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THE MANNICH REACTION—II

DERIVATIZATION OF ALDEHYDES AND KETONES USING DIMETHYL(METHYLENE)AMMONIUM SALTS

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Abstract—Aldehydes and ketones have been converted efficiently to their corresponding Mannich products by various dimethyl(methylene)ammonium salts under a range of reaction conditions. The several methods used to form these derivatives are compared. Excellent approaches to aldehyde derivatives involve treating the enol silyl ether of the carbonyl compound with methyllithium and then an iminium salt, or directly adding the iminium salt to the enol silyl ether. Ketones may be derivatized effectively by treatment with potassium hydride, followed by an iminium salt, or from the enol silyl ether by addition of the iminium reagent. Use of iminium reagents in the Mannich reaction is recommended because the yields are often good and the site of attachment on an unsymmetrical ketone is both predictable and controllable.

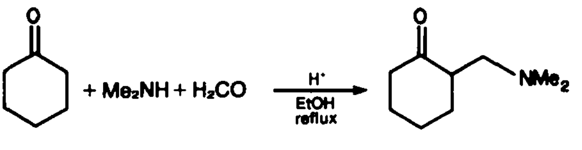
The Mannich reaction is a classic one of considerable importance in the formation of aminocarbonyl compounds either for direct medicinal applications[2] or as intermedicates in the synthesis of α,β-unsaturated products.[3] Though many conditions have been utilized, the most common approach to the reaction is to treat the carbonyl compound with the acidic mixture of dimethylamine and formaldehyde. This is generally refluxed for several days in ethanol, after which the Mannich derivative is typically isolated in 30–80% yield. It is postulated that the active aminoethylating agent is an iminium ion formed via equilibria (2).

Very recently another generic concept of effecting this transformation has emerged that differs significantly from the traditional approach. Iminium ions are used directly, rather than relying on equilibria to generate this species. This approach has three basic advantages: (1) since the concentration of iminium ion is higher than that generated via equilibria, reactions are faster; (2) lower temperatures are possible, a factor often important in the synthesis of complex molecules; and (3) aprotic conditions may be used.

Within the general approach of utilizing iminium ions there are several variations. The purpose of this work is to compare these and to comment on the use of iminium ions vs the classic conditions.

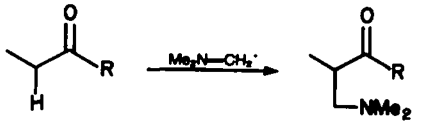
RESULTS AND DISCUSSION

The first use of iminium ions in Mannich aminomethylation may be attributed to Potier *et al.*,[4] though actually the main interest at the time was in the subsequent Polonovski reaction. Since the initial report, several variations have appeared, summarized by eqns (3)–(8).

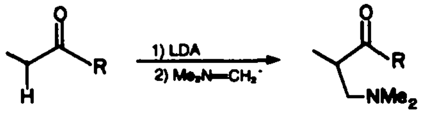


(1)

$$\mathrm{Me_2NH} \underset{}{\overset{\mathrm{H_2CO}}{\rightleftharpoons}} \mathrm{Me_2NCH_2OH} \overset{\mathrm{H^+}}{\rightleftharpoons} \mathrm{Me_2N{=}CH_2^+} + \mathrm{H_2O} \qquad (2)$$



(3)



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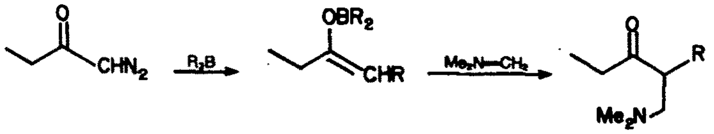
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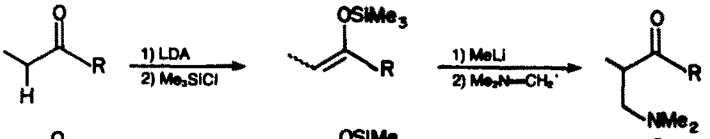
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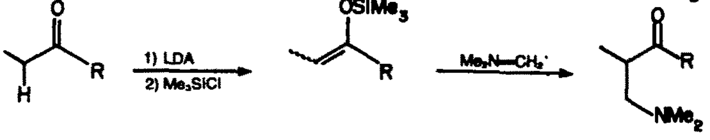
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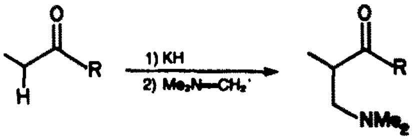

