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A New Synthesis of Alkyl and Aryl 2-Aminoimidazoles

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The condensation of cyanamide with α-aminocarbonyl compounds has been studied as a method of synthesizing alkyl and aryl 2-aminoimidazoles. Starting from *N*-alkylaminoaldehydes, 1,5-dialkyl-2-aminoimidazoles have been prepared. Starting from suitable aminoketones a variety of monosubstituted and disubstituted derivatives were obtained.

In the course of our studies on the synthesis of 2-nitroimidazoles (1,2) we have been concerned with the preparation of some 2-aminoimidazoles. A search through the literature revealed that a satisfactory method of synthesis had been described for only a few compounds of this class. Hence we have examined the possibility of preparing alkyl- and aryl-2-aminoimidazoles by condensation of cyanamide with α-aminocarbonyl compounds.

The reaction of cyanamide with α-aminoaldehydes was studied by Lawson (3). He found that starting from α-aminoacetaldehyde no crystalline material could be isolated, while α-aminopropionaldehyde gave 2,5-dimethyl-1*H*-imidazo[1,2-a]imidazole, and α-aminoisocaproic aldehyde gave 2-amino-5-isobutyl-1-(4-methyl-2-oxopentyl)imidazole. Compounds of the latter type were obtained with other alkyl- or aryl-α-aminoaldehydes.

The formation of these products, in analogy with the condensation between α-aminoaldehydes and thiocyanate (4), was interpreted as due to the reaction of two molecules of aminoaldehyde, which undergo a Schiff's base condensation, with one molecule of cyanamide. The synthesis of 2-aminoimidazole and 1-methyl-2-aminoimidazole was achieved by Lawson (3) by treating the diethyl acetals of α-amino and α-methylamino-acetaldehyde with cyanamide and hydrolyzing the intermediate guanidino derivatives.

However, protection of the carbonyl group appears unnecessary in the case of *N*-alkylaminoaldehydes, which obviously cannot give the Schiff's base condensation. In fact we have found that the condensation of cyanamide in boiling water with α-methylaminoacetaldehyde (obtained in solution by the Akabory (5,6) reduction of sarcosine ethyl ester) yields 1-methyl-2-aminoimidazole (I), identical with the product obtained by Lawson.

The extension of this reaction to other α-methylaminoaldehydes provides a useful method for the preparation of 1,5-dialkyl-2-aminoimidazoles. Starting from the ethyl ester of α-methylaminopropionic acid and of α-methylaminobutyric acid, the condensation after the Akabory reduction, yielded 1,5-dimethyl-2-aminoimidazole (II) and 1-methyl-5-ethyl-2-aminoimidazole (III), respectively.

The condensation of cyanamide with α-aminoketones was then studied, with the aim of obtaining other 2-aminoimidazole derivatives.

An attempt to prepare 4(5)-*p*-chlorophenyl-2-aminoimidazole by reacting *p*-chlorophenacylamine hydrochloride with cyanamide has been reported as unsuccessful (7). However, we have found that at slightly acidic *p*H values (between 4 and 5) 1-methyl-1-aminoacetone condenses smoothly with cyanamide in boiling water affording good yields of 4,5-dimethyl-2-aminoimidazole (IV), identical with the product obtained by Burtles and Pyman (8). The new compounds 4(5)-methyl-5(4)-phenyl-2-aminoimidazole (V) and 4(5)-methyl-5(4)-benzyl-2-aminoimidazole (VI) were prepared by the same procedure.

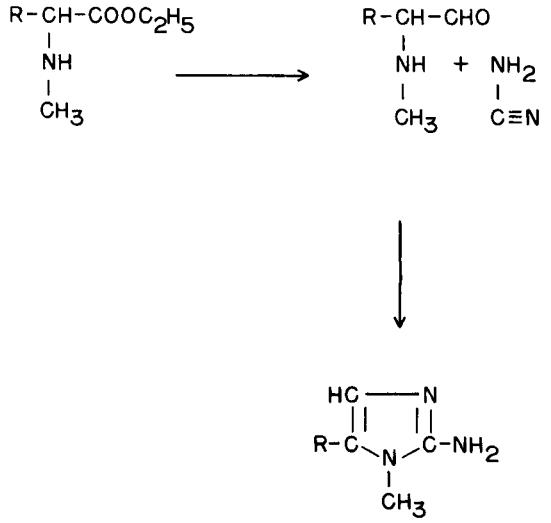
The *p*H of the reaction mixture appears to be of major importance, especially in the case of aromatic aminoketones. In fact, at strongly acidic *p*H values urea was formed and at neutral or alkaline values the condensation of two molecules of aminoketone to give symmetrical alkyl-aryl dihydropyrazines was observed.

Under similar conditions the monosubstituted 2-aminoimidazoles VII and VIII, could be prepared starting from the appropriate ketones.

