Regular Article

Spontaneous and Direct Transformation of *N,O*-Diaryl Carbamates into *N,N′*-Diarylureas

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We have discovered a spontaneous reaction of *N,O*-diaryl carbamates to afford symmetrical *N,N′*-diarylureas. Optimization of the conditions indicated that *N,N*-dimethylformamide (DMF) was the best solvent and triethylamine (Et₃N) was the best additive for this transformation. The reaction requires the presence of aryl groups on the nitrogen and oxygen atoms of carbamates. Substrates bearing an electron-donating methoxy group on either of the aryl groups reacted slowly under these conditions.

Key words   carbamate; *N,N′*-diphenylurea; triethylamine (Et₃N); isocyanate

The *N,N′*-diphenylurea skeleton is found in many biologically active compounds, including cytokinin,[1] antischistosomal agent,[2] diacylglycerol acyltransferase (DGAT)1 inhibitor,[3] vascular endothelial growth factor receptor (VEGFR)-2 inhibitor,[4] BKca channel activator,[5] and p-38-mitogen-activated protein (MAP) kinase inhibitor.[6] In addition, *N,N′*-diphenyl-substituted urea derivatives are useful components for gel-forming materials[7] and crystal engineering.[8]
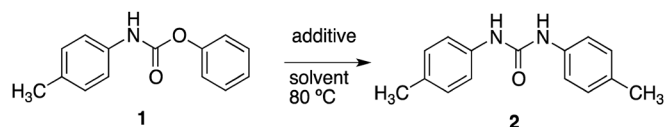
N,N′-Diphenylurea derivatives are typically synthesized by reaction of amine with aryl isocyanates or phosgene,[9] or with carbamates.[10–14] Indeed, unsymmetrically substituted ureas can be prepared from carbamate by direct reaction with amine.[13–15] Analogously with the reaction of carbamates, *N*-arylcarbamates decompose to afford phenyl isocyanate in the presence of triethylamine (Et₃N) *via* the E1cB mechanism[10] (Fig. 1a). In addition, phenyl isocyanate affords *N,N′*-diphenylurea even in the absence of amine[16–18] (Fig. 1b). However, carbamates have been known as a "blocked isocyanate,"[19] there are few examples of the synthesis of urea compounds *via* carbamate with a single-pot operation (Fig. 1c); a precedent required high temperature (200°C) and did not report isolated yield of urea.[20] Such reactions would be useful, considering the difficulty of handling highly reactive aryl isocyanates. Here, we report a spontaneous, single-step formation of symmetrical *N,N′*-diarylurea compounds from *N,O*-diaryl carbamates.

Results and Discussion

To examine the direct transformation of *N,O*-diaryl carbamate to symmetrical *N,N′*-diarylurea, we chose *N*-(4-methylphenyl)-*O*-phenyl carbamate (**1**) as a model substrate (Table 1). We were pleased to find that **1** afforded *N,N′*-bis(4-methylphenyl)urea (**2**) in 91% yield in the presence of 1 equiv of Et₃N in *N,N*-dimethylformamide (DMF) (Table 1, entry 1) in open-air environment.[21] When the reaction was performed at 50°C, the yield of **2** was decreased (Table 1 entry 2). Other less polar solvents, such as 1,4-dioxane, toluene, and dichloroethane also resulted in lower yield (Table 1, entries 3–5).

The use of dimethyl sulfoxide (DMSO) as the solvent resulted in the formation of a by-product, presumed to be the product of trimerization of isocyanate, and the yield of the desired **2** was only 32% (Table 1, entry 6). Among other polar

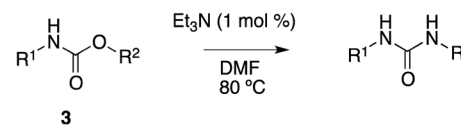Table 1. Optimization of Conditions for Direct Transformation

