# A SIMPLE OXIME-NITRONE ISOMERIZATION AND INTRAMOLECULAR CYCLOADDITION REACTION OF 2-(ALK-2-ENYL)OXY- AND 2-[*N*-(ALK-2-ENYL)BENZYLAMINO]-CYCLOHEXANONE OXIMES

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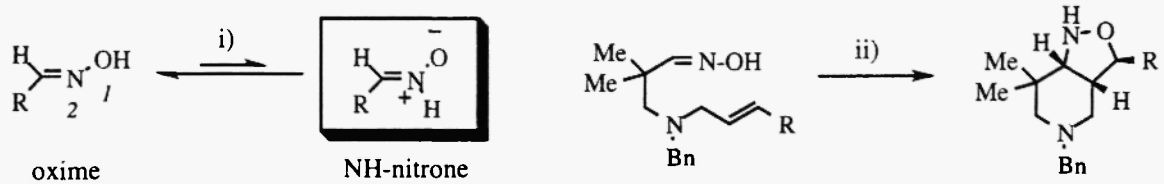
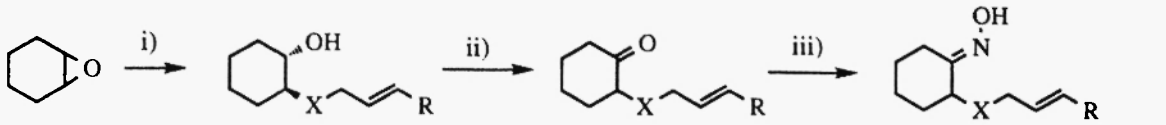
**Abstract:** Cyclohexanone oximes **6** and **7** bearing olefinic dipolarophile moieties at the 2-position underwent a thermally induced oxime-olefin cycloaddition reaction under mild conditions leading to isoxazolo[4,3-*c*]benzo[*b*]furan **8** and isoxazolo[4.3-*c*]indole derivatives **9**.

Since a new concept on the isomerization of oxime to nitrone *via* the thermal 1,2-hydrogen shift was proposed by Grigg *et al*[1] and the existence of the resultant NH-nitrone was elucidated by forming intramolecular cycloaddition products (Scheme 1), extensive investigations on the synthesis of highly functionalized isoxazolidine derivatives have been developed by many groups.[2] Recently, we have also reported the simple oxime-nitrone isomerization and intramolecular nitrone-olefin cycloaddition reaction of 3-(alk-2-enylamino)-propionaldehyde oximes, which afford isoxazolidine derivatives fused to a piperidine ring (Scheme 1).[3] In order to extend this synthetic methodology to further functionalized isoxazolidines, we examined the thermal reaction of cyclohexanone oximes bearing olefinic dipolarophile moieties at the 2-position.



