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Graphical Abstract

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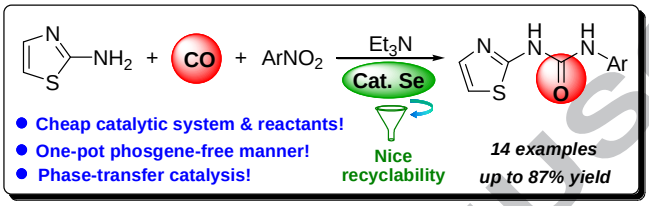

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Selenium-catalyzed carbonylation of 2-aminothiazole with nitro aromatics to *N*-aryl-*N'*-2-thiazolylureas

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ABSTRACT

An efficient, economical and phosgene-free procedure for the synthesis of *N*-aryl-*N'*-2-thiazolylureas is reported. With cheap and recyclable nonmetal selenium instead of noble metals as the catalyst, carbon monoxide instead of virulent phosgene as the carbonylation agent, the selenium-catalyzed carbonylation reaction of 2-aminothiazole can proceed smoothly in one-pot manner with a variety of nitro aromatics in the presence of triethylamine to afford the desired *N*-aryl-*N'*-2-thiazolylureas mostly in moderate to good yields. Selenium catalyst can be easily recovered due to its phase-transfer catalytic ability and reused without any significant degradation of its catalytic performance.

N-Aryl-*N'*-2-thiazolylureas, as a significant class of compounds possessing a urea linkage and a 5-member heterocycle, have attracted wide attention due to their broad spectrums of pharmacological and biological activities, such as antioxidant,[1] anticholinesterase,[1] anticancer,[2] antibacterial,[3] antiviral,[4] myorelaxant,[5] antiplasmodial,[6] and cytokinin activity,[7] etc (Figure 1). Hence, many efforts have been made towards their synthesis. The classical method relies on the phosgenation of 2-aminothiazole with aromatic amines.[8] However, the virulent nature of phosgene and the generation of corrosive HCl are the main drawbacks associated with it. Carbonyldiimidazole,[4,9] chloroformate,[10] and triphosgene[11] can also be applied as the substitutes for phosgene for this purpose, but they are limited by the low atom economy, high cost of these carbonylation reagents and the generation of corrosive HCl in some cases. Addition of 2-aminothiazole to the corresponding isocyanates provides an alternative approach to *N*-aryl-*N'*-2-thiazolylureas.[1a,5,6] Unfortunately, the significant defects accompanied with the corresponding isocyanates such as high cost, low availability, strong excitant nature, and harsh reaction conditions limit its application. Aminolysis of the corresponding carbamates with 2-aminothiazole can also realize this transformation,[10a,12] howerer, this method suffers from the drawbacks such as low atom economy, high cost and low availability of the carbamates. Recently, palladium-catalyzed cross-coupling of aryl chlorides with sodium cyanate in the presence of a biarylphosphine ligand also emerged as a practical approach to unsymmetrical *N*-arylureas (such as *N*-aryl-*N'*-2-thiazolylureas),[13] but both the catalyst and the ligand required for this approach are expensive (Scheme 1). Despite the above developments, there is still no economical and eco-friendly protocol for the synthesis of *N*-aryl-*N'*-2-thiazolylureas.

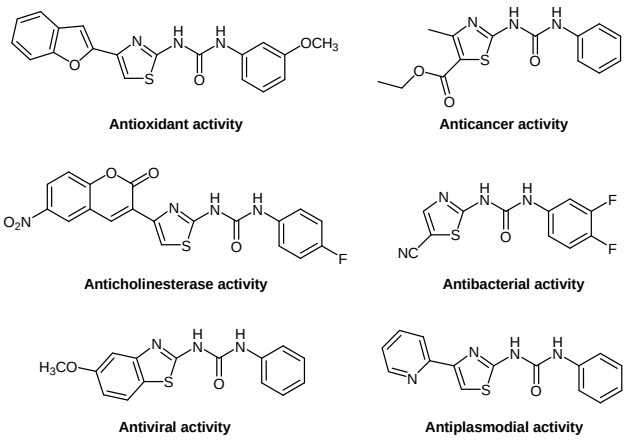

Figure 1. Select examples of bioactive *N*-aryl-*N'*-2-thiazolylureas.

