

# Phosgene-free synthesis of *N*-aryl-*N'*-(4-pyridinyl)ureas via selenium-catalyzed oxidative carbonylation of 4-aminopyridine with aromatic amines

Xiaopeng Zhang,\* Zhengwei Li, Yan Wang, Shuxiang Dong,  
Xueli Niu, and Guisheng Zhang\*

*Collaborative Innovation Center of Henan Province for Green Manufacturing of Fine Chemicals, Key Laboratory of Green Chemical Media and Reactions, Ministry of Education, School of Chemistry and Chemical Engineering, Henan Normal University, 46<sup>#</sup> Jianshe Road, Xinxiang 453 007, P. R. China*

*E-mail: [zhangxiaopengv@sina.com](mailto:zhangxiaopengv@sina.com), [zgs@htu.cn](mailto:zgs@htu.cn)*

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## Abstract

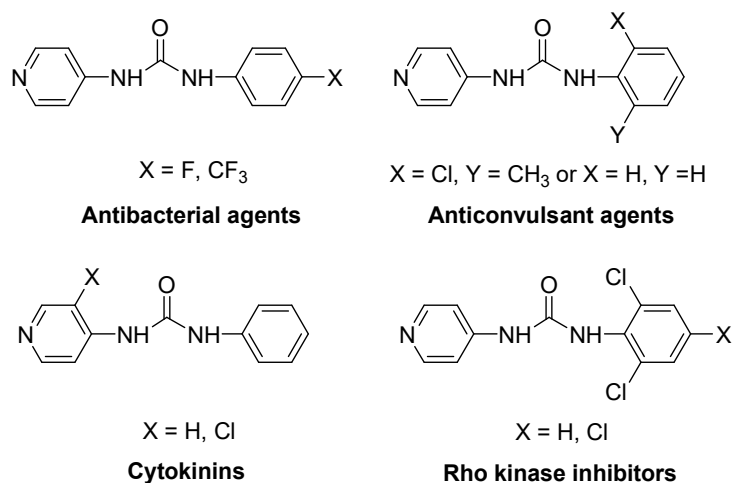
A facile, phosgene-free approach with high atom economy has been developed for the synthesis of *N*-aryl-*N'*-(4-pyridinyl)ureas. With cheap selenium as the catalyst, carbon monoxide (instead of phosgene) as the carbonyl reagent, *N*-aryl-*N'*-(4-pyridinyl)ureas can be obtained in a one-pot manner mostly in moderate to good yields via oxidative cross-carbonylation of 4-aminopyridine with a variety of aromatic amines in the presence of oxygen under atmospheric pressure. The mechanism for the synthesis of *N*-aryl-*N'*-(4-pyridinyl)ureas is also proposed.

**Keywords:** selenium, carbonylation, nitrogen heterocycles, *N*-aryl-*N'*-(4-pyridinyl)ureas, phosgene-free method

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## Introduction

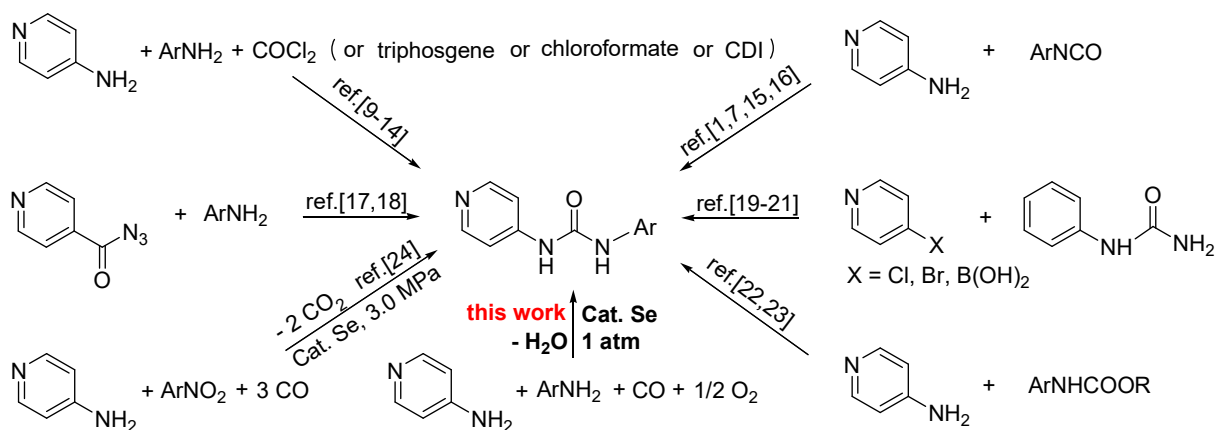
*N*-Aryl-*N'*-(4-pyridinyl)ureas are an important class of organic compounds which contain a peptide linkage and a nitrogen-containing heterocycle. Many of them exhibit distinguished biological activities, and they are frequently employed as antibacterial agents,<sup>1</sup> anticonvulsant drugs,<sup>2,3</sup> plant cytokinins,<sup>4,5</sup> and Rho kinase inhibitors (Figure 1).<sup>6</sup> In addition, these compounds can also be used as thermal latent initiators on ring-opening polymerization of epoxides in the production of epoxy resins.<sup>7,8</sup>



