Tetrahedron Letters, Vol. 22, No. 14, pp 1373 - 1376, 1981 0040-4039/81/141373-04$02.00/0
Printed in Great Britain

THE CYCLODIMERISATION OF 3-METHYL-2-BUTENENITRILE

H TUCKER*, G GOLDING and S R PURVIS
Imperial Chemical Industries Limited, Pharmaceuticals Division
Mereside, Alderley Park, Macclesfield, Cheshire, U.K.

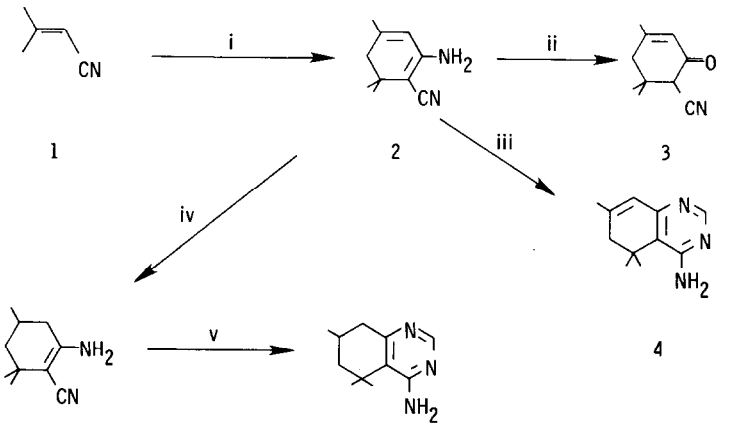
Abstract: 3-Methyl-2-butenenitrile (1) cyclodimerised on treatment with lithium diisopropylamide in dimethoxyethane at temperatures between -78°C and 0°C to 3-amino-4-cyano-1,5,5-trimethyl-1,3-cyclohexadiene (2) the structure of which was established by acid hydrolysis to the known 4-cyano-1,5,5-trimethyl-1-cyclohexene-3-one (3).

The base catalysed dimerisation of alkylidene malononitriles to cyclic enaminonitriles is well known [1,2]. Treatment of crotononitrile with potassium-benzyl, potassium[3] or tetraalkylammonium cyanides[4] yields a cyclic trimer as the major product together with a linear dimer, 3-methyl-4-hexene-1,4-dinitrile, which has arisen by Michael addition of the allylic anion via its α carbon atom to crotononitrile. We have discovered that 3-methyl-2-butenenitrile (1) undergoes facile dimerisation on treatment with lithium diisopropylamide (LDA) in dimethoxyethane or tetrahydrofuran at temperatures between -78°C to 0°C to give the cyclic enaminonitrile (2)[5,6]. On acid hydrolysis (HCl-EtOH, 1 hour at 80°C) the enaminonitrile (2) was converted into ketone (3)[7] which was identical with a sample prepared by base catalysed condensation of 5-methyl isoxazole with mesityl oxide as described by Eugster and co-workers[8] who presented unequivocal proof of its structure. The 1,2 relationship of the amino and cyano groups was further confirmed by heating (2) with formamide and formic acid at 200°C for 1 hour to give 4-amino-5,6-dihydro-5,5,7-trimethylquinoxaline (4)[9]. Enaminonitrile (2) was readily hydrogenated (5% Pd/C, atmospheric pressure) to (5)[10] which gave 4-amino-5,6,7,8-tetrahydro-5,5,7-trimethyl quinoxaline (6)[11] on reaction with formamide and formic acid at 200°C for 1 hour.

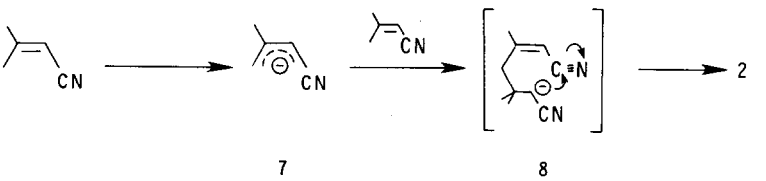
The proposed reaction mechanism involves initial deprotonation of (1) to form the allylic anion (7) which adds to a second molecule of (1) in a Michael reaction via the γ carbon atom to give anion (8) which undergoes Thorpe-Ziegler cyclisation to (2).

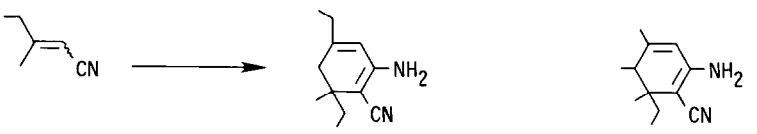
Reaction of 3-methyl-2-pentenenitrile (9) [60-40 trans/cis mixture] with LDA yielded the dimer (10) in 60% yield[12]; NMR analysis of the crude reaction mixture showed no sign of the isomeric enaminonitrile (11) which would have been formed by proton abstraction from the methylene group. Other examples of preferential deprotonation of the methyl group in similar systems have been reported. [13, 14].

