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Imidazole-2-carbaldehydes in hot ethanol undergo a decarbonylation reaction involving nucleophilic attack of the alcohol on the carbonyl to form the corresponding imidazole and ethyl formate.

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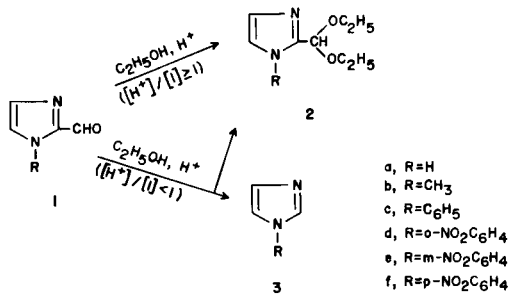
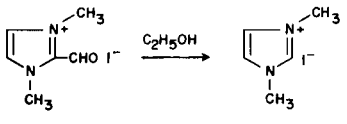
In the course of the acid catalyzed acetalyzation of imidazole-2-carbaldehydes it was observed that the yield of acetal depends on the amount of catalyst. For example, in the preparation of the ethyl acetals of imidazole-2-carbaldehydes **1a-f**, if a mole ratio (acid/aldehyde) of 1:1 or higher is used, ethyl acetals **2a-f**, respectively, are obtained in good yield. With lower amounts of catalyst, the yields of acetal decrease and at the same time a partial decarbonylation of the aldehydes occurs. When the reaction is carried out in ethanol without the catalyst, only decarbonylation takes place.

SCHEME I

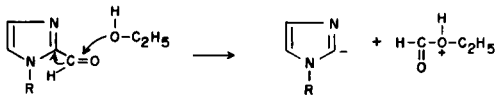


It was observed that whereas the acetalyzation rate changes within narrow limits by changing R, the decarbonylation rate depends strictly on R. In fact, as shown in Table II, the decarbonylation rate decreases remarkably in the order: Ar ≫ H > CH_3; with the exception of 1-(*o*-nitrophenyl)imidazole-2-carbaldehyde, the presence of electronegative groups on the phenyl moiety causes an increase in the decarbonylation rate. It was also observed that the quaternization of the nitrogen at position 3 makes decarbonylation easier. Thus, 1,3-dimethyl-2-formylimidazolium iodide **4** is completely decarbonylated in an hour.



In the decomposition of the aldehydes, no carbon monoxide is formed; instead, ethyl formate is obtained quantitatively.

On the basis of the experimental observations described above, it is postulated that the decarbonylation of the aldehydes occurs by a nucleophilic attack of ethanol on the carbonyl.



The formation of the intermediate carbanion in position 2 of the imidazole ring may occur easily because of the inductive effect of the nuclear nitrogen atoms as observed in exchange reactions of other azoles by Olofson, *et al.* (1), and confirmed by Wong and Keck in the deuteration of 1-methylimidazole (2). The greater resistence to decarbonylation of 1-(*o*-nitrophenyl)imidazole-2-carbaldehyde may be due to the steric hindrance of the bulky nitro group to the nucleophilic attack.

As can be seen from the results in Table II, both acetalyzation and decarbonylation reactions are acid catalyzed; however, the catalytic effect in decarbonylation is modest and lower than that observed in the formation of acetals. When the amount of acid is lower than that of aldehyde, most of the acid is employed in the protonation of heterocyclic nitrogen and so it is not available for the catalysis of the acetalyzation reaction. When the amount of acid is higher than the aldehyde, then the acetalyzation reaction prevails.

We finally ascertained that this decarbonylation reaction is limited to N_1-substituted and unsubstituted imidazole-2-carbaldehydes, whereas imidazole-4(5)-carbaldehyde and the N_1-substituted imidazole-4- and imidazole-5-carbaldehydes are stable.

EXPERIMENTAL

Melting points were taken in capillary tubes on an electrothermal apparatus and are uncorrected. The proton magnetic resonance spectra were recorded on a Jeol JNH-MH-60 spectrometer. Infrared spectra were recorded on a Perkin Elmer 257 grating spectrophotometer. A Hewlett-Packard 5730 instrument (with 2 m column packed with Porapak Q) was used for gas chromatographic analyses. Analyses were performed with a Perkin Elmer Model 240 CHN analyzer.

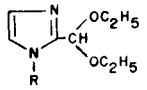
Ethyl Acetals **2a-f**.

General Procedure.

A solution of 5 g. (0.023 moles) of aldehyde and 2.1 ml. (0.023 moles) of 37% hydrochloric acid in 150 ml. of anhydrous ethanol was refluxed for several hours. The solution was then neutralized with an aqueous saturated solution of sodium carbonate and evaporated *in vacuo*; the residue was poured into water and extracted several times with ethyl acetate. Evaporation of

Table I

Preparation of Diethylacetals from Aldehydes and Hydrochloric Acid in the Mole Ratio 1:1



Compound	R	Reaction Time (Hours)	M.p. °C and Recrystallization Solvent (a)	n_D^{21}	Yield % (b)	Molecular Formula	Analysis % Calcd./Found C	H	N
2a	H	1	115-116 (c) (M)		55				
2b	CH_3	4	oil	1.4770 (d)	48				
2c	C_6H_5	2	oil	1.5288	51	$C_{14}H_{18}N_2O_2$	68.27 68.03	7.37 7.21	11.37 11.04
2d	*o*-$NO_2C_6H_4$	2	65-66 (H)		53	$C_{14}H_{17}N_3O_4$	57.72 57.45	5.88 5.63	14.43 14.18
2e	*m*-$NO_2C_6H_4$	2	39-40 (H)		45	$C_{14}H_{17}N_3O_4$	57.72 57.81	5.88 6.02	14.43 14.25
2f	*p*-$NO_2C_6H_4$	2	76-77 (B)		46	$C_{14}H_{17}N_3O_4$	57.72 57.51	5.88 6.13	14.43 14.51

(a) M = methylene chloride, H = *n*-hexane, B = benzene. (b) Yield after purification. (c) Lit. (4) m.p. 116. (d) Lit. value (4): 1.4705 at 25°.

