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A NEW SYNTHESIS OF UNSUBSTITUTED, 4(5),AND 4,5-SUBSTITUTED 1H-IMIDAZOLES.

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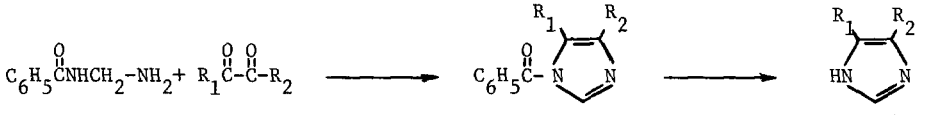
Abstract-Novel synthesis of the title compounds based on the reaction of N-(aminomethyl) benzamide with 1,2-dicarbonyl compounds is described.

During the course of another investigation it was required to examine the reaction of N-(aminomethyl) benzamide (1[1])with 1,2-dicarbonyl compounds (2a-h) in order to prepare acyl-imidazoles (3a-h) which are hydrolysed in mild acid or base to imidazoles (4a-h).

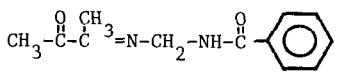


(1) (2) (3) (4)

a: R_1,R_2=H
b: R_1=H;R_2=Me
c: R_1,R_2=Me
d: R_1,R_2=n-pr
e: R_1,R_2=i-pr
f: R_1=Ph;R_2=H
g: R_1,R_2=Ph
h: R_1=benzyl,R_2=H

Whereas a variety of methods for the synthesis of imidazoles 4 can be found in the literature[2], no synthesis based on the application of this approach has yet been reported. Our exploration of this reaction for the preparation of imidazoles 4 is the subject of this report.

The cyclocondensation reactions of 1 with 2 could not be accomplished under several exploratory experiments as well as conditions which have been successful for the analogous reactions[3]. For example, when 2,3-butanedione (2c) was allowed to react with 1,either at room temperature or in refluxing solvents, starting materials were recovered unchanged. Furthermore, the same reaction in solvents containing a molar equivalent of hydrochloric acid[3] or sodium hydroxide at room temperature again afforded unchanged starting materials, whereas refluxing conditions resulted in the hydrolysis of 1 and polymerization of 2c[4]. After a series of experiments it was found that the reaction of 2c with 1 in acetic acid at 50°C gives the desired 4,5-dimethyl 1H-imidazole (4c[5]) in 42% yield together with the Schiff base 5 and compounds presumably arising from polymerization of 2c[4].



(5)

It is possible that the reaction involved the intermediacy of 3c which was hydrolysed during the reaction to 4c. The same reaction was repeated with other 1,2-dicarbonyl compounds (2a,b,d-h) and the results are summarized in table I. As expected, the yields of 1H-imidazoles decreased with increased steric bulk of 2. Consistent with these results the bulky acenaphthoquinone failed to give any detectable product upon reaction with 1.

Table I: Isolated yields of 1H-imidazoles.

	Substituent(s).	Crystallization	mp °C	yield %
a	—	C_6H_6	90(Lit[6],89-90)	60
b	4(5)-methyl	C_6H_6	59(Lit[7],56)	48
c	4,5 -dimethyl	EtOAc	121(Lit[5],117)	42
d	4,5 -dipropyl	EtOAc	67(Lit[5],66)	35
e	4,5 -diisopropyl	EtOAc	212(Lit[5],214)	27
f	4(5)-phenyl	EtOH	128(Lit[5],128)	34
g	4,5 -diphenyl	EtOH	230(Lit[5],231)	22
h	4(5)-benzyl	BuOAc	85(Lit[8],84-85)	39

General procedure for the reactions of 2 with 1.Synthesis of 4,5-dimethyl-1H-imidazole(4c). A solution of 1.5 gram (0.01mol) of 1[1] and 1ml (0.01mol) of 2c in 10ml of glacial acetic acid was stirred at 50°C for 4 hrs. The solution was then evaporated and the residue was treated with 10ml of water, neutralized with ammonia, and extracted with 3×10ml of ether. The combined organic exctracts were washed with saturated aqueous NaCl, dried (Na_2SO_4)and evaporated to dryness. The oily residue was then placed on a silica gel column and the column was eluted first with petroleum ether to remove the products arising from polymerization of 2c[4]. Next,the column was eluted with petroleum ether-benzene (5:5) to give 0.4 gram (42%) of 4c; mp 122°C (EtOAc) (Lit[5],117°C).Further elution with benzene afforded 0.34 gram (20%) of the Schiff base 5,mp 125°C (EtOH); Mass,m/e 218;IR (KBr) 3380,1800,1720,1600, 1450 Cm^{-1}. ^1H NMR(DMSO-d_6): δ2 (s,3H),2.1(s,3H),4.1(d,2H), 7.4(m,4H), 7.9(m,1H),8.8(t,1H). For the reaction of other 1,2-dicarbonyl compounds used in this work the evaporated organic extracts were not chromatographed but were crystallized from solvents indicated in table I to give the corresponding 1H-Imidazoles.

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