Tetrahedron. Vol. 30, pp. 3153 to 3157. Pergamon Press 1974. Printed in Great Britain

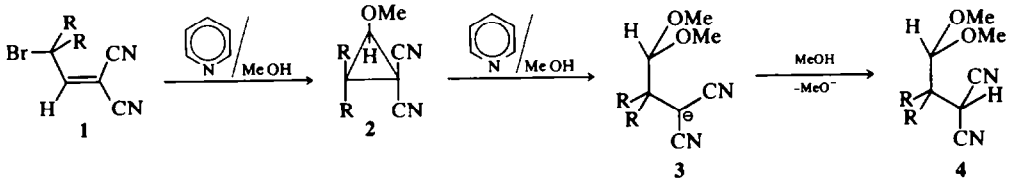
THE FORMATION OF Δ^2-PYRROLINES BY BASE CATALYSED NITRILE DIMERISATION

H. J. STORESUND* and P. KOLSAKER
Department of Chemistry, University of Oslo, Blindern, Oslo 3, Norway

(*Received in the UK 2 April 1974; Accepted for publication 7 May 1974*)

Abstract—The reaction of (1-bromocyclohexyl)methylidenemalonitrile and 2-bromo-2-methylpropylidenemalonitrile with sodium methoxide in methanol has been shown to give high yields of Δ^2-pyrrolines in a Thorpe reaction involving two initially formed nitrile products. The by-products formed, (hexahydrobenzaldehyde dimethyl acetal)-1-malonitrile and 1,1-dicyano-2,2-dimethyl-3,3-dimethoxy propane, respectively, were shown to be the only products when the malonitriles were treated with pyridine in methanol. On the action of acid, the Δ^2-pyrrolines aromatised to yield 1,2-dihydro-3H-pyrrolizine products. Structure determinations were based on IR, UV, NMR and MS. The different reaction paths have been discussed.

The formation of cyclopropanes by reaction of strong nucleophiles with allylic bromides carrying electron withdrawing γ-substituents[1,2] is in some respects analogous to the Favorskii rearrangement. In both cases the early step in the reaction appears to be the generation of a carbanion in the γ-position to the halo atom which is expelled in a subsequent (or simultaneous) ring closure reaction. Contrary to the observed stability of the cyclopropane products to the nucleophilic medium in the former reaction, the proposed cyclopropanones in the Favorskii rearrangement is readily cleaved by the base, now acting as a nucleophile. If the very reactive allylic bromide (1) is treated with a large excess of pyridine in methanol, the similarities with the Favorskii rearrangement become more obvious. Formation of the open acetal (4) is best explained by invoking nucleophilic attack on the 2-position in the initially formed cyclopropane (2):



a: R + R = $(CH_2)_5$
b: R = Me

SCHEME 1.

If the reaction was quenched after a few minutes, NMR revealed a mixture of (2) and (4) which could not, however, be separated by fractional distillation. Reactions analogous to the conversion of (2) into (4) have been reported on simple cyclopropanes having strongly electron withdrawing geminal substituents.[3]

Changing the weakly basic and nucleophilic medium pyridine/methanol to sodium methoxide in methanol, the outcome of the reaction of (1) differed significantly:

(A) R + R = $(CH_2)_5$

Addition of an equivalent amount of the base to a methanolic solution of (1) at *ca* 25° caused an immediate precipitation of an organic compound. Contrary to the essentially quantitative yield of (4) in pyridine/methanol, the yield of (4) in the latter reaction was never found to exceed *ca* 20%. At high concentration of both reactants the yield of the unknown product was practically quantitative. Its molecular weight of *ca* 414 (vapour pressure osmometric measurements) indicates a dimer.

Bearing in mind the obviously acidic properties of the acetal (4) together with the non-formation of the high molecular weight product in pyridine/methanol, the approach of characterisation was focused on the corresponding base (3) as a possible precursor for the unknown compound.

The neutral reaction of the mixture at any stage during the addition of the base, indicates an immeasurably fast rate of consumption (product formation). It is reasonable to assume that also in this medium the reaction starts by attack of methoxide on the β-position in the malonate (1)

producing the spiro compound (2). When more base is added, it competetively attacks 1 (to produce 2) and (2) to yield the acetal anion (3) which may act as a powerful nucleophile.