(8)

Treating the carbonyl compound directly with an iminium reagent (Eqn 3) has the obvious advantage of simplicity, and will work for many applications.[5] The drawbacks are: (1) no examples of aldehydes are reported; it is expected that competing aldol condensation would substantially reduce yields; (2) because of extended reaction times acid- or base-sensitive functions may not be stable; and (3) the factors controlling regiospecificity are not well known. For example, substitution of **1** is highly solvent-dependent: whereas compound **2** (95%) is formed in trifluoroacetic acid, compound **3** is the exclusive product in acetonitrile. Product **2** is the thermodynamic one and is formed more selectively than via the classic conditions.[6] Product **3** is favored kinetically, but it too is formed more selectively than would be anticipated by the usual enolate stabilities.[7] These observations underscore the importance of solvent in these phenomena. The results, however, seem to be more predictable than those obtained using traditional conditions, which have often led to contradictory claims concerning the site of attack.[8]

The approach illustrated by Eq (4) has the virtue of being a direct, "one-pot" reaction also.[9] Reaction times, compared to method 3 are much reduced. With ketones, however, both we and Poulter have found yields to be modest. Poulter has suggested that this may be due to the acidity of the Mannich products,[9] i.e. proton transfer from the Mannich product to the enolate of the starting ketone would reduce the yield, unless the reaction were performed over so long a time that the ketone itself underwent reaction. One consequence of this process is that disubstituted by-products might be formed, however, there are no reports of such products from iminium reagents. If such products are formed (they are, using classic conditions[10]), the yields are quite low. The solubility of the Mannich products makes it difficult to obtain high material balances and thus be conclusive about this point.

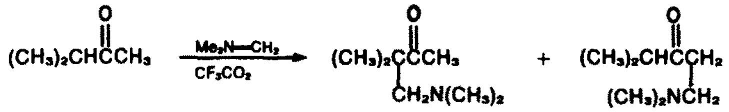
Another observation also implies that proton abstraction from the product is not the major factor in the modest yields when lithium diisopropylamide is used. Both we,[11] and others,[12] have observed that, within the limits of analysis, use of iminium ions leads to complete regiospecificity. If proton abstraction were important, loss of a substantial degree of regiospecificity would be expected.

Another explanation, for which we have found direct evidence, focuses upon the role of diisopropylamine. It is considered that the amine generated along with the enolate provides the source for an acidic hydrogen by combining with the iminium ion to form a protonated bisaminomethylene, which could protonate the enolate.

Bisaminomethylenes are well known to be intermediates under classic Mannich conditions.[13] We have obtained direct support for this interpretation from experiments in which the enolate was generated via and in the presence of disopropylamine. As the concentration of the amine increased, the Mannich yield diminished.

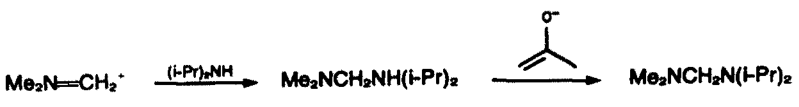
It is possible to avoid the presence of an amine by first preparing either enol borinates[12] (Eqn 5) or silylates[11] (Eqns 6 and 7). The former method is limited by having to start from a diazoketone. Silyl derivatives, on the other hand, may be prepared in high yield from a variety of aldehydes or ketones.[14]

Once the enol silyl ethers are obtained two alternatives are available. (1) The enol silyl ether may be treated with methyllithium and then the iminium reagent; cleavage of the enol silyl appears to be rate determining.

