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Efficient Synthesis of *N,N′*-Disubstituted Ureas/Thioureas Catalyzed by Iodine

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Abstract: Iodine is an efficient catalyst for the synthesis of symmetrically *N,N′*-disubstituted ureas/thioureas by heating respective amines or phenyl hydrazine and urea/thiourea on a preheated hot plate at 90–95°C, under solvent-free conditions. The yields are excellent, and the reactions go to complete within 5–10 min.

Keywords: Amines, iodine, *N,N′*-disubstituted urea/thiourea, phenyl hydrazine

INTRODUCTION

N,N′-Disubstituted urea functionality is a key structural element of many biologically active compounds such as enzyme inhibitors, peptidomimetics, neuroprotective compounds, cytokinin-like compounds, and tachykinin NK_3 selective antioxidants. These compounds also known for their significant activity as neuropeptide Y1-selective receptor antagonists and as intermediates for the preparation of pharmaceutical and agricultural chemicals.[1–3] Although the synthesis of mono- and di-substituted ureas has been documented by a variety of methods such as **reaction of unsubstituted ureas with amines in the presence of a suitable catalyst[4a] or with alkylamine hydrochloride salts,[4b,c] by the ammonolysis of isonitriles in the presence of mercuric salts[5] or ammonolysis of cyanamides,[6] by the reaction of benzotrizol-1-carboxamide with an amine in THF,[7] from phosgene and an amine *via* isocyanates,[8] from less toxic phosgene substitutes such as**

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bis(4-nitrophenyl) carbonate, di-*tert*-butyl dicarbonate, *S*,*S*-dimenthyldithiocarbonate, trihaloacetylchlorides, triphosgene and an amine[9] and by the reaction of an amine with carbamates in a suitable solvent.[10] These methods usually employ toxic, expensive reagents and relatively harsh conditions, and longer time durations are required.

Recently, Mojtahedi et al.[11] and Zheng Li et al.[12] have reported the synthesis of *N,N′*-disubstituted urea with variety of amines in the presence of $CeCl_3 \cdot 7H_2O$-KI/PEG-400, but the yields of some of the products were not satisfactory. Ranu et al.[13] reported the synthesis of *N,N′*-disubstituted thioureas catalyzed by Al_2O_3/CS_2 with good yields under microwave irradiation. This method requires careful handling and involves tedious workup procedures. Therefore, practical methods of obtaining urea-containing compounds are of great interest for the drug discovery process.

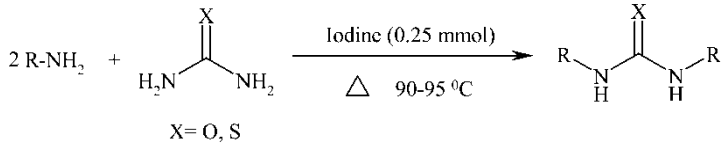
RESULTS AND DISCUSSION

Recently, we have reported the synthesis of α-iodoacetates from alkenes/ammonium acetate/I_2.[14] In continuation of our search for simple, nonhazardous methods for transformations in organic synthesis using iodine, herein we report a highly versatile and efficient synthesis of *N,N′*-disubstituted ureas/thioureas (**3**) using amines (**1**) and urea/thiourea (**2**) with catalytic amounts of iodine (Scheme 1).

To demonstrate the protocol, we selected *p*-anisidine (20 mmol) as the model substrate and treated it with urea/thiourea (10 mmol) in the presence of iodine (0.25 mmol) for 5 min to get the desired *N,N′*-bis(4-methoxyphenyl) urea (95%) (entry 4, Table 1). Several interesting features of the preparation of *N,N′*-disubstituted ureas are apparent from Tables 1 and 2. More important, the substituents such as OCH_3, Cl, Br, and NO_2 are unaffected under the reaction condition.

EXPERIMENTAL

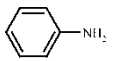
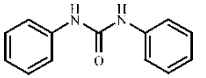
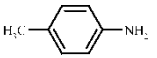
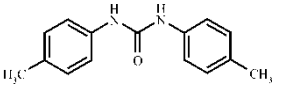
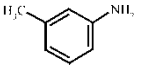
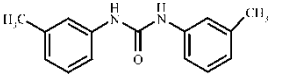
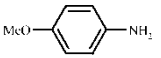
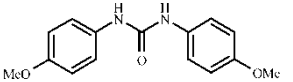
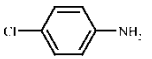
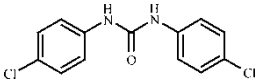
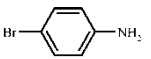
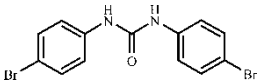
Melting points were determined on a Buchi melting-point apparatus. IR, ^1H NMR, and GC-MS spectra were recorded on Nicolet 400D FT-IR



1 **2** **3**

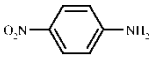
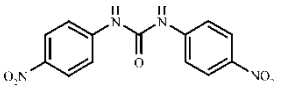
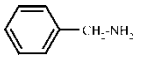
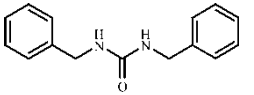
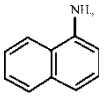
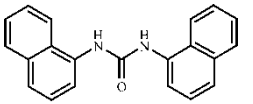
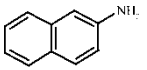
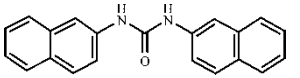
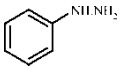
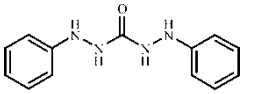
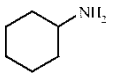
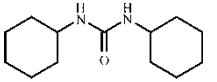
Scheme 1.

