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REACTION OF CARBONYL COMPOUND WITH ISOCYANIDE

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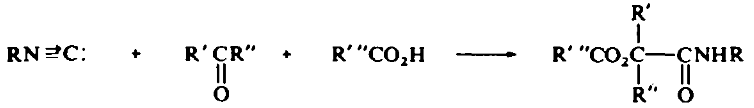
Abstract—The reaction of acetone with cyclohexyl isocyanide catalysed by BF_3-etherate at −78° yielded, after quenching with methanol, 2,3-bis(cyclohexylimino)-4,4-dimethyloxetane (II) as the main product and 2-methoxy-2-methyl-N-cyclohexylpropionamide (V) as a by-product. Based on the formation of V in the reaction of carbonyl compounds with cyclohexyl isocyanide catalysed by BF_3-etherate, a mechanistic scheme involving an imino-oxirane intermediate IV has been presented, which also offers a mechanistic explanation of the Passerini reaction. In the reaction of acetaldehyde with cyclohexyl isocyanide, catalysed by BF_3-etherate-pyridine, methyl 2-N-cyclohexylaminopropionate (VII) was detected, which also supports the formation of an imino-oxirane intermediate.

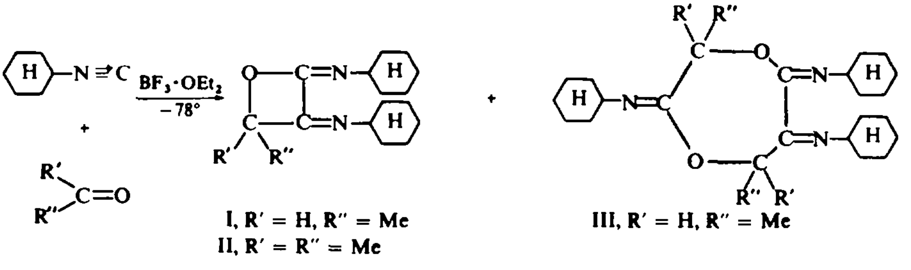
INTRODUCTION

Several mechanisms[1–4] have been proposed for the reaction of a carbonyl compound, isocyanide and carboxylic acid known as the Passerini reaction[5] which produces the amide of an α-acyloxy acid.



$$\mathrm{RN{\rightleftarrows}C{:}} \quad + \quad \mathrm{R'\underset{O}{\underset{\|}{C}}R''} \quad + \quad \mathrm{R'''CO_2H} \longrightarrow \mathrm{R'''CO_2\overset{R'}{\overset{|}{\underset{R''}{\underset{|}{C}}}}{-}\underset{O}{\underset{\|}{C}}NHR}$$

In an attempt to copolymerize acetaldehyde with cyclohexyl isocyanide in the presence of BF_3-etherate at −78°, cyclic co-oligomers, 2,3-bis(cyclohexylimino)-4-methyloxetane (I) and 2,5,6-tris(cyclohexylimino)-3,7-dimethyl-1,4-dioxacycloheptane (III) were produced in fairly high yields.[6]



I, R' = H, R'' = Me
II, R' = R'' = Me

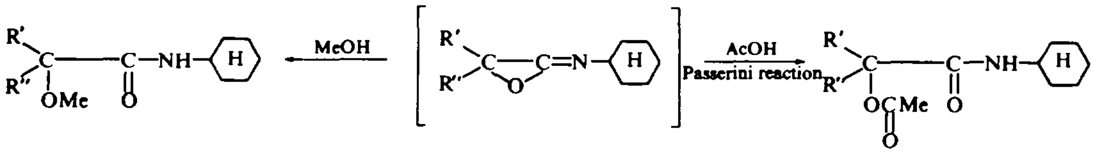
III, R' = H, R'' = Me

The formation of cyclic co-oligomers and the examination of the by-products in the reaction of cyclohexyl isocyanide with carbonyl compounds has indicated a new mechanistic scheme involving an imino-oxirane intermediate, which also serves as a mechanistic explanation of the Passerini reaction.