If the intense band at 2180 cm^{-1} in IR (see below) is due to cyano group absorbance, the existence of an enaminonitrile function in the dimer is very probable.[4] This suggests the possibility of a Thorpe-type reaction under the given conditions. The initial product in a normal Thorpe reaction involving geminal dicyano compounds, is a relatively ustable α-cyano imine which shows a great tendency to tautomerise, if possible, to a much more stable enaminonitrile. If the nitriles are equal, the Thorpe reaction is known to proceed only if catalytic amounts of a strong base are present.[5] In this particular case, however, if the nitrile (4) was subjected to Thorpe reaction conditions, no dimerisation seemed to occur. If different nitriles are used, and particularly if one is appreciably more acidic than the other, the Thorpe reaction often proceeds very smoothly.[6] If the acetal anion (3) adds in a Thorpe manner to the cyano group in the intermediate neutral spiro compound (2), the α-cyano imine (5) is formed.

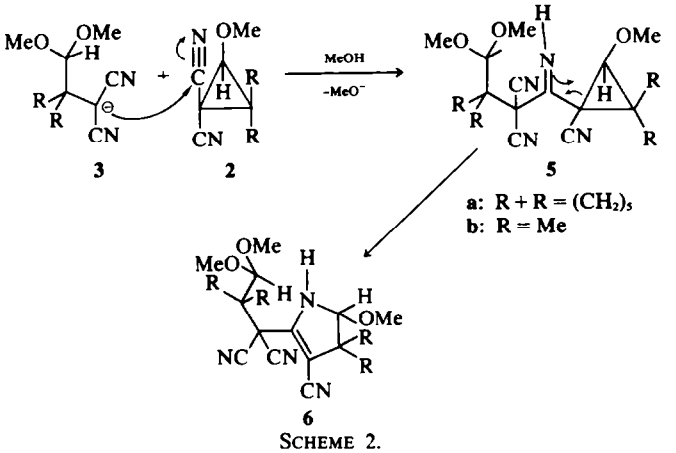
known to be characteristic of nitriles.[7]

IR (KBr) shows sharp bands at 3380 cm^{-1} (m), 2240 cm^{-1} (w), 2180 cm^{-1} (m) and 1610 cm^{-1} (s). The low-intensity band at 2240 cm^{-1} is reasonably due to the unconjugated cyano groups in 6. The strong band at 1610 cm^{-1} agrees well with the observed stretching frequencies of the carbon-carbon double bond in enaminonitriles.[4] In comparison, the enaminonitrile (7) shows nitrile absorbance at 2180 cm^{-1} (m) (conj), at 2240 cm^{-1} (w) (unconj) and a $\nu C{=}C$ at 1608 cm^{-1} (s).[4]

Replacing the N–H-proton in 6 with deuterium was effected by recrystallisation of the enaminonitrile from tetradeutromethanol. IR showed the expected shift lowering of the stretching frequency from 3380 cm^{-1} to 2450 cm^{-1}.

UV of the compound ($\lambda_{max\,6}$ 269 nm, ϵ 14·800 (MeOH), $\lambda_{max\,7}$ 263 nm, ϵ 14·400 (EtOH)) further substantiates the assignment of the enaminonitrile structure.[4]

NMR (δ-values, acetone-d_6) shows a broad 1-proton signal at *ca* 7·8 ppm, consistent with the N-H-proton in 6; a 1-proton doublet (poorly resolved) at 4·98 ppm which degenerates into a sharp 1-proton singlet simultaneously with the



SCHEME 2.

Because of

(1) the susceptibility of nucleophilic attack on the 2-position in the cyclopropane ring (analogous to the ring opening of 2),

(2) the energetically unfavourable α-cyano imine function lacking the possibility for prototropic change (no α-hydrogens),

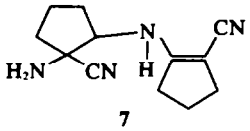
(3) a possible proximity effect,

the σ-electrons in the polarised C_1–C_2 bond in the cyclopropane ring in 5 may act as a nucleophile in the depicted way to produce the Δ^2-pyrroline (6; MW: 412; Scheme 2).