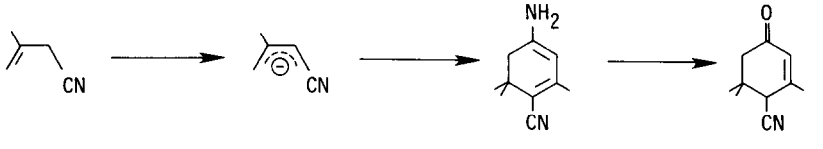
Recently Takabe and co-workers[15] reported that base catalysed dimerisation of 3-methyl-3-

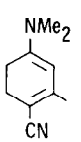


i. LDA, dimethoxyethane, -20°C ii. HCl-EtOH, 1h reflux iii. $HCONH_2$/HCOOH, 200°C 1h
iv. H_2, 5% Pd/C v. $HCONH_2$/HCOOH, 200°C 1h.









-butenenitrile (12) produced the 1,4-enaminonitrile (13) which they hydrolysed to 4-cyano-isophorone (14). The melting points and spectral data reported for (13) and (14) are virtually identical to those of (2) and (3) and since 3-methyl-3-butenenitrile and 3-methyl-2-butenenitrile should form the same allylic anion (7) on treatment with LDA, we propose that the structures (13) and (14) assigned by Takabe and co-workers to their products are incorrect. Further evidence in support of this is provided by the reported NMR spectrum of the 1,4-enaminonitrile (15)[16] in which the olefinic proton is found at δ 4.58; the olefinic proton reported for (13) is found at δ 5.5-5.66 which is comparable to the value we observed for the olefinic proton in (2) of δ 5.53-5.64.

The authors thank Mr C J Howarth for providing analytical data and Mr B Wright and Mr D Greatbanks for assistance with the NMR spectra.

References and Notes:

1. E C Taylor and A McKillop, "Advances in Organic Chemistry : Methods and Results", vol 7, Interscience (New York), 1 (1970).
2. J Mirek, M Adamczyk and M Mokrosz, Synthesis, 296 (1980).
3. J Shabtai, E Ney-Igner and H Pines, J.Org.Chem., 40, 1158 (1975).
4. D A White and M M Baizer, J.C.S. Perkin I, 2230 (1973).
5. All new compounds gave analyses for C,H, and N which were within ±0.4% of theory. Satisfactory infrared and proton magnetic resonance spectra were obtained for each new compound. TMS was used as internal standard.
6. Experimental procedure : A solution of 1 (8.1g, 0.1M) in dimethoxyethane is added to a stirred solution of lithium diisopropylamide (.05M) in dimethoxyethane maintained at -20°C The reaction mixture is allowed to warm to room temperature and is quenched with water. The product is isolated by chromatography on silica gel eluted with methylene chloride. Yield 7.4g (90%) Mp 94.5-95.5° (ether-petrol). IR ($CHCl_3$) 3500, 3390, 2180, 1660, 1620; NMR ($CDCl_3$, δ) 1.11 (6H,s); 1.83 (3H,s); 2.03 (2H,s); 4.0-4.50 (2H,bs); 5.53-5.64 (1H,m).
7. Mp 54-5°(Et_2O). Semicarbazone mp 173-4°. IR ($CHCl_3$) 2240, 1684, 1636. NMR ($CDCl_3$, δ) 1.15, 1.26 (6H,d); 1.97 (3H,s); 2.33 (2H,s); 3.30 (1H,s); 5.90-6.03 (1H,m).
8. C H Eugster, L Leichner and E Jenny, Helv.Chim.Acta, 66, 543 (1963).
9. Mp 215-220° (toluene). NMR ($CDCl_3$ δ) 1.30 (6H,s); 1.90 (3H,d); 2.21 (2H,s); 5.06 (2H,bs); 6.18 (1H,q); 8.25 (1H,s).
10. Mp 71-72.5° (petroleum-ether 60-80) NMR ($CDCl_3$ δ) 1.0 (3H,d); 1.13 (3H,s); 1.20 (3H,s); 1.4-2.4 (5H,m); 4.5 (2H,bs).

11. Mp 245° ($CHCl_3$). NMR (DMSO-d_6 δ) 1.07 (3H,d); 1.33 (3H,s); 1.58 (3H,s); 1.3-2.3 (3H, bm); 2.5-2.7 (2H,m); 6.55 (2H,bs); 8.3 (1H,s).
12. Mp 59-61° (Cyclohexane). NMR ($CDCl_3$ δ) 0.8-1.2 (9H,m); 1.38-1.62 (2H,q); 1.86-2.28 (4H,m); 4.34 (2H,bs); 5.57 (1H,s).
13. G Ege, H O Frey and E Schuck, Synthesis, 376 (1979).
14. J A Katzenellenbogen and A L Crumrine, J.A.C.S., 96, 5662 (1974).
15. K Takabe, S Ohkawa, T Sato, G H Tang and T Katagiri, Tet.Letters, 3883 (1980)
16. I I Afonina, G and F Ya Perveev, Zh.Org.Khim., 10, 1168 (1974).

(Received in UK 16 January 1981)