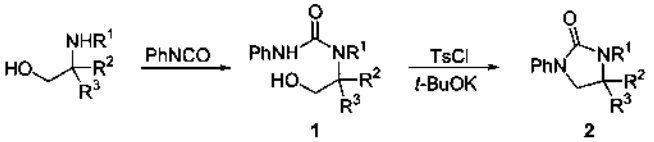
Notes

Cyclization Reaction of *N*-Aroyl-*N'*-(2-hydroxyethyl)ureas: One-Pot Synthesis of 1-Aroyl-2-imidazolidinones

Taek Hyeon Kim,* Dong Ryun Oh, and Jae Young So

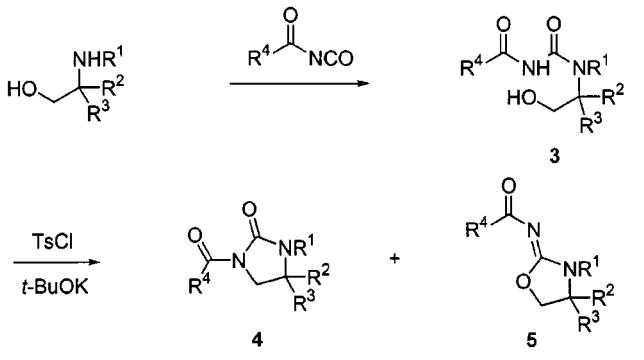
Faculty of Applied Chemistry, Chonnam National University, Kwangju 500-757, Korea
Received May 16, 2000

Cyclic ureas have recently gained much interest as pharmaceuticals for human immunodeficiency virus (HIV) protease inhibitors[1] and 5-HT_3 receptor antagonists.[2] In addition, 5- membered cyclic ureas, 2-imidazolidinones, are also used as useful chiral auxiliaries[3] in highly diastereoselective alkylation, aldol, and Diels-Alder reactions. Several synthetic routes to 2-imidazolidinones include the cyclization reaction of 1,2-diamine with phosgene,[4] phosgene derivatives,[5] dialkyl carbonate,[5] carbonyl sulfide,[6] and carbonyl selenide[7] and these methods cause the polymerization as a side reaction.[8] Recently, we reported a synthetic method for 2-imidazolidinones from 1,2-aminoalcohol by one-pot reaction of *N*-(2-hydroxyethyl)ureas with TsCl and *t*-BuOK without using phosgene gas (Scheme 1).[9] *N*-(2-Hydroxyethyl)ureas **1** were derived from 1,2-aminoalcohols and phenyl isocyanate. In this paper we examine another nucleophile such as aroylureas for this one-pot reaction. Aroylureas **3** can conceivably proceed through mild nucleophilic attack upon the tosylate intermediate in the presence of *t*-BuOK either by the nitrogen to give the 2-imidazolidinone **4** or by the oxygen atom to provide 2-oxazoline **5**. However, we expected that the increased acidity of iminodicarboyl group relative to phenylureas might favor the formation of 2-imidazolidinone.



1 2

Scheme 1



3 4 5

Scheme 2

Aroylureas **3** were readily prepared from the reaction of 1,2-aminoalcohols with benzoyl isocyanate or 2,4-dichlorobenzoyl isocyanate.[10] The next step was to achieve ring closure by activating the primary hydroxy group *via* a transfer activation[9,11] using TsCl and *t*-BuOK (Scheme 2). The cyclization of a variety of substrates **3a-3f** was examined (Table 1). Contrary to phenylureas **1**, aroylureas **3b** and **3e** prepared from *N*-unsubstituted aminoalcohols gave the unexpected mixture of both *N*- and *O*-alkylated products in low yields. In comparison to **3b**, however, aroylurea **3e** afforded more *N*-alkylated product **4e** (entries b and e), because an increase in the N-H acidity by changing the substitution pattern in the bezene ring was anticipated to increase the *N*- to *O*-alkylation ratio. With **3a**, **3c**, and **3d** prepared from *N*-substituted aminoalcohols, as expected, *N*-cyclization to 2-imidazolidinones was mainly observed with trace amount of the *O*-cyclized products regardless of the substitution pattern in the bezene ring. Aroylurea **3f** prepared from 2-aminoethanol did not undergo cyclization reaction upon this condition. The remarkable *N*-cyclization selectivity in aroylureas with α-*N*-alkyl group may occur through a buttressing effect of α-*N*-alkyl group in the cyclization.[12] The present 2-imidazolidinones **4** can be deacylated and alkylated to provide *N,N'*-disubstituted cyclic ureas, overcoming the general difficulties associated with the synthesis of tetrasubstituted ureas.[13]

