Cyclization of *N*-(2-Hydroxyethyl)-*N*-phenylmethyl-*N'*-substituted Ureas and Thioureas: Prelude to the Synthesis of 1-Aryl-substituted-2-imidazolidinones on Solid Support

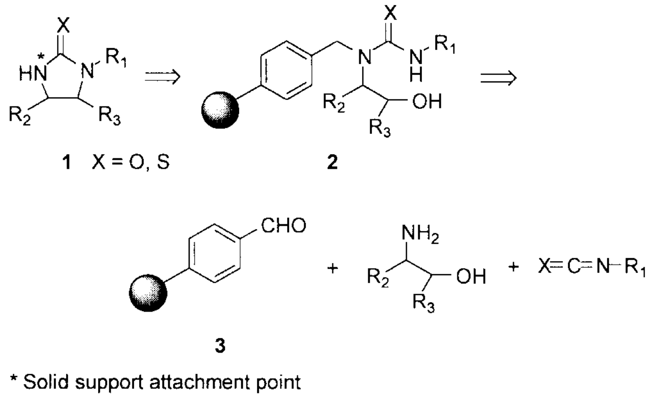
Taek Hyeon Kim,* Namgun Lee, and Jae Nyoung Kim†

Faculty of Applied Chemistry, Chonnam National University, Kwangju 500-757, Korea
†Department of Chemistry, Chonnam National University, Kwangju 500-757, Korea

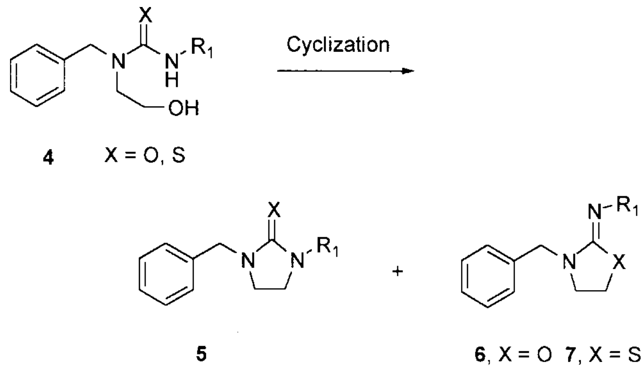
Received April 23, 2001

Keywords : 2-Imidazolidinones, 2-Imidazolidinethiones, Mitsunobu reaction, *N*-(2-Hydroxyethyl)-*N*-phenylmethylureas and *N*-(2-hydroxyethyl)-*N*-phenylmethylthioureas.

Cyclic ureas and thioureas have recently gained much interest as protease inhibitors of human immunodeficiency virus (HIV).[1] In addition, they have also found use as chiral auxiliaries for asymmetric synthesis.[2] Solid supported combinatorial chemistry methods based on library construction have proven to be useful for small acyclic and heterocyclic molecules due to their extensive utility as therapeutic agents.[3] Recently, solid-phase synthesis of 1,3,4-trisubstituted-2-imidazolidinones and 1,3,4-trisubstituted-2-imidazolidinethiones from a resin bound reduced *N*-acylated dipeptide was reported.[4] Goff also reported the synthesis of 2-imidazolidinones on solid support by tandem aminoacylation and Michael addition.[5] We reported the synthesis of 2-imidazolidinones and 2-imidazolidinethiones based on the Mitsunobu reaction of *N*-(2-hydroxyethyl)-*N'*-phenylureas and *N*-(2-hydroxyethyl)-*N'*-methylthioureas prepared from the reaction of phenyl isocyanate and methyl isothiocyanate with 1,2-aminoalcohols, respectively.[6] Depending on *N'*-substituents of ureas and thioureas, these ureas and thioureas furnished 2-imidazolidinones and 2-imidazolinethiones. Especially, only *N*-(2-hydroxyethyl)-*N*-(methyl or ethyl)-*N'*-phenylureas led to regiospecific *N*-cyclization to 2-imidazolidineones.[6a] With *N*-(2-hydroxyethyl)-*N*-(methyl or ethyl)-*N'*-methylthioureas, *N*-cyclization to 2-imidazolidinethiones was observed along with the S-cyclization products, 2-amino-2-thiazolines.[6b] From these results we became interested in devising a resin based new route to 2-imidazolidinones and 2-imidazolidinethiones. That is, if the Mitsunobu reaction of resin-bound ureas or thioureas **2** (Scheme 1) which is prepared from reductive amination of AgroGel-MB-CHO resin and aminoalcohols[7] followed by treatment of isocyanates or isothiocyanates proceeds to give *N*-cyclization products, we might develop a new synthetic method to the solid-supported 2-imidazolidinones and 2-imidazolidinethiones. This approach allows us to take advantage of the large number of commercially available and diverse 1,2-aminoalcohols and isocyanates or isothiocyanates-based building blocks. With these considerations in mind we surveyed the regioselectivity of the Mitsunobu reaction of a versatile *N*-phenylmethyl substituted ureas and thioureas **4** which bear structural features of resin bound **2** (Scheme 2) to pave the way for the generation of a wide variety of libraries based on 2-imidazolidinones and 2-imidazolidinethiones structural motif.



