Synthesis of *N*-Phenyl-*N*′-pyrimidylurea Derivatives by Selenium- or Selenium Dioxide-Catalyzed Reductive Carbonylation of Nitroaromatics

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Forty unsymmetric *N*-phenyl-*N*′-pyrimidylurea derivatives were synthesized in moderate-to-good yields by one-pot reductive carbonylation of nitroaromatics using selenium or selenium dioxide as the catalyst, aminopyrimidine derivatives as co-reagents, and carbon monoxide as the carbonyl source. The reaction parameters were investigated, as was the reusability of the catalysts. We found that selenium- or selenium dioxide-catalyzed reductive carbonylation of the nitroaromatics exhibited reaction-controlled phase-transfer phenomena of the catalysts.

Introduction

Pyrimidines are important heterocyclic compounds and it is well-known that several of their derivatives are biologically active.[1−5] In particular, pyrimidylurea derivatives containing both a peptide bond (−CONH−) and a pyrimidyl group have been widely used as immunosuppressants and anti-viral agents.[6,7] *N*-Phenyl-*N*′-pyrimidylurea derivatives are considered to be promising compounds for the treatment of autoimmune diseases and viral infection in mammals.[6,7]

The conventional methods for preparing pyrimidylurea derivatives, however, utilize highly toxic phosgene as the carbonyl source.[6] This process has many disadvantages that are particularly troublesome, such as the toxicity and corrosive nature of phosgene and the formation of hydrogen chloride as the by-product.[8,9] Accordingly, catalytic carbonylation of organic nitro compounds has been investigated recently by several industrial and academic research groups.[10,11] The major objective is to find a new catalytic process for the synthesis of these important chemicals that avoids the use phosgene. Group VIII transition metals, such as rhodium, ruthenium, and palladium, have been used commonly as catalysts for this purpose.[12,13]

Recently, non-transition metal elements and their oxides, such as selenium, sulfur, and selenium dioxide, have been found to also catalyze the carbonylation of nitroaromatics for the synthesis of urea derivatives. Franz et al. reported sulfur-catalyzed oxidative carbonylation of amines to give symmetric urea derivatives.[14,15] Sonoda et al. developed a series of selenium-catalyzed organic synthetic reactions.[16,17] Lu et al. synthesized a series of unsymmetrical phenyl ureas by one-pot reactions under relatively mild conditions.[18] Additionally, reactions catalyzed by selenium dioxide demonstrated that oxidative carbonylation of aromatic amines gives diphenylurea derivatives.[19,20] These environmentally benign reactions present many advantages over the traditional phosgene routes used for synthesis of urea derivatives. Actually, the synthesis of unsymmetrical *N*-phenyl-*N*′-pyrimidylurea derivatives by catalytic methods is even more attractive than that of symmetrical ureas, because conformational behavior of the unsymmetrical urea derivatives can be studied as model systems for polypeptides and proteins.[21]

Results and Discussion

Selenium- or Selenium Dioxide-Catalyzed Carbonylation of Nitrobenzene

Treatment of nitrobenzene with 2-aminopyrimidine in a 1:1 molar ratio, using selenium or selenium dioxide as the catalyst, in the presence of carbon monoxide led to *N*-phenyl-*N*′-(2-pyrimidyl)urea **1a** [Equation (1)]. We investigated the effects of various parameters on the reaction, such as the temperature, the amount of catalyst, the choice of organic base, and the pressure of carbon monoxide [Equation (1), Table 1].

We found that the reactions catalyzed by either selenium and selenium dioxide exhibited excellent chemoselectivity. The chemoselectivity for the formation of unsymmetrical ureas **1a** was higher than 98.1% and there was very little *N*,*N*′-diphenylurea in the crude products. We note that symmetrical *N*,*N*′-bis(2-pyrimidyl)urea was not detected in the crude products by HPLC analysis, which is different from those reported reactions, yielding a mixture of three sym-

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Table 1. Selenium- or selenium dioxide-catalyzed synthesis of *N*-phenyl-*N*′-(2-pyrimidyl)urea (**1a**)

Run	Temp. [°C]	Catalyst[a] mmol	Base (mmol)	P_{CO} [MPa]	Time [h]	Yield (%) Se	SeO_2
1	110	0.5	TEA[b] (20)	3.0	4.0	45.6	44.7
2	130	0.5	TEA (20)	3.0	4.0	70.3	76.1
3	150	0.5	TEA (20)	3.0	4.0	74.9	79.8
4	170	0.5	TEA (20)	3.0	4.0	70.8	74.6
5	150	0.01	TEA (20)	3.0	4.0	30.6	30.1
6	150	0.05	TEA (20)	3.0	4.0	51.3	52.4
7	150	0.1	TEA (20)	3.0	4.0	73.5	77.8
8	150	1.0	TEA (20)	3.0	4.0	75.1	80.8
9	150	0.5	TEA (10)	3.0	4.0	46.8	50.6
10	150	0.5	TEA (30)	3.0	4.0	76.1	79.4
11	150	0.5	TEA (40)	3.0	4.0	78.2	81.8
12	150	0.5	TPP[c] (2.0)	3.0	4.0	/	50.7
13	150	0.5	NMP[d] (20)	3.0	4.0	76.7	80.4
14	150	0.5	DABCO[e] (20)	3.0	4.0	78.3	81.1
15	150	0.5	DBN[f] (20)	3.0	4.0	81.4	84.2
16	150	0.5	DBU[g] (20)	3.0	4.0	82.3	85.9
17	150	0.5	TEA (20)	1.0	4.0	40.1	36.7
18	150	0.5	TEA (20)	2.0	4.0	66.8	67.0
19	150	0.5	TEA (20)	4.0	4.0	76.0	80.3
20	150	0.5	TEA (20)	5.0	4.0	76.8	81.3
21	150	0.5	TEA (20)	3.0	1.0	40.1	39.8
22	150	0.5	TEA (20)	3.0	2.0	68.7	69.1
23	150	0.5	TEA (20)	3.0	8.0	75.8	80.1

