BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 45, 557—561 (1972)

Studies on Stable Free Radicals. VII.[1] The Mechanism for Cyclization Reaction of α-Amino Nitriles with Carbonyl Compounds

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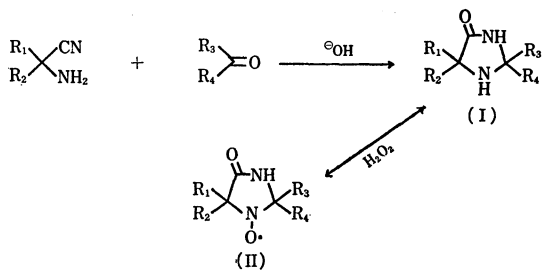
(Received July 15, 1971)

Substituted 4-oxoimidazolidines were prepared by the condensation of α-amino nitriles with carbonyl compounds, or by the self-condensation of α-amino nitriles. The mechanism of the reaction was studied. The mass spectrum of the condensation product obtained by the reaction of cyclohexanone with 1-amino-1-cyano-^{15}N-cyclohexane (III) or by the self-condensation of III, and the ESR spectrum of corresponding nitroxide radical obtained by the oxidation of the respective condensation products served to elucidate the reaction mechanisms for these condensation reactions. The mechanism for the self-condensation of α-amino nitriles proposed previously was corrected from the spectral data of the reaction product. Possible mechanisms for these condensation reactions are proposed.

In a previous paper,[2] we reported that α-amino nitriles react with aldehydes or ketones to give substituted 4-oxoimidazolidines (I) in an alcoholic solvent and the resulting products yield corresponding stable nitroxide radicals (II) by oxidation.

On the other hand, Noland *et al.*[3] reported that the self-condensation of 1-amino-1-cyanocyclohexane afforded cyclohexane-1-spiro-2′-(4′-oxoimidazolidine)-5′-spiro-1″-cyclohexane (IVa) in the presence of sodium ethoxide in ethanol containing a trace of moisture.



1) Part VI: Ref. 2,

2) T. Toda, S. Morimura, E. Mori, H. Horiuchi, and K. Murayama, This Bulletin, **44**, 3445 (1971).

3) W. E. Noland, R. J. Sundberg, and M. L. Michaelson, *J. Org. Chem.*, **28**, 3576 (1963).

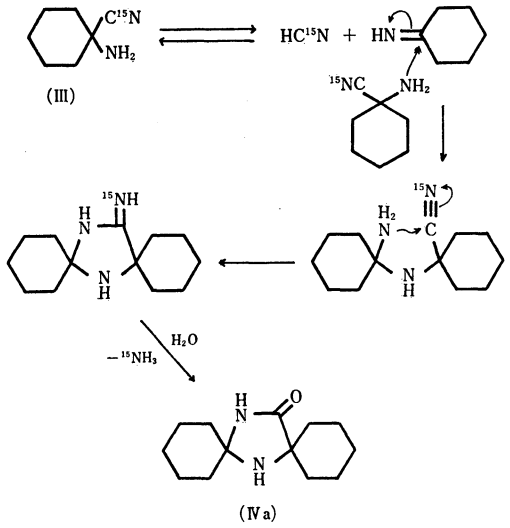


Chart 1.

They proposed for the mechanism of this self-condensation the sequence shown in Chart 1.

This paper deals with the mechanism for the cyclization reaction of α-amino nitriles with carbonyl compounds.

The reaction mechanism was clearly obtained from spectroscopic analysis of the product from the reaction of cyclohexanone with 1-amino-1-cyanocyclohexane (III) in which the nitrogen of cyano-group was replaced by ^{15}N.

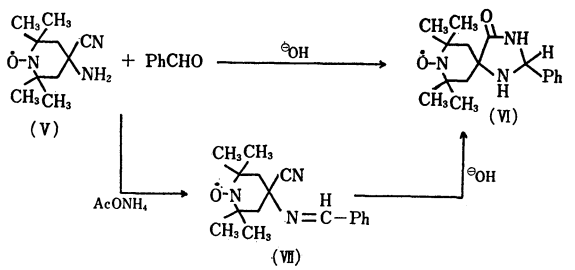
We will also discuss the reaction mechanism proposed by Noland *et al.*[3]

Results and Discussion

From our synthetic method for imidazolidinones (I), it was expected that the intermediate would be the Schiff base of an α-amino nitrile with a carbonyl compound.

