Synthetic Studies Involving 1-Aminocyclohexanecarbonitrile

WAYLAND E. NOLAND, RICHARD J. SUNDBERG,[1a] AND MARGARET L. MICHAELSON[1b]

School of Chemistry, University of Minnesota, Minneapolis 14, Minnesota

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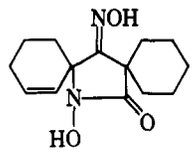
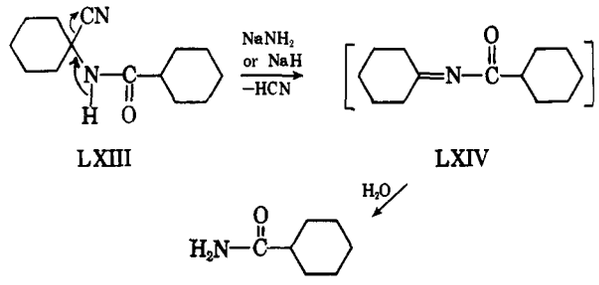
During an investigation of potential synthetic routes from 1-aminocyclohexanecarbonitrile to derivatives of the 2:2 condensation product (I)[2] of nitromethane and cyclohexanone, several interesting reactions and a new heterocyclic dispiro derivative (LXVII)[3] were encountered.



I

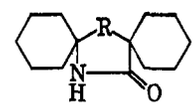
1-(Cyclohexanecarboxamido)cyclohexanecarbonitrile (LXIII, 90%) was obtained by acylation of 1-aminocyclohexanecarbonitrile with cyclohexanecarbonyl chloride in a solution of pyridine and benzene. Attempted cyclization of LXIII (through the nitrile group) with sodamide in liquid ammonia gave only unchanged LXIII. Heating of LXIII, however, with sodamide to 180° (26%), or refluxing with sodium hydride in benzene and *t*-butyl alcohol (9%), gave cyclohexanecarboxamide, assumed to result from base-catalyzed elimination of hydrogen cyanide from LXIII and subsequent hydrolysis of a resulting imine intermediate (LXIV) during the work-up procedure.



LXIII LXIV

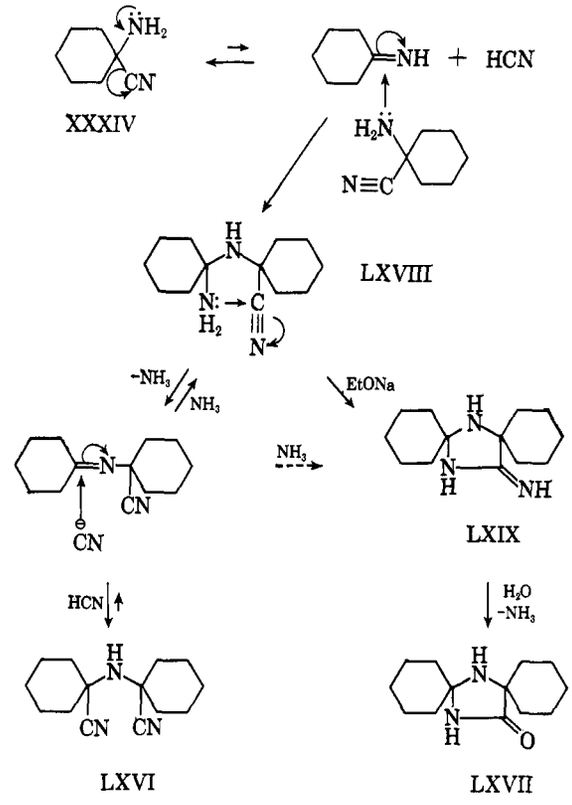
Attempted condensation of 1-aminocyclohexanecarbonitrile with the ethylene ketal of ethyl cyclohexanone-2-carboxylate (LXV) was unsuccessful, giving instead bis(1-cyanocyclohexyl)amine (LXVI, 22%), known to form from 1-aminocyclohexanecarbonitrile on standing.[4a] Repetition of the reaction under the same conditions, but in the absence of the ketal LXV, also gave LXVI in 22% yield.

