A New Method for Synthesis of Unsymmetrical Ureas Using Electrochemically Prepared Trifluoroethyl Carbamates

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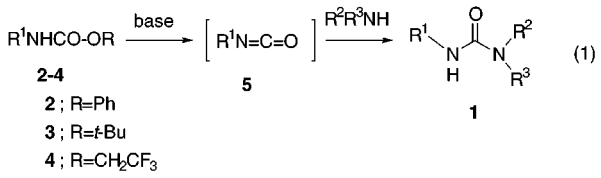
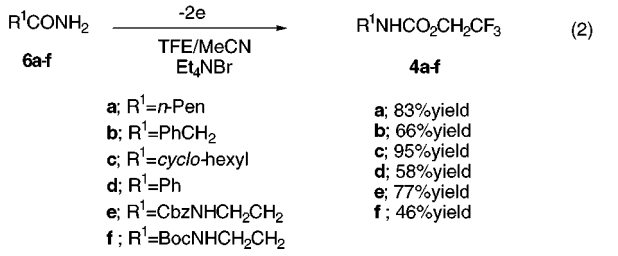
Substituted ureas have attracted much attention because of their important biological activities,[1] and thus there have been a variety of the synthetic methods.[2] However, most of the methods are limited to the preparation of symmetrical ureas and have the drawback that highly toxic reagents such as phosgene must be used. On the other hand, some methods applicable to the preparation of unsymmetrical ureas **1** without the use of any toxic reagent have been devised.[3] One promising methods is to use an aminolysis of alkoxycarbonylated amines[4] in which the OR group is a phenoxy (**2**)[5] or *tert*-butoxy group (**3**)[6] (eq 1).



Because the OR group works as a leaving group to generate an isocyanate **5** as an intermediate from alkoxycarbonylated amines, the rate of aminolysis may depend on the ability of OR as a leaving group.[7] Thus, we supposed that a new alkoxy group, possessing an ability as a leaving group different from that of a phenoxy or *tert*-butoxy group, would make the method more useful for the synthesis of substituted ureas in respect to the applicability and selectivity. This paper describes a successful result using trifluoroethyl carbamates **4**, which were easily obtained by our recently reported method (the electrochemically induced Hofmann rearrangement of amides **6**).[8] The transformation of amides **6a**−**f** to **4a**−**f** as examples are shown in eq 2.



Aminolysis of **4a**−**d** thus obtained was carried out under several reaction conditions, and the results are shown in Table 1 , which indicates the following features. The absence of NaH did not give ureas **1aa** (entry 1). On the other hand, a variety of unsymmetrical ureas **1aa**−**ae**, **bb**, **cb**, and **db** were obtained in good to moderate yields by the reaction of **4a**−**d** with primary and secondary amines such as *n*-butylamine, piperidine, piperazine, morpholine, and allylamine in the presence of NaH (entries 2−6, 9−11), whereas bulky amines such as 1-phenethylamine or diisopropylamine gave the desired product **1af** in low yield (entry 7) or did not afford the desired urea **1ag** (entry 8).

To use our new method conveniently in organic synthesis, it is necessary to clarify the advantage of **4** or the differences with the methods using **2** and **3**. In this respect, the reactivity of **4a** was compared with those of **2a** and **3a** and also with those of methyl (**7a**) and benzyl carbamates (**8a**) in the reaction with piperidine (eq 3). Table 2 summarizes the results of those competitive reactions, which show that **4a** was more reactive than **3a** (entry 2), **7a** (entry 3), and **8a** (entry 4) but was less reactive than **2a** (entry 1). The difference in the reac-

Table 1. Preparation of Unsymmetrical Ureas 1

entry	4	R^2R^3NH (2.0 equiv)	NaH (equiv)	yield of **1** (%)[a]
1	**4a**	*n*-$BuNH_2$	0	**1aa** 0[b]
2	**4a**	*n*-$BuNH_2$	2.0	**1aa** 86
3	**4a**	piperidine	1.1	**1ab** 81
4	**4a**	piperazine[c]	1.1	**1ac** 66[d]
5	**4a**	morpholine	2.0	**1ad** 80
6	**4a**	allylamine	2.0	**1ae** 42
7	**4a**	(*S*)-phenethylamine	2.0	**1af** 27
8	**4a**	diisopropylamine	2.0	**1ag** 0
9	**4b**	piperidine	1.1	**1bb** 93
10	**4c**	piperidine	1.1	**1cb** 91
11	**4d**	piperidine	1.1	**1db** 97

[a] Isolated yield. [b] Starting material was recovered. [c] 1.1 equiv to **4a**. [d] The yield is determined after the acetylation of **1ac**.

