

## 2-Oxazolines from *N*-(2-Hydroxyethyl)thioureas or -thioamides Using 1,3-Dicyclohexylcarbodiimide

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The 2-oxazoline ring system,<sup>1</sup> a simple cyclic imino ester, is of great interest in modern organic chemistry because it can be used as a masked carboxylic acid,<sup>2</sup> chiral ligand for asymmetric synthesis,<sup>3</sup> versatile synthetic intermediate<sup>4</sup> and therapeutic agent.<sup>5</sup> A number of reliable preparative methods are known. Simple cyclodehydration of a carboxylic acid and a  $\beta$ -amino alcohol can yield the oxazoline under conditions of high temperature, azeotropic water removal,<sup>6</sup> or other dehydrative means such as Appel's reaction conditions.<sup>7</sup> Also, treatment of  $\beta$ -hydroxyamide with the suitable cyclization reagents such as thionyl chloride,<sup>8</sup> phosphorotris-(1,2,4)-triazolide,<sup>9</sup> Mitsunobu conditions (DEAD/PPh<sub>3</sub>),<sup>10</sup> and phosphorous-mediated Appel reaction<sup>11</sup> has been applied in several forms.

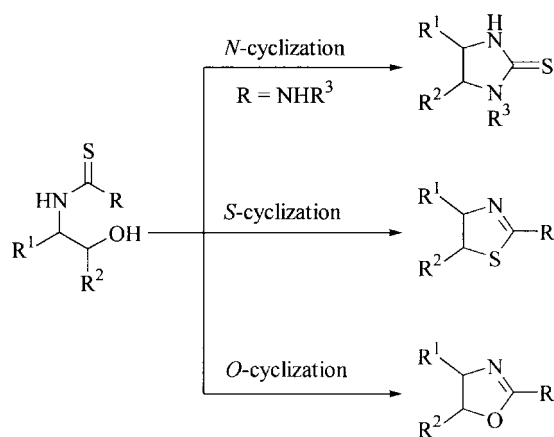
Meanwhile, 1,3-dicyclohexylcarbodiimide (DCC) was used as a good cyclization reagent for the synthesis of heterocycles such as 1,3,4-oxadiazoles,<sup>12</sup> *S*-triazolo[3,4-*a*]phthalazines,<sup>13</sup> imidazo[1,5-*a*]pyridine,<sup>14</sup> 5*H*-1,3,4-benzotriazepin-5-ones<sup>15</sup> and benzoxazoles<sup>16</sup> from the corresponding thioureas. Herein we report a synthetic route to 2-oxazolines from *N*-(2-hydroxyethyl)thioureas **2** and ring-expanded systems **5** using DCC.

The cyclization of *N*-(2-hydroxyethyl)thioureas can give different products depending on the reaction conditions and substrates (Scheme 1). Mitsunobu condition,<sup>17</sup> acidic,<sup>18</sup> or basic conditions<sup>19</sup> gave *S*-cyclized or *N*-cyclized products, but DCC mediated in our work, *O*-cyclized products **3** were obtained exclusively with high yields under the mild conditions.<sup>20</sup> Thus, known *N*-(2-hydroxyethyl)thioureas **2a-d** were prepared from the reaction of the corresponding 1,2-amino-

