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Novel Synthesis of *N*, *N*′-Dialkyl Cyclic Ureas Using Sulfur-Assisted Carbonylation and Oxidation

Takumi Mizuno, Takeo Nakai, and Masatoshi Mihara

Osaka Municipal Technical Research Institute, 1-6-50, Morinomiya, Joto-ku, Osaka 536-8553, Japan

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ABSTRACT: *The first example of cyclic urea synthesis from secondary amines by the use of sulfur-assisted carbonylation and oxidation was established. By combined sulfur-assisted carbonylation of secondary α,ω-diamines under an ambient pressure of carbon monoxide at 20°C with oxidation by molecular oxygen (0.1 MPa, 20°C), a facile synthetic method for N,N′-dialkyl cyclic ureas including 1,3-dimethyl-2-imidazolidinone was developed.* © 2009 Wiley Periodicals, Inc. Heteroatom Chem 20:64–68, 2009; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20508

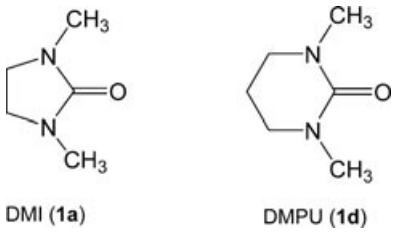
INTRODUCTION

1,3-Dimethyl-2-imidazolidinone (DMI; **1a**) (Scheme 1) is a colorless, transparent, high polar solvent with high thermal and chemical stability and noncorrosiveness. It can be used in a variety of applications (detergents, dyestuffs, and electronic materials) and in the manufacture of polymers. Its versatility can be attributed to its chemical properties, which are its excellent solubility for inorganic and organic compounds, high dielectric constant, and solvation effect [1]. Also, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (**1d**) (Scheme 1) is used as a polar, aprotic organic solvent [2]. In particular, **1a** and **1d** are suitable replacements for the carcinogenic solvent, hexamethylphosphoramide [3,4]. A variety of synthetic methods for *N*, *N*′-dialkyl cyclic ureas **1** containing **1a** and **1d** were developed, based on the carbonylation of secondary α, ω-diamines **2**. Among them, a general synthetic method for cyclic ureas **1** was based upon the carbonylation of **2** with phosgene as a carbonyl source [5,6]. However, use of this preparative method is considerably limited, because of high toxicity of phosgene. Urea and carbon dioxide in the presence of transition metal catalysts were recognized as a carbonyl source for the synthesis of **1** [7–11]. Also, cyclic ureas **1** were given by the displacement from corresponding cyclic thioureas [12,13]. Furthermore, carbon monoxide was a useful raw material for the preparation of **1**. *N*, *N*′-Dialkyl cyclic ureas **1** were afforded from secondary α, ω-diamines **2** and carbon monoxide in the presence of transition metal catalyst [14].

Recently, we found that sulfur-assisted carbonylation with carbon monoxide was strongly accelerated by *N*, *N*-dimethylformamide (DMF) or dimethyl sulfoxide (DMSO) [15] and developed a synthetic process of acyclic urea derivatives from primary amines, carbon monoxide, sulfur, and oxygen under mild conditions (0.1 MPa, 20°C) [16] or solvent-free conditions (0.1 MPa) [17]. However, this acyclic urea synthesis using sulfur-assisted carbonylation and oxidation has a serious limitation that is only applicable to the primary amines as reactants.

Therefore, our objective has been to develop a straightforward synthetic method for **1** by the

Correspondence to: Takumi Mizuno; e-mail: tmizuno@omtri.city.osaka.jp



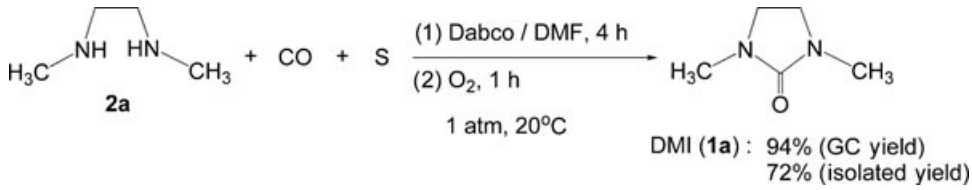
SCHEME 1 1,3-Dimethyl-2-imidazolidinone (**1a)** and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (1**d**).

carbonylation of **2** with carbon monoxide and sulfur followed by oxidation with molecular oxygen under mild conditions (0.1 MPa, 20°C). To the best of our knowledge, this is the first example of cyclic urea synthesis from secondary amines by the sulfur-assisted carbonylation with carbon monoxide and oxidation using molecular oxygen.