**Figure 1.** Selected examples of bioactive *N*-aryl-*N'*-(4-pyridinyl)ureas.

The traditional methods for the synthesis of *N*-aryl-*N'*-(4-pyridinyl)ureas mainly rely on the phosgenation of 4-aminopyridine with aromatic amines in the presence of the highly toxic and corrosive phosgene.<sup>9</sup> In recent years, great efforts have been paid to the development of phosgene-free approaches to these compounds. For example, triphosgene,<sup>9-11</sup> chloroformate,<sup>12,13</sup> and *N,N'*-carbonyldiimidazole (CDI)<sup>14</sup> have been developed as the substitutes for phosgene. However, low atom economy limits the utility of these approaches. Addition of 4-aminopyridine to the corresponding isocyanates (or addition of the corresponding amines to 4-isocyanatopyridine) is also frequently employed for this purpose,<sup>1,7,15,16</sup> but this method suffers from the drawbacks of the corresponding isocyanates such as their highly toxic and strong irritant nature, high cost, and derivation from phosgene. The reaction of isonicotinoyl azide with amines,<sup>17,18</sup> the *N*-arylation of 1-arylureas with 4-halogenated pyridine<sup>19,20</sup> or with 4-pyridinylboronic acid,<sup>21</sup> and the aminolysis of the corresponding carbamates with 4-aminopyridine<sup>22,23</sup> also have emerged as alternative approaches to *N*-aryl-*N'*-(4-pyridinyl)ureas. Nevertheless, the complex structure, high cost and low availability of the starting materials such as isonicotinoyl azide, 1-arylureas, and carbamates are the drawbacks associated with these methods. In 2003, Mei and co-workers reported a simple approach to *N*-aryl-*N'*-(4-pyridinyl)ureas via selenium-catalyzed redox carbonylation of 4-aminopyridine and aromatic nitro compounds in the presence of CO,<sup>24</sup> in which many advantages were exhibited such as phosgene-free approach, one-pot synthesis, simple, cheap and high availability of the starting materials as well as the non-metal selenium catalyst. Unfortunately, in this selenium-catalyzed redox carbonylation reaction, in addition to the pressured reaction condition (3.0 MPa), only one third of the CO consumed is transferred to the product, the other CO consumed is transformed into the greenhouse-effect gas CO<sub>2</sub> as byproduct. Therefore, further pursuit of this selenium-catalyzed carbonylation approach both to increase the utilization of CO and to avoid the formation of CO<sub>2</sub> under more moderate pressure is of great significance. In 2013, we applied this catalytic system into the synthesis of unsymmetrical 2-pyridyl ureas via the

carbonylation of 2-aminopyridine with aromatic amines and got the satisfactory results.<sup>25</sup> On this basis, herein, we present a facile one-pot, highly atom-economic, phosgene-free approach to *N*-aryl-*N'*-(4-pyridinyl)ureas via selenium-catalyzed oxidative carbonylation of 4-aminopyridine with aromatic amines in the presence of CO and O<sub>2</sub> under atmospheric pressure (Scheme 1).



**Scheme 1.** Previous and present synthetic approaches to *N*-aryl-*N'*-(4-pyridinyl)ureas.

## Results and Discussion

In our initial study, 4-aminopyridine and aniline were chosen as model substrates for optimization of the reaction conditions, and selected results are summarized in Table 1. When the reaction was conducted at 130 °C for 5 h (Table 1, Entry 1), the target product *N*-phenyl-*N'*-(4-pyridinyl)urea was obtained in 60% yield along with equivalent amounts of water together with a small amount of *N,N'*-di-(4-pyridinyl)urea and *N,N'*-diphenylurea as byproduct, indicating that accompanying the main cross-carbonylation reaction was the competitive carbonylation reaction of 4-aminopyridine and aniline themselves. With the increase of reaction temperature, the yield of *N*-phenyl-*N'*-(4-pyridinyl)urea increased accordingly. Thus, the yield of the desired product increased to 70% when the reaction was conducted at the elevated temperature of 140 °C (Table 1, Entry 2). Further increase of reaction temperature to 150 °C, the product yield remained almost unchanged (Table 1, Entry 3). When the reaction was conducted in the absence of oxygen, only 9% of the product was obtained, indicating that oxygen was necessary for this reaction (Table 1, Entry 4). Although carbon monoxide and oxygen at the ratio of 5:1 could satisfy the reaction (Table 1, Entry 5), the ratio of carbon monoxide to oxygen was finally chosen as 9:1 for safety reasons. The carbonylation reaction could not proceed at all in the absence of selenium, indicating that the selenium catalyst is essential for this reaction (Table 1, Entry 6). Higher product yields could be afforded by increasing the amount of selenium catalyst (Table 1, Entry 7), with an acceptable product yield (70%) being obtained when the selenium content was 0.25 mmol (Table 1, Entry 2). A further increase in the amount of the selenium catalyst (0.35 mmol) failed to increase the product

