Synthesis of Unsymmetrical Ureas by Sulfur-Assisted Carbonylation with Carbon Monoxide and Oxidation with Molecular Oxygen under Mild Conditions

Takumi Mizuno,* Takeo Nakai, Masatoshi Mihara

Osaka Municipal Technical Research Institute, 1-6-50, Morinomiya, Joto-ku, Osaka 536-8553, Japan
Fax +81(6)69638049; E-mail: tmizuno@omtri.city.osaka.jp
Received 17 March 2009; revised 17 April 2009

Abstract: With ambient pressure of carbon monoxide and oxygen at room temperature, *N*,*N*-dialkyl-*N*′-arylureas were selectively accessible from secondary amines, aromatic amines, and sulfur in good to excellent yields. For example, *N*-butyl-*N*-methyl-*N*′-(3,4-dichlorophenyl)urea, which is used as a herbicide (neburon), was afforded successfully from butylmethylamine (2 equiv), 3,4-dichloroaniline (1 equiv) and sulfur (1 equiv) in 79% (21.8 g) yield using carbon monoxide (0.1 MPa) and oxygen (0.1 MPa) at 20 °C in DMF.

Key words: unsymmetrical ureas, carbon monoxide, oxygen, sulfur, herbicide

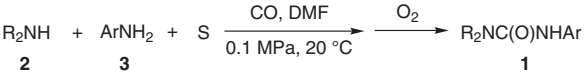
N,*N*-Dialkyl-*N*′-arylureas **1** were developed as effective herbicides that block photosynthesis of plants. These herbicides are safe for warm-blooded animals and are characterized by their high efficiency and low cost.[1] For instance, *N*-butyl-*N*-methyl-*N*′-(3,4-dichlorophenyl)urea (**1m**; neburon) has been commercially exploited as an efficient herbicide for use on wheat, alfalfa, and strawberries.[1–3]

As part of a series of sulfur-assisted carbonylations of primary amines used to prepare urea derivatives from carbon monoxide,[4–6] the synthetic methodology used for the synthesis of **1** was reported from secondary amines and aromatic amines.[7] However, this reaction requires high temperature and pressurized carbon monoxide. The *N*,*N*-diethyl-*N*′-phenylurea (**1b**) was also produced by reductive carbonylation with nitrobenzene, diethylamine (**2b**) and carbon monoxide, using sulfur and a vanadium compound as promoter.[8] Recently, piperidinecarboxanilide (**1j**) was obtained by reductive carbonylation using a catalytic amount of sulfur in ionic liquid.[9] These reactions, however, need drastic conditions (high temperature and high pressure). A similar synthesis of **1** by selenium-catalyzed reductive carbonylation of nitrobenzene with carbon monoxide and sulfur also proceeded under high pressure and temperature,[10] however, owing to the severe reaction conditions and toxicity of selenium, the use of this method is considerably limited.

Recently, solvent-assisted thiocarboxylation of amines with carbon monoxide and sulfur was reported to afford *S*-alkyl thiocarbamates in good yields.[11] In this reaction system, the thiocarboxylation of amines with carbon monoxide and sulfur was powerfully assisted by dimethyl sulfoxide (DMSO) or *N*,*N*-dimethylformamide (DMF) as solvent under mild conditions (0.1 MPa, 20 °C).

In pursuit of a synthetic methodology for generating unsymmetrical ureas **1**, a smooth synthetic method for producing symmetrical urea derivatives was recently explored through the carbonylation of amines with carbon monoxide and sulfur, followed by oxidation with molecular oxygen under mild conditions in DMF or DMSO. Using these reactions, symmetrical ureas were obtained from the corresponding primary amines in good to excellent yields under mild conditions (0.1 MPa, 20 °C).[12]

We have further extended this strategy in order to develop a user-friendly protocol for the synthesis of unsymmetrical urea derivatives **1**. Herein, we report the full results for the selective synthesis of **1** from secondary amines **2**, aromatic amines **3**, and sulfur, in DMF with 0.1 MPa of carbon monoxide and oxygen at 20 °C (Scheme 1). The preparation of *N*,*N*-dipropyl-*N*′-phenylurea (**1a**) was used as a model system for screening the influence of base and solvent on the reaction (Table 1).