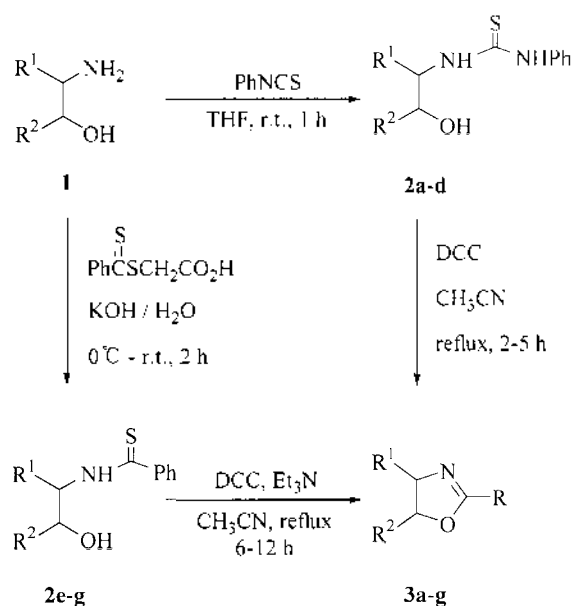
alcohols with phenyl isothiocyanate in THF at room temperature.<sup>17,20</sup> Treatment of thioureas **2a-d** with DCC in refluxing acetonitrile gave *O*-cyclized 2-phenylamino-2-oxazolines **3a-d** very successfully (Table 1). *N*-Cyclized or *S*-cyclized products were not detected in GC-mass spectral data of the crude reaction mixture. To expand this methodology, *N*-(2-hydroxyethyl)thioamides **2e-g** were prepared from the reaction of 1,2-aminoalcohols with *S*-(thiobenzoyl)thioglycolic acid in aqueous potassium hydroxide and then treated with DCC in refluxing acetonitrile in the presence of triethylamine or diethylamine for 6-12 h gave 2-oxazolines **3e-g** in excellent yields (Scheme 2).<sup>21</sup> Moreover, DCC mediated cyclization of expanded system such as **5** was

Table 1. 2-Oxazolines **3** Prepared

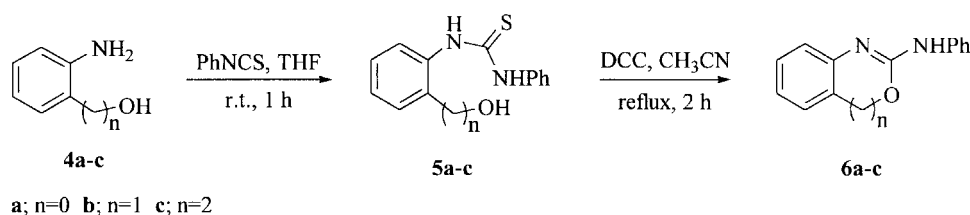
Product	R <sup>1</sup>	R <sup>2</sup>	R	Time (h)	% yield
<b>3a</b>	H	H	NHPh	5	88
<b>3b</b>	Me	H	NHPh	3	93
<b>3c</b>	Ph	H	NHPh	3	94
<b>3d</b>	H	Me	NHPh	2	92
<b>3e</b>	H	H	Ph	12	90
<b>3f</b>	Ph	H	Ph	6	91
<b>3g</b>	H	Me	Ph	9	92



Scheme 1



Scheme 2



Scheme 3

performed successfully to give desired products **6** in quite good yields (Scheme 3).<sup>16</sup>

In summary, 2-oxazolines were readily prepared from thioureas or thioamides using DCC and the scope of present study was expanded to benzo-fused ring systems.

### Experimental Section

All chemicals used were purchased from commercial sources and were used as received unless otherwise stated. Melting points were taken using an Electrothermal melting point apparatus and are uncorrected. <sup>1</sup>H NMR spectra were recorded on a Gemini 300 spectrometer. Mass spectra were obtained using a ThermoQuest Polaris Q mass spectrometer operating at 70 eV.

The known *N*-(2-hydroxyethyl)thioureas **2a-d**<sup>17,20</sup> and *N*-(2-hydroxyphenyl)-*N'*-phenylthiourea (**5a**)<sup>16</sup> were prepared following the literature procedure.

**General procedure for the preparation of *N*-(2-hydroxyethyl)thioamides **2e-g**.** To a stirred suspension of *S*-(thiobenzoyl)thioglycolic acid (2.12 g, 10 mmol) in 20 mL of water was added KOH (0.72 g, 11 mmol) at 0 °C. The mixture was stirred at ambient temperature, then ethanolamine (1.11 mmol) in water (5 mL) was added dropwise, and stirring was continued for 2 h at r.t. The reaction mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 20 mL), combined, and dried over MgSO<sub>4</sub>. The solvent was evaporated and residual material was crystallized with ether to give **2e-g**.

