Regiocontrolled Cyclization Reaction of *N*-(2-Hydroxyethyl)ureas by Transfer of Activation: One-Pot Synthesis of 2-Imidazolidinones

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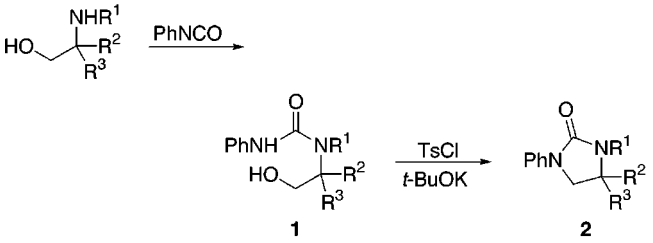
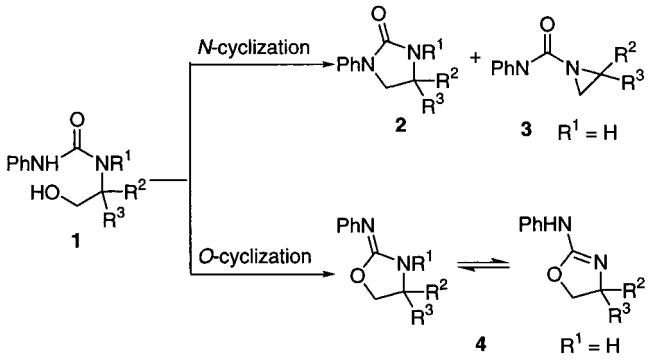
Cyclic ureas have recently gained much interest as human immunodeficiency virus (HIV) protease inhibitors[1] and $5HT_3$ receptor antagonists[2] and are expected to have increased conformational rigidity relative to the corresponding linear ureas, which are incorporated in many pharmaceuticals.[3] 5-Membered cyclic ureas, 2-imidazolidinones, are also used as useful chiral auxiliaries[4] in highly diastereoselective alkylation, aldol, and Diels−Alder reactions. 2-Imidazolidinones are generally prepared by the cyclization reaction of 1,2-diamine with phosgene[5] or its derivatives,[2] and these methods cause the polymerization as a side reaction.[6] The intramolecular cyclization of *N*-(2-hydroxyethyl)urea **1** having an ambident nucleophile using PPh_3/CCl_4 or dimethylaminosulfur trifluoride (DAST) generally leads to O-cyclized 2-oxazoline in preference to N-cyclized 2-imidazolidinone,[7] and there has been no report regarding N-cyclized 2-imidazolidinone formation with substrates **1**. In this paper, we report the result of a new and general method that gives N-cyclized products, 2-imidazolidinones **2**, as single isomers using *N*-(2-hydroxyethyl)urea **1** derived from 1,2-amino alcohol and phenyl isocyanate shown in Scheme 1.

