

Facile Synthesis of Urea Derivatives under Mild Conditions

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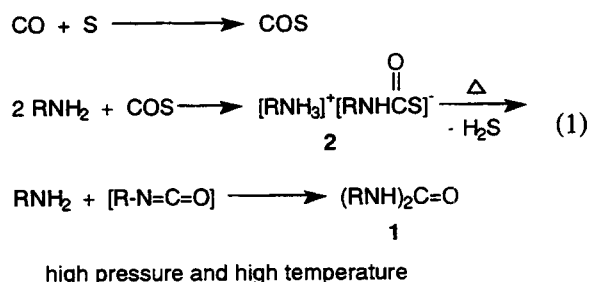
ABSTRACT

Urea derivatives were readily synthesized in good yields under quite mild conditions, i.e., at ambient pressure and room temperature by sulfur-assisted carbonylation of primary amines with carbon monoxide followed by oxidation of the resulting ammonium thiocarbamates with molecular oxygen.

INTRODUCTION

Sulfur-assisted carbonylation of primary amines with carbon monoxide to afford urea derivatives **1** was discussed about 30 years ago [1,2]. Ammonia, aliphatic, and aromatic amines react with carbon monoxide in the presence of elemental sulfur to form the corresponding ammonium thiocarbamates **2**. Elimination of hydrogen sulfide may form isocyanates as intermediates, which readily undergo aminolysis to give urea derivatives **1**, as shown in Equation 1. This carbonylation has been an important synthetic method for urea derivatives **1** because of good yields, cheap and easily available reagents, and easy operation. However, synthetic utility of this reaction on a large scale is considerably limited owing to the use of an autoclave and the drastic reaction conditions (70–500 psi, 100–130°C) required [4]. Therefore, we herein wish to report a new and convenient synthesis of urea derivatives **1** under very mild reaction conditions (1

atm, room temperature) by sulfur-assisted carbonylation of primary amines followed by treatment of the resulting product mixture with molecular oxygen.



RESULTS AND DISCUSSION

At first, we examined the efficiency of sulfur-assisted carbonylation under mild conditions. Carbonylation of butylamine with elemental sulfur and carbon monoxide was performed at 1 atm, room temperature for 20 hours followed by alkylation of the resulting butylammonium *N*-butylthiocarbamate (**2a**) with benzyl bromide to give *S*-benzyl *N*-butylthiocarbamate (**3a**) in 44% yield (Equation 2). This result suggests that sulfur-assisted carbonylation of butylamine with carbon monoxide can proceed under ordinary pressure at room temperature to form **2a** but that the drastic reaction conditions used in conventional methods may be needed for elimination of hydrogen sulfide from **2a**. Now, we have successfully accomplished a useful breakthrough to obtain urea derivatives **1**. By the combination of the sulfur-assisted carbonylation of amines using carbon monoxide with a subsequent oxidation of the resulting ammonium thiocarbamates **2** using molecular oxygen, a highly

Dedicated to Prof. Antonino Fava on the occasion of his seventieth birthday.

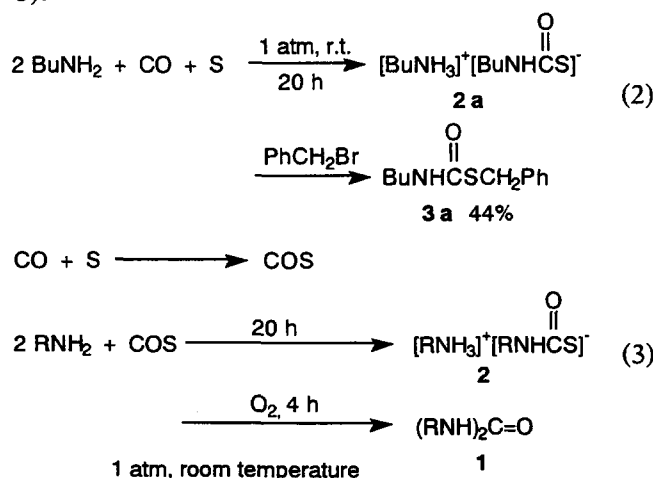
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TABLE 1 Synthesis of Urea Derivatives (1a–k)

