SHORT PAPER

J. Chem. Research (S), 2003, 442–444

Synthesis of substituted heterocyclic ureas by selenium-catalysed carbonylation using carbon monoxide†

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A series of commercially useful substituted heterocyclic ureas have been synthesised via selenium-catalysed reductive carbonylation of substituted nitrobenzezes with aminopyridine or aminopyrimidine derivatives as co-reagents and carbon monoxide as carbonylating reagent.

Keywords: ureas, carbonylation, selenium catalysis, carbon monoxide

Pyridinylureas are a known class of commercially available compounds having utility in agriculture including plant regulatory activity.[1] Phenylpyrimidylurea derivatives used as immunosuppressants and antiviral agents were found about thirty years ago.[2] These phenylpyrimidylurea derivatives provide a method of treatment of autoimmune diseases and viral infection in mammals, excluding man.

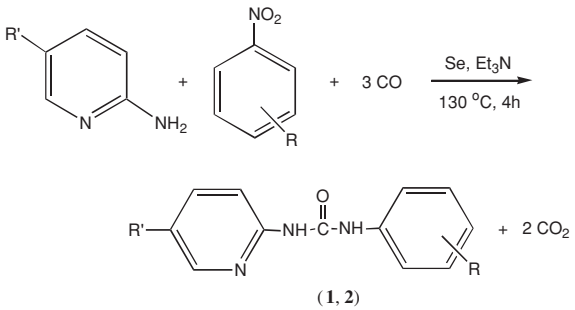
Traditionally, such compounds have been obtained by reacting amines with isocyanates, or amides with isocyanates. This route has the disadvantage of requiring an isocyanate intermediate. The most widely used method to prepare isocyanates in industry involves phosgenation of the appropriate amide or amine. However, phosgene is toxic and special handling precautions are necessary. Accordingly, there have been numerous attempts to produce urea derivatives using non-phosgene methods. Since aromatic amines are generally synthesised by the reduction of aromatic nitro compounds, one of the promising approaches is the reductive carbonylation of aromatic nitro compounds with carbon monoxide in the presence of an appropriate catalyst, give urea derivatives in a one pot reaction.

A series of patents disclose a process for preparing urea derivatives as reacting an aromatic nitro compound with amides and carbon monoxide catalysed by a Group VIII metal selected from rhodium, palladium and platinum; preference is given to the use of palladium as the catalyst.[3]

Recently, non-transition elements such as selenium and sulfur have also been found to catalyse the synthesis of urea derivatives. Franz reported sulfur-catalysed oxidative carbonylation of amines to give symmetrical ureas.[4,5] Sonoda developed a series of selenium-catalysed reactions.[6] Lu synthesised a series of unsymmetrical phenylureas in a one-pot reaction by combining the selenium-catalysed oxidative carbonylation of amines with reductive carbonylation of aromatic nitro compounds under relatively mild conditions.[7]

In this paper, the synthesis of substituted *N*-phenyl-*N*'-pyridinylurea and *N*-phenyl-*N'*-pyrimidylurea derivatives is described. Here we use aromatic nitro compounds and aminopyridine or aminopyrimidine derivatives with carbon monoxide under pressure, catalysed by selenium with triethylamine as co-catalysts to prepare the desired products according to Schemes 1–3.

Table 1 shows the oxidative and reductive carbonylation of substituted nitrobenzenes with 2-amino-5-chloropyridine to give *N*-phenyl- *N'*-(2-pyridinyl)ureas (**1a–1**). Table 2 gives the



Scheme 1 Formation of *N*-phenyl- *N'*-(2-pyridinyl)ureas.

Table 1 Carbonylation of substituted nitrobenzenes with 2-amino-5-chloropyridine[a]

Product	R'	R	M.p./°C	Yield/%
1a	Cl	H	200–203[b]	72
1b	Cl	4-Et	240	76
1c	Cl	4-Me	221[c]	80
1d	Cl	2-Me	209–212[d]	72.5
1e	Cl	3-CF_3	201–203	72
1f	Cl	4-PhO	240–242	82
1g	Cl	3-Cl	217–218[e]	88
1h	Cl	3-Me	197–199[f]	69
1i	Cl	3-Cl-2-Me	255	77
1j	Cl	3-Cl-4-Me	224	81
1k	Cl	2-$CHMe_2$	204–205	69
1l	Cl	4-$CHMe_2$	179–182	65.5