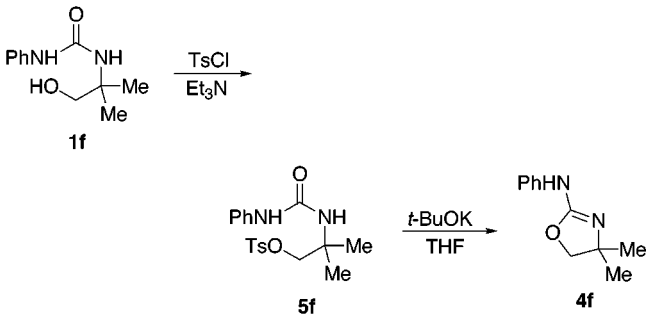
Scheme 1



Scheme 2



Scheme 3



We chose *N*-(2-hydroxyethyl)ureas **1a** and **1f** as substrates to investigate the route shown in Scheme 2 in a variety of reaction conditions. These were readily prepared from the reaction of the corresponding 1,2-amino alcohols with phenyl isocyanate, and the regioselectivities in the cyclization reaction of **1a** and **1f** were investigated as follows: These reactions are expected to give three regioisomers, namely, two N-cyclized 2-imidazolidinone **2** and aziridine (in the case of $R^1 = H$) **3** and an O-cyclized 2-oxazoline **4** depending on the nucleophilicity of the substrate and reaction conditions. Upon the Mitsunobu reaction conditions (PPh_3, EtOCON=NCOOEt), the cyclization of **1a** gave the mixtures of N-cyclized product and O-cyclized product in a ratio of 52:48 due to the low nucleophilicity of the nitrogen atom of **1a**. For activation of the hydroxyl group followed by the intramolecular reaction with some bases, we treated **1a** and **1f** with 1.2 equiv of *p*-toluenesulfonyl chloride (TsCl) in the presence of excess of Et_3N to provide the tosylate product of 55% and 62% yields, respectively, and then the intramolecular reaction of tosylate of **1a** with *tert*-butoxide (*t*-BuOK) gave no desired cyclized product while the tosylate of **1f** resulted in the O-cyclized 2-oxazoline **4f** of 84% good yield without the 2-imidazolidinone (Scheme 3). We turned to a one-pot reaction with TsCl (1.2 equiv) and *t*-BuOK (2.4

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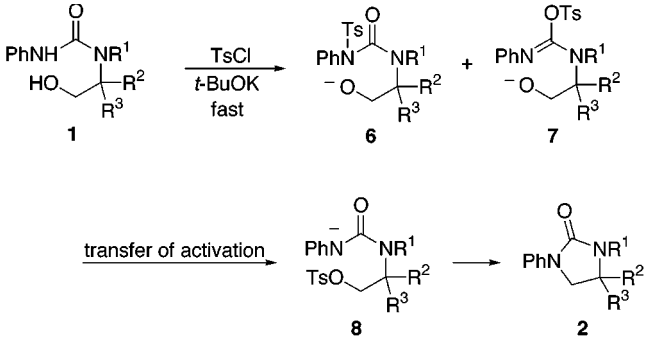
Table 1. Preparations of Ureas 1 and 2-Imidazolidinones 2

entry	R^1	R^2	R^3	yield (%) of **1**	mp of **1**	yield (%) of **2**	mp of **2**
a	H	H	H	98	123−4	71	162−3[a]
b	Me	H	H	92	105−7	88	108−10[b]
c	Et	H	H	100	104−5	89	81−2[c]
d	H	Me	H	90	115−7	65	104
e	H	Et	H	88	137−8	70	129
f	H	Me	Me	91	129−30	78	128−30
g	H	(*S*)-*i*-Pr	H	88	124	61	80−5
h	H	(*S*)-$PhCH_2$	H	85	155−6	57	115−7

[a] Lit.[8] mp 161−3 °C. [b] Lit.[9] mp 110−11 °C. [c] Lit.[9] mp 83 °C.

Scheme 4



equiv) which would avoid the inconvenience of separation of the tosylates (Scheme 1). One-pot reactions of **1a** and **1f** afforded N-cyclized product in 71% and 78% yields, respectively. Thus, in the case of **1f**, a remarkable difference on the regioselectivity of the ambident nucleophile was observed. The N-selectivity with one-pot TsCl and *t*-BuOK is noteworthy. We expected to apply this reaction condition to a general synthesis of 2-imidazolidinones.

On the basis of the above reaction conditions, the cyclization of a variety of substrates **1a**−**h** was examined that led to the 2-imidazolidinones in good yields as expected (Table 1). Any O-cyclized products were not observed in the NMR data of the crude products; that is, all reactions proceeded in good yields through regiocontrol (N-cyclization > O-cyclization) to give 2-imidazolidinone. Chiral **2g** and **2h** followed by acylation are expected to be used as the chiral auxiliaries for alkylation, aldol, and Diels−Alder reactions.[10] All ureas **1a**−**h** were prepared from the reaction of primary 1,2-amino alcohol with phenyl isocyanate in tetrahydrofuran (THF) solution at room temperature in good yields (Table 1).

The reaction mechanism for the formation of 2-imidazolidinone could be proposed as shown in Scheme 4. The sulfonamide **6** or iminosulfonate **7**[11] having alkoxide anion in an excess base is first formed, and intramolecular attack of alkoxide to the sulfonamide or iminosulfonate via seven-membered ring gives a tosylate **8** having nitrogen anion. Then the newly formed nitrogen anion affects an intramolecular regioselective nucleophilic substitution on the tosylate to provide the N-cyclized **2**. Eissenstat and Weaver used a similar reaction, which they named "transfer of activation" for preparing analogues of indol natural product pravadoline.[12] One-pot reaction of **1f** is very fast to give the corresponding 2-imidazolidinone, while the cyclization of tosylate **5f** with the same base occurs very slowly to give 2-oxazoline. So, TsCl in the one-pot reaction affects the fast formation of a tosylate having a nitrogen anion.

