REACTION OF 2-CYANOMETHYLBENZIMIDAZOLE WITH ALKYL HALIDES

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Refluxing 2-cyanomethylbenzimidazole in alcohol with alkyl halides led to low yields of N-alkylated products. Addition of base to the reaction mixture shifted the course of the reaction to form mainly N,C-dialkyl substituted products. In DMF or with an excess of alkyl halide at elevated temperature both N-mono- and N,N-dialkyl substituted materials were formed together.

1-Alkyl-2-cyanomethylbenzimidazoles can be used as intermediates in the synthesis of analytical complexing reagents [1] but there is only very restricted information concerning the alkylation of 2-cyanomethylbenzimidazole (I). The reaction of (I) with dialkyl sulfates in basic media to form 1-methyl [2] and 1-ethyl [3] derivatives has been described. According to [4] the reaction of I with benzyl halides in DMF in the presence of sodium hydride leads to a mixture of α-benzyl and 1,α-dibenzyl-2-cyanomethylbenzimidazoles but according to [5] to a mixture of starting I and three further materials, of which only 1,α,α-tribenzyl-2-cyanomethylbenzimidazole could be separated.

The aim of this work was to study the possible preparation of 1-alkyl-2-cyanomethylbenzimidazoles by treating I with alkyl halides in basic medium and in the absence of proton acceptors.

Alkylation using alkyl halides in base is the most convenient preparative method for the synthesis of 1-alkylbenzimidazoles [6]. However, for 2-cyanomethylbenzimidazole both formation of the N- anion and ionization of the cyanomethyl group can occur (NH and CH acidity values for compound I being pK_a 11.48 and 13.23, respectively). Hence, it was anticipated that the reaction course might not be simple. In fact, refluxing equimolar amounts of compound I and ethyl iodide (IIa) in absolute ethanol with potassium hydroxide led to a mixture of two compounds with similar chromatographic mobility and which could only be separated on high activity aluminum oxide. One of these was identical to 1-ethyl substituted IIIa (8.9% yield) and the other was assigned the structure 1-ethyl-2(α-cyanopropyl)benzimidazole (IV, 21%) on the basis of elemental analytical data and the PMR spectrum (which showed signals for two ethyl groups and one CH group). Use of a twofold excess of ethyl iodide basically led to an increase in the yield of N,C-diethyl substituted IV.

In aprotic polar solvents (DMSO, acetone), in which the nucleophilicity of the N- anion is markedly increased, N- and N,C-substitution also principally occurred. At the same time a further series of compounds was formed but their structure could not be demonstrated because of the difficulty of separating them in a pure state.

Alkylation in a two phase system using crown ether or quaternary ammonium salt catalysts was inhibited by the low solubility of I in those solvents normally used in such systems (see top of following page).

Thus, alkylation of I with alkyl halides in basic medium occurred nonregioselectively and cannot serve as a preparative method for synthesis of N-alkyl substituted IIIa-c.

Bearing in mind the lower basicity of I (pK 2.88) when compared with benzimidazole (pK_a 5.53) we anticipated a single course for the reaction of I with alkyl halides in the absence of proton acceptors. In fact, refluxing the reagents in ethanol gave only the mono alkyl substituted IIIa-c. However, the yields were low (not more than 20%) and there was a sharp decrease in yield in going from ethyl iodide to butyl iodide and allyl bromide. Increase in the amount of alkyl halide taken in the reaction, the duration of the reaction, or exchange of ethanol for propanol, butanol, or xylene had little influence on the yield of

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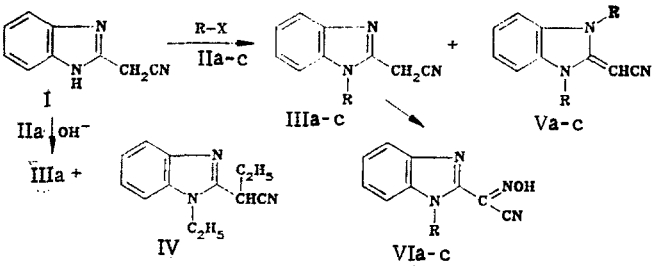

