



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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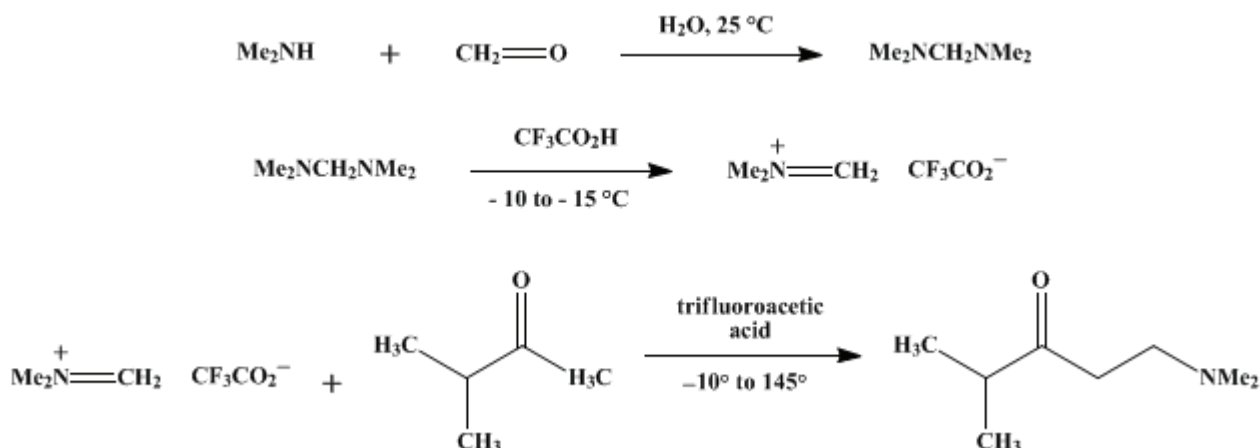
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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REGIOSELECTIVE MANNICH CONDENSATION WITH DIMETHYL(METHYLENE)AMMONIUM TRIFLUOROACETATE: 1-(DIMETHYLAMINO)-4-METHYL-3-PENTANONE

[3-Pentanone, 1-(dimethylamino)-4-methyl-]



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1. Procedure

Caution! Trifluoroacetic acid is highly toxic; consequently Part B of this procedure must be conducted in a well-ventilated hood.

A. *Bis(dimethylamino)methane*. A 500-ml., round-bottomed flask equipped with a magnetic stirring bar and a dropping funnel is charged with 100 g. (1.0 mole) of aqueous 30% formaldehyde (Note 1). The solution is stirred and cooled in an ice bath as 225 g. (2.0 moles) of a 40% solution of dimethylamine (Note 1) in water is added dropwise. The resulting aqueous solution is allowed to stand overnight at room temperature, after which it is saturated with solid potassium hydroxide. The two layers are separated, the upper layer is dried over potassium hydroxide pellets, and the drying agent is removed. Distillation at atmospheric pressure through a Vigreux column gives 85–88 g. (83–86%) of bis(dimethylamino)methane, b.p. 81.5–83°.

B. *1-(Dimethylamino)-4-methyl-3-pentanone*. A 100-ml., two-necked, round-bottomed flask equipped with a magnetic stirring bar and a pressure-equalizing dropping funnel bearing a calcium chloride drying tube is charged with 50 ml. of anhydrous trifluoroacetic acid (Note 2). The trifluoroacetic acid is stirred and cooled in an ice-salt bath at –10° to –15° while 10.2 g. (0.100 mole) of bis(dimethylamino)methane is added over a 50-minute period (Note 3). The temperature of the resulting solution of dimethyl(methylene)ammonium trifluoroacetate is kept below –10° as 8.6 g. (0.10 mole) of 3-methyl-2-butanone (Note 4) is gradually added. The cooling bath is removed and the solution is heated in an oil bath at 65° for 1.5 hours (Note 5). The temperature of the oil bath is then raised to 145° (Note 6). After 1.5 hours the solution is cooled and the trifluoroacetic acid is neutralized by adding the contents of the flask dropwise to an ice-cold solution of 100 g. of potassium carbonate in 100 ml. of water (Note 7). The crystals are collected by filtering through a sintered-glass Büchner funnel and washed with two 50-ml. portions of dichloromethane. The aqueous filtrate is extracted with four 50-ml. portions of dichloromethane. The dichloromethane extracts are combined, washed with 50 ml. of water, dried over anhydrous sodium sulfate, and concentrated with a rotary evaporator. The concentrate, which amounts to 12.7 g. (Note 8), is distilled under reduced pressure through an 18-cm. column packed with

Raschig rings (Note 9), affording 7.0–8.2 g. (49–57%) of 1-(dimethylamino)-4-methyl-3-pentanone, b.p. 49° (3 mm.) (Note 10).

