A Practical Synthesis of Ureas from Phenyl Carbamates

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Using DMSO as solvent, a mild and efficient procedure for the synthesis of unsymmetrical *N,N'*-disubstituted ureas from phenyl carbamates is described. The carbamates are treated with a stoichiometric amount of amine at ambient temperature, generating the ureas in high yield and high purity. The reaction is mild, fast, and easily scaled up.

N,N'-Unsymmetrically substituted ureas have found use in a wide variety of areas including applications in medicinal chemistry.[1] The preparation of ureas from amines is well documented[2] and it is based on the use of phosgene,[3] phosgene substitutes,[4] carbonic acid derivatives,[5,6] and isocyanates.[7] Recently, novel methods for the preparation of ureas have been described. These involve the reaction of unsymmetrical diaryl carbonates[8] or *S,S*-dimethyl dithiocarbonates with amines[9] and the treatment of ethyl carbamates with magnesium amides.[10] Others involve formation of isocyanates from *tert*-butyl carbamates using DMAP[11] or a stronger base for deprotonation.[12] Processes involving the aminolysis of alkyl carbamates have been described[13] and very often require high temperature reaction conditions.[14] Formation of ureas from phenyl carbamates is also cited in the literature,[15] but procedures often call for harsh conditions, long reaction times, and occasionally a large excess of amine.[16] Consequently, an improved general method was sought. In this communication, we wish to report optimized conditions for the synthesis of ureas via the aminolysis of phenyl carbamates under neutral and mild conditions using DMSO[17] as solvent.

Phenyl carbamates were prepared according to a known procedure[18] and obtained as stable, often crystalline, products. We found that reacting phenyl carbamates with amines (1.05 equiv), in DMSO at ambient temperature, rapidly generated urea derivatives in high yield. The only byproduct was phenol which was easily removed by a 1 M NaOH wash. Several representative examples are shown in Table 1 which include chiral, nonracemic substrates. The compatibility of a number of functional groups with the present reaction conditions was examined (Table 1). For example, the product from the reaction of prolinol with carbamate **1a** was isolated in 87% yield after only 15 minutes (entry **a**). The chiral and pharmaceutically important amine[19] (entry **d**) also gave the urea **2d** at room temperature in an excellent yield. No alcoholysis product was observed in either case. The scope of the reaction was also extended to cover amines in aqueous solution such as NH_4OH (1.1 equiv) and urea **2f** was isolated in 74% yield (entry **f**). The method was also successfully applied to secondary amines and generated the *N,N,N'*-trisubstituted ureas in high yield at ambient temperature (entries **a**, **b**, **d**, and **j**). When the HCl salt of an amine was used, it was neutralized in situ with an equimolar amount of 10 M aqueous NaOH (entry **b**). No hydrolysis product of the methyl ester of phenyl carbamate was detected in this case. Aromatic amines such as aniline (entry **c**) also reacted to form the corresponding ureas, although this reaction required heating to 85 °C for 1 hour. In accordance with the findings of Lamothe,[12,20] the reaction times were usually longer in the case of aliphatic carbamates compared to carbamates derived from aniline (60 minutes instead of 15 minutes; entries **e**, **f**, **g**, **i**). In contrast to the alternative approaches using strong base for carbamate deprotonation,[12] compounds **2e**, **2f**, and **2g** were conveniently prepared under mild and neutral conditions, in high yield, and were found to be enantiomerically pure (> 99% ee).[21] Moreover, this method is not limited to the use of sterically nonhindered amines. In fact, the use of hindered primary or secondary amines did not affect the rate of conversion and gave products **2d** and **2h** in 89 and 95% yield, respectively (entries **d**, **h**). To further explore the utility of this method, the symmetrical urea **2k** was prepared at ambient temperature in 93% yield. This result stands with that reported by Freer et al.[8] where the reaction conditions used for the same reaction required heating for several hours at 80 °C. All attempts to convert the carbamate of secondary amine **1l** into the corresponding urea failed even when heated at 190 °C for 3 hours.