I—III, V, VI a $R=C_2H_5$, b $R=C_4H_9$, c $R=CH_2CH=CH_2$; IIa,b X=I, c X=Br

the final compounds but sometimes (particularly with xylene) led to much tarring. As in the case of highly basic azoles [7] the monoalkylation of I in DMF was accompanied by N,N-dialkylation and the formation of a side product with a polymeric structure. The PMR spectra of the 1,3-dialkyl-2-cyanomethylene-2,3-dihydrobenzimidazolines (Va-c) showed a singlet signal for the CH group proton in the 2 position and double intensity signals for the alkyl group protons. In this case the yields are in the ratio ~1:4 for III and V pointing to the predominance of N,N disubstitution.

Heating 2-cyanomethylbenzimidazole (I) with an excess of alkyl halides IIb,c without solvent at 120-130°C gave the N-monosubstituted IIIb,c in higher yield (52 and 32%, respectively). Under these conditions the N,N-disubstituted Vb,c products were also formed (13 and 32%, respectively). However, this method was convenient for preparing the 1-alkyl-2-cyanomethylbenzimidazoles because of the ready separation of III and V with different chromatographic mobilities on aluminum oxide.

The IR spectra of nitriles IIIa-c show weak C≡N absorption bands in the region 2240-2280 cm^{-1} but the frequency is reduced to 2140-2160 cm^{-1} in the N,N-dialkyl substituted Va-c with a marked increase in its intensity. In these compounds this can be explained by conjunction of the cyano group with the C=C bond. The electronic spectra of III showed three distinct maxima at 213 (log ε 4.23), 275 (log ε 3.75), 283 nm (log ε 3.76) and a broad absorption in the region 247-260 nm (log ε 3.84). 1-Alkyl-2-cyanomethylbenzimidazoles IIIa-c can be protonated in acid solutions at the pyridine nitrogen atom to form the conjugate acid. The basicity of this nitrogen atom is decreased upon lengthening of the aliphatic chain of the 1-substituent, the largest effect being shown for the electron acceptor allyl group. The proteolytic equilibrium constants for 1-ethyl, 1-butyl, and 1-allyl substituted (IIIa-c) are 2.74, 2.31, and 2.05, respectively.

Upon treatment with sodium nitrite in acetic acid compounds IIIa-c were converted to the corresponding 1-alkyl-2-(α-oximino-α-cyanomethyl)benzimidazoles (VIa-c). Their IR spectra showed weak C≡N absorptions at 2230-2250 cm^{-1} and broad, diffuse bands for the chelated OH groups in the region 2400-3200 cm^{-1}.

EXPERIMENTAL

IR Spectra were recorded on a UR-20 instrument in paraffin mull and PMR spectra at 80 MHz on a Tesla BS-478 C spectrometer using HMDS as internal standard. Electronic spectra were recorded for 8.0×10^{-5} M solutions on a Specord UV-vis with ethanol solvent. Proteolytic equilibrium constants were determined by potentiometric titration of a 0.2 mmole solution in aqueous acetone (1:1, 25 ml) with HCl solution (0.1 N) using a pH-121 pH meter (μ = 0.1). Reaction monitoring and purity assessment were carried out by TLC on Al_2O_3 using $CHCl_3$ eluent and iodine vapor for visualization. Mixtures were separated using column chromatography on activity I and II grades Al_2O_3 with $CHCl_3$ eluent.