2. Notes

1. Formaldehyde and dimethylamine are available as aqueous 37% and 40% solutions, respectively, from Aldrich Chemical Company, Inc.
2. The submitters purchased trifluoroacetic acid from Prolabo, Paris, France, or E. Merck, Darmstadt, Germany, and distilled it from phosphorus pentoxide. This reagent is also available from Aldrich Chemical Company, Inc., and J. T. Baker Chemical Company.
3. The reaction between bis(dimethylamino)methane and trifluoroacetic acid is very exothermic. If the temperature is carefully controlled, a colorless solution remains when the addition is complete.
4. 3-Methyl-2-butanone was purchased from Eastman Organic Chemicals and distilled before use.
5. The progress of the reaction can be monitored by taking ¹H NMR spectra at appropriate intervals. The following absorptions for dimethyl(methylene)ammonium trifluoroacetate in trifluoroacetic acid disappear as the reaction progresses: δ (multiplicity, number of protons, assignment): 3.89 (broad m, 6H, 2 NCH₃), 8.07 (broad m, 2H, N=CH₂).
6. At this temperature 4-(dimethylamino)-3,3-dimethyl-2-butanone, which is formed initially, isomerizes to 1-(dimethylamino)-4-methyl-3-pentanone.
7. Removing trifluoroacetic acid by evaporation is tedious. The neutralization procedure given here produces insoluble salts that are readily separated by filtration.
8. The ratio of the isomeric amino ketones in the crude product can be determined from the relative intensities of the signals for the (CH₃)₂C grouping in a ¹H NMR spectrum taken in trifluoroacetic acid (see (Note 10)). In CDCl₃ these absorptions overlap.
9. To minimize losses of products during the distillation, the submitters used a circulating device to chill the condenser cooling water to 5–10°. In addition, the outlet to the vacuum line was located as far as possible from the drip tip, and the receivers were cooled in an ice bath.
10. The ¹H NMR spectrum of the product in trifluoroacetic acid shows that the isomeric purity is greater than 90%. The ¹H NMR spectra for the isomeric amino ketones in both trifluoroacetic acid and CDCl₃, δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 1-(dimethylamino)-4-methyl-3-pentanone (trifluoroacetic acid), 1.16 (d, *J* = 7, 6H, 2CCH₃), 2.98 (d, *J* = 5, 6H, 2NCH₃), 3.31 (m, 4H, CH₂CH₂); (CDCl₃), 1.10 (d, *J* = 7, 6H, 2CCH₃), 2.23 (s, 6H, 2NCH₃), 2.60 (s, 4H, CH₂CH₂); 4-(dimethylamino)-3,3-dimethyl-2-butanone (trifluoroacetic acid), 1.53 (s, 6H, 2CCH₃), 2.45 (s, 3H, COCH₃), 3.15 (d, *J* = 5, 6H, 2NCH₃), 3.40 (d, *J* = 5, 2H, CH₂N); (CDCl₃), 1.12 (s, 5H, 2CCH₃), 2.13 (s, 3H, COCH₃), 2.18 (s, 6H, 2NCH₃), 2.41 (s, 2H, CH₂N).

3. Discussion

The Mannich condensation has traditionally been carried out in the presence of water as a three-component condensation involving a carbonyl compound (or related carbon nucleophile), formaldehyde, and a primary or secondary amine.^{2,3} The initial step is a condensation between the latter two reactants to form a mono- or dialkyl(methylene)ammonium ion which subsequently serves as the electrophilic partner in the reaction. With unsymmetrical ketones aminomethylation generally occurs at both positions, giving mixtures of isomeric β -amino ketones. The ratio of the isomers depends strongly on the structure of the ketone,⁴ and the more highly branched β -amino ketone usually predominates.