R		Oxidizing Agent	Yield, % ^a
Bu	1a	O ₂	84
		air	72
		I ₂	mix.
<i>i</i> -Bu	1b	O ₂	57
<i>s</i> -Bu	1c	O ₂	39
<i>t</i> -Bu	1d	O ₂	24
Hex	1e	O ₂	77
<i>c</i> -Hex	1f	O ₂	89
Oct	1g	O ₂	97
C ₁₀ H ₂₁	1h	O ₂	64
C ₁₂ H ₂₅	1i	O ₂	63
CH ₂ =CH-CH ₂	1j	O ₂	59
Ph	1k	O ₂	9 ^b

^aIsolated yields.^bDBU (30 mmol) was added.

facile synthesis of urea derivatives **1** was successfully developed using primary amines, carbon monoxide, sulfur, and molecular oxygen under mild conditions (1 atm, room temperature) (Equation 3).



A variety of urea derivatives (**1a–k**) were prepared by the present method, as shown in Table 1. Good results were obtained by the use of molecular oxygen as an oxidizing agent to give urea derivatives (**1a–c**, **1e–g**) in moderate to excellent yields under mild reaction conditions. However, the yields of *N,N'*-di-*tert*-butylurea (**1d**) and *N,N'*-diphenylurea (**1k**) were low due to the bulkiness of the *tert*-butyl group or the low basicity of aniline, even in the presence of a strong base, DBU. Additionally, cyclic urea synthesis from diamines was also tried; however, the desired products were not obtained.

The following scheme shows a plausible pathway for the synthesis of urea derivatives under mild conditions (Scheme 1). The nucleophilic attack of an amine on S₈ (elemental sulfur) gives the zwitterion **4** which reacts with carbon monoxide to give

the carbonylated species **5**. Elimination of a smaller homologue of **4** from **5** generates carbonyl sulfide which reacts with the amine to form the ammonium thiocarbamate **2**. Oxidation of **2** with oxygen leads to the formation of the biscarbamoyl disulfide **6** as an intermediate [5], which is then subjected to aminolysis by the amine to give the urea derivative **1**.

Formation of the biscarbamoyl disulfide **6** as an intermediate may be the key step of the present synthesis of urea derivative **1** under mild conditions. However, these ideas are speculative and additional work will be needed to establish this reaction path on a firm basis. Because of the mild conditions (no need of an autoclave and heating), good yields, practical simplicity, and use of easily available and cheap reagents, the present method may provide a useful route for production of urea derivatives **1** on a large scale starting from amines, carbon monoxide, elemental sulfur, and molecular oxygen.