Reaction of 2-Cyanomethylbenzimidazole (I) with Ethyl Iodide. A. Compound I ([8], 1.57 g, 10 mmole) was added to a solution of KOH (85%, 1 g, 15 mmole) in ethanol (13 ml). Over 30 min and at 20°C ethyl iodide (0.8 ml, 10 mmole) was added with stirring. The mixture was refluxed for 2.5 h, the alcohol evaporated off, the residue treated with water (10 ml), and extracted with chloroform (3 × 10 ml). The extracts were then concentrated to 8-10 ml volume and separated on an Al_3O_3 column (50 × 4 cm). The first fraction (R_f 0.55) contained 1-ethyl-2-(α-cyanopropyl)benzimidazole (IV, 0.45 g, 21%) as snow white, shining needles with mp 119°C (from isooctane). IR Spectrum: 2240 cm^{-1} (C≡N). PMR Spectrum ($CDCl_3$); 1.15 (3H, t, CH_3); 144 (3H, t, CH_3); 2.25 (2H, m, C-CH_2); 4.03 (1H, t, CH); 4.23 (2H, q, NCH_2), 7.26, 7.67 ppm (4H, m, arom.). Found, %: C 73.0, H 7.1, N 19.8. $C_{13}H_{15}N_3$. Calculated, %: C 73.2, H 7.1, N 19.7.

The second fraction (R_f 0.4) gave the 1-ethyl substituted IIIa (0.16 g, 8.9%) with mp 160-161°C (from acetone) (lit. data [3] mp 156-157°C). IR Spectrum: 2260 cm^{-1} (C≡N). PMR Spectrum ($CDCl_3$): 1.42 (3H, t, CH_3); 3.96 (2H, s, CH_2CN); 4.18 (2H, q, NCH_2); 7.62, 7.25 ppm (4H, m, arom.). Found, %: C 71.4, H 6.0, N 22.6. $C_{11}H_{11}N_3$. Calculated, %: C 71.3, H 6.0, N 22.7.

Increase in the amount of ethyl iodide to 20 mmole and the reaction time to 3.5 h gave the N,C-diethyl substituted IV (0.66 g, 31%) and IIIa (0.18 g, 9.7%).

B. A solution of I (0.63 g, 4 mmole) and ethyl iodide (0.5 ml, 6 mmole) in absolute ethanol (5 ml) was refluxed for 6 h. The alcohol was evaporated off and the residue treated with Na_2CO_3 solution (5%, 10 ml) and extracted with $CHCl_3$ (3 × 5 ml). The unreacted I (0.28 g) was filtered off. The chloroform extracts contained I and IIIa and were chromatographed on an Al_2O_3 column (15 × 2 cm) using $CHCl_3$ eluent and the fraction with R_f 0.4 collected. The residue (0.23 g) after evaporation of solvent was crystallized in turn with acetonitrile and acetone to give the 1-ethyl substituted IIIa (0.14 g, 19%) with mp 159-160°C. An additional 0.13 g of I was eluted from the column.

C. A mixture of I (0.63 g, 4 mmole), ethyl iodide (1 ml, 12 mmole) and xylene (10 ml) was refluxed for 2 h, cooled, and the tarry precipitate separated and washed with petroleum ether. It was then treated with Na_2CO_3 solution (5%, 10 ml) and extracted with $CHCl_3$ (3 × 8 ml). Evaporation of $CHCl_3$ then gave a mixture (0.43 g) of starting I and product IIIa which was separated chromatographically (as above) to give IIIa (0.15 g, 20.3%) with mp 159-160°C and I (0.26 g). According to TLC small amounts of I along with decomposition products were present in the xylene and sodium carbonate solutions.

D. A mixture of I (1.57 g, 10 mmole) and ethyl iodide (1.2 ml, 15 mmole) in DMF (7 ml) was refluxed for 1 h, cooled, and poured into water (20 ml). The dark yellow precipitate (0.66 g), difficult to dissolve in organic solvents, was probably a polymerization product and was separated and washed with water. The mother liquors were basified with NH_4OH solution to pH 8 and extracted with $CHCL_3$ (3 × 5 ml). The chloroform extract contained a mixture of 1,3-diethyl-2-cyanomethylene-2,3-dihydrobenzimidazoline (Va) with R_f 0.8, compound IIIa, and starting I and was separated on an Al_2O_3 column (40 × 3.5 cm) to give Va (0.77 g, 36.1%) with mp 91°C (from isooctane). IR Spectrum: 2145 cm^{-1} (C≡N). PMR Spectrum (CF_3COOH): 1.25 (6H, t, 2-CH_3); 4.26 and 4.38 (6H, q, 2-NCH_2, partially obscured by the CH_2CN singlet); 7.37 ppm (4H, s, arom.). Found, %: C 73.1, H 7.0, N 19.6. $C_{13}H_{15}N_3$. Calculated, %: C 73.2, H 7.1, N 19.7. The yield of IIIa was 0.17 g (9.2%).

