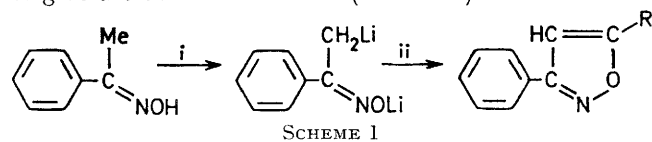


## A New Method for the Preparation of $\Delta^2$ -Isoxazolin-5-ones from the Oximes of Ketones having an $\alpha$ -Hydrogen Atom

By Jonathan S. Griffiths,\* Charles F. Beam, and the late Charles R. Hauser, Paul M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706, U.S.A.

Certain oximes having an  $\alpha$ -hydrogen atom were treated with *n*-butyl-lithium (2 mol. equiv.) to give the 1,4-dianions, which were carbonated and acid-cyclized to give the  $\Delta^2$ -isoxazolin-5-ones.

A NEW unequivocal method was recently developed in this laboratory for the synthesis of unsymmetrical isoxazoles.<sup>1</sup> This involved the conversion of an oxime, such as acetophenone oxime, into its 1,4-dilithio-salt by treatment with 2 mol equiv. of *n*-butyl-lithium. The dilithio-salts were then treated with a variety of aromatic esters, and then cyclized under acid conditions to give the desired isoxazoles (Scheme 1).



Reagents: i, 2 Bu-Li; ii, a, RCO<sub>2</sub>Me, b, HCl-H<sub>2</sub>O

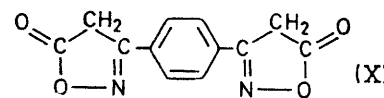
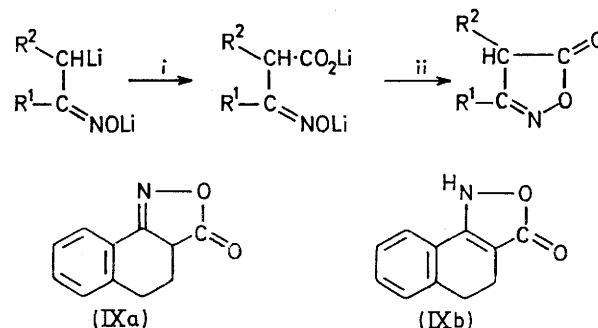
During the present investigation, the 1,4-dilithio-salts of a variety of oximes were prepared and carbonated. For the carbonation the solution containing the dianion was poured on to solid carbon dioxide. After excess of carbon dioxide had evaporated off, the resulting salts were acidified, and the assumed carboxy-oxime intermediate was cyclized to afford substituted  $\Delta^2$ -isoxazolin-5-ones (Scheme 2).

The structure of each heterocycle was established by comparison of m.p.s with those of previously reported compounds (Table), or by elemental analysis, and by i.r. and n.m.r. spectra (Experimental section). In addition, 3-phenyl- $\Delta^2$ -isoxazolin-5-one (I) was prepared by independent synthesis<sup>2</sup> from the reaction of ethyl benzoylacetate with hydroxylamine. The absorption spectra and m.p.s were identical to those of (I) prepared by the dianion-carbonation-cyclization method.

The  $\Delta^2$ -isoxazolin-5-one (IX) resulting from the carbonation-cyclization of the 1,4-dianion of  $\alpha$ -tetralone oxime was prepared in 23% yield. The n.m.r. spectra,

<sup>1</sup> C. F. Beam, M. C. D. Dyer, R. A. Schwarz, and C. R. Hauser, *J. Org. Chem.*, 1970, **35**, 1806.

taken in deuteriochloroform and in [<sup>2</sup>H<sub>6</sub>]acetone, clearly indicated that tautomer (IXa) was present in deuteriochloroform, while tautomer (IXb) was probably present in [<sup>2</sup>H<sub>6</sub>]acetone.



SCHEME 2

Reagents: i, CO<sub>2</sub>; ii, HCl-H<sub>2</sub>O

It was of further interest to treat the bis-oxime of 1,4-diacetylbenzene with 4 mol. equiv. of *n*-butyl-lithium, and to carbonate the resulting anion mixture with solid carbon dioxide. After cyclization, bis-(5-oxo- $\Delta^2$ -isoxalin-3-yl)benzene (X) was isolated in 38% yield. This compound was characterized by analysis, and i.r. and mass spectra.

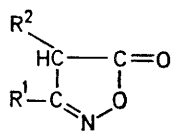
In a similar manner, the 1,4-dianions of several phenylhydrazones were prepared,<sup>3</sup> and their carbonation

<sup>2</sup> A. Hantzsch, *Chem. Ber.*, 1891, **24**, 495.

<sup>3</sup> R. S. Foote, C. F. Beam, and C. R. Hauser, *J. Heterocyclic Chem.*, 1970, **7**, 589.