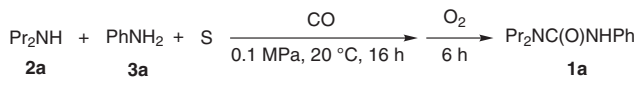
Scheme 1 Synthesis of *N*,*N*-dialkyl-*N*′-arylureas **1**

Initially, the synthesis of *N*,*N*-dipropyl-*N*′-phenylurea (**1a**) was carried out by the carbonylation of dipropylamine (**2a**; 10 mmol), aniline (**3a**), and powdered sulfur in DMF with carbon monoxide, and oxidation by molecular oxygen. The reactions proceeded smoothly under 0.1 MPa pressure, at 20 °C, to give **1a** selectively in moderate yield (66%; entry 1). Furthermore, using two equivalents of **2a**, the unsymmetrical urea **1a** was successfully obtained in a superior yield (90%; entry 2). However, shorter reaction times (4 h for carbonylation and 2 h for oxidation) led to a lower yield of **1a** (entry 3).

The effect of the base (10 mmol) on the synthesis of **1a** was then examined. By addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), triethylamine, 1-methylpyrrolidine, or triethylamine in DMF, the yields of **1a** were improved (en-

SYNTHESIS 2009, No. 15, pp 2492–2496
Advanced online publication: 29.05.2009
DOI: 10.1055/s-0029-1216863; Art ID: F05709SS

Table 1 Influence of Base and Solvent on the Synthesis of **1a**[a]



Entry	Base	Solvent	Yield (%)[b]
1	none	DMF	66
2	none	DMF	90[c]
3	none	DMF	61[c,d]
4	DBU[e]	DMF	85
5	DBN[f]	DMF	77
6	Et_3N	DMF	75
7	1-methylpyrrolidine	DMF	75
8	DABCO[g]	DMF	66
9	K_2CO_3	DMF	50
10	none	DMSO	81[c]
11	none	THF	40[c]
12	none	toluene	0[c]

[a] Reagents and conditions: Pr_2NH (1.37 mL, 10 mmol), $PhNH_2$ (0.911 mL, 10 mmol), sulfur (321 mg, 10 mmol), base (10 mmol), solvent (20 mL), CO (0.1 MPa), 20 °C, 16 h; then 6 h O_2 (0.1 MPa), 20 °C, 6 h.
[b] Isolated yields.
[c] Pr_2NH (**2a**; 2.73 mL, 20 mmol) was used.
[d] Reaction times were 4 h for carbonylation and 2 h for oxidation.
[e] 1,8-Diazabicyclo[5.4.0]undec-7-ene.
[f] 1,5-Diazabicyclo[4.3.0]non-5-ene.
[g] 1,4-Diazabicyclo[2.2.2]octane.

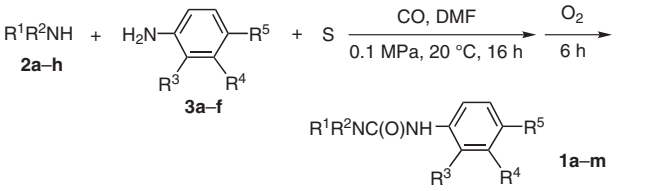
tries 4–7). It was found that one equivalent of DBU gave almost the same effect as two equivalents of **2a**, whereas, the use of 1,4-diazabicyclo[2.2.2]octane (DABCO) did not have any additional effect on the preparation (entry 8). Potassium carbonate (K_2CO_3) lowered the yield of **1a** (entry 9). The solvent used had a great impact on the reaction. **1a** was obtained in good yields using dimethyl sulfoxide (DMSO) as solvent with two equivalents of **2a** (entry 10). However, tetrahydrofuran (THF) and toluene were found to be unsuitable for the preparation of **1a** (entries 11 and 12).

In order to demonstrate the efficiency and scope of the synthetic methodology for the preparation of *N*,*N*-dialkyl-*N*′-arylureas **1**, a variety of urea derivatives **1a**–**m** were prepared under the optimized reaction conditions [dialkylamines **2a**–**h** (2.0 equiv), arylamines **3a**–**f** (1.0 equiv), DMF, 0.1 MPa CO, 20 °C, 16 h, then 0.1 MPa O_2, 20 °C, 4 h]. The results are summarized in Table 2.

Generally, unsymmetrical urea derivatives **1a**–**m** were selectively obtained in good to excellent yields under ambient pressure at room temperature. However, diisopropylamine (**2c**) gave the corresponding unsymmetrical urea **1g** in only moderate yield, presumably because of the bulkiness of **2c**. This unsymmetrical urea synthesis displayed good tolerance for several substituents on **3**. Even weakly basic 4-chloroaniline (**3d**) and 3,4-dichloroaniline (**3f**), having electron-withdrawing groups, afforded **1e** and **1m**, respectively, in good yields (entries 5 and 13). Additionally, the use of **2a**–**c** (1 equiv) and DBU (1 equiv) gave slightly lower yields of **1a**, **1b** and **1g**, respectively (entries 1, 2 and 7).