Reaction of 2-Cyanomethylbenzimidazole (I) with Butyl Iodide. A. A mixture of I (0.79 g, 5 mmole) and butyl iodide (0.57 ml, 10 mmole) in 10 ml of absolute ethanol was refluxed for 14 h, the alcohol evaporated off, and the residue treated with 10% NH_4OH solution (5 ml) and then $CHCl_3$ (5-7 ml). The unreacted I (0.63 g) was filtered off and the chloroform solution column chromatographed on Al_2O_3 collecting the fraction with R_f 0.4. Evaporation of the eluate gave 1-butyl-2-cyanomethylbenzimidazole (IIIb, 0.1 g, 9.4%) as an oil which crystallized upon trituration with petroleum ether. The snow white crystals had mp 56-57°C (from low boiling petroleum ether). IR Spectrum: 2245 cm^{-1} (C≡N). PMR Spectrum (CF_3COOH): 0.6 (3H, t CH_3); 1.1 (2H, m, CH_2•CH_3); 1.59 (2H, m, NCH_2CH_2); 4.13 (2H, t, NCH_2); 4.33 (2H, s, CH_2); 7.33 ppm (4H, s, arom.). Found, %: C 73.0, H 7.0, N 19.8. $C_{13}H_{15}N_3$. Calculated, %: C 73.2, H 7.1, N 19.7.

B. A mixture of I (3.14 g, 20 mmole) and butyl iodide (4.6 ml) was heated in a flask fitted with a short fractionating column, increasing the temperature from 20°C to 125-130°C over 30 min, and adding absolute alcohol (4 ml) (the residual I being almost completely soluble). After heating at 125-130°C for 1 h, alcohol (2 ml) was added, and the product heated for 3 h. The clear melt formed was then cooled, treated with $CHCl_3$ (15 ml) and Na_2CO_3 solution (5%, 20 ml) and the layers separated. Starting I (1.1 g, 35%) was filtered off from the aqueous layer. The chloroform layer was column chromatographed on Al_2O_3 (50 × 4 cm) to give 1,3-dibutyl-2-cyanomethylene-2,3-dihydrobenzimidazoline (Vb, 0.69 g, 12.8%) and the 1-butyl substituted IIIb (2.2 g, 51.6%), identical to that obtained by method A.

Compound Vb was purified by recrystallization from isooctane to mp 77°C and had R_f 0.8. IR Spectrum: 2140 cm^{-1} (C≡N). PMR Spectrum (CF_3COOH): 0.56 (6H, t, 2-CH_3); 1.08 (4H, m, 2 CH_2CH_3); 1.54 (4H, m, 2NCH_2CH_2); 4.15 (4H, t, 2-NCH_2); 4.31 (2H, s, CH_2); 7.33 ppm (4H, s, arom.). Found, %: C 75.8, H 8.5, N 15.8. $C_{17}H_{23}N_3$. Calculated, %: C 75.8, H 8.6, N 15.6.

Reaction of 2-Cyanomethylbenzimidazole (I) with Allyl Bromide. A mixture of I (3.14 g, 20 mmole) and allyl bromide (3.5 ml, 40 mmole) were heated in a sealed ampul for 6 h at 115-120°C. The dark, caked mass was cooled and thoroughly triturated with acetone (25-30 ml). The solid (4.5 g) was filtered off, washed with acetone (2 × 10 ml), treated with NH_4OH solution (10%, 15 ml), extracted with $CHCl_3$ (10 ml), and the extract fractionated on an Al_2O_3 column (50 × 4 cm) with collection of the fractions having R_f 0.8 and 0.4.