[a] Reaction conditions: nitrobenzene (10 mmol), 2-aminopyrimidine (10 mmol), base (10−40 mmol), CO (1.0−5.0 MPa). Catalyst: Se or SeO_2 (0.01−1.0 mmol); toluene (10 mL); 110−170 °C; 1.0−8.0 h. [b] Triethylamine. [c] Triphenylphosphane. [d] *N*-Methylpyrrolidine. [e] 1,4-Diazabicyclo[2,2,2]octane. [f] 1,5-Diazabicyclo[4,3,0]non-5-ene. [g] 1,8-Diazabicyclo[5,4,0]undec-7-ene.

metric and unsymmetrical ureas when primary amines were used as co-reagents.[16,18,22] Between the temperatures 110−170 °C, the yields of **1a** were increased as the temperature increased to 150 °C and then decreased with any further temperature increase (Table 1, runs 1−4). The decrease in yield at temperatures above 150 °C can be rationalized by presuming that **1a** decomposed faster than the occurrence of carbonylation of the remaining 2-aminopyrimidine during the reaction. The yields of **1a** were increased with increasing amounts of the catalysts (Table 1, runs 5−8).

Organic bases dramatically affect the formation of the product (Table 1, runs 9−16). In addition to triethylamine, stronger organic bases, such as 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), and the tertiary amines 1,4-diazabicyclo[2.2.2]octane (DABCO) and *N*-methylpyrrolidine (NMP), were all effective for the reductive carbonylation of nitrobenzene with 2-aminopyrimidine. Interestingly, in the presence of triphenylphosphane (Table 1, run 12), the selenium dioxide-catalyzed reaction provided **1a** in 50.7% yield, but the corresponding selenium-catalyzed reaction did not take place under the same conditions.

Reusability of the Catalysts

To test the reusability of the catalysts, the carbonylation reaction of nitrobenzene with 2-aminopyrimidine [Equation (1)] was performed using Se or SeO_2 in the presence of CO (3.0 MPa) in toluene at 150 °C for 4.0 h (Table 2). After the reaction was complete, the mixture was filtered under a nitrogen atmosphere to remove the insoluble urea derivative **1a**. The resultant liquor containing the catalyst was reused with a fresh charge of nitrobenzene and 2-aminopyrimidine. Both the selenium and selenium dioxide catalysts exhibited better activity than they did in the original runs, even after six reuses. The yields of urea **1a** increased upon recycling the catalysts, suggesting that unchanged substrates might have participated in the subsequent reaction (Table 2).

Table 2. Reusability of the catalysts

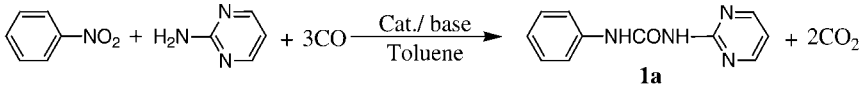
Run	Cycle	Se[a]		SeO_2[a]	
		Yield (%)	Selectivity (%)	Yield (%)	Selectivity (%)
1	0	74.9	98.3	79.8	98.4
2	1	79.8	98.1	80.1	98.1
3	2	80.1	98.1	80.3	98.2
4	3	82.4	98.2	82.3	98.1
5	4	83.5	98.2	83.6	98.1
6	5	83.8	98.1	83.7	98.1
7	6	83.7	98.3	83.8	98.2

[a] Reaction conditions: nitrobenzene (10 mmol), 2-aminopyrimidine (10 mmol), Et_3N (20 mmol), CO (3.0 MPa), Se or SeO_2 catalyst (0.5 mmol), toluene (10 mL); 140−150 °C; 4.0 h.

It is known that selenium dioxide reacts with carbon monoxide in the presence of triethylamine under very mild conditions (10 °C, 0.1 MPa), forming carbonyl selenide (COSe) in situ, and shows the same catalytic activity as selenium.[17,23] In our case, when selenium dioxide accomplished its first catalytic cycle, it demonstrated similar catalytic activity as selenium in subsequent runs, suggesting that reduction of selenium dioxide by carbon monoxide occurred in the first run to form elemental selenium (Table 2, runs 2−7).

Synthesis of *N*-Phenyl-*N*′-pyrimidylurea Derivatives

Nitroaromatics react with aminopyrimidine derivatives, using selenium or selenium dioxide as the catalyst in the presence of carbon monoxide, to form urea derivatives **2** [Equation (2)]. A series of unsymmetrical *N*-phenyl-*N*′-pyrimidylurea derivatives **2** were synthesized in one-pot reac-



1a

tions by combining catalytic oxidative carbonylation of aminopyrimidine derivatives with reductive carbonylation of nitroaromatics under relatively mild conditions (Tables 3 and 4). During the reaction the nitroaromatics also act as oxidants, thereby playing an important role in promoting the catalytic cycle. Thus, the products **2**, as well as the catalysts (Se and SeO_2), can be obtained easily by simple phase separation.