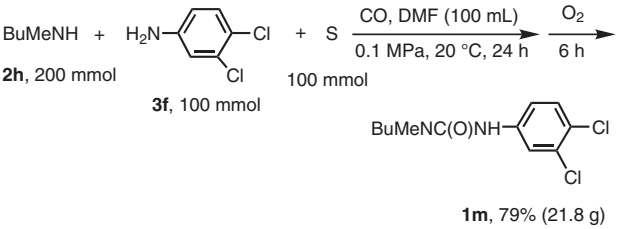
Furthermore, the unsymmetrical urea herbicide neburon (**1m**) was also prepared in reasonable yield (79%) on a larger scale (21.8 g; Scheme 2).

Table 2 Synthesis of Unsymmetrical Ureas **1a**–**m**[a]



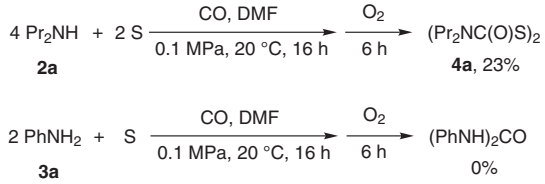
Entry	R^1	R^2		R^3	R^4	R^5			Yield (%)[b]
1	Pr	Pr	**2a**	H	H	H	**3a**	**1a**	90 (85)[c]
2	Et	Et	**2b**	H	H	H	**3a**	**1b**	82 (75)[c]
3	Et	Et	**2b**	Me	H	H	**3b**	**1c**	85
4	Et	Et	**2b**	H	H	Me	**3c**	**1d**	92
5	Et	Et	**2b**	H	H	Cl	**3d**	**1e**	90
6	Et	Et	**2b**	H	H	OMe	**3e**	**1f**	83
7	*i*-Pr	*i*-Pr	**2c**	H	H	H	**3a**	**1g**	51 (41)[c]
8	Bu	Bu	**2d**	H	H	H	**3a**	**1h**	68
9	$-(CH_2)_4-$		**2e**	H	H	H	**3a**	**1i**	64
10	$-(CH_2)_5-$		**2f**	H	H	H	**3a**	**1j**	62
11	$-(CH_2)_5-$		**2f**	H	H	Me	**3c**	**1k**	82
12	$-(CH_2)_2O(CH_2)_2-$		**2g**	H	H	H	**3a**	**1l**	65
13	Bu	Me	**2h**	H	Cl	Cl	**3f**	**1m**	73[d]

[a] Reagents and conditions: dialkylamine (20 mmol), arylamine (10 mmol), sulfur (321 mg, 10 mmol), DMF (20 mL), CO (0.1 MPa), 20 °C, 16 h; then O_2 (0.1 MPa), 20 °C, 6 h.
[b] Isolated yields.
[c] Dialkylamine (10 mmol) and DBU (10mmol) were used.
[d] Neburon (herbicide).



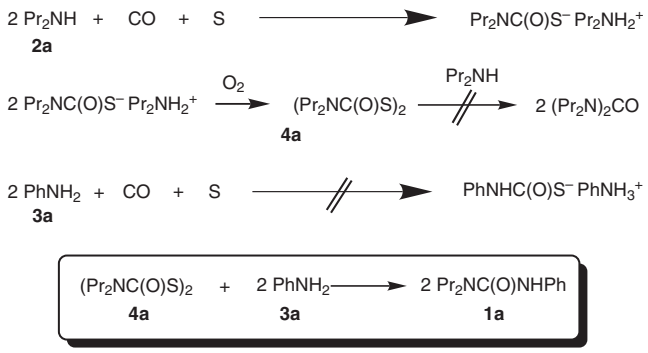
Scheme 2 Herbicide neburon (**1m**) synthesis on a large scale

In order to understand the selective formation of unsymmetrical ureas of type **1**, the following reactions with **2a** or **3a** were performed (Scheme 3). When dipropylamine (**2a**; 20 mmol) was carbonylated in the presence of sulfur (10 mmol) in DMF under 0.1 MPa of carbon monoxide at 20 °C for 16 hours then oxidized with 0.1 MPa of oxygen at 20 °C for six hours, bis(*N*,*N*-dipropylcarbamoyl)disulfide (**4a**) was formed.[13] On the other hand, a similar reaction with aniline (**3a**) did not give urea derivatives (Scheme 3). In this case, the corresponding *N*,*N*′-diphenylurea was given in moderate yield under mild conditions only in the presence of a strong base (DBU).[12]

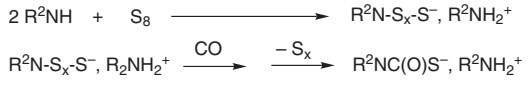


Scheme 3 Reaction of **2a** and **3a**

From these experimental clues, a possible pathway for the synthesis of **1a** was envisaged as indicated in Scheme 4. First, an *N*,*N*-dipropylthiocarbamate salt could be generated via ready reaction of the thiolate salts with carbon monoxide (Scheme 5).[14] The formed thiocarbamate salt could then be oxidized by molecular oxygen, giving bis(*N*,*N*-dipropylcarbamoyl)disulfide (**4a**). Due to the steric bulk of **4a** and **2a**, it is difficult to form the tetrapropylurea through aminolysis. In contrast, the ammonium salt of *N*,*N*′-diphenylthiocarbamate is not formed, because of the low nucleophilicity of aniline (**3a**). Therefore, the aminolysis of **4a** with **3a** leads to the selective preparation of *N*,*N*-dipropyl-*N*′-phenylurea (**1a**).



