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MANNICH REACTIONS OF π-EXCESSIVE HETEROCYCLES USING BIS-(DIALKYLAMINO)METHANES AND ALKOXYDIALKYLAMINOMETHANES ACTIVATED WITH ACETYL CHLORIDE OR SULPHUR DIOXIDE

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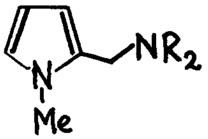
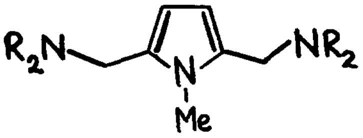
Summary: π-Excessive heterocycles react rapidly with bis(dialkylamino)methanes (aminals) and alkoxydialkylaminomethanes (aminol ethers) in acetonitrile to afford Mannich bases in good yields when activated by means of an acidic reagent such as acetyl chloride or sulphur dioxide: the principal compound studied was N-methylpyrrole.

It has been recognised for many years[1] that Mannich reactions may proceed via a number of mechanistic pathways. It has been suggested that the precise mechanism may depend on the nucleophilicity of the substrate and more particularly on the pH of the reaction medium. The concensus view is that N,N-dialkylmethyleneimonium salts are the electrophiles under acidic conditions while aminals may be involved at pH's >7 and aminol ethers have been suggested as possible intermediates in alcoholic media. It is becoming clear that a failure to isolate a Mannich base from an attempted reaction may be as a result of the reagent being of too low an electrophilicity. Thus, N-methylpyrrole is reported not to react with formaldehyde and amines when the pyrrole derivative is added to a mixture of the aldehyde and amine at 10° and the mixture is then allowed to warm to room temperature.[2] On the other hand the addition of a mixture of the aldehyde and amine hydrochloride to N-methylpyrrole results in the rapid formation of a Mannich base.[3] Similarly, although 2-methylfuran gave a Mannich base using the classical procedure, furan did not.[4]

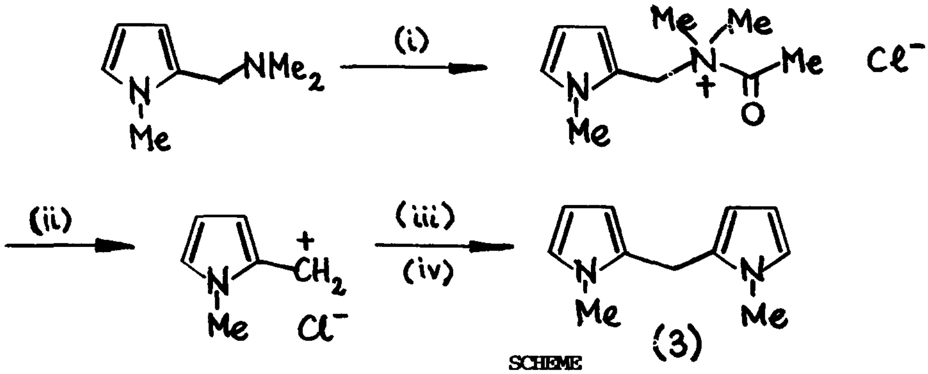
Our interest in Mannich reactions[5] carried out in aprotic solvents prompted a study of "one-pot" reactions of aminals and aminol ethers with nucleophilic aromatic compounds in the presence of non-protic acids. The generation of imonium salts using the reaction of acetyl chloride with an aminal[6] or trifluoroacetic anhydride with trimethylamine-N-oxide[7] suggested the use of acid chlorides or anhydrides. We now report our preliminary findings using acetyl chloride and sulphur dioxide. We have concentrated on N-methylpyrrole because the classical reaction only succeeds when using strongly acidic conditions.[3] N-Methylpyrrole does not afford a Mannich base with bis-(dimethylamino)methane in acetonitrile at room temperature. Our initial studies were carried out using N-methylpyrrole and aminals in acetonitrile to which acetyl chloride was then added at ca. 5°. The reaction mixtures were allowed to warm to room temperature and, after a suitable interval, the reaction mixtures were worked up and gave the yields shown in **TABLE 1**.