Table 3. Reductive carbonylation of nitroaromatics with 2-aminopyrimidine as the co-reagent

Run	R^1	Product[a] m.p. (°C) (ref.)	Yield (%) Se	SeO_2
1a	H	233−235 (221−222),[6] (225−227),[24] (233−235)[7][25]	74.9	79.8
1b	2-Me	225 (214−215)[6]	68.6	71.3
1c	3-Me	194−195	74.3	77.2
1d	4-Me	211−213 (205−206)[6]	73.9	74.9
1e	2-Cl	238−239	48.5	53.4
1f	3-Cl	226−227 (224−227)[7]	85.7	88.7
1g	4-Cl	241−243 (238),[26] (240−242)[7]	26.4	27.1
1h	2-*iPr*	193−194	33.7	35.0
1i	3-*iPr*	202−203	84.8	88.1
1j	4-*iPr*	268−269	65.5	68.6
1k	3-$COCH_3$	229−231	74.5	77.3
1l	4-$COCH_3$	252−255	62.3	63.7
1m	3-CF_3	234 (223−224)[6]	87.3	89.8
1n	2-OMe	207	55.7	60.1
1o	4-OEt	209−211	69.4	73.2
1p	4-CN	287 (273−274)[6]	55.2	61.3
1q	4-CHO	265−267	60.1	63.2
1r	4-OPh	217−218	68.7	69.9
1s	3-Cl,2-Me	264−265 (262−264)[7]	80.2	83.3
1t	3-Cl,4-Me	252−255 (251−254)[7]	83.4	87.5

[a] Reaction conditions: nitroaromatics (10 mmol), 2-aminopyrimidine (10 mmol), Et_3N (20 mmol), CO (3.0 MPa), Se or SeO_2 catalyst (0.5 mmol), toluene (10 mL); 140−150 °C; 4.0 h.

Both the selenium- and selenium dioxide-catalyzed reactions show remarkable chemoselectivity. The reaction of aminopyrimidine derivatives with nitroaromatics resulted in *N*-phenyl-*N*′-pyrimidylurea derivatives **2** in moderate-to-good yields (Tables 3 and 4). Symmetrical *N*,*N*′-bis(2-pyrimidyl)urea derivatives, however, were not detected by HPLC analysis of the crude products, which was the same observation made for reaction with 2-aminopyrimidine. In most cases, selenium dioxide showed higher catalytic activity than selenium under the same conditions, presumably because selenium dioxide forms the reactive intermediate more readily. *ortho*-Substituted nitrobenzenes such as 2-methylnitrobenzene, 2-chloronitrobenzene, 2-methoxynitrobenzene, and 2-isopropylnitrobenzene, gave relatively low yields of the expected products, suggesting that these reactions were sterically sensitive to the *ortho* substituents (Tables 3 and 4, runs 1b, 2b; 1e, 2e; 1 h, 2 h; 1n, 2n). *meta*-Substituted nitrobenzenes, such as 3-chloronitrobenzene and 3-trifluoromethylnitrobenzene, gave higher yields of the corresponding products than nitrobenzene, which reveals that these reactions are influenced electronically by the substituents on this aromatic ring (Tables 3 and 4, runs 1f, 2f and 1m, 2m). 2-Aminopyrimidine gave higher yields of the corresponding products than did 2-amino-4,6-dimethoxypyrimidine, which indicates that the reactions are also influenced electronically by substituents on the pyrimidyl rings (Tables 3 and 4).

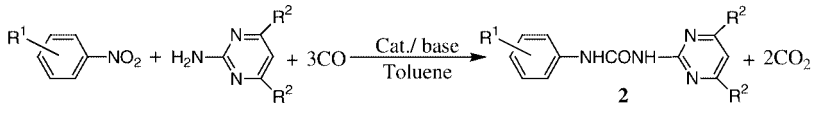
Table 4. Reductive carbonylation of nitroaromatics with 2-amino-4,6-dimethoxypyrimidine as the co-reagent

Run	R^1	Product[a] m.p. [°C]	Yield (%) Se	SeO_2
2a	H	214−216	72.3	77.1
2b	2-Me	205−207	67.1	69.9
2c	3-Me	223−224	67.9	71.0
2d	4-Me	248−249	67.8	70.5
2e	2-Cl	195−197	43.7	43.9
2f	3-Cl	227−230	83.3	86.6
2g	4-Cl	246−247	23.9	23.9
2h	2-*i*Pr	164−166	35.0	36.6
2i	3-*i*Pr	166−167	80.7	83.9
2j	4-*i*Pr	216−217	65.1	66.3
2k	3-$COCH_3$	216−218	71.3	74.9
2l	4-$COCH_3$	245−247	61.1	61.8
2m	3-CF_3	241	87.7	89.8
2n	2-OMe	175−178	51.8	53.9
2o	4-OEt	199−202	67.2	69.9
2p	4-CN	259−262	55.4	56.4
2q	4-CHO	249−251	57.3	59.1
2r	4-OPh	180−183	64.2	67.8
2s	3-Cl,2-Me	236	76.7	79.7
2t	3-Cl,4-Me	244−246	83.3	86.0

[a] Reaction conditions: nitroaromatics (10 mmol), 2-amino-4,6-dimethoxypyrimidine (10 mmol), Et_3N (20 mmol), CO (3.0 MPa), Se or SeO_2 catalyst (0.5 mmol), toluene (10 mL); 140−150 °C; 4.0 h.