Scheme 4 Reaction path for the formation of **1a**



Scheme 5 Reaction of thiolate anions with carbon monoxide

In conclusion, a useful protocol for the synthesis of unsymmetrical urea derivatives **1** in good to excellent yields has been developed. The method works under mild conditions (0.1 MPa, 20 °C) in DMF, and involves sulfur-assisted carbonylation with carbon monoxide and sulfur, and oxidation with molecular oxygen. From the viewpoint of developing an application for the practical production of **1**, including herbicide **1m**, the present method is very significant in terms of the use of easily available and cheap carbon monoxide, oxygen, sulfur and DMF, and because of the mild reaction conditions that are needed (0.1 MPa, 20 °C).

Melting points were determined on a Mettler FP 5 instrument and are uncorrected. FT-IR spectra were recorded on a JASCO FT/IR-4100 instrument. ^{1}H and ^{13}C NMR spectra were obtained on a JEOL JNM-AL300 (300 MHz, 75 MHz) instrument. Chemical shifts (δ) are reported in ppm relative to TMS. Both low and high-resolution mass spectra were measured on a JEOL JMS-600 spectrometer. Dialkylamines **2a**–**h**, arylamines **3a**–**f**, base (DBU, DBN, DABCO, Et_3N, 1-methylpyrrolidine and K_2CO_3), powdered sulfur (99.5%), and solvents (DMF, DMSO, THF, toluene) were used as purchased. CO (99.9%) and O_2 (99.9%) were also used as received.

Synthesis of *N*,*N*-Dipropyl-*N*′-phenylurea (1a); Typical Procedure

Into a 100 mL flask, Pr_2NH (**2a**; 2.73 mL, 20 mmol), aniline (**3a**; 0.911 mL, 10 mmol) and powdered sulfur (321 mg, 10 mmol) were added in DMF (20 mL) under an argon atmosphere. Ambient pressure of CO was charged and the mixture was vigorously stirred under a CO balloon (0.1 MPa) at 20 °C for 16 h (the color of the solution changed from reddish-black to pale-orange). CO was purged and O_2 (0.1 MPa) was charged at 20 °C (slightly exothermic reaction). The reaction mixture was stirred under an O_2 balloon (0.1 MPa) for an additional 6 h at 20 °C. The resulting orange emulsion was then poured into 1 M HCl (100 mL) and extracted with *t*-BuOMe (2 × 50 mL). Evaporation of solvents and purification by short-column chromatography (silica gel; EtOAc), gave *N*,*N*-dipropyl-*N*′-phenylurea (**1a**).

Yield: 1.98 g (90%); mp 68.1 °C (Lit.[10] 68–70 °C).

IR (KBr): 3320, 2962, 1639, 1541, 1447, 1239, 755 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.4 Hz, 6 H, 2 × CH_3), 1.64 (sext, *J* = 7.4 Hz, 4 H, 2 × CH_2), 3.26 (t, *J* = 7.4 Hz, 4 H, 2 × CH_2), 6.32 (br s, 1 H, NH), 7.00 (t, *J* = 7.5 Hz, 1 H, CH), 7.26 (t, *J* = 7.5 Hz, 2 H, 2 × CH), 7.37 (d, *J* = 7.5 Hz, 2 H, 2 × CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.3, 21.8, 49.4, 119.7, 122.7, 128.7, 139.3, 155.0.

MS (EI, 70 eV): *m*/*z* (%) = 220 (100) [M$^+$], 191 (11), 128 (41), 86 (10), 72 (18).

HRMS (EI, 70 eV): *m*/*z* calcd for $C_{13}H_{20}ON_2$: 220.1576; found: 220.1593.

***N*,*N*-Diethyl-*N*′-phenylurea (1b)**

Compound **1b** was purified by recrystallization (hexane–toluene).

Yield: 1.58 g (82%); mp 86.8 °C (Lit.[10] 85–87 °C).

