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A CYANIDE PROMOTED MICHAEL REACTION: THE USE OF AN AMINONITRILE AS AN ENAMINE EQUIVALENT FOR THE MICHAEL REACTON

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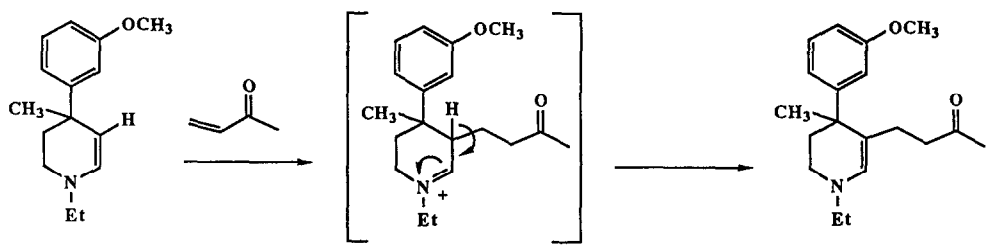
Abstract: An enamine lacking a beta-proton is shown to undergo the Michael reaction if the intermediate iminium ion is trapped with a nucleophile, such as cyanide. Reductive cleavage of the resulting nitrile affords an aminoketone product.

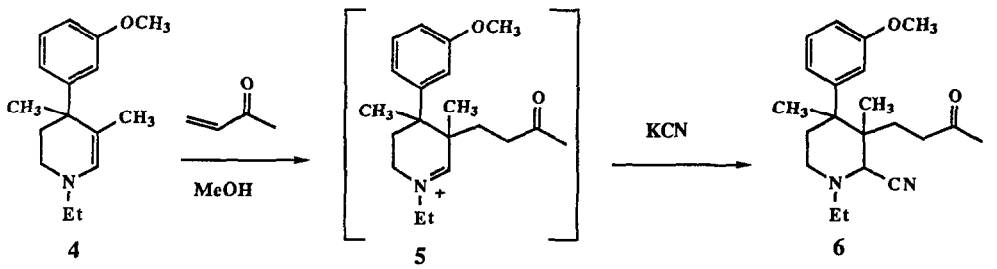
Michael reactions with enamines generally require beta-elimination of a proton (or other leaving group) from an iminium ion intermediate in order to give the usual ketoenamine products.[1] This is illustrated by the reaction between enamine **1** and methylvinylketone to give ketoenamine **3**, which presumably proceeds via iminium ion **2** as an intermediate.[2] However, it is desirable to be able to carry out such reactions with enamines lacking a beta-proton, given the versatility of enamine Michael reactions for carbon-carbon bond formation in alkaloid synthesis. This report demonstrates that an enamine lacking a beta-leaving group can undergo the Michael reaction in the presence of cyanide as a nucleophilic trap for the intermediate iminium ion. Removal of the nitrile functionality then converts the trapped aminoketonitrile to a product equivalent in terms of carbon-carbon bond formation to that from a conventional enamine-Michael reaction.



1 **2** **3**

Treatment of enamine **4** with excess methylvinylketone and KCN in methanol at room temperature for 24 h afforded the aminoketonitrile **6** in 40 % yield, presumably by cyanide trapping of intermediate **5**.[3,4,5,6] In the ^{1}H-NMR of a solution of enamine **4** and MVK in deuteriomethanol (in the absence of KCN), intermediate **5** was not observed, indicating that any equilibrium between **4** and intermediate **5** lies strongly in favor of **4**.[2] The use of cyanide

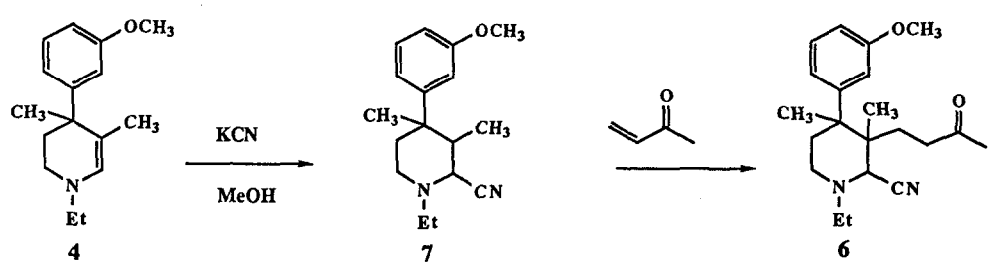
apparently overcomes this unfavorable equilibrium by trapping out intermediate **5** to give aminoketonitrile **6**.[6]



