# Preparation of 2-Isoxazolines from C(α),O-Dilithiooximes and Aldehydes and Ketones (1)

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C(α),O-Dilithiooximes were condensed with aldehydes and ketones to give β-hydroxyoximes which were usually isolated and characterized. These materials could be acid-cyclized to give the 2-isoxazoline. When the dianion was condensed with *p*-anisaldehyde, it was not necessary to isolate the intermediate; direct acid-cyclization after condensation led to the 2-isoxazoline.

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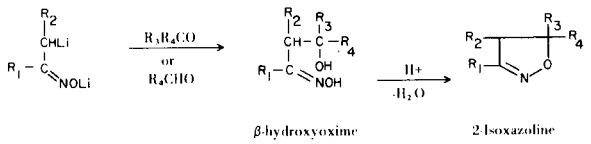
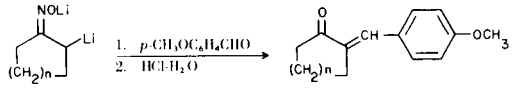
2-Isoxazolines have been prepared by the treatment of β-unsaturated ketones (4) or β-chloroketones (4) with hydroxylamine, or by the addition of nitrile oxides to olefins (4). These preparations are either not general, or require restrictive conditions, or in some cases, require reagents that are not readily available. In addition, more than one product is sometimes obtained. Recently, C(α),N-dilithiophenylhydrazones were condensed with aldehydes, followed by acid-cyclization to give 2-pyrazolines (5). This paper describes a new method for the preparation of 2-isoxazolines *via* the cyclization of β-hydroxyoximes, which, in turn, are conveniently prepared from condensation of C(α),O-dilithiooximes with aldehydes or ketones (6-9). In most instances, the β-hydroxyoximes were isolated after the condensation and characterization (Scheme I); in others, cyclizations were carried out *in situ*.

Scheme I




β-hydroxyoxime 2-Isoxazoline

Scheme II



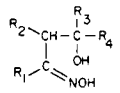

Initially, oximes of ketones containing an α-hydrogen atom were converted to their dilithio salts by treatment with two equivalents of *n*-butyllithium in tetrahydrofuran-hexane at 0° or -78°. These dilithio salts readily condensed with aldehydes such as benzaldehyde and ketones such as benzophenone to give β-hydroxyoximes which could be isolated in fair to good yield. (Table I). Simple treatment of these latter compounds with cold, concentrated sulfuric acid gave the desired 2-isoxazolines (Table II). While it was necessary to isolate the β-hydroxyoximes following the condensation with ketones and most aldehydes, it was not necessary for those reactions involving condensation with *p*-anisaldehyde. In these cases, the crude reaction mixtures were treated with 3*N* hydrochloric acid to give the 2-isoxazolines directly. Interestingly, the previously reported condensation of C(α),N-dilithiophenylhydrazones with aldehydes did not require isolation of the β-hydroxyphenylhydrazone, and the 2-pyrazoline was obtained directly by a similar procedure (5).

Similar condensations and *in situ* dehydrations of dilithiocyclohexanone and dilithiocyclopentanone oximes with *p*-anisaldehyde failed to give cyclic products. Instead, treatment of the crude reaction mixture with 3*N* hydrochlorid acid gave exomethylene derivatives of the parent ketones in yields of 37% and 41%, respectively (10-11). Possibly, 2-isoxazolines were not obtained in these examples because of steric constraint of the transition state leading to the desired product. (See Scheme II).

