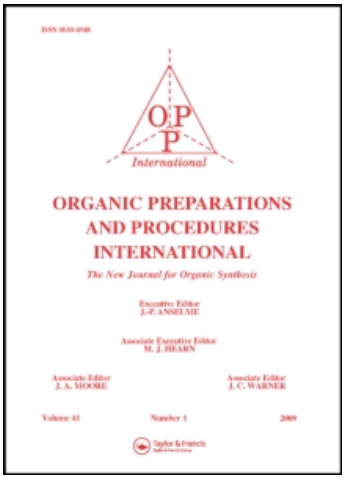

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SYNTHESIS OF 2-SUBSTITUTED 3,4-DIHYDROOXAZOLES USING S-ETHENYLSULFILIMINES†

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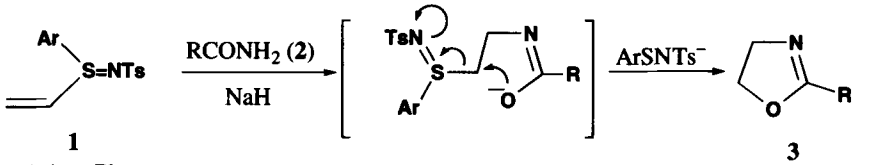
Most of O,N-,S,N- and N,N-five-membered rings are useful as intermediates for the preparation of medicinals and other functional materials. In a series of studies on the synthesis of ethenyl[1] and heterocyclic compounds[2] using S-ethenylsulfilimines (**1**), we have developed an efficient preparation of 2-substituted-3,4-dihydrooxazoles (**3**) from the reaction of **1** with nucleophilic compounds such as amides.

The cyclization involves three steps: Michael addition, prototropy (γ to α) and intramolecular S_N reaction, similar to cyclopropanation using S-ethenylsulfilimines.[3]



1
a) Ar = Ph
b) Ar = *p*-Tolyl

3
a) R = Ph b) R = *p*-Tolyl c) R = *o*-Tolyl d) R = *p*-ClPh
e) R = *m*-Py f) R = *p*-Py g) R = Me h) R = Et

S-Ethenyl-S-phenyl- (**1a**) and S-ethenyl-S-(4-methylphenyl)-N-tosylsulfilimines (**1b**) were treated with nine amides (**2**). Initially, the reaction of **1** with benzamide (**2a**) (slight excess) in the presence of equimolar amounts of sodium hydride to **2** was carried out under various conditions. Table 1 shows that the reactions in 1,2-dimethyoxyethane (DME) and tetrahydrofuran (THF) gave

TABLE 1. Reactions of **1a** with Benzamide (**2a**) to **3a**

Entry No.	**2a**/**1** (mol/mol)	NaH/**2a** (mol/mol)	Solvent	Temp/time (°C / hrs)	Yield of **3a** (%)
1	1.05	1.00	DME	rt/56	88
2	1.05	1.00	THF	rt/56	89
3	1.05	1.00	MeCN	rt/56	92
4	1.05	1.00	DME	rt/24	42
5	1.05	1.00	DME	40/10	70
6	1.05	1.00	THF	rt/24->40/5	74
7	1.05	1.00	DME	rt/24->40/5	90

high yields of the corresponding 3,4-dihydrooxazole (2-phenyl-3,4–dihydrooxazole **3a**); even acetonitrile could be used as solvent. As would be expected, the last step requires more drastic conditions than the first two. Indeed, in order to obtain high yield of **3a** from the reaction at room temperature, two or three days of reaction time were needed, while the reaction carried out at 40° for 10 hrs resulted in low yield of **3a** because of the completing reactions. The following conditions were determined to be suitable to obtain **3a** in high yield: room temperature for 24 hrs in the addition step and at 40° for 5 hrs in the others.

Table 2 shows that the reactions of **1** with aromatic amides (including nicotinamides) gave the corresponding 3,4-dihydrooxazoles **3** in high yields. With S-ethenylsulfilimines, **1b** gave higher yields of **3** than **1a**. The structural effects of **1** upon the reactivity for ring construction will be reported elsewhere. The present method gives 2-substituted, especially 2-aryl substituted 3,4-dihydrooxazoles, in high yields under mild conditions. Previously 2-substituted-3,4-dihydrooxazoles have been obtained by the cyclization of N-2-haloethylamides,[4] by the reaction of nitriles with 2-aminoethanols[5] or ethylene oxides,[6] of carboxylic acids with 2-aminoethanols followed by cyclization in the presence of triphenylphosphine,[7] of amidines with 2-aminoethanols[8] or epoxides,[9] of aldehydes with 2-azidoethanols,[10] and others.[11]

TABLE 2. Preparation of **3** by the Reaction of **1**b with **2**[a]

Entry No.	**2**	R	Temp/time (°C/hrs)	**3** mp/°C (lit.)	Yield (%)
8	b	4-$CH_3C_6H_4$	rt/24->40/5	59.5-60.5 (60)	92
9[b]	b	4-$CH_3C_6H_4$	rt/24->40/5		83
10	c	2-$CH_3C_6H_4$	rt/24->40/5	oil	89
11	d	4-ClC_6H_4	rt/24->40/5	81-83 (80-83)	97
12	e	3-Py	rt/24->40/5	66-68 (71)	98
13	f	4-Py	rt/24->40/5	113-114 (117)	95
14	g	Me	rt/90	oil	53
15	h	Et	rt/90	oil	65

a) Solvent: DME. Molar ratio **2**/**1**b: 1.05. Molar ratio NaH/**2**:1.00. b) **1a** was used.

The reactions of thioamides with S-ethenylsulfilimines gave the corresponding thiazoles in moderate yields, albeit with formation of the corresponding nitriles as by-products. A mechanistic study on the formation of the nitriles is in progress.