Reaction-Controlled Phase-Transfer Catalysis in Selenium- or Selenium Dioxide-Catalyzed Systems

During the reductive carbonylation of nitroaromatics with aminopyrimidine derivatives, the catalyst itself was not soluble in the organic solvent, but it slowly reacted with carbon monoxide to form carbonyl selenide species (SeCO)[23] that are soluble in the reaction medium, leading subsequently to homogeneous catalytic carbonylation reac tions. When the starting materials were consumed, the catalyst (elemental selenium) precipitated as a powder. This



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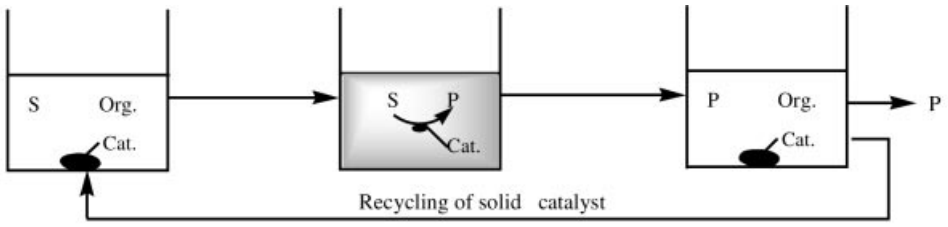


Org.: organic phase, S: substrate, Cat.: catalyst, P: product.

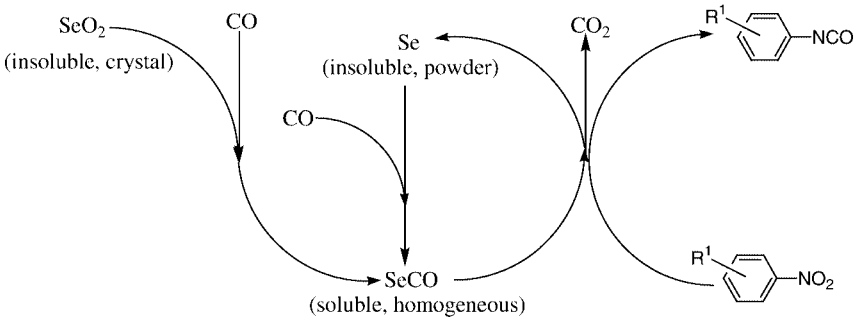
Scheme 1. Formation of urea derivatives by selenium- or selenium dioxide-catalyzed carbonylation

phenomenon manifests a solid−liquid−solid phase transfer of the catalyst that is controlled by the degree of completion of the reaction, which is in accordance with the concept of reaction-controlled phase-transfer catalysis.[27] Here, the selenium or selenium dioxide can be referred to as reaction-controlled phase-transfer catalyst. The nitro compounds can be considered as special oxidants that oxidize the intermediate carbonyl selenide species to selenium. This driven force impels the recycling of the catalyst. After the reaction reaches end, the catalyst can be separated from the product by a simple phase separation and reused as a heterogeneous catalyst (Scheme 1). That is, the reaction system changes from heterogeneous to homogeneous and then recycles to allow heterogeneous separation. Therefore, this catalytic system possesses the advantages of both homogeneous and heterogeneous catalysis.

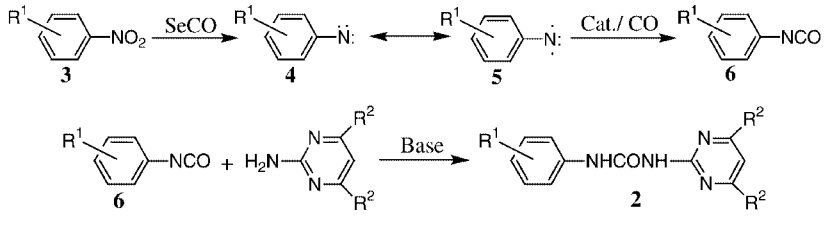
In comparison with conventional homogeneous catalysis, the catalytic system of Se/CO or SeO_2/CO is more advantageous because the catalyst can be separated from the solution after the reaction is complete. In addition, the catalyst is nonmetallic and is much cheaper than noble metal catalysts. They can be considered as "mobile" catalysts that transfer between two phases in response to the reaction process (Scheme 2). We regard the use of the catalytic systems Se/CO and SeO_2/CO as promising methods for the synthesis of unsymmetrical urea derivatives.

Proposed Reaction Pathway of Carbonylation

Although a detailed study of the reaction mechanism has not been undertaken, the present reactions can be understood mechanistically by assuming the reaction pathway shown in Scheme 3. The initial deoxygenation of substituted nitrobenzene derivative **3** with carbonyl selenide (SeCO), generated in situ by the reaction of elemental selenium or selenium dioxide with carbon monoxide in the presence of triethylamine,[23,28] results in the intermediate(s) nitrene **4** and/or nitrenoid **5** (Scheme 3), which react further with carbon monoxide to form aryl isocyanate **6**. This compound reacts with aminopyrimidine to afford the desired *N*-phenyl-*N′*-pyrimidylurea derivatives **2**.



Scheme 2. Reaction-controlled phase-transfer catalysis in the selenium or selenium dioxide-catalyzed carbonylation of nitroaromatics



Scheme 3. Proposed reaction pathway of carbonylation

Conclusion

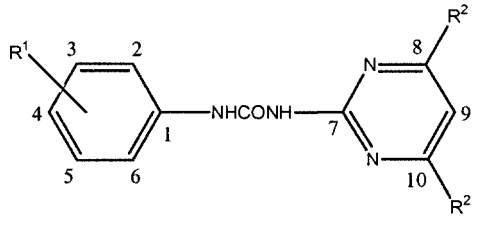
In view of the simple precursors, the mild reaction conditions, the good yields, the high chemoselectivities, the one-step synthesis, and the replacement of noxious phosgene with carbon monoxide, the present procedures seem to be very useful ones for the preparation of *N*-phenyl-*N*′-pyrimidylurea derivatives. In summary, we have developed a catalytic synthetic method for preparing unsymmetrical *N*-phenyl-*N*′-pyrimidylurea derivatives by combining reductive carbonylation of nitroaromatics with oxidative carbonylation of aminopyrimidine derivatives in a one−pot reaction.