IR (KBr): 3307, 2973, 1638, 1536, 1445, 1303, 1244, 753 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.1 Hz, 6 H, 2 × CH_3), 3.36 (q, *J* = 7.1 Hz, 4 H, 2 × CH_2), 6.34 (br s, 1 H, NH), 7.00 (t, *J* = 7.7 Hz, 1 H, CH), 7.26 (t, *J* = 7.7 Hz, 2 H, 2 × CH), 7.38 (d, *J* = 7.7 Hz, 2 H, 2 × CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 41.6, 119.8, 122.7, 128.7, 139.3, 154.6.

MS (EI, 70 eV): *m*/*z* (%) = 192 (81) [M$^+$], 100 (100), 72 (52), 58 (11).

HRMS (EI, 70 eV): *m*/*z* calcd for $C_{11}H_{16}ON_2$: 192.1263; found: 192.1257.

***N*,*N*-Diethyl-*N*′-(2-methylphenyl)urea (1c)**
Compound **1c** was purified by recrystallization (hexane–toluene).

Yield: 1.74 g (85%); mp 80.7 °C (Lit.[15] 78–79 °C).

IR (KBr): 3321, 2974, 2926, 1631, 1523, 1267, 748 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.1 Hz, 6 H, 2 × CH_3), 2.25 (s, 3 H, CH_3), 3.39 (q, *J* = 7.1 Hz, 4 H, 2 × CH_2), 6.12 (br s, 1 H, NH), 6.98 (t, *J* = 7.6 Hz, 1 H, CH), 7.13–7.20 (m, 2 H, 2 × CH), 7.77 (d, *J* = 7.6 Hz, 1 H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 17.8, 41.7, 122.2, 123.4, 126.7, 127.7, 130.2, 137.3, 154.7.

MS (EI, 70 eV): *m*/*z* (%) = 206 (83) [M^+], 100 (100), 72 (45).

HRMS (EI, 70 eV): *m*/*z* calcd for $C_{12}H_{18}ON_2$: 206.1419; found: 206.1410.

***N*,*N*-Diethyl-*N*′-(4-methylphenyl)urea (1d)**
Compound **1d** was purified by short-column chromatography (silica gel; EtOAc).

Yield: 1.90 g (92%); mp 69.0 °C (Lit.[15] 67.5–68 °C).

IR (KBr): 3336, 2979, 2930, 1636, 1518, 1418, 1244, 813, 509 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.1 Hz, 6 H, 2 × CH_3), 2.29 (s, 3 H, CH_3), 3.36 (q, *J* = 7.1 Hz, 4 H, 2 × CH_2), 6.21 (br s, 1 H, NH), 7.07 (d, *J* = 8.2 Hz, 2 H, 2 × CH), 7.26 (d, *J* = 8.2 Hz, 2 H, 2 × CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 20.7, 41.6, 120.0, 129.3, 132.3, 136.7, 154.7.

MS (EI, 70 eV): *m*/*z* (%) = 206 (87) [M^+], 100 (100), 72 (40).

HRMS (EI, 70 eV): *m*/*z* calcd for $C_{12}H_{18}ON_2$: 206.1419; found: 206.1384.

***N*,*N*-Diethyl-*N*′-(4-chlorophenyl)urea (1e)**
Compound **1e** was purified by recrystallization (hexane–toluene).

Yield: 2.03 g (90%); mp 116.5 °C (Lit.[15] 118–118.5 °C).

IR (KBr): 3328, 2984, 1633, 1494, 1304, 1243, 819, 506 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.1 Hz, 6 H, 2 × CH_3), 3.37 (q, *J* = 7.1 Hz, 4 H, 2 × CH_2), 6.24 (br s, 1 H, NH), 7.23 (d, *J* = 8.8 Hz, 2 H, 2 × CH), 7.34 (d, *J* = 8.8 Hz, 2 H, 2 × CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 41.4, 121.2, 127.5, 128.5, 138.0, 154.4.

MS (EI, 70 eV): *m*/*z* (%) = 228 (22) [M^+ + 2], 226 (67) [M^+], 100 (100), 72 (50).

HRMS (EI, 70 eV): *m*/*z* calcd for $C_{11}H_{15}ON_2Cl$: 226.0873; found: 226.0847.

***N*,*N*-Diethyl-*N*′-(4-methoxyphenyl)urea (1f)**
Compound **1f** was purified by recrystallization (hexane–toluene).

Yield: 1.84 g (83%); mp 62.0 °C (Lit.[15] 61.5–62 °C).

IR (KBr): 3283, 2970, 2932, 1633, 1514, 1296, 1235, 1168, 820 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 7.1 Hz, 6 H, 2 × CH_3), 3.35 (q, *J* = 7.1 Hz, 4 H, 2 × CH_2), 3.76 (s, 3 H, CH_3), 6.22 (br s, 1 H, NH), 6.81 (d, *J* = 8.8 Hz, 2 H, 2 × CH), 7.27 (d, *J* = 8.8 Hz, 2 H, 2 × CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 41.5, 55.5, 114.0, 122.1, 132.4, 155.0, 155.6.