Entry	Additive (eq)	Solvent	Time (h)	Yield of **2** (%)[a]
1	Et₃N (1)	DMF	25	91
2[b]	Et₃N (1)	DMF	23	71
3	Et₃N (1)	1,4-Dioxane	96	55
4	Et₃N (1)	Toluene	121	28
5	Et₃N (1)	ClCH₂CH₂Cl	65	45
6	Et₃N (1)	DMSO	32	32
7	Et₃N (1)	DMA	52	38
8	Et₃N (1)	NMP	44	45
9	Et₃N (1)	DMI	30	95
10	Et₃N (0.01)	DMF	24	93
11	None	DMF	70	82
12	DMAP (0.01)	DMF	116	75
13	2,6-Lutidine (0.01)	DMF	71	89
14	Imidazole (0.01)	DMF	67	83
15	TMEDA (0.01)	DMF	50	95

a) Isolated yield. Yields were calculated based on the assumption that 2 eq of aryl carbamate was consumed to generate 1 eq of aryl urea. *b*) The reaction was performed at 50°C.
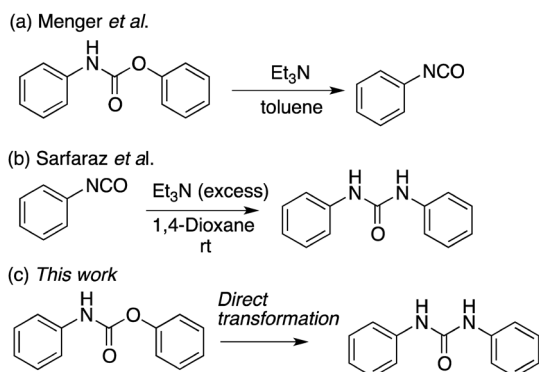
Fig. 1. Reactions of *N,O*-Diaryl Carbamate and Aryl Isocyanate

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Table 2. Substrate Scope of the Reaction

Entry	Cmpd.	R^1	R^2	Time (h)	Yield (%)[a]
1	3a	4-Nitrophenyl	C_6H_5	27	87
2	3b	4-Methoxyphenyl	C_6H_5	44	75
3	3c	Benzyl	C_6H_5	96	0
4	3d	C_6H_5	4-Nitrophenyl	20	91
5	3e	C_6H_5	4-Methoxyphenyl	44	80
6	3f	C_6H_5	Methyl	97	2

a) Isolated yield.

non-protic solvents, 1,3-dimethylimidazolidinone (DMI) afforded **2** in 95% yield (Table 1, entries 7–9) after a slightly longer reaction time. The reaction proceeded even with only a catalytic amount of Et$_3$N (1 mol %), and afforded **2** in comparable yield (Table 1, entry 10). The role of Et$_3$N in accelerating the reaction was highlighted by the reaction in the absence of Et$_3$N, which required a longer reaction time and afforded only moderate yield (Table 1, entry 11). Other amine additives, such as *N,N*-dimethylaminopyridine (DMAP), 2,6-lutidine, imidazole, and tetramethylethylenediamine (TMEDA), were less effective than Et$_3$N, and required a longer reaction time to attain a reasonable product yield (Table 1, entries 12–15).

With the optimized conditions in hand, we explored the scope of the reaction (Table 2). When the reaction was performed with **3a**, which has an electron-withdrawing nitro group on the anilino group, the outcome of the reaction was comparable with that of **1** (entry 1). In contrast, the carbamate bearing an electron-donating methoxy group on the anilino group, **3b**, reacted slowly under the same conditions, and the yield was moderate (entry 2). Replacement of the anilino moiety with a benzyl group impeded the reaction, and the desired diphenylurea product was not obtained (**3c**, entry 3); most of the starting material was recovered. This result shows the importance of the phenyl moiety for this direct transformation. Replacement of the *O*-aryl moiety with various substituted phenyl groups affected the yield of the corresponding symmetrical diphenyl urea similarly; introduction of an electron-withdrawing nitro group (**3d**) afforded a good yield of *N,N′*-diphenylurea in a shorter reaction time, while the electron-donating methoxy group (**3e**) required a longer reaction time to afford a comparable yield of the urea compound. When the *O*-aryl group was replaced with a methyl group (**3f**), only a small amount of *N,N′*-diphenylurea was obtained and most of the starting material, carbamate **3f**, remained intact. These results indicate that the presence of an aryl group on both nitrogen and oxygen of carbamate is required, and there is a preference for an electron-withdrawing substituent on the phenyl group.