The spectral and analytical data of products are as follows:

**2e**: yield 86%, mp 92-94 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.29 (s, 1H), 3.90-4.02 (m, 4H), 7.35-7.48 (m, 3H), 7.73-7.76 (m, 2H), 8.10 (s, 1H).

**2f**: yield 84%, oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.38 (br s, 1H), 4.06 (t, 2H, *J* = 4.6), 5.85 (m, 1H), 7.28-7.51 (m, 8H), 7.77-7.80 (m, 2H), 8.41 (d, 1H, *J* = 7.0).

**2g**: yield 80%, mp 93-95 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.26 (d, 3H, *J* = 6.4), 2.46 (d, 1H, *J* = 3.7), 3.56 (m, 1H), 4.11 (m, 1H), 7.33-7.47 (m, 3H), 7.72-7.74 (m, 2H), 8.14 (s, 1H).

***N*-(2-Hydroxymethyl)phenyl-*N'*-phenylthiourea (**5b**).** To a stirred solution of 2-aminobenzyl alcohol (**4b**, 1.23 g, 10 mmol) in 20 mL of THF was added phenyl isothiocyanate (1.42 g, 10.5 mmol) at r.t. After stirring for 1 h at ambient temperature, the solvent was evaporated and the precipitated solid was separated by filtration, washed with CH<sub>2</sub>Cl<sub>2</sub> to give 2.32 g (90%) of **5b** as a solid, mp 136-137 °C; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 4.52 (s, 2H), 5.25 (s, 1H), 7.14-7.50 (m, 9H), 9.30 (s, 1H), 9.88 (s, 1H).

***N*-(2-Hydroxyethyl)phenyl-*N'*-phenylthiourea (**5c**).** A solution of 2-aminophenethyl alcohol (**4c**, 1.37 g, 10 mmol) and phenyl isothiocyanate (1.42 g, 10.5 mmol) in THF (20 mL) was stirred for 1 h at r.t. The thiourea (**5c**, 2.47 g, 91%) was isolated using the same above procedure. Mp 137-139 °C; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 2.74 (t, 2H, *J* = 6.7), 3.61 (dt, 2H, *J* = 6.7, 4.6), 4.83 (t, 1H, *J* = 4.6), 7.10-7.49 (m, 9H), 9.38 (s, 1H), 9.75 (s, 1H).

**General procedure for the preparation of 2-oxazolines **3a-g**.** To a stirred solution of thiourea **2a-d** (3 mmol) in dried CH<sub>3</sub>CN (10 mL) was added DCC (0.93 g, 4.5 mmol). The reaction mixture was refluxed for the time indicated in table and then CH<sub>3</sub>CN was removed under reduced pressure. The residual material was filtered with ethyl acetate/petroleum ether (2 : 1, 3 × 15 mL) and the filtrate was concentrated and purified by column chromatography (silica gel; EtOAc : hexane, 1 : 1) to give product **3a-d**. 2-Oxazolines **3e-g** were obtained from the thioamides **2e-g** (3 mmol) using the same above procedure, except adding half equivalent of triethylamine or diethylamine.<sup>22</sup>

The spectral and analytical data of products as follows:

**3a**: yield 88%, mp 120-121 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.83 (t, 2H, *J* = 8.4), 4.36 (t, 2H, *J* = 8.4), 6.94-7.27 (m, 5H), 7.75 (br s, 1H); *m/z* (%) 162 (M<sup>+</sup>, 80), 161 (100), 104 (38), 77 (26).

