Ultrasonic Irradiated Synthesis of *N*-(5-aryl-2-furoyl)thiourea Derivatives Containing Substituted Pyrimidine Ring under Phase Transfer Catalysis

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A series of *N*-(5-aryl-2-furoyl)thiourea derivatives containing substituted pyrimidine ring were synthesized in good yield using PEG-400 as solid-liquid phase transfer catalyst under ultrasonic irradiation. The structures of all newly synthesized compounds were elucidated and confirmed by IR, ^{1}H NMR and elemental analysis. Our method has the advantage of shorter reaction time and higher reaction yield compared to the conventional heating method. Preliminary biological tests show that some of the target compounds have better inhibitory activities against roots and stalks of monocotyledon and dicotyledon plants.

Keywords: 5-Aryl-2-furoyl thiourea; 2-Amino pyrimidine; Ultrasonic irradiation; Phase transfer catalysis; Synthesis; Bioactivity.

INTRODUCTION

Various types of biological activities including pesticidal, herbicidal, fungicidal, and insecticidal activity and the promoting effect on plant growth have been established for acylthiourea derivatives[1,2,3] and which are also important intermediates in organic synthesis. In recent years, the phase transfer catalysis reaction has been widely recognized as an efficient synthetic tool and has become one of the most attractive techniques in organic synthesis.[4,5] In addition, we know that the use of ultrasonic irradiation as a method of agitating a heterogeneous reaction system is gaining recognition;[6,7] ultrasonic waves have been utilized in organic synthesis for their lower reaction temperature and simple operation as compared with the conventional heating method,[8-11] and the use of ultrasonic irradiation in the presence of PTC for organic synthesis is well documented.[12-15] Moreover, 5-aryl-2-furoic acid derivatives have been reported as better fungicides and regulators for plant growth.[16,17] In view of this, we report herein the synthesis and biological activity of 5-aryl-2-furoyl thiourea containing substituted pyrimidine ring using PEG-400 as solid-liquid phase transfer catalyst under ultrasonic irradiation. This is a facile synthesis of acylthiourea derivatives accelerated by ultrasonic irradiation. The structures of all newly synthesized compounds were elucidated and confirmed by IR, ^{1}H NMR and elemental analysis. Preliminary biological tests show that some of the target compounds have better inhibitory activities against roots and stalks of monocotyledon and dicotyledon plants.

The title compounds were synthesized by the method in Scheme I.

RESULTS AND DISCUSSION

In connection with our interest in the synthesis and biological evaluation of acylthiourea derivatives,[18-21] we now report herein a facile and efficient method for the synthesis of 5-aryl-2-furoyl thiourea derivatives under ultrasonic irradiation. In the presence of acetonitrile, 5-aryl-2-furoyl chloride directly reacted with potassium thiocynate using PEG-400 as solid-liquid phase transfer catalyst under ultrasonic irradiation to give the intermediate acyl isothiocyanate, then the intermediate undergoes a fast reaction with an added amino pyrimidine to give the corresponding 5-aryl-2-furoyl thiourea derivatives containing substituted pyrimidine ring in good to excellent yield. In our experiment, the ultrasonic and phase transfer catalysis techniques represented a better procedure in terms of good yield, milder reaction conditions, easier workup, and it was found that the ultrasonic irradiation was

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Scheme I

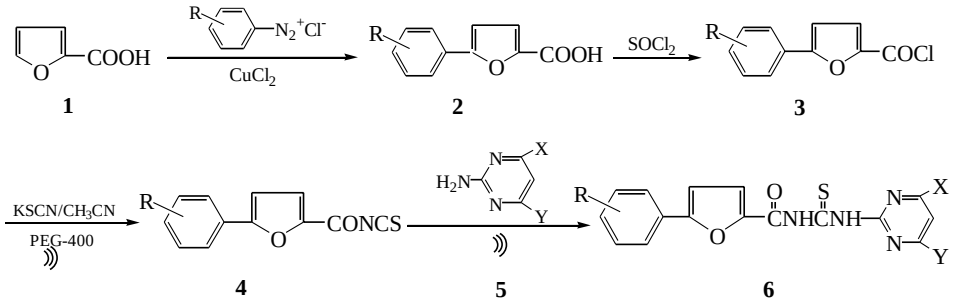

Table 1. The substituents of target compounds **6a-6j***

Compd.	**6a, 6f**	**6b, 6g**	**6c, 6h**	**6d, 6i**	**6e, 6j**
X	OCH_3	CH_3	CH_3	CH_3	OH
Y	OCH_3	CH_3	OCH_3	OC_2H_5	CH_3

* **6a-6e**, R = 4-NO_2; **6f-6j**, R = 2-Cl.

very simple and convenient for the synthesis of acylthiourea derivatives using ultrasonic cleaner with a frequency of 35 KHz.