Scheme 1



Scheme 2

The starting *N*-(2-hydroxyethyl)-*N*-phenylmethylureas and thioureas **4** were readily obtained in high yields from the reaction of the corresponding 1,2-aminoalcohols with a variety of isocyanates and isothiocyanates.

Mitsunobu reaction of ureas and thioureas **4** can give the 2-imidazolidinones and 2-imidazolidinethiones **5** only when nucleophilic attack upon the oxyphosphonium intermediate by the nitrogen atom proceeds. However, the increased nucleophilicity of sulfur atom relative to nitrogen in thioureas

*Corresponding author. E-mail: thkim@chonnam.ac.kr

Table 1. Preparation and Cyclization Reaction of *N*-(2-Hydroxyethyl)-*N*-phenylmethylureas and thioureas

Entry		R_1	X	Yield (%) of **4**	Product ratios[a]		
						Mitsunobu reaction	TsCl/NaOH[b]
1	**4a**	Et	O	88	**5a/6a**	67/33	0/100(67)
2	**4b**	Ph	O	86	**5b/6b**	100/0	100/0(76)
3	**4c**	4-MeOPh	O	65	**5c/6c**	100/0	[c]
4	**4d**	4-NO_2Ph	O	85	**5d/6d**	100/0	[c]
5	**4e**	PhCO	O	89	**5e/6e**	83/17	84/16(75/–[c])
6	**4f**	Me	S	88	**5f/7f**	54/46	30/70(18/35)
7	**4g**	Ph	S	88	**5g/7g**	95/5	69/31(50/18)
8	**4h**	PhCO	S	94	**5h/6h/7h**	61/33/6	15/81/4 (14/60/5)

[a]The ratio of product of *N*-, *S*-, and *O*-cyclization was determined by nmr data. [b]Parenthesis is the isolated yields by column chromatography. [c]Not determined.

