The Base-Catalyzed Condensation Reaction of *o*-Nitroisobutyrophenone in Liquid Ammonia

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The base-catalyzed condensation reaction of *o*-nitroisobutyrophenone (III) with sodium acetylide in liquid ammonia gave 1-ethynyl-2-methyl-1-(*o*-nitrophenyl)-1-propanol (**G**) as the main product and *o,o'*-azoxybenzamide (**C**), 2-carbamoyl-2'-carboxyazoxybenzene (**C'**), 2,2-dimethyl-3-indolinone (**D**), 1-hydroxy-2,2-dimethyl-3-indolinone (**E**), and 1-hydroxy-2,2-dimethyl-1,2-dihydro-4-quinazolone (**F**) as minor products. On the other hand, with sodium amide the ketone (III) gave Compounds **C** and **C'** as the main products and Compounds **D**, **E**, and **F** as the minor products. These products were formed by the α-proton abstraction.

The base-catalyzed condensation of *o*-nitrophenones in liquid ammonia gave rise to abnormal reactions.[1]

The treatment of *o*-nitroacetophenone (I) with sodium acetylide in liquid ammonia mainly gave Compound (**A**): 1,3-dihydroxy-3-methyl-2-(*o*-nitrophenacylidene)-indoline.[2,3] In the case of *o*-nitropropiophenone (II), 2-(1-carbamoylethyl)-1-(*o*-hydroxyphenyl)-2-methyl-3-indolinone (**B**) was obtained as the main product.[4]

In this experiment, *o*-nitroisobutyrophenone (III) was subjected to a similar reaction. The structures of these products and the mechanisms of their formations will be discussed.

Results

o-Nitroisobutyrophenone (III) was synthesized by the following two methods, analogous to these used in preparation of *o*-nitropropiophenone: 1) the hydrolytic decarboxylation of methyl *o*-nitrobenzoyldimethylacetate,[5,6] and 2) the treatment of 2-diazopropane[7] with *o*-nitrobenzaldehyde.

The treatment of III with an equimolar amount of sodium acetylide in liquid ammonia at −70 °C gave **G** as the main product and **C**, **C'**, **D**, **E**, and **F** as the minor products. On the other hand, the reaction with sodium amide gave **C** and **C'** as the main products and **D**, **E** and **F** as the minor products (Chart 1).

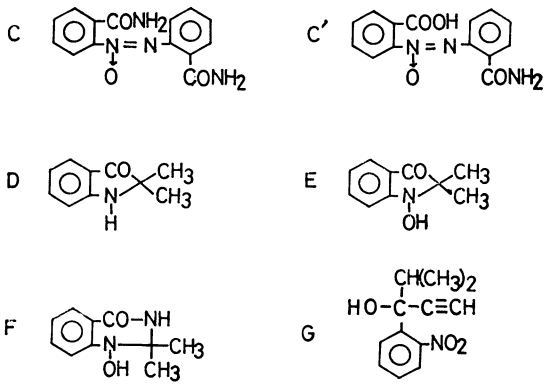


Chart 1.

Compound **C** was identified with *o,o'*-azoxybenzamide.[8] Compound **C'** was identical with the 2-carbamoyl-2'-carboxyazoxybenzene prepared by the alkaline reduction of *o*-nitrobenzamide with glucose or arsenious acid.[9]

The IR spectrum of **D** showed absorption bands of the NH group at 3380 cm^{-1} and of the C=O group at 1675 cm^{-1}. The UV spectrum of **D** revealed the absorption maxima at 237 (ε 4.33), 257 (3.78) and 398 nm (3.60) due to the 3-indolinone nucleus. Further, the NMR spectrum showed the signals for the methyl protons at δ 1.30 (s, 6H) and the imino proton at 5.15 (broad, 1H). These data were identical with those of 2,2-dimethyl-3-indolinone.[10]

The IR spectrum of **E** showed absorption bands of the OH group at 3310 cm^{-1} and of the C=O group at 1685 cm^{-1}. The UV spectrum revealed the absorption maxima at 240 (ε 4.37), 259 (3.81), and 381 nm (3.45) due to the 3-indolinone nucleus. **E** was methylated with diazomethane to give a methyl ether. The IR spectrum of the latter compound showed absorption bands due to the OCH_3 group at 2800 and 1150 cm^{-1} instead of those of the OH group at 3310 cm^{-1} of **E**. From these results, **E** was assumed to be 1-hydroxy-2,2-dimethyl-3-indolinone.