Attempted condensation of 1-aminocyclohexanecarbonitrile with ethyl cyclohexanone-2-carboxylate, catalyzed by sodium ethoxide in absolute ethanol, also was unsuccessful, giving instead what appears to be 7,14-diazadispiro[5.1.5.2]pentadecan-15-one (LXVII, 8%). Repetition of the reaction in the absence of ethyl cyclohexanone-2-carboxylate, but in ethanol containing a little moisture, gave LXVII in excellent yield (94%). Compound LXVII is an interesting self-condensation and hydrolysis product of 1-aminocyclohexanecarbonitrile and is a 7-azadispiro analog of the derivatives of I, the dispirolactams[2] II, XIV, and XV.



II, R = $CHNH_2$
XIV, R = CHOH
XV, R = C=O
LXVII, R = NH

Formation of LXVII may proceed from LXVI or, more likely, through a probable common intermediate of both compounds, the diamine LXVIII. In neutral medium the intermediate LXVIII could lose ammonia and react with cyanide ion to give LXVI; in the presence of sodium ethoxide, however, the intermediate LXVIII could readily cyclize to the iminoamide LXIX, and subsequently be hydrolyzed to LXVII by moisture present in the ethanol solvent. Analogy for the formation of compounds somewhat similar to LXVII is present in the literature of cyanohydrin chemistry.[5]



XXXIV LXVIII LXIX LXVI LXVII

(1) (a) National Science Foundation Graduate Fellow, June 1960–June 1962; Du Pont Summer Fellow, 1st Summer Session, 1962; from the Ph.D. thesis of Richard J. Sundberg, University of Minnesota, August, 1962; *Dissertation Abstr.*, **24**, 85 (1963); (b) National Science Foundation Undergraduate Research Participant, University of Minnesota, summer, 1963, supported by Grant No. NSF-GE 1143.

(2) W. E. Noland and R. J. Sundberg, *J. Org. Chem.*, **28**, 3150 (1963).

(3) Numbers of new compounds have been chosen so as not to conflict with numbers already assigned to derivatives of compound I (see ref. 2, footnote 11).

(4) (a) A. P. Snyesarev, *J. Russ. Phys. Chem. Soc.*, **46**, 206 (1914); *Chem. Abstr.*, **8**, 2550 (1914); (b) A. P. Snessarew, *J. prakt. Chem.*, [2] **89**, 361 (1914).

(5) (a) A. J. Ultée, *Rec. trav. chim.*, **28**, 257 (1909); (b) H. R. Snyder and C. T. Elston, *J. Am. Chem. Soc.*, **76**, 3039 (1954); (c) D. C. Ayres and R. A. Raphael, *J. Chem. Soc.*, 1779 (1958); (d) B. E. Betts and W. Davey, *ibid.*, 1683 (1961).

Experimental

Melting points were determined on calibrated hot stages.

1-(Cyclohexanecarboxamido)cyclohexanecarbonitrile (LXIII).—Cyclohexanecarbonyl chloride[6] (44 g., 0.300 mole) was added dropwise to a solution of 1-aminocyclohexanecarbonitrile (32 g., 0.258 mole) in pyridine (50 ml.) and benzene (120 ml.). Then the resulting solution was placed in a large water bath initially at 80°, and kept for 12 hr., during which the bath and reaction solution gradually cooled to room temperature and a white solid precipitated. Chloroform (300 ml.) and water (300 ml.) were then added, causing the entire mixture to dissolve. The chloroform layer was washed successively with 5% hydrochloric acid, 5% aqueous sodium bicarbonate solution, and water, and then dried over magnesium sulfate and evaporated, leaving a pasty solid. Crystallization from ethanol–water gave white plates (54.2 g., 90%), m.p. 161.5–164.5°. Three recrystallizations from ethanol–water yielded glistening white plates, m.p. 163–164°; ν_{NH} 3250 s, 3030 w, 1538 s, $\nu_{C\equiv N}$ 2230 vw, $\nu_{C=O}$ 1650 s, cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{14}H_{22}N_2O$ (234.33): C, 71.75; H, 9.46; N, 11.96. Found: C, 71.89; H, 9.39; N, 11.90.[7]