The difference in the reactivity of various carbamates (**3a–3d**) in Table 2 led us to investigate selective formation of *N,N′*-diarylureas from a mixture of carbamates (Fig. 2); compatibility with multiple reactive sites would be beneficial for application to polymerization. A mixture of **3a** and **3b** was reacted under similar conditions to those of Table 2, affording a complex mixture of **4**, **5** and other unidentified
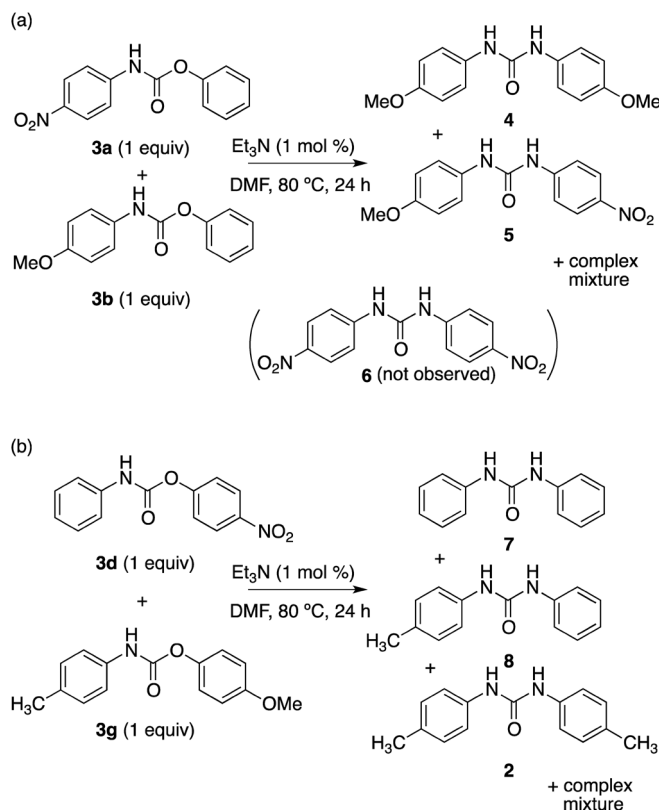

Fig. 2. Competitive Reactions

compounds (Fig. 2a). It is noteworthy that compound **6** was not observed in the crude mixture. At this stage, we think low nucleophilicity of *p*-nitroaniline generated from **3a** might be a major reason that **6** was not observed. Similar reaction of **3d** and **3g** also resulted in a complex mixture of **2**, **7**, and **8** (*ca.* **2**:**7**:**8**=1:2:1 based on the ¹H-NMR of the crude mixture), together with other unidentified products (Fig. 2b). These results may imply that the reaction involves multiple steps.

To obtain mechanistic insight into the reaction, the carbamate **3h** was reacted with *p*-toluidine under the same conditions. An unsymmetrically substituted urea, **8** was obtained selectively in 90% yield within 1 h (Fig. 3a) as expected from literatures.[22] The carbamate **3h** was also reacted with *p*-tolyl isocyanate under the same conditions. Selectivity was low, and a complex mixture of **7**, **8** and **2** (*ca.* **7**:**8**:**2**=1:2:1 from ¹H-NMR of the crude mixture) and other impurities was obtained (Fig. 3b). A comparison of reactivity in Table 2 and product ratios in Figs. 2b and 3b suggests that the product-determining step may be formation of aryl isocyanate, for which the presence of an electron-donating group would be disadvantageous.