RESULTS AND DISCUSSION

The 4-membered cyclic ether, 2,3,-bis(cyclohexylimino)-4,4-dimethyloxetane (II) was produced in 64% yield in the reaction of acetone with cyclohexyl isocyanide using BF_3–etherate as catalyst (Experimental). In this reaction, the dioxacycloheptane derivative (7-membered cyclic co-oligomer) was not formed but a small amount of a by-product detected by GLC was identified as 2-methoxy-2-methyl-N-cyclohexylpropionamide (V).

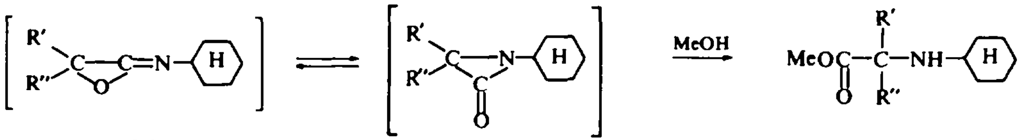
Based upon the formation of V, the imino-oxirane species (IV) may be proposed as the intermediate in the acid catalysed reaction of a carbonyl compound with the isocyanide.



V (R′ = R″ = Me) IV VI

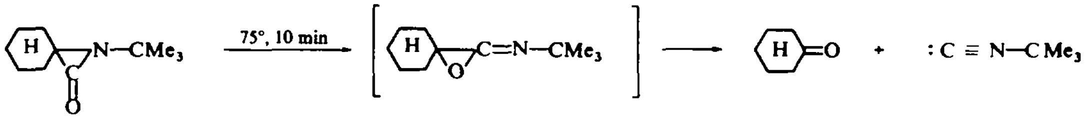
Compound V will be derived from the ring-opening reaction of IV with methanol. The ring-cleavage of IV with carboxylic acid will produce an amide of α-acyloxy acid VI which is the Passerini reaction.

The existence of the intermediate IV was substantiated by the reaction of acetaldehyde with cyclohexyl isocyanide at −78° using BF_3–etherate in the presence of a small amount of pyridine. No cyclic co-oligomer was obtained but a small amount of a product detected by GLC was identified as methyl 2-N-cyclohexylaminopropionate (VII). The latter would be derived from IV through the rearrangement of IV to α-lactam VIII.

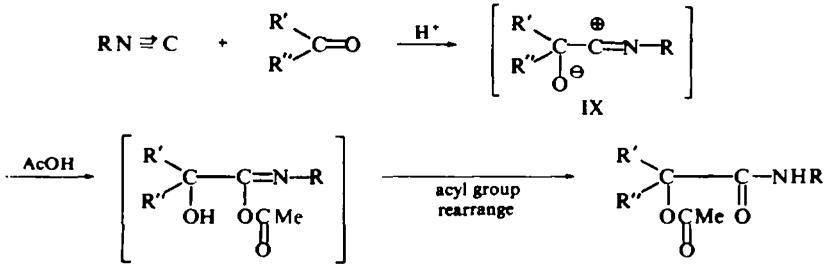


IV VIII VII (R′ = H, R″ = Me)

The rearrangement of IV into VIII is a reverse process of the rearrangment of α-lactam VIII into IV proposed by Sheehan,[7,8] to explain the pyrolysis of α-lactam into isocyanide and carbonyl compound.



For the mechanism of the Passerini reaction, the following scheme involving the zwitter ion intermediate IX followed by the acyl group rearrangement[3] has been suggested.

