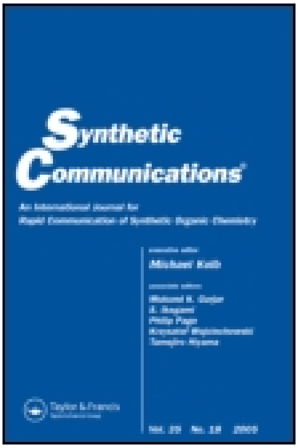

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$CeCl_3 \cdot 7H_2O$-KI-Catalyzed, Environmentally Friendly Synthesis of *N*,*N*′-Disubstituted Ureas in Water Under Microwave Irradiation

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Abstract: *N*,*N*′-Disubstituted ureas were efficiently synthesized by reactions of urea with a variety of amines in water under microwave irradiation using $CeCl_3 \cdot 7H_2O$-KI as catalyst. This protocol has advantages of not using toxic phosgene and hazardous organic solvents, high reaction rate, high yield, and a simple workup procedure.

Keywords: $CeCl_3 \cdot 7H_2O$-KI, environmentally friendly, microwave irradiation, PEG-400, *N*,*N*′-disubstituted urea, water medium

INTRODUCTION

N,*N*′-Disubstituted ureas are important subunits present in a number of naturally occurring compounds and have found numerous applications as dyes, antioxidants, pesticides, corrosion inhibitors, intermediates for the preparation of pharmaceuticals, and agricultural chemicals.[1] They can generally be synthesized from amines by phosgenation,[2] reductive carbonylation,[3] or oxidative carbonylation.[4] However, these reactions are not ecofriendly

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because of risks associated with using the toxic compounds phosgene and carbon monoxide. In addition, these reactions usually proceed in volatile organic solvents, which also cause environmental problems. Recently, Mojtahedi et al.[5] reported a solventless synthesis of disubstituted ureas by reactions of urea with arylamines. However, only diaryl-substituted ureas were given, and the yields of some examples were not satisfactory.

Organic reactions in aqueous media have been the subject of considerable attention in terms of achieving more environmentally friendly synthetic transformations.[6] In an effort to develop aqueous reactions, in this article, we report the $CeCl_3 \cdot 7H_2O$-KI-catalyzed, environmentally friendly aqueous method suitable to *N*,*N*′-diaryl, dialkyl, and diheterocyclyl substituted ureas, which utilizes a nontoxic industrial commodity (chemical urea) as starting material and microwave irradiation as heating source.

RESULTS AND DISCUSSION

In our preliminary experiments we investigated the synthesis of *N*,*N*′-diphenylurea, chosen as model process, under various conditions. When aniline (22 mmol) was treated with aqueous urea (10 mmol) in the absence of catalyst under reflux for 8 h, only 42% yield of *N*,*N*′-diphenylurea was obtained (entry 1, Table 1). The possible reason is that the poor solubility of aniline in water makes the process a heterogeneous reaction, which significantly decreases the reaction rate. To speed up the reaction and improve the yield, some phase-transfer catalysts, such as n-Bu_4NBr, n-Bu_4NI, and poly (ethylene glycol) (PEG-400) were examined (entries 2, 3, 4). However, the results were still not good enough. For this reason, some catalytic systems, for example, $CuCl_2 \cdot 2H_2O$/PEG-400, $FeCl_3 \cdot 6H_2O$/PEG-400, $CeCl_3 \cdot 7H_2O$/PEG-400, $CeCl_3 \cdot 7H_2O$-NaI/PEG-400, and $CeCl_3 \cdot 7H_2O$-KI/PEG-400, were tested for the selected reactions (entries 6–10, Table 1). Fortunately, all systems improved the reaction yields. Among these, the best result was achieved using the $CeCl_3 \cdot 7H_2O$-KI/PEG-400 system. However, a prolonged reaction period was still needed for the completion of the reaction. Therefore, we utilized a microwave-irradiation technique in the reactions (entries 11–15, Table 1). The catalytic system $CeCl_3 \cdot 7H_2O$-KI/PEG-400 gave the best yield with an approximately 30-fold increase in the reaction rate (16 min) in comparison with conventional heating (8 h). Consequently, we decided to apply $CeCl_3 \cdot 7H_2O$-KI/PEG-400 and microwave irradiation to the synthesis of all *N*,*N*′-disubstituted ureas (Scheme 1). The results are summarized in Table 2.

