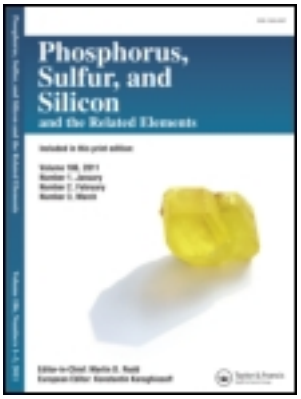

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A New Method for Synthesizing Asymmetric Urea Containing Thiazolo[5,4-b]pyridine And Applications in Agriculture

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A NEW METHOD FOR SYNTHESIZING ASYMMETRIC UREA CONTAINING THIAZOLO[5,4-b]PYRIDINE AND APPLICATIONS IN AGRICULTURE

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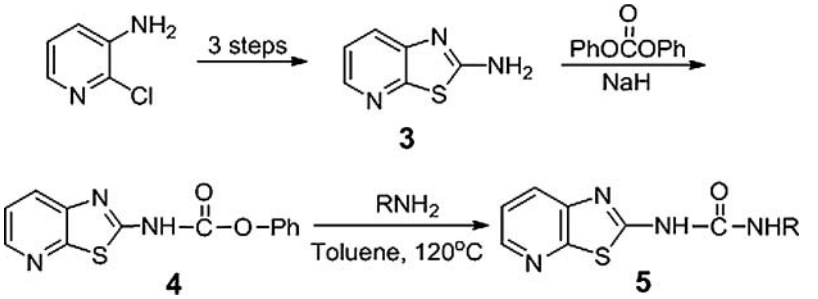
GRAPHICAL ABSTRACT



Abstract *In this article, we describe the use of diphenyl carbonate (DPC) as a carbonyl source instead of isocyanate to synthesize asymmetric substituted urea derivatives. In a study aiming to discover new lead compounds with agricultural activities, thiazole[5,4-b]pyridine ureas were prepared by this method and characterized by mass spectrometry, elemental analysis, and ^1H NMR spectroscopy. The biological activities show that the title compounds have moderate activities on herbicide, fungicide, and plant growth regulation.*

Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.*

Keywords Biological activities; diphenyl carbonate; synthesis; thiazolopyridine; urea

INTRODUCTION

Asymmetric substituted ureas play a key role in agriculture and medicine. Although there are many feasible routes for the synthesis of asymmetric urea derivatives, these

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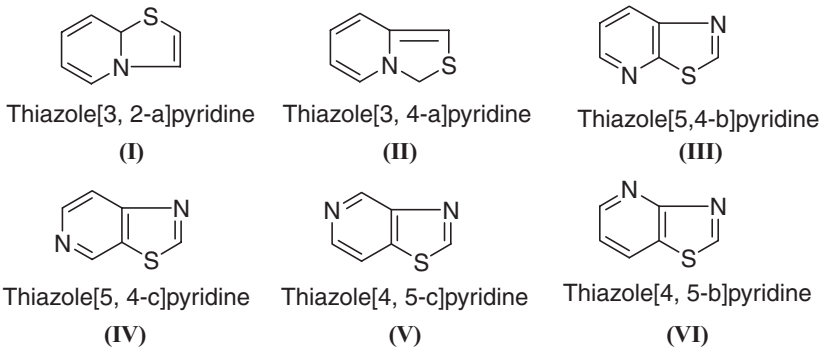
methods are generally limited to the addition of substituted amines to isocyanate from phosgene.[1,2] Because of their high toxicity and reactivity, phosgene and isocyanates are difficult to handle in the laboratory. Although alternatives for phosgene, such as triphosgene, have been developed during the last few decades,[3] it itself is prepared from phosgene. Other methods such as carbonyldiimidazole,[4] selenium-catalyzed carbonylation,[5,6] and S,S-dimethyl dithiocarbonate[2,7,8] also suffer from drawbacks, such as reagents prepared from phosgene, human carcinogens, unstable intermediates, or high pressure conditions. Alternative methods involve drastic reaction conditions, such as direct reactions of amines with dialkyl carbonates at high temperature[9] and the reaction of amines with N,N′-diphenylurea in the presence of Et_3N in refluxing DMF,[10] but only symmetric ureas can be obtained by these methods. So the development of a facile and safe procedure to synthesize asymmetric ureas is of importance and has practical application.