We also investigated the application of this method in the context of combinatorial or parallel synthesis, a subject that has recently received considerable attention.[22] Particularly interesting was the example involving the concomitant use of a primary (4-fluorobenzylamine) and a secondary (dibutylamine) amine (0.51 equiv of each amine) with one equivalent of carbamate (Scheme 1). The conversion was completed after 15 minutes and a 1:1 mixture of ureas **2m** and **2n** was isolated in 93% combined yield. Thus, this result demonstrated the potential of the method for the introduction of chemical diversity.[23] We then examined the difference in reactivity between a primary and secondary amine[24] (1 equiv of each) with 1 equivalent of carbamate **1d** under the same experimental conditions. Ureas were obtained in high combined yield (90%) and in a 3.7:1 mixture favoring the secondary amine. The greater reactivity of the latter can be rationalized by the fact that secondary amines are more nucleophilic than primary ones.[20]

We found that the rate and the yield of the reaction were highly dependent on the solvent used. The use of DMSO is critical to the mildness of the conditions as exemplified in the preparation of urea **2o** (Scheme 2, Table 2). Compared to DMSO, the reaction was much slower in MeOH, dioxane,[25] DME,[26] or CH_2Cl_2 in which the carbamate **1d** was insoluble at the beginning of the reaction. With THF as solvent, refluxing for 5 hours was required to complete the reaction. DMF[27] provided a reaction rate

Table 1. Preparation of Ureas from Phenyl Carbamates

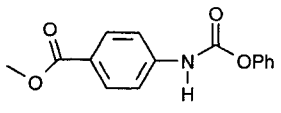
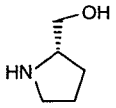
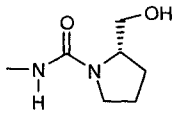
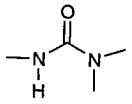
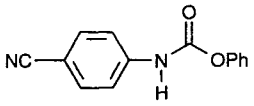
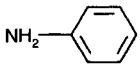
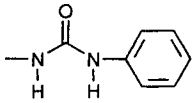
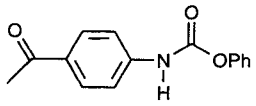
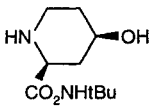
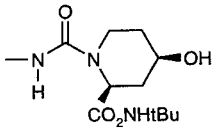
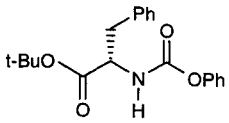
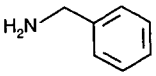
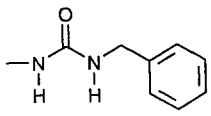
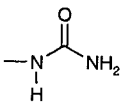
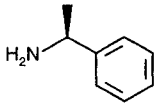
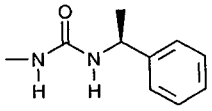
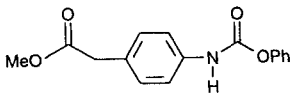
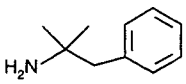
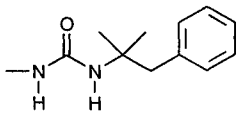
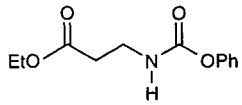
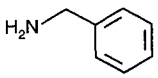
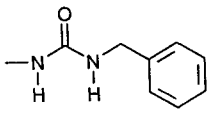
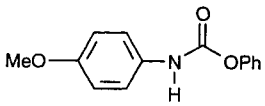
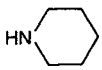
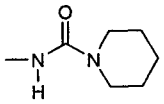
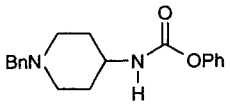
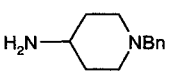
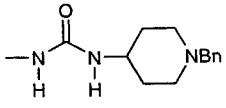
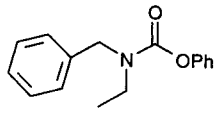
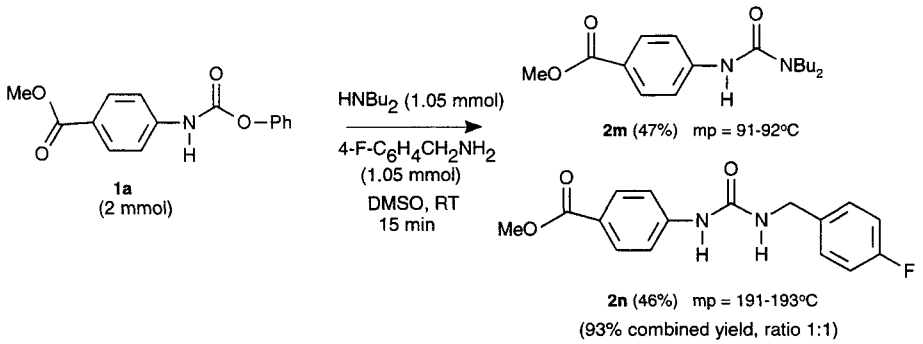
	Carbamates **1**	Amine[a]	Time[b]	Ureas **2**	Yield[c]	mp (°C)
a			15 min		87%	140–142
b		$HCl \cdot HNMe_2$[d]	30 min		80%	168–170
c			85°C, 1 h		87%	208–210
d			1.5 h		89%[f]	161–163
e			1 h		84%[f]	70–72
f		NH_4OH[e]	1 h		74%[f]	135–137
g			2.5 h		92%[f]	107–109
h			15 min		95%	105–107
i			1 h		80%	85–87
j			15 min		78%	126–128
k			3 h		93%	169–171