The first fraction gave 1,3-diallyl-2-cyanomethylene-2,3-dihydrobenzimidazoline (Vc, 1.5 g, 31.6%) as snow white crystals with mp 86°C (from isooctane). IR Spectrum: 2160 cm^{-1} (C≡N). PMR Spectrum ($CDCl_3$): 3.25 (1H, s, CHCN); 4.25 and 4.82 2 (2H, m, NCH_2); 5.12 and 5.25 2 (2H, m, CH_2); 5.83 (2H, m, 2-CH); 6.93 ppm (4H, m, arom.). Found, %: C 75.7, H 6.3, N 17.9. $C_{15}H_{15}N_3$. Calculated, %: C 75.9, H 6.4, N 17.7.

The second fraction contained 1-allyl-2-cyanomethylbenzimidazole (IIIc, 1.25 g, 31.7%) as snow white needles with mp 97-98°C (from isooctane), soluble in acetone, acetonitrile, ethyl acetate, alcohol, and $CHCl_3$. IR Spectrum: 2280 cm^{-1} (C≡N). PMR Spectrum ($CDCl_3$); 3.9 (2H, s, CH_2CN); 4.65 and 4.73 (2H, m, NCH_2); 5.0 and 5.23 (2H, m, CH_2); 5.8 (1H, m, CH); 7.2 and 7.62 ppm (3H and 1H, m, arom.). Found, %: C 73.0, H 5.4, N 21.3. $C_{12}H_{11}N_3$. Calculated, %: C 73.1, H 5.6, N 21.3.

It was shown by TLC that the acetone filtrate contained I, IIIc, Vc, and small amounts of a compound of unknown structure, contaminated by decomposition products which hindered separation of the mixture.

2-(α-Oximino-α-cyanomethyl)-1-ethylbenzimidazole (VIa). A solution of $NaNO_2$ (0.52 g, 7.5 mmole) in water (2 ml) was added with stirring to a solution of IIIa (0.93 g, 5 mmole) in acetic acid (5 ml) cooled with ice water. The mixture was left at 20°C for 2-3 h, diluted by a factor of three with water, the solid produced filtered off, thoroughly washed with water and dried at 110-120°C to give 1.06 g (99%) of pale yellow crystals with mp 209-210°C (decomp.). IR Spectrum: 2230 (C≡N), 2400-3200 cm^{-1} (OH). PMR Spectrum (CF_3COOH): 1.17 (3H, t, CH_3); 4.37 (2H, q, CH_2); 7.37 ppm (4H, s, arom.). Found, %: C 61.7, H 4.6, N 26.2. $C_{11}H_{10}N_4O$. Calculated, %: C 61.7, H 4.7, N 26.1.

Oximes VIb,c were obtained in the same way.

1-Butyl-2-(α-oximino-α-cyanomethyl)benzimidazole (VIb). Yield 91%, mp 232-233°C (decomp., from alcohol). IR Spectrum: 2235 (C≡N), 2400-3200 cm^{-1} (OH). PMR Spectrum (CF_3COOH): 0.55 (3H, t, CH_3); 1.04 (2H, m, CH_2–CH_3); 1.57 (2H, m, NCH_2CH_2); 4.32 (2H, t, NCH_2); 7.33 ppm (4H, s, arom.). Found, %: C 64.3, H 5.9, N 23.3. $C_{13}H_{14}N_4O$. Calculated, %: C 64.5, H 5.8, N 23.1.

1-Allyl-2-(α-oximino-α-cyanomethyl)benzimidazole (VIc). Yield 87.1%, mp 195-196°C (decomp., from alcohol). IR Spectrum: 1645 (C=C exo ring), 2250 (C≡N), 2400-3200 cm^{-1} (OH). PMR Spectrum (CF_3COOH): 4.98 (4H, m, CH_2, NCH_2); 5.6 (1H, m, CH); 7.38 ppm (4H, s, arom.). Found, %: C 63.5, H 4.6, N 25.0. $C_{12}H_{10}N_4O$. Calculated, %: C 63.7, H 4.4, N 24.8.

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