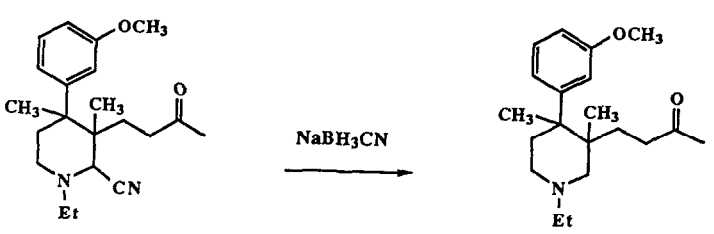
4 **5** **6**

As a practical matter, cleaner product and better yields for this reaction were obtained by using a preformed aminonitrile **7** instead of enamine **4** as the starting material.[7] Aminonitrile **7** was prepared by stirring enamine **4** and KCN in methanol for 24 hours at room temperature to give a 75% yield of **7**. Reaction of **7** with MVK in methanol at room temperature for 48 h then gave a 92% yield of aminoketonitrile **6**.

The nitrile functionality can be selectively removed in the presence of the ketone under reductive conditions to give an aminoketone **8**.[7] Treatment of aminoketonitrile **6** with $NaBH_3CN$ in refluxing methanol thus afforded **8** in 86% yield.[6,8]



4 **7** **6**



6 **8**

This process constitutes a method of carbon-carbon bond formation equivalent to that of a conventional enamine Micheal reaction and represents methodology of potential generality for alkaloid synthesis. Trapping the intermediate iminium ion with cyanide provides a driving force for the Michael reaction with an enamine lacking a beta-proton. Alternatively, an aminonitrile can be used as an enamine-like equivalent. Cleavage of the nitrile then provides an aminoketone.

REPRESENTATIVE EXPERIMENTAL PROCEDURES

Aminonitrile 7: A solution of 8.1 g (33 mmol) enamine **1** and 6.45 g (99 mmol) potassium cyanide in 100 mL methanol was stirred for 24h at room temperature under a nitrogen atmosphere. After evaporation under vaccum, 100 mL saturated $NaHCO_3$ was added to the residue and the mixture was extracted with three 150 mL portions of ethyl acetate. The combined extracts were dried over $NaCl/Na_2SO_4$ and evaporated under vacuum. The residue was chromatographed on silica gel (0.1% triethylamine, 10% ethyl acetate, 89.9% hexane, to afford 6.08 g (68%) of a colorless oil.

Aminoketonitrile 6: To a solution of 5.07 g (18.6 mmol) aminonitrile **7** in 20 mL methanol was added 26 g (372 mmol) methylvinylketone and the mixture was stirred at room temperature under a nitrogen atmosphere for 48 h. After evaporation of the solvent under vacuum, 100 mL saturated $NaHCO_3$ was added and the mixture was extracted with three 150 mL portions of ethyl acetate. The combined extracts were dried over $NaCl/Na_2SO_4$ and evaporated under vacuum. The residue was chromatographed on silica gel (0.5% triethylamine, 25% ethyl acetate, 74.5% hexane) to afford 5.83 g (92%) of a colorless oil as a 2:1 mixture of diastereomers..