**3b**: yield 93%, mp 101-102 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.26 (d, 3H, *J* = 6.4), 3.87 (dd, 1H, *J* = 7.0, 7.9), 4.12 (m, 1H), 4.43 (t, 1H, *J* = 7.9), 6.94-7.27 (m, 5H), 7.65 (br s, 1H); *m/z* (%) 176 (M<sup>+</sup>, 41), 175 (11), 161 (100), 104 (15), 77 (8).

**3c**: yield 94%, mp 148-150 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 4.13 (dd, 1H, *J* = 7.8, 8.0), 4.68 (t, 1H, *J* = 8.0), 5.16 (m, 1H), 6.95-7.34 (m, 10H); *m/z* (%) 238 (M<sup>+</sup>, 85), 237 (100), 207 (61), 161 (32), 119 (56), 91 (34), 77 (25).

**3d**: yield 94%, mp 133-134 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.42 (d, 3H, *J* = 6.1), 3.40 (m, 1H), 3.92 (m, 1H), 4.76 (m, 1H), 6.95-7.27 (m, 5H); *m/z* (%) 176 (M<sup>+</sup>, 57), 175 (100), 119 (29), 104 (37), 77 (10).

**3e**: yield 90%, oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 4.04 (t, 2H, *J* = 9.2), 4.40 (t, 2H, *J* = 9.2), 7.37-7.97 (m, 5H); *m/z* (%) 147 (M<sup>+</sup>, 80), 117 (100), 105 (17), 77 (19).

**3f**: yield 91%, oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 4.26 (t, 1H, *J* = 8.3), 4.78 (dd, 1H, *J* = 8.3, 10.1), 5.38 (dd, 1H, *J* = 8.3, 10.1), 7.24-7.50 (m, 8H), 8.03-8.06 (m, 2H); *m/z* (%) 223 (M<sup>+</sup>, 25), 193 (100), 165 (38), 89 (19), 77 (10).

**3g**: yield 92%, oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.45 (d, 3H, *J* = 6.1), 3.64 (dd, 1H, *J* = 7.3, 14.3), 4.17 (dd, 1H, *J* = 9.1, 14.3), 4.87 (m, 1H), 7.40-7.52 (m, 3H), 7.97-8.01 (m, 2H);

m/z (%) 161 ( $M^+$ , 23), 117 (100), 90 (10), 77 (12).

**General procedure for the preparation of benzo-fused heterocycles 6a-c.** To a stirred suspension of thiourea **5a-c** (3 mmol) in dried  $CH_3CN$  (20 mL) was added DCC (0.93 g, 4.5 mmol). The reaction mixture was refluxed for 2 h and then  $CH_3CN$  was removed under reduced pressure. The residual material was filtered with  $CH_2Cl_2$  and the filtrate was concentrated and purified by column chromatography (silica gel: EtOAc:hexane, 1:5) to give product **6a-c**, respectively.

The spectral and analytical data of products are as follows:

**6a:** yield 87%, mp 174-175 °C (Lit.<sup>16</sup> 162-164 °C).  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.09-7.63 (m, 9H), 8.48 (s, 1H); m/z (%) 210 ( $M^+$ , 100), 209 (94), 181 (14), 167 (9), 77 (9).

**6b:** yield 92%, mp 140-142 °C.  $^1H$  NMR ( $CDCl_3$ )  $\delta$  5.22 (s, 2H), 6.99-7.40 (m, 9H), 8.05 (bs, 1H); m/z (%) 224 ( $M^+$ , 71), 223 (56), 132 (100), 104 (23), 77 (17).

**6c:** yield 87%, mp 128-129 °C.  $^1H$  NMR ( $CDCl_3$ )  $\delta$  3.13 (t, 2H,  $J = 4.6$ ), 4.51 (t, 2H,  $J = 4.6$ ), 6.92-7.47 (m, 9H); m/z (%) 283 ( $M^+$ , 100), 237 (79), 118 (60).

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- In the case of thioamide **2g**  $Et_3NH$  was used instead of  $Et_3N$ .