Table 1. (continued)

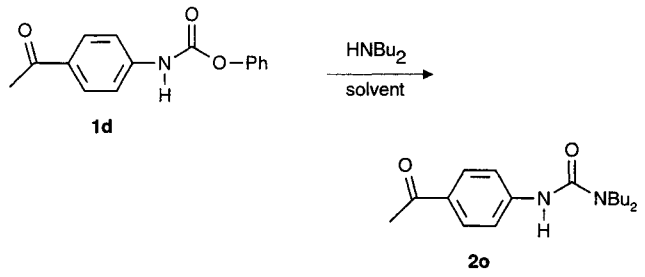
	Carbamates **1**	Amine[a]	Time[b]	Ureas **2**	Yield[c]	mp (°C)
l		$HNBn_2$	190°C, 3 h	no reaction	–	–

[a] Unless otherwise noted 1.05 equiv of amine were used.
[b] DMSO at r. t. (concentration 0.5 M) unless otherwise noted and the time values represent an upper limit.
[c] Yield of isolated pure product.
[d] 1.05 equiv of aq 10 M NaOH were used.
[e] 1.1 equiv of NH_4OH were used.
[f] See ref 30 for $[\alpha]_D$ values.



Scheme 1

similar to that of DMSO, but a lower yield of product was obtained (74 vs. 96%).



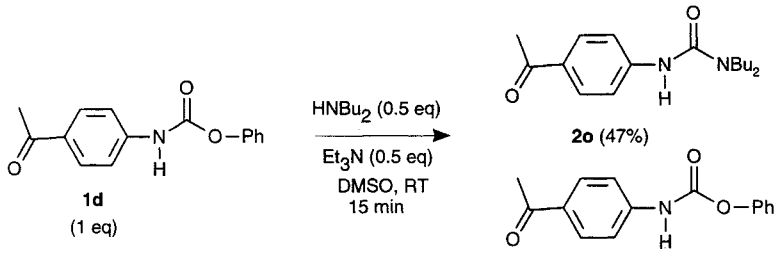
Scheme 2

Unlike isocyanates,[28] phenyl carbamates were stable in DMSO at ambient temperature. The mechanism of urea formation from phenyl carbamates has been controversial.[22,29] In an attempt to shed light on this question, carbamate **1d** was treated with half an equivalent of dibutylamine and half an equivalent of triethylamine for 15 minutes in DMSO (Scheme 3). The products isolated were the urea **2o** (47% based on carbamate) and the starting carbamate **1d** (45% recovered). The absence of isocyanate or its hydrolysis product under the conditions that generated the urea indicated that the aminolysis probably did not proceed via an E_2 mechanism. A more plausible mechanism was the direct displacement of phenoxide ion by the amine via a tetrahedral intermediate.

Table 2. Solvent Effect in Reaction of Carbamate **1d** with Dibutylamine[a]

Solvent	DMSO	DMF	THF	MeCN	Dioxane	DME	CH_2Cl_2	MeOH	Pyr
Condition	rt	rt	reflux	rt	reflux	rt	rt	rt	rt
Time[b]	15 min	15 min	5 h	1 h	5 h	24 h	24 h	24 h	2.5 h
Yield (%)[c]	96	74	92	79	65	92 (3)	90 (9)	74	85 (2)

[a] 1.05 equiv of amine were used.
[b] The time values represent an upper limit.
[c] Refers to pure isolated products (values in parentheses indicate recovered starting material).