yield (Table 1, Entry 8). The reaction failed to offer the desired product without a base (Table 1, Entry 9). When the common inorganic bases such as NaOH or K<sub>2</sub>CO<sub>3</sub> were applied in this reaction, poor product yields were obtained (Table 1, Entries 10-11). Pleasingly, the use of organic bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), diisopropylethylamine (DIPEA) or triethylamine allowed the transformation to proceed in higher yields, and of them triethylamine was found to be most effective in this transformation (Table 1, Entries 2, 12-13). It is believed that triethylamine has appropriate alkalinity to be involved in the generation of an active carbonyl selenide (COSe) complex. A screening of solvents revealed that DMF gave the best result (Table 1, Entry 2), followed by DMSO (Table 1, Entry 14), with toluene, THF, and acetone being found to be noneffective (Table 1, Entries 15-17).

**Table 1.** Optimization of the reaction conditions<sup>a</sup>

Entry	Temperature (°C)	nCO/nO <sub>2</sub>	Se (mmol)	Base	Solvent	Yield <sup>b</sup> (%)
1	130	9:1	0.25	Et <sub>3</sub> N	DMF	60
2	140	9:1	0.25	Et <sub>3</sub> N	DMF	70
3	150	9:1	0.25	Et <sub>3</sub> N	DMF	69
4	140	1:0	0.25	Et <sub>3</sub> N	DMF	9
5	140	5:1	0.25	Et <sub>3</sub> N	DMF	70
6	140	9:1	0	Et <sub>3</sub> N	DMF	0
7	140	9:1	0.15	Et <sub>3</sub> N	DMF	55
8	140	9:1	0.35	Et <sub>3</sub> N	DMF	70
9	140	9:1	0.25	-	DMF	0
10	140	9:1	0.25	NaOH	DMF	28
11	140	9:1	0.25	K <sub>2</sub> CO <sub>3</sub>	DMF	11
12	140	9:1	0.25	DBU	DMF	46
13	140	9:1	0.25	DIPEA	DMF	60
14	140	9:1	0.25	Et <sub>3</sub> N	DMSO	63
15	140	9:1	0.25	Et <sub>3</sub> N	Toluene	0
16	140	9:1	0.25	Et <sub>3</sub> N	THF	0
17	140	9:1	0.25	Et <sub>3</sub> N	Acetone	0

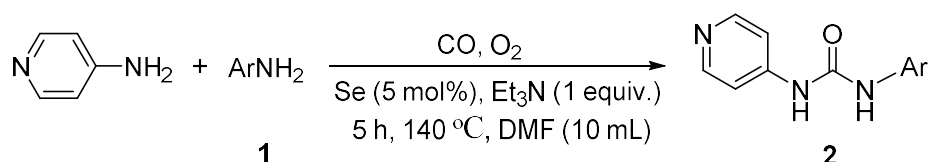
<sup>a</sup>Reaction conditions: 4-aminopyridine (5 mmol), aniline (5 mmol), base (5 mmol), solvent (10 mL), 5 h, 1 atm (CO and O<sub>2</sub>). <sup>b</sup>Isolated yield.

With the optimal conditions in hand, the scope and efficiency of the selenium-catalyzed carbonylation reaction of 4-aminopyridine with a series of amines were evaluated (Table 2). As shown in Table 2, the selenium-catalyzed oxidative carbonylation reaction of 4-aminopyridine could proceed smoothly under atmospheric pressure with many aromatic amines as well as some aliphatic amines.