To observe intermediates involved in the reaction, we monitored the reaction of **1** in the presence of 1 mol % Et$_3$N by means of ¹H-NMR in DMF-*d$_7$* in a sealed tube at 80°C (Fig. 4). The reaction was slower, and carbamate was remained even after 24 h, probably due to the lack of moisture in a sealed tube. Signals of carbamate **1** and **2** were observed in the Ph-CH$_3$ region (*ca.* 2 ppm), and those of *p*-tolyl isocyanate and *p*-toluidine were not detected. The absence of *p*-tolyl isocyanate and *p*-toluidine peaks in the reaction mixture suggests that the formation of aryl isocyanate and aniline from carbamate is slow (rate-limiting step) and/or that the equilib-
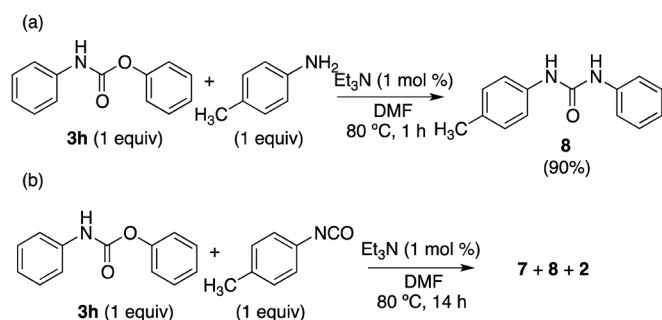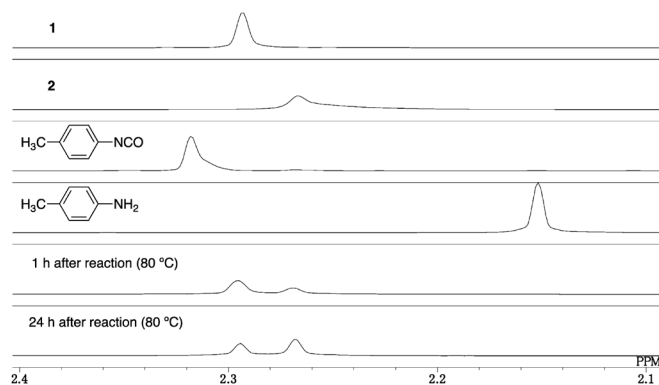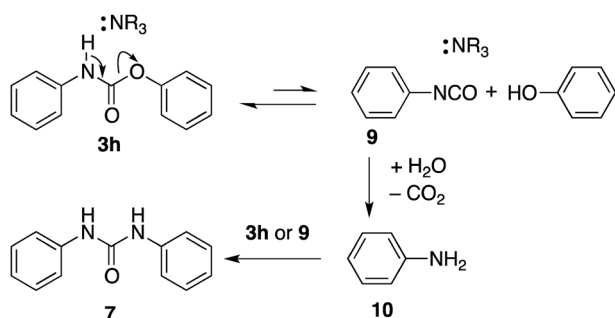
Fig. 3. Reactions of **3h** with Amine or Isocyanate

Fig. 4. ^{1}H-NMR Spectra Showing the Time Course of the Reaction

Chart 1. Proposed Reaction Mechanism

rium between carbamate and isocyanate predominantly favors carbamate,[17] so that isocyanate is undetectable by ^{1}H-NMR.

Based on the our findings and reported results,[13,17] we propose the reaction mechanism depicted in Chart 1. NR$_3$ (or Et$_3$N) catalyzes the reaction of carbamate **3h** to **9**, which favors **3h** in the equilibrium. Phenyl isocyanate **9** can be hydrolyzed by residual H$_2$O to form aniline **10**, which in turn reacts with **3h** or **9** to afford *N,N′*-diphenylurea **7**. Since absence of water, under a strict anhydrous condition, probably prevented the formation of **10**, and the reaction was not completed (*cf.* Fig. 4).

Conclusion

We found that *N,O*-diaryl carbamate is spontaneously transformed into symmetrical *N,N′*-diphenylurea in DMF in the presence of a catalytic amount of Et$_3$N. This transformation requires a presence of aryl groups on the nitrogen and oxygen atoms of the carbamate. An electron-donating group on the aryl group inhibited the reaction. We could not obtain

selective coupling products from a mixture of carbamates, apparently due to involvement of multiple intermediates in the reaction. This reaction should be useful to synthesize functional molecules with an *N,N′*-diphenylurea skeleton *via* polymerization or cyclization by employing bench-stable *N,O*-diaryl carbamate.

Experimental

General Melting points (mp) were determined by using a Yanaco melting point apparatus MP-S3 and are uncorrected. Fourier transform (FT)-IR spectra were recorded on a Horiba FT-710. ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL AL-300 or ECZ400S or Bruker AV-300M, and chemical shifts are expressed in parts per million relative to tetramethylsilane (TMS) or residual solvent peak (7.24 ppm for CDCl$_3$ (^{1}H), 77.0 ppm for CHCl$_3$ (^{13}C), 2.49 ppm for DMSO-d_6 (^{1}H), 39.5 ppm for DMSO-d_6 (^{13}C), 8.03 ppm for DMF-d_7 (^{1}H)). Mass spectra were measured on a JEOL MS700V or HX110. Silica gel (CHROMATOREX PSQ100 (Fuji Silysia Chemical Co., Inc.)) was used for all chromatographic procedures.

