Selective Decarboxylation of 1-Methyl-4,5-imidazoledicarboxylic Acid

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(Received June 22, 1979)

Synopsis. The selective decarboxylation of 1-methyl-4,5-imidazoledicarboxylic acid was carried out in various solvents. 1-Methyl-5-imidazolecarboxylic acid was obtained by heating in acetic or propionic anhydride, whereas 1-methyl-4-imidazolecarboxylic acid was obtained in *N,N*-dimethylformamide, *N,N*-dimethylacetamide, or *N*-methylpyrrolidone or by pyrolysis. The reaction mechanism is discussed.

The exhaustive decarboxylation of 4,5-imidazoledicarboxylic acids is well known, whereas the monodecarboxylation of the 1-substituted derivatives, which must lead to an isomeric product, has seldom appeared in the literature.

We have reported in a previous paper that the treatment of 1-methyl-4,5-imidazoledicarboxylic acid in an excess of boiling aniline at about 200 °C for 6—8 h gave 1-methyl-4-imidazolecarboxanilide in a yield of 56%.[1] On the other hand, Nematollahi reported the cyclic dimerization *via* the monodecarboxylation of 4,5-imidazoledicarboxylic acid in boiling acetic anhydride, yielding 5*H*,10*H*-diimidazo[3,4-*a*: 3′,4′-*d*]pyrazine-5,10-dione.[2]

The latter reaction conditions were then applied to 1-methyl-4,5-imidazoledicarboxylic acid in order to ascertain which isomer could be obtained by monodecarboxylation. The treatment in boiling acetic anhydride for only one hour gave 1-methyl-5-imidazolecarboxylic acid in a yield of 63.5%, while that at 100 °C for 4 h gave the same product in an almost quantitative yield. For the further investigation of the decarboxylation, acetic anhydride was replaced with various media; the results are summerized in Table 1.

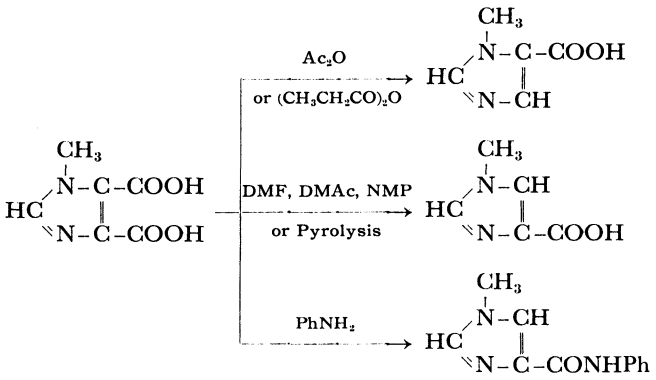


Fig. 1.

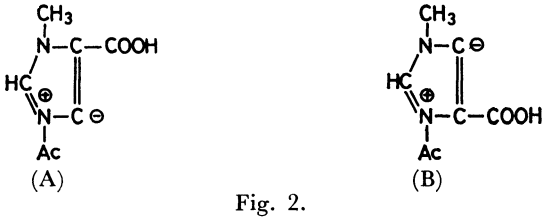
The successful effect of acetic anhydride on the selective decarboxylation seemed to suggest that the acylation of nitrogen at the 3-position is needed to promote the reaction. However, the use of anhydrides other than propionic anhydride, glacial acetic acid, acetyl chloride, and chloroacetyl chloride resulted in failure, probably because of the insolubility of the substrate in these acylating media.

On the other hand, the monodecarboxylation in such solvents as *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-methylpyrrolidone, and aniline, or by pyrolysis, where, in all cases, no electrophilic species was present, occurred at the 5-carboxyl group, giving the 4-carboxylic acid or its anilide. The reaction in *N,N*-dimethylaniline was hard to control.

Table 1. Products and conditions of decarboxylation

Reaction media	Reaction temp/°C	Reaction time/h	Product	Yield/%
Acetic anhydride	reflux	1[a]	5-COOH	63.5
	100	4[a]	5-COOH	99
Propionic anhydride	130	4	5-COOH	23.8
	100	8	5-COOH	9.5
Octanoic anhydride	130	8	none[b]	—
Palmitic anhydride	130	8	none[b]	—
Benzoic anhydride	130	4	none[b]	—
Succinic anhydride	125	15	none[b]	—
Glacial acetic acid	reflux	24	none[b]	—
Acetyl chloride	reflux	24	none[b]	—
Chloroacetyl chloride	80	30	none[b]	—
	reflux	2	decomp.	—
Aniline	reflux	6—8	4-Anilide[b]	56[1]
	100	24	none[b]	—
N,N-Dimethylaniline	reflux	5	1-Methylimidazole	—
Triethylamine	reflux	50	none[b]	—
N,N-Dimethylformamide	reflux	3[a]	4-COOH	39.7
N,N-Dimethylacetamide	reflux	3[a]	4-COOH	64.3
N-Methylpyrrolidone	130	2	4-COOH	31.7
None(Pyrolysis)	250	1 min	4-COOH	30

a) Heated until the reaction mixture became homogeneous. b) Most of the substrate was recovered.