Scheme 3

In conclusion, we have described a mild and efficient synthesis of urea derivatives under neutral conditions from primary phenyl carbamates and a stoichiometric amount of amines in DMSO at ambient temperature. The scope of the method has been assessed using a variety of aromatic and aliphatic amines including amino acid derivatives. The procedure described herein represents an improvement to existing methods and should find general applications.

Melting points were determined on a Büchi 510 apparatus and are uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker AMX 400 spectrometer using DMSO-d_6 solvent referenced at 2.50 and 39.51 ppm, respectively. Elemental

Table 3. Spectroscopic Data for Ureas **2**

Compound[a]	^{1}H NMR (DMSO-d_6) δ, J(Hz)	^{13}C NMR (DMSO-d_6) δ	MS FAB m/z (%)
2a	8.96 (br s, 1H), 7.85 (d, 2H, J = 8.7), 7.60 (d, 2H, J = 8.7), 5.34 (br s, 1H), 3.96 (br s, 1H), 3.80 (s, 3H), 3.47–3.39 (m, 4H), 1.93–1.77 (m, 4H)	166.0, 154.1, 145.3, 130.0, 122.0, 117.9, 63.5, 58.9, 51.6, 46.6, 27.7, 23.2	279 (100, MH$^+$),
2b	8.65 (s, 1H), 7.84 (d, 2H, J = 8.6), 7.63 (d, 2H, J = 8.6), 3.80 (s, 3H), 2.94 (s, 6H)	166.8, 156.0, 146.4, 130.7, 122.9, 119.2, 52.5, 37.1	223 (100, MH$^+$),
2c	9.17 (s, 1H), 8.83 (s, 1H), 7.74 (d, 2H, J = 8.7), 7.64 (d, 2H, J = 8.9), 7.46 (d, 2H, J = 8.9), 7.30 (t, 2H, J = 7.5), 7.00 (t, 1H, J = 7.5)	152.9, 145.0, 140.0, 134.1, 129.7, 123.2, 120.1, 119.4, 118.8, 104.1	238 (100, MH$^+$),
2d	8.98 (s, 1H), 7.87 (d, 2H, J = 8.9), 7.61 (d, 2H, J = 8.9), 7.31 (s, 1H), 4.83 (d, 1H, J = 4.4), 4.53 (quint., 1H, J = 6.4), 3.86 (m, 1H), 3.74 (m, 1H), 3.51 (dt, 1H, J = 13.0, 3.4), 2.50 (s, 3H), 2.05–1.98 (m, 1H), 1.86–1.80 (m, 1H), 1.71–1.53 (m, 2H), 1.25 (s, 9H)	197.1, 172.2, 156.3, 146.2, 131.1, 130.0, 119.0, 62.9, 53.8, 51.0, 38.5, 34.4, 33.0, 29.3, 27.1	362 (35, MH$^+$), 201 (50)
2e	7.30–7.18 (m, 10H), 6.54 (t, 1H, J = 6.0), 6.19 (d, 1H, J = 8.3), 4.35 (q, 1H, J = 7.2), 4.19 (d, 2H, J = 6.0), 2.91 (m, 2H), 1.33 (s, 9H)	171.6, 157.4, 140.6, 137.2, 129.3, 128.2, 128.1, 126.9, 126.5, 126.4, 80.5, 54.5, 42.8, 38.0, 27.6	355 (10, MH$^+$), 299 (60)
2f	7.31–7.14 (m, 5H), 6.18 (d, 1H, J = 8.4), 5.60 (s, 2H), 4.29 (q, 1H, J = 8), 2.90 (dd, 1H, J_{AB} = 11.7, J_{AX} = 6.6), 2.86 (dd, 1H, J_{AB} = 11.7, J_{BX} = 7.9), 1.30 (s, 9H)	171.7, 157.9, 137.2, 129.3, 128.1, 126.4, 80.4, 54.2, 38.0, 27.6	265 (20, MH$^+$), 209 (100)
2g	7.32–7.13 (m, 10H), 6.59 (d, 1H, J = 8.3), 6.03 (d, 1H, J = 8.3), 4.70 (quint., 1H, J = 7.0), 4.29 (q, 1H, J = 6.6), 2.90 (dd, 1H, J_{AB} = 11.6, J_{AX} = 6.6), 2.86 (dd, 1H, J_{AB} = 11.6, J_{BX} = 7.0), 1.33 (s, 9H), 1.30 (d, 3H, J = 7.0)	169.9, 155.0, 144.0, 135.5, 127.8, 126.6, 126.5, 124.9, 124.1, 79.0, 52.7, 47.0, 36.4, 26.0, 21.7	369 (10, MH$^+$), 313 (25), 180 (75), 120 (100)
2h	8.22 (s, 1H), 7.33–7.12 (m, 9H), 5.73 (s, 1H), 3.60 (s, 3H), 3.57 (s, 2H), 3.00 (s, 2H), 1.22 (s, 6H)	172.7, 155.3, 140.2, 139.3, 131.1, 130.4, 128.6, 127.4, 126.7, 118.3, 53.1, 52.4, 45.1, 28.3	341 (100, MH$^+$)
2i	7.32–7.19 (m, 5H), 6.41 (t, 1H, J = 6), 6.00 (t, 1H, J = 6.6), 4.19 (d, 2H, J = 6), 4.06 (q, 2H, J = 7.2), 3.25 (q, 2H, J = 6.3), 2.42 (t, 2H, J = 6.6), 1.18 (t, 3H, J = 7.2)	171.7, 157.9, 140.8, 128.1, 127.0, 126.5, 59.8, 42.9, 35.4, 34.9, 14.1	251 (100, MH$^+$)
2j	8.22 (s, 1H), 7.32 (d, 2H, J = 8.9), 6.80 (d, 2H, J = 8.9), 3.69 (s, 3H), 3.39–3.35 (m, 4H), 1.56–1.52 (m, 2H), 1.49–1.45 (m, 4H)	156.0, 155.1, 134.6, 122.3, 114.3, 55.9, 45.4, 26.3, 25.0	235 (100, MH$^+$)
2k	7.32–7.21 (m, 10H), 5.66 (d, 2H, J = 8.0), 3.42 (s, 4H), 3.38–3.30 (m, 2H), 2.67 (bd, 4H, J = 10.8), 2.00 (t, 4H, J = 10.8), 1.71 (bd, 4H, J = 10), 1.28 (q, 4H, J = 10.5)	157.4, 139.3, 129.4, 128.8, 127.5, 62.9, 52.6, 46.8, 33.2	407 (100, MH$^+$)