In order to confirm this, the following reaction was carried out: The condensation of 4-amino-4-cyano-2,2,6,6-tetramethylpiperidine-1-oxyl (V) with benzaldehyde gave 1,3,8-triaza-2-phenyl-4-oxo-7,7,9,9-tetramethyl-spiro[4.5]decane-1-oxyl (VI) in the presence of a catalytic quantity of aqueous sodium hydroxide in ethanol solution, while the reaction of V with benzaldehyde yielded the Schiff base VII under reflux in benzene using ammonium acetate as a catalyst.

The Schiff base VII thus obtained, was treated under similar conditions as in the formation of VI from V, and VI was obtained in good yield.



From the results, we assumed the mechanism for cyclization reaction of α-amino nitriles with carbonyl compounds as shown in Chart 2.

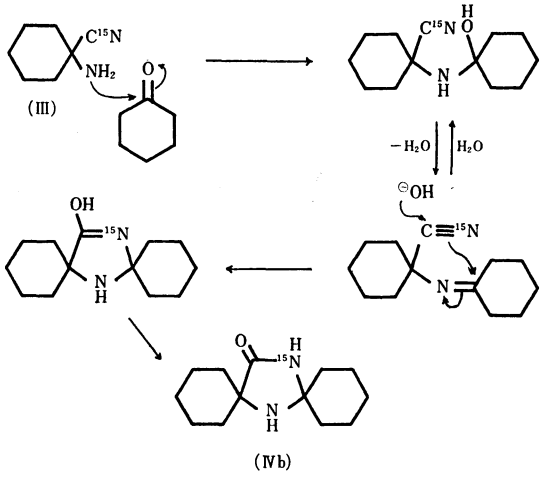


Chart 2.

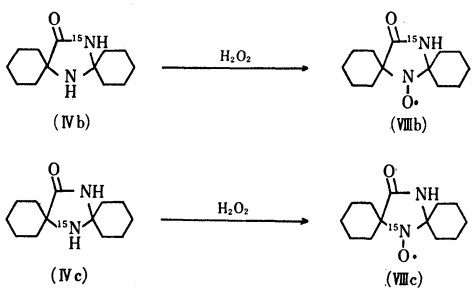
In order to confirm the assumption and the mechanism proposed by Noland and co-workers,[3] the following experiments were carried out.

The ^{15}N-substituted α-amino nitrile, 1-amino-1-cyano-^{15}N-cyclohexane (III) was prepared by the Strecker reaction of cyclohexanone with ^{15}N-sodium cyanide (95% ^{15}N content) and ammonium chloride. In a similar manner as reported previously,[2] we obtained product A by the reaction of III with cyclohexanone. Likewise, the self-condensation of III in the same way as reported by Noland *et al.*[3] afforded product B. The structures of these products A and B were both designated as cyclohexane-1-spiro-2′-[4′-oxoimidazolidine(3′-^{15}N)]-5′-spiro-1″-cyclohexane(IVb) from their IR spectra. The results are given below.

If the reaction of III with cyclohexanone follows the mechanism as shown in Chart 2, ^{15}N should be incorporated at the 3-position of the imidazolidine ring in product A.

Likewise, if the self-condensation of III proceeded as shown in Chart 1, product B would have no ^{15}N atom in the molecule.

The incorporation of ^{15}N in A or B, can be confirmed by mass spectra measurements; the position of ^{15}N in imidazolidine ring (IVb or IVc) can be determined by ESR measurements of tne corresponding nitroxide radicals (VIIIb or VIIIc) prepared by oxidation[4]



4) K. Murayama, S. Morimura, and T. Yoshioka, This Bulletin, **42**, 1640 (1969).

of A or B with hydrogen peroxide, since in the ESR spectrum triplet lines resulting from a ^{14}N nucleus are expected for VIIIb and doublet lines resulting from a ^{15}N nucleus for VIIIc, respectively.