Although satisfactory yields of 2-dialkylaminomethyl-1-methylpyrroles (**1**) were obtained using dipiperidylmethane and dimorpholinylmethane (**TABLE 1**, entries 2 and 3) we were surprised that the yield of the product obtained using bis-(dimethylamino)methane was only 18%. Very poor yields were also obtained in reactions in which acetyl chloride was added to N-methylpyrrole and aminol ethers (**TABLE** 1, entries 4 and 5). We observed a similar variation in yields of the 2,5-disubstitution products (**2**) when the same aminals and acetyl chloride (two equivalents of each) were allowed to interact with N-methylpyrrole at room temperature (**TABLE 1**, entries 6, 8, and 9). We were surprised that no disubstitution product could be isolated from the reaction of N-methylpyrrole with bis-(dimethylamino)methane 2 mol and acetyl chloride 2 mol (**TABLE** 1, entry 6). An unsatisfacory yield of 2,5-bis(dimethylaminomethyl)-1-methylpyrrole was obtained even when the reaction was conducted at -20° (**TABLE** 1, entry 7).


(1)


(2)

The most likely explanation for the failure of the latter attempted reaction is that the monosubstitution product reacts further with acetyl chloride to generate an acyl ammonium salt which fragments to N,N-dimethylacetamide and a benzylic-type cation, which then captures a second molecule of N-methylpyrrole and affords N,N'-dimethyl-2,2'-dipyrrylmethane (3). An experiment was carried out in which acetyl chloride was added to a solution of 2-N,N-dimethylaminomethyl-N'-methylpyrrole in the presence of an excess of N-methylpyrrole from which we isolated the dipyrrylmethane (3)[8] in 75% yield [**Scheme**].



SCHEME

(i) CH_3COCl; (ii) - CH_3CONMe_2; (iii) N-Methylpyrrole; (iv) - HCl

Because of the relatively poor yields obtained in reactions carried out using acetyl chloride we have begun an investigation of alternative non-protic acidic reagents. We decided to investigate the use of sulphur dioxide because it is a relatively mild reagent and in addition the expected by-products would be relatively weak acids.

TABLE 1

Reactions of N-methylpyrrole with aminals and aminol ethers together with acetyl chloride

	Reagent	Acid	Time	Product (1 or 2)[†]	Yield (%)
1.	$(Me_2N)_2CH_2$/1mol	MeCOCl/1mol	2h	2-Me_2NCH_2-	18
2.	$[(CH_2)_5N]_2CH_2$/1mol	MeCOCl/1mol	2h	2-$(CH_2)_5NCH_2$-	41
3.	$[O(CH_2CH_2)_2N]_2CH_2$/1mol	MeCOCl/1mol	2h	2-$O(CH_2CH_2)_2NCH_2$-	54
4.	$(CH_2)_5NCH_2OEt$/1mol	MeCOCl/1mol	6h	2-$(CH_2)_5NCH_2$-	9
5.	$O(CH_2CH_2)_2NCH_2OEt$/1mol	MeCOCl/1mol	6h	2-$O(CH_2CH_2)_2NCH_2$-	18
6.	$(Me_2N)_2CH_2$/2mol	MeCOCl/2mol	5days	2,5-di-(Me_2NCH_2)-	0
7.	$(Me_2N)_2CH_2$/2mol	MeCOCl/2mol	6days[*]	2,5-di-(Me_2NCH_2)-	20
8.	$[(CH_2)_5N]_2CH_2$/2mol	MeCOCl/2mol	6days	2,5-di-$(CH_2)_5NCH_2$-	82
9.	$[O(CH_2CH_2)_2N]_2CH_2$/2mol	MeCOCl/2mol	5days	2,5-di-$O(CH_2CH_2)_2NCH_2$-	87

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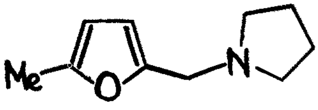
[*] Reagents mixed at -30° and kept at -20° for 6 days.