[a]Conditions: substituted nitrobenzene (10 mmol), 2-amino-5-chloropyridine (10 mmol), CO (3 MPa), Se (0.5 mmol), Et_3N (20 mmol), PhMe (10 ml), 130 °C, 4 h. [b]lit. m.p. 214 °C,[8] 206 °C,[9] 201–203 °C[10]. [c]lit.[10] m.p. 216–218 °C. [d]lit.[10] m.p. 189–191 °C. [e]lit.[10] m.p. 222–223 °C. [f]lit.[10] m.p. 193–195 °C.

Table 2 Carbonylation of substituted nitrobenzenes with 2-amino-5-methylpyridine[a]

Product	R'	R	M.p./°C	Yield/%
2a	Me	H	192–194[b]	79
2b	Me	4-Me	242	79
2c	Me	4-EtO	160–163	74
2d	Me	3-Me	202–205	79
2e	Me	3-CF_3	197–198	81
2f	Me	4-PhO	192–194	81.5
2g	Me	3-Cl-2-Me	239–240	91
2h	Me	3-Cl	209–211	84
2i	Me	2-Me	208–210	79
2j	Me	4-$CHMe_2$	177–180	83
2k	Me	2-$CHMe_2$	179–183	81
2l	Me	3-$CHMe_2$	142–144	83

[a]Conditions: substituted nitrobenzene (10 mmol), 2-amino-5-methylpyridine (10 mmol), CO (3 MPa), Se (0.5 mmol), Et_3N (20 mmol), PhMe (10 ml), 130 °C, 4 h. [b]lit.[11] m.p. 198–200 °C.

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 3 Carbonylation of substituted nitrobenzenes with 2-amino-4,6-dimethylpyrimidine[a]

Product	R	M.p./°C	Yield/%
3a	H	200–202	78.5
3b	2-Me	196–198	78
3c	3-CF_3	210–211	64.5
3d	3-Cl	195–196	76
3e	4-Cl	207–208[b]	44.5
3f	2-$CHMe_2$	180–182	70
3g	3-$CHMe_2$	150–153	46
3h	4-PhO	184–185	75
3i	3-Cl-2-Me	211–212	65
3j	3-Cl-4-Me	189–191	82.5

[a]Conditions: substituted nitrobenzene (10 mmol), 2-amino-5-methylpyridine (10 mmol), CO (3 MPa), Se (0.5 mmol), Et_3N (20 mmol), PhMe (10 ml), 150 °C, 4 h. [b]lit. m.p. 216 °C,[8] 211–212°C[12].

Table 4 Carbonylation of substituted nitrobenzenes with 4-amino-2,6-dimethylpyrimidine[a]

Product	R	M.p./°C	Yield/%
4a	H	229–231[b]	78.5
4b	2-Me	203–204[c]	78
4c	3-CF_3	229–230[d]	64.5
4d	3-Cl	221–222[e]	76
4e	4-Cl	222	44.5
4f	2-$CHMe_2$	182–183	70
4g	3-$CHMe_2$	187–189	46
4h	4-PhO	195–198	75
4i	3-Cl-2-Me	240	65
4j	3-Cl-4-Me	221–223	82.5

[a]Conditions: substituted nitrobenzene (10 mmol), 2-amino-5-methylpyridine (10 mmol), CO (3 MPa), Se (0.5 mmol), Et_3N (20 mmol), PhMe (10 ml), 150 °C, 4 h. [b]lit. m.p. 226 °C,[13] [c]lit. m.p. 205 °C,[13] [d]lit. m.p. 232 °C,[13] [e]lit. m.p. 225 °C [13]

results of a series of similar reactions between nitrobenzenes and 2-amino-5-methylpyridine, forming the corresponding ureas (**2a–l**). The yields of the substituted pyridinyl ureas are moderate to good, being somewhat better overall in the 5-methyl than in the 5-chloro series.

In a similar way, substituted nitrobenzenes reacted with 2-amino-4,6-dimethylpyrimidine and with 4-amino-2,6-dimethylpyrimidine in the presence of selenium and carbon monoxide according to Schemes 2 and 3; the results are summarised in Tables 3 and 4. The temperatures employed in these reactions were some 20° higher than in the pyridinamine reactions, but conditions were otherwise similar.

