Solvent-Free Synthesis of Urea Derivatives from Primary Amines and Sulfur under Carbon Monoxide and Oxygen at Atmospheric Pressure

Takumi Mizuno,* Masatoshi Mihara, Takeo Nakai, Toshiyuki Iwai, Takatoshi Ito
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
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Abstract: A solvent-free carbonylation and oxidation system aimed at green and sustainable chemistry was developed. With these reactions, an environmentally benign synthesis of urea derivatives could be carried out in good to excellent yields from primary amines and sulfur at ambient pressure of carbon monoxide and oxygen. For example, 1,1'-dioctylurea was prepared in 99% yield from two equivalents octylamine and one equivalent sulfur in the presence of carbon monoxide (1 atm) at 80 °C and oxygen (1 atm) at room temperature, in the complete absence of solvent.

Key words: urea derivatives, carbon monoxide, oxygen, sulfur, solvent-free

Urea derivative synthesis using carbon monoxide and sulfur was first reported in 1961.1–4 The Monsanto group introduced sulfur-assisted carbonylation of primary amines by carbon monoxide to form urea derivatives. However, this reaction requires high temperatures and pressurized carbon monoxide.

In our continuous study on the synthesis of urea derivatives under milder reaction conditions, we first reported the carbonylation of amines by carbon monoxide and sulfur, followed by oxidation by molecular oxygen to provide urea derivatives in good yields in tetrahydrofuran at 20 °C and 1 atm.4 But this carbonylation is sluggish, and the preparative method requires long reaction times. Also, its application to the synthesis of aromatic urea derivatives has remained difficult.

Recently, we reported on the solvent-assisted thiocarbonylation of amines by carbon monoxide and sulfur to afford S-alkyl thiocarbamates in good yields.5 In this reaction system, the thiocarbonylation of amines by carbon monoxide and sulfur was powerfully assisted by dimethyl sulfoxide or N,N-dimethylformamide as a solvent under mild conditions (1 atm, 20 °C). We explored a straightforward synthetic method toward urea derivatives, including aromatic urea derivatives, by the carbonylation of amines with carbon monoxide and sulfur followed by oxidation with molecular oxygen in N,N-dimethylformamide or dimethyl sulfoxide under mild conditions (1 atm, 20 °C). The corresponding urea derivatives were obtained by these reactions from primary amines in good to excellent yields under mild conditions.6

These reactions, however, need N,N-dimethylformamide or dimethyl sulfoxide as an organic solvent and accelerator of carbonylation of amines by carbon monoxide and sulfur. The increasing need for sustainable strategies in organic synthesis has led to a growing interest in reactions in the absence of solvent, and the use of water and other nonclassical solvents (such as supercritical fluids and ionic liquids).7–9 In our exploration of cleaner, green chemistry processes, we recently established a successful synthesis of 1H-quinazoline-2,4-diones in excellent yields when supercritical carbon dioxide was used as a reactant and a solvent10 or when carbon dioxide (1 atm) was used as a reactant under solvent-free conditions.11 Herein we report the full results of our research into an environmentally friendly strategy for the synthesis of urea derivatives from primary amines, carbon monoxide, sulfur, and oxygen in the absence of solvent.

First, the influence of reaction temperature and quantity of amine on the carbonylation was examined; for this the control reaction was that of octylamine (2a) leading to N,N'-dioctylurea (1a) (Scheme 1, Table 1). Initially, we examined the synthesis of N,N'-dioctylurea (1a) under solvent-free conditions by the carbonylation of octylamine (2a; 25 mmol, 1.25 equiv) with carbon monoxide (1 atm) at 20 °C, followed by oxidation with molecular oxygen (1 atm, r.t.). However, the carbonylation of 2a proceeded slowly under slurry conditions, and 1a formed in low yield (30%; Table 1, entry 1).

