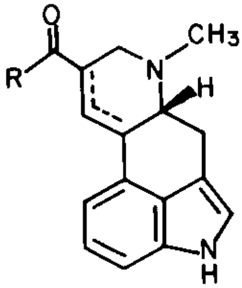
USE OF N,N-DIMETHYL(METHYLENE)AMMONIUM CHLORIDE IN THE FUNCTIONALIZATION OF INDOLES

Alan P. Kozikowski* and Hitoshi Ishida
Department of Chemistry, University of Pittsburgh
Pittsburgh, Pennsylvania 15260

The use of a preformed iminium salt has been found to provide superior yields in the generation of Mannich products from indoles.

During the course of our program geared toward the design of new strategies for the construction of various members of the ergot alkaloids,[1]

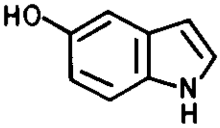


we required access to the Mannich products derived from several 4-substituted indoles. While the preparation of some related compounds had been reported by Plieninger through the use of the conventional reaction procedure which relies on the generation of the iminium ion species through equilibria involving dimethylamine, formaldehyde and acid,[2] these conditions led in the present instance to either erratic yields or to decomposition of the starting indoles due to the sensitive nature of the pendant functional groups.

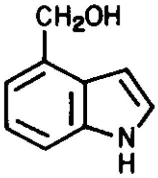
Recently, however, the use of preformed iminium salts, which function as highly reactive Mannich reagents, have proven to provide superior yields and controllable products in their reactions with enolates and/or silyl enol ethers of aldehydes, ketones and lactones.[3]

We were extremely pleased to find that the use of the preformed salt, N,N-dimethyl-(methylene)ammonium chloride (**II**), prepared by reaction of bis(N,N-dimethylamino)methane with acetyl chloride,[4] also provided an excellent solution to the present problem. All of the indoles depicted in the Table reacted rapidly and in extremely high yield to afford the desired Mannich products. Reaction of **II** with the indole derivative bearing an enol ether moiety at C-4 presented no complications and underwent reaction exclusively at the enamine-like site.

Only in two cases studied, in which the indole nucleus carried a hydroxy or hydromethyl group capable of interacting with the hydroscopic iminium salt, was reaction precluded. The starting indole IV was recovered unchanged on exposure to this salt, whereas, in contrast, the indole V underwent decomposition under these conditions.



IV



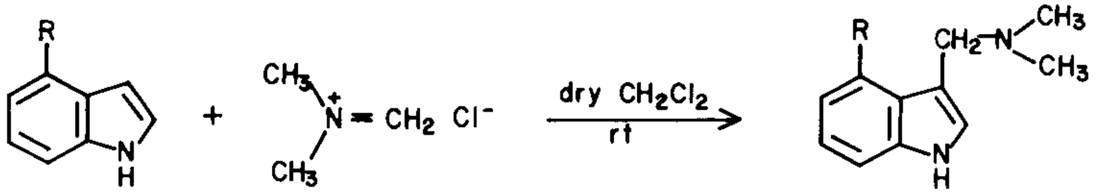
V

In summary, these results again emphasize the dramatic advantages of this approach to the Mannich reaction _vis-à-vis_ the classical method. Further transformations of these products to the ergots are presently underway and will be described in separate accounts.

General Procedure:

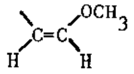
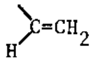
To 1 mmol of the indole and 1.3 mmol of dimethyl(methylene)ammonium chloride was added 1 ml of methylene chloride (dried by passage through neutral alumina). After stirring 10 min in a stoppered flask, the reaction mixture was quenched with 5 ml of water. After an additional 2-3 min, the aqueous phase was made basic with a 10% NaOH solution and the mixture extracted with ethyl acetate (3 x 10 ml). The combined organic extracts were washed with a saturated solution of sodium chloride and dried over $MgSO_4$. The crude isolated product obtained on rotary evaporation was purified by chromatography on activity grade III basic alumina with ethyl acetate as the eluent.

Acknowledgement. This work was supported by the National Institutes of Health through Grant HL 20579.