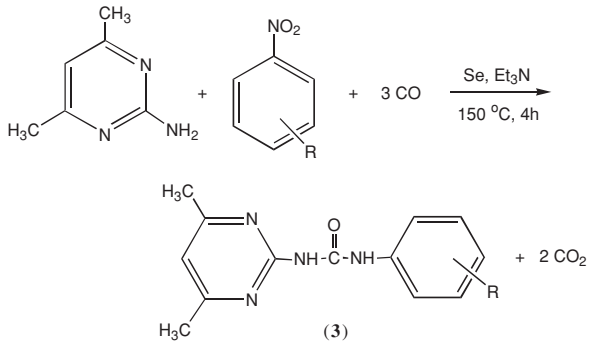
As the Tables show, both 2-amino-4,6-dimethylpyrimidine and 4-amino-2,6-dimethylpyrimidine react well and the yields are from moderate to good.

From a synthetic point of view, the mild reaction conditions, good yields, high chemoselectivity and one-step nature of the reaction, the high purity of the products, and the fact that no phosgene is employed, make the present reaction a useful method for the synthesis of heterocyclic-substituted urea derivatives.

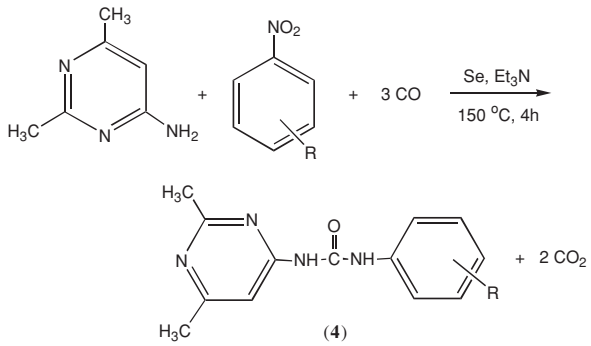
Experimental

Melting points were determined on a Taike X-4 apparatus (Beijing, China) and were uncorrected. ^1H and ^{13}C NMR spectra were obtained on a Bruker DRX 400 spectrometer. Chemical shifts were reported in ppm relative to tetramethylsilane (δ units), and dimethylsulfoxide-d_6 G.R. as solvent. Solvent toluene was reagent grade and used without further purification. Elemental selenium (99.999 %), carbon monoxide (99.9 %), nitro compounds, aminopyridines, aminopyrimidines, and triethylamine were used as purchased.

Typical procedure: *synthesis of N-phenyl-N′-(5-chloro-2-pyridinyl) urea*: Selenium (0.5 mmol), 2-amino-5-chloropyridine (10 mmol), nitrobenzene (10 mmol), triethylamine (20 mmol) and toluene (10 ml) were placed in a 100mL stainless steel autoclave. The reactor was sealed and flushed three times with 1.0 MPa of carbon monoxide.



Scheme 2 Formation of *N*-phenyl- *N′*-(2-pyrimidinyl)ureas.



Scheme 3 Formation of *N*-phenyl- *N′*-(4-pyrimidinyl)ureas.

Carbon monoxide (3.0 MPa) was introduced to the system, and the reaction vessel was placed in an oil bath preheated to 130 °C with stirring. After 4 h, the apparatus was cooled to room temperature, and the remaining carbon monoxide was evacuated. The reaction mixture was then evaporated, and the *N*-phenyl-*N′*-(5-chloro-2-pyridinyl)urea (1.78 g, 72%) was obtained and purified by flash chromatography (silica gel, hexane: AcOEt = 5:3).

Spectral data for some selected compounds: 1-Phenyl-3-(5-chloro-2-pyridinyl)urea (**1a**): ^1H NMR: δ 6.98 (t, 1H, phenyl 4), 7.29 (t, 2H, phenyl 3,5), 7.47 (d, 2H, phenyl 2,6), 7.71 (d, 1H, pyridinyl 3) 7.80 (d, 1H, pyridinyl 4), 8.26 (s, 1H, pyridinyl 6) 9.41 (s, 1H, pyridinyl-NH), 9.76 (s, 1H, phenyl-NH). ^{13}C NMR: δ 112.8 (pyridinyl 3), 118.4 (phenyl 2,6), 122.2 (phenyl 4), 123.1 (pyridinyl 5), 128.4 (phenyl 3,5), 137.7 (pyridinyl 4), 138.6 (phenyl 1), 145.1 (pyridinyl 6), 151.2 (urea C=O), 151.5 (pyridinyl 2).