The reactions of urea with aromatic amines in water promoted by microwave irradiation efficiently afforded *N*,*N*′-diaryl ureas using $CeCl_3 \cdot 7H_2O$-KI as catalyst and PEG-400 as phase-transfer catalyst (entries 1–10, Table 2). Arylamines bearing electron-donor groups, such as CH_3 and CH_3O (entries 2–4, Table 2), exhibited higher reaction rates than those

Table 1. Effect of catalytic systems and reaction conditions on the yield of *N,N′*-diphenylurea in water[a]

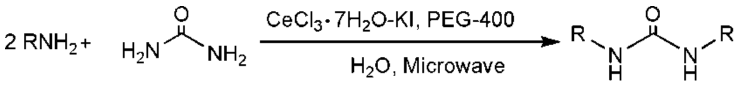
Entry	Catalytic system	Reaction condition	Reaction time	Yield[b] (%)
1	None	Reflux, 100°C	8 h	42
2	Bu_4NBr	Reflux, 100°C	8 h	50
3	Bu_4NI	Reflux, 100°C	8 h	54
4	PEG-400	Reflux, 100°C	8 h	64
5	$CeCl_3 \cdot 7H_2O$	Reflux, 100°C	8 h	76
6	$CuCl_2 \cdot 2H_2O$, PEG-400	Reflux, 100°C	8 h	87
7	$FeCl_3 \cdot 6H_2O$, PEG-400	Reflux, 100°C	8 h	89
8	$CeCl_3 \cdot 7H_2O$, PEG-400	Reflux, 100°C	8 h	91
9	$CeCl_3 \cdot 7H_2O$-NaI, PEG-400	Reflux, 100°C	8 h	96
10	$CeCl_3 \cdot 7H_2O$-KI, PEG-400	Reflux, 100°C	8 h	97
11	None	MW	16 min	51
12	PEG-400	MW	16 min	71
13	$CeCl_3 \cdot 7H_2O$	MW	16 min	83
14	$CeCl_3 \cdot 7H_2O$, PEG-400	MW	16 min	95
15	$CeCl_3 \cdot 7H_2O$-KI, PEG-400	MW	16 min	97

[a] Reaction conditions: urea (10 mmol), aniline (22 mmol), catalyst (0.2 mmol), H_2O (0.4 mL).

[b] Of isolated product.

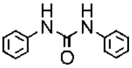
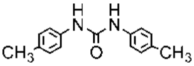
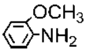
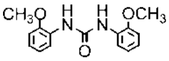
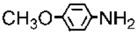
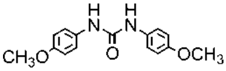
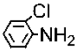
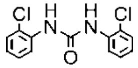
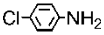
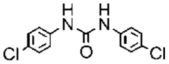
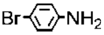
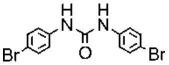
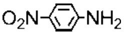
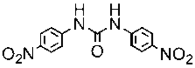
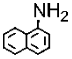
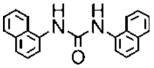
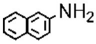
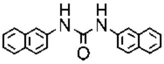
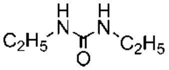
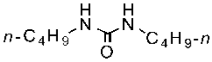
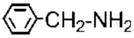
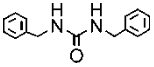
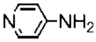
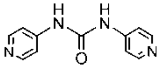
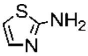
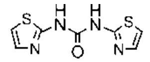
containing electron-withdrawing groups, such as NO_2 (entry 8, Table 2). Arylamines bearing *ortho* substituents (entries 3, 5, Table 2) showed certain steric hindrance compared with their *para* isomers (entries 4, 6, Table 2), which led to lower yields of the product. The reactions of urea with aliphatic amines in water (entries 11–13, Table 2) were faster than with aromatic amines. All reactions were complete within 8 min, giving high yields. The reactions of urea with heterocyclic amines (pyridine-4-amine, thiazole-2-amine) (entries 14, 15, Table 2), also efficiently produced corresponding disubstituted ureas. Furthermore, PEG-400 was not necessary for these two reactions owing to the good solubility of heterocyclic amines in water.

