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GENERAL SYNTHESIS OF C SUBSTITUTED IMIDAZOLES

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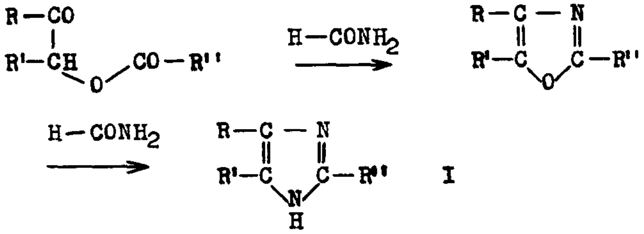
The esters of benzoin react with ammonia in acetic acid to give 2-alkyl 4,5-diphenyl oxazoles and variable amounts of the imidazoles resulting from those oxazoles (1).

Bredereck and coworkers (2) obtained oxazoles by brominating ketones in the presence of amides, and these oxazoles were transformed to imidazoles through reaction with ammonia (3).

This reaction has been extended to the synthesis of oxazoles and imidazoles by Marquez (4). Other syntheses of imidazoles have been reported (5). The present paper describes a general synthesis of C substituted imidazoles with high yields by heating formamide with esters of α-ketols. The general reaction is as follows:



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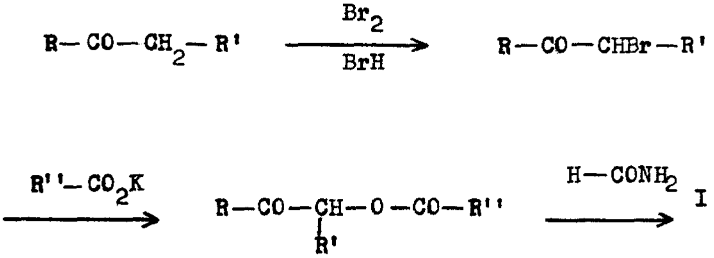
α-ketols are obtained through bromination of ketones followed by treatment with the potassium salt of the required acid.



$$R-CO-CH_2-R' \xrightarrow[BrH]{Br_2} R-CO-CHBr-R'$$

$$\xrightarrow{R''-CO_2K} R-CO-\underset{R'}{\underset{|}{CH}}-O-CO-R'' \xrightarrow{H-CONH_2} I$$

The reaction takes place through the corresponding oxazoles, as can be proved by heating the latter with formamide in the same conditions as for the α-ketol esters; they are converted quantitatively to imidazoles. See Table I.

These reactions can be illustrated with the following example:

0.6 Mole of $(NH_4)_2CO_3$ and 0.6 mole of formic acid were heated at 160º during 2 hours; 0.06 mole of the ester was added and heating was continued for 5 hours at 180-190º. After cooling and adding 60 cm3 of water, the solution was filtered and made alkaline with ammonia. The precipitate was filtered, after standing for 2-3 hours, and the imidazole was removed with hot water.

The resulting product was dried and purified. Imidazoles that were soluble in hot benzene crystallized by addition of ligroin. Others were crystallized from ethanol.

TABLE I

R	R'	R''	Yield %	M.P. °C (*)	M.P. °C bibl.			Calcd. %			Found %		
								N	C	H	N	C	H
C_6H_5	H	CH_3	75	157	152(4)	161(5)	$C_{10}H_{10}N_2$	17,72	75,95	6,32	17,80	76,0	6,23
C_6H_5	CH_3	CH_3	85	230	190(4)	227(5)	$C_{11}H_{12}N_2$	16,20	76,74	6,97	16,11	76,6	6,85
C_6H_5	C_2H_5	CH_3	80	139	134(4)	---	$C_{12}H_{14}N_2$	15,05	77,41	7,52	14,95	77,7	7,23
C_6H_5	H	C_2H_5	70	131	131(4)	133(5)	$C_{11}H_{11}N_2$	16,20	76,74	6,97	16,10	76,5	6,94
C_6H_5	CH_3	C_2H_5	90	150	178(4)	130(5)	$C_{12}H_{14}N_2$	15,05	77,41	7,52	15,00	77,5	7,30
C_6H_5	CH_3	H	65	187	187(2)	185(5)	$C_{10}H_{10}N_2$	17,72	75,95	6,32	17,55	75,9	6,27
C_6H_5	H	H	50	129	129(2)	133(5)	$C_9H_8N_2$	19,44	75,00	5,55	--	--	--

(*) All melting points were taken on a Fisher - Johns apparatus and are uncorrected.