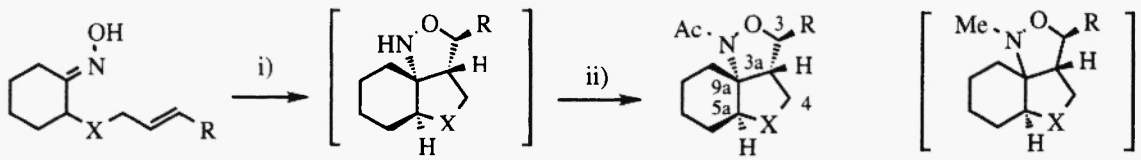

**Scheme 1** *Reaction and conditions:* i) 1,2-H shift; ii) EtOH or BuOH, reflux, 8–36 h, good to excellent yields

Cyclohexanones **4** and **5** were prepared from cyclohexene oxide (**1**) accordingly to the method reported by Mori *et al*[4]; a nucleophilic ring-opening of epoxide **1** with alcohols and amines was accomplished by neutral alumina catalyst[5] to give cyclohexanols **2** and **3**, respectively. A Jones oxidation of cyclohexanols **2** and **3** gave cyclohexanones **4** and **5**, which were converted to the desired oximes **6** and **7** by usual treatment with hydroxylamine (Scheme 2). A solution of **6a** in butan-1-ol (BuOH) was heated under reflux for 4 days and a successive work-up gave the oxime-olefin cycloadduct, perhydroisoxazolo[4,3-*c*]benzo[*b*]furan, **8a** in 64% yield together with unchanged **6a** (30%). Similarly, the thermal reaction of oximes **6b** and **6c** in refluxing BuOH or toluene gave tricyclic products **8b** and **8c**, respectively (Table 1). In every case, the starting oximes **8** were not



**1** **2:** X= O **3:** X= N-Bn **4:** X= O **5:** X= N-Bn **6:** X= O **7:** X= N-Bn **a:** R= H **b:** R= Me **c:** R= Ph

**Scheme 2** *Reagents and conditions:* i) alk-2-enyl alcohols or *N*-(alk-2-enyl)benzylamines (each 1.1 equiv.), $Al_2O_3$ (neut. W-H), dry ether; reflux, overnight, 48–90%; ii) Jones reagent (2.0 equiv.), acetone, 0–15 °C, 0.5 h, 40–72%; iii) $H_2NOH{\bullet}HCl$ (1.5 equiv.), NaOAc (1.5 equiv.), MeOH, rt, 4–6 h, 73–98%



**6:** X= O **7:** X= N-Bn **8:** X= O **9:** X= N-Bn **10:** X= O **11:** X= N-Bn **12:** X= O **13:** X= N-Bn

**Scheme 3** *Reagents and conditions:* i) in refluxing solvent; ii) $Ac_2O$ (1.0 equiv.), pyridine (2.0 equiv.), benzene, rt, 5 h, 57–89%

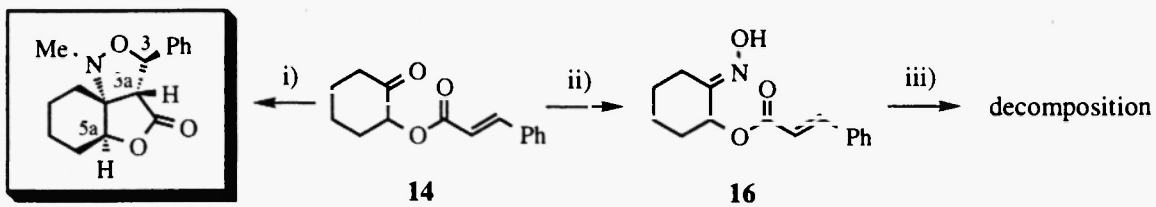
**Table 1.** Thermal reaction of 2-[*N*-(alk-2-enyl)oxy]- (**6**) and 2-[*N*-(alk-2-enyl)benzylamino]-cyclohexanone oximes (**7**)

| Run | Oxime | X | R | Solvent | Time/ h | Cycloadduct (Yield/ %) | Recovered oxime |
|---|---|---|---|---|---|---|---|
| 1 | **6a** | O | H | BuOH | 96 | **8a** (64) | **6a** (30) |
| 2 | **6a** | O | H | toluene | 96 | **8a** (75) | **6a** (16) |
| 3 | **6b** | O | Me | BuOH | 72 | **8b** (50) | **6b** (36) |
| 4 | **6b** | O | Me | toluene | 72 | **8b** (71) | **6b** ( 9) |
| 5 | **6c** | O | Ph | EtOH | 48 | **8c** (50) | **6c** (41) |
| 6 | **6c** | O | Ph | BuOH | 48 | **8c** (57) | **6c** (33) |
| 7 | **6c** | O | Ph | toluene | 48 | **8c** (72) | **6c** (11) |
| 8 | **7a** | N-Bn | H | BuOH | 48 | **9a** (56) | **7a** (16) |
| 9 | **7b** | N-Bn | Me | BuOH | 21 | **9b** (48) | a) |
| 10 | **7b** | N-Bn | Me | toluene | 10 | **9b** (40) | a) |
| 11 | **7c** | N-Bn | Ph | EtOH | 70 | **9c** (55) | a) |
| 12 | **7c** | N-Bn | Ph | toluene | 48 | **9c** (64) | a) |

a) A mixture of unidentified products was also obtained.