The IR spectrum of **F** showed absorption bands of the NH group at 3200 cm^{-1} and of the C=O group at 1655 cm^{-1}. The UV spectrum of **F** revealed the absorption maxima characteristic of the quinazoline nucleus at 228 (ε 4.42) and 328 nm (3.41). From the above results, **F** was assumed to be 1-hydroxy-2,2-dimethyl-1,2-dihydro-4-quinazolone, which was synthesized by the condensation of *o*-hydroxylaminobenzamide with acetone in acetic acid.

The IR spectrum of **G** showed the absorption bands of the C≡CH group at 3300 and 2101 cm^{-1}, of the NO_2 group at 1535, 1375, and 850 cm^{-1}, and of the OH group at 3550 cm^{-1}. The NMR spectrum of **G** showed the signals for the proton of alkyne at δ 2.77 (s, 1H), for the methyl protons at 1.05 (d, 3H), and 1.10 (d, 3H), for the methine proton at 2.75 (m, 1H), and for the hydroxyl proton at 3.00 (s, 1H). From the results, **G** was assumed to be 1-ethynyl-2-methyl-1-(*o*-nitrophenyl)-1-propanol.

Consequently, the reaction of III with sodium acetylide gave the normal condensation product without the participation of the nitro group.

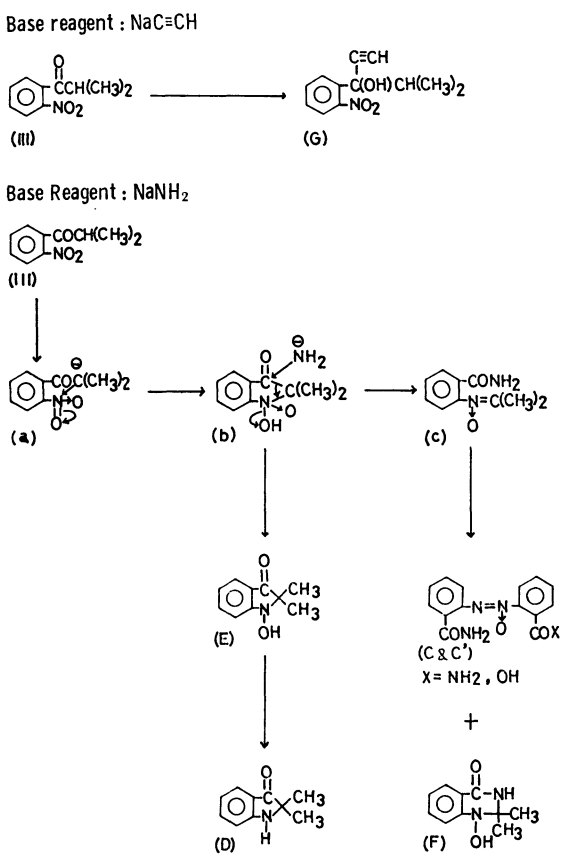
G was oxidized to confirm its structure. The ozonolysis of **G** gave an acid, 2-hydroxy-3-methyl-2-(*o*-nitrophenyl)butyric acid, and a neutral fraction having the absorption band of the CHO group at 1700 cm^{-1}. The latter compound was immediately oxidized with silver oxide or aqueous hydrogen peroxide to the same

acid which was obtained from the acid fraction. These acid fractions were further oxidized with lead tetraacetate to yield III. Further, the oxidation of **G** with potassium permanganate gave the acid described above.

Discussion

It has been pointed out that the base-catalyzed condensations of *o*-nitrobenzoyl derivatives undergo cyclization to isatogenes.[1]

The reaction of *o*-nitroisobutyrophenone (III) with sodium acetylide gave Compound **G** as the main product and Compounds **C**, **C'**, **D**, **E**, and **F** as minor products (Scheme 1).[1]



Scheme 1.

Various reasons for the results described above may be considered.[11,12] First, the increase in the number of alkyl groups on the α carbon of the carbonyl group decreases the acidity of the α-proton. Consequently, *o*-nitroisobutyrophenone (III) will react with the acetylide anion through nucleophilic addition at the carbonyl group rather than through the α-proton abstraction.

Second, in the *o*-nitrophenones, the increase in the steric hindrance between the alkyl and nitro groups competes with the repulsion by dipole-dipole interaction between the carbonyl and nitro groups.

In acetophenone or propiophenone, with small alkyl groups, the nitro group may be located in the neighborhood of the alkyl group undergoing the abstraction of the α-proton, but in the case of *o*-nitroisobutyrophenone, with a larger alkyl group, the situation is reversed.

On the other hand, with sodium amide the ketone (III) gave Compounds **C** and **C'** as the main products and Compounds **D**, **E** and **F** as the minor products.