Experimental Section

General. ^{1}H NMR and ^{13}C NMR spectra were recorded

Table 1. Preparations of Aroylureas **3** and 1-Aroyl-2-imidazolidinones **4**

Entry	R^1	R^2	R^3	R^4	yield (%) of **3**[a]	mp of **3**	yield (%) of **4**
a	Et	H	H	Ph	85	158-160	82
b	H	Me	Me	Ph	95[b]	122-124	11 (33/67)[c]
c	Et	H	H	2,4-Cl_2Ph	92	124-126	94
d	Me	H	H	2,4-Cl_2Ph	83	153-155	81
e	H	Me	Me	2,4-Cl_2Ph	84	203-205	48 (70/30)[c]
f	H	H	H	2,4-Cl_2Ph	83	126-128	nc[d]

[a]Isolated yield by recrystallization. [b]Isolated yield by column chromatography. [c]The ratio of 2-imidazolidinone **4** and 2-oxazoline **5** was determined with ^{1}H NMR data. [d]nc means no cyclization reaction

using 300 MHz and 75 MHz NMR spectrometer; chemical shifts are reported in ppm using TMS as internal standard. Melting points were determined on a capillary apparatus and uncorrected. Analytical TLC was performed on 0.25 mm precoated silica gel plates. Flash column chromatography was carried out with 230-400 mesh silica gel.

General Procedure for Preparation of Aroylureas 3.

A solution of aroyl isocyanate (2.4 mmol) in tetrahydrofuran (5 mL) was added over 10 min to a solution of 2-aminoethanol (2.4 mmol) in tetrahydrofuran (15 mL) cooled in an ice bath. The reaction mixture was stirred for 30 min and evaporated. The crude products except **3b** were purified by the recrystallization in n-hexane/small amount of acetone or ethanol.

1-Benzoyl-3-ethyl-3-(2-hydroxyethyl)urea (3a). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86-7.83 (m, 2H), 7.50-7.45 (m, 1H), 7.40-7.35 (m, 2H), 3.90 (t, 2H, J = 4.3 Hz), 3.47 (t, 2H, J = 4.3 Hz), 3.33(q, 2H, J = 7.2 Hz), 1.16 (t, 3H, J = 7.2 Hz).

1-Benzoyl-3-[(2-hydroxy-1,1-dimethyl)ethyl]urea (3b). R_f = 0.3 (ethyl acetate/n-hexane 1 : 1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.04 (bs, 2H), 7.91-7.89 (m, 2H), 7.64-7.58 (m, 1H), 7.54-7.48 (m, 2H), 3.88 (s, 1H), 3.68 (d, 2H, J = 6.1 Hz), 1.40 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 154.5, 133.2, 132.3, 128.9, 127.9, 70.4, 55.6, 24.5.

1-(2,4-Dichlorobenzoyl)-3-ethyl-3-(2-hydroxyethyl)urea (3c). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, 1H, J = 8.3 Hz), 7.37 (d, 1H, J = 1.9 Hz), 7.29 (dd, 1H, J = 1.9, 8.3 Hz), 3.87-3.84 (m, 2H), 3.53-3.49 (m, 2H), 3.34 (q, 2H, J = 6.9 Hz), 1.16 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 153.3, 137.5, 131.9, 130.2, 129.6, 127.6, 127.3, 61.9, 49.1, 42.4, 12.8.

1-(2,4-Dichlorobenzoyl)-3-methyl-3-(2-hydroxyethyl)urea (3d). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, 1H, J = 8.3 Hz), 7.39 (d, 1H, J = 2.0 Hz), 7.30 (dd, 1H, J = 2.0, 8.3 Hz), 3.88-3.85 (m, 2H), 3.55-3.52 (m, 2H), 2.98 (s, 3H).

1-(2,4-Dichlorobenzoyl)-3-[(2-hydroxy-1,1-dimethyl)-ethyl]urea (3e). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.19 (bs, 1H), 8.79 (s, 1H), 7.57 (d, 1H, J = 8.3 Hz), 7.48 (d, 1H, J = 1.9 Hz), 7.36 (dd, 1H, J = 1.9, 8.3 Hz), 3.61 (s, 2H), 1.33 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 153.1, 138.4, 132.0, 131.4, 130.9, 130.6, 127.7, 70.2, 55.8, 24.5.