I II III

Table. Reaction of 4-Substituted Indoles with N,N-Dimethyl(methylene)ammonium Chloride

Entry	R	Isolated Yield (%)	m.p. °C	Spectral Data[5]
1	-H	98	—[6]	ir($CHCl_3$) 3500, 2950, 2800, 1220 cm^{-1}; nmr ($CDCl_3$) 8.79 (bd s, 1H), 7.79 (d of d, 1H, J = 3 and 7 Hz), 6.97-7.40 (m, 4H), 3.67 (s, 2H), 2.30 (s, 6H).
2	$-CH_2OAc$	98	123-124	ir($CHCl_3$) 3500, 3000, 2800, 1730, 1260-1200 cm^{-1}; nmr ($CDCl_3$) 8.00 (bd s, 1H), 6.86-7.33 (m, 4H), 4.96 (s, 2H), 3.77 (s, 2H), 2.23 (s, 6H), 2.07 (s, 3H).
3	-CHO	91	oil	ir($CHCl_3$) 3500, 3000, 2800, 1680, 1220 cm^{-1}; nmr ($CDCl_3$) 10.53 (s, 1H), 6.87-7.73 (m, 4H), 3.63 (s, 2H), 2.20 (s, 6H).
4	$-CO_2CH_3$	100	—[7]	ir($CHCl_3$) 3500, 3000, 2800, 1720, 1300, 1280, 1200 cm^{-1}; nmr ($CDCl_3$) 9.45 (bd s, 1H), 6.87-7.62 (m, 4H), 3.89 (s, 3H), 3.72 (s, 2H), 2.18 (s, 6H).
5	 $C(H)=C(H)OCH_3$	100	133-134	ir($CHCl_3$) 3500, 2960, 2800, 1640, 1280, 1220, 1020 cm^{-1}; nmr ($CDCl_3$) 8.00 (bd s, 1H), 7.63 (t, 1H, J = 4 Hz), 6.83-7.16 (m, 3H), 6.23 (ABq, 2H, J = 7 Hz, $\Delta\gamma_{AB}$ = 8.5), 3.70 (s, 3H), 3.53 (s, 2H), 2.23 (s, 6H).
6	 $C(H)=CH_2$	96	114-116	ir($CHCl_3$) 3500, 3050, 2800, 1605, 1220, 1010, 910 cm^{-1}; nmr ($CDCl_3$) 8.20 (bd s, 1H), 7.73 (d of d, 1H, J = 11 and 18 Hz), 6.93-7.36 (m, 4H), 5.70 (d of d, 1H, J = 2 and 18 Hz), 5.28 (d of d, 1H, J = 2 and 11 Hz), 3.60 (s, 2H), 2.19 (s, 6H).

References and Notes

1. A. P. Kozikowski and M. P. Kuniak, *J. Org. Chem.*, 1978, **43**, 2083.
2. H. Plieninger and W. Müller, *Chem. Ber.*, 1960, **93**, 2024; H. Plieninger, C. Wagner and H. Immel, *Liebigs Ann. Chem.*, 1971, **743**, 95.
3. The use of dimethyl(methylene)ammonium iodide was first described by Eschenmoser in the functionalization of the corrin chromophore, see J. Schrieber, H. Maag, N. Hashimoto and A. Eschenmoser, *Angew. Chem., Int. Ed. Engl.*, 1971, **10**, 330; S. Danishefsky, T. Kitahara, R. McKee and P. F. Schuda, *J. Am. Chem. Soc.*, 1976, **98**, 6715; N. L. Holy and Y. F. Wang, *J. Am. Chem. Soc.*, 1977, **99**, 944; N. Holy, R. Fowler, E. Burnett and R. Lorenz, *Tetrahedron*, 1979, **35**, 613.
4. G. Kinast and L.-F. Tietze, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 239; H. Böhme and K. Hartke, *Chem. Ber.*, 1960, **93**, 1305.
5. The ^{1}H NMR spectra were taken on a Varian T-60A instrument using tetramethylsilane as the internal standard. IR spectra were recorded on a Perkin-Elmer 700 spectrometer.
6. H. Kühn and O. Stein, *Chem. Ber.*, 1937, **70**, 567.
7. F. C. Uhle, C. M. McEwen, H. Schröter, C. Yuan and B. W. Baker, *J. Am. Chem. Soc.*, 1960, **82**, 1200.

Received, 15th October, 1979