Experimental Section

General Remarks: The organic solvents were all reagent grade and used without further purification. Aminopyrimidines, elemental selenium (99.999%), selenium dioxide (98.0%), carbon monoxide (99.9%), nitroaromatics, triethylamine, and other organic bases were all used as received. The purity and selectivity of products were determined by using a Waters HPLC with MeOH/H_2O as eluent. Melting points were determined on a Taike X-4 apparatus (Beijing, China) and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DRX 400 MHz spectrometer. Chemical shifts are reported in ppm relative to tetramethylsilane (δ scale). [D_6]Dimethylsulfoxide was the solvent.

The carbonylation reaction was carried out in a 100-mL stainless-steel autoclave that was placed in a thermostatic oil bath. The stirring rate was kept constant for all the experiments. Reaction materials, including aminopyrimidine, nitro compound, organic solvent, selenium or selenium dioxide as catalyst, triethylamine or other organic base as co-catalyst, were introduced successively into the autoclave. The reactor was sealed, flushed three times with carbon monoxide (1.0 MPa), pressurized with carbon monoxide, and then placed in an oil bath preheated at the stated temperature. After the reaction was finished, the apparatus was cooled to ambient temperature, and the remaining carbon monoxide was evacuated. The reaction mixture was filtered, and *N*-phenyl-*N*′-pyrimidylurea derivatives were collected and further purified by flash chromatography (silica gel: hexane/ EtOAc, 10:3).

Data of Some Representative *N*-Phenyl-*N*′-pyrimidylurea Derivatives



***N*-Phenyl-*N*′-(2-pyrimidyl)urea (1a):** M.p. 233−235 °C. ^{1}H NMR (400 MHz, [D_6]DMSO, 23 °C): δ = 7.06 (t, *J* = 7.2 Hz, 1 H, 4-H), 7.12 (t, *J* = 4.8 Hz, 1 H, 9-H), 7.33 (t, *J* = 7.6 Hz, 2 H, 3-H/5-H), 7.59 (d, *J* = 8.0 Hz, 2 H, 2-H/6-H), 8.67 (d, *J* = 4.8 Hz, 2 H, 8-H/10-H), 9.94 (s, 1 H, PyN*H*), 11.36 (s, 1 H, PhN*H*) ppm. ^{13}C NMR (400 MHz, [D_6]DMSO, 23 °C): δ = 114.60 (C-9), 119.18 (C-2, C-6), 122.66 (C-4), 128.42 (C-3, C-5), 138.20 (C-1), 151.00 (C=O), 157.50 (C-7), 157.70 (C-8, C-10) ppm.

***N*-(2-Methylphenyl)-*N*′-(2-pyrimidyl)urea (1b):** M.p. 225 °C. ^{1}H NMR (400 MHz, [D_6]DMSO, 23 °C): δ = 2.36 (s, 3 H, CH_3), 7.00 (t, *J* = 4.8 Hz, 1 H, 9-H), 7.15 (t, *J* = 4.8 Hz, 1 H, 4-H), 7.20 (d, *J* = 8.0 Hz, 1 H, 3-H), 7.25 (t, *J* = 8.0 Hz, 1 H, 5-H), 8.09 (d, *J* = 8.0 Hz, 1 H, 6-H), 8.70 (d, *J* = 4.8 Hz, 2 H, 8-H/10-H), 10.26 (s, 1 H, PyN*H*), 11.41 (s, 1 H, PhN*H*) ppm. ^{13}C NMR (400 MHz, [D_6]DMSO, 23 °C): δ = 18.13 (*C*H_3), 114.98 (C-9), 120.34 (C-6), 123.12 (C-4), 126.38 (C-5), 127.16 (C-2), 130.25 (C-3), 137.12 (C-1), 151.48 (C=O), 157.82 (C-7), 158.18 (C-8, C-10) ppm.

***N*-(2-Chlorophenyl)-*N*′-(2-pyrimidyl)urea (1e):** M.p. 238−239 °C. ^{1}H NMR (400 MHz, [D_6]DMSO, 23 °C): δ = 7.08 (t, *J* = 4.6 Hz, 1 H, 9-H), 7.17 (t, *J* = 4.8 Hz, 1 H, 4-H), 7.35 (t, *J* = 7.8 Hz, 1 H, 5-H), 7.54 (d, *J* = 8.0 Hz, 1 H, 3-H), 8.39 (d, *J* = 8.0 Hz, 1 H, 6-H), 8.72 (d, *J* = 4.8 Hz, 2 H, 8-H/10-H), 10.43 (s, 1 H, PyN*H*), 12.12 (s, 1 H, PhN*H*) ppm. ^{13}C NMR (400 MHz, [D_6]DMSO, 23 °C): δ = 115.33 (C-9), 120.97 (C-6), 122.16 (C-2), 123.91 (C-4), 127.77 (C-5), 129.27 (C-3), 135.84 (C-1), 151.38 (C=O), 157.53 (C-7), 158.24 (C-8, C-10) ppm.