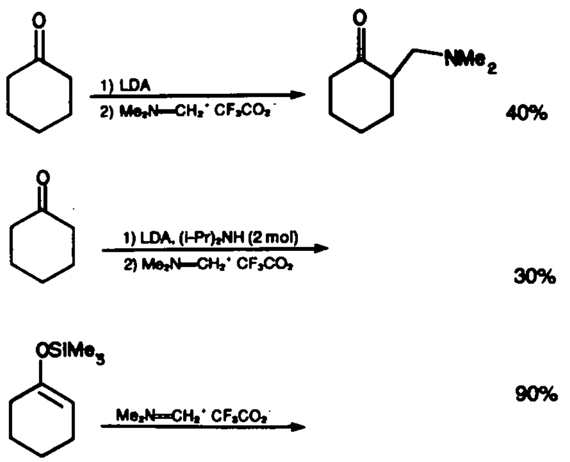


$$(CH_3)_2CH\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow[CF_3CO_2]{Me_2N{=}CH_2} (CH_3)_2\underset{CH_2N(CH_3)_2}{C}\overset{O}{\overset{\|}{C}}CH_3 + (CH_3)_2CH\overset{O}{\overset{\|}{C}}\underset{(CH_3)_2NCH_2}{C}H_2$$

1 **2** **3**



$$Me_2N{=}CH_2^+ \xrightarrow{(i\text{-}Pr)_2NH} Me_2NCH_2NH(i\text{-}Pr)_2 \longrightarrow Me_2NCH_2N(i\text{-}Pr)_2$$

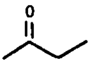
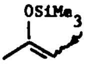
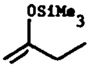
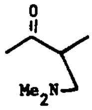
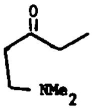
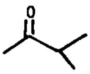
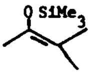
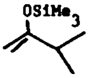
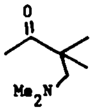
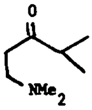
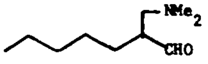
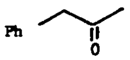
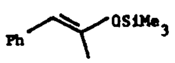
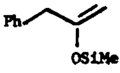
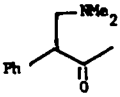
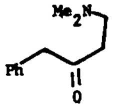


Reactions are performed at low temperature and are regiospecific, and the yields are fair (Table 1). The spectra give some evidence for side-products (formed in quite low yield and not isolated). (2) Alternatively, methyllithium, which could have a deleterious effect on several functional groups, may be avoided.[15] Mannich derivatives are formed by simply combining the enol silyl ether and the iminium salt at room temperature, with reaction times of a few minutes to a few hours (Table 2). It is important to follow the reactions closely (TLC or NMR) because if excessive times are permitted, lower yields result.

In the methods described thus far, several choices must be made. One concerns which iminium counterion to use. Table 2 indicates results with I^-, Cl^- and $CF_3CO_2^-$ counterions. Reactions were performed for short times to permit rate differences to appear. In dry DMF, in which all three reagents are highly soluble, the product yields are virtually identical. In dichloromethane only the trifluoroacetate is completely soluble; yield differences likely reflect reagent solubility because reactions over longer periods produced equivalent yields. Ether is a poor solvent choice, presumably because of the insolubility of the halide salts. Because of the convenience of product isolation, methylenechloride is easily the solvent of choice.