Preparation of 1 Et$_3$N (0.80 mL, 5.7 mmol) and phenyl chloroformate (1.0 mL, 7.9 mmol) were added dropwise to a solution of *p*-toluidine (1.00 g, 9.3 mmol) in CH$_2$Cl$_2$ (10 mL) under cooling in an ice bath. The mixture was stirred for 1 h, and then evaporated to dryness. The residue was recrystallized from *n*-hexane to afford **1** (660 mg, 51%) as colorless needles. ^{1}H-NMR and mp were consistent with reported data.[23]

Phenyl *N*-(4-Methylphenyl)carbamate (**1**)

mp 119.0–120.0°C; ^{1}H-NMR (300 MHz, CDCl$_3$) 2.33 (s, 3H), 7.13–7.24 (m, 5H), 7.32–7.42 (m, 4H).

General Procedure for the Reaction of 1 (Table 1) Et$_3$N (1.4 µL, 0.01 mmol) was added to a solution of **1** (227 mg, 1.0 mmol) in DMF (4 mL), and the mixture was stirred at 80°C without Ar displacement (open-air) until the reaction was complete, as determined by TLC analysis. Then, Et$_2$O (200 mL) was added, and the mixture was washed with sat. NH$_4$Cl aq. (200 mL) and 10% NaOH aq. (200 mL) twice, dried over Na$_2$SO$_4$, and filtered. The filtrate was evaporated under reduced pressure to afford **2** as a colorless powder. ^{1}H-NMR was consistent with reported data.[24]

N,N′-Bis(4-methylphenyl)urea (**2**)

^{1}H-NMR (300 MHz, DMSO-d_6) 2.22 (s, 6H), 7.06 (d, J=8.4 Hz, 4H), 7.31 (d, J=8.4 Hz, 4H), 8.49 (br s, 2H).

Preparation of 3a Pyridine (0.77 mL, 9.6 mmol) and phenyl chloroformate (1.1 mL, 8.8 mmol) were added dropwise to a solution of *p*-nitroaniline (1.11 g, 8.0 mmol) in CH$_2$Cl$_2$ (50 mL), and the reaction mixture was stirred for 1 h at room temperature (r.t.). Then, 10% HCl (1 mL) and H$_2$O (40 mL) were added. The organic layer was dried over Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent, AcOEt–hexane=1:3) to afford **3a** as a yellow solid (1.69 g, 81%). ^{1}H-NMR and mp were consistent with reported data.[25]

Phenyl *N*-(4-Nitrophenyl)carbamate (**3a**)

mp 158.0–159.0°C; ^{1}H-NMR (300 MHz, CDCl$_3$) 7.20 (d, J=9.0 Hz, 2H), 7.31 (m, 2H), 7.40–7.45 (m, 2H), 7.62 (d, J=9.0 Hz, 2H), 8.24 (d, J=9.0 Hz, 2H).

Preparation of 3b Compound **3b** was synthesized in a similar manner to that described for **3a**, except that *p*-methoxyaniline was used in place of *p*-nitroaniline. It was

purified by recrystallization from CH_2Cl_2 to afford colorless needles (71%). ^{1}H-NMR and mp were consistent with reported data.[25)

Phenyl *N*-(4-Methoxyphenyl)carbamate (**3b**)

mp 150.5–151.0°C; ^{1}H-NMR (300 MHz, CDCl$_3$) 3.80 (s, 3H), 6.82 (br s, 1H), 6.88 (d, *J*=9.0 Hz, 2H), 7.18–7.23 (m, 3H), 7.35–7.42 (m, 4H).

Preparation of 3c A solution of phenyl chloroformate (1.2 mL, 9.5 mmol) in CH_2Cl_2 (5 mL) and tetrahydrofuran (THF) (5 mL) was added to a solution of benzylamine (1.0 mL, 9.15 mmol) and *N,N*-diisopropylethylamine (3.2 mL, 18.3 mmol) and in CH_2Cl_2 (10 mL) and THF (10 mL) in an ice bath. The mixture was stirred for 23 h at r.t., and then evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent, AcOEt–hexane=1:7) to afford **3c** as a colorless solid (1.31 g, 63%). ^{1}H-NMR and mp were consistent with reported data.[26)

Phenyl *N*-Benzylcarbamate (**3c**)

mp 77.0–78.0°C; ^{1}H-NMR (300 MHz, CDCl$_3$) 4.47 (d, *J*=6.0 Hz, 2H), 5.33 (br s, 1H), 7.14–7.23 (m, 3H), 7.28–7.4l (m, 7H).

