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SYNTHESIS OF 1-ALKYLIMIDAZOLES

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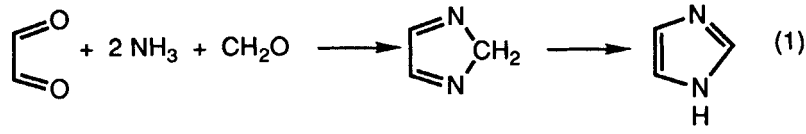
ABSTRACT: A mechanistic investigation of the synthesis of imidazole and 1-alkylimidazoles has led to an improved synthesis starting from glyoxal, formaldehyde and alkylammonium chlorides.

The synthesis of imidazole was historically carried out by means of the reaction shown in equation 1, though this was not the highest yield method and the equation, as written, conveys little information about the course of the reaction.



(1)

The low yields of reaction 1 (typically less than 15%) discourage its wide usage, though researchers continue to be tempted by the low cost of reagents and apparent simplicity of the process.[1-5] Analysis of reaction 1 leads to the conclusion that imidazole should be the main product of the reaction of glyoxal with aldehyde and

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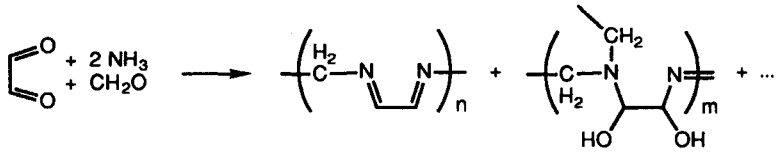
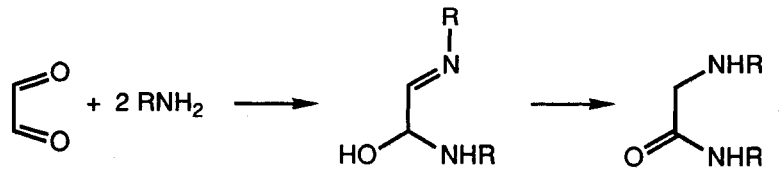
ammonia; the aromaticity of imidazole and the cyclic structure of the intermediates should promote imidazole formation. We have carried out a comparative analysis of side reactions in an effort to define optimum conditions for the reaction.

The observed high viscosity of the products from equation 1 could be due to the formation of linear and branched Schiff-bases according to equation 2:



(2)

A 10-20% increase of the yield of imidazole upon heating the products of reaction 1 in the presence of Pd and molecular hydrogen under pressure is evidence of reaction 2.[6] Under these conditions, methylene and azomethylene groups are hydrogenated and imidazolynes are dehydrogenating giving imidazoles.[7] Both processes convert the linear and branched products (reaction 2) to the cyclic, aromatic imidazole. Another side reaction in imidazole synthesis in basic media is the intermolecular Cannizzaro rearrangement of the Schiff-bases (equation 3):[8]



(3)

Under these conditions, the glyoxal also undergoes undesirable side reactions.[1,2]

We decided that the most probable method for improving the yield of imidazole would be to carry out the reaction between ammonia and the aldehydes in the presence of acid. The acid medium would suppress the rearrangement of

reaction 3 and the hydrolysis of azomethylenes back to starting amine and aldehyde species. The stability of glyoxal is also increased under acidic conditions.[1] Hydrolysis not only impedes the synthesis of linear azomethylenes but also of imidazole which has a cyclic Schiff-base intermediate. By adjusting the conditions such that the rate of the hydrolysis of linear products is equal to the rate of condensation, we can expect accumulation of imidazole due to its stability toward acid hydrolysis.

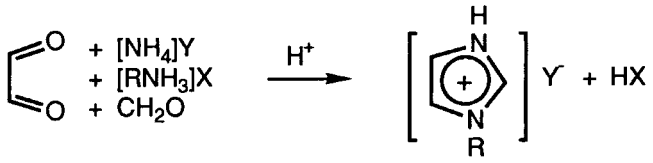
The first investigation of the influence of the reaction medium acidity on reaction 1 was by Davidson who synthesized 4,5-diarylimidazoles in quantitative yield by replacing water with glacial acetic acid as solvent.[9] Unfortunately, these yields are obtained only in the case of diarylglyoxals. The yield of imidazole decreases to 50% if dialkylglyoxals are used.[10,11] In case of unsubstituted glyoxal, yields decrease substantially. We attribute these observations to the lower reactivity of substituted α-diketones relative to glyoxal, which makes the acidity of acetic acid sufficient to prevent most side reactions during the synthesis of 4,5-diarylimidazoles and to a lesser extent, 4,5-dialkylimidazoles.