EXPERIMENTAL SECTION

All melting points are uncorrected. The IR spectra were recorded on a Shimadzu IR-435 spectrophotometer and ^1H NMR spectra on a JNM-GSX270 spectrometer using TMS as the internal standard in $CDCl_3$ without limitation. All amides (Tokyo Kasei Kogyo Co., Ltd) were used after purification. Solvent DME and ether were used after drying by ordinal methods. S-Aryl-S-ethenyl-N-tosylsulfilim-

ines were prepared by reported methods.[12, 13] (**1a**: mp. 111-112°, lit.[13] 111-113°. **1b**: mp. 128-129°, lit.[13] 128.5-129.5°).

Preparation of 3. General Procedure.- To a stirred solution of 2.0 mmol of **1** and 2.1 mmol of **2** in 25 mL of DME was added 2.1 mmol of sodium hydride at room temperature. After stirring at room temperature for 24 hrs followed by stirring at 40° for 5 hrs, 25 mL of ether was added to the solution and the resulting precipitate was removed by filtration or decantation. The organic phase was evaporated to give an oil or semi-solid residue of **3**. The residue was purified by a suitable method to it [in the case of column chromatography, silica gel C200 (Wako Chemical Co. Ltd.) and benzene were used] and the structure of **3** was confirmed by IR and NMR spectra and in agreement of melting point of its picrate with the literature value.

2-Phenyl-3,4-dihydrooxazole (3a): oil. IR (neat): 1645 (C=N), 1062 (C-O-C) 740 and 690 cm^{-1} (arom). ^1H NMR: δ 4.02 (t, 2H, J = 6.9 Hz), 4.38 (t, 2H, J = 6.9 Hz), 7.33- 8.00 (m, 5H); picrate of **3a**: mp. 177-178° (from 50% EtOH aq), lit.[8] 177°.

2-(4-Methylphenyl)-3,4-dihydrooxazole (3b): mp. 59.5-60.5° (from Et_2O-hexane), lit.[15] 60° (from the same solvents). ^1H NMR: δ 2.38 (s, 3H), 4.03 (t, 2H, J = 9.5 Hz), 4.40 (t, 2H, J = 9.5 Hz), 7.20 (d, 2H, J = 8.4 Hz), 7.82 (d, 2H, J = 8.4 Hz); picrate of **3b**: mp. 184-186° (from 50% EtOH aq), lit.[14] 187-188°.

2-(2-Methylphenyl)-3,4-dihydrooxazole (3c): oil.[14] ^1H NMR: δ 2.58 (s, 3H), 4.06 (t, 2H, J = 9.5 Hz), 4.35 (t, 2H, J = 9.5 Hz), 7.18-7.35 (m, 2H), 7.29 (d,1H, J = 7.3 Hz), 7.78 (d, 1H, J = 8.1 Hz); picrate of **3c**: mp. 142-143°, lit.[14]144-145°.

2-(4-Chlorophenyl)-3,4-dihydrooxazole (3d): mp. 81-83° (from Et_2O-hexane), lit.[16] 80-83° (from the same solvents). ^1H NMR: δ 4.06 (t, 2H, J = 9.6 Hz), 4.43 (t, 2H, J = 9.6 Hz), 7.39 (d, 2H, J = 8.9 Hz), 7.87 (d, 2H, J = 8.9 Hz); picrate of **3d**: mp. 191-193° (from EtOH - Et_2O), lit.[15] 194-196°.

2-(3-Pyridyl)-3,4-dihydrooxazole (3e): mp. 66-68° (from Et_2O-hexane), lit.[16] 71° (from dil EtOH aq). IR (KBr): 1640 (C=N), 1060 cm^{-1} (C-O-C). ^1H NMR: δ 4.08 (t, 2H, J = 9.5 Hz), 4.46 (t, 2H, J = 9.5 Hz), 7.35 (dd, 1H, J = 8.1 and 4.9 Hz), 8.23 (d, 1H, J = 8.1 Hz), 8.70 (d, 1H, J = 4.9 Hz), 9.14 (s, 1H); picrate of **3e**: mp.180-181° (from 50% EtOH aq), lit.[17] 181°.

2-(4-Pyridyl)-3,4-dihydrooxazole (3f): mp. 113-114° (from Et_2O-hexane). lit.[16] 117° (from dil EtOH aq). IR (KBr): 1645 (C=N), 1060 cm^{-1} (C-O-C). ^1H NMR: δ 4.10 (t, 2H, J = 9.5 Hz), 4.48 (t, 2H, J = 9.5 Hz), 7.78 (d, 2H, J = 6.3 Hz), 8.71 (d, 2H, J = 6.3 Hz); picrate of **3f**[17]: mp. 185-187° (from 50% EtOH aq).

2-Methyl-3,4-dihydrooxazole (3g): oil; picrate of **3g**: mp. 155-157°, lit.[17] 157-159°. ^1H NMR (DMSO-d_6): δ 2.13 (s, 3H), 3.21 (t, 2H, J = 5.5 Hz), 4.29 (t, 2H, J = 5.5 Hz), 8.00 (broad s, 1H), 8.75 (s, 2H).

2-Ethyl-3,4-dihydrooxazole (3h): oil; picrate of **3h**: mp. 152-153°, lit.[18] 154°. ^1H NMR (DMSO-d_6): δ 1.10 (t, 3H, J = 8.5 Hz), 2,43 (t, 2H, J = 8.5 Hz), 3.25 (t, 2H, J = 5.4 Hz), 4.30 (t, 2H, J = 5.4 Hz), 8.00 (broad s, 1H), 8.71 (s, 2H).

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