Preparation of 3d Phenyl isocyanate (0.8 mL, 7.3 mmol) was added to a solution of *p*-nitrophenol (1.00 g, 7.2 mmol) in CH_2Cl_2 (20 mL) in an ice bath. The reaction mixture was stirred for 19 h at r.t., and then evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent, CH_2Cl_2–hexane=5:1) to afford **3d** as a colorless solid (0.569 g, 31%). ^{1}H-NMR and mp were consistent with reported values.[27)

4-Nitrophenyl *N*-Phenylcarbamate (**3d**)

mp 146.0–147.0°C; ^{1}H-NMR (300 MHz, CDCl$_3$) 6.9l (br s, 1H), 7.16 (t, *J*=7.2 Hz, 1H), 7.35–7.46 (m, 6H), 8.29 (d, *J*=9.0 Hz, 2H).

Preparation of 3e Compound **3e** was synthesized in a similar manner to that described for **3d**, except that *p*-methoxyphenol was used in place of *p*-nitrophenol. The product was purified by recrystallization from ethanol to afford a colorless solid (56%).

4-Methoxyphenyl *N*-Phenylcarbamate (**3e**)

mp 138.0–139.0°C; ^{1}H-NMR (300 MHz, CDCl$_3$) 3.81 (s, 3H), 6.38–6.93 (m, 3H), 7.08–7.13 (m, 3H), 7.34 (t, *J*=7.5 Hz, 2H), 7.44 (d, *J*=7.5 Hz, 2H); ^{13}C-NMR(75 MHz, CDCl$_3$) 55.6, 114.4, 118.7, 122.5, 123.8, 129.1, 137.4, 144.1, 152.0, 157.2; IR (KBr) 3344, 2924 2856, 1722, 1606, 1549, 1502, 1448, 1381, 1317, 1213, 1022, 904, 839, 758, 696, 663, 519 cm^{-1}; high resolution (HR)-MS (electron ionization (EI)$^+$) Calcd for $C_{14}H_{13}NO_3$ (M$^+$) 243.0890. Found 243.0889.

Preparation of 3f Phenyl isocyanate (2.7 mL, 25 mmol) was added to dry methanol (40 mL) in a two-necked flask under Ar. The solution was stirred at 80°C for 30 min, and evaporated under reduced pressure. The residue was cooled in a dry ice-acetone bath, affording a colorless solid **3f** (3.67 g, 98%). ^{1}H-NMR and mp were consistent with reported data.[28)

Methyl Phenylcarbamate (**3f**)

mp 43.0–44.0°C; ^{1}H-NMR (300 MHz, CDCl$_3$) 3.78 (s, 3H), 6.61 (br s, 1H), 7.07 (t, *J*=7.5 Hz, 1H), 7.31 (t, *J*=7.5 Hz, 2H), 7.38 (t, *J*=7.5 Hz, 2H).

Preparation of 3g Et$_3$N (0.8 mL, 5.7 mmol) and *p*-tolyl isocyanate (1.5 mL, 12 mmol) were added to a solution of *p*-methoxyphenol (1.50 g, 12 mmol) in toluene (57 mL) at r.t. The reaction mixture was stirred for 3 h at r.t., and then evaporated

under reduced pressure. The crude product was recrystallized from ethanol to afford **3g** as colorless needles (2.18 g, 71%). ^{1}H-NMR and mp were consistent with reported data.[29,30)

4-Methoxyphenyl *N*-(4-Methylphenyl)carbamate (**3g**)

mp 164.5–165.0°C; ^{1}H-NMR (300 MHz, CDCl$_3$) 2.32 (s, 3H), 3.80 (s, 3H), 6.90 (d, *J*=9.0 Hz, 2H), 7.08–7.14 (m, 4H), 7.32 (m, 2H).