With our present knowledge, the reactions of acyl isothiocyanates with nucleophiles are complex, since addition to the –N=C=S system and nucleophilic substitution at the carbonyl-carbon atom may compete with one another.[22] Acyl isothiocyanates have been prepared under liquid-liquid phase transfer catalysis using tetrabutylammonium bromide as the catalyst, which after isolation reacted with aniline to give the corresponding thiourea derivatives.[23] However, in the presence of water, hydrolysis of the acyl chloride may occur, and the yield of the acyl isothiocyanate is decreased. Harrison has also reported that polymer-supported thiocyanate treated with benzoyl chloride in benzene yielded benzoyl isothiocyanate, but the preparation of the polymer-supported reagent required long reaction times and vacuum conditions.[24] In search of improving methods to prepare acylthiourea by reacting acyl isothiocyanates with nucleophiles, we have found the ultrasonic vibration of a mixture of acyl chloride, potassium thiocyanate and 3% PEG-400 in acetonitrile can obtain acyl isothiocyanates in good yield. In this paper, we have conducted our reaction using ultrasonic irradiation in the presence of PTC; this modified method shortened the reaction time from 5-6 h to 1-1.5 h and improved yield compared with the conventional method.

All the structures of the newly synthesized compounds **6** were assigned on the basis of their elemental analyses and spectroscopic data, IR and ^{1}H NMR. The IR (KBr) spectrum displayed absorptions at about 3225 cm^{-1}, 1650 cm^{-1} and 1200 cm^{-1}, which are assigned to N-H, C=O and C=S functions, respectively. The medium-strong $\nu_{C=O}$ band in the IR spectra of all the compounds appears at about 1650 cm^{-1}, apparently decreasing in wavenumber compared with the ordinary carbonyl absorption (1710 cm^{-1}). The ^{1}H NMR (DMSO-d_6) spectrum revealed signals at about δ 12.90 and 12.20 that were attributed to the protons of N-H, in addition to, the singlet and multiplet signals at about δ 6.50 and δ 7.20-8.50 were assigned to pyrimidine-CH and aromatic protons, respectively. Based on the foregoing spectral data, the target compounds were assigned the structure **6**. Some compounds are very soluble in chloroform and dichloromethane; the others can be dissolved in DMF, DMSO and other nonprotic solvents.

All physical data for the target compounds **6** are given in Table 2, and the ^{1}H NMR and IR data of the target compounds **6** can be obtained in Table 3.

Biological activity

The biological activities of compounds **6a-6j** have been determined by the flat-utensil method according to the standard bioactivity test procedures of the Shanghai Branch of the National Pesticide R&D South Central in China. Compounds **6e**, **6j**, etc. showed inhibitory activities against roots and stalks of dicotyledon and monocotyledon plants used. The inhibition percentage of some compounds is shown in Table 4. The results revealed that compound **6e** has high inhibitory activities against roots and stalks of dicotyledon plants (such as *Chenopodium serotinum L.*) and active against roots and stalks of monocotyledon plants (such as *Digitaria sanguinalis (L.) Scop*) in higher concentrations (1.0×10^{-4}), and the inhibitory rate to the root and stalk attain 100% and 90%, respectively; compound **6j** has good inhibitory activi-

