

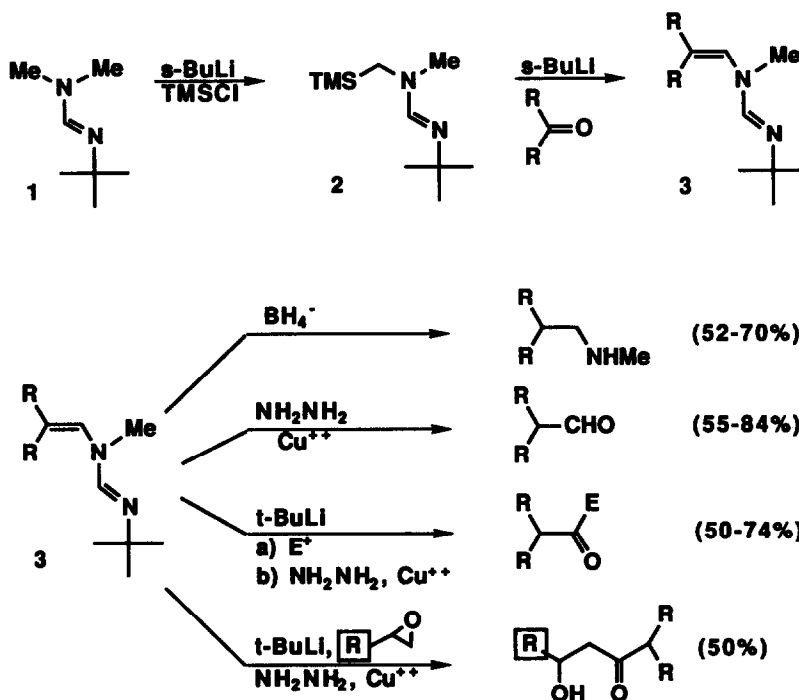
Formamidine Anions in Synthesis. The One-Carbon Homologation of Aldehydes and Ketones to Nitriles

Braulio Santiago¹ and A. I. Meyers*

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523 U. S. A.

Summary: Treatment of various carbonyl compounds with the carbanion of the 2-trimethylsilylmethyl formamidine **2** gives the enamidine **3** which is readily transformed into the homologated nitriles **6**.

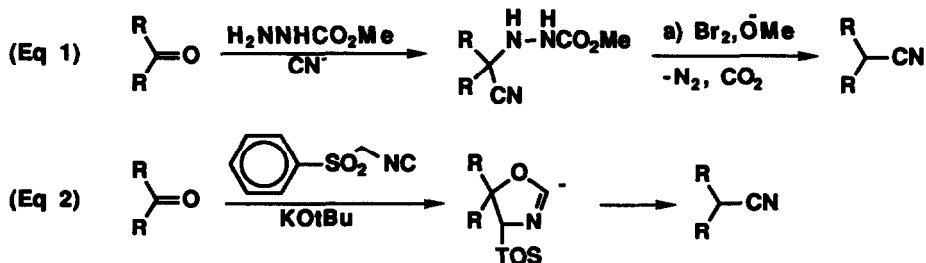
The chemistry of chiral and achiral formamidines has been amply demonstrated during recent years to afford routes to a variety of alkaloids² and related materials.³ Furthermore, the versatile enamidine **3**, readily available by Peterson olefination⁴ of the lithio derivative of **2**, has been shown to furnish a host of homologated carbonyl compounds as outlined in Scheme 1.³ The key reaction which allows this process rests with the facile exchange of **3** with hydrazine



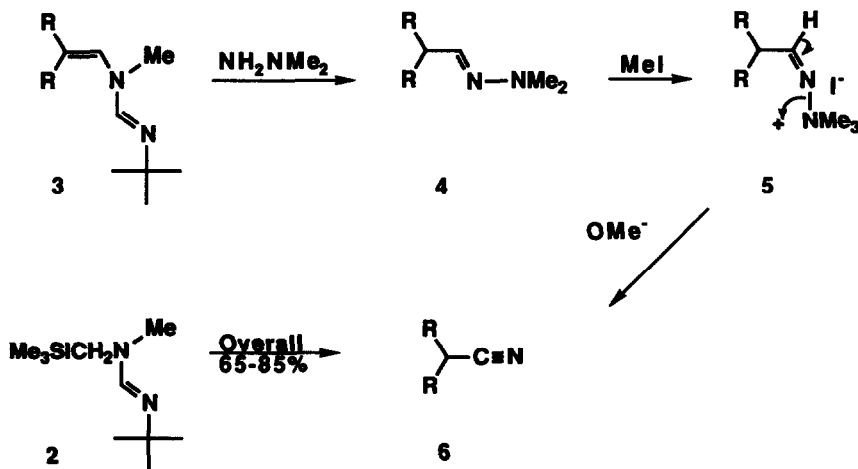
Scheme 1

producing the corresponding hydrazones. The latter are readily cleaved to the carbonyl compounds with Cu(II).

Although the reactions in the scheme are important, there has been a long interest in transforming various carbonyls to the homologated nitrile and this effort has been expended by others using a variety of means. Most notable is the work of Ziegler⁵ and Van Leusen⁶ who homologated ketones via their α -cyanohydrazides or Tosmic adducts (eq 1 and 2, respectively). In the TosMIC reaction, low yields were generally observed with α,β -unsaturated aldehydes but a recent modification⁷ using O,O-diethylcyano phosphate has solved this problem.