In conclusion, we have succeeded in the development of a new and general synthetic method for 2-imidazolidinones from 1,2-amino alcohol through the regiocontrol of *N*-(2-hydroxyethyl)ureas without using phosgene gas. Furthermore, the present reaction would be applicable as a new synthetic method for 1,2-diamine from 1,2-amino alcohol by acid hydrolysis of 2-imidazolidinones.[13]

Experimental Section

General Methods. ^1H NMR and ^{13}C NMR spectra were recorded using 300 and 75 MHz NMR spectrometers; chemical shifts are reported in ppm using $CDCl_3$ as solvent and TMS as internal standard. Melting points were determined on a capillary apparatus and are uncorrected. All chemicals were products of Aldrich. Analytical TLC was performed on 0.25 mm precoated silica gel plates. Flash chromatography was carried out with 230−400 mesh silica gel.

Intramolecular Cyclization of 5f. To a stirred solution of **5f** (1.3 g, 3.6 mmol) in THF (10 mL) under nitrogen in an ice bath was added potassium *tert*-butoxide (1.2 g, 10.8 mmol). The reaction mixture was stirred in an ice bath for 2 h, and then at room temperature overnight, monitored by TLC. For disappearance of **5f** the stirring was continued in reflux for 2 h, quenched with water, and extracted with ether. The crude product was purified by flash column chromatography to give **4f**.

4,4-Dimethyl-4,5-dihydro-*N*-phenyl-2-oxazolamine(4f): mp 127−8 °C; ^1H NMR (300 MHz, $CDCl_3$) 7.36−7.25 (m, 4H), 7.05−6.95 (m, 1H), 4.03 (s, 2H), 1.32 (s, 6H); ^{13}C NMR ($CDCl_3$) 155.4, 128.8, 122.2, 120.1, 78.6, 28.1; IR ($CDCl_3$) 1688 (s) cm^{-1}; HRMS calcd for $C_{11}H_{14}N_2O$ 190.1106, found 190.1109.

Intramolecular Cyclization of *N*-(2-Hydroxyethyl)urea. General Procedure. To a stirred suspension of potassium *tert*-butoxide (0.4 g, 3.6 mmol) and urea (1.5 mmol) in THF (20 mL) under nitrogen in an ice bath was added a solution of *p*-toluenesulfonyl chloride (0.34 g, 1.8 mmol) in THF (5 mL) dropwise with a syringe. The reaction mixture was stirred in an ice bath for 10 min, quenched with water (20 mL), and extracted with ether (25 mL ×2). The crude product was purified by flash column chromatography.

1-Phenyl-2-imidazolidinone (2a): ^1H NMR (300 MHz, $CDCl_3$) 7.56−7.52 (m, 2H), 7.37−7.26 (m, 2H), 7.08−7.06 (m, 1H), 3.97−3.92 (m, 2H), 3.62−3.55 (m, 2H); ^{13}C NMR ($CDCl_3$) 159.9, 140.0, 128.8, 122.3, 117.9, 45.3, 37.5; IR ($CDCl_3$) 1684 (s) cm^{-1}; HRMS calcd for $C_9H_{11}N_2O$ 162.0793, found 162.0726.

1-Methyl-3-phenyl-2-imidazolidinone (2b): ^1H NMR (300 MHz, $CDCl_3$) 7.57−7.53 (m, 2H), 7.35−7.26 (m, 2H), 7.04−6.99 (m, 1H), 3.81−3.76 (m, 2H), 3.47−3.42 (m, 2H), 2.89 (s, 3H); ^{13}C NMR ($CDCl_3$) 158.2, 140.6, 128.7, 122.2, 117.2, 44.1, 42.3, 31.2; IR ($CDCl_3$) 1696 (s) cm^{-1}.