MS (EI, 70 eV): *m*/*z* (%) = 222 (94) [M^+], 149 (19), 100 (100), 91 (10), 72 (47), 58 (14).

HRMS (EI, 70 eV): *m*/*z* calcd for $C_{12}H_{18}O_2N_2$: 222.1368; found: 222.1361.

***N*,*N*-Di-*i*-propyl-*N*′-phenylurea (1g)**
Compound **1g** was purified by recrystallization (hexane–toluene).

Yield: 1.12 g (51%); mp 116.1 °C (Lit.[16] 113–115 °C).

IR (KBr): 3287, 2968, 1633, 1527, 1447, 1336, 1248, 1148, 758 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.33 (d, *J* = 6.8 Hz, 12 H, 4 × CH_3), 3.99 (sept, *J* = 6.8 Hz, 2 H, 2 × CH), 6.19 (br s, 1 H, NH), 7.00 (t, *J* = 7.7 Hz, 1 H, CH), 7.27 (t, *J* = 7.7 Hz, 2 H, 2 × CH), 7.36 (dd, *J* = 7.7, 1.2 Hz, 2 H, 2 × CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5, 45.5, 119.7, 122.7, 128.8, 139.3, 154.7.

MS (EI, 70 eV): *m*/*z* (%) = 220 (100) [M^+], 128 (55), 120 (10), 93 (27), 86 (90).

HRMS (EI, 70 eV): *m*/*z* calcd for $C_{13}H_{20}ON_2$: 220.1576; found: 220.1587.

***N*,*N*-Dibutyl-*N*′-phenylurea (1h)**
Compound **1h** was purified by recrystallization (hexane).

Yield: 1.68 g (68%); mp 83.4 °C (Lit.[10] 83–84 °C).

IR (KBr): 3297, 2957, 1637, 1533, 1446, 1408, 1223, 754 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.4 Hz, 6 H, 2 × CH_3), 1.36 (sext, *J* = 7.4 Hz, 4 H, 2 × CH_2), 1.60 (quin, *J* = 7.4 Hz, 4 H, 2 × CH_2), 3.29 (t, *J* = 7.4 Hz, 4 H, 2 × CH_2), 6.29 (br s, 1 H, NH), 7.00 (t, *J* = 7.7 Hz, 1 H, CH), 7.26 (t, *J* = 7.7 Hz, 2 H, 2 × CH), 7.37 (dd, *J* = 7.7, 1.0 Hz, 2 H, 2 × CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 20.2, 30.8, 47.5, 119.7, 122.7, 128.8, 139.3, 154.9.

MS (EI, 70 eV): *m*/*z* (%) = 248 (100) [M^+], 205 (20), 156 (93), 100 (25), 93 (17), 86 (71), 57 (96).

HRMS (EI, 70 eV): *m*/*z* calcd for $C_{15}H_{24}ON_2$: 248.1889; found: 248.1911.

***N*-Phenyl-1-pyrrolidinecarboxamide (1i)**
Compound **1i** was purified by short-column chromatography (silica gel; EtOAc).

Yield: 1.21 g (64%); mp 129.9 °C (Lit.[10] 130–132 °C).

IR (KBr): 3296, 2973, 2873, 1642, 1537, 1442, 1380, 1241, 761 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.87–1.92 (m, 4 H, 2 × CH_2), 3.41 (t, *J* = 6.7 Hz, 4 H, 2 × CH_2), 6.40 (br s, 1 H, NH), 6.98 (td, *J* = 7.7, 0.9 Hz, 1 H, CH), 7.24 (t, *J* = 7.7 Hz, 2 H, 2 × CH), 7.41(d, *J* = 7.7 Hz, 2 H, 2 × CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.4, 45.6, 119.5, 122.5, 128.6, 139.3, 154.0.

MS (EI, 70 eV): *m*/*z* (%) = 190 (39) [M^+], 98 (100), 92 (21), 77 (23), 70 (25), 65 (29), 56 (37), 55 (72).

HRMS (EI, 70 eV): *m*/*z* calcd for $C_{11}H_{14}ON_2$: 190.1106; found: 190.1092.

***N*-Phenyl-1-piperidinecarboxamide (1j)**
Compound **1j** was purified by washing with hexane.

Yield: 1.27 g (62%); mp 168.3 °C (Lit.[10] 168–170 °C).