Typically, *para*-substituted anilines gave higher yields of the desired products (Table 2, Entries 4, 8, 12) compared to their *ortho*-substituted analogues (Table 2, Entries 2, 6, 11), indicating that this reaction was sensitive to steric factors. Thus, it was understandable that when the carbonylation reaction proceeded with 2,6-dimethylaniline (**1j**) and *N*-methylaniline (**1n**), the corresponding product yields were obtained only in 25% (**2j**) and 22% (**2n**), respectively (Table 2, Entries 10, 14), mostly probably due to their high steric hindrance. Similar to aromatic amines, when the aliphatic amine with less steric hindrance such as butylamine (**1r**) was used, moderate yield of the desired product was obtained (Table 1, Entry 18). The bulkier the aliphatic amines were, the more difficult it became for them to participate in the reaction (Table 2, Entries 19-21). Thus, when the reaction proceeded with those with high steric hindrance such as dimethylamine (**1t**) or diethylamine (**1u**), no desired product was obtained (Table 2, Entries 20-21).

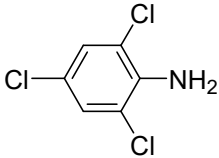
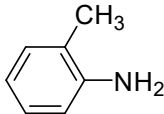
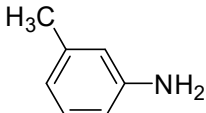
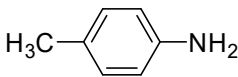
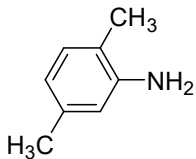
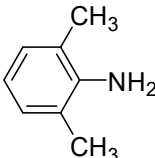
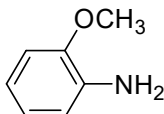
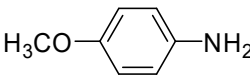
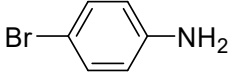
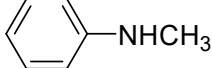
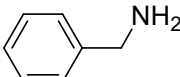
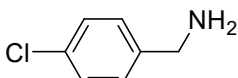
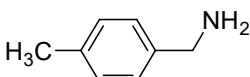
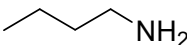
The method was also found to work smoothly with those anilines bearing electron-donating groups (Table 2, Entries 6-8, 11-12). In contrast, lower products yields were obtained when those anilines bearing electron-withdrawing groups were applied (Table 2, Entries 2-4, 13), suggesting that this reaction was also sensitive to electronic factors. Therefore, it was not surprising that this reaction failed to proceed with 2,4,6-trichloroaniline (Table 2, Entry 5), most probably due to the combined effects of steric and electronic factors. The carbonylation reaction also worked smoothly with benzylamine, *p*-chlorobenzylamine and *p*-methylbenzylamine, affording the desired products in moderate yields (Table 2, Entries 15-17). In addition, polycyclic aromatic amines such as 1-naphthylamine (**1v**) and heterocyclic amines such as 2-aminopyridine (**1w**) also tolerate the catalytic system well and afforded the desired products in 60% and 66% yields, respectively (Table 2, Entries 22-23).

**Table 2.** Selenium-catalyzed carbonylation of 4-aminopyridine with amines<sup>a</sup>

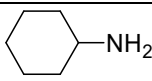
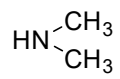
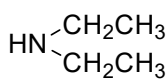
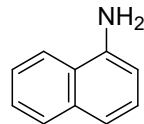
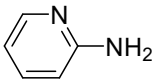


Entry	Amine	Product	Yield <sup>b</sup> (%)
1		<b>1a</b> → <b>2a</b>	70
2		<b>1b</b> → <b>2b</b>	33
3		<b>1c</b> → <b>2c</b>	49
4		<b>1d</b> → <b>2d</b>	41

Table 2 (continued)