Heterocyclic compounds also play a key role in the research and development of new pesticides because of their special chemical structures and physical properties, and now they have become important for new pesticides. There are a lot of commercial pesticides containing heterocyclic structures: for example, neonicotinoid insecticides imidacoprid and acetamiprid, super-high efficient herbicide sulfonylurea, triazolopyrimidine and imidazolinone, and the fungicides Triadimefon and Triadimenol.

Fused systems containing a pyridine ring, in particular thiazolopyridines, are widely used as base structures in the design of various biologically active compounds possessing antiviral, anticarcinogenic, antiphlogistic, and antispasmodic properties.[11–14] There are six isomeric thiazolopyridine systems reported in the literature (Scheme 1).[15] Depending on the fusion of the thiazole moiety to the pyridine ring, thiazolopyridines can be classified into the following classes: thiazolo[3,2-a]pyridine (**I**), thiazolo[3,4-a]pyridine (**II**), thiazolo[5,4-b]pyridine (**III**), thiazolo[5,4-c]pyridine (**IV**), thiazolo[4,5-c]pyridine (**V**), and thiazolo[4,5-b]pyridine (**VI**). Several thiazolo[5,4-b]pyridines have been evaluated as antibacterials,[16–20] antibiotics,[21,22] antivirals,[23] bronchospasmolytics,[24] leukotriene antiagonists,[25] antiulcer agents,[26,27] and as azo dyes.[28]



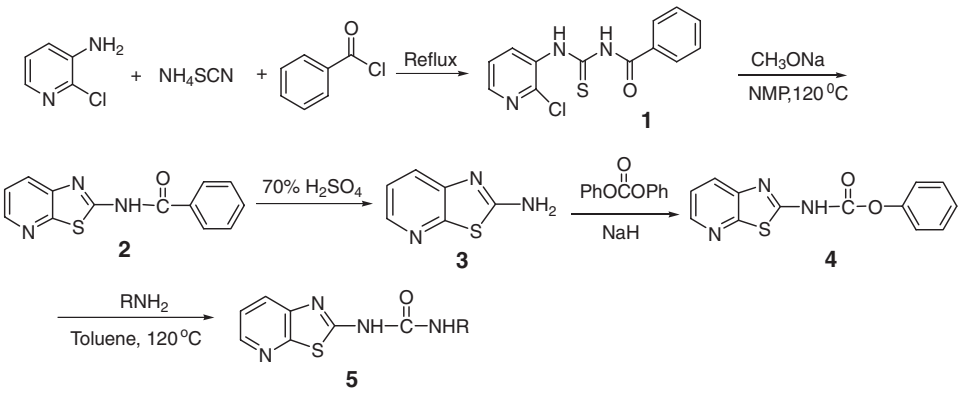
Scheme 1 Structures of six thiazolopyridines.

To develop a convenient method to synthesize asymmetric ureas, obtain the multifunctional libraries of 1,3-disubstituted asymmetric urea derivatives, and optimize the structure of urea derivative to find a new lead compound, in this article we report another asymmetric urea derivative, thiazolo[5,4-b]pyridine urea, from substituted amino compounds, and

phenyl thiazolo[5,4-b]pyridine-2-yl carbamate under refluxing in toluene, as well as their biological activities.

RESULTS AND DISCUSSION

We used diphenyl carbonate (DPC) as a carbonyl source to synthesize the title compounds. Diphenyl carbonate, a key raw material utilized in the phosgene-free polycarbonate manufacturing process, has been one of the foci of research in chemistry and chemical engineering in recent decades. It is also used as a solvent and chemical intermediate, and it is easy and safe to handle in the laboratory as a carbonyl source, instead of phosgene. The synthetic route to the title compounds **5** is outlined in Scheme 2.



Scheme 2 Synthetic route for the preparation of compounds **5**.

