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단 신

TsCl/NaOH 존재하에서 *N*-(2-Hydroxyethyl)-*N*'-phenylthioureas로부터 2-Phenylamino-2-oxazolines의 합성

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2-Phenylamino-2-oxazolines from *N*-(2-Hydroxyethyl)-*N*-phenylthioureas using TsCl/NaOH

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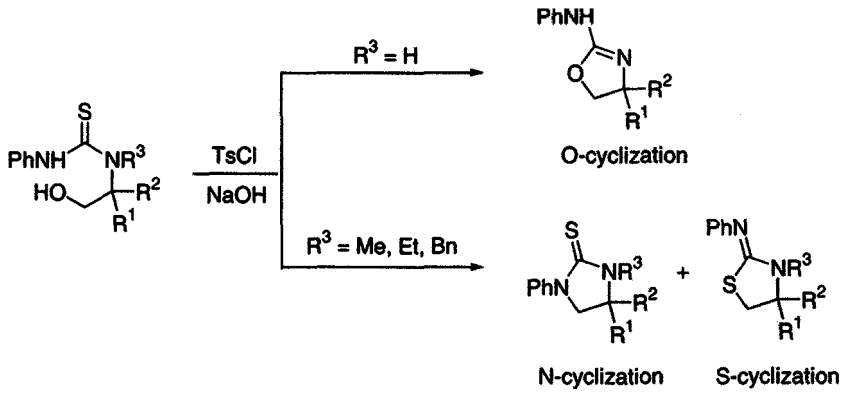
주제어: 2-페닐아미노-2-오사졸린, *N*-(2-하이드로시에틸)-*N*'-페닐티오우레아, TsCl/NaOH

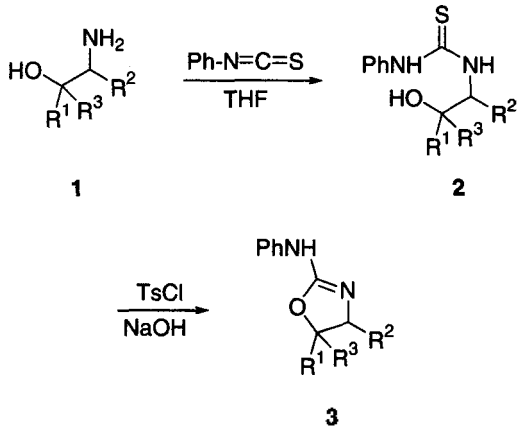
Keywords: 2-Phenylamino-2-oxazoline, *N*-(2-Hydroxyethyl)-*N*'-phenylthioureas, TsCl/NaOH

2-Amino-2-oxazolines have received considerable attention as biologically active molecules such as a potent adrenoceptor agonist,[1] imidazoline receptor agonist,[2] and octopaminergic agonist.[3] This interest has stimulated considerable research in the preparation of a variety of compounds. 2-Amino-2-oxazolines are generally prepared by the following methods: cyclization of *N*-(2-haloethyl)ureas[1a,4] or *N*-(2-hydroxyethyl)guanidine,[5] ring opening of aziridines with isocyanates,[6] reaction between 2-aminoalcohol and cyano bromide,[7] cyclization of *N*-(2-hydroxyethyl)thiopseudoureas with sodium ethoxide in reflux,[5a,8] and cyclodesulfurization of *N*-(2-hydroxyethyl)thioureas with mercuric oxide[9] or superoxide radical anion.[10] Recently we reported that 2-phenylamino-2-oxazolines were synthesized by cyclodesulfurization of *N*-(2-hydroxyethyl)-*N*-phenylthioureas using TsCl and NaOH.[11] However, only thioureas derived from *N*-unsubstituted amino alcohol and phenyl isothiocyanate provided the regiocontrolled O-cyclization products, while thioureas from *N*-substituted amino alcohol gave the mixture of *N*- and S-cyclization product (*Scheme* 1). Thus, this cyclic reaction is depending on the N-substituent of thiourea. Thioureas used in these ring closures were prepared exclusively from primary hydroxy groups. In this article, we examined the cyclization of *N*-(2-hydoxyethyl)thioureas **2** derived from secondary and tertiary hydroxyl groups to explore the generality and scope of the above cyclodesulfurization.