The overall advantage of the syntheses of the hetero-

Table I

β-Hydroxyoximes



| Compound Number | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Empirical Formula | Yield (%) | Mp. (a) (°C) | Elemental Analysis (b) | C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|
| I | $C_6H_5$ | H | $C_6H_5$ | $C_6H_5$ | $C_{21}H_{19}NO_2$ | 69 | 162-164 | Calcd. | 79.47 | 6.03 | 4.41 |
| | | | | | | | | Found | 79.62 | 5.94 | 4.41 |
| II | $C_6H_5$ | H | H | $p$-$CH_3OC_6H_4$ | $C_{16}H_{17}NO_3$ | 24 | 96-98 | Calcd. | 70.85 | 6.27 | 5.16 |
| | | | | | | | | Found | 70.61 | 6.35 | 5.02 |
| III | $C_6H_5$ | H | H | $p$-$ClC_6H_4$ | $C_{16}H_{14}ClNO_2$ | 52 | 140-142 | Calcd. | 65.34 | 5.12 | 5.08 |
| | | | | | | | | Found | 65.13 | 4.97 | 4.88 |
| IV | $p$-$CH_3OC_6H_4$ | H | H | $p$-$CH_3OC_6H_4$ | $C_{17}H_{19}NO_4$ | 48 | 160-161 | Calcd. | 67.76 | 6.35 | 4.65 |
| | | | | | | | | Found | 67.78 | 6.31 | 4.41 |
| V | $C_6H_5$ | $C_6H_5$ | H | $p$-$CH_3OC_6H_4$ | $C_{22}H_{21}NO_3$ | 50 | 163-165 | Calcd. | 76.06 | 6.09 | 4.03 |
| | | | | | | | | Found | 75.88 | 6.36 | 3.90 |
| VI | $C_6H_5$ | H | H | $C_6H_5$ | $C_{15}H_{15}NO_2$ | 60 | 115-116 | Calcd. | 74.65 | 6.23 | 5.80 |
| | | | | | | | | Found | 74.61 | 6.34 | 5.74 |
| VII | $C_6H_5$ | H | H | $m$-$CH_3C_6H_4$ | $C_{16}H_{17}NO_2$ | 64 | 147-149 | Calcd. | 75.27 | 6.71 | 5.49 |
| | | | | | | | | Found | 75.38 | 6.91 | 5.31 |
| VIII | $C_6H_5$ | H | H | $o$-$CH_3C_6H_4$ | $C_{16}H_{17}NO_2$ | 72 | 122-124 | Calcd. | 75.27 | 6.71 | 5.49 |
| | | | | | | | | Found | 74.98 | 6.76 | 5.37 |
| IX | $p$-$CH_3OC_6H_4$ | H | $C_6H_5$ | $p$-$CH_3C_6H_4$ | $C_{23}H_{23}NO_3$ | 77 | 183-184 | Calcd. | 76.48 | 6.41 | 3.88 |
| | | | | | | | | Found | 76.33 | 6.30 | 3.67 |

(a) Recrystallized from 95% ethanol. (b) Infrared spectra (Nujol); two hydroxyl peaks between 2.89-3.13 μ.

forward, leads to one isomer, and requires readily available starting materials.

## EXPERIMENTAL

Combustion analyses were performed by the Robertson Laboratory, Florham Park, New Jersey 07932, M-H-W Laboratories, Garden City, Michigan 48135, and Galbraith Laboratories, Knoxville, Tennessee 37921. Infrared spectra were obtained from Perkin-Elmer 137 and 700 Infrared Spectrometers. Nmr spectra were obtained from a Varian Associates A-60 nmr Spectrometer, and chemical shifts are reported in parts per million (δ) downfield from an internal TMS standard. Melting points were obtained in a Thomas-Hoover melting point apparatus and are uncorrected. *n*-Butyllithium was obtained from Alfa Inorganics, Inc., Beverly, Massachusetts and Lithium Corporation of America, Bessemer City, North Carolina. Tetrahydrofuran was obtained from Matheson, Coleman, and Bell, and it could be distilled from lithium aluminum hydride or used as supplied. The oximes were prepared by a standard method (15) and were recrystallized from ethanol and water.

Preparation of β-Hydroxyoximes.

The following description for the conversion of dilithioacetophenone oxime to β-hydroxyoxime may be considered general for those cases where isolation of the β-hydroxyoxime is desired. A solution of 3.38 g. (0.025 mole) of acetophenone oxime in 25 ml. of THF was added under nitrogen during 5 minutes to a mixture of 32 ml. (0.05 mole) of 1.6 M *n*-butyllithium in hexane and 200 ml. of THF at -78° or 0° (16) (see Table I). After 1 hour, the clear orange-yellow solution was treated during 5 minutes with a solution of 4.55 g. (0.025 mole) of benzophenone in 25 ml. of THF to produce a light green solution. After 30 minutes the mixture was treated with 100 ml. of water (17) and the layers were separated. The aqueous layer was extracted with three 50-ml. portions of ether and the extracts were combined, dried, and concentrated to afford a white solid. Recrystallization of this solid from ethanol gave 5.41 g. (69%) of (diphenylhydroxymethyl)acetophenone oxime (I), m.p. 162-164°.