EXPERIMENTAL

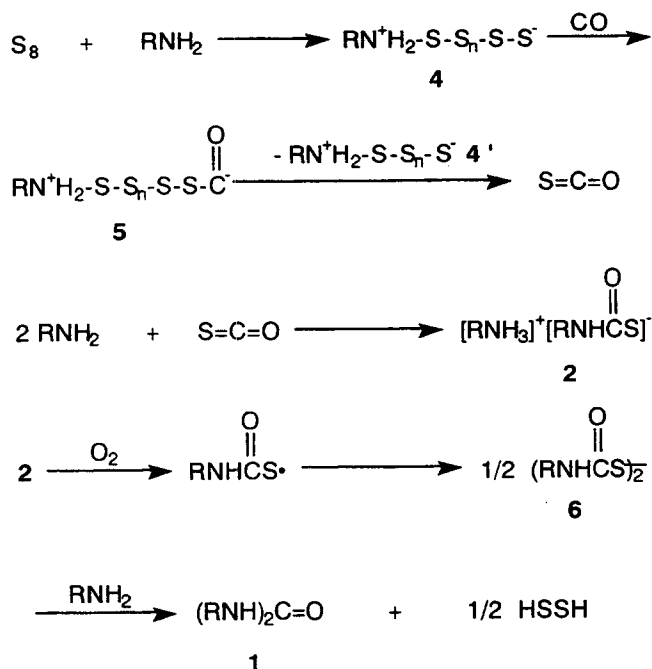
General

Melting points were determined on a Mettler FP 5 instrument and were uncorrected. Infrared (IR) spectra were recorded on a JASCO A-3 spectrometer. ¹H NMR spectra were obtained on a JEOL JNM-EX270 (270 MHz) instrument. Chemical shifts were reported relative to tetramethylsilane (δ -units). Mass spectra were recorded on a JEOL JMS-DX303HF spectrometer. Amines were dried over potassium hydroxide and purified by distillation. THF was dried over sodium wire before use and purified by distillation. Powdered sulfur (99.5%), carbon monoxide (99.9%), and oxygen (99.5%) were used as purchased.

Typical Procedure for Synthesis of *N,N'*-Dibutylurea (**1a**)

Elemental sulfur (0.32 g, 10 mmol) was added to a THF solution (20 mL) of butylamine (2.47 mL, 25 mmol), and the solution was vigorously stirred at 20°C for 20 hours under carbon monoxide (1 atm). After evacuation of the unreacted carbon monoxide, oxidation of the mixture with molecular oxygen (1 atm) was performed at 20°C with stirring for an additional 4 hours. Then, evaporation of the solvent and an excess amount of butylamine, followed by purification by short-column chromatography (silica gel, AcOEt), gave **1a** in a 84% yield (1.45 g).

N,N'-Dibutylurea (**1a**). Mp 72.8°C (Ref. [7], 71°C); IR (KBr) 3340 (N-H), 1615 (C=O), 1575 cm⁻¹ (N-H); ¹H NMR (CDCl₃) δ 0.91 (t, *J* = 7 Hz, 6H), 1.27–1.52 (m, 8H), 3.14 (q, *J* = 7 Hz, 4H), 4.93 (brs,



SCHEME 1

2H); MS, m/z (%), 172 (M^+ , 100), 129 (37), 100 (33), 57 (47).

N,N'-Diisobutylurea (**1b**). Mp 131.6°C (Ref. [1b], 128–130°C); IR (KBr) 3350 (N-H), 1625 (C=O), 1575 cm^{-1} (N-H); $^1\text{H NMR}$ (CDCl_3) δ 0.90 (d, $J = 7$ Hz, 12H), 1.68–1.75 (m, 2H), 2.98 (t, $J = 7$ Hz, 4H), 5.09 (brs, 2H); MS, m/z (%), 172 (M^+ , 100), 157 (36), 129 (26), 56 (65).

N,N'-Di-*sec*-butylurea (**1c**). Mp 135.8°C (Ref. [1b] 135°C); IR (KBr) 3340 (N-H), 1625 (C=O), 1575 cm^{-1} (N-H); $^1\text{H NMR}$ (CDCl_3) δ 0.91 (t, $J = 7$ Hz, 6H), 1.10 (d, $J = 7$ Hz, 6H), 1.39–1.49 (m, 4H), 3.61–3.71 (m, 2H), 4.49 (brs, 2H); MS, m/z (%), 172 (M^+ , 33), 143 (100), 72 (29), 58 (84).

N,N'-Di-*tert*-butylurea (**1d**). Mp 232.3°C (sublimation) (Ref. [1b], 245°C); IR (KBr) 3360 (N-H), 1635 (C=O), 1560 cm^{-1} (N-H); $^1\text{H NMR}$ (d_6 -DMSO) δ 1.19 (s, 18H), 5.43 (brs, 2H); MS, m/z (%), 172 (M^+ , 3), 157 (11), 58 (100); exact MS calcd 172.1576, found 172.1605.