In the high resolution mass spectrum of product A, the expected molecular ion peak at *m/e* 223.171 assigned to $C_{13}H_{22}ON^{15}N$, and a fragment peak at *m/e* 180.116 to $C_{10}H_{15}ON^{15}N$ were found, while in the case of the imidazolidinone IVa containing no ^{15}N, the corresponding peaks at *m/e* 222.277 ($C_{13}H_{22}ON_2$) and 179.119 ($C_{10}H_{15}ON_2$) were observed.

Oxidation of compound IVa by hydrogen peroxide afforded the corresponding nitroxide radical (VIIIa).[4] Similarly, oxidation of product A gave the nitroxide radical (VIIIb) which was given the following assignment.

Since triplet lines (a_N=14.1 gauss) were observed in the ESR spectrum of this oxidation product, the structure of product A was assigned to IVb. Thus, the mechanism shown in Chart 2 is plausible for the cyclization reaction of α-amino nitriles with carbonyl compounds.

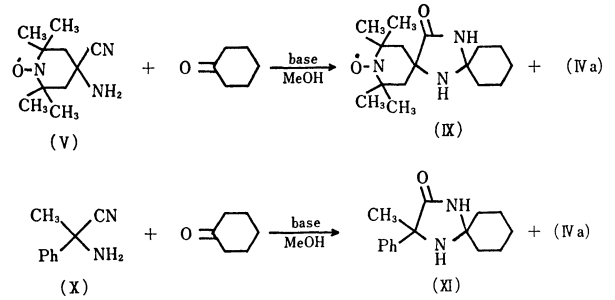
On the other hand, the structure of product B was also assigned to IVb from the mass spectrum of product B and ESR spectrum of the corresponding nitroxide radical.

This shows that the self-condensation reaction of α-amino nitrile does not follow the mechanism (Chart 1) proposed by Noland *et al.*,[3] but might proceed by a mechanism as shown in Chart 5 for the following reasons.

In the cyclization reaction of α-amino nitriles with carbonyl compounds, we found that imidazolidinone compounds I having different substituents from those expected from the mechanism (Chart 2) were obtained.

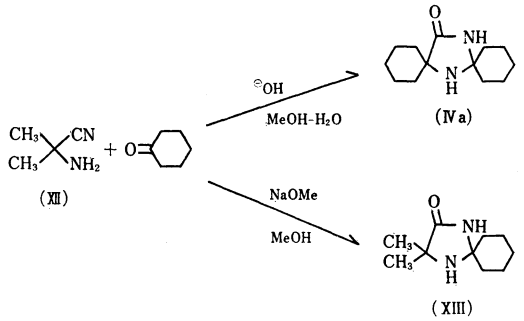
Treatment of amino nitrile V with cyclohexanone under the same conditions mentioned above gave the normal reaction product, cyclohexane-1-spiro-2′-(4′-oxoimidazolidine)-5′-spiro-4″-(2″,2″,6″,6″-tetramethylpiperidine-1″-oxyl) (IX) and the abnormal reaction product with exchanged substituents IVa, in 44.5% and 36.0% yield, respectively.

Similarly, the reaction of α-amino-α-phenylpropionitrile (X) with cyclohexanone afforded the normal product 1,4-diaza-2-methyl-2-phenyl-3-oxo-spiro-[4.5]-decane (XI) and the same substituent-exchanged product IVa.



Further experiments showed that in these reactions, the presence of a small amount of water increased the yield of the substituent-exchanged product IVa.

The reaction of α-amino-isobutyronitrile (XII) with cyclohexanone in the presence of basic catalyst was carried out in water free methanol and in methanol containing a small quantity of water. In the former case the normal reaction product 1,4-diaza-2,2-dimethyl-3-oxo-spiro[4.5]decane (XIII) was obtained in 90% yield, while in the latter the substituent-exchanged product IVa in 80% yield.



Two possible processes are considered for these exchange reactions: iminopropane reacts with cyclohexanone to give iminocyclohexane (Chart 3); iminopropane is decomposed by water to acetone and ammonia (Chart 4). Cyclohexanone is then converted into 1-amino-1-cyanocyclohexane in the reaction system and the exchange reaction product IVa is formed by the mechanism shown in Chart 2.