[a] Satisfactory microanalyses obtained: C ± 0.38, H ± 0.15, N ± 0.15.

analyses (C,H,N) were carried out using a Fisons Instruments EA 1108 CHN elemental analyzer. MS and HRMS were recorded on a Micromass Autospec. Specific optical rotations were measured in MeOH using the Na lamp (589 nm) of a Perkin Elmer 241 polarimeter. HPLC analyses were performed on a Vydac C-18 column using $MeCN/H_2O$ gradients with 0.06% TFA. All solvents used were anhydrous grade. Phenyl chloroformate and the various amines were from commercial sources and used as received. The phenyl carbamates used were analytically pure based on HPLC, elemental analysis and/or high resolution mass spectroscopy. The yields reported in this work were of isolated, purified products.

Typical Procedure for Carbamate Formation; Phenyl *N*-(4-Acetylphenyl)carbamate (1d):
A dry, 500-mL flask equipped with an N_2 inlet adapter, a rubber septum, and a magnetic stirring bar, was charged with 4-aminoacetophenone (13.5 g, 100 mmol) in anhyd THF (200 mL) and cooled to 0 °C. Pyridine (10.1 mL, 125 mmol) and phenyl chloroformate (12.9 mL, 103 mmol) were added to the mixture. The resulting suspension was stirred at 0 °C for 5 min and allowed to warm to r.t. for 1 h. EtOAc (600 mL) was added and the suspension was washed successively with 1 M HCl (100 mL), H_2O (100 mL), sat. aq $NaHCO_3$ (200 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give the crude product, which was triturated with Et_2O/hexane (hot) and furnished **1d** as an ivory solid; yield: 23.9 g (94%); mp 167–169 °C.