MS of the dimer gave M + 1(*m/e* 413) and, like the acetal (4), a base peak at *m/e* 75 likely to be due to the formation of the stable dimethoxy carbonium ion from the acetal function in the molecule. The (M + 1)-peak, formed by ion-molecule reaction, is

disappearance of the N-H-proton on the addition of deuterium oxide. This is in accordance with the expected behaviour of the two protons in the pyrroline ring in 6. A 1-proton singlet recorded at 4·15 ppm corresponds well with the acetal proton and so does the 20-proton multiplet at 1·0–2·3 ppm with the cyclohexyl protons. The three 3-proton singlets at 3·52, 3·48 and 3·33 ppm must be due to the three methoxy groups in 6. As the chiral centre in the molecule is relatively far away from the acetal group, it is somewhat difficult to explain why the acetal OMe groups should have detectably different magnetic environments. MS and the chemical properties, however, support the presence of an acetal group in the molecule.

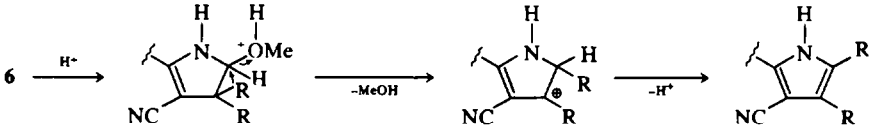
In order to confirm the presence of an acetal function in the molecule, the dimer was treated



7

with TFA at room temperature. An immediate reaction occurred leading to a single product which gave $M^+(m/e$ 348) by MS and thus indicated that the pyrroline (**6**) looses two molecules of methanol under acidic conditions. This could be verified by NMR (δ-values, TFA) showing a 1-proton singlet at 5·5 ppm, a 3-proton singlet at 3·6 ppm, a *ca* 4-proton multiplet at 2·6–3·1 ppm and a *ca* 16-proton multiplet at 1·2–2·3 ppm.

IR (KBr) shows the absence of N-H-absorbance, but there are still two nitrile absorbances at 2240 cm^{-1}(w) and at 2215 cm^{-1}(m); the band at 1610 cm^{-1} in the parent compound has vanished but instead two new bands at 1570 cm^{-1}(m) and at 1525 cm^{-1}(m) have appeared. A Raman-spectrum of the product did not show additional bands but intensity of the two new bands in the C=C region was greatly increased. The low νC=C frequencies in IR (Raman) suggest cyclic conjugation which was confirmed by UV analysis of the compound giving λ_{max} 225 nm, ϵ 7700 and λ_{max} 263 nm, ϵ 5800 (MeOH). The spectroscopic data correspond well with the spectroscopic properties of pyrrols reported in the literature.[8,9] The aromatisation of the pyrroline system is best illustrated by a concerted 1,2-alkyl shift and expulsion of methanol followed by elimination of a proton as depicted below:

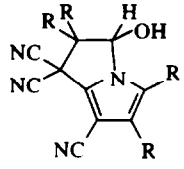


SCHEME 3.

The elimination of a further molecule of methanol is explained by invoking nucleophilic attack on a protonated acetal group by the N atom which in pyrrols is much less basic than ether oxygens. The spectroscopic data observed for the product are all in excellent agreement with those expected for the 1,2-dihydro-3H-pyrrolizine derivative (**8**).

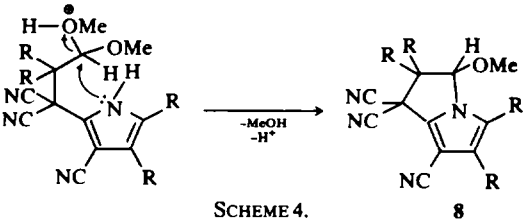
On treatment of the pyrroline (**6**) with *aqueous* TFA, a much slower reaction occurred. The final product gave a UV spectrum identical to that of **8**. The IR spectrum showed, contrary to the spectrum of **8**, a strong OH absorbance at 3500 cm^{-1}. MS gave $M^+(m/e$ 334) and NMR (δ-values, TFA) showed a 1-proton singlet at 6·0 ppm, a *ca* 4-proton multiplet at 2·6–3·1 ppm and a *ca* 16-proton multiplet at 1·2–2·3 ppm.