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(4) Basha, A. *Tetrahedron Lett.* **1988**, *29*, 2525.

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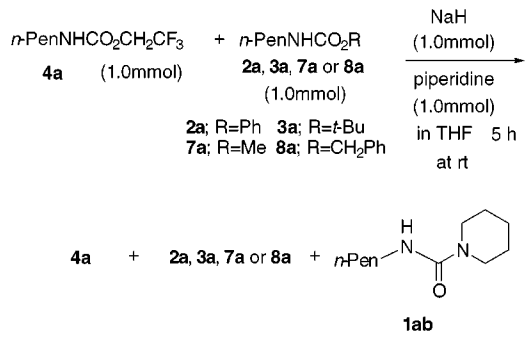
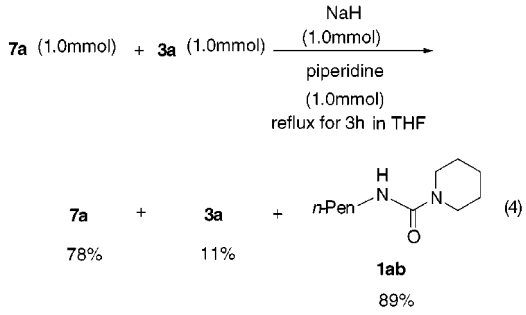


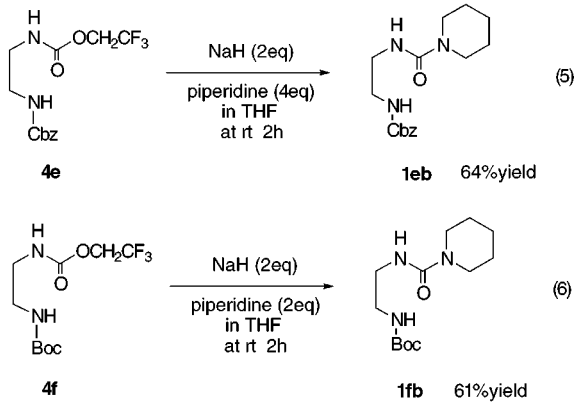
tivities of those carbamates is explainable in terms of the acidity of phenol, 2,2,2-trifluoroethanol, and normal alcohols.[9]

Furthermore, the competitive reaction between **3a** and **7a** showed that **3a** was more reactive than **7a** (eq 4). Also,



8a was found to be slightly reactive than **7a** by the competitive reaction between **7a** and **8a**.[10] Those results indicate the order of the reactivities of alkyl carbamates **2**−**4**, **7**, and **8** as shown in Scheme 1.

On the basis of this finding, subjecting unsymmetrically protected diamines **4e** and **4f** to a condition containing NaH and piperidine gave unsymmetrical ureas **1eb** and **1fb**, in which only the amino group protected with CF_3CH_2OCO group was converted to the corresponding ureido group (eqs 5 and 6).



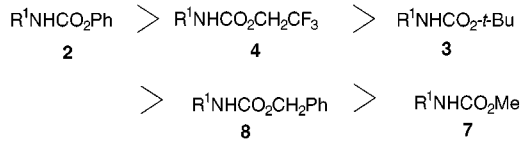
In summary, trifluoroethyl carbamates **4** obtained by the electrochemically induced Hofmann rearrangement of amides **6** could be used as good precursors for the preparation of unsymmetrical ureas **1**, and **4** showed reactivities different from that of phenyl and *tert*-butyl carbamates.

Table 2. Comparison of the Reactivity of 4a with that of 2a, 3a, 7a, or 8a

entry	recoveries of **4a**, **2a**, **3a**, **7a,** or **8a** (%)	yield[a] of **1ab** (%)
1	75 (**4a**)	0 (**2a**)	81
2	0 (**4a**)	87 (**3a**)	69
3	3 (**4a**)	89 (**7a**)	83
4	4 (**4a**)	90 (**8a**)	74

[a] The yields of urea were based on the amount of piperidine.