We now report that we have been successful in carrying out this important transformation by a variation on the sequence shown in Scheme 1. Thus, the trimethylsilyl formamidine **2**, after treatment with *sec*-BuLi at -30°C , gave the appropriate carbanion which, when treated with the carbonyl compound (Table 1), gave, after workup, good yields of the enamidine **3**. It was found that addition of 2.0 equiv of HMPA prior to the addition of *enolizable* carbonyl compounds gave good yields of the Peterson olefination for in its absence significant quantities of starting carbonyls were recovered.

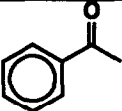
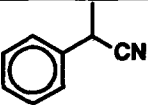
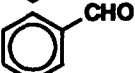
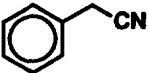
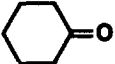
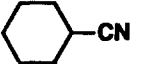
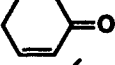
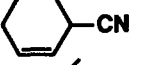
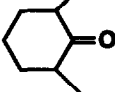
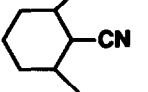
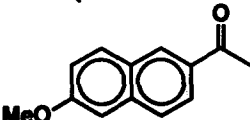
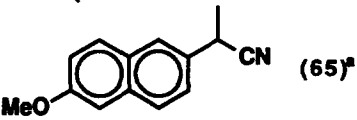


Scheme 2

The exchange of the formamidine by *N,N*-dimethylhydrazine was smoothly accomplished by heating in aqueous acetic acid for several hours producing the hydrazones **4**. Taking the cue from an earlier study⁸ which reported that trimethylammonium hydrazones **5**, when treated with base readily underwent hetero-Hoffmann elimination to the nitrile, it was felt that this would indeed be a useful route to the nitriles. This was based on the fact that it was quite convenient to transform carbonyls to the enamidines and exchange the latter for dimethyl hydrazones as shown earlier.³ In that event, the hydrazones **4** were treated with methyl iodide to give the quaternary salts and subjected to methoxide ion elimination producing the nitriles in good overall yields. In the Table the last three entries were performed without purification of any of the intermediates while the first three examples were purified at each stage.

As seen from the examples in the Table, a variety of carbonyls were examined. Noteworthy is the conjugated ketone (entry 4) which gives pyrroles when the TosMIC method is employed.⁶

Table. Homologation of Carbonyls to Nitriles.

| Entry | Carbonyl | Enamidine 3 (%) | Nitrile 6 (%) |
|-------|---|------------------------|--|
| 1 |  | 76 |  (82) |
| 2 |  | 84 |  (75) ^b |
| 3 |  | 87 |  (89) |
| 4 |  | -- |  (66) ^a |
| 5 |  | -- |  (85) ^a |
| 6 |  | -- |  (65) ^a |

a) Prepared without isolation-purification of intermediates **3**, **4**, **5**. b) Yield for stepwise isolation-purification of **3**, **4**, **5**. When carried out without isolation overall yield was 55% (not optimized).

A typical procedure is given which eliminates the need for isolation of any of the intermediates (entries 4, 5, 6).

To a solution of 5.0 mmol of **2⁹** in 15 mL of dry THF cooled to -78° C was added in a dropwise manner 6.4 mmol of *s*-BuLi in hexane. The solution was allowed to slowly warm to -20° C and stirred for 1.5 h. After recooling to -78° C the carbonyl component (1.3 eq) was added dropwise. If the carbonyl was enolizable then 2.0 equiv HMPA was added prior to the addition of

the carbonyl. After 45 min the mixture was warmed to 0° C, stirred for 2-3 h, and 10 mL of sat. K₂CO₃ added. The layers were separated, the aqueous extracted with CH₂Cl₂, combined, dried (K₂CO₃) and concentrated and the residue passed through silica gel using 10% Et₃N-Hexane to remove any HMPA. The enamidine **3**, thus obtained, was dissolved in EtOH-H₂O (10 mL, 70% v/v) and N,N-dimethylhydrazine (37.5 mmol, 3.5 equiv) was added followed by acetic acid (13.13 mmol, 3.5 equiv). The mixture was heated (60° C, 6 h), cooled, and diluted with brine (25 mL). The mixture was extracted with CH₂Cl₂, dried (K₂CO₃) and concentrated to give the hydrazone **4**. Quaternization with methyl iodide was performed by dissolving the hydrazone in 3 mL of benzene and adding 3.0 mmol of MeI, heating for 7 h, and removing all the volatiles under aspirator. The solid residue was dissolved in methanol (4 mL) and NaOMe (4.56 mmol, 2.0 equiv) was added and the solution heated at reflux (4 h), cooled, added to water (25 mL) to dissolve all the solids, and extracted with ethyl acetate (4x20 mL). After drying (K₂CO₃) the solvent were removed and the nitrile obtained by kugelrohr distillation.

Acknowledgment. The authors are grateful to the National Science Foundation for financial support.

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(Received in USA 18 May 1993; accepted 15 July 1993)