consumed and partially recovered. Interestingly, slightly better results in yields of the oxime-olefin cycloadducts **8** were obtained by the reaction in refluxing toluene in contrast to those which have been reported by us.[3] Oximes **7a–c** were also allowed to react and gave perhydroisoxazolo[4,3-*c*]indoles **9a–c** in moderate

yields. Cycloadducts **8** and **9** were obtained as viscous oils except for **9b**. Although the TLC and/or HPLC of **8** and **9** suggested that they should be isolated as single isomers, some of their $^1$H and $^{13}$C-NMR spectra did not give any available information on the stereochemistry of the isoxazolidine ring due to the signal broadening.[6] In order to obtain further information on this respect, we examined the reaction of cyclohexanones **4** and **5** with *N*-methylhydroxylamine in EtOH under reflux to give the corresponding *N*-methylnitrone cycloadducts **12** and **13** in 54–85% yields. However, the stereochemistry of cycloadducts **12** and **13** could not be made clear also due to the signal broadening in their NMR spectra. So, the crude products **8** and **9** were treated with acetic anhydride in benzene to afford *N*-acetylated products **10** and **11**. The structures of *N*-acetylated **10** and **11**, fortunately, could be fully characterized by their $^1$H-NMR spectroscopic data compared with those of a related compound. The reaction of **14**, prepared in a similar manner to cyclohexanones **4** and **5**, with *N*-methylhydroxylamine gave the nitrone-cycloadduct **15**, the structure of which was unambiguously confirmed by its single-crystal analysis.[7] The signal patterns and coupling constants in the $^1$H-NMR spectra of **10** and **11** are consistent with those of **15** (Table 2). The treatment of ketone **14** with hydroxylamine gave the corresponding oxime **16**. The reaction of oxime **16** in refluxing EtOH gave, unfortunately, an inseparable mixture of products probably due to decomposition of the starting oxime.




**15**
(X-ray structure analysis)

**14** **16**

**Scheme 4** *Reagents and conditions:* i) MeNHOH•HCl (1.5 equiv.), NaOAc (1.5 equiv.), EtOH, reflux, 3 h, 42%; ii) $H_2NOH$•HCl (1.5 equiv.), NaOAc (1.5 equiv.), MeOH, rt, 6 h, 80%; iii) EtOH, reflux, 4 h

**Table 2.** Selected $^1$H-NMR spectroscopic data for products **10**, **11**, and **15**.

| | | | | Chemical shifts/ δ | | | Coupling constants/ Hz | |
|---|---|---|---|---|---|---|---|---|
| Run | Product | X | R | 3-H | 3a-H | 5a-H | $J_{3\text{-}3a}$ | $J_{5a\text{-}6}$ |
| 1 | **10a** | O | H | 3.95 and 4.04 | 3.03 | 4.44 | 0 and 4.3 | 6.3 and 7.9 |
| 2 | **10b** | O | Me | *ca.* 4.1[a)] | 2.73 | 4.61 | ud[b)] | 6.0 and 6.3 |
| 3 | **10c** | O | Ph | 5.06 | 3.16 | 4.73 | 4.3 | 6.3 and 7.9 |
| 4 | **11a** | N-Bn | H | 3.83 and 3.94 | 2.85 | 3.41 | 1.0 and 4.6 | 5.0 and 7.6 |
| 5 | **11b** | N-Bn | Me | 4.01 | *ca.* 2.4[a)] | 3.26 | 4.3 | 5.6 and 7.6 |
| 6 | **11c** | N-Bn | Ph | 4.87 | 2.88 | 3.45 | 4.0 | 5.0 and 7.6 |
| 7 | **15** | | | 5.27 | 3.27 | 3.93 | 4.0 | 5.9 and 6.3 |

a) Overlapped with another signal. b) ud: undetermined.