Scheme 1



Experimental Section

General. All solvents were dried by standard techniques. Sodium hydride, *n*-butylamine, piperidine, piperazine, morpholine, allylamine, 1-phenethylamine, diisopropylamine, carboxamides **6a**−**d**, and *β*-alaninamide hydrochloride were commercially available. Compounds **6e**,**f** were prepared according to conventional known methods as shown below. 2,2,2-Trifluoroethyl carbamates **4a**−**f** were prepared according to the reported method by us.[8] Ureas **1bb** (39531-35-6) and **1db** (2645-36-5) are known compounds.[11]

3-Benzyloxycarbonylaminopropanoxamide (6e). Into a solution of methylene chloride (20 mL) containing *β*-alaninamide hydrochloride (8 mmol), DMAP (1 mmol), and triethylamine (26 mmol) was added benzyl chloroformate (18 mmol) at 0 °C under a nitrogen atmosphere, and the resulting solution was stirred at room temperature for 6 h. The solution was worked up with aqueous NH_4Cl, and the organic portion was extracted with methylene chloride. Evaporation of the solvent in vacuo gave a residue, which was subjected on a column chromatography (silica gel, methanol/AcOEt =1/1) to give **6e** in 20% yield: mp 160−162 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.48 (t, J = 6.2 Hz, 2H), 3.49 (t, J = 6.0 Hz, 2H), 5.09 (s, 2H), 5.40 (br s, 2H), 5.60 (br s, 1H), 7.23−7.40 (m, 5H); IR (neat) 3378, 3333, 3193, 1684, 1646 cm^{-1}. Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.21; H, 6.28; N, 12.46.

3-*N*-Boc-aminopropanoxamide (6f). Di-*tert*-butyl dicarbonate (18 mmol) was added to solution of methylene chloride (20 mL) containing *β*-alaninamide hydrochloride (8 mmol), triethylamine (26 mmol), and DMAP (1 mmol). After being stirred for 6 h at room temperature, the solution was worked up with an aqueous NH_4Cl solution, and the organic portion was extracted with methylene chloride. Evaporation of the solvent in vacuo gave a residue, which was subjected on a column chromatography (silica gel, methanol/AcOEt =1/1) to give **6f** in a 30% yield: mp 160−161 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9H), 2.46 (t, J = 5.9 Hz, 2H), 3.42 (q, J = 6.0 Hz, 2H), 5.13 (br s, 1H), 5.35 (br s, 1H), 5.71 (br s, 1H); IR (Nujol) 3343, 3200, 1692, 1634 cm^{-1}. Anal. Calcd for $C_8H_{16}N_2O_3$: C, 51.05; H, 8.57; N, 14.88. Found: C, 50.71; H, 8.17; N, 15.05.

Electrochemically Induced Hofmann Rearrangement. Typical Procedure. A solution of **6a** (2.5 mmol) and Et_4NBr (1.25 mmol) in acetonitrile (10 mL) containing 2,2,2-trifluoroethanol (12.5 mmol) was charged in a one-compartment cell equipped with platinum plate anode and cathode (1 cm × 2 cm), and a constant current (100 mA) was passed through the cell at ambient temperature (30−40 °C) until 2.2 F/mol of electricity was passed. After the removal of acetonitrile, the residue was extracted with methylene chloride. The extract was dried on $MgSO_4$, and the solvent was evaporated in vacuo to give a mixture of carbamate **4a** and a small amount of recovered **6a**.

(9) Riddick, J. A.; Bunger, W. B.; Sakano, T. K. In *Organic Solvents*, 4th ed.; John Wiley & Sons: New York, 1986; p 700.

(10) Carbamate **8a** was 2 times reactive than **7a** in the reaction with piperidine in THF in the presence of NaH (reflux, 3 h).

(11) Nec, R. *Chem. Prum.* **1979**, *29*, 589.

The mixture was subjected to column chromatography (silica gel) with *n*-hexane/ethyl acetate to give **4a**.

***N*-2,2,2-Trifluoroethoxycarbonylpentylamine (4a):** 83%; oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.90 (t, J = 6.7 Hz, 3H), 1.23−1.65 (m, 6H), 3.21 (q, J = 6.8 Hz, 2H), 4.45 (q, J = 8.5 Hz, 2H), 4.79−4.98 (br s, 1H); IR (neat) 3361, 2963, 1750, 1550 cm^{-1}; HRMS calcd for $C_8H_{14}F_3NO_2$ 213.0976, found 213.0977. Anal. Calcd for $C_8H_{14}F_3NO_2$: C, 45.07; H, 6.62; N, 6.57. Found: C, 45.07; H, 6.70; N, 6.57.