Most *N,N′*-disubstituted ureas can be readily separated from the final reaction mixture by hot filtration of aqueous solutions, except entries 11, 12, and 14, which required the cooling of the aqueous solutions to room temperature before filtration.



Scheme 1.

Table 2. $CeCl_3.7H_2O$-KI-catalyzed synthesis of *N*,*N*′-disubstituted ureas in water under microwave irradiation[a,b]

Entry	Amine	Product	Irradiation time (min)	Mp (°C)	Yield[c] (%)
1			16	242	96
2			12	269	95
3			12	185	82
4			12	240	96
5			16	225–226	86
6			16	302	94
7			16	295	95
8			20	305–306	83
9			20	277–278	93
10			20	293–294	94
11[d,e]	$C_2H_5NH_2$		4	121–122	87
12	n-$C_4H_9NH_2$		8	71–72	95
13			8	165–166	95
14[d]			8	197–198	88
15[d]			12	222–223	85

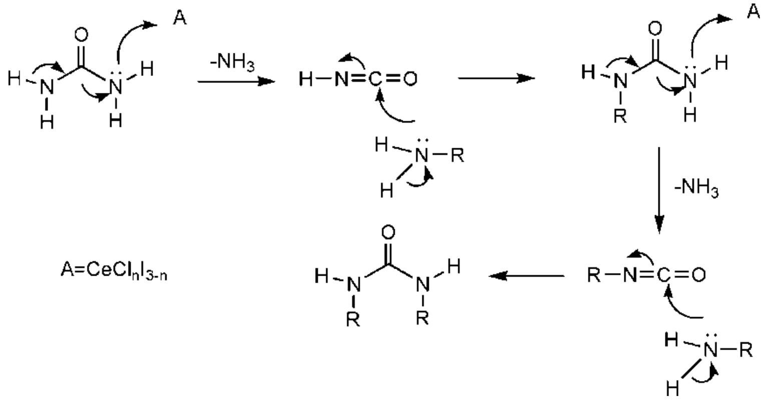
[a] Reaction conditions: urea (10 mmol), aniline (22 mmol), $CeCl_3 \cdot 7H_2O$ (0.2 mmol), PEG-400 (0.2 mol), H_2O (0.4 mL).

[b] All products were identified by ^1H NMR, IR, and elemental analyses and compared with authentic samples.

[c] Yields refer to the isolated products.

[d] No PEG-400 was added.

[e] The aqueous solution of ethylamine (70%) was used as starting material.



Scheme 2.

A plausible reaction mechanism for the title reactions is illustrated in Scheme 2. Urea reacts with one molecule of amine, librating one molecule of ammonia, and is transformed to monosubstituted urea **1**. Subsequently, the monosubstituted urea is converted to an isocyanate **2** with loss of another molecule of ammonia. Then, the isocyanate reacts with another amine molecule to produce *N*,*N*′-disubstituted urea. The $CeCl_3 \cdot 7H_2O$-KI is possibly first converted to $CeCl_nI_{3-n}$ (n = 0, 1, 2), which functions as a Lewis acid[7] to efficiently promote the elimination of ammonia.