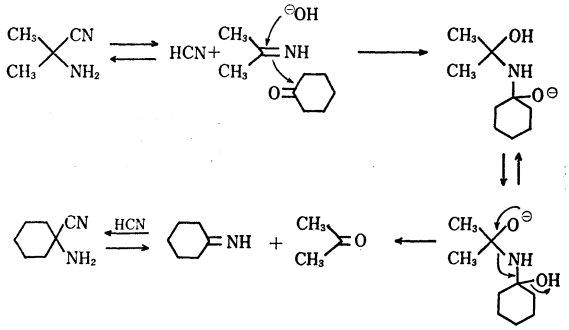


Chart 3.

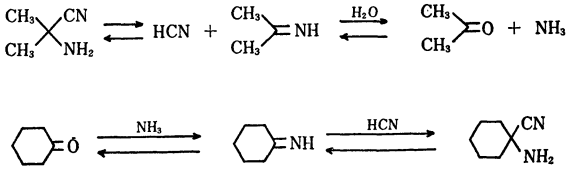


Chart 4.

The second assumption would be more reasonable in explaining the effect of water in promoting the formation of IVa.

In the case of the self-condensation of α-amino nitrile III, iminocyclohexane might also decompose into cyclohexanone and ammonia, and subsequently, the cyclohexanone thus formed would react with the amino nitrile III to give the imidazolidinone IVb by Chart 2 mechanism.

Consequently, the self-condensation reaction[3] of 1-amino-1-cyanocyclohexane might proceed by the mechanism shown in Chart 5.

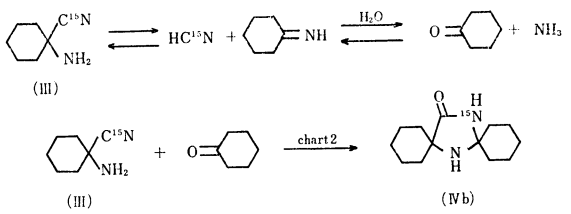


Chart 5.

Presumably the decomposition of iminopropane by water take place faster than that of iminocyclohexane, and cyclohexanone forms an α-amino nitrile more easily than other dialkyl ketones. This hypothesis can be supported by the fact that the reaction of the α-amino nitrile XII with methylisobutyl ketone gave only the normal product 2,2,5-trimethyl-2-isobutyl-4-oxoimidazolidine.[2]

Experimental

Melting points are uncorrected. The IR spectra were determined by means of nujol mulls and liquid films. The mass spectra were obtained using a JEOL-JMS-OIS mass spectrometer. The ESR spectra were recorded on a Hitachi MES 4001 type X-band spectrometer employing 100 kc modulation. Splitting constants were measured relative to the aqueous solution of Fermy's salt.

4-Cyano-4-benzilidenimino-2,2,6,6-tetramethylpiperidine-1-oxyl (VII). A solution of 2.0 g (10 mmol) of 4-amino-4-cyano-2,2,6,6-tetramethylpiperidine-1-oxyl (V)[2] and 1.1 g (10 mmol) of benzaldehyde in 50 m*l* of benzene containing 0.2 g of ammonium acetate was heated under reflux using a Dean-Stark water separator for 8 hr. The solution was cooled to room temperature, washed with water, dried over sodium sulfate and evaporated under reduced pressure to give 2.5 g (86.3%) of crude crystals VII. Recrystallization from benzene gave an analytical sample: mp 84.5°C. Found: C, 71.75; H, 7.82; N, 14.71%. Calcd for $C_{17}H_{22}ON_3$: C, 71.80; H, 7.81; N, 14.77%. IR (cm^{-1}): $\nu_{C\equiv N}$ 2230, $\nu_{C=N}$ 1648.