***N*-2,2,2-Trifluoroethoxycarbonylbenzylamine (4b):** 66%; mp 59 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.45 (q, J = 8.5 Hz, 2H), 3.35 (d, J = 5.9 Hz, 2H) 7.19−7.41 (m, 5H); IR (neat) 3326, 1701, 1673, 1279, 1254, 1183 cm^{-1}. Anal. Calcd for $C_{10}H_{10}F_3NO_2$: C, 51.51; H, 4.32; N, 6.01. Found: C, 51.64; H, 4.40; N, 6.06.

***N*-2,2,2-Trifluoroethoxycarbonylcyclohexylamine (4c):** 95%; mp 73 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.03−1.48 (m, 4H), 1.56−1.82 (m, 4H), 1.85−2.03 (m, 2H), 3.37−3.60 (m, 1H), 4.44 (q, J = 8.5 Hz, 2H), 4.63−4.85 (br s, 1H); IR (neat) 3440, 1794, 1748, 1383, 1095 cm^{-1}. Anal. Calcd for $C_9H_{14}F_3NO_2$: C, 48.00; H, 6.27; N, 6.22. Found: C, 48.12; H, 6.19; N, 6.22.

***N*-2,2,2-Trifluoroethoxycarbonylaniline (4d):** 58%; mp 57 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.56 (q, J = 8.4 Hz, 2H), 6.78−6.93 (br s, 1H), 7.20−7.48 (m, 5H); IR (KBr) 3058, 2982, 1748, 1277, 1171, 1100 cm^{-1}. Anal. Calcd for $C_9H_8F_3NO_2$: C, 49.32; H, 3.68; N, 6.39. Found: C, 49.08; H, 3.75; N, 6.31.

***N*-Benzyloxycarbonyl-*N*′-2,2,2-trifluoroethoxycarbonyl-1,2-ethanediamine (4e):** 77%; mp 115−117 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.25−3.40 (m, 4H), 4.44 (q, J = 8.4 Hz, 2H), 5.00−5.20 (m, 3H), 5.40 (br s, 1H), 7.23−7.42 (m, 5H); IR (neat) 3328, 1706, 1694 cm^{-1}. Anal. Calcd for $C_{13}H_{15}F_3N_2O_4$: C, 48.75; H, 4.72; N, 8.75. Found: C, 49.05; H, 4.91; N, 8.70.

***N*-Boc-*N*′-2,2,2-trifluoroethoxycarbonyl-1,2-ethanediamine (4f):** 46%; mp 133−135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 3.20−3.40 (m, 4H), 4.46 (q, J = 8.7 Hz, 2H), 4.81 (br s, 1H), 5.44 (br s, 1H); IR (neat) 3324, 1680 cm^{-1}. Anal. Calcd for $C_{10}H_{17}F_3N_2O_4$: C, 41.96; H, 5.99; N, 9.79. Found: C, 41.98; H, 5.70; N, 9.75.

Urea Formation. Typical Procedure. Into a dry, 50 mL flask equipped with a nitrogen inlet adapter, a rubber septum, and a magnetic stirring bar was placed **4a** (0.5 mmol) and *n*-butylamine (1 mmol) in THF. Sodium hydride (1 mmol) was added to the mixture at 0 °C. The resulting solution was stirred at room temperature, and after 5 h aqueous NH_4Cl was added to the mixture. After the removal of the solvent in vacuo, the residue was extracted with ethyl acetate. The extract was dried on $MgSO_4$, and the solvent was evaporated in vacuo to give a residue, which was subjected to column chromatography (silica gel) with *n*-hexane/ethyl acetate to give *N*-*n*-butyl-*N*′-pentylurea (**1aa**) in 86% yield.

***N*-*n*-Butyl-*N*′-*n*-pentylurea (1aa):** mp 51−52 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.89 (t, J = 7.0 Hz, 3H), 0.92 (t, J = 6.8 Hz, 3H), 1.13−1.60 (m, 10H), 3.05−3.25 (m, 4H), 4.53−4.83 (br s, 1H); IR (neat) 3335, 1622 cm^{-1}; HRMS calcd for $C_{10}H_{22}N_2O$ 186.1732, found 186.1733. Anal. Calcd for $C_{10}H_{22}N_2O$: C, 64.47; H, 11.90; N, 15.04. Found: C, 64.32; H, 11.83; N, 14.96.