Table 2. Physical constants of compounds **6a-6j**

Compd.	Molecular formula Formula weight	Appearance	M.P. (°C)	Yield (%)	Analytical data. Calcd. (%) (Found)		
					C	H	N
6a	$C_{18}H_{15}N_5O_6S$ 429	light yellow powder	186-187	78	50.35 (50.27)	3.50 (3.38)	16.32 (16.41)
6b	$C_{18}H_{15}N_5O_4S$ 397	white powder	196-198	80	54.41 (54.56)	3.78 (3.65)	17.63 (17.52)
6c	$C_{18}H_{15}N_5O_5S$ 413	yellow powder	202-204	82	52.30 (52.43)	3.63 (3.54)	16.95 (17.02)
6d	$C_{19}H_{17}N_5O_5S$ 443	light yellow powder	208-209	74	51.47 (51.35)	3.84 (3.92)	15.80 (15.68)
6e	$C_{17}H_{13}N_5O_5S$ 399	light yellow powder	225-227	86	51.13 (51.04)	3.26 (3.39)	17.54 (17.42)
6f	$C_{18}H_{15}ClN_4O_4S$ 418.5	white powder	188-189	88	51.61 (51.70)	3.58 (3.47)	13.38 (13.25)
6g	$C_{18}H_{15}ClN_4O_2S$ 386.5	light yellow powder	193-195	84	55.89 (55.96)	3.88 (3.91)	14.49 (14.35)
6h	$C_{18}H_{15}ClN_4O_3S$ 402.5	light yellow powder	209-210	85	53.66 (53.74)	3.73 (3.64)	13.91 (14.02)
6i	$C_{19}H_{17}ClN_4O_3S$ 432.5	white powder	190-191	80	52.72 (52.85)	3.93 (3.87)	12.95 (13.02)
6j	$C_{17}H_{13}ClN_4O_3S$ 388.5	white powder	213-215	77	52.51 (52.60)	3.35 (3.28)	14.41 (14.49)

Table 3. IR and ^{1}H NMR data of compounds **6a-6j***

Compd.	IR (ν_{max}/cm^{-1}, KBr)			^{1}H NMR (δ, ppm)					
	N-H	C=O	C=S	Ar-H	Py-H	N-H	N′-H	OCH_3/CH_2	CH_3
6a	3190	1615	1260	7.54-8.38 (m, 6H)	6.08 (s, 1H)	12.18 (s, 1H)	12.85 (s, 1H)	3.83 (s, 6H)	----
6b	3205	1650	1252	7.05-8.40 (m, 6H)	6.80 (s, 1H)	12.62 (s, 1H)	12.87 (s, 1H)	----	2.40 (s, 6H)
6c	3217	1645	1215	7.10-8.23 (m, 6H)	6.44 (s, 1H)	12.42 (s, 1H)	12.78 (s, 1H)	3.80 (s, 3H)	2.25 (s, 3H)
6d	3215	1630	1230	7.14-8.28 (m, 6H)	6.38 (s, 1H)	12.35 (s, 1H)	12.83 (s, 1H)	4.21 (q, 2H)	1.18; 2.32 (t, 3H; s, 3H)
6e	3245	1660	1226	7.32-8.36 (m, 6H)	6.28 (s, 1H)	12.25 (s, 1H)	12.74 (s, 1H)	----	2.36 (s, 3H)
6f	3195	1648	1235	7.24-7.86 (m, 6H)	6.12 (s, 1H)	12.18 (s, 1H)	12.52 (s, 1H)	3.86 (s, 6H)	----
6g	3210	1640	1218	7.18-7.81 (m, 6H)	6.75 (s, 1H)	12.15 (s, 1H)	12.64 (s, 1H)	2.35 (s, 6H)	----
6h	3213	1632	1212	7.15-7.84 (m, 6H)	6.43 (s, 1H)	12.36 (s, 1H)	12.75 (s, 1H)	3.88 (s, 3H)	2.31 (s, 3H)
6i	3185	1652	1235	7.23-7.94 (m, 6H)	6.36 (s, 1H)	12.21 (s, 1H)	12.84 (s, 1H)	4.12 (q, 2H)	1.15; 2.36 (t, 3H; s, 3H)
6j	3200	1647	1245	7.10-8.12 (m, 6H)	6.34 (s, 1H)	12.30 (s, 1H)	12.81 (s, 1H)	----	2.42 (s, 3H)

*Abbreviations: s = singlet, t = triplet, q = quarterlet, m = multiplet, Py = pyrimidine.

Table 4. The inhibition percentage of some active compounds to kinds of plants

Compd.	Conc. (ppm)	Inhibition	*Echinochloa crusgallis L.*	*Sorghum bicolot*	*Digitaria sanguinalis (L.) scop*	*Chenopodium serotinum L.*	*Amaranthus retroflexus L.*
6e	10	The stalk	0	30	70	70	80
		The root	70	50	90	60	85
	50	The stalk	0	40	80	80	85
		The root	80	90	90	80	90
	100	The stalk	10	40	90	100	90
		The root	90	90	90	100	90
6j	10	The stalk	0	0	0	0	0
		The root	0	20	0	0	0
	50	The stalk	0	10	60	20	20
		The root	20	20	70	20	20
	100	The stalk	30	10	70	100	20
		The root	80	10	80	100	20

ties against roots and stalks of dicotyledon plants (such as *Chenopodium serotinum L.*) in higher concentrations (1.0×10^{-4}), and the inhibitory percentage to the root and stalk attain 100%.