may favor 2-aminothiazoline formations **7**. The Mitsunobu reaction was achieved with triphenylphosphine (TPP) and diethyl azodicarboxylate (DEAD) in THF (Table 1). The DEAD was added to a mixture of the TPP and **4** at room temperature. The reactions were complete within 30 min. With *N'*-ethylurea **4a** and *N'*-benzoylurea **4e**, the Mitsunobu reaction produced the mixture of *N*- and *O*-cyclization (entries 1 and 5). On the other hand, *N'*-phenylurea **4b** led to a regiospecific *N*-cyclization product, 2-imidazolidinone **5b** (entry 2). All thioureas gave the mixture of cyclization products (entries 6-8). *N'*-Benzoylthiourea **4h**, contrary to *N'*-methylthiourea **4f** and *N'*-phenylthiourea **4g**, yielded the *O*-cyclization to give 2-oxazoline **6h** presumably due to the formation of isothiourea intermediate (entry 8).[9] Unfortunately most of ureas and thioureas upon the cyclization gave the mixtures. However, it is noteworthy that the ring closure of *N'*-phenylurea **4b** provided regiocontrolled 2-imidazolidinone **5b** without the mixtures. Thus, we made further efforts with another *N'*-arylureas to establish the generality of this transformation. Both *N'*-4-methoxyphenylurea **4c** and *N'*-4-nitrophenylurea **4d** also yielded only the regiocontrolled *N*-cyclization products regardless of the introduction of an electron donating or withdrawing substituent in benzene ring (entries 3 and 4). The separation and purification of the Mitsunobu reaction products were not convenient because the by-products, triphenylphosphine oxide and 1,2-dicarbethoxyhydrazine have similar R_f values to products, which would be no problems in solid phase synthesis. To obtain the authentic samples of cyclization products we performed the cyclization reaction of ureas and thioureas using TsCl and aqueous NaOH[8] and the product ratio of mixtures of Mitsunobu reaction was determined on the base of isolated authentic products as shown in Table 1.

In conclusion, we confirmed that the Mitsunobu reaction of *N'*-aryl-*N*-(2-hydroxyethyl)-*N*-phenylmethylureas furnished the regiospecific *N*-cyclization products. Thus, the Mitsunobu reaction may be applicable to obtain the libraries of 1-aryl substituted imidazolidinones from **2** on solid support. Applications of this protocol to the synthesis of 1-aryl-2-imidazolidinones on solid support will be reported in due course.

Experimental Section

^{1}H NMR and ^{13}C NMR spectra were recorded using 300 MHz and 75 MHz NMR spectrometer; chemical shifts are reported in ppm using TMS as an internal standard. Melting points were measured in a glass capillary apparatus and uncorrected. Mass spectra were recorded on a HP 5983B GC/Mass spectrometer. Elemental analysis was performed in the Korea Basic Science Institute, Kwangju, Korea. Analytical TLC was performed on 0.25 mm precoated silica gel plates. Flash chromatography was carried out with 230-400 mesh silica gel.

General procedure for the preparation of urea and thiourea 4. To a stirred solution of 1,2-aminoalcohol (4.59 mmol) in THF (10 mL) under nitrogen at room temperature was added a solution of isocyanate or isothiocyanate (4.18 mmol) in THF (5 mL) dropwise for 5 min with a syringe. The reaction mixture was stirred for 30 min and evaporated. The crude products were purified by column chromatography to give the requisite product.

***N'*-Ethyl-*N*-(2-hydroxyethyl)-*N*-phenylmethylurea (4a)**. Yield 88%; pale yellow oil; R_f = 0.3 (ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 7.36-7.22 (m, 5H), 4.48 (s, 2H), 3.67 (t, 2H, J = 4.8), 3.39 (t, 2H, J = 4.8), 3.20 (dq, 2H, J = 5.4, 6.9), 1.07 (t, 3H, J = 6.9); ^{13}C NMR ($CDCl_3$) δ 160.1, 137.8, 128.6, 127.3, 127.0, 61.7, 51.1, 50.2, 35.6, 15.2; EIMS *m/z* 65.0 (91), 91.0 (100), 105.0 (87), 120.0 (75), 132.0 (74), 189.1 (49), 204.1 (52), 222.1 (27, MW).

***N*-(2-Hydroxyethyl)-*N'*-phenyl-*N*-phenylmethylurea (4b)**. Yield 86%; white solid; mp 95-97 °C; R_f = 0.6 (ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 7.37-7.18 (m, 10H), 7.00 (t, 1H, J = 7.3), 4.30 (s, 2H), 3.61 (bs, 2H), 3.30 (bs, 3H); ^{13}C NMR ($CDCl_3$) δ 157.7, 139.7, 137.5, 128.8, 128.7, 127.5, 122.4, 119.2, 61.4, 50.3, 49.7; EIMS *m/z* 65.0 (88), 91.0 (100), 119.0 (93), 132.0 (73), 177.1 (20), 252.1 (26), 270.1 (14, MW).