These data are all consistent with the 1,2-dihydro-3H-pyrrolizine (**9**). As the pyrrolizine (**8**) was shown to be stable in aqueous TFA (**8**, **9**), the most plausible way to explain the formation of **9** is to consider hydrolysis of the acetal group (to yield an aldehyde) prior to the ring closure reaction.



9

a: R + R = $(CH_2)_5$
b: R = Me



SCHEME 4. **8**

(B) R = CH_3

The original aim of this investigation was to prepare the *spiro* compound (**2A**) planned used for conformational studies.[10] As the outcome of this reaction turned out to be rather unexpected, a simpler system was sought in order to verify the conclusions drawn above. Replacing the cyclohexyl group in **1A** with two Me substituents might give a clearer picture of the reactions and particularly the aromatisation process.

When the allylic bromide (**1**) was added sodium methoxide in exactly the same way as in the cyclohexyl case, no precipitation of a dimer took place. A yield of only 5% of a soluble dimer together with *ca* 90% of the acetal (**4**) could be isolated. The spectroscopic properties of the dimer are all in complete agreement with the Δ^2-pyrroline structure **6** (Scheme 2).

Any process leading to deviation from unity in the ratio of 2/3 will cause a reduced yield of the dimer. It is apparent in the present case that the cleavage of the methyl substituted cyclopropane occurs more readily than the nucleophilic ring opening of the spiro analog (Scheme 1). The difference in reactivity can reasonably be attributed to the different degree of steric hindrance to nucleophilic approach in the two cyclopropanes. To make the base more indiscriminate, it was added to the bromide in one portion. The yield of the dimer thus increased to *ca* 60%.

The acid catalysed aromatisation (Scheme 3), which could be followed by NMR by measuring the gradual appearance of the two down-field singlets due to the Me groups attached to the aromatic system, turned out to be a much slower process than the corresponding reaction in the cyclohexyl analog. Furthermore, contrary to the unambiguous formation of **8** from the cyclohexyl substrate, the final product in this case was shown to be a mixture of **8** *and* **9** the ratio of which being dependent on the concentration of the dimer. The observed rate difference in the two aromatisation processes, in which the alkyl shift clearly is the rate-determining step, must be ascribed to the greater migratory aptitude of a secondary alkyl group. Furthermore, the product composition in the latter reaction shows that the hydrolysis of the acetal function now competes with the ring closure reaction.

Except hydrolysis of the acetal group, no other reactions seemed to take place on prolonged (>72 h) treatment of the dimer with *aqueous* TFA.

It thus appears that the ring closure reaction (Scheme 4) occurs *after* the aromatisation indicating a lower nucleophilicity of the nitrogen atom in the pyrroline as compared with the reactivity of the pyrrole nitrogen.

EXPERIMENTAL

General. The spectroscopic data quoted in this investigation were recorded on a Varian A-60A NMR spectrometer, Perkin-Elmer 457 IR spectrophotometer, Perkin-Elmer UV spectrophotometer, Cary 81 Raman spectrophotometer and AEI MS 902 mass spectrometer. Knauer Vapour Pressure Osmometer was used in the molecular weight determination.

The mps given are all uncorrected.

(1-*Bromocyclohexyl*)*methylidenemalonitrile* (**1A**). Preparation of **1A** was effected by refluxing the corresponding nonbrominated analog with NBS in CCl_4 using dibenzoyl peroxide as catalyst and UV irradiation from an external lamp. After *ca* 13 h the precipitated succinimide was filtered off and the reddish soln was washed with water and $Na_2S_2O_3$aq. The dried soln was then refluxed for ½ h with active charcoal. The resulting semi-solid material was extracted several times with ether (5%) in light petroleum (40–60°) at 30° and the combined extracts cooled to −60°. Light yellow needles of **1**, m.p. 50–52° were obtained (yield 45%). (Found: C 50·4, H 4·4, N 11·6. Calc. for $C_{10}H_{11}N_2Br$: C 50·2, H 4·6, N 11·7%).

