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The reaction of  $C\alpha,O$ -Dilithiooximes **2** and  $\alpha$ -chloroketones afforded 5-(hydroxymethyl)- $\Delta^2$ -isoxazolines **4**.  $\alpha,\beta$ -Unsaturated aldehydes and ketones reacted with **2** to give the corresponding acyclic 1,2-addition products **5**. The latter were cyclized with phosphorus pentoxide to 5-vinyl- $\Delta^2$ -isoxazolines **6**.

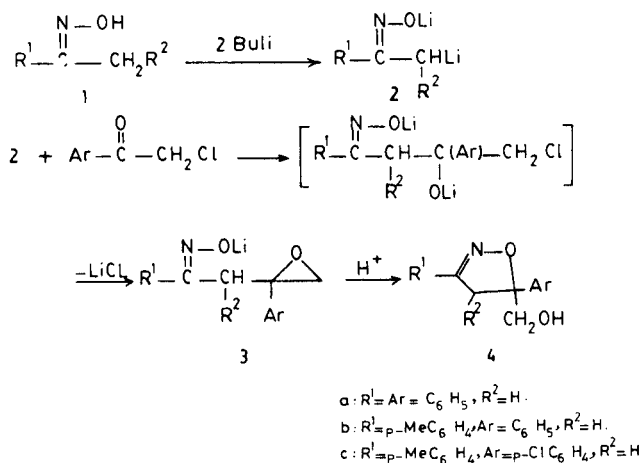
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In continuation of a study [1] to explore the synthetic aspects of the reaction of oxime dianions **2** [2] with functionalized carbonyl compounds, we now investigate the reaction of **2** with  $\alpha$ -chloroketones and  $\alpha,\beta$ -unsaturated aldehydes and ketones.

#### Reaction of **2** with $\alpha$ -Chloroketones.

The reaction of oxime dianions **2** and  $\alpha$ -chloroketones, at low temperature, was found to yield 5-(hydroxymethyl)- $\Delta^2$ -isoxazolines **4**. An oxirane intermediate, **3**, is assumed to intervene in this reaction. This intermediate is transformed *via* fast ring expansion, in a manner similar to that proposed elsewhere [3], to the final product **4** (Scheme 1).

Scheme 1



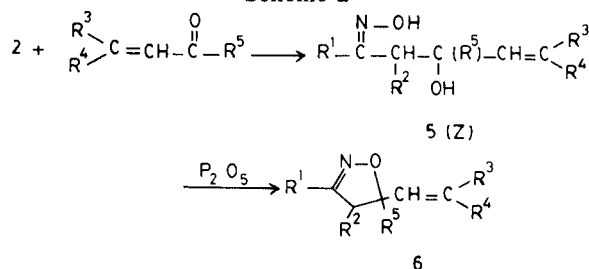
Compounds **4** were characterized by analytical and spectral data. In their ir spectra, O-H and C=N bond stretchings were observed respectively at 3410-3490 and 1605-1615  $\text{cm}^{-1}$ . The pmr spectrum of compound **4c** exhibited two doublets ( $J = 16 \text{ Hz}$ ) at 3.90 (1H) and 3.20 ppm (1H), assigned to the diastereotopic C-4 methylene protons. The broadened doublet at about 3.7 ppm (2H), which collapses to a singlet upon addition of deuterium oxide, is assigned to the two hydroxymethyl protons at C-5, showing mutual coupling with the adjacent O-H proton. The latter proton appeared as a doublet of doublet,

centered at about 2.5 ppm, which disappeared upon exchange with deuterium oxide. The mass spectra of compounds **4** display, besides weak molecular ion peaks, base peaks corresponding to  $[\text{M} - \text{CH}_2\text{OH}]^+$  ions. Such fragmentation pattern is common for primary alcohols, having their  $\text{CH}_2\text{OH}$  group attached to a quaternary carbon [4], which resemble the present compounds.