(A) (B)

Fig. 2.

(C) (D)

Fig. 3.

From the above results, the reaction mechanism can be thought to be as follows, on the basis of the adjacent charge effect: in the presence of such electrophilic species as acetic anhydride, the decarboxylated transition state (A) must be more stable than (B), consequently yielding the 5-carboxylic acid, while in the absence of electrophilic species, (D) must be preferable to (C), giving the 4-carboxylic acid or its derivative. Such a consideration on the basis of the electrostatic interaction has appeared in a paper by Cohen and his coworkers.[3] They studied the exchange reaction of ring hydrogens in 1-methylimidazole by NMR and concluded that the 5-carbanion was preferable to the 4-carbanion because of the electrostatic repulsion.

The present work provides a route to synthesize 1-methyl-4- and -5-imidazolecarboxylic acids and their derivatives which is more convenient than the known syntheses.[4]

Experimental

Decarboxylation in Acetic Anhydride. Into 100 ml of acetic anhydride, 3.4 g (0.02 mol) of 1-methyl-4,5-imidazoledicarboxylic acid was added, after which the suspension was heated at 100 °C for 4 h. After the reaction mixture became homogeneous, it was concentrated to dryness under reduced pressure. The resulting residue was washed with acetone and recrystallized from ethanol to give 1-methyl-5-imidazolecarboxylic acid in a yield of 2.5 g (99%); mp 256—257 °C (dec) (uncorr.) (lit,[4] 275—277 °C (dec)).

Decarboxylation in Propionic Anhydride. 1-Methyl-4,5-imidazoledicarboxylic acid (1.7 g, 0.01 mol) in 100 ml of propionic anhydride was heated, after which the reaction mixture was treated in the same way as that in acetic anhydride.

Decarboxylation in N,N-*Dimethylformamide.* Into 50 ml of *N,N*-dimethylformamide, a 1.7 g portion(0.01 mol) of 1-methyl-4,5-imidazoledicarboxylic acid was added, after which the suspension was heated under reflux for 3 h. The reaction mixture was then concentrated to dryness under reduced pressure. The resulting residue was washed with benzene and recrystallized from ethanol to give 1-methyl-4-imidazolecarboxylic acid in a yield of 0.5 g(39.7%); mp 246—247 °C (dec)(uncorr.)(lit,[2] 246—247 °C(dec)).

Decarboxylations in N,N-*Dimethylacetamide and* N-*Methylpyrrolidone.* The decarboxylations in *N,N*-dimethylacetamide and *N*-methylpyrrolidone were carried out in the same way as that in *N,N*-dimethylformamide.

Pyrolysis. In a test tube, 0.85 g (0.005 mol) of 1-methyl-4,5-imidazoledicarboxylic acid was placed and heated in a silicone oil bath at 250 °C for 1 min. The reaction mixture was then washed with benzene and recrystallized from ethanol to give 1-methyl-4-imidazolecarboxylic acid in a yield of 0.19 g (30%).

Isomeric Identification of the Monocarboxylic Acids. The carboxylic acids obtained were transformed to their methyl esters, which were then compared gas-chromatographically with authentic methyl 1-methyl-4- and -5-imidazolecarboxylates.

Methylation of 1-Methyl-4- and -5-imidazolecarboxylic Acids. Into 50 ml of thionyl chloride, a 2.5 g portion(0.02 mol) of 1-methyl-5-imidazolecarboxylic acid was added; the suspension was then heated under reflux for about 6 h till the mixture became clear. Immediately after the thionyl chloride has been distilled off, a 50 ml portion of methanol was added and the mixture was refluxed for 1 h. The reaction mixture was then cooled in an ice bath, and powdery sodium carbonate was added to make it alkaline. The solution was concentrated to dryness under reduced pressure, and the residue was extracted with chloroform. The chloroform layer was concentrated again, and the resulting residue was recrystallized from hexane to give methyl 1-methyl-5-imidazolecarboxylate in a yield of 1 g (35.7%); mp 54—56 °C (uncorr.) (lit,[4] 56—57 °C, 68—70 °C, 39—40 °C).

The methylation of the 4-carboxylic acid was carried out in a similar way. The methyl ester was obtained in a yield of 45%; mp 103—104 °C (lit,[1] 103—104 °C).

Preparation of Authentic Samples. Methyl 1-methyl-5-imidazolecarboxylate was prepared from methyl 4-imidazolecarboxylate with dimethyl sulfate according to Pyman's method,[4] while the 4-isomer was prepared from 1-methyl-4-imidazolecarboxanilide through hydrolysis, followed by esterification.[1] The isomeric structure of these authentic samples has previously been determined by a study of the Nuclear Overhauser Effect on NMR.[1]

Gas Chromatography. Gas chromatography was performed on a Shimadzu GC-6AMP instrument equipped with a 3 mm × 1000 mm glass column of OV-17 (5%) on DMCS. The column temperature was raised at a rate of 4 °C/min starting from 100 °C, and the flow rate was 30 ml of helium/min. The retention times of methyl 1-methyl-4- and -5-imidazolecarboxylates were 21 and 10 min, respectively.

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