

a) The stereochemistry of **2d** and **2e**, and **2f** and **2g** (diastereomers each other) are undecided yet. b) Stirred magnetically. c) Yield of isolated product.

major product, which showed a pair of doublets at $\delta=3.80$ ($C_3\text{-H}$, $J=2.0$ Hz) and 4.20 ($C_2\text{-H}$, $J=2.0$ Hz) and a minor isomer (**5a**) which showed a pair of doublets at $\delta=3.70$ ($J=2.0$ Hz) and 3.80 ($J=2.0$ Hz) were obtained. In **4a**, NOE between *O*-benzyl methylene and $C_2\text{-H}$ was observed. Hence, the configuration of the benzyloxy group of **4a** is *syn* and **5a** is *anti* to the oxirane ring, respectively. On the other hand, the configuration of oxime **3a** can be confirmed to be identical to that of **4a** by a comparison of its NMR spectra. (**3a**: $\delta=3.83$ ($J=2.0$ Hz), 4.27 ($J=2.0$ Hz), and 8.70 (s))

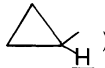
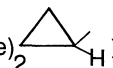
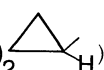
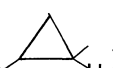
When **3a** and **4a** were allowed to react with hydroxylamine hydrochloride in methanol at 40°C for 4 h, **2a** was obtained in quantitative yield; **5a**, however, was recovered unchanged under similar reaction

conditions, and under a refluxing condition gave only a resinous substance.

The reaction of *trans*-2-aryl- and 2-cyclopropyl-3-benzoyloxiranes with hydroxylamine hydrochloride may be explained by saying that the initially-formed oxiranyl *syn*-oxime suffers an intramolecular attack on the 2-position of the oxirane ring by oxygen nucleophile of the oxime to afford the corresponding 2-isoxazolin-4-ols.

In order to extend this reaction for the synthesis of 2-isoxazolin-4-ol bearing other than aryl and cyclopropyl, *trans*-2-benzoyl-3-methyloxirane (**1h**) was allowed to react with hydroxylamine similarly to **1a** to give *trans*-5-methyl-3-phenyl-2-isoxazolin-4-ol (**2h**) in only 10% yield; the corresponding *syn*-*O*-benzyloxime

Table 2. NMR Data and Elemental Analyses of **2**

Compound	^1H NMR (in CDCl_3 , δ , J/Hz)	^{13}C NMR (in CDCl_3 , δ)	Anal. C, H, N
2a	2.63 (d, 1H, 8.9, 4-OH) 5.37 (dd, 1H, 8.9, 9.3, 4-H) 5.56 (d, 1H, 3.0, 5-H)	84.7 (C_4), 90.3 (C_5) 157.2 (C_3 , C=N)	($\text{C}_{15}\text{H}_{13}\text{NO}_2$)
2b	2.53 (d, 1H, 8.9, 4-OH) 5.35 (dd, 1H, 8.9, 3.3, 4-H) 5.49 (d, 1H, 3.3, 3,5-H)	84.5 (C_4), 90.1 (C_5) 159.7 (C_3 , C=N)	($\text{C}_{16}\text{H}_{15}\text{NO}_3$)
2c	1.70—1.80 (m, 1H, ) 2.40 (d, 1H, 8.7, 4-OH) 4.78 (dd, 1H, 8.7, 4.0, 4-H) 5.30 (d, 1H, 4.0, 5-H)	6.9, 7.2, 7.3 () 85.6 (C_4), 88.8 (C_5) 161.8 (C_3 , C=N)	($\text{C}_{12}\text{H}_{13}\text{NO}_2$)
2d	1.35 (dd, 1H, 5.8, 8.3, (Me) ₂ ) 2.40 (d, 1H, 9.0, 4-OH) 4.85 (dd, 1H, 9.0, 4.2, 4-H) 5.29 (d, 1H, 4.2, 5-H)	20.1, 20.15, 20.7 ((Me) ₂ ) 22.5, 26.7 (CH_3) 87.3 (C_4), 88.6 (C_5) 160.0 (C_3 , C=N)	($\text{C}_{14}\text{H}_{17}\text{NO}_2$)
2e	1.55 (dd, 1H, 5.8, 8.2, (Me) ₂ ) 2.45 (d, 1H, 9.0, 4-OH) 4.77 (dd, 1H, 9.0, 4.3, 4-H) 5.33 (d, 1H, 4.3, 5-H)	19.1, 19.7, 21.9 ((Me) ₂ ) 21.9, 26.5 (CH_3) 87.7 (C_4), 88.7 (C_5) 160.2 (C_3 , C=N)	($\text{C}_{14}\text{H}_{17}\text{NO}_2$)
2f	2.70—2.80 (m, 1H, Ph ) 2.45 (d, 1H, 9.0, 4-OH) 4.90 (dd, 1H, 9.0, 4.0, 4-H) 5.40 (d, 1H, 4.0, 5-H)	20.2, 21.0, 33.1 (Ph ) 87.5 (C_4), 88.8 (C_5) 160.2 (C_3 , C=N)	($\text{C}_{18}\text{H}_{17}\text{NO}_2$)
2g	2.80—2.90 (m, 1H, Ph ) 2.45 (d, 1H, 9.0, 4-OH) 4.85 (dd, 1H, 9.0, 4.0, 4-H) 5.42 (d, 1H, 4.0, 5-H)	20.0, 20.5, 32.1 (Ph ) 87.3 (C_4), 88.6 (C_5) 160.0 (C_3 , C=N)	($\text{C}_{18}\text{H}_{17}\text{NO}_2$)
2h	1.53 (d, 3H, 6.6 Hz) 2.13 (d, 1H, 9.6, 4-OH) 4.47 (dq, 1H, 6.6, 6.6, 5-H) 5.15 (dd, 1H, 6.6, 9.6, 4-H)	11.2 (CH_3), 76.8 (C_5) 81.3 (C_4), 159.3 (C_3 , C=N)	($\text{C}_{10}\text{H}_{11}\text{NO}_2$)