Other ureas were prepared by similar procedures. In the case of *N*,*N*-(3-azapentamethylenediyl)-*N*′-*n*-pentylurea **1ac**, Et_3N (4 equiv to **1ac**) and acetyl chloride (4 equiv to **1ac**) were added to the reaction mixture after it was stirred for 5 h, and then the usual working up afforded *N*,*N*-1,5-(4-acetyl-4-azapentamethylenediyl)-*N*′-*n*-pentylurea (**acetyl-1ac**). Ureas **1eb** and **1fb** were prepared by adding NaH (2 mmol) to a solution of piperidine (4 mmol) in THF and then adding **4e**,**f** (1 mmol) to the solution. Then, the resulting solution was stirred at room temperature for 2 h.

***N*,*N*-1,5-Pentamethylenediyl-*N*′-*n*-pentylurea (1ab):** 81%; mp 52−53 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J = 6.7 Hz, 3H), 1.12−1.43 (m, 4H), 1.43−1.67 (m, 8H), 3.16−3.26 (m, 4H), 3.27−3.36 (m, 4H), 4.48−4.60 (br s, 1H); IR (neat) 3343, 1624 cm^{-1}. Anal. Calcd for $C_{11}H_{22}N_2O$: C, 66.61; H, 11.19; N, 14.13. Found: C, 66.61; H, 11.22; N, 13.96.

***N*,*N*-1,5-(4-Acetyl-4-azapentamethylenediyl)-*N*′-*n*-pentylurea (acetyl-1ac):** 66%; colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J = 7.0 Hz, 3H), 1.22−1.45 (m, 4H), 1.45−1.61 (m, 2H), 2.11 (s, 3H), 3.21 (q, J = 5.6 Hz, 2H), 3.33 (t, J = 5.5 Hz, 2H), 3.40 (s, 4H), 3.62 (t, J = 5.5 Hz, 2H), 4.80−4.92 (br s, 1H); IR (neat) 3357, 1653 cm^{-1}; HRMS calcd for $C_{12}H_{23}N_3O_2$ 241.1790, found 241.1774. Anal. Calcd for $C_{12}H_{23}N_3O_2$: C, 59.72; H, 9.61; N, 17.41. Found: C, 59.35; H, 9.45; N, 17.25.

***N*,*N*-1,5-(3-Oxapentamethylenediyl)-*N*′-*n*-pentylurea (1ad):** 80%; colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.90 (t, J = 6.8 Hz, 3H), 1.22−1.43 (m, 4H), 1.43−1.60 (m, 2H), 3.23 (q, J = 6.5 Hz, 2H), 3.33 (t, J = 4.8 Hz, 4H), 3.69 (t, J = 4.8 Hz, 4H), 4.35−4.61 (br s, 1H); IR (neat) 3335, 1664 cm^{-1}. Anal. Calcd for $C_{10}H_{20}N_2O_2$: C, 59.97; H, 10.06; N, 13.99. Found: C, 59.66; H, 9.92; N, 13.86.

***N*-Allyl-*N*′-*n*-pentylurea (1ae):** 42%; mp 31−32 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.89 (t, J = 6.6 Hz, 3H), 1.19−1.39 (m, 4H), 1.39−1.58 (m, 2H), 3.15 (q, J = 6.8 Hz, 2H), 3.74−3.86 (m, 2H), 4.66−4.98 (br s, 2H), 5.05−5.28 (m, 2H), 5.75−5.98 (m, 1H); IR (neat) 3339, 1593 cm^{-1}; HRMS calcd for $C_9H_{18}N_2O$ 170.1419, found 170.1400. Anal. Calcd for $C_9H_{18}N_2O$: C, 63.49; H, 10.66; N, 16.45. Found: C, 63.16; H, 10.38; N, 16.06.