N,N'-Dihexylurea (**1e**). Mp 75.0°C (Ref. [1b] 73–74°C); IR (KBr) 3330 (N-H), 1610 (C=O), 1575 cm^{-1} (N-H); $^1\text{H NMR}$ (CDCl_3) δ 0.88 (t, $J = 7$ Hz, 6H), 1.23–1.36 (m, 12H), 1.42–1.49 (m, 4H), 3.13 (q, $J = 7$ Hz, 4H), 5.12 (brs, 2H); MS, m/z (%), 228 (M^+ , 100), 199 (53), 185 (66), 128 (45).

N,N'-Dicyclohexylurea (**1f**). Mp 230.7°C (Ref. [1b], 229–230°C); IR (KBr) 3330 (N-H), 1625 (C=O),

1575 cm^{-1} (N-H); $^1\text{H NMR}$ (CD_3OD) δ 1.06–2.04 (m, 20H), 3.40–3.50 (m, 2H); MS, m/z (%), 224 (M^+ , 26), 143 (21), 99 (39), 56 (100).

N,N'-Dioctylurea (**1g**). Mp 90.0°C (Ref. [1b], 89–90°C); IR (KBr) 3330 (N-H), 1610 (C=O), 1580 cm^{-1} (N-H); $^1\text{H NMR}$ (d_6 -DMSO) δ 0.86 (t, $J = 7$ Hz, 6H), 1.25–1.37 (m, 24H), 2.95 (q, $J = 7$ Hz, 4H), 5.62 (brs, 2H); MS, m/z (%), 284 (M^+ , 100), 227 (70), 213 (70), 55 (71).

N,N'-Didecylurea (**1h**). Mp 99.0°C (Ref. [1b], 99–100°C); IR (KBr) 3340 (N-H), 1615 (C=O), 1580 cm^{-1} (N-H); MS, m/z (%), 340 (M^+ , 100), 255 (62), 99 (79), 55 (84).

N,N'-Didodecylurea (**1i**). Mp 105.1°C (Ref. [1b], 105–106°C); IR (KBr) 3350 (N-H), 1615 (C=O), 1575 cm^{-1} (N-H); MS, m/z (%), 396 (M^+ , 68), 99 (100), 55 (79).

N,N'-Diallylurea (**1j**). Mp 96.1°C (Ref. [8], 95°C); IR (KBr) 3330 (N-H), 1620 (C=O), 1585 cm^{-1} (N-H); $^1\text{H NMR}$ (CDCl_3) δ 3.75–3.80 (m, 4H), 5.05–5.21 (m, 4H), 5.40 (brs, 2H), 5.76–5.90 (m, 2H); MS, m/z (%), 140 (M^+ , 5), 98 (11), 85 (10), 56 (100).

N,N'-Diphenylurea (**1k**). Mp 242.8°C (Ref. [9], 241–242°C); IR (KBr) 3330 (N-H), 1645 (C=O), 1595 (C=C), 1550 cm^{-1} (N-H); $^1\text{H NMR}$ (d_6 -DMSO) δ 6.96 (t, $J = 7$ Hz, 2H), 7.27 (t, $J = 8$ Hz, 4H), 7.45 (d, $J = 8$ Hz, 4H), 8.64 (brs, 2H); MS, m/z (%), 212 (M^+ , 15), 119 (10), 93 (100), 66 (15).

S-Benzyl *N*-butylthiocarbamate (**3a**). Mp 59.4°C; IR (KBr) 3275 (N-H), 1635 (C=O); $^1\text{H NMR}$ (CDCl_3) δ 0.91 (t, $J = 7$ Hz, 3H), 1.26–1.40 (m, 2H), 1.44–1.55 (m, 2H), 3.29 (q, $J = 6$ Hz, 2H), 4.16 (s, 2H), 5.33 (brs, 1H), 7.20–7.35 (m, 5H); MS, m/z (%), 223 (M^+ , 12), 124 (39), 91 (100), 57 (12); exact MS calcd 223.1031, found 223.1001.

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