IR (KBr): 3289, 2925, 2855, 1630, 1536, 1449, 1243, 754 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.60–1.63 (m, 6 H, 3 × CH_2), 3.44 (s, 4 H, 2 × CH_2), 6.58 (br s, 1 H, NH), 7.01(tt, *J* = 7.7, 1.6 Hz, 1 H, CH), 7.27 (tt, *J* = 7.7, 1.6 Hz, 2 H, 2 × CH), 7.33–7.37 (m, 2 H, 2 × CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.3, 25.6, 45.4, 119.8, 122.9, 128.8, 139.2, 154.9.

MS (EI, 70 eV): *m*/*z* (%) = 204 (12) [M$^+$], 112 (54), 92 (64), 77 (70), 69 (100), 65 (69), 56 (63).

HRMS (EI, 70 eV): *m*/*z* calcd for $C_{12}H_{16}ON_2$: 204.1263; found: 204.1265.

_N_-4-Tolyl-1-piperidinecarboxamide (1k)

Compound **1k** was purified by washing with hexane.

Yield: 1.79 g (82%); mp 146.9 °C (Lit.[17] 146–148 °C).

IR (KBr): 3286, 2928, 2847, 1631, 1598, 1531, 1427, 1245, 811, 508 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.63 (s, 6 H, 3 × CH_2), 2.29 (s, 3 H, CH_3), 3.42 (s, 4 H, 2 × CH_2), 6.68 (br s, 1 H, NH), 7.07(d, *J* = 8.2 Hz, 2 H, 2 × CH), 7.24 (dt, *J* = 8.2, 2.0 Hz, 2 H, 2 × CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.7, 24.2, 25.4, 45.6, 120.1, 129.3, 132.6, 136.4, 154.9.

MS (EI, 70 eV): *m*/*z* (%) = 218 (100) [M$^+$], 174 (14), 112 (97), 84 (13), 69 (40).

HRMS (EI, 70 eV): *m*/*z* calcd for $C_{13}H_{18}ON_2$: 218.1419; found: 218.1404.

_N_-Phenyl-1-morpholinecarboxamide (1l)

Compound **1l** was purified by washing with toluene.

Yield: 1.33 g (65%); mp 160.4 °C (Lit.[18] 161.5–162 °C).

IR (KBr): 3269, 2953, 2858, 1634, 1541, 1444, 1251, 1115, 746 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.44 (t, *J* = 4.8 Hz, 4 H, 2 × CH_2), 3.68 (t, *J* = 4.8 Hz, 4 H, 2 × CH_2), 6.60 (br s, 1 H, NH), 7.04 (t, *J* = 7.0 Hz, 1 H, CH), 7.24–7.35 (m, 4 H, 4 × CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.2, 66.4, 120.2, 123.3, 128.8, 138.8, 155.2.

MS (EI, 70 eV): *m*/*z* (%) = 206 (100) [M$^+$], 114 (81), 77 (16), 70 (55), 57 (25).

HRMS (EI, 70 eV): *m*/*z* calcd for $C_{11}H_{14}O_2N_2$: 206.1055; found: 206.1069.

Large-Scale Preparation of _N_-Butyl-_N_-methyl-_N′_-(3,4-dichlorophenyl)urea (1m)

A dark-red solution containing *N*-butylmethylamine (**2h**; 23.6 mL, 200 mmol), 3,4-dichloroaniline (**3f**; 16.2 g, 100 mmol), and powdered sulfur (3.21g, 100 mmol) in DMF (100 mL), was vigorously stirred under CO (0.1 MPa) at 20 °C for 24 h. Into the resulting red solution, molecular O_2 (0.1 MPa) was charged at 20 °C (exothermic reaction). The reaction mixture was stirred for an additional 6 h at 20 °C. The resulting red solution was then poured into 1 M HCl (200 mL) and the deposited white solid was washed with hexane (200 mL). *N*-Butyl-*N*-methyl-*N′*-(3,4-dichlorophenyl)urea (**1m**) was purified by recrystallization (hexane–toluene).

Yield: 21.8 g (79%); mp 100.9 °C (Lit.[3] 101.5–103 °C).

IR (KBr): 3300, 2959, 2930, 1642, 1581, 1475, 1297, 875 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.4 Hz, 3 H, CH_3), 1.34 (sext, *J* = 7.4 Hz, 2 H, CH_2), 1.56 (quin, *J* = 7.4 Hz, 2 H, CH_2), 2.99 (s, 3 H, CH_3), 3.33 (t, *J* = 7.4 Hz, 2 H, CH_2), 6.48 (br s, 1 H, NH), 7.20 (dd, *J* = 8.8, 2.3 Hz, 1 H, CH), 7.29 (d, *J* = 8.8 Hz, 1 H, CH), 7.61 (d, *J* = 2.3 Hz, 1 H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 20.0, 30.1, 34.6, 48.9, 119.0, 121.4, 125.8, 130.1, 132.4, 138.9, 154.8.