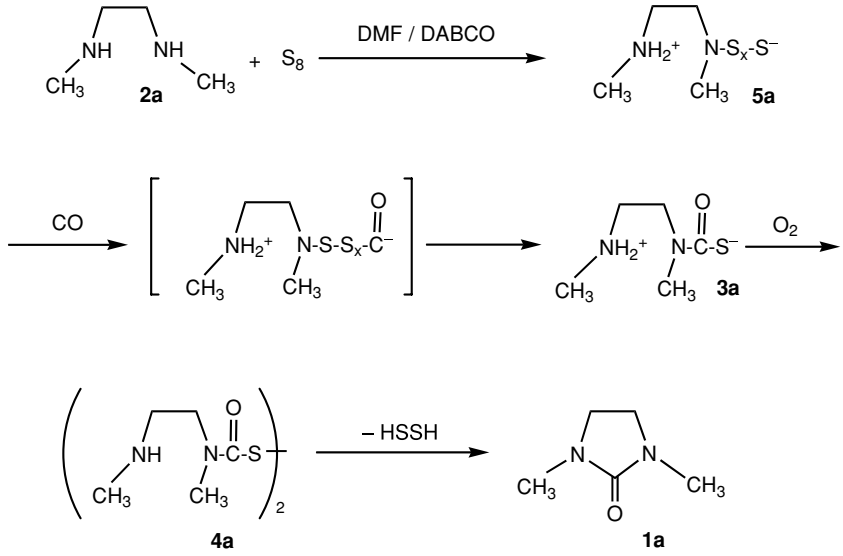
RESULTS AND DISCUSSION

Our investigation into the sulfur-assisted carbonylation and oxidation of secondary α,ω-diamines **2** employing *N*, *N*-dimethylformamide as a solvent led to the successful synthesis of *N*, *N*′-dialkyl cyclic ureas **1** (Schemes 2 and 3). *N*, *N*′-Dimethylethylenediamine (**2a**) readily reacted with carbon monoxide (0.1 MPa) and sulfur (1.5 equiv.) in the presence of 1,4-diazabicyclo[2.2.2]octane (Dabco®) (0.5 equiv.) at 20°C for 4 h in *N*, *N*-dimethylformamide solvent. Then, the generated thiocarbamate salt **3a** in the DMF solution was oxidized by molecular oxygen under an ambient pressure at 20°C for 1 h. Finally, 1,3-dimethyl-2-imidazolidinone (**1a**) was obtained in 94% yield (GC yield) based on **2a**.

First, the influence of base and solvent was examined on the synthesis of **1a** by the sulfur-assisted carbonylation and oxidation of **2a** (Table 1). In the absence of additional base, **1a** was obtained in good yield in *N*, *N*-dimethylformamide solvent (Entry 1). By addition of 0.5 equiv. of Dabco®, 1-methylpyrrolidine, or triethylamine in DMF, yields of **1a** were improved (Entries 2–4). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) did not have an additional effect for the preparation of **1a** (Entry 5), and potassium carbonate (K_2CO_3) lowered the yield of **1a**, because of low



SCHEME 2 Synthesis of 1,3-dimethyl-2-imidazolidinone (**1a**).



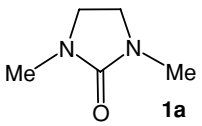
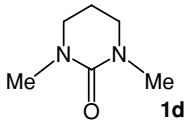
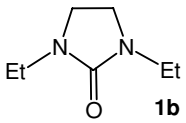
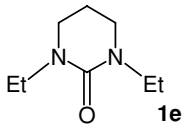
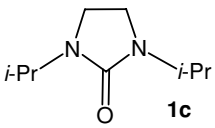
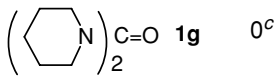
SCHEME 3 Proposed pathway for the synthesis of 1,3-dimethyl-2-imidazolidinone (**1a**).

TABLE 1 Effect of Base and Solvent on Synthesis of DMI (**1a**)

Entry	*Base*	*Solvent*	*Yield (%)*[a]
1	None	DMF	81
2	Dabco	DMF	94
3	1-Methylpyrrolidine	DMF	92
4	Triethylamine	DMF	87
5	DBU	DMF	81
6	K_2CO_3	DMF	27
7	Dabco	DMAc	87
8	Dabco	DMSO	73
9	Dabco	THF	17
10	Dabco	MTBE	0
11	Dabco	Toluene	0

Reaction conditions: *N*, *N*′-dimethylethylenediamine (**2a**) (1.07 mL, 10 mmol), sulfur (481 mg, 15 mmol), base (5 mmol), solvent (20 mL), CO (1 atm), 20°C, 4 h for carbonylation, and O_2 (1 atm), 20°C, 1 h for oxidation.
[a]GC yields.

