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Communications

Condensation of Halophenols with Primary Amines and Formaldehyde in Aprotic Solvent

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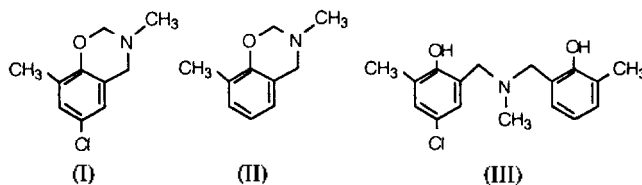
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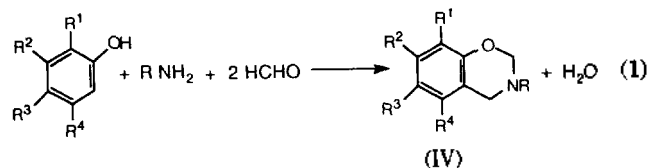
The Mannich reaction has been widely used^{1,2} to introduce substituted aminomethyl groups into a variety of organic compounds. Many examples of transaminomethylation with Mannich bases have been observed. This reaction, like other amine-carbonyl condensations, can be applied to biomimetic synthetic strategies.³ The Mannich reaction involving phenols, formaldehyde, and primary amines has been used as a convenient source for a variety of compounds. Quarternization of the Mannich base, followed by elimination, provides a method for introducing an exocyclic methylene next to a carbonyl group. The course of this generally facile condensation reaction is, however, greatly influenced by a number of variables.^{4,5} In particular, the size of the *ortho* substituent on the phenol has been shown to play an important role. The study of the aminoalkylation of *ortho*-cresol was of particular interest since this phenol contains both a free *ortho* and a free *para* position. Reaction of equimolar quantities of 6-chloro-3,4-dihydro-3,8-dimethyl-2H-1,3-benzoxazine(I) and *ortho*-cresol led to the isolation of single aminoalkylation product(III) in 60% yield.⁶ The same compound was obtained by an alternative aminoalkylation involving the condensation of 3,4-dihydro-3,8-dimethyl-2H-1,3-benzoxazine(II) with 4-chloro-2-methylphenol, which has a free *ortho* position but no free *para* position. This indicated that *o*-cresol was aminoalkylated in the *ortho* position.

The use of 4-*t*-butylphenol in place of 2,4-dimethylphenol, however resulted in high yield of a benzoxazine. In contrast, efforts to prepare benzoxazines from a phenol having an *o*-*t*-butyl substituent were unsuccessful, and only the bis(hydroxy)amine was obtained.⁴



In the view of the fact that the course of the condensation reaction can be shifted by steric factors in the striking manner, it could be of interest to determine the effect of varying the electrophilic character of substituents on the phenol. A comparison of *o*-cresol with *o*-halophenol in such studies appeared to have attractive possibilities for substantially eliminating steric factors⁵ since the chloro and a further variation in electronegative effects was visualized through use of di- as well as monohalophenols.

Herein, we report the preparation of new dihydro-1,3-benzoxazines with a number of phenols, and primary amines together with formaldehyde. The promised extension⁶ of the earlier work to include reactions with aromatic compounds other than phenols has not been reported. We have previously shown that chlorosilane derivatives may be used in '*in situ*' reaction with amines and aminol ethers to afford Mannich bases after reaction with electron rich aromatic compounds.⁹ We have used the dihydro-1,3-benzoxazines(IV) in reactions with 2-methylfuran using chlorosilane derivatives in a non-protic solvent. Benzoxazines were prepared by the reaction of *ortho*-cresol, *para*-cresol, di- and tri-chlorophenols with formaline or *para* formaldehyde and primary amines in dioxane, by the known Burke's procedure.⁴ Dihydro-1,3-benzoxazines were prepared, as described in equation 1 and the results are shown in Table 1.



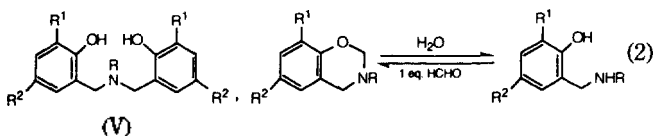
The results show that higher yield is obtained when the *para*-formaldehyde rather than formaline was used. Apparently due to the reverse reaction shown in equation 2, their yields increased in order of *meta*-, *para*-, *ortho*-cresols and