The starting *N*-(2-hydroxyethyl)thioureas **2** were readily obtained in high yields from the reaction of the corresponding 1,2-aminoalcohols with phenyl isothiocyanate, which provided exclusively the desired products under mild conditions, thus avoiding the need for O-protection (*Scheme* 2).[11] The cyclization of various substrates **2a-2f** using 1.1 equiv of TsCl and 2.5 equiv of NaOH was performed at room temperature and the results are shown in *Table* 1. With thioureas **2a-2d** prepared from 1,2-amino secondary alcohols, 2-phenylamino-2-oxazolines **3a-3d** through O-cyclization were regioselectively obtained (entries 1-4). Even **2e** and **2f** derived from tertiary alcohols also furnished O-cyclization products. All 2-oxazolines were identified with spectroscopic data, and the comparison of authentic sample data.[12] It is



Scheme 1.



Scheme 2.

noteworthy in the above reactions to note that the ring closure of the substrates **2a**-**2f** having secondary and tertiary hydroxyl groups using TsCl/NaOH proceeded through the cyclodesulfurization to provide regiocontrolled 2-phenylamino-2-oxazolines.

The mechanism for the formations of O-cyclized products could be proposed as the pathway of carbodiimide intermediate[13] as reported in our previous paper.[11b] Thus, this reaction might be considered to be able to proceed regardless of the classification of hydroxyl groups.

In conclusion, the ring closure of *N*-(2-hydroxyethyl)-*N*-phenylthioureas **2** using NaOH and TsCl. is proven to furnish 2-pheylamino-2-oxazolines **3**. We have found an entry to the synthesis of 2-phenylamino-2-oxazolines by a mild one-pot cyclization of *N*-(2-hydroxyethyl)-*N*-phenylthioureas prepared from *N*-unsubstituted 1,2-amino secondary and tertiary alcohols and phenyl isothiocyanate. Chiral 2-phenylamino-2-oxazolines like **3c**, **3e** and **3f** to be applied as chiral auxiliaries[14] are in progress.

EXPERIMENTAL SECTION

General methods. ^{1}H NMR and ^{13}C NMR spectra were recorded using 300 MHz and 75 MHz NMR spectrometer; chemical shifts are reported in ppm using TMS as an internal standard. Melting points were measured in a glass capillary apparatus and uncorrected. Mass spectra were recorded on a HP 5983B GC/Mass spectrometer. Analytical TLC was

Table 1. Cyclization of *N*-(2-hydroxyethyl)-*N*-phenylthioureas **2**

entry	R1	R2	R3	thioureas	yields %a of 2	2-oxazolines	yields %a of 3
1	Me	H	H	2a	96	3a	96
2	Et	H	H	2b	97	3b	85
3	(S)-Ph	(R)-Me	H	2c	94	3c	75
4	-(CH2)4-	H	2d	90	3d	71	
5	Me	(S)-i-Pr	Me	2e	85	3e	80
6	Ph	(S)-i-Pr	Ph	2f	99	3f	99

performed on 0.25 mm precoated silica gel plates. Flash chromatography was carried out with 230-400 mesh silica gel.

General procedure for the preparation of thioureas 2. To a stirred solution of 1,2-aminoalcohol (4.59 mmol) in THF (10 mL) under nitrogen at room temperature was added a solution of phenyl isothiocyanate (0.50 mL, 4.18 mmol) in THF (5 mL) dropwise for 5 min with a syringe. The reaction mixture was stirred for 30 min and evaporated. The crude product was purified by flash column chromatography to afford corresponding thiourea.

***N*-(2-Hydroxypropyl)-*N'*-phenylthiourea (2a).** yield 96%; white solid, mp 108-109 °C; R_f = 0.3 (ethyl acetate/hexane 1:1); IR ($CDCl_3$, cm^{-1} 2142 (N=C=N); ^1H NMR ($CDCl_3$) δ 8.13 (1H, bs), 7.44-7.22 (5H, m), 6.58 (1H, bs), 4.04-4.01 (1H, m), 3.92-3.88 (1H, m), 3.48-3.41 (1H, m), 2.35 (1H, bs), 1.20 (3H, d, *J*=6.2 Hz); ^{13}C NMR ($CDCl_3$) δ 180.6, 136.2, 130.1, 127.2, 124.9, 67.1, 52.0, 21.1; HRMS calcd for $C_{10}H_{14}N_2OS$: 210.0827. Found 210.0826.

***N*-(2-Hydroxybutyl)-*N'*-phenylthiourea (2b).** yield 97%; white solid, mp 102-103 °C; R_f = 0.5 (ethyl acetate/hexane 1:1); ^1H NMR ($CDCl_3$) δ 7.82 (1H, bs), 7.46-7.21 (5H, m), 6.52 (1H, bs), 3.97-3.85 (1H, m), 3.80-3.74 (1H, m), 3.51-3.45 (1H, m), 2.01 (1H, bs), 1.58-1.42 (2H, m), 0.98 (3H, t, *J*=7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 180.9, 136.1, 130.2, 127.2, 125.0, 72.4, 50.6, 28.1, 9.7; HRMS calcd for $C_{11}H_{16}N_2OS$: 224.0983. Found 224.0974.