1-Ethyl-3-phenyl-2-imidazolidinone (2c): ^1H NMR (300 MHz, $CDCl_3$) 7.57−7.54 (m, 2H), 7.35−7.26 (m, 2H), 7.04−6.99 (m, 1H), 3.82−3.78 (m, 2H), 3.49−3.44 (m, 2H), 3.31 (q, 2H, J = 7.2 Hz), 1.17 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) 157.6, 140.2,

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(10) Recently, Prasad reported that chiral N-acylated **2g** and **2f** were prepared from the ring opening of oxazolines with aniline followed by cyclization with phosgene and used for highly diastereoselective benzylations and methylations; see: Konigsberger, K.; Prasad, K.; Repic, O.; Blacklock, T. J. *Tetrahedron: Asymmetry* **1997**, *8*, 2347. We found these compounds were readily prepared from a convenient short course via acylation of **2g** and **2f**, and its results will be published in another paper.

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128.6, 122.0, 117.1, 42.3, 41.0, 38.5, 12.5; IR ($CDCl_3$) 1701 (s) cm^{-1}; HRMS calcd for $C_{11}H_{14}N_2O$ 190.1106, found 190.1098.

4-Methyl-1-phenyl-2-imidazolidinone (2d): ^1H NMR (300 MHz, $CDCl_3$) 7.54−7.51 (m, 2H), 7.36−7.26 (m, 2H), 7.07−7.02 (m, 1H), 4.04−3.87 (m, 1H+1H), 3.51−3.43 (m, 1H), 1.34 (d, 3H, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$) 159.1, 140.1, 128.7, 122.5, 117.8, 52.5, 44.8, 21.7; IR ($CDCl_3$) 1700 (s) cm^{-1}.

4-Ethyl-1-phenyl-2-imidazolidinone (2e): ^1H NMR (300 MHz, $CDCl_3$) 7.56−7.52 (m, 2H), 7.36−7.26 (m, 2H), 7.07−7.02-(m, 1H), 4.02−3.96 (m, 1H), 3.77−3.68 (m, 1H), 3.55−3.50 (m, 1H), 1.70−1.60 (m, 2H), 0.99 (t, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) 159. 1, 140. 1, 128.7, 122.4, 117.7, 50.6, 50.4, 28.9, 9.4; IR ($CDCl_3$) 1698 (s) cm^{-1}.

4,4-Dimethyl-1-phenyl-2-imidazolidinone (2f): ^1H NMR (300 MHz, $CDCl_3$) ^1H NMR (300 MHz, $CDCl_3$) 7.55−7.52 (m, 2H), 7.36−7.26 (m, 2H), 7.07−7.02 (m, 1H), 5.95 (bs, 1H), 3.65 (s, 2H), 1.36 (s, 6H); ^{13}C NMR ($CDCl_3$) 158.1, 140.2, 128.8, 122.5, 117.7, 58.2, 51.3, 28.6; IR ($CDCl_3$) 1700 (s) cm^{-1}; HRMS calcd for $C_{11}H_{14}N_2O$ 190.1106, found 190.1110.

(4*S*)-4-(1-Methylethyl)-1-phenyl-2-imidazolidinone (2g): ^1H NMR (300 MHz, $CDCl_3$) 7.56−7.53 (m, 2H), 7.35−7.12 (m, 2H), 7.05−7.02(m, 1H), 6.32 (bs, 1H), 3.95−3.88 (m, 1H), 3.57−3.47 (m, 2H), 1.79−1.69 (m, 1H), 0.98 (d, 3H, J = 6.7 Hz), 0.92 (d, 3H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$) 159.3, 140.2, 128.7, 122.3, 117.6, 54.8, 49.0, 33.1, 18.0, 17.0; IR ($CDCl_3$) 1716 (s) cm^{-1}.

(4*S*)-1-Phenyl-4-phenylmethyl-2-imidazolidinone (2h): ^1H NMR (300 MHz, $CDCl_3$) 7.53−7.20 (m, 10H), 4.95 (bs, 1H), 4.04−3.95 (m, 2H), 3.65−3.61 (m, 1H), 2.92−2.84 (m, 2H); ^{13}C NMR ($CDCl_3$) 158.7, 139.9, 136.6, 129.3, 129.1, 128.9, 128.8, 128.5, 127.0, 122.7, 117.8, 50.4, 50.4, 42.2; IR ($CDCl_3$) 1705 (s) cm^{-1}; HRMS calcd for $C_{16}H_{16}N_2O$ 252.1263, found 252.1266.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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