***N*-(2-Hydroxyethyl)-*N'*-(4-methoxyphenyl)-*N*-phenylmethylurea (4c)**. Recrystallization (hexane/acetone) Yield 65%; white solid; mp 121-123 °C; R_f = 0.5 (ethyl acetate/hexane 1/1); ^{1}H NMR ($CDCl_3$) δ 7.86 (bs, 1H), 7.36-7.22 (m, 6H), 6.82 (bd, 2H), 4.42 (s, 2H), 3.78 (s, 2H), 3.70-3.66 (bt, 2H), 3.41-3.38 (bt, 2H).

***N*-(2-Hydroxyethyl)-*N'*-(4-nitrophenyl)-*N*-phenylmethylurea (4d)**. Yield 85%; yellow solid; mp 140-141 °C; R_f = 0.5 (ethyl acetate/hexane 1/1); ^{1}H NMR ($CDCl_3$) δ 8.17-8.14 (m, 2H), 7.49-7.46 (m, 2H), 7.37-7.30 (m, 5H), 4.57 (s, 2H), 3.82-3.79 (bt, 2H), 3.52-3.49 (bt, 2H).

***N'*-Benzoyl-*N*-(2-hydroxyethyl)-*N*-phenylmethylurea (4e)**. Yield 89%; pale yellow solid; mp 119-121 °C; R_f = 0.3 (ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 7.87-7.80 (m, 2H), 7.47-7.24 (m, 9H), 4.46 (bs, 2H), 3.85-3.82 (m, 2H), 3.39 (bs, 2H); ^{13}C NMR ($CDCl_3$) d 166.2, 154.7, aromatics, 61.0, 50.0, 49.2; EIMS *m/z* 77.0 (90.0), 91.0 (100), 105.0 (84), 120.0 (47), 147.0 (31), 176.1 (19), 280.2 (4, MW-H_2O).

N-(2-Hydroxyethyl)-N'-methyl-N-phenylmethylthiourea (4f). Yield 88%; pale yellow oil; R_f = 0.3 (ethyl acetate/hexane 1/1); ^{1}H NMR ($CDCl_3$) δ 7.38-7.27 (m, 5H), 5.00 (s, 2H), 3.82 (s, 4H), 3.09 (d, 3H, J = 4.4); ^{13}C NMR ($CDCl_3$) δ 185.4, 136.2, 128.9, 127.7, 127.0, 61.5, 54.9, 53.0, 33.0; EIMS m/z 70.1 (61), 91.0 (72), 104.5 (56), 206.1 (6), 224.2 (1, MW).

N-(2-Hydroxyethyl)-N'-phenyl-N-phenylmethylthiourea (4g). Yield 88%; white solid; mp 117-119 °C; R_f = 0.4 (ethyl acetate/hexane 1/1); ^{1}H NMR ($CDCl_3$) δ 7.43-7.29 (m, 10H), 7.15 (t, 1H, J = 7.3), 5.16 (m, 2H), 3.75 (bs, 4H); ^{13}C NMR ($CDCl_3$) δ 183.8, 140.2, 136.2, 128.7, 128.4, 127.6, 127.4, 124.8, 124.1, 61.0, 55.1, 52.3; EIMS m/z 65.0 (91), 91.0 (100), 119.0 (94), 177.1 (30), 252.1 (36), 270 (8, MW-H_2O).