1,3,8-Triaza-2-phenyl-4-oxo-7,7,9,9-tetramethyl-spiro[4.5]-decane-8-oxyl (VI). (A) To a solution of 19.6 g (0.1 mol) of V[2] and 10.6 g (0.1 mol) of benzaldehyde in 30 m*l* of ethanol was added 1 m*l* of aqueous sodium hydroxide (40%) and the solution were stirred at room temperature for five days. After removal of ethanol under reduced pressure, the resulting crystalline solid was washed with water and dried in a vacuum. VI was obtained analytically pure by recrystallization from methanol: mp 184—185°C, yield 19.2 g (63.5%). Found: C, 67.46; H, 7.92; N, 13.81%. Calcd for $C_{17}H_{24}O_2N_3$: C, 67.52; H, 8.00; N, 13.90%. IR (cm^{-1}): $\nu_{C=O}$ 1703, ν_{NH} 3250 and 3350.

(B) A solution of 2.0 g (7 mmol) of VII and 1 m*l* of aqueous sodium hydroxide (40%) in 20 m*l* of methanol was stirred at room temperature for five days. A yield of 1.8 g (85.0%) of VI was obtained by a similar work-up to that mentioned above. The IR spectrum of the product was consistent with the authentic sample obtained in (A).

1-Amino-1-cyano-^{15}N-cyclohexane (III). A solution of 7.4 g (75 mmol) of cyclohexanone in 30 m*l* of methanol saturated with ammonia was added slowly to a stirred solution of 5.0 g of sodium cyanide-^{15}N (^{15}N content 95%)[5] and 9.3 g of ammonium chloride in 80 m*l* of aqueous ammonia (28%) at 0—5°C. Stirring was continued for 24 hr at room temperature. The resulting precipitate was removed by filtration and the methanol filtrates were evaporated under reduced pressure. The organic layer was extracted with 200 m*l* of diethyl ether, dried over potassium carbonate and evaporated under reduced pressure. The residual oil was distilled to give 5.5 g (64.6%) of III: bp 76—78°C/1 mmHg. IR (cm^{-1}): $\nu_{C\equiv N}$ 2200, ν_{NH} 3350, 3280, and 3200. Mass spectrum: $M^+=125$.

Cyclization Reaction of III with Cyclohexanone. To a solution of 1.5 g (12 mmol) of III and 1.4 g (12 mmol) of cyclohexanone in 10 m*l* of methanol was added 1 m*l* of a solution of sodium methoxide prepared by adding sodium (2.8 g) to 80 m*l* of methanol, with stirring at room temperature. Stirring was continued for 24 hr. After the solvent had been evaporated under reduced pressure, the resulting crystals were washed with water, dried *in vacuo*. Recrystallization from cyclohexane gave an analytical sample: mp 219—220°C, yield 2.2 g (79.1%). IR (cm^{-1}): $\nu_{C=O}$ 1687, ν_{NH} 3310, 3140, and 3010.

Self-condensation of III. To a solution of 3.8 g (30 mmol) of III in 15 m*l* of 98% (by weight) methanol was added 1 m*l* of a solution of sodium methoxide prepared as above, with stirring at room temperature. Stirring was continued for 24 hr. An analytical sample was obtained by a similar procedure as described above: mp 219—220°C, yield 2.8 g (80.0%). IR (cm^{-1}): $\nu_{C=O}$ 1687, ν_{NH} 3310, 3140, and 3010. Mass spectrum: $M^+=223.173$, $(M-C_3H_7)^+=180.115$.

Oxidation Reaction. (A) To a stirred solution of 0.6 g (27 mmol) of product A (IVb) in 4 m*l* of acetic acid was added 10 mg of ethylenediaminetetraacetic acid (EDTA) and 15 mg of sodium tungstate and then slowly 4 m*l* of aqueous solution of hydrogen peroxide (30%) at room temperature. The solution was stirred for additional 12 hr at room temperature. The resulting precipitate was separated by filtration, washed with water, and dried *in vacuo* to give 0.5 g (77.6%) of VIIIb: mp 227—228°C. IR (cm^{-1}): $\nu_{C=O}$ 1708, ν_{NH} 3160 and 3050. ESR (in benzene): $a_N=14.1$ gauss. (B). By a similar method to that described in (A), 0.5 g (77.6%) of VIIIb was obtained from 0.6 g (27 mmol) of the product B (IVb): mp 227—228°C. IR (cm^{-1}): $\nu_{C=O}$ 1708, ν_{NH} 3160 and 3050. ESR (in benzene): $a_N=14.1$ gauss.