Preparation of 3h Compound **3h** was synthesized in a similar manner to that described for **1**, except that aniline was used in place of *p*-toluidine. The product was purified by silica gel column chromatography (eluent, AcOEt–hexane=1:3), then recrystallization from CH_2Cl_2 to afford **3h** as colorless prisms (19%). ^{1}H-NMR and mp were consistent with reported data.[23)

Phenyl *N*-Phenylcarbamate (**3h**)

mp 130.0–131.0°C; ^{1}H-NMR (300 MHz, CDCl$_3$) 6.91 (br s, 1H), 7.11 (t, *J*=7.5 Hz, 1H), 7.18–7.47 (m, 9H).

Compound Data Related to Table 2

N,N′-Bis(4-methoxyphenyl)urea (**4**)

^{1}H-NMR was consistent with reported data[31); ^{1}H-NMR (300 MHz, DMSO-*d$_6$*) 3.70 (s, 6H), 6.84 (d, *J*=8.1 Hz, 4H), 7.32 (d, *J*=8.1 Hz, 4H), 8.36 (br s, 2H).

N,N′-Bis(4-nitrophenyl)urea (**6**)

^{1}H-NMR was consistent with reported data[32); ^{1}H-NMR (300 MHz, DMSO-*d$_6$*) 7.72 (d, *J*=9.1 Hz, 4H), 8.22 (d, *J*=9.1 Hz, 4H), 9.65 (br s, 2H).

N-Phenyl-*N′*-(4-methylphenyl)urea (**8**)

^{1}H-NMR was consistent with reported data[33); ^{1}H-NMR (300 MHz, DMSO-*d$_6$*) 2.23 (s, 3H), 6.94 (t, *J*=7.4 Hz, 1H), 7.07 (d, *J*=8.1 Hz, 2H), 7.26 (t, *J*=8.1 Hz, 2H), 7.32 (d, *J*=8.4 Hz, 2H), 7.43 (d, *J*=8.1 Hz, 2H), 8.52 (br s, 1H), 8.59 (br s, 1H).

Preparation of 5 Synthesized for the purpose of comparison in the ^{1}H-NMR experiment in Fig. 2a. A solution of *p*-anisidine (246 mg, 2.0 mmol) in Et$_2$O (2 mL) was added to a solution of *p*-nitrophenyl isocyanate (328 mg, 2.0 mmol) in Et$_2$O (5 mL) in an ice bath. The mixture was stirred for 16 h at r.t., then the precipitate was collected by suction, and washed with Et$_2$O. The crude product was recrystallized from methanol to afford **5** as a colorless powder (134 mg, 24%).

N-(4-Methoxyphenyl)-*N′*-(4-nitrophenyl)urea (**5**)

mp 236.5–238.0°C; ^{1}H-NMR (400 MHz, DMSO-*d$_6$*) 3.71 (s, 3H), 6.88 (d, *J*=9.2 Hz, 2H), 7.37 (d, *J*=9.2 Hz, 2H), 7.67 (d, *J*=9.2 Hz, 2H), 8.17 (d, *J*=8.1 Hz, 2H), 8.73 (br s, 1H), 9.37 (br s, 1H); ^{13}C-NMR (100 MHz, DMSO-*d$_6$*) 55.2, 114.0, 117.3, 120.5, 125.2, 131.9, 140.8, 146.6, 152.1, 154.9; IR (KBr) 2954, 1691, 1645, 1614, 1593, 1552, 1506, 1468, 1406, 1342, 1304, 1228, 1167, 1109, 1032, 858, 761, 744, 688, 548 cm^{-1}; HR-MS (EI$^+$) Calcd for $C_{14}H_{13}N_3O_4$ (M$^+$) 287.0901. Found 287.0906.

Reaction Monitoring by ^{1}H-NMR (Fig. 4) A mixture of **1** (42.6 mg, 0.187 mmol) and Et$_3$N (2.6 µL, 1.9 µmol) in DMF-*d$_7$* (0.675 mL) was heated in an NMR tube in an oil bath at 80°C. The ^{1}H-NMR spectrum of the mixture was measured at the indicated times.

Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials. Detail and ^{1}H-NMR spectrums of competitive reaction in Figs. 2 and 3; ^{1}H- and ^{13}C-NMR spectrums of compound **3e**.

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