#### Reaction of **2** with $\alpha,\beta$ -Unsaturated Aldehydes and Ketones.

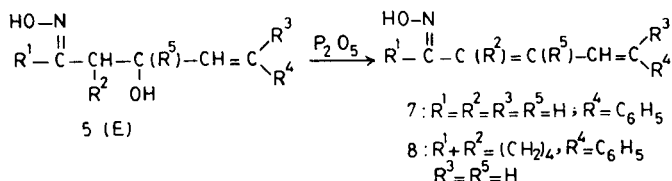
With  $\alpha,\beta$ -unsaturated aldehydes and ketones, oxime dianions **2** were found to undergo nucleophilic 1,2-addition at the carbonyl group, leading to  $\beta$ -hydroxy- $\gamma$ -en-1-one oximes **5** (Scheme 2). This addition is reminiscent of the reaction of **2** with simple carbonyl compounds [5]. Compounds **5** exhibited O-H absorptions at 3160-3520 and a C=C stretching band at 1618-1665  $\text{cm}^{-1}$ , but no C=O stretching bands. They gave correct elemental analysis and exhibited the correct molecular ions in their mass spectra. The pmr spectra of these compounds revealed that the vinylic protons of the unsaturated carbonyl compound were retained in the reaction products. In compounds **5a-c,f,g** the vinylic C-4 proton appeared as a doublet of doublet, centered at about 6.23 ppm, due to coupling with the neighbouring protons at C-3 and C-5. In compounds **5d,e,h**, this proton gave a multiplet in the range 5.23-6.13 ppm. The exchangeable doublet at about 4.1-4.4 ppm, and the singlet at 9.6-10.5 ppm were assigned, respectively, to the C-OH and N-OH protons. The C-3 proton in compounds **5a-c,e,g** showed a multiplet, centered at 4.54 ppm, due to coupling with the vicinal protons at C-2 and C-4, as well as with the O-H proton.

Scheme 2



Mild dehydration of compounds **5** with phosphorus pentoxide at 0° resulted in the formation of 5-vinyl- $\Delta^2$ -isoxazolines **6** (Scheme 2). Except for the absence of the exchangeable O-H signals, the pmr spectra of compounds **6** were similar to those of their acyclic precursors **5**. Their ir spectra revealed no absorptions in the region 3600-3200  $\text{cm}^{-1}$ , indicating the absence of O-H groups in these compounds.

Scheme 3



Compound **5f** was a mixture of the (*Z*)- and (*E*)-isomeric forms, as indicated from its pmr spectrum and chemical behaviour [6]. Upon dehydration, this mixture gave two

Table 1

Physical Data for Compounds **4**, **6**, **7** and **8**

| Compound  | mp (°C) | Yield (%)<br>(Solvent) | Calcd./ (Found)  |                |                |
|-----------|---------|------------------------|------------------|----------------|----------------|
|           |         |                        | C                | H              | N              |
| <b>4a</b> | 114     | 68 (C + P)             | 75.87<br>(75.85) | 5.97<br>(5.97) | 5.53<br>(5.55) |
| <b>4b</b> | 123     | 62 (C + P)             | 76.38<br>(76.17) | 6.41<br>(6.39) | 5.24<br>(5.28) |
| <b>4c</b> | 136     | 77 (C + P)             | 67.66<br>(67.46) | 5.34<br>(5.33) | 4.64<br>(4.57) |
| <b>6a</b> | 126     | 93 (C + P)             | 81.90<br>(81.94) | 6.06<br>(6.03) | 5.62<br>(5.70) |
| <b>6b</b> | 175     | 89 (C + P)             | 82.10<br>(81.45) | 6.51<br>(6.50) | 5.32<br>(5.37) |
| <b>6c</b> | 184     | 96 (C + P)             | 62.21<br>(62.55) | 4.30<br>(4.30) | 4.27<br>(4.31) |
| <b>6d</b> | oil     | 88 —                   | 78.56<br>(78.18) | 8.35<br>(8.40) | 6.11<br>(6.09) |
| <b>6e</b> | 63      | 79 (H)                 | 76.98<br>(76.62) | 7.00<br>(6.93) | 7.48<br>(7.56) |
| <b>6f</b> | 108     | 45 (C + P)             | 76.28<br>(75.93) | 6.40<br>(6.39) | 8.09<br>(8.12) |
| <b>6g</b> | 112     | 88 (T + H)             | 79.26<br>(79.61) | 7.54<br>(7.57) | 6.16<br>(6.12) |
| <b>7</b>  | 145     | 38 (C + P)             | 76.28<br>(76.40) | 6.40<br>(6.42) | 8.09<br>(8.09) |
| <b>8</b>  | 187     | 54 (M + W)             | 79.26<br>(79.60) | 7.54<br>(7.50) | 6.16<br>(6.16) |

C, chloroform; P, petroleum ether; H, hexane; T, carbon tetrachloride; M, methanol; W, water.

products, which were separated and identified as compounds **6f** and **7**. The latter acyclic compound is assumed to originate from the (*E*)-isomer, in which the two O-H groups are unsuitably located for intramolecular cyclization (Scheme 3). In one case, **5g**, the (*Z*) and (*E*)-isomers could be separated and identified [7]. Dehydration of (*Z*)-**5g** gave the cyclic product **6g**, while the (*E*)-isomer was transformed to the acyclic compound **8** upon dehydration.

