ 331, $[\text{M}-\text{COOC}_2\text{H}_4]^+$ 274, $\text{CH}_2=\text{N}^+\text{Et}_2$ 86.

5-(N,N-Diethylamino)-1-carboethoxy-(4-fluorophenyl)-1-cyanopentane (Ie) was obtained by a process similar to that described in [1] from (4-fluorophenyl)acetonitrile and diethylcarbonate in the presence of sodium ethylate, followed by treatment of the sodium salt of the ethyl ether of (4-fluorophenyl)cianoacetic acid with 1,4-dibromobutane and the interaction of 5-bromo-1-carboethoxy-1-(4-fluorophenyl)-1-cyanopentane with diethylamine.

IR spectrum, thin film (ν , cm^{-1}): 2240 ($\text{C}\equiv\text{N}$), 1600, 1510 1460 ($\text{CH}=\text{CH}$ arom., CH_2); mass spectrum (m/z): $[\text{M}^+]$ 334, $[\text{M}-\text{Me}]^+$ 319, $[\text{M}-\text{COOEt}]^+$ 261, $\text{CH}_2=\text{N}^+\text{Et}_2$ 86.

(4-Fluorophenyl)acetonitrile. To a suspension of 4.57 g (0.0933 mole) of sodium cyanide in 20 ml DMSO was added with stirring a solution of 9 g (0.0622 mole) of 4-fluorobenzylchloride in 12 ml DMSO (upon which the temperature spontaneously increases to 65 – 70°C during 20 min). The reaction medium was heated to 80 – 85°C, kept at this temperature for 1 h, cooled down to room temperature, and poured

onto ice. Then the mixture was extracted with benzene (2 \times 50 ml). The benzene extracts were combined, washed with 50 ml of water, and dried over magnesium sulfate. The drying agent was separated by filtration and the solution was washed with 50 ml of benzene. Finally, benzene was distilled off and the residue distilled in vacuum to yield 7 g (83.2%) of (4-fluorophenyl)acetonitrile; b.p., 100 – 110°C (15 Torr).

4-Fluorobenzylchloride. To 12 g (0.0951 mole) of 4-fluorobenzyl alcohol [8] was added 24 ml of concentrated hydrochloric acid, the mixture heated to 70°C and stirred for 3.5 h. Then the reaction mixture was cooled to room temperature and extracted with benzene (2 \times 40 ml). The benzene extracts were combined, washed with a 4% solution of sodium carbonate, and dried over calcium chloride. The drying agent was separated by filtration and the solution was washed with 30 ml of benzene. Finally, benzene was distilled off and the residue distilled in vacuum to yield 10 g (72.7%) of (4-fluorobenzylchloride; b.p., 82°C (26 Torr).

1-Phenyl-1-cyanopropane (Iif). To a solution of 258 g (4.5983 mole) of potassium hydroxide in 387 ml of water at 45°C was added with stirring 4.39 g (0.0193 mole) of TE-BAC and 232.65 g (1.0708 mole) of the ethyl ether of phenylethylcianoacetic acid (If) [9]. The reaction mixture was stirred at 45 – 50°C for 2 h and cooled down to room temperature. Then the bottom aqueous – alkaline layer was removed and the upper layer was washed with water (2 \times 200 ml) to yield 154.44 g (99.3%) of compound Iif.

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