Table 1. Iodine-catalyzed synthesis of *N,N′*-disubstituted ureas

Entry	Amines	Time (min)	Product[a]	Yield (%)[b]	Melting point (°C)	
					Found	Reported[c]
1		5		98	242	242
2		5		96	267–268	269
3		5		90	263–264	264
4		5		95	237	240
5		5		95	298	302
6		5		96	298	295

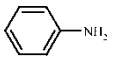
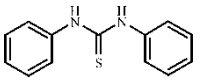
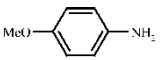
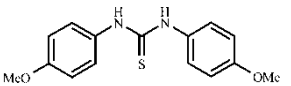
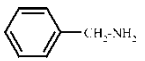
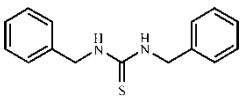
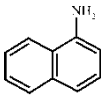
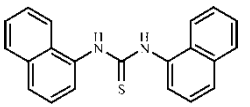
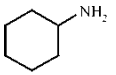
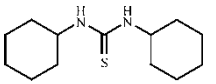
(*continued*)

Table 1. Continued

Entry	Amines	Time (min)	Product[a]	Yield (%)[b]	Melting point (°C)	
					Found	Reported[c]
7		10		90	300–301	305–306
8		8		98	168	165–166
9		10		95	280	277–278
10		10		95	288	293–294
11		10		96	170	171–173
12		10		95	205	205–206

[a]All the products are known, characterized by IR and ^{1}H NMR spectral analysis, and compared with the authentic samples.
[b]Isolated yields.
[c]Melting points of compounds are consistent with reported values (Refs. 12, 15, and 16).

Table 2. Iodine-catalyzed synthesis of *N,N′*-disubstituted thioureas

Entry	Amines	Time (min)	Product[a]	Yield (%)[b]	Melting point (°C)	
					Found	Reported[c]
1		10		92	151	150–153
2		10		94	200	201–203
3		10		95	148	148
4		10		90	197	198
5		10		95	182	182.5

[a]All the products are known, characterized by IR and ^{1}H NMR spectral analysis, and compared with the authentic samples.
[b]Isolated yields.
[c]Melting points of compounds are consistent with reported values (Refs. 13, 15, and 16).

spectrophotometer, 400-MHz Brucker spectrometer, and Shimadzu GC-MS QP 5050A, respectively. All amines, urea and thioureas, and iodine were commercial products and used without further purification.

General Procedure for *N,N′*-Disubstituted Urea/Thiourea

p-Anisidine (2.46 g, 20 mmol), urea/thiourea (0.60/0.76 g, 10 mmol), and iodine (0.063 g, 0.25 mmol) were mixed and heated on a hot plate at 90–95°C for a given period of time (Tables 1 and 2). After completion of the reaction, contents were cooled to room temperature, poured onto crushed ice, filtered, and washed with a 10% $Na_2S_2O_3$ solution. The crude product was further purified by recrystallization (hot MeOH) to afford pure *N,N′*-bis(4-methoxyphenyl)urea (5.17 g, 95%)/*N,N′*-bis(4-methoxyphenyl)thiourea (5.42 g, 94%).

Data

***N,N′*-bis(4-Methoxyphenyl)urea** (entry 4, Table 1): ^{1}H NMR (DMSO-d_6) 8.32 (s, 2H), 6.65 (d, $J = 8.8$ Hz, 4H), 7.25 (d, $J = 8.8$ Hz, 4H), 3.72 (s, 6H); ^{13}C NMR δ179.9, 163.2, 135.5, 134.8, 122.1, 60.5; MS (M^+) 272.02; IR (KBr, ν, cm^{-1}): 3310, 1606.

***N,N′*-bis(4-Methoxyphenyl)thiourea** (entry 2, Table 2): ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ9.40 (s, 2H), 7.25 (d, $J = 8.8$ Hz, 4H), 6.84 (d, $J = 8.8$ Hz, 4H), 3.72 (s, 6H); ^{13}C NMR δ185.9, 162.2, 137.5, 131.8, 119.1, 60.5; MS (M^+) 288.84; IR (KBr, ν, cm^{-1}): 3220, 1613.

CONCLUSION

In conclusion, we demonstrated an efficient synthesis of *N,N′*-disubstituted urea/thiourea using a catalytic amount of iodine under mild conditions.

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and *N,N′*-bis-(3,4-methylenedioxyphenyl) urea enhance adventitious root formation in apple rootstock M26 (*Malus pumila* Mill). *Plant Sci.* **2001**, *160*, 1055–1065.

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