## EXPERIMENTAL

Melting points were uncorrected. The ir spectra (potassium bromide pellets) were recorded on a Perkin-Elmer 577. Pmr spectra were taken on a Varian T-60. Mass spectra were measured by the direct inlet technique on a Varian MAT 112 spectrometer at 70 eV. *n*-Butyllithium (in hexane) was a product of Aldrich Chemical Company. Tetrahydrofuran (THF) was dried over sodium-potassium alloy and distilled just before use. Other solvents were used without purification.

Preparation of Compounds **4**.

The appropriate  $\alpha$ -chloroketone or aldehyde (25 mmoles) in THF (20 ml) was dropwise added (within 10 minutes) to a cold ( $-78^\circ$ ), stirred solution of the oxime dianion (25 mmoles) in THF (50 ml)/hexane (32 ml). Stirring was continued for 2 hours at the same temperature. The mixture was allowed to warm up to 0°, and then neutralized with 3M hydrochloric acid. The organic layer was separated, washed with water (2 x 30 ml), and dried (anhydrous sodium sulfate). The residue left after evaporation of the solvent *in vacuo* was crystallized from chloroform/petroleum spirit.

Preparation of Compounds **5**.

The appropriate unsaturated aldehyde or ketone (25 mmoles) in dry THF (50 ml) was dropwise added to a stirred cold (ice-bath) solution of the oxime dianion (25 mmoles) in THF (50 ml)/hexane (32 ml). The mixture was stirred for 30 minutes at 0°, and then neutralized carefully with 3M hydrochloric acid. The organic layer was separated, washed with water (2 x 30 ml), dried (anhydrous sodium sulfate), and the solvent was evaporated *in vacuo*. The solid residue was finally crystallized from the appropriate solvent.

Preparation of Compounds **6**.

Phosphorus pentoxide (6.0 g) was portionwise added to a cold (ice-bath) stirred solution of compound **5** (1.0 g) in chloroform (50 ml). After completion of the reaction, as indicated by thin-layer chromatography, excess phosphorus pentoxide was destroyed by dropwise addition of methanol. The mixture was then washed with water (2 x 50 ml). The solvent was finally removed under reduced pressure, and the residue was crystallized from the appropriate solvent.

## REFERENCES AND NOTES

[1] Taken from MS Thesis of A. S. Madi, Chemistry Department, University of Jordan, 1987. Part I, A. Q. Hussein, A. A. Jarrar and A. S. Madi, *Heterocycles*, in press.

[2] For reactions of **2** with organic substrates, see F. E. Henoch, K. G. Hampton and C. R. Hauser, *J. Am. Chem. Soc.*, **91**, 676 (1969); *ibid.*, **89**,