Schulze[12] obtained imidazole and 4-methylimidazole in 69% yield by heating ammonium sulfate, glyoxal and formaldehyde in water. When we reproduced this synthesis, we observe a pH decrease from ~5 to ~1 during the course of the reaction. Because imidazole supports only a monocationic charge but the reaction under acidic conditions consumes two cations, imidazole formation liberates protons to the reaction medium and thus the pH changes. Reaction 3 causes the same change of pH for the similar reasons.

As the side reactions of the imidazole synthesis are suppressed in an acidic medium, it follows that the by-products are formed mainly during the first stages of the process when medium is not yet acidic enough. Initial acidification of the

reaction mixture should minimize formation of by-products and raise the yield of the imidazole. Experimental examination of this assumption showed direct dependence of the imidazole yield on the acidity of the medium. At initial pH = 0.5, the yield reached the value of 85%. Hence, a pH ≈ 1 should be close to optimum for imidazole synthesis. This observation explains the low yield of unsubstituted imidazole obtained by the Davidson[9] method.

Acidification of the reaction mixture also allows the synthesis of N-substituted imidazoles via one-step process from glyoxal:



(4)

In contrast to unsubstituted imidazole, pH = 2 is found to be optimum when employing the substituted ammonium compounds of reaction 4.

As in the synthesis of imidazole above, the HX acid is liberated during synthesis. Hence, the value of the dissociation constant of this acid should be taken into consideration because it influences the pH of the medium. Types of ammonium and alkylammonium salts are chosen so that accumulated HX does not change pH value from the optimum. Thus in the synthesis of N-unsubstituted imidazole, hydrochloric acid was used, and phosphoric acid was employed for the synthesis of N-alkylimidazole derivatives. The yield of N-alkylimidazoles by reaction 4 is about 50% of distilled material and purities of at least 95% can be realized after a single distillation (Table 1). It is clear that unsubstituted imidazole will be a by-product of reaction 4. Its quantity increases when the ammonium salt solution is added slowly into a well-stirred reaction mixture containing the other reagents.

N-substituted imidazoles are usually prepared by alkylation of 1H-imidazole with haloalkyls or activated esters in basic media.[13,14] Yields of N-alkylimidazole from normal haloalkyls are usually 30-40%, and they decrease dramatically for branched alkyls. Applying special methods, such as carrying out the reaction in liquid ammonia,[15] in a solution of polyethyleneglycol and ethanol,[16] in a THF or DMF solution in presence of NaH,[17,18] or in an autoclave under pressure,[19] the yield of N-alkylimidazole can be increased to 80%. Yields of N-alkylimidazoles with hindered alkyls improve very little under these conditions. For example, alkylation of imidazole to give N-*tert*-butylimidazole under a variety of conditions gave yields in the range of 5-12%.[20-22] Hence, synthesis of N-alkylimidazoles by alkylation can be estimated as appropriate only in case of *n*-alkyl derivatives. Moreover, relatively expensive reagents and procedures are needed to be applied to gain high yield of the alkylimidazole. The method reported in the present article is simpler and good to moderate yields are obtained even in the synthesis of imidazoles with hindered alkyl substitutes. As shown in Table 1, the yield changes only slightly in going from *n*-alkylimidazoles to *sec*-alkylimidazoles. Even in case of *tert*-alkylimidazole, the yield remains as high as 25%. Subsequent to this work, Arduengo reported the synthesis of imidazolium salts from α-dicarbonyls, aldehydes and monoalkylamines under acidic conditions.[23]

Experimental Section

Distilled water and reagent grade materials have been used without additional purification except the ethyl acetate which was distilled prior to use. ^{1}H NMR spectra were obtained on a Tesla BS-487 C spectrometer (80 Mhz) using TMS as internal standard. IR spectra were recorded using a Specord M-80 in CCl_4 solution. Spectroscopic parameters are presented in Table 2.

TABLE 1. Synthetic details of the imidazoles.