These products are formed by the α-proton abstraction. The conjugate base of *o*-nitroisobutyrophenone causes an intramolecular reaction with the nitro group containing the electrophilic center to form an intermediate (b) of the 3-indolinone type, which is subsequently reduced to form the products, **D** and **E**.

In the next step, the addition of the amide anion to the carbonyl group of the intermediate (b) cleaved the heterocyclic ring to form a nitrone (c). The nitrone was derived to Compound **F**, an unknown product of the weak acidity, by the addition of the amide group to the C=N double bond of the nitrone.[13,14]

On the other hand, Compounds **C** and **C'** were assumed to be formed by the oxidation-reduction reaction of *o*-hydroxylaminobenzamide, which was formed by the cleavage of the intermediate (c).

Experimental

The IR spectra were measured with JASCO IR-E and Hitachi EPI-2 spectrophotometers, using neat or Nujol mull; the UV spectra, with a Hitachi EPS-2 spectrophotometer, using 95% EtOH as the solvent, and the NMR spectra, with JEOLCO C-60, using $CDCl_3$ as the solvent.

Preparation of o-Nitroisobutyrophenone (III). Methylation Method: A solution of 42 g (0.18 mol) of methyl *o*-nitrobenzacetate in 60 ml of absolute methanol was added in one portion to a sodium methoxide solution prepared from 4.1 g of sodium metal, followed by the drop-by-drop addition of an absolute methanol solution of methyl iodide (0.36 mol); then the mixture was refluxed at 65 °C for 30 min. The reaction mixture was cooled with ice–water, and then another molar equivalent of sodium methoxide was added in one portion. The mixture was subsequently treated with methyl iodide and refluxed at 65 °C for 3 h. The insoluble material was filtered off, and the filtrate was evaporated to give a residue, which was taken up with ether and washed thoroughly with 10% aqueous sodium hydroxide. This product was refluxed with a mixture of 13.5 ml of acetic acid, 7.5 ml of concd hydrochloric acid, and 7ml of water for 75 min. After being made alkaline with 20% aqueous sodium hydroxide, the reaction product was extracted with ether; the subsequent evaporation of the ethereal layer gave a crude product, which was distilled under reduced pressure; bp 115—130 °C/4 Torr. It was recrystallized from petroleum benzine; mp 46—47 °C; yield, 65—81%.

2-Diazopropane Method[7]: A solution of 25.7 g (0.17 mol) of *o*-nitrobenzaldehyde in an arbitrary volume of dry ether was added to 0.17 mol of 2-diazopropane (prepared from acetone-hydrazone) at −20 °C. The reaction mixture was stirred for 2 h at the same temperature and then warmed to room temperature. The insoluble material was removed by filtration. The filtrate was washed with a saturated sodium hydrogen sulfite solution to remove the unchanged aldehyde. The evaporation of the ether layer gave colorless crystals (mp 46—48 °C) from petroleum benzine; yield, 65—72%. IR (cm^{-1}): 1705 (C=O); 1530, 1350, and 860 (NO_2). Found: C, 62.52; H, 5.88; N, 7.23%. Calcd for $C_{10}H_{11}NO_3$: C, 62.16; H, 5.74; N, 7.25%.

The Condensation of o-*Nitroisobutyrophenone (III) with Sodium Acetylide.* A mixture of 0.23 g (0.01 g-atom) of sodium and 100—150 ml of liquid ammonia was saturated with dry acetylene. The mixture was cooled at −70 °C, and then a solution of 1.93 g (0.01 mol) of *o*-nitroisobutyrophenone in 10 ml of dry ether was added in one portion. After the mixture had stood at −60 °C for one hour, during which it turned from grey to yellow, ammonium chloride (1.0 g) was added; then the liquid ammonia was evaporated while 50 ml of dry ether was added. Next, 50 ml of water was added, the reaction mixture was filtered to remove an insoluble material (a), and the ethereal layer (b) was separated from the aqueous layer (c). The insoluble material (a) was recrystallized from water or dilute alcohol to give Compound **C** in a 0.2-g yield; mp 245—246 °C (lit,[8] mp 242 °C). Found: C, 59.10; H, 4.41; N, 19.52%. Calcd for $C_{14}H_{12}N_4O_3$: C, 59.15; H, 4.26; N, 19.71%. The aqueous layer (c) was acidified with 6M-HCl and continuously extracted with ether. The extract was evaporated and recrystallized from methanol to give Compound **C'** (mp 209—211 °C) in a 50-mg yield. Found: C, 59.04; H, 3.90; N, 14.79%. Calcd for $C_{14}H_{11}N_3O_4$: C, 58.94; H, 3.89; N, 14.79%. The ethereal layer (b) was successively extracted with aqueous sodium hydrogen carbonate and aqueous sodium hydroxide to leave a neutral fraction as the organic layer (d), which was purified by column chromatography on silica gel with chloroform to give **G** in 1.04 g (60.1%). Found: C, 65.31; H, 6.03; N, 6.39%. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39%.