N'-Benzoyl-N-(2-hydroxyethyl)-N-phenylmethylthiourea (4h). Yield 94%; pale yellow oil; R_f = 0.5 (ethyl acetate/hexane 1/1); ^{1}H NMR ($CDCl_3$) δ 7.94-7.80 (m, 2H), 7.88-7.23 (m, 9H), 5.26 (bs, 1H), 4.85 (bs, 1H), 4.15-3.67 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 181.2, 164.8, aromatics, 60.1, 55.4, 52.4; EIMS m/z 77.0 (74), 91.0 (100), 105.0 (64), 191.1 (17), 296.2 (4, M-H_2O).

Cyclization of N-(2-hydroxyethyl)-N-phenylmethylurea and N-(2-hydroxyethyl)-N-phenylmethylthiourea 4. A: TsCl/NaOH. To a stirred solution of urea or thiourea (0.88 mmol) in THF (10 mL) under nitrogen at room temperature was added a solution of NaOH (88 mg, 2.2 mmol) in water (3 mL) and TsCl (0.18 g, 0.97 mmol) in THF (5 mL) dropwise for 5 min with a syringe. The reaction mixture was stirred for 30 min at room temperature, quenched with water (30 mL), and extracted with ether (50 mL × 3). The organic layer was dried, filtered, evaporated, and purified by flash column chromatography to give the cyclized product.

B: the Mitsunobu reaction. To a stirred solution of urea or thiourea (1.49 mmol) and triphenylphosphine (0.59 g, 2.24 mmol) in THF (20 mL) under nitrogen at room temperature was added a solution of diethyl azodicarboxylate (0.46 mL, 2.24 mmol) in THF (10 mL) dropwise for 5 min with a syringe. The reaction mixture was stirred for 30 min and evaporated to give the crude product.

3-Phenylmethyl-2-ethyliminooxazolidine (6a). Yield 67 %; pale yellow oil; R_f = 0.4 (ethyl acetate/methanol 7/1); ^{1}H NMR ($CDCl_3$) δ 7.33-7.25 (m, 5H), 4.38 (s, 2H), 4.25-4.20 (m, 2H), 3.28 (q, 2H, J = 7.3), 3.24-3.19 (m, 2H), 1.16 (t, 3H, J = 7.3); ^{13}C NMR ($CDCl_3$) δ 154.3, 137.3, 128.5, 128.2, 127.4, 64.0, 49.7, 45.9, 40.9, 17.1; EIMS m/z 65.0 (89), 90.8 (100), 120.0 (82), 149.0 (55), 204.1 (21, MW).

1-Phenyl-3-phenylmethyl-2-imidazolidinone (5b). Yield 76%; white solid; R_f = 0.6 (ethyl acetate/hexane 1/1); ^{1}H NMR ($CDCl_3$) δ 7.60-7.56 (m, 2H), 7.36-7.30 (m, 7H), 7.05-7.02 (m, 1H), 4.46 (s, 2H), 3.78-3.73 (m, 2H), 3.37-3.30 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 157.7, 140.5, 136.9, 128.8, 128.6, 128.2, 127.5, 122.3, 117.3, 48.1, 42.3, 41.1; EIMS m/z 65.0 (58), 77.0 (57), 91.0 (100), 104.0 (40), 132.0 (33), 161.0 (27), 223.1 (21), 252.2 (43, MW).

1-Benzoyl-3-phenylmethyl-2-imidazolidinone (5e). Yield 75%; oil; R_f = 0.8 (ethyl acetate/hexane 1/1); ^{1}H NMR ($CDCl_3$) δ 7.63-7.60 (m, 2H), 7.50-7.25 (m, 8H), 4.41 (s, 2H), 3.99-3.95 (m, 2H), 3.40-3.35 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 170.4, 154.2, 135.7, 134.6, 131.3, 128.9, 128.7, 128.3, 128.0, 127.5, 47.8, 40.6, 40.4; EIMS m/z 77.0 (100), 91.0 (85), 105.0 (96), 175.1 (60), 280.2 (41, MW).