1-Phenyl-3-(5-methyl-2-pyridinyl)urea (**2a**): ^1H NMR: δ 2.23 (s, 3H, CH_3), 7.02 (d, 1H, pyridinyl 3), 7.32 (t, 2H, phenyl 3,5), 7.41 (t, 1H, phenyl 4), 7.53 (d, 1H, pyridinyl 4), 7.55 (d, 2H, phenyl 2,6), 8.11 (s, 1H, pyridinyl 6), 9.37 (s, 1H, pyridinyl-NH), 10.59 (s, 1H, phenyl-NH). ^{13}C NMR: δ 17.1 (CH_3), 111.5 (pyridinyl 3), 118.7 (phenyl 2,6), 122.4 (phenyl 4), 126.2 (pyridinyl 5), 128.8 (phenyl 3,5), 139.2 (phenyl 1), 139.2 (pyridinyl 4), 146.3 (pyridinyl 6), 150.8 (urea C=O), 157.7 (pyridinyl 2).

1-(3-Trifluoromethylphenyl)-3-(5-methyl-2-pyridinyl)urea (**2e**): ^1H NMR: 2.24 (s, 3H, CH_3), 7.35 (d, 1H, pyridinyl 3), 7.42 (t, 1H, phenyl 5), 7.53 (d, 1H, phenyl 4), 7.61 (d, 1H, phenyl 6), 7.62 (s, 1H, phenyl 2), 7.65 (d, 1H, pyridinyl 4), 8.14 (2, 1H, pyridinyl 6), 9.48 (s, 1H, pyridinyl-NH), 10.81 (s, 1H, phenyl-NH). ^{13}C NMR: δ 17.1 (CH_3), 111.6 (pyridinyl 3), 114.6 (phenyl 2), 118.7 (CF_3), 122.4 (phenyl 4), 126.6 (phenyl 6), 129.2 (phenyl 4), 129.5 (phenyl 3), 125.5 (pyridinyl 5), 139.2 (pyridinyl 4), 140.0 (phenyl 1), 146.4 (pyridinyl 6), 150.4 (urea CO), 152.2 (pyridinyl 2).

1-Phenyl-3-(4,6-dimethyl-2-pyrimidyl)urea (**3a**): ^1H NMR: δ 2.41 (s, 6H, CH_3), 6.84 (s, 1H, pyrimidyl 5), 7.04 (t, 1H, phenyl 4), 7.33 (t, 2H, phenyl 3,5), 7.56 (d, 2H, phenyl 2,6), 9.18 (s, 1H, phenyl-NH), 11.51 (s, 1H, pyrimidyl-NH), ^{13}C NMR: δ 22.7 (CH_3), 113.1 (pyrimidyl 5), 118.8 (phenyl 2,6), 122.4 (phenyl 4), 128.3 (phenyl 3,5), 138.2 (phenyl 1), 150.9 (urea C=O), 157.0 (pyrimidyl 4,6), 167.0 (pyrimidyl 2).

1-Phenyl-3-(2,6-dimethyl-4-pyrimidyl)urea (**4a**): ^{1}H NMR: δ 2.39 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 7.02 (s, 1H, pyrimidyl 5), 7.04 (t, 1H, phenyl 4), 7.30 (t, 2H, phenyl 3,5), 7.50 (d, 2H, phenyl 2,6), 9.67 (s, 1H, phenyl-NH), 10.73 (s, 1H, pyrimidyl-NH). ^{13}C NMR: δ 23.6 (CH_3), 25.2 (CH_3), 103.5 (pyrimidyl 5), 118.6 (phenyl 2,6), 122.4 (phenyl 4), 128.2 (phenyl 3,5), 138.0 (phenyl 1), 151.5 (urea C=O), 158.1 (pyrimidyl 4), 164.9 (pyrimidyl 6), 166.2 (pyrimidyl 2).

Received 7 October 2002; accepted 18 April 2003
Paper 02/1567

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