The key intermediate thiazolo[5,4-b]pyridin-2-yl amine **3**, which was obtained from 2-chloropyridinyl-3-amine in three steps according to a modified literature procedure,[29] was treated with diphenyl carbonate and NaH in anhydrous THF to give phenyl thiazolo[5,4-b]pyridin-2-yl carbamate **4** in an acceptable yield. The title compounds **5** were produced by aminolysis of compound **4** and diversified amine in refluxing toluene for about 20 h in good yield. They were easy to isolate by filtration or recrystallization and seldom needed silica gel column chromatography.

As a control, the synthesis of phenyl carbamate **4** was attempted from **3** by treatment with phenyl chloroformate and Et_3N in THF. However, this procedure did not work well, and no desired product was monitored from TLC. It is possible that phenyl chloroformate is so active that many side products were formed under these conditions. In this article, the benzothiazole amine **3** was first converted to the sodium salt and then treated with diphenyl carbonate to give moderate yield of the desired phenyl carbamate.

To evaluate the biological activity of the title compounds, we tested the insecticidal, herbicidal, fungicidal, and plant growth regulation activities. The results show that the title compounds have no insecticidal activities against Oriental armyworm and *Culex pipiens pallens*. Most compounds possess moderate herbicidal activities against Amaranthus tricolor L at post-emergence and very lower activities against *Echinochloa crusgalli*, *Brassica napus L.*, *Medicago sativa L.*, and *Digitaria sanguinalis(Linn)Scop.*, but have some fungicidal inhibition against *Fusarium graminearum*, *Alternaria solani*, *Cercospora arachidicol*, *Botryosphaeria berengeriama*, and *Fusarium oxysporum*. Most compounds

have inhibition on rooting of cucumber cotyledon, while compound **5n** has plant growth regulation activities on rooting of cucumber cotyledon at 101.5%. The detailed biological results are listed in Tables S1 and S 2 (see the Supplemental Materials, available online).

CONCLUSIONS

In summary, we have described the novel phosgene-free synthesis of asymmetric urea containing thiazole[5,4-b]pyridine with agricultural activities (herbicide, fungicide, and plant growth regulation). This method is safe, convenient, and easy to scale up in laboratory. The final synthesized compounds were characterized by spectral data (^{1}H NMR, ESI-MS, and elemental analysis). Further investigations of these compounds are in progress.

EXPERIMENTAL

Melting points were determined using an X-4 Digital Microscope Melting Point Apparatus (Beijing Taike Co. Ltd.) and were uncorrected. Nuclear magnetic resonance spectra were recorded on Varian Mecury Plus 400 NMR or Bruker Avance-300 NMR instrument in $CDCl_3$ or $(CD_3)_2SO$. Chemical shifts (δ_H) are reported in parts per million (ppm), relative to TMS as internal standard. Elemental analyses were carried out on an MF-3 automatic analyzer instrument. Flash-column chromatography was performed using commercial grades of silica gel 200∼300 meshes. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 F254 plates, and spot visualization was accomplished by UV light (254 nm) or phosphomolybdic acid solution.

Solvents were obtained from commercial sources and purified according to the literature[30] if necessary.

Preparation of Phenyl Thiazolo[5,4-b]pyridin-2-ylcarbamate 4[29]

To the mixture of ammonium isothiocyanate (8.9 g, 116.68 mmol, 1.0 eq) and benzoyl chloride (16.4 g, 116.68 mmol, 1.0 eq) in acetone (100 mL), 2-chloropyridin-3-amine (10 g, 77.78 mmol, 0.5 eq) in acetone (50 mL) was added with a mechanical stirrer and then heated to reflux for 8 h. After cooling to room temperature, the solvent was removed under reduced pressure, and the residue was dissolved in hot ethanol and filtered. The solid was washed with water and diethyl ether successively, and dried at room temperature to obtain the desired compound **1**, mp 152–154°C, yield 85%, ^{1}H NMR [DMSO, 400MHz] δ/ppm: 8.51–8.52 (m, 1H), 8.16–8.18 (m, 1H), 8.11–8.13 (m, 2H), 7.63–7.67 (m,1H), 7.51–7.58 (m, 3H), 5.32 (brs, 2H, 2×NH).