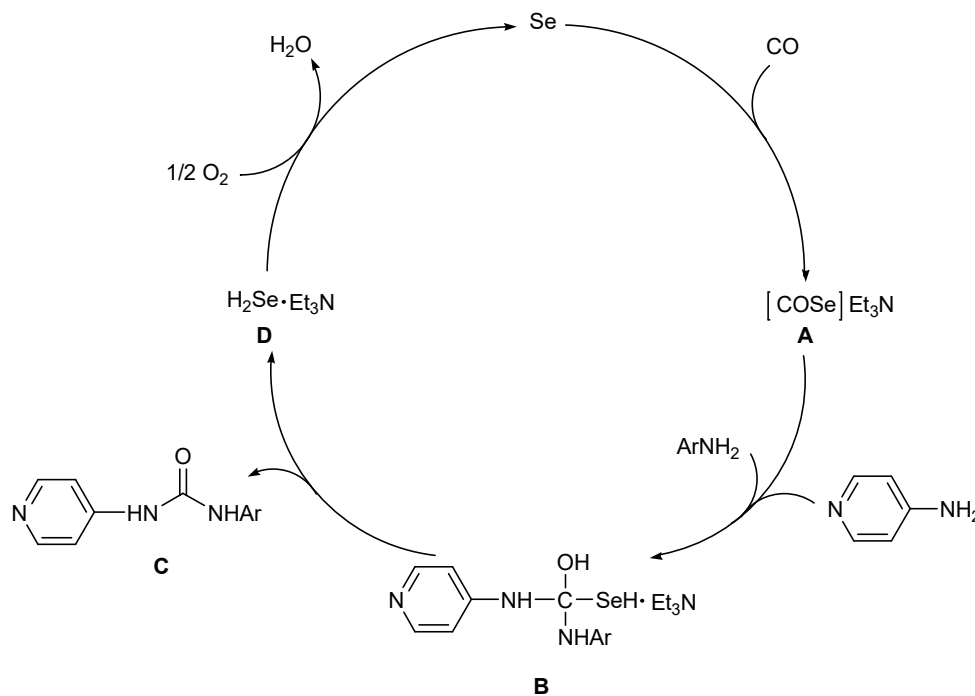
Entry	Amine	Product	Yield <sup>b</sup> (%)
5		<b>1e</b> → <b>2e</b>	0
6		<b>1f</b> → <b>2f</b>	50
7		<b>1g</b> → <b>2g</b>	60
8		<b>1h</b> → <b>2h</b>	74
9		<b>1i</b> → <b>2i</b>	41
10		<b>1j</b> → <b>2j</b>	25
11		<b>1k</b> → <b>2k</b>	41
12		<b>1l</b> → <b>2l</b>	74
13		<b>1m</b> → <b>2m</b>	48
14		<b>1n</b> → <b>2n</b>	22
15		<b>1o</b> → <b>2o</b>	54
16		<b>1p</b> → <b>2p</b>	54
17		<b>1q</b> → <b>2q</b>	53
18		<b>1r</b> → <b>2r</b>	51

**Table 2 (continued)**

Entry	Amine	Product	Yield <sup>b</sup> (%)
19		<b>1s</b> → <b>2s</b>	28
20		<b>1t</b> → <b>2t</b>	0
21		<b>1u</b> → <b>2u</b>	0
22		<b>1v</b> → <b>2v</b>	60
23		<b>1w</b> → <b>2w</b>	66

<sup>a</sup> 4-aminopyridine (5 mmol), amine (5 mmol), Se 0.25 mmol, Et<sub>3</sub>N (5 mmol), DMF (10 mL), 5 h, 140 °C, 1 atm (n<sub>CO</sub>:n<sub>O<sub>2</sub></sub> = 9:1). <sup>b</sup> Isolated yield.

On the basis of previous studies and our observations, a possible mechanism for the reaction is illustrated (Scheme 2).

**Scheme 2.** Proposed reaction mechanism.

The first step of the selenium-catalyzed carbonylation reaction involves the formation of carbonyl selenide **A** through the reaction of carbon monoxide with selenium in the presence of triethylamine.<sup>26</sup> Then **A** accepts the nucleophilic attack of 4-aminopyridine and the amine to afford the intermediate **B**.<sup>27</sup> Subsequently, species **B** undergoes elimination to generate the target *N*-aryl-*N'*-(4-pyridinyl)urea product **C**, accompanied by the formation of hydrogen selenide **D**, which is then oxidized by oxygen to provide selenium for the next catalytic cycle.<sup>27</sup>

## Conclusions

We have developed a facile, one-pot, phosgene-free strategy for the synthesis of *N*-aryl-*N'*-(4-pyridinyl)ureas. With cheap and readily available selenium as the catalyst, triethylamine as the cocatalyst, and carbon monoxide (instead of phosgene) as the carbonylation reagent, the carbonylation reaction of 4-aminopyridine proceeds smoothly with many amines under atmospheric pressure to afford the corresponding unsymmetrical 4-pyridinylureas mostly in moderate to good yields. The low cost, high atom economy, no generation and emission of carbon dioxide, one-pot and phosgene-free conditions should make this strategy very promising.

## Experimental Section

**General.** <sup>1</sup>H and <sup>13</sup>C spectra were recorded on a Bruker DPX-400 spectrometer using DMSO-*d*<sub>6</sub> or CDCl<sub>3</sub> as the solvent. Coupling constants (*J*) are reported in Hz. Column chromatography was performed on silica gel (200–300 mesh). All melting points were determined with a Keyi XT4 apparatus (Beijing, China). Carbon monoxide (99.9%) and selenium (99.95%) were used as purchased. All other chemicals were AR grade and were used without further purification.