4(5)-Phenyl-2-aminoimidazole (VIII) had been previously described by Pyl, *et al.* (9). 4(5)-Methyl-2-aminoimidazole (VII) had been obtained in very poor yields by reduction of 2-*p*-bromophenylazo-4(5)-methylimidazole and characterized only as the picrate (8). Although our reaction yields were fairly good, attempts at crystallizing this product as the base or the hydrochloride or sulfate were unsuccessful. Recovery from the reaction mixture was then achieved via the picrate salt, from which a purified solution of the hydrochloride was obtained using the routine procedure (10). Lyophilization of this solution afforded 4(5)-methyl-2-aminoimidazole hydrochloride (VII) in a fairly pure state.

The reaction can be applied to the synthesis of the previously unknown 1,4-disubstituted-2-aminoimidazoles. In fact, 1-methyl-4-phenyl-2-aminoimidazole (IX, fig. 3) was obtained in good yields from *N*-methylaminoacetophenone.

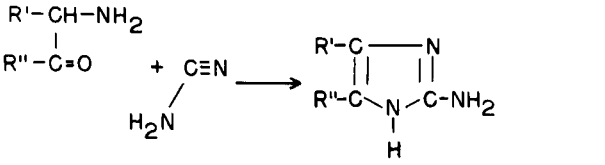
It can be therefore concluded that the condensation of cyanamide with α-aminocarbonyl compounds provides a general method for the preparation of aryl- and alkyl-2-aminoimidazoles.



I R = H

II R = CH_3

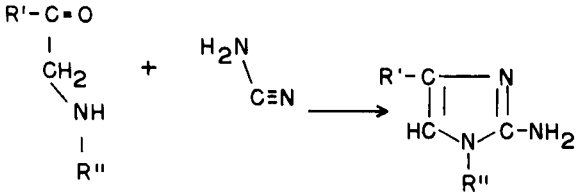
III R = C_2H_5



IV R' = R" = CH_3

V R' = CH_3 R" = C_6H_5

VI R' = CH_3 R" = C_6H_5-CH_2



VII R' = CH_3 R" = H

VIII R' = C_2H_5 R" = H

IX R' = C_6H_5 R" = CH_3

EXPERIMENTAL

1-Methyl-2-aminoimidazole Hydrochloride (I).

To a solution containing 4.6 g. of sarcosine ethyl ester hydrochloride in 35 ml. of water, 200 g. of 2.5% sodium amalgam were added over one hour, maintaining the *p*H acid by addition of 15% hydrochloric acid, and keeping the temperature between -5° and 0° by addition of solid carbon dioxide. The mixture was stirred at 0° for a further 30 minutes and then the mercury was separated. To the resulting solution of methylaminoacetaldehyde, 3.5 g. of cyanamide were added. The *p*H was brought to 4.5, the solution heated for one hour on a steam bath and then evaporated to dryness under reduced pressure. The residue was washed with ether to remove the unreacted cyanamide, dissolved in a small volume of water and added to a boiling solution of picric acid in water. The picrate, obtained on cooling, weighed 2.2 g. after recrystallization from methanol and melted at 208-210° (reported (3) m.p. 212°). The picrate was dissolved in a boiling mixture of 150 ml. of water, 10 ml. of concentrated hydrochloric acid and 300 ml. of benzene. The organic phase was separated, the inorganic phase was extracted several times with benzene and evaporated to dryness. Recrystallization of the residue from ethanol-ether afforded 0.7 g. of the product, m.p. 84-85° (reported (3) m.p. = 84°).

Anal. Calcd. for $C_4H_8ClN_3$: C, 35.96; H, 6.04; N, 31.46; Cl, 26.54. Found: C, 36.08; H, 5.85; N, 31.40; Cl, 26.66.

1,5-Dimethyl-2-aminoimidazole Hydrochloride (II).

A solution of α-*N*-methylaminopropionaldehyde was prepared by reducing 4 g. of ethyl-α-methylaminopropionate as above. After the addition of 3.5 g. of cyanamide, the *p*H was brought to 4.5, the solution heated on a steam bath for one hour and evaporated to dryness. The residue was taken up in 100 ml. of anhydrous ethanol and the sodium chloride removed by filtration. The solution was concentrated to 20 ml. and made acid with 5 ml. of ethanol saturated with hydrogen chloride. On addition of ether, a precipitate was obtained. Recrystallization of the solid product from ethanol-ether yielded 2.5 g. of white crystals, m.p. 257° (dec.).

Anal. Calcd. for $C_5H_{10}ClN_3$: C, 40.68; H, 6.83; N, 28.47; Cl, 24.02. Found: C, 40.87; H, 6.70; N, 28.29; Cl, 24.14.

1-Methyl-5-ethyl-2-aminoimidazole Hydrochloride (III).

The reaction was performed as described above for the dimethyl derivative. Starting from 8.8 g. of ethyl α-methylaminobutyrate, 3.05 g. of pure product was obtained, m.p. 201-203°.

Anal. Calcd. for $C_6H_{12}ClN_3$: C, 44.58; H, 7.48; N, 21.94; Cl, 26.0. Found: C, 44.46; H, 7.68; N, 22.14; Cl, 25.69.

2-Amino-4,5-dimethylimidazole Hydrochloride (IV).