In a 100 mL of flask, the above compound **1** (2.20 g, 7.5 mmol, 1.0 eq) and $NaOCH_3$ (0.81 g, 15 mmol, 2.0 eq) were placed in N-methyl-2-pyrrolidone) (NMP, 15 mL). After refluxing for 8 h, the mixture was poured into cool water (30 mL). The precipitate was filtered and washed with water and diethyl ether successively, and dried at room temperature to give the intermediate **2**, yield 75%. ^{1}H NMR [DMSO, 300MHz] δ/ppm: 13.00 (brs, 1H, NH), 8.49–8.51 (m, 1H), 8.13–8.16 (m, 3H), 7.65–7.71 (m, 1H), 7.49–7.60 (m, 3H).

The above intermediate **2** (10 g, 40 mmol) in 70% sulfuric acid (50 mL) was heated to reflux for 3–4 h. After cooling to room temperature, the mixture was poured into water (125mL), and neutralized with 30% NaOH. The precipitate was filtered and washed with water and diethyl ether to give the desired product, yield 56%, mp 241–243°C (lit.[31]

Table 1 Physical constants and microanalytical data of thiazole[5,4-b]pyridine ureas 5

				Elemental Analysis					
				C%		H%		N%	
Compound	R	Yield (%)	Mp (°C)	Calc.	Found	Calc.	Found	Calc.	Found
5a	Pyridin-2-yl	65	290–292	53.13	53.52	3.34	3.41	25.81	25.64
5b	6-Methyl-pyridin-2-yl	68	285–286	54.72	54.62	3.89	3.72	24.55	24.54
5c	5-Methyl-pyridin-2-yl	70	296–297	54.72	54.55	3.89	3.64	24.55	24.67
5d	4-Methyl pyridin-2-yl	72	294–295	54.72	54.83	3.89	3.52	24.55	24.56
5e	*p*-Tolyl	65	287–288	59.14	59.84	4.25	4.32	19.70	19.46
5f	5-Bromo-pyridin-2-yl	68	>300	41.16	40.98	2.30	2.32	20.00	19.79
5g	5-Chloro-pyridin-2-yl	75	290–292	47.14	47.16	2.64	2.50	22.91	22.68
5h	2-Chloro-pyridin-3-yl	75	286–288	47.14	47.23	2.64	2.65	22.91	22.86
5i	2,4,5-Trichlorophenyl	80	295–297	41.79	41.57	1.89	2.04	14.99	15.24
5j	4-Bromophenyl	78	290–292	44.71	44.47	2.60	2.57	16.04	15.85
5k	4-Chlorophenyl	71	286–288	51.23	51.35	2.98	3.12	18.38	18.30
5l	5-Nitro-pyridin-2-yl	66	296–298	45.57	45.73	2.55	2.82	26.57	26.68
5m	*o*-Tolyl	60	260–262	59.14	58.96	4.25	4.22	19.70	19.61
5n	Benzyl	62	263–265	59.14	59.32	4.25	4.25	19.70	19.83
5o	*n*-Butyl	86	220–222	52.78	52.81	5.64	5.58	22.38	22.47
5p	*n*-Propyl	72	220–222	50.83	51.13	5.12	5.12	23.71	23.81
5q	*i*-Propyl	74	218–220	50.83	51.02	5.12	5.36	23.71	23.72
5r	Pyrimidin-2-yl	60	290–292	48.52	48.72	2.96	3.24	30.86	31.02
5s	4-Methyl pyrimidin-2-yl	54	>300	50.34	50.16	3.52	3.56	29.35	29.32
5t	4-Nitrophenyl	58	286–288	49.52	49.42	2.88	2.68	22.21	22.38

Table 2 Characteristic ESI-MS and ^{1}H NMR data of thiazole[5,4-b]pyridine ureas 5