***N*-[(1*R*, 2*S*)-2-Hydroxy-1-methyl-2-phenylethyl]-*N'*-phenylthiourea (2c).** yield 94%; white solid, mp 137-138 °C; R_f = 0.2-0.3 (ethyl acetate/hexane 3:7); ^1H NMR ($CDCl_3$) δ 7.82 (1H, bs), 7.44-7.17(10H, m), 6.20 (1H, d, *J*=7.3 Hz), 5.08-5.07 (1H, m), 4.90 (1H, bs), 2.80 (1H, bs), 1.01 (3H, d, *J*=6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 179.6, 140.4, 135.9, 130.1, 128.3, 127.6, 127.2, 126.1, 125.0, 75.6, 56.1, 13.8; HRMS calcd for $C_{16}H_{18}N_2OS$: 286.1140. Found 286.1151.

***N*-(2-Hydroxycyclohexyl)-*N'*-phenylthiourea (2d).** yield 90%; white solid, mp 141-142 °C; R_f = 0.6 (ethyl acetate/hexane 1:1); ^1H NMR ($CDCl_3$) δ 8.02 (1H, s), 7.44-7.21 (5H, m), 6.60 (1H, d, *J*=8.1 Hz), 4.43-4.42 (1H, m), 4.08-4.05 (1H, m), 1.99 (1H, bs), 1.82-1.25 (8H, m); ^{13}C NMR ($CDCl_3$) δ 179.2, 136.3, 130.2, 127.0, 124.6, 68.7, 56.4, 31.9, 26.6, 23.7, 19.6; HRMS calcd for $C_{13}H_{18}N_2OS$: 250.1140. Found 250.1136.

***N*-[(1S)-1-(Dimethylhydroxymethyl)-2-methylpropyl]-*N'*-phenylthiourea (2e).** yield 85%; white solid, mp 206-207 °C; R_f = 0.7 (ethyl acetate/hexane 1:1); ^1H NMR ($CDCl_3$) δ 8.74 (1H, s), 7.43-7.26 (5H, m), 6.58 (1H, d, *J*=10.0), 4.42 (1H, dd, *J*=10.0, 2.7 Hz), 2.20-2.10 (2H, m), 1.24 (6H, s), 1.01 (3H, d, *J*=6.8 Hz), 0.78 (3H, d, *J*=6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 181.2, 136.2, 129.8, 126.9, 125.0, 74.1, 65.3, 29.3, 28.8, 26.9, 22.2, 17.4; HRMS calcd for $C_{14}H_{22}N_2OS$: 266.1453. Found 266.266.1453.

***N*-[(1S)-1-(Diphenylhydroxymethyl)-2-methylpropyl]-*N'*-phenylthiourea (2f).** yield 99%; white solid, mp 75-76 °C; R_f = 0.2-0.3 (ethyl acetate/hexane 1:4); ^1H NMR ($CDCl_3$) δ 8.15 (1H, bs), 7.58-7.16 (15H, m), 6.76 (1H, d, *J*=7.5 Hz), 5.54 (1H, d, *J*= 7.9 Hz), 2.98 (1H, bs), 1.97-1.89 (1H, m), 0.86 (3H, d, *J*=8.0 Hz), 0.71 (3H, d, *J*=6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 181.3, 145.2, 144.7, 135.8, 130.0, 128.5, 128.4, 127.4, 127.2, 125.7, 125.6, 125.4, 82.9, 63.7, 31.0, 23.6, 18.5; HRMS calcd for $C_{24}H_{26}N_2OS$: 390.1766. Found 390.390.1764.

Cyclization of *N*-(2-hydroxyethyl)thioureas. To a stirred solution of thiourea (0.88 mmol) in THF (10 mL) under nitrogen at room temperature was added a solution of NaOH (88 mg, 2.2 mmol) in water (3 mL) and TsCl (0.18 g, 0.97 mmol) in THF (5 mL) dropwise for 5 min with a syringe. The reaction mixture was stirred for 30 min at room temperature, quenched with water (30 mL), and extracted with ether (50 mL×3). The organic layer was dried, filtered, evaporated. The crude product was purified by flash column chromatography to give the cyclized product.