1-Methyl-3-phenylmethyl-2-imidazolidinethione (5f). Yield 18%; pale yellow solid, mp 109-111 °C; R_f = 0.8 (ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 7.34-7.27 (m, 5H), 4.84 (s, 2H), 3.57-3.50 (m, 2H), 3.43-3.37 (m, 2H), 3.19 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 183.2, 136.5, 128.6, 128.2, 127.6, 51.8, 48.3, 45.4, 35.1; EIMS m/z 44.2 (89), 65.1 (73), 91.0 (100), 115.0 (35), 145.1 (30), 206.1 (74, MW). Anal Calcd for $C_{11}H_{14}N_2S$: C, 64.04; H, 6.84; N, 13.58; S, 15.54. Found: C, 63.90; H, 6.79; N, 13.10; S, 15.20.

3-Phenylmethyl-2-methyliminothiazolidine (7f). Yield 35%; colorless oil, R_f = 0.5 (ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 7.32-7.25 (m, 5H), 4.50 (s, 2H), 3.34-3.29 (m, 2H), 3.12-3.07 (m, 2H), 3.10 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 160.2, 137.7, 128.5, 128.0, 127.2, 50.3, 50.2, 41.4, 26.7; EIMS m/z 43.2 (75), 74.9 (100), 90.9 (90), 177.9 (44), 206.0 (59, MW). Anal Calcd for $C_{11}H_{14}N_2S$: C, 64.04; H, 6.84; N, 13.58; S, 15.54. Found: C, 63.83; H, 6.68; N, 13.42; S, 15.12.

1-Phenyl-3-phenylmethyl-2-imidazolidinethione (5g). Yield 50%; white solid, mp 119-121 °C (lit.[14] mp 125-126 °C); R_f = 0.7 (ethyl acetate/hexane 1 : 1); ^{1}H NMR ($CDCl_3$) δ 7.56-7.53 (m, 2H), 7.43-7.25 (m, 8H), 4.95 (s, 2H), 4.00-3.94 (m, 2H), 3.59-3.53 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 181.7, 140.9, 136.2, 129.0, 128.3, 127.6, 126.2, 124.9, 51.7, 48.8, 45.6; EIMS m/z 77.1 (51), 91.1 (100), 136.0 (32), 148.0 (35), 182.1 (14), 239.2 (10), 268.2 (29, MW). Anal Calcd for $C_{16}H_{16}N_2S$: C, 71.60; H, 6.01; N, 10.44; S, 11.95. Found: C, 71.15; H, 5.90; N, 10.06; S, 11.50.

3-Phenylmethyl-2-phenyliminothiazolidine (7g). Yield 18%; white solid, mp 93-95 °C (lit.[14] mp 92-94 °C); R_f = 0.8 (ethyl acetate/hexane 1 : 1); ^{1}H NMR ($CDCl_3$) δ 7.36-7.24 (m, 7H), 7.04-6.97 (m, 3H), 4.71 (s, 2H), 3.49-3.44 (m, 2H), 3.10-3.06 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 159.0, 152.2, 137.2, 128.8, 128.6, 128.2, 127.4, 123.0, 122.0, 50.2, 50.1, 26.8; EIMS m/z 77.1 (58), 91.1 (100), 207.2 (33), 268.3 (45, MW). Anal Calcd for $C_{16}H_{16}N_2S$: C, 71.60; H, 6.01; N, 10.44; S, 11.95. Found: C, 71.26; H, 5.88; N, 10.34; S, 11.74.

1-Benzoyl-3-phenylmethyl-2-imidazolidinethione (5h). Yield 14%; white solid, mp 113-114 °C; R_f = 0.8 (ethyl acetate/hexane 1 : 1); ^{1}H NMR ($CDCl_3$) δ 8.19-8.16 (m, 2H), 7.50-7.35 (m, 8H), 5.22 (s, 2H), 4.15-4.12 (m, 2H), 3.60-3.57 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 178.2, 177.4, 135.8, 134.2, 132.1, 129.6, 128.9, 128.2, 65.8, 57.5, 47.9; EIMS m/z 77.0 (100), 91.5 (77), 105.0 (85), 191.1 (28), 267.1 (22), 296.2 (26, MW). Anal Calcd for $C_{17}H_{16}N_2OS$: C, 68.89; H, 5.44; N, 9.45; S, 10.82. Found: C, 68.45; H, 5.12; N, 9.69; S, 10.40.

