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A NOVEL MANNICH TYPE REACTION USING AMINALS IN ALKALINE MEDIUM

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Abstract: A one-step synthesis of 1,3-bis[2'-hydroxy-5'-substituted-benzyl]imidazolidines (3a-d) using a Mannich type reaction in basic media is described.

Mannich reactions[1] of phenols have generally been accomplished using equimolar amounts of formaldehyde and a primary or secondary amine, usually as the free base in ethanol solutions[2]. o-Alkylaminomethylphenols[3], N,N-bis (2-hydroxybenzyl)alkyl or arylamines[4,5] and 3,4-dihydro-3,6-di-substituted-2H-1,3-benzoxazines[6] are obtained depending upon the condensation conditions and the employed specific reactants. In spite of the accumulation of considerable knowledge on the possible course of the Mannich reaction[7], its mechanism, particulary in basic

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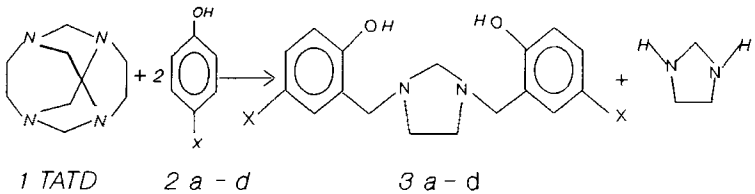
media, has been the subject of considerable discussion. Under basic conditions methylene-bis-amines[8], N-hydroxymethylamines or N-alkoxymethylamines[9] are assumed to be the aminomethymethylating agents. To our knowledge, only Cummings and Shelton[10] have proposed a plausible mechanism for the Mannich reaction in basic media. However, although this mechanism, based on kinetics studies, involves the formation of dimethylaminomethylols, it was not useful to solve the question of deciding among methylene-bis-amines, N-alkoxymethylamines or N-hydroxymethylamines as the intermediate in the Mannich reaction.



1 TATD 2 a - d 3 a - d

#	a	b	c	d
X	H	Cl	COOMe	Me

Scheme 1

In connection with our synthetic studies on heterocyclic compounds[11] we now describe a Mannich-type condensation in basic media of **p**-substituted phenols with ethylenediamine and formaldehyde. Our results prompted us the hypothesis that **aminals** might be the aminomethylating agents, since we have successfully reacted 1,3,6,8-

tetraazatricyclo[4.4.1.1.^{3,8}]dodecane **(TATD)** (1) with a number of **p**-substituted phenols (2a-d) by heating the reactants in aqueous dioxane solution. As shown in scheme 1 the obtained Mannich bases were 1,3-bis[2'-hydroxy-5'-substituted-benzyl]imidazolidines (3a-d). Evidence for their structures has been obtained by spectroscopical methods and mass spectral fragmentation. Our results provide the first examples of a Mannich reaction between cyclic aminals and phenols under mild basic conditions, and a simple one-step general synthesis of the above mentioned compounds from readily available materials.

EXPERIMENTAL.

Mass spectra were obtained using a Shimadsu 9020 mass spectrometer in low resolution (LR) electron impact (EI) mode. Melting points (uncorrected) were determined on a Fisher-Jons melting point apparatus. IR spectra were performed on a Perkin-Elmer FT-IR spectrophotometer. ^{1} NMR spectra were taken from $CDCl_3$ solutions at room temperature on a Varian XL-300 GS instrument. The ^{1}H chemical shifts are reported in ppm downfield from TMS. ^{13}C NMR spectra were run on the same instrument operating at 75.25 MHz and the respective chemicals shifts are reported as above. The 1,3,6,8-tetraazatricyclo[4.4.1.1.^{3,8}] dodecane **(TATD)** (1) was prepared as described[12] from

ethylenediamine and formaldehyde and was further purified by recrystallisation from benzene. All new compounds gave satisfactory elemental analysis. Standard reagents and solvents were used direct from bottles or purified by usually procedures as necessary.

General procedure for the condensation of TATD (1) with phenols.

The 1,3-bis[2'-hydroxy-5'-substituted-benzyl]imidazolidines (3a-d) were prepared as follows: To a solution of TATD (2.0 g ,12 mmol) in water (5 ml) was added the appropriate phenol (see table 1) dissolved in 1,4-dioxane (10 mL). The weakly basic reaction mixture was stirred for variable time at 40-42°C. The reaction was monitored by TLC. The crude product thus obtained was further purified by CC on silica gel eluting with benzene: ethyl acetate mixtures. For melting points and yields see table 1.