The choice of which iminium reagent is most convenient can be narrowed to two: the trifluoroacetate and the iodide. The trifluoroacetate can be prepared in a few hours from anhydrous trimethylamine oxide and also (in lower yield) from the dihydrate by adding trifluoroacetic anhydride to a solution of the oxide in methylene chloride and then heating.[5] The trifluoroacetate, however, does have one drawback: it must be distilled to

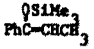
Table 1. Aminoethylation by treatment with methyllithium, then adding dimethyl(methylene)ammonium trifluoroacetate

Carbonyl Compound		Enol Silyl Ether[a]		Mannich Product[b]		Yield
						
	A[c]	81	19	80	20	50
	B[d]	48	52	48	52	53
						
	A	61	39	61	39	61
	B	20	80	20	80	65
						48
						
	A	100	0	100	0	70
	B	50	50	50	50	65

[a] Isomeric distribution determined by GLC. [b] Isomeric distribution determined by ^1H NMR, accurate to ±5%.

[c] Procedure A, ref 14. [d] Procedure B, ref 14.

Table 2. Treatment of enol silyl ethers with various dimethyl (methylene ammonium salts)

Entry	Enol Silyl Ether (mmol)	X^-	mmol	Time (min)	Solvent	Products (%)
1	 $PhC(OSiMe_3){=}CHCH_3$ (1.03)	$CF_3CO_2^-$	2.00	30	CH_2Cl_2	 $PhC(=O)CH(CH_3)CH_2NMe_2$ (75)
2	"	I^-	2.00	30	CH_2Cl_2	" (65)
3	"	Cl^-	2.03	30	CH_2Cl_2	" (43)
4	"	$CF_3CO_2^-$	2.00	8	DMF	" (60)
5	"	I^-	2.02	8	DMF	" (55)
6	"	Cl^-	2.06	8	DMF	" (41)
7	"	$CF_3CO_2^-$	2.02	50	Et_2O	" (55)
8	"	I^-	1.98	50	Et_2O	" (0)
9	"	Cl^-	2.03	50	Et_2O	" (0)

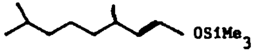
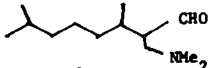
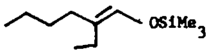
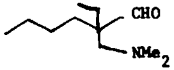
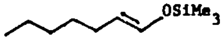
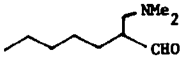
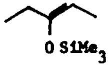
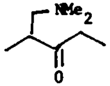
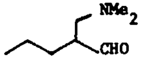
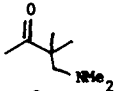
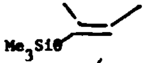
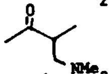
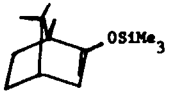
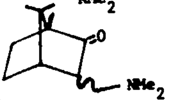
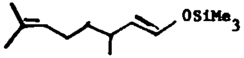
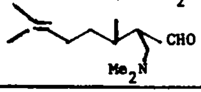
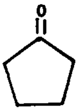
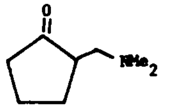
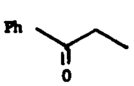
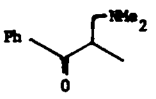
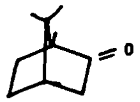
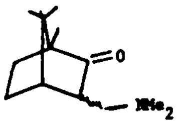
10		(2.06)	$CF_3CO_2^-$	4.3	50	CH_2Cl_2		(55)
11		(2.01)	I^-	4.1	480	CH_2Cl_2		(40)
12		(3.50)	$CF_3CO_2^-$	5.9	60	DMF Et_3N		(70)
13		(1.22)	$CF_3CO_2^-$	2.4	10	CH_2Cl_2		(60)
14		(4.01)	$CF_3CO_2^-$	4.7	25	CH_2Cl_2		(60)
15		(8.00)	$CF_3CO_2^-$	8.2	60	CH_2Cl_2		(80)
16		(1.98)	$CF_3CO_2^-$	4.0	15	CH_2Cl_2		(80)
17		(2.01)	I^-	4.0	2000	CH_2Cl_2		(40)
18		(1.99)	I^-	4.1	80	CH_2Cl_2		(85)

Table 3. Aminomethylation of ketones using potassium hydride

Ketone	Mannich Product	Yield (%)
		60
		75
		70

obtain good yields of Mannich products; this presumably removes traces of trifluoroacetic acid. It is advisable to check the iminium product by NMR before it is distilled to be sure that the trimethylamine oxide is totally converted. If clearly detectable amounts of the oxide are present the yield of the distilled iminium reagent is substantially reduced. The reagent must then be distilled at or below 0.05 mm; at this pressure the reagent will boil around 120–140° and the yield is 75–90%. If the temperature of the vapors reaches 170°, decomposition ensues. The distilled reagent has been stored in a refrigerator under nitrogen for long periods without decomposition.