**General procedure for the synthesis of *N*-aryl-*N'*-(4-pyridinyl)ureas **2**.** 4-Aminopyridine (5 mmol), aromatic amine (5 mmol), Se (0.25 mmol), Et<sub>3</sub>N (5 mmol) and DMF (10 mL) were added to a 50 mL three-necked flask equipped with a condenser. Next, the gaseous mixture of carbon monoxide and oxygen (*n*<sub>CO:n</sub><sub>O<sub>2</sub></sub> = 9:1, 20 mL/min) was bubbled into the reaction mixture with vigorous stirring at 140 °C for 5 h. Upon completion of the reaction, the mixture was cooled to room temperature, followed by stirring for 30 min in the atmosphere to precipitate Se, which was collected by suction filtration. The filtrate was evaporated under reduced pressure to remove DMF, and the residue was purified by column chromatography (silica gel, EtOAc-CH<sub>3</sub>OH, 10:1) to give the desired *N*-phenyl-*N'*-(4-pyridinyl)urea product.

***N*-Phenyl-*N'*-(4-pyridinyl)urea (**2a**).** Colorless needles, mp 164-165 °C (Lit.<sup>3</sup> mp 166-167 °C). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.11 (s, 1 H), 8.87 (s, 1 H), 8.37 (d, *J* 5.1 Hz, 2 H), 7.48 (dd, *J* 11.4, 6.7 Hz, 4 H), 7.30 (t, *J* 7.6 Hz, 2 H), 7.00 (t, *J* 7.0 Hz, 1 H) ppm. <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 152.19, 150.23, 146.60, 139.19, 128.92, 122.48, 118.63, 112.35 ppm. CAS registry number: 1932-35-0.



***N*-(2-Chlorophenyl)-*N'*-(4-pyridinyl)urea (2b)**. Colorless needles, mp 178-179 °C (Lit.<sup>3</sup> mp 174-176 °C). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.80 (s, 1H), 8.48 (s, 1H), 8.39 (d, *J* 5.3 Hz, 2H), 8.16 (d, *J* 8.2 Hz, 1H), 7.54-7.37 (m, 3H), 7.29 (t, *J* 7.7 Hz, 1H), 7.03 (t, *J* 7.6 Hz, 1H) ppm. <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 151.90, 150.31, 146.30, 135.50, 129.30, 127.64, 123.88, 122.49, 121.70, 112.36 ppm. CAS registry number: 20949-44-4.

***N*-(3-Chlorophenyl)-*N'*-(4-pyridinyl)urea (2c)**. Colorless needles, mp 208-209 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.20 (s, 1H), 9.08 (s, 1H), 8.37 (d, *J* 4.6 Hz, 2H), 7.74 (s, 1H), 7.46 (d, *J* 4.6 Hz, 2H), 7.28 (d, *J* 8.0 Hz, 2H), 7.02 (d, *J* 6.4 Hz, 1H) ppm. <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 152.13, 150.27, 146.44, 140.81, 133.45, 130.45, 122.12, 118.08, 117.06, 112.54 ppm. CAS registry number: 13208-37-2.

***N*-(4-Chlorophenyl)-*N'*-(4-pyridinyl)urea (2d)**. Colorless needles, mp 245-246 °C (Lit.<sup>3</sup> mp 242-243 °C). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.17 (s, 1H), 9.03 (s, 1H), 8.36 (d, *J* 6.0 Hz, 2H), 7.51 (d, *J* 8.8 Hz, 2H), 7.45 (d, *J* 6.1 Hz, 2H), 7.33 (d, *J* 8.8 Hz, 2H) ppm. <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 152.09, 150.20, 146.46, 138.19, 128.75, 126.05, 120.12, 112.41 ppm. CAS registry number: 13208-60-1.

***N*-(2-Methylphenyl)-*N'*-(4-pyridinyl)urea (2f)**. Colorless needles, mp 185-186 °C (Lit.<sup>3</sup> mp 189-190 °C). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.43 (s, 1H), 8.35 (s, 2H), 8.12 (s, 1H), 7.77 (d, *J* 7.9 Hz, 1H), 7.43 (d, *J* 5.7 Hz, 2H), 7.23-7.12 (m, 2H), 6.99 (t, *J* 7.4 Hz, 1H), 2.24 (s, 3H) ppm. <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 152.31, 150.20, 146.63, 136.75, 130.30, 128.13, 126.24, 123.46, 121.72, 112.03, 17.84 ppm. CAS registry number: 13289-27-5.

***N*-(3-Methylphenyl)-*N'*-(4-pyridinyl)urea (2g)**. Colorless needles, mp 200-201 °C (Lit.<sup>3</sup> mp 203-204 °C). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.09 (s, 1H), 8.79 (s, 1H), 8.35 (d, *J* 4.5 Hz, 2H), 7.44 (s, 2H), 7.31 (s, 1H), 7.24 (d, *J* 7.3 Hz, 1H), 7.17 (t, *J* 7.7 Hz, 1H), 6.83 (d, *J* 6.0 Hz, 1H), 2.28 (s, 3H) ppm. <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 152.09, 150.14, 146.55, 139.02, 138.08, 128.70, 123.18, 119.08, 115.76, 112.26, 21.21 ppm. CAS registry number: 13143-41-4.