Compound	ESI-MS $(M-1)^-$ (%)	^{1}H NMR (DMSO, 300MHz or 400MHz, δ/ppm)
5a	270 (100)	(300M Hz): 12.36(s, 1H, NH), 10.07(s, 1H, NH), 8.43(t, J = 2.0Hz, 1H), 8.07(d, J = 3.9Hz, 1H), 8.07(d, J = 8.1Hz, 1H), 7.87–7.82(m, 1H), 7.57(d, J = 7.8Hz, 1H), 7.48–7.45(m, 1H), 7.13(t, J = 11.7Hz, 1H)
5b	284 (100)	(300M Hz): 12.42(s, 1H, NH), 10.04(s, 1H, NH), 8.43(t, J = 4.8Hz, 1H), 8.08(d, J = 8.1Hz, 1H), 7.72(t, J = 7.8Hz, 1H), 7.48–7.44(m, 1H), 7.35(t, J = 3.6Hz, 1H), 7.00(d, J = 7.5Hz, 1H), 2.48(s, 3H)
5c	284 (100)	(300M Hz): 12.30(s, 1H, NH), 9.96(s, 1H, NH), 8.42(s, 1H), 8.18(s, 1H), 8.07(s, 1H), 7.66(d, J = 2.7Hz, 1H), 7.47(d, J = 1.0Hz, 2H), 2.26(s, 3H)
5d	284 (100)	(300M Hz): 12.49(s, 1H, NH), 10.04(s, 1H, NH), 8.43(d, J = 3.3Hz, 1H), 8.23(d, J = 5.1Hz, 1H), 8.07(d, J = 8.1Hz, 1H), 7.49–7.45(m, 1H), 7.36(s, 1H), 6.98(d, J = 4.8Hz, 1H), 2.34(s, 3H)
5e	283 (100)	(300M Hz): 10.90(s, 1H, NH), 9.08(s, 1H, NH), 8.39(d, J = 5.1Hz, 1H), 8.01(d, J = 6.9Hz, 1H), 7.40(d, J = 8.1Hz, 3H), 7.15(d, J = 7.5Hz, 2H), 2.27(s, 3H)
5f	348 (100), 350 (95)	(300M Hz): 11.65(s, 1H, NH), 9.98(s, 1H, NH), 8.45(t, J = 8.4Hz, 2H), 8.07–8.05(m, 2H), 7.76–7.74(m, 1H), 7.49–7.45(m, 1H)
5g	304 (100)	(300M Hz): 11.64(s, 1H, NH), 9.99(s, 1H, NH), 8.43(t, J = 3.9Hz, 2H), 8.06(t, J = 2.4Hz, 1H), 7.96(t, J = 2.1Hz, 1H), 7.83–7.81(m, 1H), 7.47(t, J = 3.0Hz, 1H)
5h	270 (100) $(M-Cl)^-$	(300M Hz): 12.36(s, 1H, NH), 10.07(s, 1H, NH), 8.42(d, J = 3.3Hz, 1H), 8.37(s, 1H), 8.06(d, J = 7.5Hz, 1H), 7.84(t, J = 6.6Hz, 1H), 7.56(d, J = 6.9Hz, 1H), 7.47(d, J = 4.5Hz, 1H), 7.14(d, J = 4.2Hz, 1H)
5i	371 (100), 373 (80)	(300M Hz): 11.66(s, 1H, NH), 9.19(s, 1H, NH), 8.40(d, J = 15.4Hz, 2H), 8.02(d, J = 7.2Hz, 1H), 7.89(s, 1H), 7.43(d, J = 3.2Hz, 1H)
5j	348 (100)	(400M Hz): 10.98(s, 1H, NH), 9.31(s, 1H, NH), 8.37–8.36(t, J = 2.2Hz, 1H), 7.98(d, J = 3.2Hz, 1H), 7.48(s, 4H), 7.43–7.40(m, 1H)
5k	303 (100)	(300M Hz): 11.06(s, 1H, NH), 9.34(d, J = 1.6Hz, 1H), 8.45–8.39(m, 1H), 8.01–7.99(t, J = 8.8Hz, 1H), 7.57–7.37(m, 4H)
5l	315 (100)	(300M Hz): 8.46(d, J = 3.9Hz, 2H), 8.06–8.04(t, J = 3.8Hz, 2H), 7.49–7.47(t, J = 3.8Hz, 2H)
5m	283 (50)	(300M Hz): 8.23(s, 1H, NH), 7.79(d, J = 8.4Hz, 2H), 7.18–7.13(m, 3H), 6.96(d, J = 7.2Hz, 1H), 2.26(s, 3H)
5n	285 (100)	(400M Hz): 10.96(s, 1H, NH), 8.33(d, J = 4.4Hz, 1H), 7.93(d, J = 8.0Hz, 1H), 7.39–7.24(m, 6H), 4.35(d, J = 5.6Hz, 2H)
5o	249 (100)	(400M Hz): 10.76(s, 1H, NH), 8.31(d, J = 3.6Hz, 1H), 7.92(d, J = 8.0Hz, 1H), 7.38–7.35(m, 1H), 6.75(s, 1H), 3.16–3.11(m, 2H), 1.46–1.38(m, 2H), 1.33–1.23(m, 2H), 0.88–0.85(t, J = 7.2Hz, 3H)
5p	235 (100)	(400M Hz): 10.76(s, 1H, NH), 8.32(d, J = 4.4Hz, 1H), 7.92(d, J = 8.0Hz, 1H), 7.38–7.35(m, 1H), 6.77(s, 1H), 3.12–3.07(m, 2H), 1.48–1.42(m, 2H), 0.86–0.83(t, J = 7.2Hz, 3H)
5q	235 (100)	(400M Hz): 10.57(s, 1H, NH), 8.31(d, J = 4.4Hz, 1H), 7.92(d, J = 8.0Hz, 1H), 7.38–7.35(m, 1H), 6.63(d, J = 7.2Hz, 1H), 3.83–3.75(m, 1H), 1.11(d, J = 6.8Hz, 6H)
5r	270 (90) 271 (20)	(400M Hz): 8.76(d, J = 4.4Hz, 1H), 8.43–8.39(m, 2H), 8.03–8.01(m, 1H), 7.46–7.42(m, 2H)
5s	287 (100)	(400M Hz): 8.40–8.39(t, J = 2.2Hz, 2H), 8.43–8.39(d, J = 8.0Hz, 1H), 7.46–7.42(m, 2H)
5t	314 (100)	(400M Hz): 12.24(s, 1H, NH), 8.38(s, 2H), 8.23–8.19(m, 1H), 8.03–7.99(t, J = 7.6Hz, 1H), 7.769(s, 1H), 7.45–7.40(m, 2H)