Increasing the temperature of the carbonylation from 60 to 150 °C did have an effect on the yield of 1a (Table 1). At temperatures between 80 and 120 °C (Table 1, entries 3, 8, and 11), N,N'-dioctylurea (1a) was obtained in good yield (60–68%) from 1.25 equivalents of 2a. Use of an excess of octylamine (2a) resulted in remarkable improvements in the yield of 1a, with 2.0 equivalents of...
In this solvent-free reaction system, octylamine (2a) giving 1a in almost quantitative yield (Table 1, entries 5, 10, and 13).

Next, the effect of the addition of tertiary amines (20 mmol) readily reacted with carbon monoxide (1 atm) and sulfur (10 mmol, 1.0 equiv) at 80 °C within four hours, followed by oxidation with molecular oxygen under ambient pressure at 20 °C within one hour. Finally, N,N'-dicotylyurea (1a) was obtained as a pure white solid in 99% yield, based on sulfur (Scheme 1; Table 1, entry 5).

Next, the effect of the addition of tertiary amines (20 mmol, 1.0 equiv) to the reaction with 1.0 equivalent (20 mmol) of octylamine (2a) was tested. The addition of triethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene had no effect, with the yield of 1a remaining at 66% and 56% respectively (Table 1, entries 6 and 7). Therefore, an excess of primary amine 2a is necessary for the synthesis of urea 1a in quantitative yield.

To demonstrate the efficiency and scope of the solvent-free synthetic method, we investigated the preparation of a variety of urea derivatives 1a–p from the corresponding amines 2a–p (2.0 equiv) under carbon monoxide (1 atm) at 80 °C for four hours, followed by oxidation with oxygen (1 atm) at 20 °C for one hour (Scheme 2; Table 2).

Primary amines 2a–f and 2h–j were suitable reagents for this synthetic method, and provided the corresponding N,N'-dialkylureas 1a–f and 1h–j in good to excellent yields under solvent-free condition (Table 2, entries 1–6 and 8–10). However, N,N'-bis(1,1,3,3-tetramethylbutyl)urea (1g) was obtained in a low yield (17%), because of the bulkiness of (1,1,3,3-tetramethylbutyl)amine (2g) (Table 2, entry 7). N,N'-Diphenylureas 1k–m were obtained in low yields from aromatic amines 2k–m in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (Table 2, entries 11–13), but in the absence of 1,8-diazabicyclo[5.4.0]undec-7-ene, there was no formation of 1k (Table 2, entry 11). The low yields of N,N'-diphenylureas at 80 °C for four hours, followed by oxidation with oxygen (1 atm) at 20 °C for one hour (Scheme 2; Table 2).

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1k–n (Table 2, entries 11–14) are the consequence of the basicity of anilines 2k–n. 3-Nitroaniline (2n), with an electron-withdrawing group on the ring, formed no N,N-bis(3-nitrophenyl)urea (1n) under these conditions (Table 2, entry 14).

We also examined the reactions of secondary amines 2o and 2p under these conditions, but urea derivatives 1o and 1p did not form (Table 2, entries 15 and 16). Under similar solvent-free conditions, S-methyl N,N-dialkylthiocarbamates 4o and 4p were obtained in moderate yields (43 and 53%, respectively) by esterification of N,N-dialkylthiocarbamate salts 3o and 3p with methyl iodide (Scheme 3). Therefore, 3o and 3p could not be oxidized with oxygen.

![Scheme 3](image)

Scheme 3 Synthesis of thiocarbamates 4o and 4p

Possible pathways for this synthesis of urea derivatives 1 from amines 2 by carbonylation followed by oxidation are shown in Schemes 4 and 5. For the carbonylation step (Scheme 4), on the basis of our finding that salts of thiolate anions 5 readily react with carbon monoxide to form salts of thiocarbamates 3, we suggest a plausible pathway via thiolate anions 5 for this solvent-free carbonylation of amines 2 in the presence of carbon monoxide and sulfur.

![Scheme 4](image)

Scheme 4 Proposed pathway for the synthesis of thiocarbamates 3 by carbonylation of amines 2

At the reaction stage where amines 2 are carbonylated, elemental sulfur undergoes S–S bond fission by the reaction with amines 2, and ammonium salts of thiolate anions 5 form (Scheme 4). The reaction of thiolate anions 5 with carbon monoxide gives the carbonylated species. Through an intramolecular rearrangement of the carbonylated species (Scheme 4, path A) or elimination of carbonyl sulfide from the carbonylated species (path B), ammonium salts of thiocarbamates 3 are generated. This reaction proceeds at high temperature under liquid conditions.

