Notes

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

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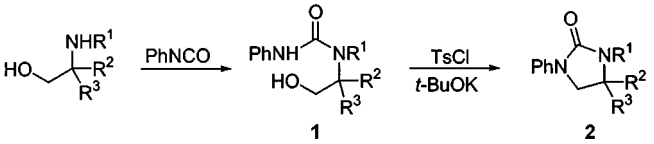
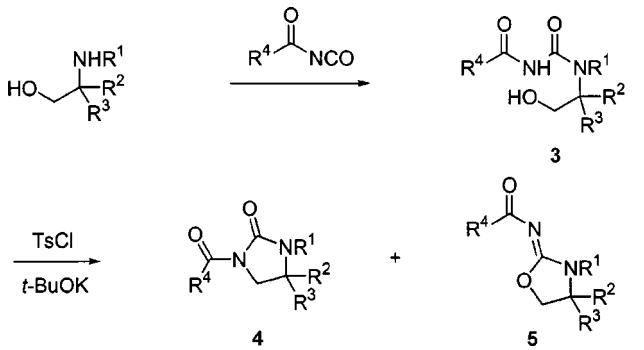
Cyclic ureas have recently gained much interest as pharmaceuticals for human immunodeficiency virus (HIV) protease inhibitors[1] and 5-HT_3 receptor antagonists.[2] In addition, 5- membered cyclic ureas, 2-imidazolidinones, are also used as useful chiral auxiliaries[3] in highly diastereoselective alkylation, aldol, and Diels-Alder reactions. Several synthetic routes to 2-imidazolidinones include the cyclization reaction of 1,2-diamine with phosgene,[4] phosgene derivatives,[2] 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.

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