Compound	Yield	$T_{boil/mm\ Hg}$		η_d^{20}	Analysis		Formula	Calculated	
	%	Obs.	Lit.		C	H		C	H
1-Methyl imidazole	56	86/12	94/15 [21]	1.4960	58.7	7.1	$C_4H_6N_2$	58.50	7.37
1-Isopropyl imidazole	46	97/12	–	1.4811	65.6	9.3	$C_6H_{10}N_2$	65.41	9.15
1-Cyclohexyl imidazole	49	155/12	–	1.5153	72.2	9.1	$C_9H_{14}N_2$	71.95	9.39
1-*tert*-Butyl imidazole	25	105/12	70/0.8	1.4785	67.9	9.6	$C_7H_{12}N_2$	67.69	9.74
1-*n*-Butyl imidazole	55	114/12	120/20	1.4798	67.8	9.7	$C_7H_{12}N_2$	67.69	9.74

Imidazole. Glyoxal (0.1 mol, 16.2 mL of 30% aqueous solution), formaldehyde (0.1 mol, 15 mL of 20% aqueous solution) and ammonium chloride (0.2 mol, 11.1 g) were added to a 100 mL flask equipped with stirrer and reflux condenser. The reaction slurry was acidified with a few drops of concentrated hydrochloric acid until the pH = 0-1 and was kept at 95 °C for 60 min. The resulting dark brown mixture was chilled, treated with solid KOH and extracted with ethyl acetate seven times. The combined extract was evaporated in vacuum at 50 °C and then at 100 °C. The resulting slightly brown residue (5.8 g) is ≈95% pure imidazole (85% yield). The sublimed product had mp = 90 °C.

1-Alkylimidazoles. A 100 mL flask equipped with mechanical stirrer, dropping funnel and reflux condenser was loaded with glyoxal (0.1 mol, 11.5 mL of 40%

TABLE 2. Spectroscopic characterization of the imidazoles.

Compound	NMR Spectra		IR Spectrum
	Observed	Literature	
1-methyl imidazole	3.75 (3H, s, CH_3), 6.93 (1H, s, 5-H), 7.10 (1H, s, 4-H), 7.51 (1H, s, 2-H)	3.68 (s), 6.88 (s), 7.05 (s), 7.42 (s) [22]	904 (C=C), 1076, 1110, 1232, 1284 (CH_3), 1512 (C=N)
1-isopropyl imidazole	1.27 (6H, d, CH_3), 4.40 (1H, m, CH), 6.93 (1H, s, 5-H), 7.69 (1H, s, 2-H) 7.04 (1H, s, 4-H)	1.34 (d) 4.29 (m) 6.93 (s) 7.50 (s) 7.00 (s) [21]	908 (C=C), 1014, 1072, 1112, 1226, 1300, 1372 (CH_3), 1404, (CH_3), 1456, 1492 (C=N)
1-cyclohexyl imidazole	1.70 (10H, m, CH_2), 4.05 (1H, m, CH), 6.92 (1H, s, 5-H), 7.12 (1H, s, 4-H), 7.60 (1H, s, 2-H)		894, 908 (C=C), 992, 1076, 1112, 1230, 1274, 1448 (CH_2), 1492 (C=N)
1-*tert*-butyl imidazole	1.49 (9H, s, CH_3), 6.91 (1H, s, 5-H), 7.27 (1H, s, 4-H), 7.73 (1H, s, 2-H)	1.56 (s), 7.06 (s), 7.07 (s), 7.62 (s) [19]	906 (C=C), 1008, 1080, 1113, 1238, 1274, 1372 (CH_3), 1487 (C=N)
1-*n*-butyl imidazole	0.90 (9H, t, CH_3), 1.28 (2H, m(6) $C\underline{H}_2CH_3$), 1.71 (2H, m(5), $N\text{-}CH_2C\underline{H}_2$), 3.89 (2H, t, $N\text{-}CH_2$), 6.87 (1H, s, 5-H), 7.01 (1H, s, 4-H) 7.42 (1H, s, 2-H)		905.6 (C=C), 1030.4, 1076, 1110, 1228, 1278 (CH_2, CH_3), 1367 (CH_2, CH_3), 1387, 1458, 1542 (C=N)

aqueous solution), formaldehyde (0.1 mol, 15 mL of 20% aqueous solution) and alkylammonium salt (0.1 mol), which had been obtained by acidification of the appropriate alkylamine solution in 8-15 mL of water with phosphoric acid until the pH ≈ 2. The reaction mixture was warmed to 90-95 °C and a saturated aqueous solution of 0.1 mol ammonium chloride was added to the stirred reaction mixture over a period of 60-75 min. After an additional 10 min of stirring at 95 °C, the crimson reaction mixture was chilled, solid KOH was added and the mixture was extracted with ethyl acetate three times. The combined extract was evaporated and distilled in vacuum (see Table 1 and 2).

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