To a solution of 3.8 g. of 1-methyl-1-aminoacetone hydrochloride, obtained as a syrup by the Dakin and West method (11), in 40 ml. of water, 3.5 g. of cyanamide was added. The *p*H was brought to 4.5 with 1 *N* sodium hydroxide solution and the solution was heated on a steam bath for one hour. Evaporation under reduced pressure gave a syrupy residue which, on treatment with anhydrous ether and acetone, became a brownish powder. Crystallization from ethanol made acid with hydrogen chloride yielded 3.5 g. of pure IV, m.p. 289° (reported (8) m.p. 289°).

Anal. Calcd. for $C_5H_{10}ClN_3$: C, 40.68; H, 6.83; N, 28.47; Cl, 24.02. Found: C, 40.50; H, 6.58; N, 28.25; Cl, 23.85.

2-Amino-4(5)-methyl-5(4)-phenylimidazole Hemisulfate (V).

A solution containing 2.5 g. of 1-amino-1-phenylacetone hydrochloride (12) and 5 g. of cyanamide in 25 ml. of water was brought to *p*H 4.5 with 1 *N* sodium hydroxide solution, heated on a steam bath for one hour and then evaporated to dryness under reduced pressure. The residue was triturated with ether and then dissolved in 10 ml. of water. On addition of 2 ml. of concentrated sulfuric acid and cooling, a white product crystallized. After recrystallization from water the product was filtered and dried at 70° under reduced pressure for several hours, yield 1.72 g., m.p. 167-169°.

Anal. Calcd. for $C_{10}H_{11}N_3 \cdot \frac{1}{2}H_2SO_4$: C, 54.04; H, 5.44; N, 18.91; S, 7.21. Found: C, 53.75; H, 5.69; N, 18.70; S, 7.02.

The picrate melted at 217°.

2-Amino-4(5)-methyl-5(4)-benzylimidazole Hemisulfate (VI).

From 3 g. of 1-benzyl-1-aminoacetone hydrochloride (12) and 3 g. of cyanamide, by the procedure described above for the methylphenyl derivative, 2.98 g. of white crystals were obtained, m.p. 246-248°.

Anal. Calcd. for $C_{11}H_{13}N_3 \cdot \frac{1}{2}H_2SO_4$: C, 55.91; H, 5.97; N, 17.78; S, 6.79. Found: C, 55.68; H, 6.14; N, 17.54; S, 6.58.

4(5)-Methyl-2-aminoimidazole Hydrochloride (VII).

To a solution of 5 g. of aminoacetone hydrochloride in 30 ml. of water, 5 g. of cyanamide was added. The *p*H was brought to 4.5 with 10% sodium hydroxide solution, the solution was heated on a steam bath for one hour and then evaporated to dryness. The residue was washed with ether, dissolved in a few milliliters of water and

added to a boiling solution of 10 g. of picric acid in 200 ml. of water. The picrate of VII, obtained on cooling, was recrystallized from methanol. Yield 12.2 g., m.p. 184-185° (reported (8) m.p. 186-187°). The product was dissolved in a boiling mixture of one liter of 1 *N* hydrochloric acid and 2 liters of benzene. The organic phase was separated and the inorganic phase extracted several times with benzene. Lyophilization of the aqueous solution afforded 4.8 g. of a pinkish hygroscopic powder, m.p. 115-117°.

Anal. Calcd. for $C_4H_8ClN_3$: C, 35.96; H, 6.04; N, 31.46; Cl, 26.54. Found: C, 35.44; H, 6.24; N, 30.95; Cl, 26.01.

4(5)-Phenyl-2-aminoimidazole (VIII).

To a mixture of 3.4 g. of aminoacetophenone and 3 g. of cyanamide in 30 ml. of water, 2 ml. of acetic acid was added and the *p*H brought to 4.5 with 10% sodium hydroxide solution. The solution was heated on a steam bath for one hour, cooled, filtered and made slightly alkaline with ammonium hydroxide. The precipitate was collected and crystallized from water. Yield 1.4 g., m.p. 166-168° (reported (9) m.p. 168°).

Anal. Calcd. for $C_9H_9N_3$: C, 67.9; H, 5.70; N, 26.40. Found: C, 68.00; H, 5.46; N, 26.13.

The hydrochloride, after crystallization from ethanol-ether melted at 207-209°.

The picrate had a melting point of 228°.

1-Methyl-4-phenyl-2-aminoimidazole (IX).

To a solution of 5.6 g. of ω-methylaminoacetophenone hydrochloride and 2 g. of cyanamide in 60 ml. of water, 2 ml. of acetic acid and 30 ml. of 1 *N* sodium hydroxide solution was added. The resulting *p*H was 4.5. The solution was heated on a steam bath for one hour and then cooled and made slightly alkaline by the addition of ammonium hydroxide. The crude precipitate, crystallized from water, yielded 4 g. of white crystals, m.p. 204-206°.

Anal. Calcd. for $C_{10}H_{11}N_3$: C, 69.34; H, 6.40; N, 24.26. Found: C, 69.50; H, 6.50; N, 23.94.

The picrate had a melting point of 246-248°.

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