2-*Bromo*-2-*methylpropylidenemalonitrile* (**1B**). The Me analog was made in the same way as described above. The crude product was distilled, b.p. 65–66°/0·04 mm Hg and the distillate was made crystalline by treatment with ether at −30°, m.p. 28–29°C (yield 30%). (Found: 42·2, H 3·5. Calc. for $C_7H_7N_2Br$: C 42·2, H 3·5%).

(*Hexahydrobenzaldehyde dimethyl acetal*)-1-*malonitrile* (**4A**). Malonate (**1A**—0·01 mole), dissolved in MeOH (25 ml), was added pyridine (0·1 mole) in MeOH (25 ml). After being kept at 25° for 24 h, the mixture was poured into water/ether, the ether layer being washed several times with water. The crude product gave on distillation in *vacuo* **4A**, b.p. 135°/0·25 mm Hg (yield 75%). MS gave M-31 (*m/e* 191) (base peak, *m/e* 75). NMR (δ in ppm, $CDCl_3$) 1·0–2·3, 10 H, m; 3·58, 6 H, s; 4·42, 1 H, s; 4·08, 1 H, s. (Found: C 65·0, H 7·9, N 12·8. Calc. for $C_{12}H_{18}O_2N_2$: C 64·8, H 8·1, N 12·6%).

Acetal (**4A**-1 mM) was dissolved in MeOH (5 ml) and the mixture added to saturated solution of 2,4-dinitrophenylhydrazine in 2 N HCl (20 ml). The yellow hydrazone was recrystallised from EtOAc at −35° yielding orange crystals m.p. 226–227°. (Found: C 54·1, H 4·5. Calc. for $C_{16}H_{16}O_4N_6$: C 53·9, H 4·5%).

1,1-*Dicyano*-2,2-*dimethyl*-3,3-*dimethoxy propane* (**4B**). The same procedure was adopted as the one described above. B.p. 98–100°/0·6 mm Hg (yield 80%). MS gave M-31 (*m/e* 151) (base peak, *m/e* 75). NMR (δ in ppm, $CDCl_3$) 1·65, 6 H, s; 3·60, 6 H, s; 4·10, 1 H, s; 4·38, 1 H, s (Found: C 59·1, H 7·8. Calc. for $C_9H_{14}O_2N_2$: C 59·3, H 7·7%).

Δ^2-*Pyrroline* (**6A**). Malonate (**1A**—10 mM), dissolved in abs MeOH (20 ml), was added an equivalent amount of NaOMe in MeOH (5 ml) during 5 min at 25°. The dimer, that started to precipitate during the addition of the base, was filtered off after 10 h and recrystallised from MeOH M.p. 222–3° (yield 65%). (Found: C 67·1, H 7·8, N 13·6. Calc. for $C_{23}H_{32}N_4O_3$: C 67·0, H 7·8, N 13·6%).

Δ^2-*Pyrroline* (**6B**). Malonate (**1B**—10 mM), dissolved in abs MeOH (20 ml), was added in one portion the equiv amount of NaOMe in MeOH (5 ml). After *ca* 2 h, the mixture was poured into ether (500 ml) which then was washed with water. On evaporation of the dried ether soln, the dimer started to crystallise. It was filtered off and recrystallised from MeOH to yield nice, colourless crystals, m.p. 152–3° (57% yield). MS gave M-31 (*m/e* 301) (base peak, *m/e* 75). NMR (δ in ppm, $CDCl_3$), 1.28, 3 H, s; 1·32, 6 H, s; 1·50, 3 H, s; 3·35, 3 H, s; 3·55, 6 H, s; 4·10, 1 H, s; 4·41, 1 H, d (poorly resolved); *ca* 7·9 1 H (broad). IR (KBr) 3380 cm^{-1} (m), 2240 cm^{-1} (w), 2180 cm^{-1} (m) and 1610 cm^{-1} (s). UV (MeOH) λ_{max} 266 nm, ϵ 15·300. (Found: C 61·4, H 7·4, N 16·9. Calc. for $C_{17}H_{24}O_3N_4$: C 61·4, H 7·3, N 16·9%).

