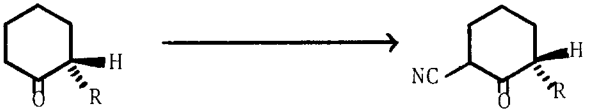
Tetrahedron Letters,Vol.22,No.50,pp 5011-5014,1981 0040-4039/81/505011-04$02.00/0
Printed in Great Britain

# KINETIC CYANATIONS OF KETONE ENOLATES

Daniel Kahne and David B. Collum*
Department of Chemistry, Cornell University, Ithaca, NY 14853

Summary: Kinetic cyanations of ketone enolates using p-toluenesulfonyl cyanide provide efficient routes to β-ketonitriles.

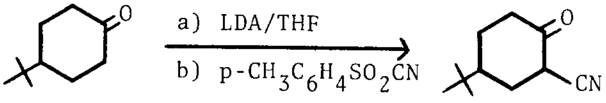
During the course of a natural product synthesis study going on in our laboratory we required a means of effecting the ketone cyanation illustrated in equation 1. Examination of existing methodologies used to prepare β-ketonitriles failed to uncover a completely acceptable solution.[1-5] The majority of these procedures would seriously jeopardize the integrity of the asymmetric center at the α' carbon of our substrate. The high yielding isoxazole route (1. NaOMe-HCOOMe 2. $NH_2OH{\cdot}HCl$ 3. NaOMe) developed by Stock and Claisen,[4] which has been refined and utilized throughout the past nine decades,[2,3] possibly could be adapted to kinetic enolate trapping conditions.[6] However, the number of transformations required seemed somewhat cumbersome.



(1)

In 1970, Kuehne and Nelson reported that ketone enolates could be trapped using cyanogen chloride to provide β-ketonitriles albeit in low (11-42%) yields.[3] Feeling that their approach was conceptually sound, we pursued this strategy with the hope that a more efficient trapping procedure might arise from the proper combination of cyanation reagent and reaction conditions.

Initial attempts to cyanate ketone enolates using cyanogen bromide[7] or phenyl cyanate ($C_6H_5OCN$)[8] proved fruitless. However, we found that p-toluenesulfonyl cyanide[9] (p-TsCN, 1) was effective.[10] Thus, *inverse addition* of the lithium enolate of 4-t-butylcyclohexanone (2) to 2.0 equivalents of p-TsCN (1) in anhydrous tetrahydrofuran (THF) at -78°C provided β-ketonitrile 3 in 80% yield after chromatography (equation 2). We recovered less than 2% of the starting ketone 2, indicating that deprotonation of the acidic product by the enolate was not a problem. To elucidate the scope and limitations of this procedure we cyanated several substrates under analogous conditions. The results appear in the Table. We were able to achieve fair to good results. For the most part, no serious problems arose from proton transfer processes. However, attempts to cyanate kinetic enolates derived from a variety of methyl ketones (e.g. Entry 5) provided significant amounts of recovered starting ketones (∿20%) and meager mass balances. Previously observed[5] facile polymerizations of the acylacetonitrile products could account for these poor results.



2 1 3

(2)

ref. 13

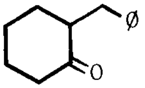
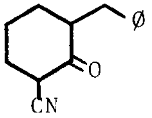
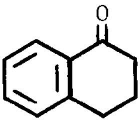
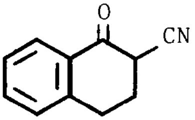
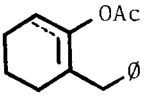
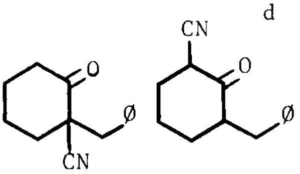
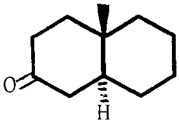
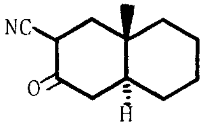
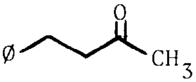
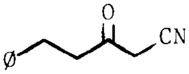
A representative experimental procedure is as follows: To a solution of lithium diisopropyl amide (1.15 mmol) in anhydrous tetrahydrofuran (1.0 ml) at -78°C under nitrogen was added 4-t-butylcyclohexanone (154 mg, 1.00 mmol) in dry THF (1.0 ml). After 20 minutes, the solution containing the enolate was drawn up by gas-tight syringe and added to a solution of p-toluenesulfonyl cyanide (1, 368 mg, 2.00 mmol) in THF at -78°C over a period of about 30 seconds. After quenching with concentrated ammonium hydroxide (0.5 ml) and warming the vessel to room temperature to decompose the residual p-toluenesulfonyl cyanide, acidification with 10% HCl and usual extractive workup (diethyl ether) afforded crude β-ketonitrile 3 contaminated with very polar sulfone-containing material. Flash chromatography[10] afforded pure 3 (80% yield) which was identical to a sample of 3 prepared by a literature procedure.[3]

