A Simple Synthetic Method of *trans*-5-Aryl and 5-Cyclopropyl Derivatives of 2-Isoxazolin-4-ol via Intramolecular Ring Opening of α,β-Epoxy Ketone Oximes

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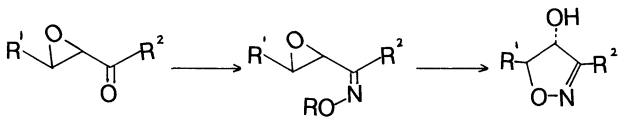
(Received April 23, 1990)

Synopsis. *trans*-5-Aryl and 5-cyclopropyl derivatives of 2-isoxazolin-4-ol were conveniently prepared from *trans*-2-aryl- and 2-cyclopropyl-3-benzoyloxiranes and hydroxylamine hydrochloride in the presence of pyridine via an intramolecular opening of oxirane by the oxygen nucleophile of the oxyimino group.

2-Isoxazolin-4-ols are not available by nitrile oxide cycloaddition to enol ethers or esters since 2-isoxazolin-5-ols are formed.[1] Although a useful synthetic method for 2-isoxazolin-4-ol has been reported,[2] the method is unable to be employed for a compound which is susceptible to a strong base.[3] Reported herein is a convenient method for producing *trans*-5-aryl and 5-cyclopropyl derivatives of 2-isoxazolin-4-ol via an intramolecular ring opening oxirane by the oxygen nucleophile of the oxyimino group.

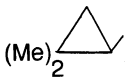
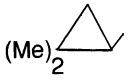
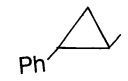
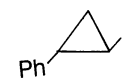
An ethanol solution of *trans*-2-benzoyl-3-phenyloxirane (**1a**) was refluxed with 1.5 equivalent of hydroxylamine hydrochloride in the presence of pyridine for 5 h. After the usual treatment a crystalline compound (**2a**) was given in 72% yield together with a small amount of oxime (**3a**, 7%). The ^{1}H NMR spectrum of **2a** did not show a hydroxyl signal of oxime, but, rather, showed a doublet of the hydroxyl signal (δ=2.63, J=8.9 Hz) and a C_4-hydrogen signal being coupled to two hydrogens (δ=5.37, dd, J=8.9, 3.0 Hz) and a doublet of C_5-hydrogen signal (δ=5.56, J=3.0 Hz). In addition, a treatment of the *p*-toluenesulfonate of **2a** with sodium methoxide in methanol gave 3,5-diphenylisoxazole quantitatively; hence, **2a** was identified to be *trans*-3,5-diphenyl-2-isoxazolin-4-ol. The results of the formation of *trans*-5-aryl and 5-cyclopropyl derivatives of 2-isoxazolin-4-ol are summarized in Table 1.

When an ethanol solution of **1a** was stirred with 1.2 equivalent of hydroxylamine hydrochloride and 2 equivalents of sodium acetate in water, oxime **3a** was obtained in 70% yield. When **1a** was stirred with *O*-benzylhydroxylamine hydrochloride, anhydrous methanol and pyridine, an *O*-benzylhydroxime (**4a**) as the



1a—1h **3**: R=H **4**: R=CH_2Ph **2a—2h**

Table 1. One-Pot Synthesis of 5-Aryl and 5-Cyclopropyl Derivatives of 2-Isoxazolin-4-ol

2-Isoxazolin-4-ol	R_1	R_2	Reaction		Yield[c]	Mp
			Temp/°C	Time/h	%	°C
2a	C_6H_5	C_6H_5	Reflux	5	72	167—168
2b	C_6H_5	C_6H_4-*p*-OMe	25	10[b]	60	132—133
2c		C_6H_5	Reflux	5	62	99—100
2d[a]		C_6H_5	Reflux	5	84	137—138
2e[a]		C_6H_5	Reflux	5	72	92— 93
2f[a]		C_6H_5	Reflux	5	65	114—115
2g[a]		C_6H_5	Reflux	5	55	106—107

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.

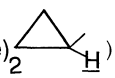
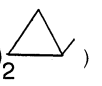
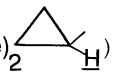
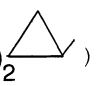
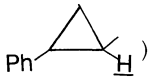
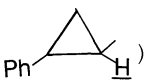
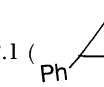
major product, which showed a pair of doublets at δ=3.80 (C_3-H, J=2.0 Hz) and 4.20 (C_2-H, J=2.0 Hz) and a minor isomer (**5a**) which showed a pair of doublets at δ=3.70 (J=2.0 Hz) and 3.80 (J=2.0 Hz) were obtained. In **4a**, NOE between *O*-benzyl methylene and C_2-H was observed. Hence, the configuration 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**: δ=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	^{1}H 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)	($C_{15}H_{13}NO_2$)
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)	($C_{16}H_{15}NO_3$)
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)	($C_{12}H_{13}NO_2$)
2d	1.35 (dd, 1H, 5.8, 8.3, ) 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 () 22.5, 26.7 (CH_3) 87.3 (C_4), 88.6 (C_5) 160.0 (C_3, C=N)	($C_{14}H_{17}NO_2$)
2e	1.55 (dd, 1H, 5.8, 8.2, ) 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 () 21.9, 26.5 (CH_3) 87.7 (C_4), 88.7 (C_5) 160.2 (C_3, C=N)	($C_{14}H_{17}NO_2$)
2f	2.70—2.80 (m, 1H, ) 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 () 87.5 (C_4), 88.8 (C_5) 160.2 (C_3, C=N)	($C_{18}H_{17}NO_2$)
2g	2.80—2.90 (m, 1H, ) 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 () 87.3 (C_4), 88.6 (C_5) 160.0 (C_3, C=N)	($C_{18}H_{17}NO_2$)
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)	($C_{10}H_{11}NO_2$)

(**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 ketone[6] 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**≈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**≈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-Isoxazolin-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 evaported under reduced pressure and the residue extracted with ether after the addition of 1 mol dm^{-3} HCl; the solusion was then washed with water and dried over sodium solfate. 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*-Benzyloxime 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*-benzyloxime (**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.

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