[†] All new compounds reported in this letter have been fully characterised by spectroscopic methods and elemental analysis or accurate mass measurement of the molecular ion.

When we determined the ^{13}C nmr spectrum of bis-(dimethylamino)methane in a mixture of sulphur dioxide and CD_3CN we observed no change in the spectrum over a period of about 24h. However, on addition of 1 mol equivalent of N-methylpyrrole the spectrum showed after about 1h that additional signals were present that could be assigned to 2-N,N-dimethylaminomethyl-1-methylpyrrole and N,N-dimethylaminosulphinate. When reactions were carried out on a preparative scale in the presence of an excess of sulphur dioxide we were able to isolate useful yields of mono-substituted derivatives from N-methylpyrrole and from a number of other heterocycles, including 2-methylfuran (**4**), indole (5), and N-methylindole (6) (**TABLE 2**).



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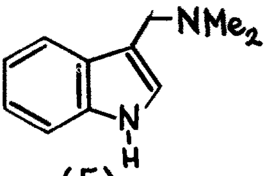

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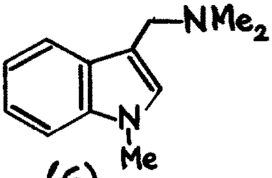


(6)

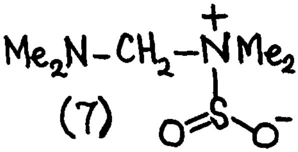
We failed to obtain a Mannich base from an attempted reaction between furan and ethoxypyrrolidinylmethane in the presence of sulphur dioxide. We did, however, isolate dipyrrolidinylmethane from this latter reaction and conclude that the intermediate, of type (**8**), formed between the aminol ether and sulphur dioxide, although not electrophilic enough to react with furan, does fragment to afford dipyrrolidinylmethane.

TABLE 2

Reactions of heterocycles with aminals and an aminol ether in the presence of sulphur dioxide

	Heterocycle	Reagent	Time	Product(s)	Yield (%)
1.	N-Me-pyrrole	$(Me_2N)_2CH_2$	2h	2-$(Me_2N)CH_2$-	40
2.	N-Me-pyrrole	$(Me_2N)_2CH_2$	4days	2-$(Me_2N)CH_2$-	58
3.	N-Me-pyrrole	$[(CH_2)_5N]_2CH_2$	4days	{ 2-$(CH_2)_5NCH_2$-	74
				{+2,5-di-$(CH_2)_5NCH_2$-	7
4.	N-Me-pyrrole	$[O(CH_2CH_2)_2N]CH_2$	3days	{ 2-$O(CH_2CH_2)_2NCH_2$-	49
				{+2,5-di-$O(CH_2CH_2)_2NCH_2$-	10
5.	N-Me-pyrrole	$[(CH_2)_4N]_2CH_2$	4days	2-$(CH_2)_4NCH_2$-	83
6.	indole	$(Me_2N)_2CH_2$	4days	3-$(Me_2N)CH_2$-	96
7.	N-Me-indole	$(Me_2N)_2CH_2$	2days	3-$(Me_2N)CH_2$-	80
8.	2-Me-furan	$[(CH_2)_4N]_2CH_2$	2days	2-$(CH_2)_4NCH_2$-,5-Me-	34
9.	2-Me-furan	$(CH_2)_4NCH_2OEt$	2days	2-$(CH_2)_4NCH_2$-,5-Me-	68

Although the mechanism, or mechanisms, involved in these reactions are not clearly established it is most likely that free imonium salts are not involved and that acyl ammonium salts are involved in the reactions using acetyl chloride. In certain other investigations where imonium salts are known to be involved they appear as precipitates on mixing the reagents. In the reactions using sulphur dioxide, dipolar species, for example (7) and (8), are the most likely reactive intermediates.



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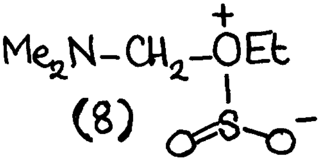

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