The ammonium salts of thiocarbamates 3 thus formed are then converted into urea derivatives 1, via isocyanate intermediates 7, and ammonium hydrogensulfide salts 6 (Scheme 5). Therefore, excess amounts of amines 2 (>1.5 equiv) are needed for the quantitative synthesis of ureas 1. The ammonium hydrogensulfide salts 6 forming from 3 are oxidized by molecular oxygen, and thus sulfur and amines 2 are recovered with water (Scheme 5). The reaction path via isocyanates 7 is supported by the attempted reactions of secondary amines 2o and 2p, which did not form the corresponding ureas 1o and 1p, because oxidation of the corresponding thiocarbamate salts 3o and 3p did not proceed.

An environmentally benign method for the synthesis of urea derivatives 1 in good to excellent yields under ambient pressure has been developed. It includes the solvent-free carbonylation of amines 2 with carbon monoxide and sulfur, and the oxidation of the resulting ammonium salts of hydrogensulfide 6 with molecular oxygen. This synthetic method of 1 is very significant in terms of green and sustainable chemistry, proceeding without organic solvent, under atmospheric pressure, and requiring easily available and inexpensive carbon monoxide, oxygen, and sulfur.

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. 1H (300 MHz) and 13C NMR (75 MHz) spectra were obtained on a JEOL JNM-AL300 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. Amines 2a–p, Et3N, DBU, sulfur (99.5%), CO (99.9%), and O2 (99.9%) were used as purchased.
**N,N'-Diocetylurea (1a); Typical Procedure**

Octylamine (2a; 6.63 mL, 40 mmol) and powdered sulfur (321 mg, 10 mmol) were placed in a 100-mL flask under an argon atmosphere. The flask was charged with an ambient pressure of CO, and vigorously stirred under CO from a balloon (1 atm) at 80 °C for 4 h. The color of the soln then changed from reddish black to pale yellow. The flask was purged of CO, and charged with O2 (1 atm) at 20 °C (slightly exothermic reaction). The reaction mixture was stirred under O2 from a balloon (1 atm) for another 1 h at 20 °C. The resulting pale yellow solid was then poured into 1 M HCl (200 mL), and the deposited white solid was washed with toluene (100 mL) and MTBE (100 mL); this gave pure 1a.

Yield: 2.816 g (99%); mp 91.0 °C (Lit.2 89–90 °C).

**1H NMR (300 MHz, DMSO-d6, 60 °C):** δ = 0.94 (s, 18 H, 6 CH3), 1.21 (t, J = 6.6 Hz, 4 H, 2 CH2), 5.32 (br s, 2 H, 2 NH), 5.77 (t, J = 5.6 Hz, 2 H, 2 NH).

**13C NMR (75 MHz, DMSO-d6, 60 °C):** δ = 13.3, 21.8, 28.6, 29.7, 39.1, 158.0.

**MS (EI, 70 eV):** m/z (% = 200 (100) [M+], 171 (46), 144 (24), 101 (16).

**HRMS (EI, 70 eV):** m/z calcld for C15H32ON2: 256.2515; found: 256.2518.

**N,N'-Dicyclohexylurea (1e)**

Yield: 2.006 g (90%); mp 231.7 °C (Lit.2 229–230 °C).

**IR (KBr):** 3327, 2928, 2850, 1617, 1576, 1311, 1244, 1089 cm−1.

**MS (EI, 70 eV):** m/z (% = 256 (100) [M+], 213 (45), 199 (39), 158 (29).

**HRMS (EI, 70 eV):** m/z calcld for C15H32ON2: 256.2515; found: 256.2518.

**N,N'-Dipentylurea (1b)**

Compound 1b was purified by short-column chromatography (sila- gel, EtOAc).

Yield: 1.517 g (76%); mp 85.6 °C (Lit.14 88 °C).