Acknowledgment: This work was supported by Cornell University and indirectly by Research Corporation and the Petroleum Research Fund. D.B.C. would like to thank the E.I. Du Pont de Nemours Company for a Young Faculty Grant.

## References and Footnotes:

1. von R.E. Meyer, Helv. Chim. Acta, 16, 1291 (1933); I.B. Johns and H.R.D. Pietro, J. Org. Chem., 29, 1970 (1964); J.K. Rasmussen and A. Hassner, Synthesis, 682 (1973); M.E. Kuehne, J. Amer. Chem. Soc., 81, 5400 (1959).
2. M.E. Kuehne and J.A. Nelson, J. Org. Chem., 35, 161 (1970); M.E. Kuehne, J. Org. Chem., 35, 171 (1970).

Table

| Entry | Starting Ketone | Product[d] | Yield[a] |
|---|---|---|---|
| 1 |  |  d | 67% |
| 2 |  |  | 78% |
| 3 |  (89:11 mixture)[b] |  d<br>9:1 | 56% |
| 4 |  |  c,d | 80% |
| 5 |  |  | < 5% |

[a] All products were purified by flash chromatography (ref. 10), shown to be homogeneous by gas chromatography (OV-101), and characterized by IR, proto NMR, and mass spectroscopy.

[b] The enolate was generated by the method of House _et_ _al_. (ref. 11).

[c] The regiochemical assignment was based on literature analogy (ref. 12).

[d] Ref. 13.

W.S. Johnson and W.E. Shelberg, *J. Amer. Chem. Soc.*, **67**, 1745 (1945); *Ibid.*, 1754 (1945); W.S. Johnson, J.W. Petersen and C.D. Geutsche, *Ibid.*, **69**, 2942 (1947); A. Chatterjee, D. Roy and S.K. Chatterjee, *Synthesis*, 449 (1981).

4. L. Claisen and R. Stock, *Ber.*, **24**, 130 (1891).

5. F.J. Vinick, Y. Pan and H.W. Gschwend, *Tetrahedron Lett.*, 4221 (1978).

6. For selected examples of ketone enolate acylation see:
G. Stork, P. Rosen, M.L. Goldman, R.V. Coombs and J. Tsuji, *J. Amer. Chem. Soc.*, **87**, 275 (1965); S. Bernasconi, P. Gariboldi, G. Jommi and M. Sisti, *Tetrahedron Lett.*, 2337 (1980); W.P. Jackson and S.V. Ley, *Chem. Comm.*, 732 (1979).

7. Bromination products predominated.

8. R.E. Murray and G. Zweifel, *Synthesis*, 150 (1980).

9. Prepared by the method of J.M. Cox and R. Ghosh, *Tetrahedron Lett.*, 335 (1969).
See also: H. Westmijze and P. Vermeer, *Synthesis*, 784 (1977).

10. W.C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).

11. H.O. House, M. Gall and H.D. Olmstead, *J. Org. Chem.*, **36**, 2361 (1971).

12. C. Agami, J. Levisalles and B. Lo Cicero, *Tetrahedron*, **35**, 961 (1979).

13. The β-ketonitrile products existed as a mixture of keto and enol tautomeric forms.

(Received in USA 8 September 1981)