^{1}H NMR (DMSO-d_6): δ = 10.62 (s, 1H), 7.94 (d, 2H, J = 9.0 Hz), 7.65 (d, 2H, J = 9.0 Hz), 7.46–7.43 (m, 2H), 7.30–7.24 (m, 3H), 2.53 (s, 3H).

^{13}C NMR (DMSO-d_6): δ = 196.5, 151.6, 150.3, 143.2, 131.5, 129.6, 129.5, 125.6, 121.9, 117.6, 26.4.

MS FAB: m/z (%) = 256 (100) $[MH]^+$.

HRMS: m/z Calcd for $C_{15}H_{14}NO_3$ 256.0973; found 256.0965.

Typical Procedure for Urea Formation; *N*-(4-Acetylphenyl)-*N'*,*N'*-dibutylurea (2o):
To a dry, 100-mL flask equipped with an N_2 inlet adapter, a rubber septum, and a magnetic stirring bar, was placed phenyl *N*-(4-acetylphenyl)carbamate (**1d**; 6.38 g, 25 mmol) in DMSO (50 mL). Dibutylamine (4.42 mL, 26.25 mmol) was slowly added to the mixture. The resulting solution was stirred at r.t. for 15 min, after which time EtOAc (250 mL) was added to the mixture. The latter was washed successively with H_2O (2 × 50 mL), 1 M HCl (100 mL), H_2O (100 mL), 1 M NaOH (100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a crude solid, which was triturated with Et_2O/hexane and furnished **2o** as a white solid; yield: 6.98 g (96%); mp 90–92 °C.

^{1}H NMR (DMSO-d_6): δ = 8.50 (s, 1H), 7.84 (d, 2H, J = 8.7 Hz), 7.62 (d, 2H, J = 8.7 Hz), 3.32–3.29 (m, 4H), 2.49 (s, 3H), 1.48–1.44 (m, 4H), 1.30–1.27 (m, 4H), 0.89 (t, 6H, J = 7.5 Hz).

^{13}C NMR (DMSO-d_6): δ = 196.2, 154.3, 145.6, 130.1, 129.0, 118.3, 46.1, 30.2, 26.2, 19.5, 13.8.

MS FAB: m/z (%) = 291 (100) $[MH]^+$.

***N*,*N*-Dibutyl-*N'*-[4-(methoxycarbonyl)phenyl]urea (2m) and *N*-[(4-fluorophenyl)methyl]-*N'*-[4-(methoxycarbonyl)phenyl]urea (2n):**
A dry, 25-mL flask equipped with an N_2 inlet adapter, a rubber septum, and a magnetic stirring bar, was charged with carbamate **1a** (542.5 mg, 2 mmol) in DMSO (3.5 mL). To the mixture was added a combination of dibutylamine (178 µL, 1.05 mmol) and 4-fluorobenzylamine (120 µL, 1.05 mmol) in DMSO (0.5 mL). The resulting solution was stirred at r.t. for 15 min, after which time EtOAc (60 mL) was added to the mixture. The organic layer was washed successively with H_2O (2 × 25 mL), 1 M HCl (2 × 25 mL), 1 M NaOH (2 × 25 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a white solid, which was purified by flash chromatography (1:30; *i*-PrOH/CH_2Cl_2) and yielded **2m** (288 mg, 47%) as a white solid and **2n** (278 mg, 46%) as a white solid.

Urea 2m: (R_f = 0.24; 1:30; *i*-PrOH/CH_2Cl_2); mp 91–92 °C.

^{1}H NMR (DMSO-d_6): δ = 8.49 (s, 1H), 7.83 (d, 2H, J = 8.9 Hz), 7.63 (d, 2H, J = 8.9 Hz), 3.80 (s, 3H), 3.32 (t, 4H, J = 7.6 Hz), 1.52–1.44 (m, 4H), 1.32–1.23 (m, 4H), 0.89 (t, 6H, J = 7.6 Hz).

^{13}C NMR (DMSO-d_6): δ = 165.9, 154.3, 145.3, 129.7, 121.9, 118.4, 51.6, 46.0, 30.1, 19.4, 13.7.

MS FAB: m/z (%) = 307 (100) $[MH]^+$.

Urea 2n: (R_f = 0.14; 1:30; *i*-PrOH/CH_2Cl_2); mp 191–193 °C.