240–242°C). ^{1}H NMR [DMSO, 300MHz] δ/ppm: 8.06 (m, 1H), 7.61 (m, 1H), 7.25 (m, 1H).

To dry THF (50 mL), NaH (2.30 g, 0.10 mol, 6.0 eq) was added under an ice-water bath and stirred for 30 min. Then thiazolo[5,4-b]pyridin-2-amine (2.52 g, 16.7 mmol, 1.0 eq) in 50 mL dry THF was added dropwise to the above mixture. After stirring for 1.5 h, diphenyl carbonate (4.2 g, 20.0 mmol, 1.2 eq) was added and stirred overnight. The solvent was removed under reduced pressure, and the residue was diluted with ethyl acetate (100 mL), washed with brine (50 mL × 3), and dried over Na_2SO_4. The solvent was evaporated, and the residue was separated by flash silica gel column chromatograph to give white solid 2.4 g, yield 54%, ^{1}H NMR [DMSO, 300MHz] δ/ppm: 12.81 (brs, 1H, NH), 8.44–8.47 (m, 1H), 8.10–8.13 (m, 1H), 7.45–7.51 (m, 3H), 7.30–7.35 (m, 3H).

Preparation of Title Compounds 5

A mixture of phenyl thiazolo[5,4-b]pyridin-2-ylcarbamate **4** (1.0 eq) and aliphatic or aromatic amine (1∼1.5 eq) in toluene (40 mL) was refluxed for 20 h. When the solution was cooled, the precipitate from the reactant was filtered and washed with ethanol to yield one part of the desired product. The filtrate was concentrated and recrystallized from the appropriate solvents or purified by flash silica gel column chromatography (hexane and ethyl acetate as eluent) to yield another part of product. All physical constants and spectral data are outlined in Tables 1 and 2.

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