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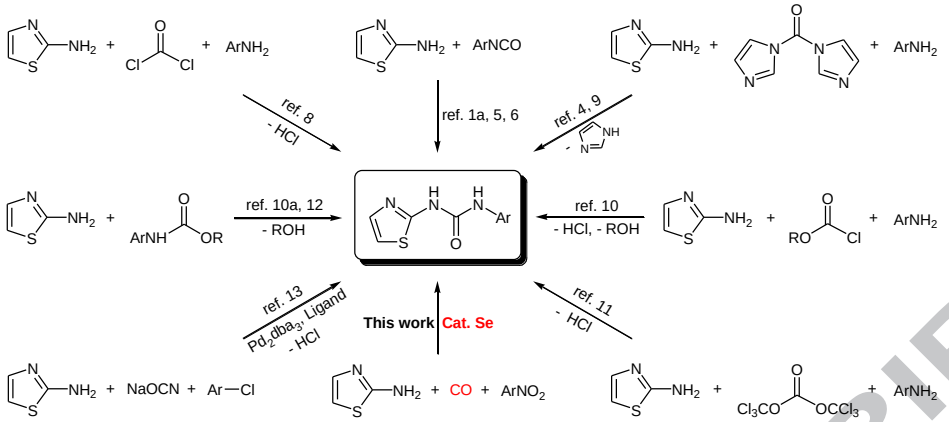
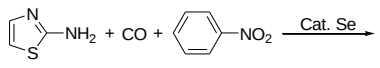


Scheme 1. Previous and present synthetic approaches to *N*-aryl-*N'*-2-thiazolylureas.

Over the past decades, catalyzed by transition metals, carbon monoxide has been used as a readily available and cheap C1 source to prepare various carbonyl containing products.[14] However, high cost and poor recyclability of the transition metal catalysts are the unavoidable weakness presented in this catalytic system. Thus, further pursuit of a cheap and recyclable catalyst for this carbonylation approach is highly desirable. Fortunately, cheap and readily available nonmetal selenium was found by Sonoda[15] to be an effective catalyst for carbon monoxide at this stage. Henceforth, Se/CO catalytic system has been widely used for the synthesis of a variety of carbonyl containing products such ureas,[16] carbamates,[16a,17] thiocarbamates,[16a,18] and carbonates,[16a,19] etc. To the best of our knowledge, there are no literature examples of the synthesis of *N*-aryl-*N'*-2-thiazolylureas with Se/CO catalytic system. Herein, we wish to report an efficient and economical approach to these target products via one-pot carbonylation of 2-aminothiazole with nitro aromatics using cheap and easily available selenium as the catalyst and carbon monoxide as the carbonylation agent in the presence of triethylamine (Scheme 1).

Initially, the carbonylation of 2-aminothiazole with nitrobenzene (**1a**) was chosen as a model reaction for optimizing the reaction conditions (Table 1). The reaction failed to proceed in the absence of selenium (Table 1, entry 1), which indicated that selenium catalyst was essential for this carbonylation reaction. Next, the selenium load was screened and the results revealed that 0.25 mmol was the best choice (Table 1, entries 2-4). Generally, selenium-catalyzed carbonylation reaction should proceed in a proper alkaline condition, which is believed to promote the formation of the active carbonyl selenide (COSe). As expected, no desired product was obtained when the reaction conducted in the absence of a base (Table 1, entry 5). Both the common inorganic bases such as NaOH and K_2CO_3 and organic bases such as Et_3N and pyridine were test for the present catalytic system, and among them, Et_3N was found to be most effective

Table 1. Optimization of the reaction conditions[a]



1a **2a**

Entry	Se (mmol)	Base	Temperature (°C)	Material ratio[b]	CO pressure (MPa)	Solvent	Yield[c] (%)
1	-	Et_3N	130	1:1	3	Toluene	0
2	0.15	Et_3N	130	1:1	3	Toluene	62
3	0.25	Et_3N	130	1:1	3	Toluene	77
4	0.35	Et_3N	130	1:1	3	Toluene	75
5	0.25	-	130	1:1	3	Toluene	0
6	0.25	NaOH	130	1:1	3	Toluene	49
7	0.25	K_2CO_3	130	1:1	3	Toluene	53
8	0.25	Pyridine	130	1:1	3	Toluene	72
9	0.25	Et_3N	90	1:1	3	Toluene	39
10	0.25	Et_3N	110	1:1	3	Toluene	68
11	0.25	Et_3N	150	1:1	3	Toluene	78
12	0.25	Et_3N	130	1:2	3	Toluene	23
13	0.25	Et_3N	130	2:1	3	Toluene	78
14	0.25	Et_3N	130	1:1	2	Toluene	55
15	0.25	Et_3N	130	1:1	4	Toluene	74
16	0.25	Et_3N	130	1:1	3	EtOAc	35
17	0.25	Et_3N	130	1:1	3	THF	52
18	0.25	Et_3N	130	1:1	3	Acetone	50