TABLE 2 Synthesis of *N*, *N*′-Dialkyl Cyclic Ureas (**1a–e**) and Acyclic Ureas (**1f–g**)

Product	*Yield (%)*[a]	*Product*	*Yield (%)*[a]
 **1a**	94	 **1d**	17
	72[b]		
 **1b**	70	 **1e**	Trace
 **1c**	41	$(Pr_2N)_2C{=}O$ **1f**	0[b–d]
		 **1g**	0[c]

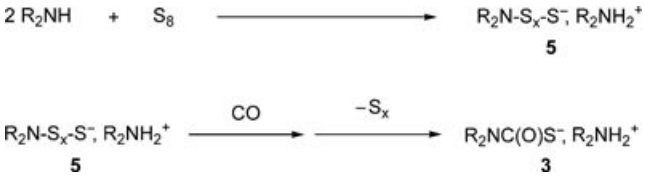
Reaction conditions: Amine (10 mmol), sulfur (481 mg, 15 mmol), Dabco (561 mg, 5 mmol), DMF (20 mL), CO (1 atm), 20°C, 4 h for carbonylation, and O_2 (1 atm), 20°C, 1 h for oxidation.
[a]GC yields.
[b]Isolated yields.
[c]Amine (20 mmol) was used.
[d]Bis(*N*, *N*-dipropylcarbamoyl) disulfide (**4f**) was formed in 36% (1.81 mmol).

solubility of K_2CO_3 in DMF (Entry 6). Using *N*, *N*-dimethylacetoamide (DMAc) or dimethyl sulfoxide as a solvent in the presence of Dabco®, **1a** was given in good yields (Entries 7,8). However, tetrahydrofuran (THF), *t*-butyl methyl ether (MTBE), and toluene were unsuitable for the preparation of 1,3-dimethyl-2-imidazolidinone (**1a**) (Entries 9–11).

Next, several *N*, *N*′-dialkyl cyclic ureas (**1a–d**) including **1a** were synthesized by the sulfur-assisted carbonylation with carbon monoxide and oxidation with molecular oxygen under mild condition (0.1 MPa. 20°C) (Table 2). 1,3-Dimethyl-2-imidazolidinone (**1a**) and 1,3-diethyl-2-imidazolidinone (**1b**) were obtained in good to excellent yields. However, the yield of **1c** was lowered by bulkiness of *N*-isopropyl groups. Furthermore, the present method was ineffective in the formation of six-membered rings (**1d** and **1e**).

Under similar mild conditions, *S*-methyl *N*, *N*-dipropylthiocarbamate was obtained in excellent yield by esterification of *N*, *N*-dipropylthiocarbamates salt (**3f**) with methyl iodide [15]. However, secondary amines, dipropylamine (**2f**), and piperidine (**2g**) did not give acyclic ureas (**1f, g**) at all. In the case of **2f**, bis(*N*, *N*-dipropylcarbamoyl) disulfide (**4f**) was formed in place of tetrapropylurea (**1f**). Therefore, **4f** could not receive the nucleophilic substitution of **2f** by the bulkiness of **2f** and **4f**.

Scheme 3 shows possible pathways for the synthesis of **1a** by the carbonylation of **2a** followed by oxidation of the thiocarbamate **3**a. We have found that thiolate salts **5** readily react with carbon monoxide to give thiocarbamate salts **3** (Scheme 4) [18], and therefore we propose that a plausible pathway for this sulfur-assisted carbonylation of **2a** with carbon monoxide is via thiolate anion **5a**. At first, elemental sulfur undergoes S–S bond fission by the reaction with **2a**, to form ammonium thiolate (**5a**). The reaction of **5a** with carbon monoxide gives the carbonylated species. Through an intramolecular rearrangement or elimination of carbonyl sulfide from the carbonylated species, thiocarbamate salt (**3a**) is generated. The thus formed thiocarbamate salt (**3a**) is oxidized by molecular oxygen, giving **1a** via dicarbamoyl disulfide (**4a**). Indeed, in the case of the reaction with **2f**, bis(*N*, *N*-dipropylcarbamoyl) disulfide (**4f**) was obtained in place of **1f**.



SCHEME 4 The reaction of thiolate aniones 5 with carbon monoxide.