The iodide is conveniently prepared by the Eschenmoser approach.[16] Its only drawbacks are that (1) a long reaction time is necessary to prepare the intermedicate ammonium iodide and (2) the reagent is a solid and cannot be transferred by syringe. The salt is reasonably hydroscopic and it is advisable to transfer samples in a dry atmosphere; lower yields of Mannich products do result if the reagent is contaminated with moisture. The chloride is even less convenient because it is highly hydroscopic. A potential problem with enol silyl ethers containing esters, ethers, alcohols, of ketals is that these functions are known to react with trimethylsilyl iodide.[17]

Finally, the method reported by Poulter[9] (Eqn 8) employing potassium hydride works very well for ketones and results in high yields (Table 3). It is a one pot procedure and appears to be the best method, where applicable. In unsymmetrical ketones, the thermodynamic product is favored; thus, this method is unsuitable if the kinetic product is desired. This approach presumably will not work for aldehydes because of the competing aldol condensation.

Since the use of iminium reagents has been investigated in several laboratories with consistent results, this approach to the Mannich reaction is demonstrated and reliable. Because of distinct advantages compared to the classical approach, the use of iminium reagents may replace the traditional method. But before this possibility may be evaluated, additional examples, expecially involving the synthesis of complex molecules, will be necessary.

EXPERIMENTAL

M. ps (taken on a Fisher-Johns block) and b. ps are uncorrected. IR spectra were obtained using a Perkin-Elmer 710 instrument. NMR spectra were recorded on a Varian A-60A instrument with TMS as an internal standard.

Procedure A (*potassium hydride*). To a stirred slurry of KH (10% excess over ketone) in 5–10 ml of dry THF was added at 0°, a soln of the ketone in 5 ml THF. After 10 min the contents of the flask were transferred via syringe to a cooled addition funnel (−78°) and slowly added to a rapidly stirred slurry of dimethyl(methylene)ammonium iodide (100% excess) in 10 ml of dry THF at −78°. After the addition was complete, the contents of the flask were permitted to warm to room temp. (30 m) and stirring was continued for 30 min. Sat. NaCl aq (5–10 ml) was added, along with sufficient water to dissolve the salts. The layers were separated, and the THF was removed at reduced pressure. The pH of the aqueous layer was adjusted to 10 and extracted four times with pentane. The extracts combined with the THF evaporation residue and cooled to 5° before extracting with *cold* 5N HCl. The aqueous layer was washed twice with cold pentane before addition of cold 10N NaOH (just enough to make the solution basic). The soln was extracted four times with pentane and the combined extracts were dried over Na_2SO_4. Removal of the solvent and analysis by IR and NMR gave results consistent with the Mannich derivatives.

Procedure B (*silyl enol ether*). Silyl enol ethers, prepared according to the method of House,[14] and dissolved in 5–10 ml of solvent at room temp. were treated with a 100% excess of the Me_2NCH_2 salt and stirred for the times indicated in Table 2. Analysis by NMR indicated product yields. In some cases the products were isolated by the method outlined in procedure A.

For the reactions performed with MeLi, the soln of enol silyl ether was cooled in a dry ice bath before MeLi was added. A 10% molar excess of MeLi was added dropwise over 5 min. After stirring for 1 hr at −78°, a 100% excess of the Me_2NCH_2 salt was added. The contents of the flask were permitted to warm to room temp. and stirring was continued for 30 min. Isolation techniques were according to procedure A.

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