Table 2  
Physical and Spectral Data for Compounds 5

| Compound      | R <sub>1</sub>                     | R <sub>2</sub>                  | R <sub>3</sub>                | R <sub>4</sub> = R <sub>5</sub> | mp         | Yield % | Calcd./Found (%)<br>C H N            | C <sup>2</sup> -H | R <sub>2</sub>     | R <sub>1</sub>               | R <sub>3</sub> | R <sub>4</sub>    | R <sub>5</sub>    |
|---------------|------------------------------------|---------------------------------|-------------------------------|---------------------------------|------------|---------|--------------------------------------|-------------------|--------------------|------------------------------|----------------|-------------------|-------------------|
| <b>5a</b>     | C <sub>6</sub> H <sub>5</sub>      | H                               | C <sub>6</sub> H <sub>5</sub> | H                               | 130<br>C+P | 77      | 76.38 6.41 5.24<br>67.03 6.40 5.33   | 3.16<br>2H,d      | 6.77-7.50<br>10H,m | 6.72-7.68/2.30<br>9H,m/3H,s  | 6.60<br>1H, d  | 6.59 [a]<br>1H, d | 4.76 [a]<br>1H, m |
| <b>5b</b>     | p-Me-C <sub>6</sub> H <sub>4</sub> | H                               | C <sub>6</sub> H <sub>5</sub> | H                               | 137<br>C+P | 74      | 76.84 6.81 4.98<br>76.45 6.73 4.95   | 3.12<br>2H,d      | 7.13-7.83<br>9H,m  | 7.06-7.53/2.33<br>4H/m/3H, s | 1.56<br>3H, d  | 6.61<br>1H, d     | 4.72 [a]<br>1H, m |
| <b>5c</b>     | p-Br-C <sub>6</sub> H <sub>4</sub> | H                               | C <sub>6</sub> H <sub>5</sub> | H                               | 129<br>C+P | 79      | 58.98 4.66 4.05<br>59.22 4.61 4.03   | 3.12<br>2H,d      | 7.00-7.50<br>4H,d  | 7.06-7.53/2.33<br>4H/m/3H, s | 1.56<br>3H, d  | 6.60<br>1H, d     | 4.71 [a]<br>1H, m |
| <b>5d</b>     | p-Me-C <sub>6</sub> H <sub>4</sub> | H                               | Me                            | Me                              | 78<br>T+H  | 63      | 72.84 8.56 5.66<br>72.46 8.61 5.70   | 3.19<br>2H,d      | 7.00-7.50<br>4H,d  | 7.06-7.53/2.33<br>4H/m/3H, s | 1.56<br>3H, d  | 1.78<br>3H, d     | 1.28 [b]<br>3H, s |
| <b>5e</b>     | p-Me-C <sub>6</sub> H <sub>4</sub> | H                               | H                             | H                               | 105<br>C+P | 73      | 70.22 7.37 6.82<br>69.94 7.28 6.85   | 3.08<br>2H,m      | 6.79<br>1H,dd      | 6.72-6.98<br>5H, m           | 6.60<br>1H, d  | 6.56<br>1H, d     | 4.48 [b]<br>1H, m |
| <b>5f</b>     | H                                  | H                               | C <sub>6</sub> H <sub>5</sub> | H                               | 89<br>C+P  | 53      | 69.09 6.85 7.33<br>68.87 6.74 7.30   | 2.53<br>2H,m      | 1.11-2.23<br>8H,m  | 6.56<br>1H, d                | 6.60<br>1H, d  | 6.60<br>1H, d     | 4.53 [a]<br>1H, m |
| <b>(Z)-5g</b> | (CH <sub>2</sub> ) <sub>4</sub>    | (CH <sub>2</sub> ) <sub>4</sub> | C <sub>6</sub> H <sub>5</sub> | H                               | 148<br>M+W | 80      | 73.44 7.81 5.71<br>73.17 7.78 5.76   | 2.23<br>1H,m      | 0.88-2.42<br>8H,m  | 6.60<br>1H, d                | 6.60<br>1H, d  | 6.60<br>1H, d     | 4.50 [c]<br>1H, m |
| <b>(E)-5g</b> | (CH <sub>2</sub> ) <sub>4</sub>    | (CH <sub>2</sub> ) <sub>4</sub> | C <sub>6</sub> H <sub>5</sub> | H                               | 177<br>M+W | 15      | 73.44 7.81 5.71<br>73.33 7.79 5.76   | 3.58<br>1H,m      | 1.11-2.33<br>8H,m  | 6.60<br>1H, d                | 6.60<br>1H, d  | 6.60<br>1H, d     | 4.33 [c]<br>1H, m |
| <b>5h</b>     | (CH <sub>2</sub> ) <sub>4</sub>    | (CH <sub>2</sub> ) <sub>4</sub> | Me                            | Me                              | 118<br>C+P | 71      | 68.21 10.02 6.63<br>68.20 10.04 6.66 | 3.41<br>1H,m      | 1.11-2.33<br>8H,m  | 1.85<br>3H, d                | 1.85<br>3H, d  | 1.85<br>3H, d     | 1.36 [b]<br>3H, s |

[a] In acetone-d<sub>6</sub>. [b] In deuteriochloroform. [c] In deuteriochloroform/DMSO-d<sub>6</sub>.

463 (1967); J. Brown, K. L. Sides, T. D. Fulmer and C. F. Beam, *J. Heterocyclic Chem.*, **16**, 1669 (1979).

[3] N. Matsumura, A. Kunugihara and S. Yoneda, *J. Heterocyclic Chem.*, **22**, 1169 (1985).

[4] K. Biemann, "Mass Spectrometry", 1962, p 96, McGraw Hill; E. Stenhagen, S. Abrahamsson and F. W. McLafferty, "Registry of Mass Spectral Data", Vol **1**, John Wiley, 1974, p 55.

[5] C. A. Park, C. F. Beam, E. M. Kaiser, R. J. Kaufmann, F. E. Henoch and C. R. Hauser, *J. Heterocyclic Chem.*, **13**, 449 (1976).

[6] The primary adduct exists initially in the (*Z*)-configuration, partial isomerization during workup of the reaction mixture would give a mixture of both (*Z*) and (*E*)-isomers; see R. E. Gawaley and T. Nagg, *Tetrahedron Letters*, 263 (1984); R. E. Lyle and H. M. Fribush, *J. Org. Chem.*, **43**, 1275 (1978); M. E. Jung, P. A. Blair and J. A. Lowe, *Tetrahedron*, **18**, 1439 (1976).

[7] The assignment of the (*Z*)- and (*E*)-configurations here is consistent with the pmr spectra; see G. J. Karabatsos and R. A. Taller, *Tetrahedron*, **24**, 3347 (1968).