***N*-(3-Chlorophenyl)-*N*′-(2-pyrimidyl)urea (1f):** M.p. 226−227 °C. ^{1}H NMR (400 MHz, [D_6]DMSO, 23 °C): δ = 7.13 (t, *J* = 4.6 Hz, 1 H, 9-H), 7.16 (d, *J* = 7.6 Hz, 1 H, 4-H), 7.36 (t, *J* = 7.6 Hz, 1 H, 5-H), 7.51 (d, *J* = 7.6 Hz, 1 H, 6-H), 7.84 (s, 1 H, 2-H), 8.70 (d, *J* = 4.8 Hz, 2 H, 8-H/10-H), 10.03 (s, 1 H, PyN*H*), 11.67 (s, 1 H, PhN*H*) ppm. ^{13}C NMR (400 MHz, [D_6]DMSO, 23 °C): δ = 115.26 (C-9), 117.91 (C-6), 118.84 (C-2), 122.75 (C-4), 130.55 (C-5), 133.30 (C-3), 140.15 (C-1), 151.50 (C=O), 157.75 (C-7), 158.28 (C-8, C-10) ppm.

***N*-(2-Isopropylphenyl)-*N*′-(2-pyrimidyl)urea (1h):** M.p. 193−194 °C. ^{1}H NMR (400 MHz, [D_6]DMSO, 23 °C): δ = 1.21 [d, *J* = 6.8 Hz, 6 H, -CH(CH_3)$_2$], 2.51−2.54 [m, 1 H, -C*H*(CH$_3$)$_2$], 7.09 (t, *J* = 4.8 Hz, 1 H, 4-H), 7.12 (t, *J* = 4.6 Hz, 1 H, 9-H), 7.29 (t, *J* = 8.0 Hz, 1 H, 5-H), 7.61 (d, *J* = 8.0 Hz, 1 H, 3-H), 7.96 (d, *J* = 8.0 Hz, 1 H, 6-H), 8.67 (d, *J* = 4.8 Hz, 2 H, 8-H/10-H), 10.24 (s, 1 H, PyN*H*), 11.41 (s, 1 H, PhN*H*) ppm. ^{13}C NMR (400 MHz, [D_6]DMSO, 23 °C): δ = 22.65 [-CH(*C*H$_3$)$_2$], 33.74 [-*C*H(CH$_3$)$_2$], 115.01 (C-9), 122.14 (C-6), 123.97 (C-4), 125.17 (C-5), 126.03 (C-3), 135.76 (C-1), 139.73 (C-2), 151.78 (C=O), 157.90 (C-7), 158.17 (C-8, C-10) ppm.

***N*-(3-Isopropylphenyl)-*N*′-(2-pyrimidyl)urea (1i):** M.p. 202−203 °C. ^{1}H NMR (400 MHz, [D_6]DMSO, 23 °C): δ = 1.22 [d, *J* = 6.8 Hz, 6 H, -CH(CH_3)$_2$], 2.86−2.89 [m, 1 H, -C*H*(CH$_3$)$_2$], 6.96 (d, *J* = 7.6 Hz, 1 H, 4-H), 7.15 (t, *J* = 4.6 Hz, 1 H, 9-H), 7.25 (t, *J* = 7.6 Hz, 1 H, 5-H), 7.44 (d, *J* = 7.6 Hz, 1 H, 6-H), 7.47 (s, 1 H, 2-H), 8.70 (d, *J* = 4.8 Hz, 2 H, 8-H/10-H), 10.16 (s, 1 H, PyN*H*), 11.42 (s, 1 H, PhN*H*) ppm. ^{13}C NMR (400 MHz, [D_6]DMSO, 23 °C): δ = 23.90 [-CH(*C*H$_3$)$_2$], 33.55 [-*C*H(CH$_3$)$_2$], 115.00 (C-9), 117.12 (C-6), 117.53 (C-2), 121.04 (C-4), 128.82 (C-5), 138.50 (C-1), 149.27 (C-3), 151.50 (C=O), 157.88 (C-7), 158.24 (C-8, C-10) ppm.

***N*-(4-Acetylphenyl)-*N*′-(2-pyrimidyl)urea (1l):** M.p. 252−255 °C. ^{1}H NMR (400 MHz, [D_6]DMSO, 23 °C): δ = 2.53 (s, 3 H, -COCH_3), 7.18 (t, *J* = 5.0 Hz, 1 H, 9-H); 7.76 (d, *J* = 8.4 Hz, 2 H, 2-H/6-H), 7.96 (d, *J* = 8.4 Hz, 2 H, 3-H/5-H), 8.71 (d, *J* = 4.8 Hz, 2 H, 8-H/10-H), 10.37 (s, 1 H, PyN*H*), 11.82 (s, 1 H, PhN*H*) ppm. ^{13}C NMR (400 MHz, [D_6]DMSO, 23 °C): δ = 26.47 (*C*H_3), 115.32 (C-9), 118.53 (C-2, C-6), 129.65 (C-3, C-5), 131.54 (C-4), 143.08 (C-1), 151.33 (NH*C*ONH), 157.61 (C-7), 158.30 (C-8, C-10), 196.53 (Ph-*C*OCH$_3$) ppm.

