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 inhibitors4 and 5-HT3 receptor antagonists.2 In addition, 5-membered cyclic ureas, 2-imidazolidinones, are also used as useful chiral auxiliaries3 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 selenide7 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.

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 activation9,11 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 benzene 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 benzene ring. Aroylurea 3f prepared from 2-aminoethanol did not undergo cyclization reaction under 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. 1H NMR and 13C NMR spectra were recorded

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<th>Entry</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>R4</th>
<th>Yield (%) of 3</th>
<th>mp of 3</th>
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<td>Et</td>
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<td>Me</td>
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<td>H</td>
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<td>126-128</td>
<td>nc†</td>
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*Isolated yield by recrystallization. †Isolated yield by column chromatography. The ratio of 2-imidazolidinone 4 and 2-oxazoline 5 was determined with 1H NMR data. 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 dropwise using a syringe. 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, CDCl3) 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)urea (3b).

1,2-Benzoyl-3-ethyl-2-imidazolidinone (4a). 1 H NMR (300 MHz, CDCl3) 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, CDCl3) 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-Benzoyl-3-ethyl-2-imidazolidinone (4b). 1 H NMR (300 MHz, CDCl3) 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-methyl-3-(2-hydroxyethyl)urea (3d).

1-(2,4-Dichlorobenzoyl)-3-(2-hydroxy-1,1-dimethyl)urea (3e).

1-Benzoyl-3-ethyl-2-oxazolamine (5b).

5% yield; Rf = 0.5 (acetone/chloroform 3:1); mp 164-166 °C; 1 H NMR (300 MHz, CDCl3) 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, CDCl3) 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. Rf = 0.4 (acetone/chloroform 3:1).

4,4-Dimethyl-4-dihydro-N-benzoyl-2-oxazolamine (5b).

42% yield; Rf = 0.4 (ethyl acetate/n-hexane 1:1); mp 79-81 °C; 1 H NMR (300 MHz, CDCl3) δ 9.62 (bs, 1H, 8.52-8.23 (m, 2H), 7.49-7.38 (m, 3H), 4.15 (s, 2H), 1.42 (s, 6H); 13 C NMR (75 MHz, CDCl3) 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-(2,4-Dichlorobenzoyl)-3-methyl-2-imidazolidinone (4d).

1-(2,4-Dichlorobenzoyl)-4,4-dimethyl-2-imidazolidinone (4e).

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