4, 5-Dihydro-5-methyl-*N*-phenyl-2-oxazolamine (3a). yield 96%; white solid, mp 133-134 °C (lit.[12] mp 133-134 °C); R_f = 0.1 (ethyl acetate/hexane 1:1); IR ($CDCl_3$, cm^{-1}) 1649; ^1H NMR ($CDCl_3$) δ 7.28-6.95 (5H, m), 4.79-4.72 (1H, m), 3.95-3.89 (1H, m), 3.43-3.37 (1H, m), 1.42 (3H, d, *J*=6.2 Hz); ^{13}C NMR ($CDCl_3$) δ 157.2, 142.3, 128.8, 122.0 119.9, 76.1, 55.3, 20.4; HRMS calcd for $C_{10}H_{12}N_2O$: 176.0950.

Found 176.0949.

4, 5-Dihydro-5-ethyl-*N*-phenyl-2-oxazolamine (3b). yield 85%; white solid, mp 83-85 °C; R_f= 0.2 (ethyl acetate); IR ($CDCl_3$, cm^{-1}) 1643; H NMR ($CDCl_3$) δ 7.33-6.95 (5H, m), 4.57-4.53 (1H, m), 3.97-3.90 (1H, m), 3.53-3.47 (1H, m), 1.82-1.63 (2H, m), 1.03 (2H, t, *J*=7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 157.3, 128.9, 122.0, 119.7, 81.0, 54.4, 27.8, 9.33; HRMS calcd for $C_{11}H_{14}N_2O$: 190.1106. Found 190.1106.

(4*R*,5*S*)-Dihydro-4-methyl-5-phenyl-*N*-phenyl-2-oxazolamine (3c). yield 75%; oil; R_f= 0.2-0.3 (ethyl acetate/hexane 1:1); IR ($CDCl_3$, cm^{-1}) 1685; ^1H NMR ($CDCl_3$) δ 7.39-6.99 (10H, m), 5.64 (1H, d, *J*=8.4 Hz), 4.41-4.37 (1H, m), 0.80 (3H, d, *J*=6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 156.5, 142.0, 136.4, 128.8, 128.3, 128.0, 126.1, 122.2, 120.3, 83.6, 59.6, 18.1; HRMS calcd for $C_{16}H_{16}N_2O$: 252.1263. Found 252.1262.

3a,4,5,6,7,7a-Hexahydro-*N*-phenyl-2-benzoxazolamine (3d). yield 71%; white solid, mp 124-125 °C; R_f = 0.2 (ethyl acetate); IR ($CDCl_3$, cm^{-1}) 1683; ^1H NMR ($CDCl_3$) δ 7.29-6.98 (5H, m), 4.60-4.55 (1H, m), 3.83-3.61 (1H, m), 1.83-1.55 (8H, m); ^{13}C NMR ($CDCl_3$) δ 156.9, 144.4, 128.8, 124.8, 122.2, 121.7, 78.2, 55.4, 28.8, 26.8, 20.3, 20.0; HRMS calcd for $C_{13}H_{16}N_2O$: 216.1263. Found 216.1268.

(4*S*)-4, 5-Dihydro-5, 5-dimethyl-4-(1-methylethyl)-*N*-phenyl-2-oxazolamine (3e). yield 80%; R_f = 0.3 (ethyl acetate/hexane 7:3); ^1H NMR ($CDCl_3$) δ 7.33-6.96 (5H, m), 4.6 (1H, bs), 3.22 (1H, d, *J*= 8.1), 1.84-1.77 (1H, m), 1.48 (3H, s), 1.25 (3H, s), 1.01 (3H, d, *J*=6.0 Hz), 0.92 (3H, d, *J*=6.6 Hz); HRMS calcd for $C_{14}H_{20}N_2O$: 232.1576. Found 232.1575.

(4*S*)-4, 5-Dihydro-5, 5-diphenyl-4-(1-methylethyl)-*N*-phenyl-2-oxazolamine (3f). yield 99%; white solid, mp 75-76 °C; R_f=0.5 (ethyl acetate/hexane 7:3); IR ($CDCl_3$, cm^{-1}) 1685; ^1H NMR ($CDCl_3$) δ 7.50-6.97 (15H, m), 4.57 (1H, d, *J*=3.3 Hz), 1.85-1.75 (1H, m), 0.93 (3H, d, *J*=6.8 Hz), 0.66 (3H, d, *J* =6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 154.6, 144.7, 141.4, 140.3, 128.8, 128.3, 127.8, 127.2, 126.6, 126.2, 122.0, 119.5, 92.1, 74.2, 30.9, 21.5, 16.4; HRMS calcd for $C_{24}H_{24}N_2O$: 356.1889. Found 356.1889.

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