***N*-*n*-Pentyl-*N*′-(*S*)-α-phenetylurea (1af):** 27%; mp 45−47 °C; $[\alpha]^{19}_D$ −14.7 (c 0.97, MeOH), (uncorrected); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85 (t, J = 5.8 Hz, 3H), 1.05−1.53 (m, 6H), 1.42 (d, J = 6.6 Hz, 3H), 2.94−3.22 (m, 2H), 4.43−4.72 (br s, 1H), 4.69−4.84 (m, 1H), 4.85−5.10 (br s, 1H); IR (neat) 3335, 1633 cm^{-1}; HRMS calcd for $C_{14}H_{22}N_2O$ 234.1732, found 234.1714. Anal. Calcd for $C_{14}H_{22}N_2O$: C, 71.76; H, 9.46; N, 11.95. Found: C, 71.52; H, 9.49; N, 11.66.

***N*-Benzyl-*N*′,*N*′-*1*,5-pentamethylenediylurea (1bb):**[11] 93%; mp 98−99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49−1.65 (m, 6H), 3.24−3.40 (m, 4H), 4.43 (d, J = 5.4 Hz, 3H), 4.65−4.83 (br s, 1H), 7.24−7.39 (m, 5H); IR (neat) 3334, 1624 cm^{-1}; HRMS calcd for $C_{13}H_{18}N_2O$ 218.1419, found 218.1418.

***N*-Cyclohexyl-*N*′,*N*′-1,5-pentamethylenediylurea (1cb):** 91%; mp 140−141 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.97−1.44 (m, 6H), 1.44−1.85 (m, 8H), 1.85−2.02 (m, 2H), 3.22−3.37 (m, 4H), 3.54−3.75 (m, 1H), 4.27 (br d, J = 7.2 Hz, 1H); IR (neat) 3332, 1615 cm^{-1}; HRMS calcd for $C_{12}H_{22}N_2O$ 210.1732, found 210.1741. Anal. Calcd for $C_{12}H_{22}N_2O$: C, 68.53; H, 10.54; N, 13.32. Found: C, 68.42; H, 10.32; N, 13.19.

***N*,*N*-1,5-Pentamethylenediyl-*N*′-phenylurea (1db):**[11] 97%; mp 160−161 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52−1.75 (m, 6H), 3.36−3.53 (m, 4H), 6.33−6.48 (br s, 1H), 6.97−7.04 (m, 1H), 7.22−7.32 (m, 2H), 7.32−7.43 (m, 2H); IR (neat) 3324, 1650 cm^{-1}; HRMS calcd for $C_{12}H_{16}N_2O$ 204.1262, found 204.1272.

***N*-2-Benzyloxycarbonylaminoethyl-*N*′,*N*′-1,5-pentamethylenediylurea (1eb):** 64%; mp 106−108 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.42−1.62 (m, 6H), 3.23−3.40 (m, 8H), 5.08 (s, 2H), 5.19 (br s, 1H), 5.60 (br s, 1H), 7.30−7.42 (m, 5H); IR (neat) 3320, 1718, 1638 cm^{-1}. Anal. Calcd for $C_{16}H_{23}N_3O_3$: C, 62.93; H, 7.59; N, 13.76. Found: C, 62.68; H, 7.57; N, 13.65.

***N*-2-Boc-aminoethyl-*N*′,*N*′-1,5-pentamethylenediylurea (1fb):** 61%; mp 132−133 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.46−1.66 (m, 6H), 3.20−3.40 (m, 8H), 5.03 (br s, 1H), 5.25 (br s, 1H); IR (neat) 3359, 1694, 1622 cm^{-1}. Anal. Calcd for $C_{13}H_{25}N_3O_3$: C, 57.54; H, 9.29; N, 15.49. Found: C, 57.38; H, 9.02; N, 15.25.

Comparison of Reactivity of Carbamates (2a−3a, 4a, 7a, 8a). Typical Procedure. Into a dry, 50 mL flask equipped with a nitrogen inlet adapter, a rubber septum, and a magnetic stirring bar were placed **4a** (0.5 mmol), **2a** (0.5 mmol), and piperidine (0.5 mmol) in THF. Sodium hydride in oil (0.5 mmol) was added to the mixture at 0 °C. The resulting solution was stirred at room temperature for 5 h, and then aqueous NH_4Cl was added to the mixture. After the removal of the solvent, the residue was extracted with ethyl acetate. The extract was dried on $MgSO_4$, and the solvent was evaporated in vacuo to give a mixture of **4a**, **2a**, and **1ab**. The yields were determined by integral intensity of ^{1}H NMR spectra.

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