[a] Reaction conditions: 2-aminothiazole (5 mmol), base (10 mmol), solvent (10 mL), 8 h.

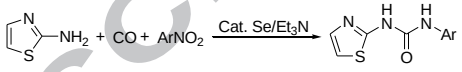
[b] n(2-aminothiazole) : n(nitrobenzene).

[c] Isolated yield of *N*-phenyl-*N'*-2-thiazolylurea.

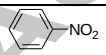
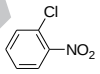
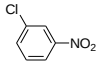
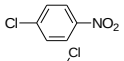
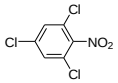
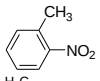
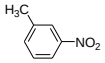
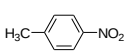
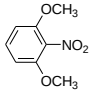
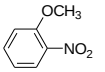
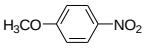
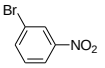
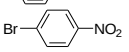
(Table 1, entries 3, 6-8). The reaction seemed to be very sensitive to temperature. When it proceeded at 90 °C, only 39% of the desired product was obtained (Table 1, entry 9). The product yield increased with the rise of temperature and could reach a satisfactory value at 130 °C. Further increase of the reaction temperature failed to improve the product yield significantly (Table 1, entries 3, 10, 11). Next, the raw material ratio of 2-aminothiazole to nitro benzene was investigated and 1:1 was found a proper proportion (Table 1, entries 3, 12, 13). The influence of CO pressure was also checked and the results indicating that 3 MPa could satisfy the reaction (Table 1, entries3, 14, 15). Finally, the solvents such as toluene, EtOAc, THF and acetone were screened for this reaction and toluene provided the best results (Table 1, entries 3, 16-18).

With the optimized reaction conditions in hand, we then turned to explore the scope and efficiency of the present catalytic system (Table 2). In general, the selenium-catalyzed carbonylation reaction of 2-aminothiazole could proceed smoothly with a variety of nitro aromatics, affording the corresponding *N*-aryl-*N'*-2-thiazolylureas mostly in moderate to good yields. And accompanied by the target products, a little symmetrical diaryl urea and di(2-thiazo1yl)urea could be detected existing in the reaction mixture, which indicated that the competitive self-carbonylation of nitro aromatics and 2-aminothiazole also occurred. The present carbonylation reaction seemed very sensitive to steric factors. Typically, ortho-substituted nitro benzenes led to lower product yields (Table 2, entries 2, 6, 10) compared to their meta- and para-substituted analogues (Table 2, entries 3, 4, 7, 8, 11). The higher the steric hindrance, the lower the product yields. As a result, it was understandable that no desired products were obtained when the carbonylation reaction proceed with 1e and 1i (Table 2, entries 5, 9). In addition, electronic effects of the nitro substrates also exerted an important influence on the present reaction. According to the results, the nitro benzenes with electron-donating groups (Table 2, entries 6-8, 10, 11) could proceed more efficiently than those with electron-withdrawing groups (Table 2, entries 2-4, 12, 13) in higher yields. In addition to the benzenoid nitro aromatics, 1-nitronaphthalene was also tested as an typical example of polycyclic nitro aromatics and was found to be amenable to the carbonylation reaction well (Table 2, entry 14).

Table 2. Selenium-catalyzed carbonylation of 2-aminothiazole with nitro aromatics[a]



1 2

Entry	Substrate		Product	Yield[b] (%)
1		**1a**	**2a**	77
2		**1b**	**2b**	35
3		**1c**	**2c**	51
4		**1d**	**2d**	64
5		**1e**	**2e**	0
6		**1f**	**2f**	43
7		**1g**	**2g**	69
8		**1h**	**2h**	87
9		**1i**	**2i**	0
10		**1j**	**2j**	47
11		**1k**	**2k**	82
12		**1l**	**2l**	54
13		**1m**	**2m**	65
14		**1n**	**2n**	72

[a] Reaction conditions: 2-aminothiazole (5 mmol), nitro aromatic (5 mmol), Se (0.25 mmol), Et_3N (10 mmol), CO (3 MPa), toluene (10 mL), 130 °C, 8 h.