***N*-(2-Methyl-3-chlorophenyl)-*N*′-(2-pyrimidyl)urea (1s):** M.p. 264−265 °C. ^{1}H NMR (400 MHz, [D_6]DMSO, 23 °C): δ = 2.10 (s, 3 H, Ph-CH_3), 6.86 (d, *J* = 7.6 Hz, 1 H, 4-H), 7.16 (t, *J* =

4.8 Hz, 1 H, 9-H), 7.25 (t, *J* = 7.8 Hz, 1 H, 5-H), 7.71 (d, *J* = 8.0 Hz, 1 H, 6-H), 8.70 (d, *J* = 4.8 Hz, 2 H, 8-H/10-H), 10.33 (s, 1 H, PyN*H*), 11.54 (s, 1 H, PhN*H*) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 23 °C): δ = 14.78 (Ph-*C*H$_3$), 112.70 (C-6), 115.12 (C-9), 118.25 (C-4), 127.20 (C-5), 133.57 (C-2), 138.63 (C-3), 148.34 (C-1), 151.46 (C=O), 158.01 (C-7), 158.21 (C-8, C-10) ppm

***N*-(3-Chloro-4-methylphenyl)-*N′*-(2-pyrimidyl)urea (1t):** M.p. 252−255 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 23 °C): δ = 2.29 (s, 3 H, Ph-C*H*$_3$), 7.14 (t, *J* = 4.8 Hz, 1 H, 9-H), 7.30 (d, *J* = 6.0 Hz, 1 H, 5-H), 7.69 (d, *J* = 6.0 Hz, 1 H, 6-H), 8.21 (s, 1 H, 2-H), 8.78 (d, *J* = 4.8 Hz, 2 H, 8-H/10-H), 10.22 (s, 1 H, PyN*H*), 11.55 (s, 1 H, PhN*H*) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 23 °C): δ = 18.91 (Ph-*C*H$_3$), 115.17 (C-9), 117.13 (C-6), 118.04 (C-2), 129.61 (C-4), 131.29 (C-5), 133.22 (C-3), 139.05 (C-1), 151.34 (C=O), 157.73 (C-7), 158.25 (C-8, C-10) ppm.

***N*-phenyl-*N′*-(4,6-dimethoxy-2-pyrimidyl)urea (2a):** M.p. 214−216 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 23 °C): δ = 3.95 (s, 6 H, -OC*H*$_3$), 5.91 (s, 1 H, 9-H), 7.06 (t, *J* = 7.2 Hz, 1 H, 4-H), 7.324 (t, *J* = 8.0 Hz, 2 H, 3-H/5-H), 7.54 (d, *J* = 8.0 Hz, 2 H, 2-H/6-H), 9.99 (s, 1 H, PyN*H*), 11.11 (s, 1 H, PhN*H*) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 23 °C): δ = 54.39 (Py-O*C*H$_3$), 82.70 (C-9), 119.25 (C-2, C-6), 123.10 (C-4), 129.00 (C-3, C-5), 138.34 (C-1), 151.14 (C=O), 156.81 (C-7), 171.23 (C-8, C-10) ppm.

***N*-(3-Methylphenyl)-*N′*-(4,6-dimethoxy-2-pyrimidyl)urea (2c):** M.p. 223−224 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 23 °C): δ = 2.29 (s, 3 H, Ph-C*H*$_3$), 3.94 (s, 6 H, Py-OC*H*$_3$), 5.91 (s, 1 H, 9-H), 6.89 (d, *J* = 6.8 Hz, 1 H, 4-H), 7.21 (t, *J* = 7.6 Hz, 1 H, 5-H), 7.30 (d, *J* = 7.2 Hz, 1 H, 6-H), 7.39 (s, 1 H, 2-H), 9.96 (s, 1 H, PyN*H*), 11.04 (s, 1 H, PhN*H*) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 23 °C): δ = 21.23 (Ph-*C*H$_3$), 54.40 (Py-O*C*H$_3$), 82.64 (C-9), 116.45 (C-2), 119.75 (C-4), 123.84 (C-6), 128.84 (C-5), 137.22 (C-3), 138.25 (C-1), 151.10 (C=O), 156.82 (C-7), 171.24 (C-8, C-10) ppm.

***N*-(4-Methylphenyl)-*N′*-(4,6-dimethoxy-2-pyrimidyl)urea (2d):** M.p. 248−249 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 23 °C): δ = 2.25 (s, 3 H, Ph-C*H*$_3$), 3.94 (s, 6 H, Py-OC*H*$_3$), 5.90 (s, 1 H, 9-H), 7.14 (d, *J* = 8.0 Hz, 2 H, 3-H/5-H), 7.42 (d, *J* = 8.0 Hz, 2 H, 2-H/6-H), 9.94 (s, 1 H, PyN*H*), 11.03 (s, 1 H, PhN*H*) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 23 °C): δ = 20.40 (Ph-*C*H$_3$), 54.38 (Py-O*C*H$_3$), 82.61 (C-9), 119.26 (C-2, C-6), 129.38 (C-3, C-5), 132.04 (C-4), 135.79 (C-1), 151.21 (C=O), 156.91 (C-7), 171.22 (C-8, C-10) ppm.

***N*-(3-Chlorophenyl)-*N′*-(4,6-dimethoxy-2-pyrimidyl)urea (2f):** M.p. 227−230 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 23 °C): δ = 3.95 (s, 6 H, Py-OC*H*$_3$), 5.92 (s, 1 H, 9-H), 7.13 (d, *J* = 7.6 Hz, 1 H, 4-H), 7.34 (t, *J* = 7.8 Hz, 1 H, 5-H), 7.49 (d, *J* = 8.0 Hz, 1 H, 6-H), 7.82 (s, 1 H, 2-H), 10.10 (s, 1 H, PyN*H*), 11.19 (s, 1 H, PhN*H*) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 23 °C): δ = 54.42 (Py-O*C*H$_3$), 82.87 (C-9), 117.77 (C-6), 118.71 (C-2), 122.80 (C-4), 130.64 (C-5), 133.32 (C-3), 139.82 (C-1), 151.16 (C=O), 156.74 (C-7), 171.26 (C-8, C-10) ppm.