In conclusion, we have developed a rapid, high-yield synthesis of *N*,*N*′-diaryl, dialkyl, and diheterocyclyl substituted ureas by reactions of urea with a variety of amines in water under microwave irradiation, which efficiently circumvents the use of toxic phosgene and volatile organic solvents. The synthesis is an environmentally friendly alternative to previous methods.

EXPERIMENTAL

IR were recorded using KBr pellets on an Alpha Centauri FTIR spectrophotometer and ^{1}H NMR spectra on an Avanci-D2X-200 instrument using $(CD_3)_2SO$ as solvent and Me_4Si as internal standard. Elemental analyses were performed on a Vario E1 elemental-analysis instrument. Mass spectra were recorded on a QP-1000A GC-MS using the impact mode (70 eV). Melting points were observed in an electrothermal melting-point apparatus and are uncorrected.

Preparation of *N*,*N*′-Diphenylurea under Microwave Irradiation

A mixture of urea (0.60 g, 10 mmol), aniline (2.05 g, 22 mmol), $CeCl_3 \cdot 7H_2O$ (0.07 g, 0.2 mmol), KI (0.03 g, 0.2 mmol), PEG-400 (0.08 g, 0.2 mmol) in

0.4 mL of water was charged in a round-bottom glass flask fitted with a reflux condenser attached to a water aspirator to remove ammonia. Then, the flask was placed in a modified microwave oven and subjected to microwave irradiation at 700 W for an appropriate time (Table 2). After the reaction was complete, the flask was removed from the microwave oven, the resulting mixture was quickly filtered, and the solid was washed with water to give white solid as product. An analytical sample was obtained by recrystallization from ethanol.

The other *N*,*N*′-disubstituted ureas were prepared in a similar way except the following:

Entries 11, 14, 15: no PEG-400 added.

Entry 8 product was recrystallized from DMF.

Entry 15 product was recrystallized from ethyl acetate.

Entries 11, 12, 14 products were recrystallized from water.

All products were identified by ^{1}H NMR, IR, and elemental analyses and compared with authentic samples. The physical and spectral data of some representative compounds are given here:

N,*N*′-Di(2-methoxyphenyl)urea: ^{1}H NMR: (DMSO-d$_6$, 200 MHz): δ 8.36 (2H, s, NH, exchangeable with D_2O), 6.84 (4H, d, $^3J = 8.8$ Hz, Ar-H), 7.32 (4H, d, $^3J = 8.8$ Hz, Ar-H), 3.69 (3H, s, CH_3); IR (KBr, ν, cm^{-1}): 3312 (N-H), 1606 (C=O). MS: m/z, 272 (M^+). Anal. calcd. for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.09; H, 5.98; N, 10.33.

N,*N*′-Di(4-bromophenyl)urea: ^{1}H NMR: (DMSO-d$_6$, 200 MHz): δ 8.48 (2H, s, NH, exchangeable with D_2O), 6.93 (4H, d, $^3J = 8.9$ Hz, Ar-H), 7.44 (4H, d, $^3J = 8.9$ Hz, Ar-H); IR (KBr, ν, cm^{-1}): 3288 (N-H), 1640 (C=O). MS: m/z, 340 (M^+). Anal. calcd. for $C_{13}H_{10}Br_2O$: C, 45.65; H, 2.95; N, 4.68. Found: C, 45.72; H, 2.89; N, 4.63.

N,*N*′-Di(pyrid-4-yl)urea: ^{1}H NMR: (DMSO-d$_6$, 200 MHz): δ 9.32 (2H, s, NH, exchangeable with D_2O), 8.37 (4H, d, $^3J = 6.0$ Hz, Py-H), 7.44 (4H, d, $^3J = 6.0$ Hz, Py-H); IR (KBr, ν, cm^{-1}): 3340 (N-H), 1740 (C=O). MS: m/z, 214 (M^+). Anal. calcd. for $C_{11}H_{10}N_4O$: C, 61.67; H, 4.71; N, 26.15. Found: C, 61.73; H, 4.78; N, 26.09.

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