# Regioselective Synthesis of Mannich Bases from Unsymmetrical Ketones and Immonium Salts

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*Summary* Isomeric Mannich bases derived from unsymmetrical ketones can be synthesised regioselectively simply by selecting the reaction conditions; reaction of dimethyl(methylene)ammonium trifluoroacetate in trifluoroacetic acid yields the more substituted aminoketone while reaction of di-isopropyl(methylene)ammonium perchlorate in acetonitrile leads to the less substituted aminoketone.

The Mannich reaction with ketones has been studied for a long time, but with unsymmetrical ketones the problem of regiospecificity is still controversial. Numerous erroneous results have been reported and recently corrected.[1]†

We report here conditions under which an unsymmetrical ketone reacts in high yield and with good regioselectivity either at the less or at the more substituted α-position. We have used immonium ions (*cf.* ref. 2) in anhydrous solvents as suggested by Jacques *et al.*[3] The results are in the Table.

Table

| Immonium salt | Solvent | Ketone RCOMe R | Total yield (%) | Ratio of (**3**) : (**4**)[a] |
|---|---|---|---|---|
| (**1**) | $CF_3CO_2H$ | Cyclopentyl | 90 | **95 : 5** |
| | | Isopropyl | 90 | **85 : 15** |
| | | Cyclohexyl[b] | 70 | **69 : 31** |
| (**2b**) | MeCN | Cyclopentyl | 80 | 0 : 100 |
| | | Isopropyl | 95 | 0 : 100 |
| | | Cyclohexyl | 90 | 0 : 100 |

[a] Isomeric ketones were identified by their n.m.r. spectra and properties of their picrates. The proportions of the isomers were evaluated from the n.m.r. spectra of the crude extracts.

[b] Reaction is not complete after 48 h.

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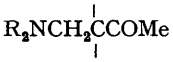
† Striking differences in the solubilities of isomeric aminoketones may account for the observed discrepancies. For instance the aminoketone (**3c**) derived from methyl isopropyl ketone is much more soluble in ether than its isomer (**4c**).

$Me_2\overset{+}{N}{=}CH_2\ CF_3CO_2^-$
(1)

$Pr^i_2\overset{+}{N}{=}CH_2\ X^-$
(2) **a**; X = $CF_3CO_2^-$
**b**; X = $ClO_4^-$

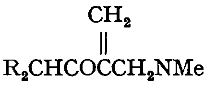

$R_2NCH_2\overset{|}{\underset{|}{C}}COMe$

(**3**) **c**; R = Me
**d**; R = $Pr^i$

$>CHCOCH_2CH_2NR_2$

(**4**) **c**; R = Me
**d**; R = $Pr^i$

The reaction in trifluoroacetic acid with the immonium trifluoroacetate (**1**), gives products containing very high amounts of the more substituted isomeric amino-ketones (**3c**). Conversely, reaction occurs mainly at the less substituted position in an aprotic solvent such as acetonitrile. However, in this solvent significant amounts of the aminomethylene ketone (**5**) are obtained with the trifluoroacetate (**1**) [arising from decomposition of the diaminoketone (**6**)]. This can be overcome by use of a bulkier immonium salt such as (**2b**) which leads to isomerically pure aminoketones (**4d**) in high yields.


$R_2CHCO\overset{CH_2}{\overset{\|}{C}}CH_2NMe_2$
(5)

$R_2CHCOCH(CH_2NMe_2)$
(6)

The immonium trifluoroacetate (**1**) is prepared conveniently in quantitative yield, by the method of Potier *et al.*[2] [reaction (1)], and an equimolar mixture of (**1**) and (**7**) and

$$(Me_2N)_2CH_2 + 2CF_3CO_2H \rightarrow (1) + \underset{(7)}{Me_2NH_2CF_3CO_2^-} \qquad (1)$$

the ketone (0·5M‡) is heated in boiling $CF_3CO_2H$ for 48 h. We have been unable to synthesise the trifluoroacetate (**2a**) by using reaction (1), and instead we used the perchlorate

$$Pr^i_2NMe + Ph_3CClO_4 \rightarrow (2b) + Ph_3CH \qquad (2)$$

(**2b**) [reaction (2)].[4] A 1 : 1 ratio of the ketone§ and (**2b**) is heated in boiling acetonitrile for 72 h.

We are currently extending this study to other unsymmetrical ketones and immonium ions to improve selectivity and reactivity. Preliminary results with the immonium trifluoroacetate from morpholine indicate that in trifluoroacetic acid the orientations are similar to those observed with (**1**) but that the reaction is faster.

Apart from preparative interest,¶ our results raise an interesting mechanistic problem. We think that the differences we observe may reflect the influence of the conditions on the relative rates of the enolization step and of the addition step. We are now determining these relative rates.

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‡ In trifluoroacetic acid, use of higher concentrations increases the proportion of the less substituted aminoketones. Isomerization may be responsible for this.

§ In acetonitrile, the orientation is not concentration dependent from 0·1 to 2M.

¶ A regiospecific synthesis of Mannich bases has been recently described by Hooz *et al.*[5] but this synthesis is indirect involving diazoketones.

[1] H. L. Brown, G. L. Buchanan, A. C. W. Curran, and G. W. McLay, *Tetrahedron*, 1968, **24**, 4565; G. L. Buchanan, A. C. W. Curran, and T. R. Wall, *Tetrahedron*, 1969, **25**, 5503 and references cited.
[2] A. Ahond, A. Cave, C. Kan-Fan, and P. Potier, *Bull. Soc. chim. France*, 1970, 2707.
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[4] H. Volz and H. H. Kilz, *Tetrahedron Letters*, 1970, **22**, 1917.
[5] J. Hooz and J. N. Bridson, *J. Amer. Chem. Soc.*, 1973, **95**, 602.