3-Phenylmethyl-2-benzoyliminooxazolidine (6h). Yield 60%; white solid, mp 83-84 °C; R_f = 0.1 (ethyl acetate/hexane 1 : 1); ^{1}H NMR ($CDCl_3$) δ 8.25-8.22 (m, 2H), 7.47-7.32 (m, 8H), 4.68 (s, 2H), 4.55-4.49 (m, 2H), 3.50-3.45 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 175.0, 159.7, 137.2, 135.3, 131.6, 129.7, 128.9, 128.3, 128.2, 127.9, 65.8, 49.1, 44.3; EIMS m/z

77.1 (76), 91.1 (100), 105.1 (73), 132.1 (26), 175.2 (18), 280.3 (14, MW). Anal Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.83; H, 5.63; N, 9.66.

3-Phenylmethyl-2-benzoyliminothiazolidine (7h). Yield 5%; white solid, mp 122-124 °C; $R_f = 0.5$ (ethyl acetate/hexane 1 : 1); ^{1}H NMR ($CDCl_3$) δ 8.33-8.30 (m, 2H), 7.50-7.34 (m, 8H), 5.00 (s, 2H), 3.62-3.57 (m, 2H), 3.18-3.12 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 175.9, 172.2, 136.7, 135.8, 131.9, 129.7, 128.9, 128.2, 128.0, 51.2, 48.8, 26.9; EIMS *m/z* 77.1 (100), 91.1 (62), 105.1 (75), 191.2 (18), 296.4 (8, MW). Anal Calcd for $C_{17}H_{16}N_2OS$: C, 68.89; H, 5.44; N, 9.45; S, 10.82. Found: C, 68.47; H, 5.47; N, 9.2; S, 10.48.

Acknowledgment. This work was supported by the grant No. (2001-1-12300-004-1) from the Basic Research Program of the Korea Science and Engineering Foundation and by the grant from the Brain Korea 21 program of the Ministry of Education.

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. (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.
3. (a) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449. (b) Fruchtel, J. S.; Jung, G. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 17. (c) Thomson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555.
4. Nefzi, A.; Ostresh, J. M.; Giulianotti, M.; Houghten, R. A. *J. Comb. Chem.* **1999**, *1*, 195.
5. Goff, D. *Tetrahedron Lett.* **1998**, *39*, 1477.
6. (a) Kim, T. H.; Lee, G.-J.; Cha, M.-H. *Synth. Comm.* **1999**, *29*, 2753. (b) Kim, T. H.; Cha, M. -H. *Tetrahedron Lett.* **1999**, *40*, 3125.
7. (a) Kung, P.-P.; Swayze, E. *Tetrahedron Lett.* **1999**, *40*, 5651. (b) Krchňák, V.; Smith, J.; Vágner, J. *Tetrahedron Lett.* **2001**, *42*, 2443. (c) Krchňák, V.; Smith, J.; Vágner, J. *Tetrahedron Lett.* **2001**, *42*, 1627. (d) Krchňák, V.; Szabo, L.; Vágner, J. *Tetrahedron Lett.* **2000**, *41*, 2835.
8. Kim, T. H.; Lee, G. -J. *J. Org. Chem.* **1999**, *64*, 2941.
9. (a) Mitsunobu, O.; Kato, K.; Kakese, F. *Tetrahedron Lett.* **1969**, 2473. (b) Mitsunobu, O.; Kato, K.; Tomari, M. *Tetrahedron* **1970**, *26*, 5731.