1-(2,4-Dichlorobenzoyl)-3-(2-hydroxyethyl)urea (3f). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (bs, 1H), 7.62 (d, 1H, J = 8.4 Hz), 7.48 (d, 1H, J = 2.0 Hz), 7.36 (dd, 1H, J = 2.0, 8.4 Hz), 3.82-3.78 (m, 2H), 3.55-3.49 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 153.8, 138.5, 131.9, 131.1, 130.6, 127.8, 62.2, 42.8, 30.9

General Procedure for Intramolecular Cyclization of 3.

To a stirred suspension of potassium *t*-butoxide (0.4 g, 3.6 mmol) and aroylurea (1.5 mmol) in tetrahydrofuran (20 mL) under the nitrogen in an ice bath was added a solution of *p*-toluenesulfonyl chloride (0.34 g, 1.8 mmol) in tetrahydrofuran (5 mL) dropwise using a syringe. The reaction mixture was stirred in an ice bath for 30 min, quenched with water (20 mL), and extracted with ether (25 mL × 2). The crude product was purified by flash column chromatography.

1-Benzoyl-3-ethyl-2-imidazolidinone (4a). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86-7.83 (m, 2H), 7.50-7.45 (m, 1H), 7.40-7.35 (m, 2H), 3.92-3.89 (m, 2H), 3.48-3.44 (m, 2H), 3.32 (q, 2H, J = 7.2 Hz), 1.16 (t, 3H, J = 7.2 Hz); HRMS calcd for $C_{12}H_{14}N_2O_2$ 218.1055, found 218.1045.

1-Benzoyl-4,4-dimethyl-2-imidazolidinone (4b). 11% yield; R_f = 0.5 (acetone/chloroform 3 : 10); mp 164-166 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62-7.58 (m, 2H), 7.47-7.44 (m, 1H), 7.40-7.35 (m, 2H), 6.00 (bs, 1H), 3.75 (s, 2H), 1.29 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 155.0, 134.6, 131.2, 128.6, 127.4, 56.3, 51.2, 28.3; MS (EI) m/e 219 (M+1, 56), 218 (M, 95), 203 (87), 190 (66), 175 (67), 113 (93), 105 (100), 77 (93). The starting material **3b** was recovered in 12% yield. R_f = 0.4 (acetone/chloroform 3 : 10).

4,4-Dimethyl-4,5-dihydro-*N*-benzoyl-2-oxazolamine (5b). 42% yield; R_f = 0.4 (ethyl acetate/n-hexane 1 : 1); mp 79-81 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.62 (bs, 1H), 8.25-8.23 (m, 2H), 7.49-7.38 (m, 3H), 4.15 (s, 2H), 1.42 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.8, 166.0, 136.7, 131.9, 129.4, 128.2, 76.7, 58.4, 27.3; MS (EI) m/e 218 (M, 40), 217 (94), 141 (96), 105 (100), 77 (88).

1-(2,4-Dichlorobenzoyl)-3-ethyl-2-imidazolidinone (4c). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.22 (m, 3H), 4.07-4.01 (m, 2H), 3.55-3.53 (m, 2H), 3.31 (q, 2H, J = 7.2 Hz), 1.174 (t, 3H, J = 7.2 Hz); HRMS calcd for $C_{12}H_{12}Cl_2N_2O_2$ 286.0276, found 286.0257.

1-(2,4-Dichlorobenzoyl)-3-methyl-2-imidazolidinone (4d). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.21 (m, 3H), 4.06-4.00 (m, 2H), 3.55-3.50 (m, 2H), 2.84 (s, 3H); HRMS calcd for $C_{11}H_{10}Cl_2N_2O_2$ 272.01193, found 272.01199.

1-(2,4-Dichlorobenzoyl)-4,4-dimethyl-2-imidazolidinone (4e). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.21 (m, 3H), 3.84 (s, 2H), 1.42 (s, 6H); HRMS calcd for $C_{12}H_{12}Cl_2N_2O_2$ 286.0276, found 286.0286.

Acknowledgment. Financial support from the Brain Korea 21 program of the Ministry of Education is gratefully acknowledged. Spectroscopic analyses were performed in the Korea Basic Science Institute.