In our previous reports [16,17] of urea synthesis from primary amines by sulfur-assisted carbonylation using carbon monoxide and oxidation with oxygen, isocyanate intermediates were suggested in this oxidation stage. Therefore, because of difficulty of aminolysis of bulky dicarbamoyl disulfides **4**, the formation of ureas **1** from the thiocarbamate salts **3** generated from primary amines is generally much easier, compared with from secondary amines.

CONCLUSION

In summary, a novel synthetic method for *N*, *N*′-dialkyl cyclic ureas **1**, especially 1,3-dimethyl-2-imidazolidinone (**1a**), has been developed under mild conditions (0.1 MPa, 20°C) in DMF, in which includes the sulfur-assisted carbonylation of secondary diamines **2** with carbon monoxide, and the oxidation of resulting thiocarbamate salts **3** with molecular oxygen. From the viewpoint of application to practical production of **1a**, the present method is very significant in terms of the use of easily available and cheap carbon monoxide, oxygen, sulfur, and DMF, and mild reaction conditions (0.1 MPa, 20°C).

EXPERIMENTAL

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, 75 MHz) instrument. Chemical shifts were reported in ppm relative to tetramethylsilane (δ-units). Mass and exact mass spectra were measured on a JEOL JMS-600 spectrometer. Amines **2a–g**, DMF, DMAc, DMSO, THF, MTBE, toluene, Dabco®, 1-methylpyrrolidine, triethylamine, DBU, K_2CO_3, sulfur (99.5%), carbon monoxide (99.9%), and oxygen (99.9%) were used as purchased.

Typical Procedure for the Synthesis of DMI **1a**

A dark red solution containing *N*, *N*′-dimethylethylenediamine (**2a**; 2.13 mL, 20 mmol), Dabco® (1.12 g, 10 mmol), and powdered sulfur (962 mg, 30 mmol) in DMF (20 mL) was vigorously stirred under CO (0.1 MPa) at 20°C for 4 h. Into the resulting brown emulsion of thiocarbamate salt (**3a**), O_2 (0.1 MPa) was charged at 20°C (exothermic reaction). The reaction mixture was stirred for an additional 1 h at 20°C. DMF was evaporated from the resulting brown emulsion, and 1,3-dimethyl-2-imidazolidinone (**1a**) was given by distillation.

1,3-Dimethyl-2-imidazolidinone (**1a**). Yield: 1.64 g (72%) yield; bp 107–109°C, 30 hPa (Lit. [1] 106–108°C, 23 hPa); ^{1}H NMR ($CDCl_3$): δ (ppm) 2.78 (s, 6H, CH_3), 3.27 (s, 4H, CH_2); ^{13}C NMR ($CDCl_3$): δ (ppm) 31.3, 44.9, 161.9; MS *m/z* (%): 114 (M^+, 100), 113 (54), 85 (11), 72 (10), 58 (14), 56 (21).

For the identification of **1a**, retention time of GC and NMR and MS spectra of **1a** was compared with those of commercially available DMI.

Procedure for the Formation of Bis(N,N-dipropylcarbamoyl) Disulfide **4f**

Dipropylamine (**2f**; 2.73 mL, 20 mmol), Dabco® (561 mg, 5 mmol), powdered sulfur (481 mg, 15 mmol), and DMF (10 mL) 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 (0.1 MPa) at 20°C for 4 h. The color of the solution then changed from red to reddish black. The flask was purged of CO and charged with O_2 (0.1 MPa) at 20°C (slightly exothermic reaction). The reaction mixture was stirred under O_2 from a balloon (0.1 MPa) for another 1 h at 20°C. The resulting orange solution was then poured into 1 M HCl (100 mL) and extracted by *t*-butyl methyl ether (200 mL). Bis(*N*, *N*-dipropylcarbamoyl) disulfide (**4f**) was purified as an oil, by short-column chromatography (silica gel, EtOAc).

Bis(N,N-dipropylcarbamoyl) Disulfide (**4f**). Yield: 581 mg (36%, 1.81 mmol) yield; IR (neat, cm^{-1}): ν 2964, 2874, 1681(C=O), 1467, 1404, 1218, 1118; ^{1}H NMR ($CDCl_3$): δ (ppm) 0.82–1.03 (m, 12H, CH_3), 1.53–1.80 (m, 8H, CH_2), 3.36 (br s, 8H, CH_2); ^{13}C NMR ($CDCl_3$): δ = 11.1, 20.9, 22.0, 50.3, 163.3; MS *m/z* (%): (ppm) 320 (M^+, 15), 129 (13), 128 (100), 86 (41); Exact MS: calcd for $C_{14}H_{28}O_2N_2S_2$: 320.1592; found: 320.1611.

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