1,2-*Dihydro*-3H-*pyrrolizine* (**8A**). Δ^2-pyrroline (**6A**—1 mM) was dissolved in anhyd TFA (5 ml) and kept at 20° for 2 h. The mixture was then extracted with ether/$NaHCO_3$aq and worked up in the usual way. The colourless product was recrystallised from MeOH, m.p. 259–260° (yield 80%). (Found: C 72·2, H 7·2, N 16·0. Calc. for $C_{21}H_{24}N_4O$: C 72·4, H 6·9, N 16·1%).

1,2-*Dihydro*-3*H*-*pyrrolizine* (**9A**). Δ^2-pyrroline (**6A**—1 mM) was dissolved in TFA/20% H_2O (10 ml) and kept at 20° for 24 h. The usual work-up yielded a colourless product which on recrystallisation from MeOH gave **9A**, m.p. 228–9° (75% yield). (Found: C 71·8, H 6·4. Calc. for $C_{20}H_{22}N_4O$: C 71·8, H 6·6%).

1,2-*Dihydro*-3H-*pyrrolizine* (**8B** and **9B**). Δ^2-pyrroline (**6B**—1 mM) was dissolved in anhyd TFA (10 ml) and kept at 20° for 18 h. The usual work-up yielded a colourless oil which consisted of a *ca* 1:1 ratio of **8B** and **9B**. CCl_4 dissolved **8B** completely leaving behind the crystalline, insoluble **9B** which was recrystallised from ether at −30°, m.p. 177–8°. MS gave M^+ (*m/e* 254). NMR (δ in ppm, $CDCl_3$), 1·40, 3 H, s; 1·58, 3 H, s; 2·08, 3 H, s; 2·22, 3 H, s; 4·10, 1 H, s; 5·40, 1 H, s. IR (KBr) 3500 cm^{-1} (s), 2240 cm^{-1} (w), 2215 cm^{-1} (m), 1570 cm^{-1} (m) and 1525 cm^{-1} (m). UV (MeOH) λ_{max} 227 nm, ϵ 7900, λ_{max} 266 nm, ϵ 6000. (Found: C 66·0, H 5·6, N 21·9. Calc. for $C_{14}H_{14}N_4O$: C 66·2, H 5·5, N 22·0%).

The CCl_4 filtrate contained almost pure **8B** which also was recrystallised from ether at low temp, m.p. 121–3°. MS gave M^+ (*m/e* 268). NMR (δ in ppm, $CDCl_3$), 1·38, 3 H, s; 1·60, 3 H, s; 2·12, 3 H, s; 2·28, 3 H, s; 3·55, 3 H, s;

4·95, 1 H, s. IR (KBr) 2240 cm^{-1} (w), 2215 cm^{-1} (m), 1570 cm^{-1} (m) and 1525 cm^{-1} (m). The UV spectrum was identical to that of **9B**. (Found: C 67·1, H 5·8. Calc. for $C_{15}H_{16}N_4O$: C 67·2, H 5·9%).

REFERENCES

[1]P. Kolsaker and H. J. Storesund, *Chem. Comm.* 375 (1972)

[2]H. J. Storesund and P. Kolsaker, *Tetrahedron Letters* 2255 (1972)

[3]J. M. Stewart and H. H. Westberg, *J. Org. Chem.* **30**, 1951 (1965)

[4]S. Baldwin, *J. Org. Chem.* **26**, 3288 (1961)

[5]Z. Rappoport, *The Chemistry of the Cyano Group.* Interscience (1970)

[6]A. Dornow, I. Kuhlcke and F. Baxmann, *Chem. Ber.* **82**, 254 (1949)

[7]F. W. McLafferty, *Analyt. Chem.* **34**, 26 (1962)

[8]U. Eisner and R. L. Erskine, *J. Chem. Soc.* 971 (1958)

[9]U. Eisner and P. H. Gore, *Ibid.* 922 (1958)

[10]P. Kolsaker, H. J. Storesund, J. Schaug, G. Wøien Larsen, *Acta Chem. Scand.* **27**, 1460 (1973)