MS (EI, 70 eV): *m*/*z* (%) = 276 (42) [M$^+$ + 2], 274 (65) [M$^+$], 187 (10), 161 (11), 114 (100), 58 (16), 57 (88).

HRMS (EI, 70 eV): *m*/*z* calcd for $C_{12}H_{16}ON_2Cl_2$: 274.0640; found: 274.0635.

Bis(_N_,_N_-dipropylcarbamoyl)disulfide (4a)

Pr_2NH (**2a**; 2.73 mL, 20 mmol), powdered sulfur (321 mg, 10 mmol), and DMF (20 mL) were placed in a 100 mL flask under an argon atmosphere. The flask was charged with CO (0.1 MPa), and the mixture was vigorously stirred under a balloon of CO (0.1 MPa) at 20 °C for 16 h. The flask was purged of CO, and charged with O_2 (0.1 MPa) at 20 °C, then the solution was stirred under a balloon of O_2 (0.1 MPa) for an additional 6 h at 20 °C. The resulting orange solution was poured into 1 M HCl (100 mL), and extracted with *t*-BuOMe (2 × 50 mL). Bis(*N*,*N*-dipropylcarbamoyl)disulfide (**4a**) was purified as an oil, by short-column chromatography (silica gel; EtOAc).

Yield: 374 mg (23%); oil.[13]

IR (NaCl): 2964, 2933, 2874, 1681, 1404, 1218, 1119, 708 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90–0.92 (m, 12 H, 4 × CH_3), 1.58–1.72 (m, 8 H, 4 × CH_2), 3.36 (br s, 8 H, 4 × CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.2, 20.9, 22.1, 50.5, 163.4.

MS (EI, 70 eV): *m*/*z* (%) = 320 (29) [M$^+$], 129 (27), 128 (100), 86 (77).

HRMS (EI, 70 eV): *m*/*z* calcd for $C_{14}H_{28}O_2N_2S_2$: 320.1592; found: 320.1576.

References

(1) *Bioorganic Chemistry of Pesticides*; Eto, M., Ed.; Soft Science Publications: Tokyo, **1985**, 73.
(2) *Pesticide Data Book*, 3rd ed.; Uesugi, Y.; Ueji, M.; Koshioka, M., Eds.; Soft Science Publications: Tokyo, **1997**, 288.
(3) *Merck Index*, 14th ed.; O'Neil, M. J.; Heckelman, P. E.; Koch, C. B.; Roman, K. J., Eds.; Merck & Co., Inc.: Whitehouse Station NJ, **2006**, 6435.
(4) Franz, R. A.; Applegath, F. *J. Org. Chem.* **1961**, *26*, 3304.
(5) Franz, R. A.; Applegath, F.; Morriss, F. V.; Baiocchi, F. *J. Org. Chem.* **1961**, *26*, 3306.
(6) Franz, R. A.; Applegath, F.; Morriss, F. V.; Baiocchi, F.; Bolze, C. *J. Org. Chem.* **1961**, *26*, 3309.
(7) Franz, R. A.; Applegath, F.; Morriss, F. V.; Baiocchi, F.; Breed, L. W. *J. Org. Chem.* **1962**, *27*, 4341.
(8) Macho, V.; Kralik, M.; Ligac, G.; Bojsova, E.; Vojcek, L. *Collect. Czech. Chem. Commun.* **1996**, *61*, 381.
(9) Wang, X.; Lu, S. *J. Mol. Catal.* **2006**, *255*, 25.
(10) Yang, Y.; Lu, S. *Tetrahedron Lett.* **1999**, *40*, 4845.
(11) Mizuno, T.; Iwai, T.; Ishino, Y. *Tetrahedron* **2005**, *61*, 9157.
(12) Mizuno, T.; Mihara, M.; Iwai, T.; Ito, T.; Ishino, Y. *Synthesis* **2006**, 2825.
(13) Mizuno, T.; Nakai, T.; Mihara, M. *Heteroat. Chem.* **2009**, *20*, 64.
(14) Mizuno, T.; Daigaku, T.; Nishiguchi, I. *Tetrahedron Lett.* **1995**, *36*, 1533.
(15) Ozaki, S.; Nagoya, T. *Bull. Chem. Soc. Jpn.* **1957**, *30*, 444.
(16) Lee, S.-H.; Matsushita, H.; Clapham, B.; Janda, K. D. *Tetrahedron* **2004**, *60*, 3439.
(17) Hoffmann, R. W.; Hagenbruch, B.; Smith, D. M. *Chem. Ber.* **1977**, *110*, 23.
(18) Henry, R. A.; Dehn, W. M. *J. Am. Chem. Soc.* **1949**, *71*, 2297.