CONCLUSIONS

In this paper, we have conducted our reaction using PEG-400 as solid-liquid phase transfer catalyst under ultrasonic irradiation; PEG-400 as a phase transfer catalyst is indispensable for these reactions. It can easily react with KSCN to form complex [PEG-400-K^+]SCN^-, which makes it possible for SCN^- to readily react with 5-aryl-2-furoyl chloride and leads to the formation of intermediate **4**. In summary, this is a facile and convenient method for the synthesis of acyl thiourea derivatives containing substituted pyrimidine ring, with the advantages of simple operation, short reaction times and good yields over the typical method, which can make this procedure a useful and attractive alternative to the currently available methods. In addition our ultrasonic irradiation method distinctly improves the efficiency of the synthetic process and shortens the reaction time. The catalyst PEG-400 is inexpensive, relatively nontoxic, highly stable and easily available.

EXPERIMENTAL SECTION

All starting materials are commercial products of chemical or analytical grade purity. Sulfuric chloride was distilled before use and potassium thiocyanate was baked before use. 2-Amino-4,6-disubstitute-pyrimidine **5** was prepared by the literature method.[25]

The melting points were determined on an XT4A micro digital melting point apparatus and are uncorrected. The isolated compounds **6** were characterized by elemental microanalyses. The C, H and N analyses were repeated twice. The result of elemental analyses are listed in Table 2. IR spectra were obtained on a Nicolet 5DX FT-IR spectrophotometer in the region 4000-400 cm^{-1} KBr discs. ^1H NMR spectra were recorded on a Varian-300-54 spectrometer with d_6-DMSO as the solvent. Chemical shift values are reported in ppm (δ) relative to TMS as internal standard. Thin layer chromatography (TLC) analyses were carried out on 5 × 20 cm plates coated with silica gel GF_{254} type 60 (50-250 mesh) using a ethyl acetate-petroleum ether mixture (1:2) as solvent. Ultrasonic irradiation was performed within a CQ-250S ultrasonic cleaner (35 ± 5% KHz, 250 W, made in Shanghai J&L Ultrasonic Ltd., Shanghai, P. R. China).

Synthesis of 5-aryl-2-furoic acid (2)

To an ice cold solution of substituted phenylamine (0.05 mol), water (10 mL) and concentrated hydrochloric acid (14 mL), a solution containing 3.45 g (0.05 mol) sodium nitrite in 10 mL water was cooled to 0 °C and slowly added dropwise over a 20 min period with stirring, and then the reaction mixture was stirred at 0-5 °C for about 30 min. Thereafter, the reaction mixture was filtered to yield a clear solution. Then furoic acid (0.03 mol), acetone (25 mL), copper

chloride (2.10 g), water (10 mL) and the clear solution were placed in a round-bottomed flask containing a magnetic stirrer and stirred at room temperature for several hours; the precipitate solid was filtered off, and then dissolved in the solution of sodium hydrogen carbonate; the mixture was filtered off, and the filtrate was acidified by hydrochloric acid to yield precipitate, the resulting precipitate was collected and recrystallized from DMF-C_2H_5OH-H_2O to obtain pure 5-aryl-2-furoic acid **2**. 5-(4-nitro-phenyl)-2-furoic acid, m.p. 252-253 °C, Yield, 45%; 5-(2-chloro-phenyl)-2-furoic acid, m.p. 203-205 °C, Yield, 53%.

Synthesis of 5-aryl-2-furoyl chlorides (3)

5-Aryl-2-furoic acid **2** (0.05 mol) and sulfuric chloride (15 mL) were placed in a dried round-bottomed flask containing a magnetic stirrer bar and stirred at 50 °C for 2 h. Then the excessive sulfuric chloride was removed under reduced pressure, and the residue left to cool to room temperature to obtain the precipitate. The resulting precipitate was collected by filtration and washed with petroleum ether, then recrystallized from EtOH-H_2O to yield 5-aryl-2-furoyl chlorides **3**. 5-(4-nitro-phenyl)-2-furoyl chloride, m.p. 141-143 °C, Yield, 82%; 5-(2-chloro-phenyl)-2-furoyl chloride, m.p. 69-70 °C, Yield, 86%.