Aminoketone 8: A solution of 4.55 g (13.3 mmol) ketonitrile **6** and 1.67 g (26.6 mmol) sodium cyanoborohydride in 50 mL methanol was heated at reflux for 6 h. After cooling to room temperature, the solvent was evaporated under vacuum and then 100 mL saturated $NaHCO_3$ was added to the residue. The mixture was extracted with three 150 mL portions of ethyl acetate. The combined extracts were dried over $NaCl/Na_2SO_4$ and evaporated. The residue was chromatographed on silica gel (0.5% triethylamine, 50% ethyl acetate, 49.5% hexane; increased by gradient to 0.5%triethylamine, 99.5% ethyl acetate), to afford 3.6 g (86% yield) of **8** as a 2:1 mixture of diastereomers.

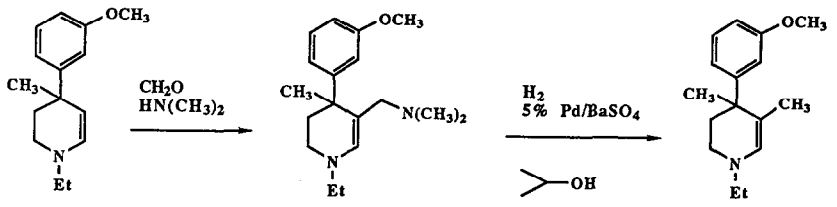
REFERENCES AND NOTES

1) (a) Stork, G.; Brizzolara,A.; Landesman, H.; Szmuszkovicz,J.; Terrell, R. J. Am. Chem. Soc. **1963**, 85, 207. (b) Szmuszkovicz,J. Adv. Org. Chem. **1963**, 4, 1. (c) Kuehne, M. E. Synthesis **1970**, 510. (d) Cook, A. G., Ed. Enamines: Synthesis, Structure and Reactions, Marcel Dekker, New York, 1969.

2) While the involvement of a dihydropyran intermediate has been implicated in many enamine Michael reactions, such an intermediate has not been detected in the present work (see ref. 1).

3) For the preparation of 4-arylpiperidine endocyclic enamines and their synthetic applications see: (a) Evans, D.A.; Mitch, C. H.; Thomas, R. C.; Zimmerman, D. M.; Robey, R. L. J.Am. Chem. Soc. **1980**, 102, 5955. (b) Evans, D. A.; Mitch, C. Tetrahedron Lett. **1982**, 285. (c) Shenvi, A. B.; Ciganek, E. J. Org. Chem. **1984**, 49, 2942.

4) Enamine **4** was prepared by Mannich reaction with 1-ethyl-4-methyl-4-(3-methoxyphenyl-1,2,3,4-tetrahydropiperidine (see ref. 5 for its preparation), dimethylamine and formaldehyde, followed by hydrogenolysis of the Mannich adduct with 5% $Pd/BaSO_4$ (1 atm. H_2, isopropanol): Barnett, C. J. Eur. Pat. Appl. E.P. 136,863; Chem Abstr. **1985**, 103, 195998g.



5) CAUTION: The N-ethyl compound is used to avoid the neurotoxicity associated with N-methyl-4-aryl-1,2,3,6-tetrahydropyridines (MPTP), as an intermediate in the preparation of **4**: Zimmerman, D.M.; Cantrell, B. E.; Reel. J. K.; Heimrick-Luecke, S.K.; Fuller, R.W. J. Med. Chem. **1986**, 29, 1517.

6) By 13-C NMR, **6** was found to consist of an approximately 2:1 mixture of diastereomers. Similarly, after removal of the nitrile functionality, **8** is also found to be a 2:1 mixture of diastereomers, indicative of each set of diastereomers being isomeric at C-3.

7) For leading references to some recent applications of aminonitriles as iminium ion equivalents see: (a) Flann, C.; Malone, T. C.; Overman, L. E. J. Am. Chem. Soc. **1987**, 109, 6097. (b) Greirson, D. S.; Harris, M.; Husson, H. P. J. Am. Chem. Soc. **1980**, 102, 1064. (c) Bosch, J.; Rubiralta, M.; Bolos, J. Tetrahedron **1987**, 43, 391.

8) Alternatively, reductive cleavage of the nitrile functionality was carried out by hydrogenolysis (5% Pd/C, 1 atm. H_2) though yields were not as high using this method (see ref. 7).

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