Cyclization of β-Hydroxyoxime to Afford 2-Isoxazoline.

This procedure for the conversion of β-hydroxyoxime to isoxazoline may also be considered general.

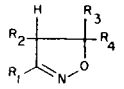
To 10 ml. of concentrated sulfuric acid at 0° was added with swirling, in small portions, 0.003 mole of β-hydroxyoxime. After all the solid had been added, the yellow-orange solution was allowed to stand for 1 hour at 0°. The solution was then poured into 150 ml. of ice-water, and a solid usually formed. After filtration on a Buchner funnel, the solid was recrystallized from the appropriate solvent (see Table II).

Condensation of Anion with *p*-Anisaldehyde and Acid-Cyclization to 2-Isoxazoline.

A 0.025-mole sample of dilithioacetophenone oxime was treated with 3.4 g. (0.025 mole) of anisaldehyde in 25 ml. of

Table II

2-Isoxazolines



| Compound Number | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Name (-2-Isoxazoline) | Empirical Formula | Yield (%) | M.p. (°C) (a) | Nmr Spectral δ (p.p.m.) (l) |
|---|---|---|---|---|---|---|---|---|---|
| I | $C_6H_5$ | H | $C_6H_5$ | $C_6H_5$ | 3,5,5-triphenyl | $C_{21}H_{17}NO$ | 76 | 140.5-142 (b) | ($CDCl_3$): 3.95 (s, 2H, $-CH_2-$) and 7.20-7.58 (m, 15H, ArH). |
| II | $C_6H_5$ | H | H | *p*-$CH_3OC_6H_4$ | 5(*p*-Anisyl)-3-phenyl | $C_{16}H_{15}NO_2$ | 53 (c) | 105 (d) | ($CDCl_3$): 2.97-3.88 (m, 2H, $-CH_2-$) 3.8 (s, $OCH_3$), 5.43-5.76 (m, 1H, -CH-), and 6.73-7.75 (m, 9H, ArH). |
| III | $C_6H_5$ | H | H | *p*-$ClC_6H_4$ | 5(*p*-Chlorophenyl),3-phenyl | $C_{15}H_{12}ClNO$ | 70 | 110-111.5 (e) | ($CDCl_3$-$CF_3COOH$): 3.22-4.02 (m, 2H, $-CH_2-$), 5.17-5.47 (m, 1H, -CH-), and 7.25-7.88 (m, 9H, ArH). |
| IV | *p*-$CH_3OC_6H_4$ | H | H | *p*-$CH_3OC_6H_4$ | 3,4-Di(*p*-Anisyl)- | $C_{17}H_{17}NO_3$ | 60 | 138-140 (f) | ($CDCl_3$): 3.25-3.92 (m, $-CH_2-$), 3.78 (s, $OCH_3$), 3.82 (s, $OCH_3$) 5.40-5.83 (m, -CH), and 6.72-7.75 (m, ArH). |
| V | $C_6H_5$ | $C_6H_5$ | H | *p*-$CH_3OC_6H_4$ | 5(*p*-Anisyl)-3,-4-diphenyl- | $C_{22}H_{19}NO_2$ | 33 | 130-132 (g) | ($CDCl_3$): 3.78 (s, 3H, $OCH_3$), 3.83 (d, 1H, CH), 5.47 (d, 1H, CH), and 6.80-7.67 (m, 10H, ArH). |
| VI | $C_6H_5$ | H | H | $C_6H_5$ | 3,5-Diphenyl- | $C_{15}H_{13}NO$ | 57 | 72-74 (h) | ($CDCl_3$): 3.08-4.05 (m, 2H, $-CH_2-$), 5.50-5.88 (m. 1H, CH), and 7.17-7.80 (m, 10H, ArH). |
| VII | $C_6H_5$ | H | H | *m*-$CH_3C_6H_4$ | 3-Phenyl-5-(*m*-tolyl)- | $C_{16}H_{15}NO$ | 76 | 55-57 (i) | ($CDCl_3$-$CF_3COOH$): 2.39 (s, $CH_3$), 3.40-4.43 (m, $-CH_2$), 5.72-6.05 (m, CH), and 7.11-7.85 (m, ArH). |
| VIII | $C_6H_5$ | H | H | *o*-$CH_3C_6H_4$ | 3-Phenyl-5-(*o*-tolyl)- | $C_{16}H_{15}NO$ | 55 | 62-64 (j) | ($CDCl_3$-$CF_3COOH$): 2.32 (s, 3H, $CH_3$), 3.43-3.78 (m, 2H, $-CH_2-$), 5.48-5.80 (m, 1H, -CH), and 7.10-7.78 (m, 9H, ArH). |