In conclusion, we have described here that cyclohexanone oximes **6** and **7** underwent an oxime-nitrone isomerization *via* 1,2-hydrogen shift and that the resultant NH-nitrones were trapped intramolecularly with the

olefinic dipolarophiles to give tricyclic cycloadducts **8** and **9**. These sequences should be utilized as a key step for the synthesis of highly functionalized heterocyclic systems.

## Typical Procedures and Spectroscopic Data

A solution of **6c** (0.12 g; 0.49 mmol) in toluene (5 ml) was heated under reflux for 48 h and the solvent was evaporated off. The residue was subjected to a column chromatography on silica gel to give cycloadduct **8c** (0.086 g, 72%) and unchanged **6c** (11%) as elution of hexane-ethyl acetate (4/1). **8c:** Pale yellow oil; IR (NaCl) $\nu_{max}/cm^{-1}$ 3190 (NH); $^1H$ NMR ($CDCl_3$) $\delta$ = 1.20–1.80 (8 H, ov, 6-, 7-, 8- and 9-$H_2$), 2.10 (1 H, 4-H), 2.61 (1 H, 3a-H), 2.76 (1 H, 5a-H), 3.02 (1 H, 4-H), 3.52–3.81 (2 H, C$H_2$Ph), 4.74 (1 H, d, $J$ = 4.6 Hz, 4-H), 6.00 (1 H, br s, NH), and 7.24–7.34 (10 H, ov, Ph); $^{13}C$ NMR ($CDCl_3$) $\delta$ = 21.9, 22.6, 25.8, 31.5 (br), 60.1, 71.6 (br), 77.2, 78.5, 78.8 (br), 126.1, 128.0, 128.7, and 139.3.

A mixture of **8c** (0.10 g, 0.40 mmol), pyridine (0.080 ml, 0.80 mmol), and acetic anhydride (0.038 ml, 0.40 mmol) in benzene (5 ml) was stirred at room temperature for 5 h and usual purification with silica-gel column chromatography gave *N*-acetylated **10c** (0.105 g, 89%) as elution of hexane-ethyl acetate (3/1). **10c:** Pale yellow oil (Found: C, 70.70; H, 7.15; N, 4.68%. $C_{17}H_{21}NO_3$ requires: C, 71.05; H, 7.37; N, 4.87%); IR (NaCl) $\nu_{max}/cm^{-1}$ 1630 (CO), $^1H$ NMR ($CDCl_3$) $\delta$ = 1.19–1.74 (7 H, ov, 6-, 7-, and 8-$H_2$ and 9-H), 2.20 (3 H, s, Me), 2.35 (1 H, m, 9-H), 3.16 (1 H, m, 3a-H), 3.88 (1 H, dd, $J$ = 4.0 and 9.6 Hz, 4-H), 4.24 (1 H, dd, $J$ = 7.6 and 9.6 Hz, 4-H), 4.73 (1 H, dd, $J$ = 6.3 and 7.9 Hz, 5a-H), 5.06 (1 H, d, $J$ = 4.3 Hz, 3-H), and 7.33–7.43 (5 H, ov, Ph); $^{13}C$ NMR ($CDCl_3$) $\delta$ = 20.5 and 21.9 (6- and 7-C), 22.4 (*Me*CO), 27.2 (8-C), 29.7 (9-C), 59.6 (3a-C), 69.8 (4-C), 75.3 (9a-C), 79.5 (5a-C), 86.0 (3-C), 125.5, 128.5, 128.8, and 137.8 (Ph C), and 165.9 (Me*C*O).

## References and Notes

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(7) Crystallographic data for the structure of **15** have been deposited with the Cambridge Crystallographic Data Centre. 12 Union Road, Cambridge CB2 1EZ, UK.

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