RESULTS AND DISCUSSION

Condensation of ethylenediamine with formaldehyde in alkaline medium yields the macrocyclic aminal whose structure was established by Rydell and Murray-Rust[13] as 1,3,6,8-tetraazatricyclo[4.4.1.1.^{3,8}]dodecane **(TATD)** (1). This

TABLE 1
Mannich reactions of phenolic compounds with TATD[a]

Phenol (mM)	pKa Phenol	pH Range	Comp. (mp °C)	Yield (%)
2a (24)	9.2	7.5-8.0	3a (125-126)	26.4
2b (24)	10.1	8.0-7.5	3b (80-82)	28.1
2c (24)	9.9	8.0-7.5	3c (103-105)	27.0
2d (24)	8.5	7.0-6.5	3d (148-150)	21.4

[a] Molar ratio phenol to TATD =2:1

compound, related to the well known hexamethylenetetramine (urotropine), reacts under mild alkaline conditions in absence of any aqueous base with two equivalents of the appropriate phenol (2a-d) to provide in a one-step reaction the 1,3-bis[2'-hydroxy-5'-substituted-benzyl]imidazolidines (3a-d) in yields varying 20-30%. The structures of compounds 3a-d were assigned on the basis of IR, ^{1}H and ^{13}C-NMR (see tables 2 and 3) and MS spectra. The phenolic hydroxyl groups in the compounds was detected with Folin-Ciocalteu reagent[14] and from the intense 3400-2500 cm^{-1} (broad, hydrogen-bonded OH) bands in IR spectra. In the ^{1}H-NMR spectra aromatic protons showed complex splitting patterns. Chemical shifts assignments were performed on the basis of coupling patterns and aromatic substituent effects. Both,

TABLE 2
^{1}H-NMR Chemical Shift Data of 3a-d

comp.	H-C2	Ph-CH_2	H-C4 H-C5	H-C3′	H-C4′	H-C6′
3a	3.53	3.85	2.97	6.78	7.13	6.96
3b	3.52	3.82	2.97	6.75	7.12	6.96
3c	3.55	3.89	2.97	6.76	7.17	6.97
3d	3.62	4.05	3.05	6.91	7.92	7.82

TABLE 3
^{13}C-NMR Chemical Shifts Data of 3a-3d.

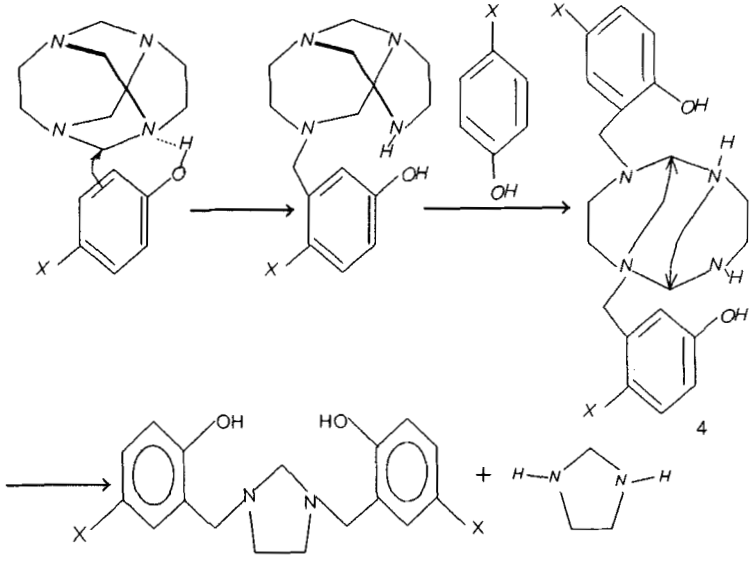
No	C2	C4-5	C1′	C2′	C3′	C4′	C5 ′	C6′	Benz
3a	74.5	51.5	122.6	156.1	117.7	128.0	123.9	129.0	57.7
3b	74.6	51.5	121.4	157.6	116.5	128.3	119.7	129.0	58.1
3c	74.6	51.5	121.3	157.5	116.2	128.3	119.2	129.1	58.2
3d	74.6	51.4	120.7	161.8	116.9	130.1	122.1	131.2	57.9

TABLE 4
Mass Spectra of Compounds 3a-d

Comp.	Mass spectrum m/z (rel.int.)
3a	284(M^+,14),283(28),177(26),107(100),77(30)
3b	352(M^+,32),354(M^++2,20),356(M^++4,2),351(20) 211(40),170(50),141(100),77(80),71(63)
3c	400(M^+,52),399(90),235(48),207(66),165(100)
3d	312(M^+,100),311(60),191(80),163(64),121(88)

methylene protons of the heterocyclic ring and benzylic protons were assigned by confronting their chemical shifts values with those calculated using the Shoolery additivity rule[15] and with the reported[16] data for similar substances. The assignement of ^{13}C-NMR spectra

was done by means of theoretical calculations of both proton decoupled and "off resonance" spectra. The mass spectra (see table 4) revealed that all compounds have the expected molecular weight. The fragmentation pattern was similar for all compounds. In view of these results results we proposed a plausible mechanism process outlined in Scheme 2. First, when phenol is added to TATD the initially formed hydrogen bond could undergo monoprotonation of any of the four nitrogen atoms. Althought the interactions of lone pairs in diamines is always repul-



Scheme 2

sive or antibonding this can be changed to a bonding interaction by protonation because the lone pairs become coplanar[17]. Introduction of a proton between nitrogens

leads to polarization of the adjacent methylene (aminalic) groups. In agreement with known electrophilic substitution to aromatic rings, the reaction involves the suscesive attack of two molecules of the phenol. The posible intermediate (4), not yet isolated, undergoes intramolecular condensation to gain stability.

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