

MANNICH REACTIONS OF FURAN AND 2-METHYLFURAN USING PRE-FORMED IMONIUM SALTS

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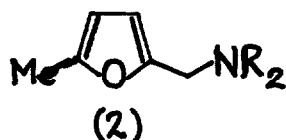
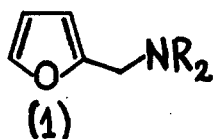
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Summary: Good yields of 2-dialkylaminomethylfurans are obtained when *N,N*-dialkylmethylenium chlorides are allowed to interact with furan in acetonitrile at room temperature; similar results are obtained using 2-methylfuran.

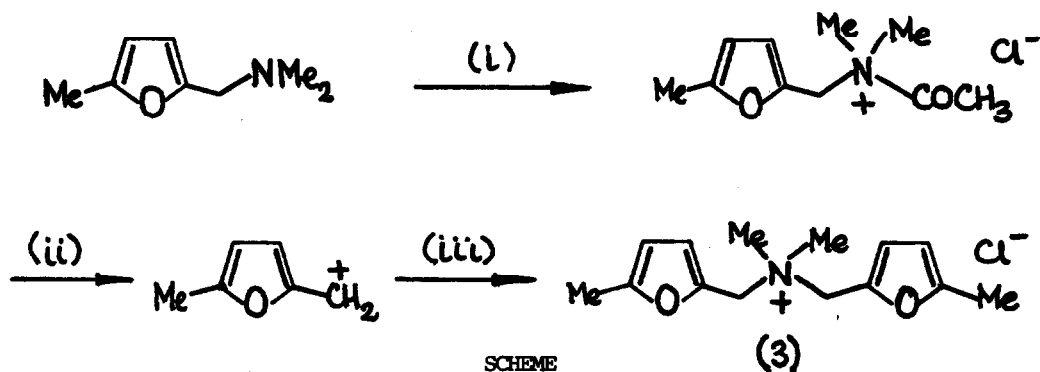
Mannich reactions¹ of 2-methylfuran have been reported to afford good yields of 2-*N,N*-dialkylaminomethyl-5-methylfuran using aqueous formaldehyde and secondary amines under various reaction conditions.² Thus 2-methylfuran, formaldehyde, and dimethylamine in aqueous acetic acid at 100° gives 2-*N,N*-dimethylaminomethyl-5-methylfuran in 69-76% yield.^{2c} Remarkably, it is reported^{2b} that the application of the Mannich reaction to furan yielded no liquid amine. It has been suggested^{3a} that this reaction can be carried out only with alkyl substituted furans, and it has been pointed out^{3b} that this reflects the marked activating effect of methyl substitution on electrophilic addition with elimination reactions.

Competition data for trifluoroacetylation using trifluoroacetic anhydride at 75° gave the relative rates: thiophene (1.0), furan (1.4×10^2), 2-methylfuran (1.2×10^5), and pyrrole (5.3×10^7).⁴ Similar values [thiophene (1.0), furan (3.0×10^3), and pyrrole (5×10^5)] were obtained for reactions using [$C_6H_7Fe(CO)_3$]⁺.⁵ That thiophene affords the expected Mannich product⁶ when it is heated in acetonitrile with *N,N*-dimethylmethylenium chloride suggests that Mannich reactions with furan should succeed.

We now report that good yields of the expected Mannich products can be isolated when furan and 2-methylfuran are allowed to interact with pre-formed *N,N*-dialkylmethylenium salts in acetonitrile at room temperature (TABLE). The majority of the *N,N*-dialkylmethylenium salts used in this study are easily prepared from the corresponding bis(dialkylamino)methane by reaction with acetyl chloride in ether.⁷ However, like previous workers,⁸ we have not been able to prepare a pure sample of bis(di-isopropylamino)methane. On the other hand we have prepared ethoxy-di-isopropylaminomethane in good yield from di-isopropylamine, ethanol, and paraformaldehyde. The aminol ether affords *N,N*-di-isopropylmethylenium chloride in good yield using the method reported recently by Duboudin and her co-workers.⁹ We have not optimized the reaction conditions in the Mannich reactions that we now report. We have carried out some reactions for short times and the results suggest that some of the reaction times indicated in the TABLE could be reduced.



It has been our habit to extract the Mannich bases from aqueous solutions using dichloromethane. When solutions of the Mannich base (2, R = Me) were allowed to stand over magnesium sulphate for ca. 12h before isolation we isolated variable amounts of the quaternary salt (3). We presume that the salt (3) is formed by the displacement of dimethylamine from a salt. In separate experiments we showed that the salt (3) is formed when the free base (2, R = Me) is allowed to stand for several days in dichloromethane in the presence of magnesium sulphate and that it is also formed from a mixture of the free base (2, R = Me) and its hydrochloride. We have also prepared the salt (3) in 98% yield from 2-N,N-dimethylaminomethyl-5-methylfuran by reaction with acetyl chloride (0.5 mol) SCHEME. The free bases may be isolated more conveniently by extraction with ether.