References

1. (a) Lam, P. Y. S.; Jadhav, P. K.; Eyermann, C. J.; Hodge, C. N.; Ru, Y.; Bacheler, L. T.; Meek, J. L.; Otto, M. J.; Rayner, M. M.; Wong, Y. N.; Chang, C-H.; Weber, P. C.; Jackson, D. A.; Sharpe, T. R.; Erickson-Viitanen, S. *Science* **1994**, *263*, 380. (b) Wilkerson, W. W.; Dax, S.; Cheatham, W. W. *J. Med. Chem.* **1997**, *40*, 4079. (c) Patel, M.; Bacheler, L. T.; Rayner, M. M.; Cordova, B. C.; Klabe, R. M.; Erickson-Viitanen, S.; Seitz, S. P. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 823.
2. Heidempergher, F.; Pillan, A.; Pinciroli, V.; Vaghi, F.; Arrigoni, C.; Bolis, G.; Caccia, C.; Dho, L.; McArthur, R.; Varasi, M. *J. Med. Chem.* **1997**, *40*, 3369.
3. (a) (4*R*,5*S*)-1,5-Dimethyl-4-phenyl-2-imidazolidinone: Guillena, G.; Najera, C. *Tetrahedron: Asymmetry* **1998**, *9*, 1125, and references cited therein. (b) (4*S*)-4-(1-Methylethyl or phenymethyl)-1-phenyl-2-imidazolidinone: Taguchi, T.; Shibuya, A.; Sasaki, H.; Endo, J.; Morikawa, T.; Shiro, M. *Tetrahedron: Asymmetry* **1994**, *5*, 1423, and references

cited therein. (c) *trans*-4,5-Tetramethylene-2-imidazolidinone: Davies, S. G.; Evans, G. B.; Mortlock, A. A. *Tetrahedron: Asymmetry* **1994**, *5*, 585. (d) Camphor-derived 2-imidazolidinone: Palomo, C.; Oiarbide, M.; Gonzalez, A.; Garcia, J. M.; Berree, F. *Tetrahedron Lett.* **1996**, *37*, 4565. (e) (4*S*)-4-Carboxylate-2-imidazolidinone: Kubota, H.; Kubo, A.; Takahashi, M.; Shimizu, R.; Da-te, T.; Okamura, K.; Nunami, K. *J. Org. Chem.* **1995**, *60*, 6776.

4. (a) Birkofer, L.; Kuhlthau, H. P.; Ritter, A. *Chem. Ber.* **1960**, *93*, 2810. (b) Hayward, R. J.; Meth-Cohn, O. *J. Chem. Soc., Perkin Trans. 1* **1975**, 212. (c) Maclaren, J. A. *Aust. J. Chem.* **1977**, *30*, 455. (d) Kim, J-M.; Wilson T. E.; Norman, T. H.; Schultz, P. G. *Tetrahedron Lett.* **1996**, *37*, 5309.
5. Takeda, K.; Ogura, H. *Synth. Comm.* **1982**, *12*, 213.
6. Ulrich, H.; Tucker, B.; Richter, R. *J. Org. Chem.* **1978**, *43*, 1544.
7. Kondo, K.; Yokoyama, S.; Miyoshi, N.; Murai, S.; Sonoda, N. *Angew. Chem., Intl. Ed. Engl.* **1979**, *18*, 692.
8. Davies, S. G.; Mortlock, A. A. *Tetrahedron* **1993**, *49*, 4419.
9. Kim, T. H.; Lee, G.- J. *J. Org. Chem.* **1999**, *64*, 2941.
10. Procedure for the preparation of 2,4-dichlorobenzoyl isocyanate. See: Weikert, R. J.; Bingham, Jr., S.; Emanuel, M. A.; Fraser-Smith, E. B.; Loughhead, D. G.; Nelson, P. H.; Poulton, A. L. *J. Med. Chem.* **1991**, *34*, 1630.
11. For a general discussion of the transfer of activation, see: (a) Sobolov, S. B.; Sun, J.; Cooper, B. A. *Tetrahedron Lett.* **1998**, *39*, 5685. (b) Eissenstat, M. A.; Weaver, J. D. *Tetrahedron Lett.* **1995**, *36*, 2029.
12. Park, K. H.; Kurth, M. J. *Tetrahedron Lett.* **1999**, *40*, 5841.
13. Katritzky, A. R.; Pleynet, D. P. M.; Yang, B. *J. Org. Chem.* **1997**, *62*, 4155.