Table II

Decarbonylation Reaction

Starting Compound	Solvent (a)	Reaction Time (Hours)	% Starting Compound (b)	% imidazole (b)	% diethylacetal (b)
1a	E	100 (c)	57	21	15
	E-H	100 (c)	16	25	
1b	E	100 (c)	65	27	11
	E-H	100 (c)	36	21	
1c	E	26	traces	60	18
	E-H	10		36	
1d	E	100	traces	65	21
	E-H	10		38	
1e	E	12	traces	71	23
	E-H	4		42	
1f	E	10	traces	78	25
	E-H	3.5		39	

(a) E = ethanol, E-H = ethanol-hydrochloric acid (mole ratio acid/aldehyde 0.1:1). (b) Yield after purification. (c) The reaction was stopped after 100 hours.

the solvent gave a residue which was chromatographed on a silica gel column with ethyl acetate as eluent. Evaporation of the first fraction of eluate gave the acetal. Yields and analytical data are given in Table I.

Decarbonylation Reaction, Identification of Products.

a) In Ethanol.

A solution of 0.01 mole of aldehyde in 100 ml. of anhydrous ethanol was refluxed for several hours (see Table II). The residue obtained by evaporation of the solvent chromatographed on silica gel, gave the respective imidazole which was identified by comparison with authentic samples (5,6).

Ethyl formate was identified by gas chromatographic analysis. The formation of ethyl formate was confirmed by its transformation in formic acid which was identified through its derivative benzimidazole. A typical experiment will be described. A solution of **1** (0.01 mole) in 150 ml. of ethanol was refluxed for 10 hours and then made basic (*p*H 12) by 2*N* sodium hydroxide. The mixture was steam distilled to remove volatile non-acidic materials. The residue was acidified to *p*H 2 with sulfuric acid and distilled. The distillate was made basic with 2*N* sodium hydroxide and evaporated to dryness. The method of Phillips was used to convert the sodium formate residue into benzimidazole, m.p. 170-171°, no depression in m.p. with an authentic sample (3).

b) In Ethanol with Hydrochloric Acid in the Mole Ratio (Acid/Aldehyde) 0.1:1.

A solution of 10 mmoles of aldehyde and 1 mmole of hydrochloric acid in 150 ml. of anhydrous ethanol was refluxed for several hours (Table II). After cooling, the reaction mixture was neutralized with 2*N* sodium hydroxide and evaporated *in vacuo*; the residue obtained was chromatographed on silica gel with ethyl acetate as eluent. Evaporation of the first fraction gave unreacted aldehyde; evaporation of the second and third fractions gave diethyl acetal **2a-f**, respectively, and imidazole **3**, which was identified by comparison with an authentic sample.

1,3-Dimethyl-2-formylimidazolium Iodide (**4**).

To 0.01 moles of **1b** in 100 ml. of acetone, 1.25 ml. (0.02 moles) of methyl iodide were added. After 5 days at room temperature, the quaternary salt, which separated as crystals, was filtered and washed several times with acetone; m.p. 270-271° dec.; ir (nujol): 1690 (s) cm^{-1}; ^1H nmr (deuteriomethanol): 4.00 (6H, s), 6.15 (1H, s), 7.60 (2H, s).

Anal. Calcd. for $C_6H_9IN_2$: C, 30.53; H, 3.84; N, 11.86. Found: C, 30.28; H, 4.07; N, 11.71.

1,3-Dimethylimidazolium Iodide (**5**).

A solution of 1 g. of **4** in 20 ml. of anhydrous ethanol was refluxed for 1 hour. Evaporation of the solvent *in vacuo* gave an oily residue which was recrystallized from ethyl acetate; m.p. 84-86° lit. (7) 86.5-88°.

REFERENCES AND NOTES

(1) R. Olofson, J. M. Landesberg, K. N. Houk and J. S. Michelman, *J. Am. Chem. Soc.*, **88**, 4265 (1966).

(2) J. L. Wong and J. H. Keck, Jr., *J. Org. Chem.*, **39**, 2398 (1974).

(3) M. A. Phillips, *J. Chem. Soc.*, 2393 (1928).

(4) P. E. Iversen and H. Lund, *Acta Chem. Scand.*, **20**, 2649 (1966).

(5) A. Wohl and W. Marckwald, *Chem. Ber.*, **22**, 568 (1889); W. Marckwald, *ibid.*, **25**, 2354 (1892).

(6) A. L. Johnson, J. C. Kauer, D. C. Sharma and R. I. Dorfman, *J. Med. Chem.*, **12**, 1024 (1969).

(7) C. G. Overberger, J. C. Salamone and S. Yaroslavsky, *J. Org. Chem.*, **30**, 3580 (1965).