Although ^1H [δ = 2.31, s., 6H; 3.28, s., 6H; 4.98, s., 4H; 6.05, d. (J = 3.3 Hz); and 6.83, d. (J = 3.3 Hz) ppm] and ^{13}C [δ = 13.5 (Me); 49.3 (Me); 59.4 (CH_2); 107.4 (CH); 118.4 (CH); 140.7 (C); and 155.4 (C) ppm] nmr spectroscopy and elemental analysis indicated the structure of the salt (3) we were unable to observe the molecular ion by electron impact mass spectrometry. The mass spectrum obtained was almost identical to that observed for the compound (2, R = Me). We were only able to observe the molecular ion by using chemical ionisation (C.I.) or fast atom bombardment (F.A.B.) mass spectrometry.

The reasons for the failure to obtain the Mannich product in the previous study remain obscure. We have shown that the amine may be re-isolated after treatment with aqueous acid under conditions such that 2-hydroxymethylfuran is converted into laevulinic acid,¹⁰ as well as under the conditions previously reported^{2c} for the successful aminoalkylation of 2-methylfuran.

We were unable to isolate a Mannich base from an attempted reaction between furan and *N,N*-di-isopropylmethyleneimmonium chloride, the only basic product isolated was di-isopropylamine which we assume to result from the hydrolysis of the immonium salt.

Certain of the Mannich bases that we have obtained are considerably more volatile than we anticipated and it may be that earlier difficulties relate to this property. It is noteworthy that in certain of the reactions we have detected the presence of aminals as contaminants of the Mannich bases. The imonium salts used in the reactions were not contaminated by unreacted aminal and therefore the most obvious explanation for this observation is that nucleophilic displacement of secondary amine occurs from the Mannich base hydrochloride and that this then forms the aminal by interaction with unreacted imonium salt.

TABLE

Reactions of furan and 2-methylfuran with *N,N*-dialkylmethyleneimmonium chlorides

| heterocycle | imonium salt † | time | bp [‡] /mm | % yield of (1) or (2) * |
|-------------------|--|--------|---------------------|----------------------------|
| 1. furan | $\text{Me}_2\overset{\dagger}{\text{N}}=\text{CH}_2 \text{ Cl}^- \text{ (a)}$ | 5 days | 65/15 | 66 |
| 2. furan | $(\text{CH}_2)_5\overset{\dagger}{\text{N}}=\text{CH}_2 \text{ Cl}^- \text{ (a)}$ | 5 days | 67-8/1 | 74 |
| 3. furan | $(\text{CH}_2)_5\overset{\dagger}{\text{N}}=\text{CH}_2 \text{ Cl}^- \text{ (a)}$ | 1 day | 67-8/1 | 66 |
| 4. furan | $\text{O}(\text{CH}_2\text{CH}_2)_2\overset{\dagger}{\text{N}}=\text{CH}_2 \text{ Cl}^- \text{ (a)}$ | 5 days | 55-8/1 | 67 |
| 5. furan | $(\text{CH}_2)_4\overset{\dagger}{\text{N}}=\text{CH}_2 \text{ Cl}^- \text{ (a)}$ | 5 days | 67-8/3.5 | 66 |
| 6. furan | $(\text{CH}_2)_4\overset{\dagger}{\text{N}}=\text{CH}_2 \text{ Cl}^- \text{ (a)}$ | 1 h | 67-8/3.5 | 48 |
| 7. furan | $(\text{CH}_2)_4\overset{\dagger}{\text{N}}=\text{CH}_2 \text{ Cl}^- \text{ (a)}$ | 7 h | 67-8/3.5 | 56 |
| 8. 2-methylfuran | $\text{Me}_2\overset{\dagger}{\text{N}}=\text{CH}_2 \text{ Cl}^- \text{ (a)}$ | 3 days | 53-5/17 | 84 |
| 9. 2-methylfuran | $\text{Me}_2\overset{\dagger}{\text{N}}=\text{CH}_2 \text{ Cl}^- \text{ (a)}$ | 2 h | 53-5/17 | 78 |
| 10. 2-methylfuran | $(\text{CH}_2)_5\overset{\dagger}{\text{N}}=\text{CH}_2 \text{ Cl}^- \text{ (a)}$ | 3 days | 126-9/4 | 67 |
| 11. 2-methylfuran | $\text{O}(\text{CH}_2\text{CH}_2)_2\overset{\dagger}{\text{N}}=\text{CH}_2 \text{ Cl}^- \text{ (a)}$ | 3 days | 139-41/4.5 | 85 |
| 12. 2-methylfuran | $(\text{CH}_2)_4\overset{\dagger}{\text{N}}=\text{CH}_2 \text{ Cl}^- \text{ (a)}$ | 3 days | 102-4/4 | 94 |
| 13. 2-methylfuran | ${}^i\text{Pr}_2\overset{\dagger}{\text{N}}=\text{CH}_2 \text{ Cl}^- \text{ (b)}$ | 3 days | 94-6/4.5 | 65 |

† prepared from bis-(dialkylamino)methane by reaction with acetyl chloride (a)⁷
or from dialkylamino ethoxymethane by reaction with methyl trichlorosilane (b)⁹
‡ Kugelrohr distillation

* all new compounds have been fully characterised by spectroscopic methods and by means of elemental analysis or accurate mass measurement on the molecular ion.