The Condensation of o-*Nitroisobutyrophenone (III) with Sodium Amide.* Sodium amide was prepared from 0.23 g (0.01 g-atom) of sodium and 100—150 ml of liquid ammonia, using ferric nitrate($9H_2O$) as a catalyst. The mixture was cooled at −70 °C, and then a solution of 1.93 g (10 mmol) of *o*-nitroisobutyrophenone in 10 ml of dry ether was added in one portion. After standing at −60 °C for one hour, ammonium chloride (1.0 g) was added, and then the liquid ammonia was evaporated while 50 ml of dry ether was added. The post-treatment was then carried out as has been described above. The insoluble material (a) gave 1.7 g (23%) of **C** (mp 254—256 °C), and the aqueous layer (c) gave 0.9 g (12%) of **C'** (mp 209—211 °C). The ethereal layer (b), after have been washed an alkaline solution, gave 0.5—0.9 g (10—19%) of **D** (mp 86—87 °C) from petroleum ether. Found: C, 74.29; H, 6.90; N, 8.69%. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69%. The acid fraction obtained by the extraction with aqueous sodium hydroxide, after purification by column chromatography on silica gel with chloroform, gave 0.4 g (9.5%) of **F** (mp 196—197 °C (chloroform or ether)) and 0.1 g (2.3%) of **E** (mp 102—103 °C (petroleum benzine)). **E**, Found: C, 67.45; H, 6.32; N, 7.89%. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.29; N, 7.91%. **F**, Found: C, 62.10; H, 6.13%. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.29%. This compound was identified with the synthetic specimen (see below) by IR spectroscopy.

Preparation of F. A solution of 20 ml of acetone and 20 ml of acetic acid was added to 1.5 g (0.02 mol) of *o*-hydroxylaminobenzamide during refluxing at 85—86 °C for about 13 h. The black solution was evaporated under reduced pressure to leave a tar substance, which was then chromatographed on silica gel with chloroform. The first fraction was recrystallized from ether to give pearl grey and twinkle crystals; mp 197—200 °C; yield, 725 mg. IR (cm^{-1}): 3160 (OH), 1655, 1600 (CONH), and 1380 (CH_2). Found: C, 62.18; H, 6.36; N, 14.32%. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.29; N, 14.58%.

Ozonolysis of G. Ozone gas was passed into a solution of 2.8 g (13 mmol) of **G** in acetic acid at 5—6 °C for 30 min. The reaction mixture was then diluted with water and heated in a water bath. The solvent was removed under reduced pressure, and the residue was separated into acid and neutral fractions by the usual method. The oil from the acid part solidified in due time and was recrystallized from ether and petroleum benzine to give white crystals; mp 143—145 °C (1.0 g, 40.7%). The oil from the neutral part was oxidized with silver oxide or hydrogen peroxide in an alkaline solution to form the same product as the acid part. The IR spectrum of the acid part (cm^{-1}): 3550 (OH), 2900, 2500, 930 (COOH), 1720 (C=O), 1540, 1375, 825 (NO_2), and 770 (*o*-subst. benzene). Found: C, 55.70; H, 5.61 N, 5.83%. Calcd for $C_{11}H_{13}NO_5$: C, 55.23; H, 5.48; N, 5.86%.

Oxidation of G with $KMnO_4$. *Formation of the Acid Fraction*: Into an acetone (10 ml) solution of 32 mg (0.15 mmol) of **G** we added a small amount of $KMnO_4$; the purple color disappeared at once. The addition of $KMnO_4$ was continued at room temperature until the purple color remained ($KMnO_4$: 47 mg in total). The filtered reaction mixture was evaporated to remove the acetone, acidified with 2 M-HCl, and extracted with ether; the extract was then evaporated to give the acid compound.

Oxidation of Acid Compound with Lead Tetraacetate. Formation of III: A mixture of 100 mg (0.44 mmol) of an acid compound and 203 mg of $Pb(OAc)_4$ in 20 ml of dry benzene was stirred at reflux for 8 h. The reaction mixture was then cooled, and the $Pb(OAc)_2$ was filtered off and washed with ether. The combined filtrates were washed with a sodium hydrogen carbonate solution, dried with sodium sulfate, and evaporated to give 407 mg of III (mp 41—42 °C).

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