[b] Isolated yield of *N*-aryl-*N'*-2-thiazolylurea.

Compared to the difficulty in recovering the catalyst from the common homogeneous system, one prominent advantage of the present catalytic system is that selenium catalyst can be easily recovered for further use due to its role as a phase-transfer catalyst. Specifically, selenium power is insoluble in the catalytic system prior to the carbonylation reaction; then selenium reacts with CO to from carbonyl selenide in situ to initiate the carbonylation reaction, which can dissolve in the reaction mixture to form a homogeneous catalytic system during the reaction process; after the reaction, selenium power can be precipitate out of the reaction medium conveniently by oxidization. Thus, catalyst selenium can easily be recovered by simple filtration and drying, and more importantly, which can be recycled in subsequent reactions. The reusability of the recovered selenium was tested by taking the carbonylation reaction of 2-aminothiazole with nitrobenzene as an example. As shown in Table 3, the yield of the desired *N*-phenyl-*N'*-2-thiazolylurea only dropped from 77% to 73% after four cycles, indicating that the catalytic performance of the recovered selenium was almost the same as that of the fresh selenium considering its small loss in each recovery step.

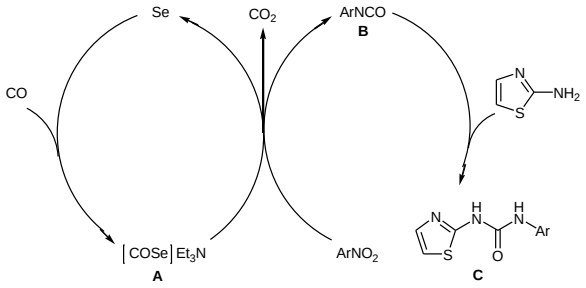
Table 3. Recyclability test of selenium catalyst[a]

Entry	Cycle	Yield[b] (%)
1	0	77
2	1	75
3	2	74
4	3	74
5	4	73

[a] Reaction conditions: 2-aminothiazole (5 mmol), nitrobenzene (5 mmol), Se (0.25 mmol), Et_3N (10 mmol), CO (3 MPa), toluene (10 mL), 130 °C, 8 h.

[b] Isolated yield of *N*-phenyl-*N'*-2-thiazolylurea.

A possible mechanism for this selenium-catalyzed carbonylation reaction has been outlined in Scheme 2. First, the carbonylation reaction is initiated by the active species carbonyl selenide (**A**), which is generated in situ by the reaction of carbon monoxide with selenium in the presence of triethylamine.[16a,20] Then, nitro aromatic reacts with **A** to afford the corresponding isocyanate (**B**), accompanied by the releasing of carbon dioxide, while A is transformed back to selenium for the coming catalytic cycle.[21] Finally, the addition of 2-aminothiazole to **B** generates the desired product *N*-aryl-*N'*-2-thiazolylurea (**C**).



Scheme 2. Proposed reaction pathway to *N*-aryl-*N'*-2-thiazolylureas.

In conclusion, an efficient, economical and phosgene-free procedure for the synthesis of *N*-aryl-*N'*-2-thiazolylureas has been established. With cheap and recyclable nonmetal selenium instead of noble metals as the catalyst, carbon monoxide instead of virulent phosgene as the carbonylation agent, the selenium-catalyzed carbonylation reaction of 2-aminothiazole can proceed smoothly in one-pot manner with a variety of nitro aromatics in the presence of triethylamine to afford the desired *N*-aryl-*N'*-2-thiazolylureas mostly in moderate to good yields. Low cost, high atom economy, phosgene-free conditions, no generation of corrosive waste, and simple procedure should make this approach very promising.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures, compound characterization data and copies of ^{1}H NMR spectra for all products) associated with this article can be found, in the online version, at http://dx.doi.org/

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Highlights

1. Cheap catalytic system and reactants!
2. One-pot phosgene-free manner!
3. Phase-transfer catalysis!
4. Nice recyclability of catalyst selenium!
5. Broad substrate scope!