^{1}H NMR (DMSO-d_6): δ = 9.0 (s, 1H), 7.84 (d, 2H, J = 8.9 Hz), 7.54 (d, 2H, J = 8.9 Hz), 7.36–7.32 (m, 2H), 7.17–7.13 (m, 2H), 6.78 (t, 1H, J = 5.7 Hz), 4.28 (d, 2H, J = 5.7 Hz), 3.31 (s, 3H).

^{13}C NMR (DMSO-d_6): δ = 165.9, 162.3, 159.9, 154.7, 145.0, 136.2, 130.2, 129.1, 129.0, 121.7, 116.7, 115.0, 114.8, 51.6, 42.0.

MS FAB: m/z (%) = 303 (100) $[MH]^+$.

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(1) Matsuda, K. *Med. Res. Rev.* **1994**, *14*, 271.
(2) Sandler, S.R.; Karo, W. In *Organic Functional Group Preparations*; Academic: New York, 1971; Vol. II, pp 152–191.
(3) Shriner, R.L.; Horne, W.H.; Cox, R.F. *Org. Synth.* **1943**, *2*, 453.
Nowick, J.S.; Powell, N.A.; Nguyen, T.M.; Noronha, G. *J. Org. Chem.* **1992**, *57*, 7364.
(4) Kurita, K.; Matsumura, T.; Iwakura, Y. *J. Org. Chem.* **1976**, *41*, 2070.
Kurita, K.; Iwakura, Y. *In Org. Synth. Coll. VI*; Wiley: New, York, 1988; p 715.
Eckert, H.; Forster, B. *Angew. Chem.* **1987**, *99*, 992; *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 894.
Randad, R.S.; Majer, P. *J. Org. Chem.* **1994**, *59*, 1937.
Cotarca, L.; Delogu, P.; Nardelli, A.; Šunjic, V. *Synthesis* **1996**, 553.
(5) Gante, J. *Chem. Ber.* **1965**, *98*, 3334.
Izdebski, J.; Pawlak, D. *Synthesis* **1989**, 423.
Lipkowski, A.W.; Tam, S.W.; Portoghese, P.S. *J. Med. Chem.* **1986**, 29, 1222.
Adamiak, R.W.; Stawinski, J. *Tetrahedron Lett.* **1977**, *18*, 1935.
(6) Staab, H.A. *Liebigs Ann. Chem.* **1957**, *609*, 75.
Wang, X.C.; Kempf, D.J. *202nd ACS National Meeting* New York, 25–30 August, 1991 (Abstract 106).
(7) Ozaki, S. *Chem. Rev.* **1972**, *72*, 457.
(8) Freer, R.; McKillop, A. *Synth. Commun.* **1996**, *26*, 331.
(9) Leung, M.-K.; Lai, J.-J.; Lau, K.-H.; Yu, H.-H.; Hsiao, H.-J. *J. Org. Chem.* **1996**, *61*, 4175.
(10) Basha, A. *Tetrahedron Lett.* **1988**, *29*, 2525.
(11) Knölker, H.-J.; Braxmeier, T.; Schlechtingen, G. *Synlett* **1996**, 502.
Knölker, H.-J.; Braxmeier, T.; Schlectingen, G. *Angew. Chem.* **1995**, *107*, 2746; *Angew. Chem., Int. Ed. Engl.* **1995**, 34, 2497.
(12) Lamothe, M.; Perez, M.; Colovray-Gotteland, V.; Halazy, S. *Synlett* **1996**, 507.
(13) Henson, T.R.; Timberlake, J.F., U.S. Patent 4294774; *Chem. Abstr.* **1982**, *96*, 7220n.
Hassan, A.A.; Mourad, A.E. *Indian J. Chem.* **1992**, *31B*, 277.
(14) Crosby, D.G.; Nieemann, C. *J. Am. Chem. Soc.* **1954**, *76*, 4458.
Forbes, I.T.; Jones, G.E.; Murphy, O.E.; Holland, V.; Baxter, G.S. *J. Med. Chem.* **1995**, *38*, 855.
Carceller, E.; Merlos, M.; Giral, M.; Almmansa, C.; Bertolli, J.; Garcia-Rafanel, J.; Forn, J. *J. Med. Chem.* **1993**, *36*, 2984.
(15) Kimura, T.; Watanabe, N.; Matsui, M.; Hayashi, K.; Tanaka, H.; Ohtsuka, I.; Saeki, T.; Kogushi, M.; Kabayashi, H.; Akasaka, K.; Yamagishi, Y.; Saitou, I.; Yamatsu, I. *J. Med. Chem.* **1993**, *36*, 1641.
Lampe, J.W.; Hana, R.G.; Piscitelli, T.A.; Chou, Y-L.; Erhart,

