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

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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\(^1,4\) or \(N\)-(2-hydroxyethyl)guanidine,\(^5\) ring opening of aziridines with isocyanates,\(^6\) reaction between 2-aminooalcohol and cyanobromo,\(^7\) cyclization of \(N\)-(2-hydroxyethyl)thiopseudoureas with sodium ethoxide in reflux,\(^8,9\) 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)-\(N\)′-phenylthiourea 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-hydroxyethyl)thiourea 2 derived from secondary and tertiary hydroxyl groups to explore the generality and scope of the above cyclodesulfurization.

The starting \(N\)-(2-hydroxyethyl)thiourea 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
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 as reported in our previous paper. 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-phenylamino-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 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
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; Rf = 0.3 (ethyl acetate/hexane 1:1); IR (CDCl3, cm⁻¹) 2142 (N=C=N); ¹H NMR (CDCl3) 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); ¹³C NMR (CDCl3) δ 180.6, 136.2, 130.1, 127.2, 124.9, 67.1, 52.0, 21.1; HRMS calcd for C14H12N2O: 210.0827. Found 210.0826.

**N-(2-Hydroxybutyl)-N'-phenylthiourea (2b).** yield 97%; white solid, mp 102-103 °C; Rf = 0.5 (ethyl acetate/hexane 1:1); ¹H NMR (CDCl3) 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); ¹³C NMR (CDCl3) δ 180.9, 136.1, 130.2, 127.2, 125.0, 72.4, 50.6, 28.1, 9.7; HRMS calcd for C16H18N2O: 224.0983. Found 224.0974.

**N-[(1R, 2S)-2-Hydroxy-1-methyl-2-phenylethyl]-N’-phenylthiourea (2c).** yield 94%; white solid, mp 137-138 °C; Rf = 0.2-0.3 (ethyl acetate/hexane 3:7); ¹H NMR (CDCl3) 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); ¹³C NMR (CDCl3) 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 C16H18N2O: 286.1140. Found 286.1151.

**N-(2-Hydroxycyclohexyl)-N'-phenylthiourea (2d).** yield 90%; white solid, mp 141-142 °C; Rf = 0.6 (ethyl acetate/hexane 1:1); ¹H NMR (CDCl3) 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); ¹³C NMR (CDCl3) 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 C16H18N2O: 250.1140. Found 250.1136.

**N-[(1S)-1-(Dimethylhydroxymethyl)-2-methylpropyl]-N'-phenylthiourea (2e).** yield 85%; white solid, mp 206-207 °C; Rf = 0.7 (ethyl acetate/hexane 1:1); ¹H NMR (CDCl3) δ 8.74 (1H, s), 7.43-7.26 (5H, m), 6.58 (1H, d, J=10.0 Hz), 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); ¹³C NMR (CDCl3) 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 C18H22N2O: 266.1453. Found 266.266.1453.

**N-[(1S)-1-(Diphenylhydroxymethyl)-2-methylpropyl]-N'-phenylthiourea (2f).** yield 99%; white solid, mp 75-76 °C; Rf = 0.2-0.3 (ethyl acetate/hexane 1:4); ¹H NMR (CDCl3) 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); ¹³C NMR (CDCl3) 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 C24H29N2O: 390.1766. Found 390.390.1764.

**Cyclization of N-(2-hydroxyethylthiourea.** 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-1-phenyl-2-oxazoline (3a).** yield 96%; white solid, mp 133-134 °C; IR (CDCl3, cm⁻¹) 3168, 3074, 1653, 1595, 1498, 1460, 1383, 1303, 1248, 1192, 1049, 839, 746; ¹H NMR (CDCl3) δ 8.02 (1H, s), 7.54-7.41 (1H, t, J=8.1 Hz), 6.71 (1H, d, J=8.1 Hz); ¹³C NMR (CDCl3) 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 C16H18N2O: 176.0950.
4. 5-Dihydro-5-ethyl-N-phenyl-2-oxazoline (3b). yield 85%; white solid, mp 83-85 °C; Rf = 0.2 (ethyl acetate); IR (CDCl3, cm⁻¹) 1643; H NMR (CDCl3) 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); 13C NMR (CDCl3) δ 157.3, 128.9, 122.0, 119.7, 81.0, 54.4, 27.8, 9.33; HRMS calc'd for C15H16N2O: 252.1263. Found 252.1262.

3a,4,5,6,7,7a-Hexahydro-N-phenyl-2-benzoxazoline (3d). yield 71%; white solid, mp 124-125 °C; Rf = 0.2 (ethyl acetate); IR (CDCl3, cm⁻¹) 1683; 1H NMR (CDCl3) 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); 13C NMR (CDCl3) 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 calc'd for C15H16N2O: 252.1263. Found 252.1262.

(4S)-4, 5-Dihydro-5, 5-dimethyl-4-(1-methyl-ethyl)-N-phenyl-2-oxazoline (3e). yield 80%; Rf = 0.3 (ethyl acetate/hexane 7:3); 1H NMR (CDCl3) δ 7.33-6.96 (5H, m), 4.61 (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 calc'd for C15H16N2O: 232.1576. Found 232.1575.

(4S)-4, 5-Dihydro-5, 5-diphenyl-4-(1-methyl-ethyl)-N-phenyl-2-oxazoline (3f). yield 99%; white solid, mp 75-76 °C; Rf = 0.5 (ethyl acetate/hexane 7:3); IR (CDCl3, cm⁻¹) 1685; 1H NMR (CDCl3) 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); 13C NMR (CDCl3) 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 calc'd for C23H22N2O: 356.1889. Found 356.1889.

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