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appeared to be effected by pouring the solutions of the dianion on to solid carbon dioxide, or by bubbling carbon dioxide into solution of the dianion solutions; however,

 $\Delta^2$ -Isoxazolin-5-ones

Compd.	R <sup>1</sup>	R <sup>2</sup>	Yield (%)	M.p.	Lit. m.p.
(I)	Ph	H	45	152—153 <sup>b</sup>	152 <sup>a</sup>
(II)	Ph	Ph	60	156—158	155—156 <sup>b</sup>
(III)	<i>p</i> -MeO·C <sub>6</sub> H <sub>4</sub>	H	57	141—144	141—144 <sup>c</sup>
(IV)	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	H	57	131—134	131—133 <sup>c</sup>
(V)	<i>o</i> -MeC <sub>6</sub> H <sub>4</sub>	H	43	93—95	
(VI)	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	H	42	151—153	152 <sup>d</sup>
(VII)	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub>	H	30	141—143	141—143 <sup>e</sup>
(VIII)	<i>p</i> -FC <sub>6</sub> H <sub>4</sub>	H	50	133—135	

<sup>a</sup> L. Claisen and W. Zedel, *Chem. Ber.*, 1891, **24**, 142. <sup>b</sup> R. Scarpati and G. Speroni, *Gazzetta*, 1959, **89**, 1511. <sup>c</sup> V. H. Wallingford and A. H. Homeyer, U.S.P. 2,407,942/1946 (*Chem. Abs.*, 1947, **41**, 1699). <sup>d</sup> A. Wahl and J. Rolland, *Ann. chim.*, 1928, **10**, 5. <sup>e</sup> Cz. Belzecki and T. Urbanski, *Roczniki Chem.*, 1958, **32**, 779.

only trace amounts of  $\Delta^2$ -pyrazolin-5-ones were isolated.\*

The synthetic method described in the present work is a new route to a variety of  $\Delta^2$ -isoxazolin-5-ones, which can be prepared from readily available starting materials. The reaction conditions used are compatible with a variety of substituents (Table), and the synthesis has a short and simple experimental procedure. In addition, the new method appears to be the first procedure for the preparation of the  $\Delta^2$ -isoxazolin-5-ones, (V), (VIII), (IX), and (X).

## EXPERIMENTAL

All analyses were performed by M-H-W Laboratories, Garden City, Michigan. I.r. spectra were obtained on Perkin-Elmer 137 and 237 spectrometers. N.m.r. spectra were obtained with Varian A-60 and T-60 spectrometers, and shifts are reported in  $\delta$  p.p.m. downfield from an internal tetramethylsilane (TMS) standard. The mass spectrum was taken at the Research Triangle Institute for Mass Spectrometry, Durham, N.C., on an MS-902 mass spectrometer. M.p.s were taken on samples in open capillary tubes in a Thomas-Hoover melting point apparatus. Tetrahydrofuran (THF) was distilled from lithium aluminium hydride immediately before use. n-Butyl-lithium, obtained from Alfa Inorganics, Inc., Beverly, Massachusetts, and Foote Mineral Co., Exton, Pennsylvania, was used as supplied.

*General Procedure for the Preparation of  $\Delta^2$ -Isoxazolin-5-ones.*—To a stirred solution of oxime (0.025 mol) in tetrahydrofuran (100 ml), which was cooled to 0° under nitrogen, was added n-butyl-lithium (0.05 mol), during 5 min. After 30 min, the solution, which was assumed to contain 0.025 mol of dilithio-salt, was poured into a 1-l flask containing freshly powdered solid carbon dioxide (ca. 1/2 lb). Excess of carbon dioxide was allowed to evaporate off, and the mixture was acidified (100 ml of 3N-hydrochloric acid). The resulting mixture was heated under reflux for 1 h, cooled, and separated, and the aqueous layer was extracted with small portions of chloroform (ca. 25 ml). The organic layers were combined, concentrated, and recrystallised.

3-Phenyl- $\Delta^2$ -isoxazolin-5-one (I) (from 95% ethanol) had  $\nu_{\max}$  (CHCl<sub>3</sub>) 5.51  $\mu$ m (C=O);  $\delta$  (CDCl<sub>3</sub>) 3.97 (s, 2H, CH<sub>2</sub>) and 7.80 (m, 5H, ArH) p.p.m.

3,4-Diphenyl- $\Delta^2$ -isoxazolin-5-one (II) (from 95% ethanol) had  $\nu_{\max}$  (CHCl<sub>3</sub>), 5.52 and 5.57  $\mu$ m (C=O);  $\delta$  (CDCl<sub>3</sub>) 4.93 (s, CH) and 7.28—8.01 (m, ArH) p.p.m.

3-(*p*-Methoxyphenyl)- $\Delta^2$ -isoxazolin-5-one (III) (from chloroform-acetone) had  $\nu_{\max}$  (CHCl<sub>3</sub>) 5.57  $\mu$ m (C=O);  $\delta$  (CDCl<sub>3</sub>) 3.60 (s, 2H, CH<sub>2</sub>), 3.87 (s, 3H, OMe), and 6.90—7.75 (m, 4H, ArH) p.p.m.