(4h), however, was converted to 2h in 75% yield by a treatment with titanium tetrachloride in dichloromethane.

Experimental

General. All melting points are uncorrected. The NMR spectra were obtained on a JNM-GX270 spectrometer using TMS as the internal standard.

Preparation of 1. Cyclopropyl methyl ketone,⁴ 2,2-dimethylcyclopropyl methyl ketone,⁵ and 2-phenylcyclopropyl methyl ketone⁶ were prepared according to methods described in the literature. Condensations of cyclopropyl methyl ketones with benzaldehyde were carried out according to methods described in the literature.⁷ The α,β -epoxy ketones 1a–g were prepared from the corresponding α,β -unsaturated ketones.⁸ 1a: mp 89–90 °C (hexane–ethyl acetate)(lit.⁸ mp 90 °C) 1b: mp 89 °C (methanol), 90%. 1c: mp 167–168 °C (hexane–ether), 70%. The mixture of diastereomers (98%, 1d:1e $\approx$ 1:1), was chromatographed on silica gel, using hexane–ether. 1d: oil, R_f 0.35 (hexane: ether 94:6) 1e: oil, R_f 0.28 (hexane: ether 94:6). The mixture of diastereomers (100%, 1f:1g $\approx$ 1:1) was chromatographed on silica gel, using hexane–ether. 1f: mp 69–70 °C, R_f 0.57 (hexane: ether 5:1) 1g: mp 62–63 °C, R_f 0.48 (hexane: ether 5:1).

One-Pot Synthesis of 2-Isioxazolin-4-ols. General Method: An ethanol (30 ml) solution of *trans*-2-benzoyl-3-phenyloxirane (1a, 2.2 g, 10 mmol) was refluxed with hydroxylamine hydrochloride (1.04 g, 15 mmol) in the presence of pyridine (7 ml) for 5 h. After cooling, the reaction mixture was evaporated under reduced pressure and the residue extracted with ether after the addition of 1 mol dm⁻³ HCl; the solution was then washed with water and dried over sodium sulfate. After evaporation of the ether, the residue was purified by recrystallization to afford 2a in 72% yield. From the filtrate, oxime 3a, mp 155–156 °C, was isolated in 7% yield.

Oxime of 1a. An ethanol (30 ml) solution of 1a (2.2 g, 10 mmol) was stirred with hydroxylamine hydrochloride (0.83 g, 12 mmol), sodium acetate (1.64 g, 20 mmol) and water (3 ml), at 40 °C for 2 h. After cooling, the reaction mixture was poured into water. The precipitate was recrystallized from methanol to afford an oxime in 70% yield. The melting point of the oxime was not depressed upon admixture with 3a.

O-Benzylloxime of 1a. After a methanol (40 ml) solution of 1a (2.2 g, 10 mmol) was stirred with *O*-benzylhydroxylamine hydrochloride (1.92 g, 12 mmol), and pyridine (10 ml) at room temperature for 24 h, the reaction mixture was poured into water. The precipitate was recrystallized from methanol to afford *syn*-*O*-benzylloxime (4a), mp 71 °C, in 70% yield. From the filtrate, the *anti*-isomer (5a), mp 63 °C, was isolated in 15% yield.

3,5-Diphenylisoxazole from *p*-Toluenesulfonate of 2a.

p-Toluenesulfonate of 2a was prepared from 2a in the usual manner, mp 127 °C (EtOH). After a methanol (10 ml) solution of the *p*-toluenesulfonate (200 mg) was stirred with sodium methoxide (50 mg) at room temperature for 1 h, the reaction mixture was poured into water to give 3,5-diphenylisoxazole, quantitatively. mp 141–142 °C (EtOH)-(lit.⁹ mp 141–143 °C).

5-Methyl-3-phenyl-2-isoxazolin-4-ol (2h). Similarly to 1a, 2-benzoyl-3-methyloxirane(1h) gave 2h in 10% yield, mp 140 °C (hexane–ethyl acetate)(lit.² mp 102–105 °C). Similarly to 4a, 1h gave 4h. *syn*-4h: R_f 0.58 (benzene), 70% *anti*-5h: R_f 0.18 (benzene), 16%. A dichloromethane (10 ml) solution of *syn*-4h (200 mg) was stirred with titanium tetrachloride (100 mg) under a nitrogen atmosphere at room temperature for 24 h. The dichloromethane solution was washed with water and dried over sodium sulfate. After evaporation of the solvent, the residue was purified by recrystallization from hexane–ethyl acetate to afford 2h in 75% yield.

References

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