Table 1. Reaction of phenols with primary amines and formaldehyde in dioxane

R	R ¹	R ²	R ³	R ⁴	HCHO Type	Yield %
CH ₃ ^a	CH ₃	H	H	H	A	76
CH ₃ ^a	H	CH ₃	H	H	A	59
CH ₃ ^a	H	H	CH ₃	H	A	68
C ₂ H ₅	H	H	CH ₃	H	A	68
n-C ₃ H ₇	H	H	CH ₃	H	B	88
i-C ₄ H ₉	H	H	CH ₃	H	A	66
C ₆ H ₅ CH ₂	H	H	CH ₃	H	A	40
CH ₃	Cl	H	Cl	H	A	61
C ₂ H ₅	Cl	H	Cl	H	A	42
n-C ₃ H ₇	Cl	H	Cl	H	A	31
i-C ₄ H ₉	Cl	H	Cl	H	A	89
t-C ₄ H ₉	Cl	H	Cl	H	B	96
C ₆ H ₅ CH ₂	Cl	H	Cl	H	B	75
n-C ₃ H ₇	CH ₃	H	Cl	H	B	92
i-C ₄ H ₉	CH ₃	H	Cl	H	B	90
t-C ₄ H ₉	CH ₃	H	Cl	H	B	77
C ₆ H ₅ CH ₂	CH ₃	H	Cl	H	B	85
CH ₃	Cl	H	Cl	Cl	A	54
C ₂ H ₅	Cl	H	Cl	Cl	A	36
n-C ₃ H ₇	Cl	H	Cl	Cl	A	32
n-C ₄ H ₉	Cl	H	Cl	H	B	72

^a40% methylamine aqueous solution. A=Aqueous formaldehyde=30% formaline, B=paraformaldehyde

2,4-dichloro-, 2,4,5-trichloro-phenol for halophenols. We monitored dimerization(V) of benzoxazines and phenols by thermal initiation. Since dihydro-1,3-benzoxazines has been shown to undergo cleavage in hot ethanol,⁵ it was envisaged that treatment of such reagents with chlorosilanes would readily generate reactive Mannich intermediates.



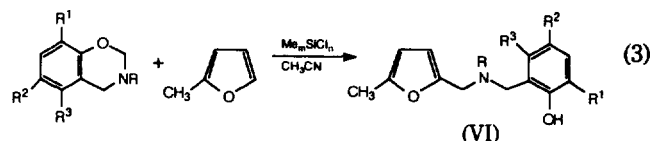
Although important recent modifications⁷ to the experimental methods used in Mannich reactions involve the use of preformed methylene-ammonium salts.⁸ The reaction was carried out with π -excessive heterocycle, 2-methylfuran and dihydro-1,3-benzoxazines using as an activator, chlorosilanes in aprotic solvent, acetonitrile.

Thus it can be seen that dihydro-1,3-benzoxazines will function readily as Mannich reagents under the conditions described as above, yielding Mannich bases with phenol substituents. Hence a series of reactions of dihydro-1,3-benzoxazines with electron-rich heterocycle, 2-methylfuran, was shown to yield new Mannich bases(VI) as described in equation 3 and Table 2.

The addition of trichloromethylsilane gave the better yield of Mannich bases. Among several chloromethylsilanes tested in this study, the addition of trichloromethylsilane gave the best results, although similar Lewis acids such as dichlorome-

Table 2. Reactions of 2-Methylfuran with Dihydro-1,3-Benzoxazines in the Presence of Silicon Reagents

R	R ¹	R ²	R ³	Silanes Me _m SiCl _n	Mannich base Yield %
CH ₃	CH ₃	H	H	m=1, n=3	80
CH ₃	CH ₃	H	H	m=2, n=2	74
CH ₃	CH ₃	H	H	m=3, n=1	65
n-C ₃ H ₇	Cl	Cl	H	m=1, n=3	74
n-C ₃ H ₇	Cl	Cl	H	m=2, n=2	76
n-C ₃ H ₇	Cl	Cl	H	m=3, n=1	82
n-C ₄ H ₉	Cl	Cl	H	m=2, n=2	82
C ₆ H ₅ CH ₂	Cl	Cl	H	m=2, n=2	94
n-C ₃ H ₇	Cl	Cl	Cl	m=1, n=3	80
n-C ₃ H ₇	Cl	Cl	Cl	m=2, n=2	64
n-C ₃ H ₇	Cl	Cl	Cl	m=3, n=1	61
n-C ₄ H ₉	Cl	Cl	Cl	m=3, n=1	60
C ₆ H ₅ CH ₂	Cl	Cl	Cl	m=2, n=2	92



thylsilane and chlorotrimethylsilane were also effective to some extent.

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