3-(*p*-Tolyl)- $\Delta^2$ -isoxazolin-5-one (IV) (from chloroform-hexane) had  $\nu_{\max}$  (CHCl<sub>3</sub>) 5.57  $\mu$ m (C=O);  $\delta$  (CDCl<sub>3</sub>) 2.40 (s, 3H, Me) 3.73 (s, 2H, CH<sub>2</sub>), and 7.22—7.67 (m, 4H, ArH) p.p.m.

3-(*o*-Tolyl)- $\Delta^2$ -isoxazolin-5-one (V) (from 95% ethanol) (Found: C, 68.3; H, 4.9; N, 7.8. C<sub>10</sub>H<sub>9</sub>NO<sub>2</sub> requires C, 68.6; H, 5.2; N, 8.0%) had  $\nu_{\max}$  (CHCl<sub>3</sub>) 5.57  $\mu$ m (C=O);  $\delta$  (CDCl<sub>3</sub>) 2.42 (s, 3H, Me), 3.83 (s, 2H, CH<sub>2</sub>), and 7.32—7.50 (m, 4H, ArH) p.p.m.

3-(*p*-Chlorophenyl)- $\Delta^2$ -isoxazolin-5-one (VI) (from chloroform-acetone) had  $\nu_{\max}$  (CHCl<sub>3</sub>), 5.55  $\mu$ m (C=O);  $\delta$  (CDCl<sub>3</sub>) 3.83 (s, 2H, CH<sub>2</sub>) and 7.32—7.78 (m, 4H, ArH) p.p.m.

3-(*p*-Bromophenyl)- $\Delta^2$ -isoxazolin-5-one (VII) (from chloroform-hexane) had  $\nu_{\max}$  (CHCl<sub>3</sub>), 5.58  $\mu$ m (C=O);  $\delta$  (CDCl<sub>3</sub>) 3.80 (s, CH<sub>2</sub>) and 7.30—7.80 (m, ArH) p.p.m.

3-(*p*-Fluorophenyl)- $\Delta^2$ -isoxazolin-5-one (VIII) (from benzene-hexane) (Found: C, 66.3; H, 3.5; N, 8.6. C<sub>9</sub>H<sub>6</sub>FO<sub>2</sub> requires C, 66.3; H, 3.7; N, 8.5%) had  $\nu_{\max}$  (CHCl<sub>3</sub>), 5.55  $\mu$ m (C=O);  $\delta$  (CDCl<sub>3</sub>) 3.80 (s, 2H, CH<sub>2</sub>) and 7.07—7.88 (m, 4H, ArH) p.p.m.

4,5-Dihydro-naph[1,2-c]isoxazol-3(3aH)-one (IX) (from chloroform) (Found: C, 70.4; H, 4.9; N, 7.5. C<sub>11</sub>H<sub>9</sub>NO<sub>2</sub> requires C, 70.6; H, 4.9; N, 7.5%) had  $\nu_{\max}$  (CHCl<sub>3</sub>), 5.59  $\mu$ m (C=O);  $\delta$  (CDCl<sub>3</sub>) 2.43 (m, 2H, CH<sub>2</sub>), 2.98 (t, 2H, CH<sub>2</sub>Ar), 3.50 (m, 1H, CH), and 7.17—7.93 (m, 4H, ArH) p.p.m.;  $\delta$  [(CD<sub>3</sub>)<sub>2</sub>CO] 2.52 (m, 2H, CH<sub>2</sub>), 3.05 (t, 2H, CH<sub>2</sub>Ar), 5.40 (s, 1H, NH), and 7.37—7.70 (m, 4H, ArH) p.p.m.

1,4-Bis-(5-oxo- $\Delta^2$ -isoxazolin-3-yl)benzene (X).—To a solution of 1,4-diacetylbenzene oxime (4.71 g, 0.025 mole) and tetrahydrofuran (200 ml), which was cooled to 0° under nitrogen, was added, during 10 min, n-butyl-lithium (0.1 mol). After 90 min, the solution was poured into a 1-l flask containing freshly powdered solid carbon dioxide (ca. 1/2 lb.). Excess of carbon dioxide was allowed to evaporate off, and the mixture was acidified (100 ml of 3N-hydrochloric acid). The resulting mixture was heated under reflux for 1 h, cooled, and separated. The organic layer, which contained suspended material, was further concentrated to give a *solid*, m.p. 283° (decomp.) (from dimethylformamide-95% ethanol) (2.3 g, 38%) [Found: C, 58.9; H, 3.3; N, 11.3%;  $M^+$  (mass spectrum) 244.0479. C<sub>12</sub>H<sub>9</sub>N<sub>2</sub>O<sub>4</sub> requires C, 59.0; H, 3.3; N, 11.5%;  $M$  244.0483];  $\nu_{\max}$  (KBr), 5.57 and 5.59  $\mu$ m (C=O).

We thank the Army Research Office (Durham) and the Petroleum Research Fund administered by the American Chemical Society for support, Dr. David Rosenthal for the mass spectral determination, which was supported by a grant from the National Institutes of Health, and Dr. C. H. Lochmüller for constructive discussions.

[0/1626 Received, September 21st, 1970]

\* R. S. Foote, this laboratory.