Table II (Continued)

| Compound Number | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Name (-2-Isoxazoline) | Empirical Formula | Yield (%) | M.p. (°C) | Nmr (Spectral δ (p.p.m.) |
|---|---|---|---|---|---|---|---|---|---|
| IX | *p*-$CH_3OC_6H_4$ | H | $C_6H_5$ | *p*-$ClH_3$-$C_6H_5$ | 3(*p*-Anisyl)-5-phenyl-5(*p*-tolyl) | $C_{22}H_{20}NO_2$ | 99 | 132-134 (k) | ($CDCl_3$-$CF_3COOH$): 2.35 (s, 3H, $CH_3$), 3.92 (s, 3H, $OCH_3$), 4.33 (s-minor splitting, 2H, $-CH_2$), and 6.97-7.78 (m, 13H, ArH). |

(a) Recrystallized from 95% ethanol. (b) Lit. m.p. 140°, see reference (12). (c) Thirty-nine percent yield if isolated β-hydroxyoxime and then cyclized. (d) Lit. m.p. 103°, see reference (12). (3) *Anal.* Calcd.: C, 69.99; H, 4.66; N, 5.43. Found: C, 70.13; H, 4.58. N, 5.45. (f) Lit. m.p. 137-138°, see reference (13). (g) *Anal.* Calcd.: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.45; H, 5.95; N, 4.19. (h) Lit. m.p. 75°, see reference (14). (i) *Anal.* Calcd.: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.70; H, 6.58; N, 5.80. (j) *Anal.* Calcd.: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.70; H, 6.53; N, 5.81. (k) *Anal.* Calcd.: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.57; H, 6.29; N, 4.09. (l) Nmr spectra were obtained on a Varian Associates A-60 Nmr Spectrometer and chemical shifts are reported in p.p.m. (δ) downfield from an internal TMS standard.

THF at 0°. After 30 minutes, the resulting mixture was treated with 100 ml. of 3*N* hydrochloric acid and heated under reflux for 1 hour. Work-up as with the β-hydroxyoximes gave 2-isoxazolines (see Table II).

Preparation of Exomethylene Derivatives.

A 0.025-mole sample of either cyclopentanone or cyclohexanone oxime was dissolved in 100 ml. of THF, cooled to 0°, blanketed with nitrogen, and treated with 0.055 mole of *n*-butyllithium. After stirring the solution for 30-45 minutes, 0.030 mole of *p*-anisaldehyde dissolved in 50 ml. of THF was added at a fast dropwise rate. After stirring for 15 minutes, the mixture was neutralized with 100 ml. of 3*N* hydrochloric acid and heated under reflux for 1 hour. After cooling and work-up as described above, the products were recrystallized from ethanol to give anisylidene-cyclopentanone (41%), m.p. 63-65°. [Lit. m.p. 68-69°; see reference (10)]; nmr (deuteriochloroform): δ 1.80-3.10 (m, 6H, $-CH_2-$), 3.83 (s, 3H, $OCH_3$), and 6.83-7.67 (m, ArH, + vinyl); and ansylidene-cyclohexanone (37%), m.p. 74-76° [Lit. m.p. 72°; see reference (11)]; nmr (deuteriochloroform): δ 1.63-2.15 and 2.38-2.07 (m, $-CH_2-$, 8H), 3.82 (s, 3H, $OCH_3$), and 6.87-7.60 (m, ArH and vinyl).

72°; see reference (11)]; nmr (deuteriochloroform): δ 1.63-2.15 and 2.38-3.07 (m, $-CH_2-$, 8H), 3.82 (s, 3H, $OCH_3$), and 6.87-7.60 (m, ArH and vinyl).

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(16) The base may also be added to the oxime, see references (7) and (8).

(17) A 10-15% solution of ammonium chloride could also be used.