**IR (KBr):** 3366, 2955, 2932, 2861, 1623, 1579 cm−1.

**1H NMR (300 MHz, DMSO-d6):** δ = 0.85 (t, J = 6.9 Hz, 6 H, 2 CH3), 1.17–1.38 (m, 12 H, 6 CH2), 2.93 (q, J = 6.5 Hz, 4 H, 2 CH2), 5.68 (t, J = 5.6 Hz, 2 H, 2 NH).

**13C NMR (75 MHz, DMSO-d6, 60 °C):** δ = 13.9, 21.8, 28.6, 29.7, 39.1, 158.0.

**HRMS (EI, 70 eV):** m/z (% = 200 (100) [M+], 171 (46), 144 (24), 101 (16).

**N,N'-Bis(3-methoxypropyl)urea (1c)**

Compound 1c was purified by recrystallization from hexane.

Yield: 1.983 g (97%); mp 52.5 °C (Lit.2 47–49 °C).

**IR (KBr):** 3366, 2930, 2874, 1639, 1571, 1120 cm−1.

**1H NMR (300 MHz, DMSO-d6):** δ = 1.57 (quin, J = 6.5 Hz, 4 H, 2 CH2), 2.99 (q, J = 6.5 Hz, 4 H, 2 CH2), 3.20 (s, 6 H, 2 CH3), 3.30 (t, J = 6.5 Hz, 4 H, 2 CH2), 5.77 (t, J = 5.6 Hz, 2 H, 2 NH).

**13C NMR (75 MHz, DMSO-d6, 60 °C):** δ = 30.0, 36.5, 57.8, 69.7, 158.0.

**HRMS (EI, 70 eV):** m/z (% = 204 (36) [M]+, 189 (100), 90 (38), 88 (39).

**N,N'-Dihexylurea (1d)**

Compound 1d was purified by short-column chromatography (sila- gel, EtOAc).

Yield: 2.031 g (89%); mp 76.1 °C (Lit.2 73–74 °C).

**IR (KBr):** 3332, 2957, 2931, 2856, 1617, 1577, 1478, 1462, 1251, 1222 cm−1.
\[ \text{N,N'-Dibenzy lurea (1l)} \]

Compound 1l was purified by washing with toluene.

Yield: 1.978 g (82%); mp 169.4 °C (Lit.2 169–171 °C).

HRMS (EI, 70 eV): \[ m/z (%): 340 (100) [M^+] \], 296 (26), 179 (100), 91 (63).

\[ \text{N,N'-Bis(4-methoxybenzyl)urea (1j)} \]

Compound 1j was purified by washing with toluene and MTBE.

Yield: 2.087 g (70%); mp 173.8 °C (Lit.2 176–177 °C).

HRMS (EI, 70 eV): \[ m/z (%): 296 (30) [M^+] \], 135 (26), 120 (100), 91 (30).

\[ \text{S-Methyl N,N-Dipropylthiocarbamate (4o)} \]

Compound 4o was purified by short-column chromatography (silica gel, EtOAc).

Yield: 761 mg (43%); oil.\[^{16}\]

IR (neat): 2964, 2931, 2875, 1650, 1406, 1222, 1123 cm\(^{-1}\).

HRMS (EI, 70 eV): \[ m/z (%): 175 (29) [M^+] \], 123 (58), 122 (100), 108 (62), 80 (32), 69 (39).

\[ \text{S-Methyl Piperidinecarbothioate (4p)} \]

Compound 4p was purified by short-column chromatography (silica gel, EtOAc).

Yield: 838 mg (53%); oil.\[^{16}\]

IR (neat): 2935, 2855, 1650, 1412, 1250, 1209 cm\(^{-1}\).

HRMS (EI, 70 eV): \[ m/z (%): 159 (56) [M^+] \], 112 (100), 75 (18), 69 (72), 56 (13).

References

(13) In the previous report on urea synthesis from primary amines and carbon monoxide in the presence of a selenium catalyst, the same reaction pathway was suggested: Sonoda, N. *Pure Appl. Chem.* 1993, 65, 699.