***N*-(4-Methylphenyl)-*N'*-(4-pyridinyl)urea (2h)**. Colorless needles, mp 188-189 °C (Lit.<sup>3</sup> mp 188-189 °C). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.11 (s, 1H), 8.80 (s, 1H), 8.36 (d, *J* 5.3 Hz, 2H), 7.45 (d, *J* 5.6 Hz, 2H), 7.37 (d, *J* 8.1 Hz, 2H), 7.09 (d, *J* 8.0 Hz, 2H), 2.23 (s, 3H) ppm. <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 152.19, 150.15, 146.71, 136.30, 131.37, 129.31, 118.70, 112.29, 20.41 ppm. CAS registry number: 13256-77-4.

***N*-(2,5-Dimethylphenyl)-*N'*-(4-pyridinyl)urea (2i)**. Colorless needles, mp 208-209 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.48 (s, 1H), 8.34 (d, *J* 6.2 Hz, 2H), 8.12 (s, 1H), 7.61 (s, 1H), 7.44 (dd, *J* 4.9, 1.4 Hz, 2H), 7.06 (d, *J* 7.6 Hz, 1H), 6.80 (d, *J* 7.6 Hz, 1H), 2.25 (s, 3H), 2.19 (s, 3H) ppm. <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 152.30, 150.16, 146.68, 136.55, 135.18, 130.08, 125.23, 124.06, 122.27, 112.14, 20.88, 17.44 ppm. CAS registry number: 905034-63-1.

***N*-(2,6-Dimethylphenyl)-*N'*-(4-pyridinyl)urea (2j)**. Colorless needles, mp 166-167 °C (Lit.<sup>3</sup> mp 168-170 °C). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.26 (s, 1H), 8.34 (d, *J* 5.9 Hz, 2H), 7.97 (s, 1H), 7.45 (d, *J* 6.3 Hz, 2H), 7.08 (s, 3H), 2.21 (s, 6H) ppm. <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 152.70, 150.09, 147.06, 135.66, 134.82, 127.81, 126.33, 112.12, 18.24 ppm. CAS registry number: 97627-20-8.

***N*-(2-Methoxyphenyl)-*N'*-(4-pyridinyl)urea (2k).** Colorless needles, mp 196-197 °C (Lit.<sup>3</sup> mp 196-197 °C). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 10.25 (s, 1H), 8.58 (s, 1H), 8.35 (s, 2H), 8.10 (d, *J* 6.7 Hz, 1H), 7.47 (s, 2H), 7.09-6.79(m, 3H), 3.85 (s, 3H) ppm. <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 152.19, 150.16, 148.07, 146.72, 128.13, 122.48, 120.52, 118.75, 112.05, 110.87, 55.79 ppm. CAS registry number: 76947-68-7.

***N*-(4-Methoxyphenyl)-*N'*-(4-pyridinyl)urea (2l).** Colorless needles, mp 168-169 °C (Lit.<sup>3</sup> mp 175-176 °C). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 10.09 (s, 1H), 9.61 (s, 1H), 8.32 (d, *J* 4.8 Hz, 2H), 7.40 (dd, *J* 18.9, 6.8 Hz, 4H), 6.87 (d, *J* 8.5 Hz, 2H), 3.71 (s, 3H) ppm. <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 154.63, 152.57, 150.09, 146.90, 132.44, 119.91, 114.03, 111.93, 55.20 ppm. CAS registry number: 20949-48-8.

***N*-(4-Bromophenyl)-*N'*-(4-pyridinyl)urea (2m).** Colorless needles, mp 168-169 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.17 (s, 1H), 9.04 (s, 1H), 8.36 (d, *J* 4.8 Hz, 2H), 7.52-7.38 (m, 6H) ppm. <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 151.99, 150.18, 146.33, 138.55, 131.60, 120.48, 113.89, 112.35 ppm. CAS registry number: 13142-16-0.

***N*-Methyl-*N*-phenyl-*N'*-(4-pyridinyl)urea (2n).** Colorless needles, mp 147-148 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.63 (s, 1H), 8.32-8.27 (m, 2H), 7.48-7.40 (m, 4H), 7.34-7.25 (m, 3H), 3.28 (s, 3H) ppm. <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 154.13, 149.73, 147.16, 143.50, 129.36, 126.40, 126.25, 113.28, 37.79 ppm. CAS registry number: 80194-82-7.