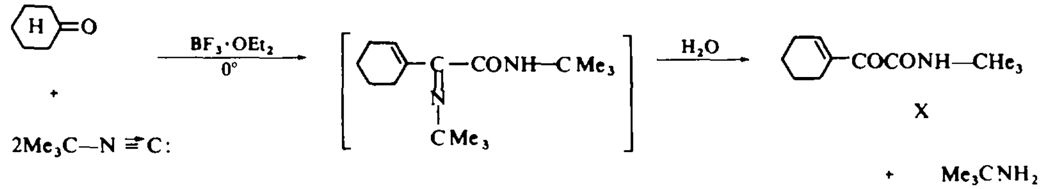


IX

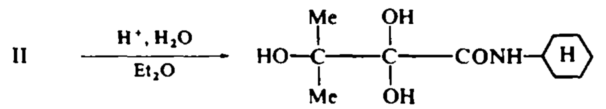
This scheme, however, is not applicable to the formation of V and VII in the present study, but on the other hand, the imino-oxirane species IV which is derived by the ring-closure of IX may be regarded as a common intermediate leading to the amide of α-acyloxyl acid (Passerini reaction) and to the two products, V and VII, in the reaction of a carbonyl compound with isocyanide.

In addition, the oxetane products (I and II) may be formed by the reaction of the oxirane intermediate with a second molecule of isocyanide. Again, the dioxacycloheptane product (III) may be derived from I and IV.

The 4-membered cyclic co-oligomer may be the precursor of the product in the ketone-isocyanide-BF_3 reaction reported by Müller *et al.*[9] 1-Cyclohexenyl-N-t-butylglyoxylamide (X) was isolated in the reaction of cyclohexanone and t-butyl isocyanide with equimolar amount of BF_3-etherate followed by the hydrolysis of reaction mixture.



The formation of X is explained more reasonably by assuming that the oxetane derivative is the precursor, i.e. the acid hydrolysis of the oxetane derivative from one mole of cyclohexanone and two moles of t-butyl isocyanide yields X. In fact, 2,2,3-trihydroxy-3-methyl-N-cyclohexylbutyramide (XI) was produced in the treatment of II with hydrochloric acid.



XI

EXPERIMENTAL

IR spectra were taken by two spectrophotometers, IR-S and 402G, of Japan Spectroscopic Co. NMR spectra were taken at 60 Mc/s with TMS as the internal standard by using a Varian A-60 spectrometer. UV spectra were determined in EtOH on a SV-50A spectrophotometer of Shimazu Co. (Japan). GLC analyses were made with a GC-2C instrument of Shimazu Co. (Japan). Mol wts were determined by a Mechrolab Model 302 vapor pressure osmometer in benzene. M.ps and b.ps were uncorrected.

Materials. Cyclohexyl isocyanide was prepared by the method of Ugi *et al.*[10] and rectified prior to use, b.p. 42–44°/3 mm (lit.[10] 56–58°/11 mm). Acetone was dried on Drierite and rectified. All other reagents used were obtained commercially.

Reaction of acetone with cyclohexyl isocyanide. To a soln of acetone (2·2 ml, 30 mmoles) and cyclohexyl isocyanide (3·6 ml, 30 mmoles) in diethyl ether (20 ml), diethyl ethyl (5 ml) containing of BF_3-etherate (2 mmoles) was added dropwise at −78° under N_2. After standing 1 day at the same temp, the reaction was stopped by the addition of MeOH (5 ml). From the ether-soluble part, 2·65 g of II was obtained by recrystallization, yield 64% (based on isocyanide), m.p. 59–60°; M.W. 278, calc 276. (Found: C, 73·57; H, 10·42; N, 10·06. $C_{17}H_{28}N_2O$ requires: C, 73·87; H, 10·21; N, 10·13%); UV spectrum λ_{max} 241 mμ (ε 7450). NMR spectrum (in pyridine): 5·88 and 6·50 (two broad ms, 2H, —CH—), 8·46 (s, 6H, CH_3—), 8–9 τ (complex, 20H, —CH_2— of cyclohexyl ring). IR spectrum (KBr): 1738 (s) ($\nu_{C=N}$), 1705 (s) ($\nu_{C=N}$), and 1100 cm^{-1} (s) (ν_{C-O-C}). No absorption in the 3600–3000 cm^{-1} region.