In recent years a number of methods have been developed for the preparation of dialkyl(methylene)ammonium salts (Mannich reagents),^{5,6,7,8,9} and their use in Mannich-type condensation reactions under anhydrous conditions has improved the scope and efficiency of this important synthetic process.^{6,7,8,9,10,11,12,13} However, the orientation of the Mannich reaction may nevertheless be difficult to control. Apart from the work of the submitters, the preparation of isomerically pure Mannich bases has only been achieved by indirect methods in which specific enol derivatives are generated and allowed to react with dialkyl(methylene)ammonium salts.^{10,12,14} The Mannich reaction of β -keto esters affords isomerically pure β -dimethylamino β' -keto esters which may in turn be converted to specific α -methylene ketones.¹⁵ However, the β -amino ketones themselves are not as yet available by this method.

The submitters have found that the orientation of the reaction of Mannich reagents with

unsymmetrical ketones in anhydrous solvents is highly dependent on the experimental conditions, the solvent, and the structures of the ketone and iminium ion reactants.¹¹ Under conditions of kinetic control, the reaction of methyl ketones with dimethyl(methylene)ammonium trifluoroacetate in trifluoroacetic acid leads to amino ketones in which the more highly substituted isomer predominates (\geq 85% when the α '-position is tertiary and 80% when the α '-position is secondary). In contrast, reaction with diisopropyl(methylene)ammonium perchlorate in acetonitrile gives almost exclusively the less highly substituted isomer (100% when the α '-position is tertiary and 90% when it is secondary). Although the latter method directly affords the less highly substituted Mannich bases in yields greater than 80%, it cannot be utilized safely in large-scale preparative reactions owing to the hazardous nature of perchlorate salts.

The less highly substituted Mannich bases can also be prepared directly from ketones and dimethyl(methylene)ammonium trifluoroacetate by the procedure reported here, which takes advantage of the isomerization of Mannich bases in trifluoroacetic acid.¹¹ (In acetic acid the Mannich bases undergo elimination of dimethylamine to give α -methylene ketones.) This method is rapid and affords products, having an isomeric purity of at least 90%, without difficult separations. The 49–57% yield of 1-(dimethylamino)-4-methyl-3-pentanone obtained with this procedure compares favorably with the overall yields of amino ketones prepared by the indirect routes mentioned previously.

1-(Dimethylamino)-4-methyl-3-pentanone has been prepared by addition of isopropyl-magnesium bromide to methyl 3-(dimethylamino)propionate,¹⁶ by reduction of 1-(dimethylamino)-4-methyl-1-penten-3-one with lithium aluminum hydride,¹⁷ and by displacement of chloride from 1-chloro-4-methyl-3-pentanone with dimethylamine.¹⁸ Although the preparation of 1-(dimethylamino)-4-methyl-3-pentanone by Mannich condensation of 3-methyl-2-butanone with dimethylamine hydrochloride and formaldehyde has been reported,¹⁹ the product evidently is a mixture of the two isomeric β -dimethylamino ketones.^{4,18}

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

potassium carbonate (584-08-7)

acetic acid (64-19-7)

acetonitrile (75-05-8)

formaldehyde (50-00-0)

sodium sulfate (7757-82-6)

potassium hydroxide (1310-58-3)

dimethylamine (124-40-3)

dimethylamine hydrochloride (506-59-2)

dichloromethane (75-09-2)

3-methyl-2-butanone (563-80-4)

isopropyl-magnesium bromide (920-39-8)

lithium aluminum hydride (16853-85-3)

Bis(dimethylamino)methane (51-80-9)

trifluoroacetic acid (76-05-1)

DIMETHYL(METHYLENE)AMMONIUM TRIFLUOROACETATE

1-(DIMETHYLAMINO)-4-METHYL-3-PENTANONE,
3-Pentanone, 1-(dimethylamino)-4-methyl- (5782-64-9)

4-(dimethylamino)-3,3-dimethyl-2-butanone

diisopropyl(methylene)ammonium perchlorate

methyl 3-(dimethylamino)propionate (3853-06-3)

1-(dimethylamino)-4-methyl-1-penten-3-one

1-chloro-4-methyl-3-pentanone

phosphorus pentoxide (1314-56-3)