Condensation of 4-Amino-4-cyano-2,2,6,6-tetramethylpiperidine-1-oxyl (V) with Cyclohexanone. A solution of 19.6 g (0.1 mol) of V[2] and 9.8 g (0.1 mol) of cyclohexanone and 1 m*l* of aqueous sodium hydroxide (40%) in 50 m*l* of methanol was stirred at room temperature for three days. After removal of methanol, 50 m*l* of benzene was added and the mixture was stirred at room temperature. After 1 hr, 8.0 g (36.0%) of crude crystals IVa separated; the precipitate was filtrated and washed with water. The crude material was recrystallized from ethanol to give a pure sample IVa which was confirmed by comparison of its IR spectrum with that of an authentic sample. The filtrate was dried over potassium carbonate, evaporated *in vacuo* to give 13.1 g (44.5%) of crude crystals IX. Recrystallization from petroleum ether gave an analytically pure sample: mp 201—202°C. Found: C, 65.22; H, 9.57; N, 14.26%. Calcd for $C_{16}H_{28}O_2N_3$: C, 65.27; H, 9.59; N, 14.27%. IR (cm^{-1}): $\nu_{C=O}$ 1705, ν_{NH} 3280.

Condensation of α-Amino-α-phenylpropionitrile (X) with Cyclohexanone. A mixture of 7.3 g (50 mmol) of α-amino-α-phenylpropionitrile (X) and 4.9 g (50 mmol) of cyclohexanone was heated at 50—60°C in the presence of

5) Available from the Institute of Physical and Chemical Research, Wako-shi, Saitama, Japan.

1 m*l* of sodium methoxide solution mentioned above. After 25 hr, 1.2 g (24.1%) of crude crystals IVa were separated by filtration, washed with water and dried *in vacuo*. By recrystallization from ethanol, IVa was obtained pure as shown by comparison of its IR spectrum and melting point with those of an authentic sample. The filtrate was dissolved in 50 m*l* of benzene, washed with water, dried over potassium carbonate and evaporated under reduced pressure. The residual oil was crystallized on adding petroleum ether to give 3.2 g (40.0%) of crude crystals XI. The crude material was recrystallized from petroleum ether to give an analytical sample: mp 130—131°C. Found: C, 73.69; H, 8.35; N, 11.21%. Calcd for $C_{15}H_{20}ON_2$: C, 73.77; H, 8.25; N, 11.21%. IR (cm^{-1}): $\nu_{C=O}$ 1695, ν_{NH} 3350, 3200 and 3095.

Condensation of α-Aminoisobutyronitrile (XII) with Cyclohexanone. (A). A solution of 8.4 g (0.1 mol) of α-aminoisobutyronitrile (XII) and 9.8 g (0.1 mol) of cyclohexanone and 1 m*l* of aqueous sodium hydroxide (40%) in 50 m*l* of 95% methanol (by weight) were stirred for three days at room temperature. A similar work-up as described above provided 17.8 g (85.0%) of IVa as shwon by comparison of its IR spectrum and melting point with those of an authentic sample. (B). The methanol used was distilled into a receiver containing dried anhydrous sodium sulfate and was used immediately. In a 100 m*l* flask was placed a solution of 8.4 g (0.1 mol) of α-aminoisobutyronirile (XII) and 9.8 g (0.1 mol) of cyclohexanone in 50 m*l* methanol and 1 m*l* of sodium methoxide solution was added. The flask was stoppered to exclude moisture and was heated at 40—50°C with stirring for 6 hr. After removal of methanol under reduced pressure, the resulting crystals were washed with water and dried *in vacuo*. Recrystallization from ethanol gave an analytical sample: mp 193—194°C, yield 16.4 g (90.0%). Found: C, 65.77; H, 9.84; N, 15.14%. Calcd for $C_{10}H_{18}ON_2$: C, 65.89; H, 9.96; N, 15.37%. IR (cm^{-1}): $\nu_{C=O}$ 1693, ν_{NH} 3190 and 3070.

The authors wish to thank Prof. Makoto Okawara, Tokyo Institute of Technology, for his valuable comments and Dr. G. Sunagawa, director of these laboratories, for his encouragement.