***N*-(3-Isopropylphenyl)-*N′*-(2-pyrimidyl)urea (2i):** 166−167 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 23 °C): δ = 1.20 [d, *J* = 6.8 Hz, 6 H, -CH(C*H*$_3$)$_2$], 2.83−2.89 [m, 1 H, -C*H*(CH$_3$)$_2$], 3.96 (s, 6 H, Py-OC*H*$_3$), 5.90 (s, 1 H, 9-H), 6.96 (d, *J* = 7.6 Hz, 1 H, 4-H), 7.24 (t, *J* = 7.8 Hz, 1 H, 5-H), 7.37 (d, *J* = 8.0 Hz, 1 H, 6-H), 7.40 (s, 1 H, 2-H), 9.96 (s, 1 H, PyN*H*), 11.09 (s, 1 H, PhN*H*) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 23 °C): δ = 23.82 [-CH(*C*H$_3$)$_2$], 34.53 [-*C*H(CH$_3$)$_2$], 54.34 (Py-O*C*H$_3$), 82.70 (C-9), 116.82 (C-6), 117.20 (C-2), 121.19 (C-4), 128.92 (C-5), 138.32 (C-1), 149.27 (C-3), 151.11 (C=O), 156.84 (C-7), 171.23 (C-8, C-10) ppm.

***N*-(4-Isopropylphenyl)-*N′*-(2-pyrimidyl)urea (2j):** 216−217 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 23 °C): δ = 1.19 [d, *J* = 6.8 Hz, 6 H, -CH(C*H*$_3$)$_2$], 2.83−2.89 [m, 1 H, -C*H*(CH$_3$)$_2$], 3.94 (s, 6 H, Py-OC*H*$_3$), 5.58 (s, 1 H, 9-H), 7.20 (d, *J* = 6.0 Hz, 2 H, 3-H/5-H), 7.43 (t, *J* = 6.0 Hz, 2 H, 2-H/6-H), 9.88 (s, 1 H, PyN*H*), 11.21 (s, 1 H, PhN*H*) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 23 °C): δ = 23.97 [-CH(*C*H$_3$)$_2$], 32.83 [-*C*H(CH$_3$)$_2$], 54.35 (Py-O*C*H$_3$), 82.65 (C-9), 119.34 (C-2, C-6), 126.71 (C-3, C-5), 135.92 (C-1), 143.22 (C-4), 151.14 (C=O), 156.90 (C-7), 171.22 (C-8, C-10) ppm.

***N*-(3-Acetylphenyl)-*N′*-(4,6-dimethoxy-2-pyrimidyl)urea (2k):** M.p. 216−218 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 23 °C): δ = 2.54 (s, 3 H, -COC*H*$_3$), 3.96 (s, 6 H, Py-OC*H*$_3$), 5.85 (s, 1 H, 9-H), 7.46 (t, *J* = 7.8 Hz, 1 H, 5-H), 7.64 (d, *J* = 7.6 Hz, 1 H, 4-H), 7.75 (d, *J* = 8.0 Hz, 1 H, 6-H), 8.09 (s, 1 H, 2-H), 9.49 (s, 1 H, PyN*H*), 11.00 (s, 1 H, PhN*H*) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 23 °C): δ = 25.97 (-CO*C*H$_3$), 53.80 (Py-O*C*H$_3$), 82.40 (C-9), 118.21 (C-2), 122.44 (C-4), 123.29 (C-6), 128.76 (C-5), 137.46 (C-3), 138.42 (C-1), 150.63 (C=O), 156.44 (C-7), 171.06 (C-8, C-10), 196.87 (Ph-*C*OCH$_3$) ppm.

***N*-(3-Trifluoromethylphenyl)-*N′*-(4,6-dimethoxy-2-pyrimidyl)urea (2m):** M.p. 241 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 23 °C): δ = 3.94 (s, 6 H, Py-OC*H*$_3$), 5.30 (s, 1 H, 9-H), 7.40 (d, *J* = 7.2 Hz, 1 H, 4-H), 7.57 (t, *J* = 7.8 Hz, 1 H, 5-H), 7.61 (d, *J* = 8.0 Hz, 1 H, 6-H), 8.13 (s, 1 H, 2-H), 10.16 (s, 1 H, PyN*H*), 11.31 (s, 1 H, PhN*H*) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 23 °C): δ = 54.41 (Py-O*C*H$_3$), 82.92 (C-9), 115.26 (C-6), 118.61 (Ph-*C*F$_3$), 119.43 (C-2), 122.95 (C-4), 129.20 (C-3), 130.18 (C-5), 139.19 (C-1), 151.29 (C=O), 156.66 (C-7), 171.25 (C-8, C-10) ppm.

***N*-(3-Chloro-4-methylphenyl)-*N′*-(4,6-dimethoxy-2-pyrimidyl)urea (2t):** M.p. 244−246 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 23 °C): δ = 2.26 (s, 3 H, Ph-C*H*$_3$), 3.94 (s, 6 H, Py-OC*H*$_3$), 5.91 (s, 1 H, 9-H), 7.30 (d, *J* = 6.0 Hz, 1 H, 5-H), 7.68 (d, *J* = 6.0 Hz, 1 H, 6-H), 8.80 (s, 1 H, 2-H), 10.06 (s, 1 H, PyN*H*), 11.11 (s, 1 H, PhN*H*) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 23 °C): δ = 18.82 (Ph-*C*H$_3$), 54.38 (Py-O*C*H$_3$), 82.76 (C-9), 117.08 (C-6), 118.15 (C-2), 128.40 (C-4), 131.17 (C-5), 133.11 (C-3), 138.59 (C-1), 152.26 (C=O), 156.66 (C-7), 171.23 (C-8, C-10) ppm.

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