***N*-Benzyl-*N'*-(4-pyridinyl)urea (2o).** Colorless needles, mp 260-261 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.56 (s, 1H), 8.28 (d, *J* 5.0 Hz, 2H), 7.40 (d, *J* 5.4 Hz, 2H), 7.32 (d, *J* 6.7, 4H), 7.23 (dd, *J* 15.3, 6.5 Hz, 2H), 4.31 (d, *J* 5.9 Hz, 2H) ppm. <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 154.81, 149.81, 147.30, 139.89, 128.28, 127.05, 126.73, 111.79, 42.61 ppm. CAS registry number: 353543-01-8.

***N*-(4-Chlorobenzyl)-*N'*-(4-pyridinyl)urea (2p).** Colorless needles, mp 139-140 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.12 (s, 1H), 8.30 (s, 2H), 7.45-7.34 (m, 4H), 7.32 (d, *J* 8.5 Hz, 2H), 6.94 (s, 1H), 4.31 (s, 2H) ppm. <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 154.71, 149.98, 147.06, 139.07, 131.40, 128.96, 128.24, 111.98, 42.13 ppm. CAS registry number: 945473-80-3.

***N*-(4-Methylbenzyl)-*N'*-(4-pyridinyl)urea (2q).** Colorless needles, mp 159-160 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.02 (s, 1H), 8.29 (d, *J* 5.9 Hz, 2H), 7.39 (d, *J* 6.2 Hz, 2H), 7.23-7.08 (m, 4H), 6.82 (t, *J* 5.8 Hz, 1H), 4.26 (d, *J* 5.8 Hz, 2H), 2.27 (s, 3H) ppm. <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 154.60, 149.98, 147.06, 136.81, 135.85, 128.86, 127.13, 111.86, 42.48, 20.66 ppm. CAS registry number: 1790317-56-4.

***N*-Butyl-*N'*-(4-pyridinyl)urea (2r).** Yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 9.31 (s, 1H), 8.22 (d, *J* 5.5 Hz, 2H), 7.36 (d, *J* 5.9 Hz, 2H), 6.25 (s, 1H), 3.19 (d, *J* 6.1 Hz, 2H), 1.41 (q, *J* 7.4 Hz, 2H), 1.31-1.21 (m, 2H), 0.82 (t, *J* 7.3 Hz, 3H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 155.56, 149.07, 148.24, 112.69, 39.53, 31.94, 19.98, 13.69 ppm. CAS registry number: 752151-87-4.

***N*-Cyclohexyl-*N'*-(4-pyridinyl)urea (2s).** Yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 9.41 (s, 1H), 8.18 (d, *J* 6.1 Hz, 2H), 7.38 (d, *J* 6.3 Hz, 2H), 6.23 (s, 1H), 3.65-3.50 (m, 1H), 1.83 (d, *J* 9.2 Hz, 2H), 1.57 (d, *J* 13.2 Hz, 2H), 1.47 (d, *J* 12.7 Hz, 1H), 1.29-0.98 (m, 5H) ppm. <sup>13</sup>C NMR (100 MHz,

CDCl<sub>3</sub>):  $\delta$  154.66, 148.89, 148.71, 112.81, 48.58, 33.26, 25.36, 24.60 ppm. CAS registry number: 148806-83-1.

***N*-(1-Naphthalenyl)-*N'*-(4-pyridinyl)urea (2v)**. Colorless needles, mp 247-248 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  9.68 (s, 1H), 9.12 (s, 1H), 8.38 (d, *J* 5.8 Hz, 2H), 8.13 (d, *J* 8.4 Hz, 1H), 7.95 (t, *J* 7.2 Hz, 2H), 7.69 (d, *J* 8.2 Hz, 1H), 7.62-7.47 (m, 5H) ppm. <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  152.74, 150.20, 146.65, 133.77, 133.72, 128.41, 126.41, 126.00, 125.87, 125.81, 123.72, 121.54, 118.42, 112.27 ppm. CAS registry number: 13256-93-4.

***N*-(2-Pyridinyl)-*N'*-(4-pyridinyl)urea (2w)**. Colorless needles, mp 193-194 °C (Lit.<sup>6</sup> mp 192-194 °C). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  10.68 (s, 1H), 9.57 (s, 1H), 8.40 (d, *J* 5.3 Hz, 2H), 8.29 (d, *J* 3.7 Hz, 1H), 7.76 (t, *J* 7.0 Hz, 1H), 7.53 (dd, *J* 20.9, 7.1 Hz, 3H), 7.10-6.92 (m, 1H) ppm. <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  152.34, 151.90, 150.22, 147.03, 145.81, 138.58, 117.97, 112.81, 112.05 ppm. CAS registry number: 188738-94-5.

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