Compound V was detected as a main by-product by the GLC analysis (column: PEG (3 m), at 170°; carrier gas, H_2, flow rate, 60 ml/min) and was isolated by preparative GLC. (Found: C, 65·95; H, 10·19; N, 6·85. $C_{11}H_{21}NO$ requires: C, 66·29; H, 10·62; N, 7·03%); NMR spectrum (in $DCCl_3$): 6·74 (s, 3H, CH_3O—), 8·65 (s, 6H, CH_3—), 6·28 (broad m, 1H, CH—) and 8–9 τ (complex, 10H, —CH_2— of cyclohexyl ring). IR spectrum (neat): 3280 (m) (ν_{N-H}), 1650 (s) ($\nu_{C=O}$), 1520 (m) (δ_{N-H}) and 1070 cm^{-1} (s) (ν_{C-O-C}).

Preparation of methyl 2-N-*cyclohexylaminopropionate* VII. To a mixture of acetaldehyde (5·6 ml, 100 mmoles), cyclohexyl isocyanide (11 ml, 90 mmoles), and pyridine (0·8 ml, 10 mmoles) in diethyl ether (30 ml), a soln of BF_3–etherate (0·5 ml, 4 mmoles) in diethyl ether (5 ml) was added dropwise at −78°. The reaction mixture was kept at −78° for 24 hr, and then was treated with MeOH (5 ml) at the same temp. No residue was observed in the ether-soluble fraction, but VII was detected by GLC analysis (column: Silicone (3 m); at 150°; carrier gas: H_2; flow rate: 60 ml/min) and was isolated by preparative GLC. The structure of VIII was identified by the comparison of the GLC retention time, IR, and NMR spectra with an authentic sample.

2,2,3-*Trihydroxy*-3-*methyl*-N-*cyclohexylbutyramide* XI. To an ethereal soln (15 ml) of II (3 g, 11 mmoles) 2N HCl (13 ml) was added dropwise with stirring at 0° and stirring continued for 6 hr at room temp. The ether layer of the reaction mixture was separated and neutralized with Na_2CO_3aq. The ether was evaporated, and the residue washed with petrol. Recrystallization of the residue with acetone yielded 1·83 g of XI, m.p. 68–70° dec. (Found: C, 57·20; H, 9·20; N, 6·04. $C_{11}H_{21}NO_4$ requires: C, 57·12; H, 9·15; N, 6·06%); NMR spectrum (in pyridine): 4·06 (s, 2H, —OH), 8·30 (s, 6H, CH_3—), 6·05 (broad m, 1H, CH—), 8–9 τ (complex, 10H, —CH_2— of cyclohexyl ring). IR spectrum (KBr): 3470 (m) and 3385 (m) (ν_{OH}), 3225 (m) (ν_{N-H}), 1640 (s) ($\nu_{C=O}$), 1550 (s) (δ_{N-H}), 1128 (s), 1085 (s) and 1015 cm^{-1} (s) (ν_{C-O}).

REFERENCES

[1] M. Passerini, *Gazz. Chim. Ital.* **61**, 964 (1931).

[2] R. H. Baker and D. Stanonis, *J. Am. Chem. Soc.* **73**, 699 (1951).

[3] I. Ugi and R. Meyr, *Chem. Ber.* **94**, 2229 (1961).

[4] I. Hagedorn and U. Eholzer, *Chem. Ber.* **98**, 936 (1965).

[5] M. Passerini, *Gazz. Chim. Ital.* **51**, 126 (1921).

[6] T. Saegusa, N. Taka-ishi and H. Fujii, *Polymer Letters* **5**, 779 (1967).

[7] J. C. Sheehan and I. Lengyel, *J. Am. Chem. Soc.* **86**, 746 (1964).

[8] J. C. Sheehan and I. Lengyel, *Ibid.* **86**. 1356 (1964).

[9] E. Müller and B. Zeeh, *Liebigs Ann.* **696**, 72 (1966).

[10] I. Ugi and R. Meyr, *Chem. Ber.* **93**, 239 (1960).