

DIECKMANN AND THORPE REACTIONS IN DIMETHYL SULFOXIDE^{1,2}

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In earlier work we have demonstrated the efficacy of sodium hydride as base and dimethyl sulfoxide (DMSO) as solvent in alkylation⁴ and acylation⁵ reactions.

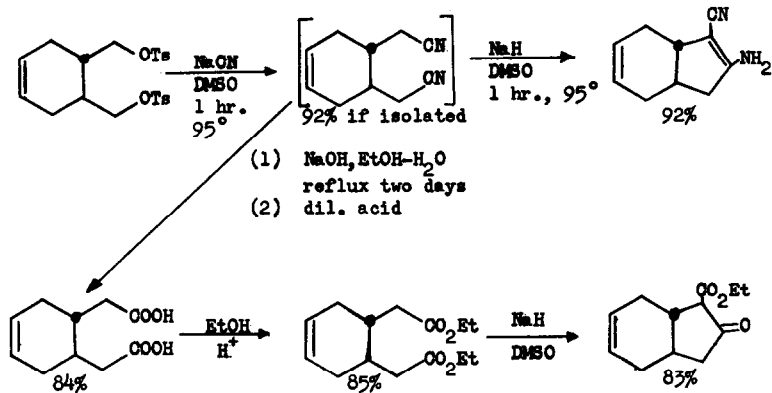
We have now determined in the course of an unrelated investigation, that this combination also provides reasonable yields in the Dieckmann condensation. Of more interest, however, is the discovery that 1,4 dinitriles (prepared from dihalides or ditosylates and sodium cyanide in DMSO⁶) can be cyclized directly to β -cyanoenamino nitriles⁷ by the addition of sodium hydride. This is an especially useful technique because it permits direct conversion of a ditosylate to the cyclic Thorpe product in a single reaction vessel in a period of two or three hours compared to the two or three day period necessary to prepare the corresponding β -ketoester.

In a typical reaction, conducted under dry, oxygen-free nitrogen 45 g. (0.1 mole) of trans-4,5-bis-hydroxymethylcyclohexene ditosylate⁸ was added over 15 minutes to a stirred slurry of 14.7 g. (0.3 mole) of dry sodium cyanide

in 200 ml. of dry^{4,5} DMSO heated at 90-95°. After one hour at 95° the reaction mixture was cooled and 2.4 g. (0.10 mole) of sodium hydride (from a 50% oil dispersion washed free of oil with dry benzene) slurried in 50 ml. of DMSO was added over 30 minutes. After an additional period of heating at 90-100° with continuous stirring the reaction mixture was poured onto 1.5 liters of ice and water. The crude enamino nitrile, 14.8 g. (92.5%), m.p. 195-197°, was recrystallized three times from benzene-hexane, m.p. 195.4-196.0°. Anal. Calcd. for C₁₀H₁₂N₂: C, 74.96; H, 7.55; N, 17.49. Found: C, 75.03; H, 7.41; N, 17.32.

The yield of dinitrile isolated by omission of the sodium hydride step was also 92.5% therefore the conversion in the cyclization reaction is 100%. Similar conversions were found in the other examples.

The procedure outlined provides a useful alternative to the Dieckmann synthesis of cyclic ketones provided suitable means are available for hydrolysis of the cyano-enamines. This problem has been discussed in detail and a variety of methods for effecting the hydrolysis has been described.¹¹ The overall result is a rapid method of considerable potential in natural product synthesis because a great variety of starting diols are available from Diels-Alder reaction of appropriate dienes with substituted maleic anhydrides followed by lithium aluminum hydride reduction in tetrahydrofuran.



The table below summarizes some of the results of our study.⁹

<u>Starting Material</u>	<u>Product</u>	<u>Yield, %</u>
		<u>cis</u> - 74 <u>trans</u> - 92.5
		<u>cis</u> - 85 ¹⁰
		78
		<u>cis</u> - 75 <u>trans</u> - 85
		65-75

REFERENCES AND FOOTNOTES

- (1) This work was partially supported by National Science Foundation Grant GP 260.
- (2) Discussed at the Ninth Tetrasectional meeting in Tulsa, Oklahoma, March 16, 1963.
- (3) National Science Foundation Undergraduate Research Participant summer 1962 and academic year 1962-1963.
- (4) J. J. Bloomfield, J. Org. Chem. 26, 4112 (1961).
- (5) J. J. Bloomfield, J. Org. Chem. 27, 2742 (1962).
- (6) (a) Cf., R. A. Smiley and C. Arnold, J. Org. Chem., 25, 257 (1960) and
(b) L. Friedman and H. Schecter, J. Org. Chem., 25, 877 (1960).
- (7) We have found that all of our cyclization products exist primarily in the enamine form by examination of their n.m.r. spectra which show no protons alpha to nitrile and two protons on nitrogen. See also Q. E. Thompson, J. Am. Chem. Soc., 80, 5483, (1958).
- (8) D. C. Ayres and R. A. Raphael, J. Chem. Soc., 1779 (1958).
- (9) Satisfactory analyses have been obtained on all the compounds shown.
- (10) Methanesulfonic esters are not satisfactory. Only partial displacement occurs (under usual reaction conditions) producing a mixture of mono and dinitrile.
- (11) S. Baldwin, J. Org. Chem., 26, 3280 (1961) and references cited therein.