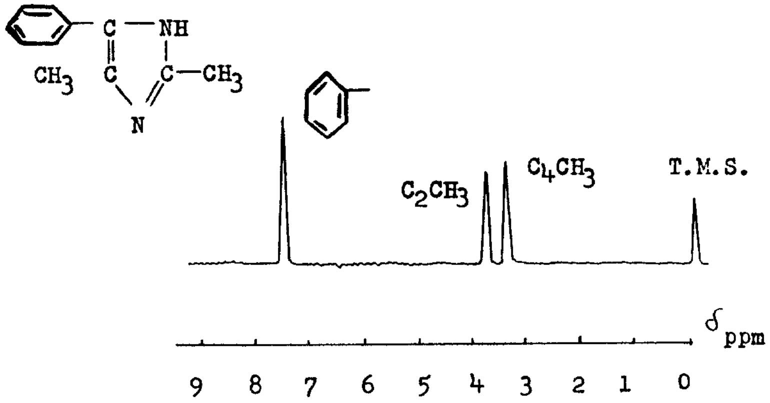
Localization of substituents in the imidazole ring by nuclear magnetic resonance

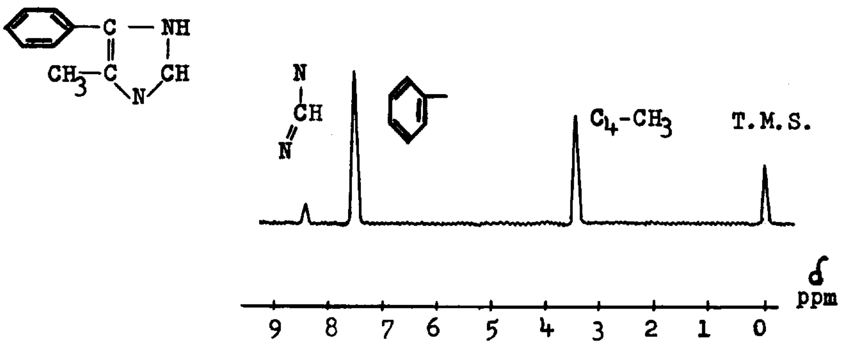
The evidence for the assigned structures was obtained through N.M.R. spectra studies.

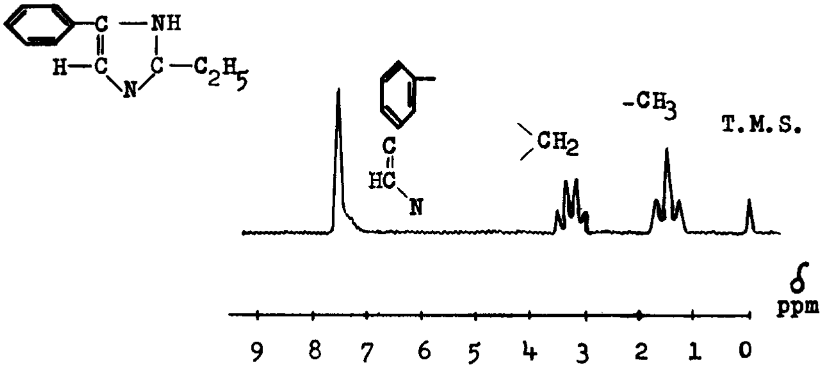
The spectra were recorded at 60 Mc/s and electronically integrated on a Varian A - 60 spectrometer using trifluor acetic acid as solvent. The chemical shifts are expressed as δ-values (ppm) downfield from internal tetramethylsilane ($\delta = 0$).

In all cases the $\text{C-}\underset{\substack{| \\ \text{C}}}{\text{N}}\text{H}$ group produces no signal. Whilst the $\text{N=}\underset{\substack{| \\ \text{N}}}{\text{C}_2}\text{H}$ group produces a signal at $\delta = 8,5$, the $\text{C=}\underset{\substack{| \\ \text{N}}}{\text{C}_4}\text{H}$ group shows at $\delta = 7,4$. The $-CH_3$ groups bound to C_2 and C_4 produce different signals; the $\text{N-}\underset{\substack{\| \\ \text{N}}}{\text{C}_2}\text{-CH}_3$ group shows at $\delta = 2,8$ and the $\text{C=}\underset{\substack{| \\ \text{N}}}{\text{C}_4}\text{-CH}_3$ at $\delta = 2,5$.

The results are illustrated with the following examples:







References

1. D.Davidson, M.Weiss and M.Jelling, Org.Chem., *2*,319(1937)
2. H.Bredereck, F.Effenberger, F.Marquez and K.Ockewitz, *Chem.Ber.*, *93*,2083 (1960)
3. H.Bredereck, R.Gompper and H.Wild, *Chem.Ber.*, *88*,1351 (1955)
4. F.Marquez, *An.Real Soc.Esp.Fis.y Quim.*, *57 B*,723 (1962)
5. Cons.Ed.Arnold Weissberger, *The Chemistry of Heterocyclic Compounds. Imidazole and Derivatives*, part I, page 33, Inters.Publish. 1953.