Attempted Cyclization of LXIII with Base: Cleavage to Cyclohexanecarboxamide. A. With Sodamide.—Compound LXIII (2.1 g., 0.0090 mole) and sodamide (0.2 g., 0.0051 mole) were heated together to 180° for 1 hr. At about 150° a violent evolution of gas occurred. After the mixture had cooled, it was dissolved in ethanol and the solution diluted with water and made acid with dilute hydrochloric acid. White needles (0.297 g., 26%) precipitated, which had an infrared spectrum (Nujol) identical with that of authentic cyclohexanecarboxamide. Recrystallization from ethanol–water, sublimation under reduced pressure, and two additional recrystallizations from chloroform–light petroleum ether (b.p. 60–68°) yielded **cyclohexanecarboxamide** as shiny white plates, m.p. 190–191°; lit.[8] m.p. 184°, lit.[9] 185–186°; ν_{NH} 3340 s, 3160 s, $\nu_{C=O}$ 1635 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_7H_{13}NO$ (127.18): C, 66.10; H, 10.30; N, 11.01. Found: C, 66.18; H, 10.34; N, 9.75.

B. With Sodium Hydride.—Compound LXIII (2.10 g., 0.00895 mole) and solid sodium hydride (0.3 g., 0.012 mole) were refluxed in benzene (30 ml.) for 20 hr. Then absolute ethanol (1 ml.), *t*-butyl alcohol (1 ml.), and sodium (0.03 g., 0.0013 g.-atom) were added, and the solution was refluxed for 4 hr. more. Evaporation of the solvents left an orange oily residue, which was partitioned between chloroform and dilute hydrochloric acid. The chloroform layer was concentrated, and then diluted with light petroleum ether (b.p. 60–68°). The solid which precipitated was sublimed under reduced pressure, yielding **cyclohexanecarboxamide** (0.103 g., 9%), m.p. 189–190°, having an infrared spectrum (Nujol) identical with that of an authentic sample and with that of the sample prepared with sodamide (part A.).

Ethyl Cyclohexanone-2-carboxylate.—The compound was obtained[10] in 59% yield (from cyclohexanone) as a colorless liquid, $n^{28}D$ 1.4762; lit.[10] 59–62%, $n^{25}D$ 1.476–1.479; $\nu_{C=O}$ 1731 s, 1710 s, 1650 vs, $\nu_{C=C}$ 1618 vs cm.$^{-1}$ on the liquid.

Ethylene Ketal of Ethyl Cyclohexanone-2-carboxylate. Ethyl 1,4-Dioxaspiro[4.5]decane-6-carboxylate (LXV).—*p*-Toluenesulfonic acid (0.2 g.) was added to a solution of ethyl cyclohexanone-2-carboxylate (34.0 g., 0.200 mole) and ethylene glycol (16.7 g., 0.269 mole) in benzene (100 ml.), and the solution was refluxed for 3 hr., during which time water (4.5 ml., 124%) was collected in a Dean–Stark water trap. The benzene solution was then washed with aqueous sodium bicarbonate solution, dried over sodium bicarbonate, and distilled, giving a colorless liquid (39.3 g., 92%), b.p. 95–104° (1 mm.), $n^{30}D$ 1.4634. Redistillation through a 10-cm. spiral wire column yielded a colorless liquid (35.7 g., 83%), $n^{28}D$ 1.4632, $\nu_{C=O}$ 1733 s cm.$^{-1}$ on the liquid.

Anal. Calcd. for $C_{11}H_{18}O_4$ (214.25): C, 61.66; H, 8.47. Found: C, 61.17; H, 8.60.