P.W.; Lumma, W.C., Jr.; Greenberg, S.G.; Ingebretsen, W.R.; Marshall, D.C.; Wiggins, J. *J. Med. Chem.* **1990**, *33*, 1688.
(16) Glamkowski, J.E.; Chiang, Y. *J. Heterocycl. Chem.* **1987**, *24*, 733.
(17) For a review on DMSO see: Martin, D.; Weise, A.; Niclas, H.-J. *Angew. Chem.* **1967**, *79*, 340; *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 318.
(18) Corey, E.J.; Suggs, W. *J. Org. Chem.* **1973**, *38*, 3223.
(19) Gillard, J.; Abraham, A.; Anderson, P.C.; Beaulieu, P.L.; Bogri, T.; Bousquet, Y.; Grenier, L.; Guse, I.; Lavallée, P. *J. Org. Chem.* **1996**, *61*, 2226.
(20) Menger, F.M.; Glass, L.E. *J. Org. Chem.* **1974**, *39*, 2459.
(21) The enantiomeric excess (%ee) of urea **2e** was found to be >99% (chiral column) by comparison with its racemate which was prepared from the racemic carbamate. The de of **2g** (>99%) was confirmed by ^{1}H NMR and HPLC analysis using two solvent systems:
– Vydac (Protein & Peptide C18); reverse phase with TFA (0.06%) in MeCN, 230 nm, 1.5 mL/min.
– Waters (Milford, MA, Symmetry C8); reverse phase with NaH_2PO_4 (50 mM) in MeCN, 215 nm, 1 mL/min.
– Chiral Pak AS (DAICEL 4.6×250 mm); 10% EtOH/hexane, 205 nm, 0.5 mL/min.
(22) For example, see: Ellman, A.J. *Acc. Chem. Res.* **1996**, *29*, 132.
(23) When two primary amines (butylamine and isoamylamine) and two secondary amines (dibutylamine and diisoamylamine) were used, a similar reactivity effect was observed. The combined yield (94 and 90%) and a ratio of 1:1 mixture were obtained respectively.
(24) Dibutylamine and butylamine were used under the same conditions.
(25) Shawali, A.S.; Hrhash, A.; Sidky, M.M.; Hassaneen, H.M.; Elkaadi, S.S. *J. Org. Chem.* **1986**, *51*, 3498.
(26) Gregory, W.A.; Brittelli, D.R.; Wang, C.-L.J.; Wuonola, M.A.; McRipley, R.J.; Eustice, D.C.; Eberly, V.S.; Bartholenew, P.T.; Slee, A.M.; Forbes, M. *J. Med. Chem.* **1989**, *32*, 1673.
(27) Jones, G.H.; Venuti, M.C.; Alvarez, R.; Bruno, J.J.; Berks, A.H.; Prince, A. *J. Med. Chem.* **1987**, *30*, 295.
(28) Carleton, P.S.; Farrissey, W.J., Jr. *Tetrahedron Lett.* **1969**, *10*, 3485.
(29) Hegarty, A.F.; Frost, L.N. *J. Chem. Soc., Chem. Commun.* **1972**, 500.
Bender, M.L.; Homer, R.B. *J. Org. Chem.* **1965**, 30, 3975.
(30) Optical rotations for ureas: **2a**: $[\alpha]_D^{24}$ −97.7° (*c* = 2.12, MeOH); **2d**: $[\alpha]_D^{24}$ −153.6° (*c* = 1.01, MeOH); **2e**: $[\alpha]_D^{22}$ +16.5° (*c* = 1.1, MeOH); **2f**: $[\alpha]_D^{22}$ +20.4° (*c* = 1.1, MeOH); **2g**: $[\alpha]_D^{24}$ +5.9° (*c* = 0.66, MeOH).