General procedures for the synthesis of the target compounds 6a-6j were as follows

To a solution of potassium thiocyanate (3 mmol) in 10 mL of acetonitrile, an equimolar quantity of 5-aryl-2-furoyl chloride **3** and four drops of polyethylene glycol-400 (PEG-400) were added. The reaction mixture was immersed into the water bath of an ultrasonic cleaner at refluxed temperature for about 0.5 h and then the reaction mixture was filtered off to yield an orange-red solution **4**. Then an equimolar quantity of 4,6-disubstituted-2-amino pyrimidine **5** was added, then put under ultrasonic irradiation for about 15-20 min; the reaction was monitored by TLC. At the end of the reaction, the resulting precipitate was collected by filtration and recrystallized from DMF-EtOH-H_2O to yield compound **6**.

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REFERENCES

1. Sarkis, G. Y.; Faisal, E. D. *J. Heterocyclic Chem.* **1985**, *22*, 137.
2. Wegner, P.; Hans, R.; Frank, H.; Joppien, H. *Eur. Pat.* **1986**, 190611.
3. Upadlgaya, J. S.; Srivastava, P. K. *J. Indian Chem. Soc.* **1982**, *59(6)*, 767.
4. Starks, C. M.; Liotta, C. *Phase Transfer Catalysis*; Academic Press: New York, 1978.
5. Illi, V. O. *Tetrahedron Lett*, **1979**, *20*, 2431.
6. Azuma, T.; Yanagida, S.; Sakurai, H. *Synth. Commun.* **1982**, *12*, 137.
7. Luche, J. L.; Petrier, C. *J. Org. Chem*. **1983**, *48*, 3837.
8. Yasui, S.; Noguchi, A.; Yokoyama, Y. *Jpn. Kokai Tokkyo Koho Tp* 04 36750, 1992.
9. Li, J. T.; Li, L. J.; Li, T. S.; Wang, J. Z. *Indian J. Chem*. **1998**, *378*, 298.
10. Li, J. T.; Chem, G. F.; Wang, J. X.; Li, T. S. *Synth. Commun.* **1999**, *29*, 965.
11. Davidson, R. S.; Safdar, A.; Spencer, J. P.; Robinson, B. *Ultrasonics.* **1987**, *25*, 35.
12. Diez-Barra, E.; De la Hoz, A.; Diaz-Ortiz, A.; Prieto, P. *Synlett*. **1992**, 893.
13. Peng, Y.; Song, G. *Green Chemistry* **2002**, *4*, 349.
14. Li, X.; Wang, J.; Mason, R.; Bu, X. R.; Harrison, J. *Tetrahedron*. **2002**, *58*, 3747.
15. Bhatkhande, B. S.; Samant, S. D. *Ultrasonics Sonochemistry* **1998**, *5*, 7.
16. Wei, T. B.; Chen, J. C.; Wang, X. C.; Yang, S. Y. *Chem. Abstr.* **1993**, *128*, 191447P.
17. Dai, Y. J.; Li, Y. J.; Chen, J. C. *Chinese J. Org. Chem*. **1988**, *8*, 443.
18. Xue, S. J.; Zou, J. S.; Yang, H. J. *Chin. Chem. Lett.* **2000**, *11(1)*, 19.
19. Wei, T. B.; Chen, J. C.; Wang, X. C.; Yang, S. Y. *J. Chem. Chin. Univ.* **1992**, *13*, 1217.
20. Xue, S. J.; Duan, L. P.; Ke, S. Y.; Jia, L. B. *Chem. J. on. Internet*. **2003**, *8*, 67.
21. Xue, S. J.; Ke, S. Y.; Duan, L. P. *Chin. J. Org. Chem*. **2004**, *24(2)*, 227.

22. Hoggarth, E. *J. Chem. Soc*. **1949**, 1160.
23. Reeves, W. P.; Simmons, A. Jr.; Rudis, J. A.; Bothwell, C. Tim. *Synth. Commun.* **1981**, *11*, 781.
24. Harrison, C. R.; Hodge, P. *Synthesis.* **1980**, 299.
25. Xue, S. J.; Tan, D. Y. *J. Central China Norm. Univ. (Nat. Sci).* **1998**, *28(1)*, 77.