Bis(1-cyanocyclohexyl)amine (LXVI).—1-Aminocyclohexanecarbonitrile (20.0 g., 0.161 mole; prepared[2] in 87% yield from ammonia and cyclohexanone cyanohydrin) was kept at room temperature for 40 hr. and at 90° for 20 hr. The now reddish liquid was cooled in ice, causing crystallization to a mass of yellowish crystals. After 1 hr. a solution (20 ml.) of 1:1 ether–light petroleum ether (b.p. 60–68°) was added, leaving undissolved white crystals (4.04 g., 22%), m.p. 135–136°. Two recrystallizations from chloroform–light petroleum ether yielded white plates, m.p. 137–138°, lit.[4] m.p. 136°; ν_{NH} 3310 ms, $\nu_{C\equiv N}$ 2200 w cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{14}H_{21}N_3$ (231.33): C, 72.68; H, 9.15; N, 18.17. Found: C, 73.07; H, 9.23; N, 18.42.

7,14-Diazadispiro[5.1.5.2]pentadecan-15-one (LXVII).—1-Aminocyclohexanecarbonitrile[2] (21.0 g., 0.169 mole) was added to a solution of sodium ethoxide prepared by adding sodium (2.8 g., 0.122 g.-atom) to 98.4% (by weight) ethanol (80 ml.). White needles, which began to form after a few minutes at room temperature, had filled the solution within 2 hr. After a total of 21 hr. the needles were filtered, and three more crops were collected, giving a total of 17.66 g. (94%), m.p. 219–222°, having an infrared spectrum identical with that of the analytical sample. Two recrystallizations from chloroform–light petroleum ether (b.p. 60–68°) yielded the analytical sample as white needles, m.p. 219°; ν_{NH} 3300 w, 3220 m, 3020 w, $\nu_{C=O}$ 1687 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{13}H_{22}N_2O$ (222.32): C, 70.23; H, 9.97; N, 12.60. Found: C, 70.14; H 10.04; ,N, 12.65.

(6) A. C. Cope and E. Ciganek, *Org. Syn.*, **39**, 19 (1959).

(7) The compound, although pure, gave erratic nitrogen analyses. Two other analyses on a single sample of m.p. 163–164° gave N, 13.42, 10.53.

(8) (a) O. Aschan, *Ann.*, **271**, 231 (1892); (b) J. S. Lumsden, *J. Chem. Soc.*, **87**, 90 (1905).

(9) W. Markownikoff, *Ber.*, **25**, 3355 (1892).

(10) H. R. Snyder, L. A. Brooks, and S. H. Shapiro, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 531.

A New Type of Reaction of Phenylmagnesium Bromide with a Sterically Hindered Cyclobutanone

RAYMOND D. KIMBROUGH, JR.

School of Chemistry, Georgia Institute of Technology, Atlanta 32, Georgia

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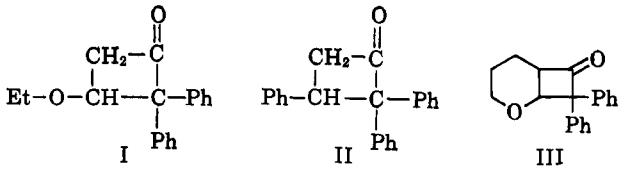
Unhindered cyclobutanones react normally with carbonyl reagents and give the expected phenylhydrazones, semicarbazones, and like derivatives. Certain sterically hindered cyclobutanones, such as the cycloaddition products of diphenylketene with ethyl vinyl ether,[1] I, with styrene,[2] II, and with dihydropyran,[1] III, do not react with phenylhydrazine or semicarbazide, presumably because the two phenyl groups hinder the carbonyl carbon and prevent any reaction from occurring at this position.[1,2]



Such sterically hindered cyclobutanones are known to undergo two types of reaction with Grignard reagents. A methylmagnesium halide gives a normal reaction,[3] while the bulkier phenylmagnesium halide gives a ring-opening reaction.[3] Here the phenylmagnesium bromide acts as a base and removes the weakly acidic α-hydrogen to produce the cyclobutanone enolate which undergoes ring opening to give a more stable enolate.

(1) C. D. Hurd and R. D. Kimbrough, *J. Am. Chem. Soc.*, **82**, 1373 (1960).

(2) H. Staudinger and E. Suter, *Ber.*, **53**, 1092 (1920).

(3) H. Staudinger and A. Rheiner, *Helv. Chim. Acta*, **7**, 8 (1924).