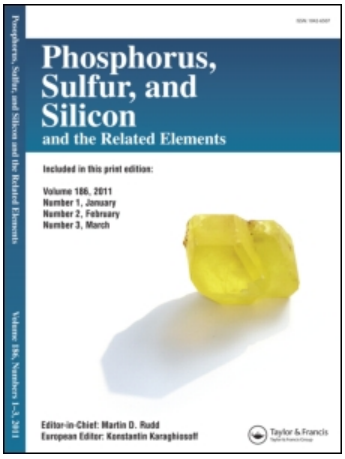

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Biological Activities Studies and Phase Transfer Catalysts Promoting the One-Pot Synthesis of *N*-Aryl-*N'*-(4-Ethyloxy Benzoyl)-Thiourea Derivatives

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A series of N-aryl-N′-(4-ethyloxybenzoyl)-thiourea 3a–h was synthesized under phase transfer catalysis and r.t. conditions. The chemical structure of all compounds were established by IR, ^{1}H NMR, and ^{13}C NMR studies, and all of the compounds were investigated for plant-growth regulating activity. Excitingly, they remarkably enhance root elongation.

Keywords Biological activities; N-aryl-N′-(4-ethyloxybenzoyl)-thiourea; one-pot synthesis; phase transfer catalysis

INTRODUCTION

During the last few decades, thiourea and its derivatives, especially acyl-thiourea compounds, have been sisterly studied for their potential use in agriculture, extraction, separation, medicine, and analytical chemistry.[1] For example, owing to their strong coordination ability, many are extensively utilized as collectors for copper and precious metals in mining.[2–3] Moreover, considerable attention has been devoted to the synthesis of N-acyl-thiourea derivatives possessing such comprehensive bioactivities as herbicides, inaecticides, and plant-growth

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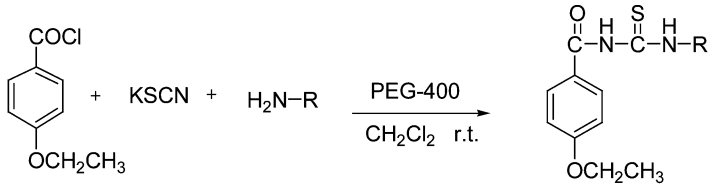
regulators.[4] In view of these facts and as a part of our work of the synthesis plant-growth regulators,[5–9] herein we report a one-pot facile, efficient, and high-yield method for the synthesis of N-aryl-N′-(4-ethyloxybenzoyl)-thiourea under the condition of solid-liquid phase-transfer catalysis using polyethylene glycol-400 (PEG-400) as the catalyst Scheme 1, and their biological activities were investigated.



1 **2** **3**

3	R	3	R
3a	3-$NO_2C_6H_4$	**3e**	2-HOC_6H_4
3b	2-$MeOC_6H_4$	**3f**	3-HOC_6H_4
3c	3-MeC_6H_4	**3g**	4-HOC_6H_4
3d	-$(CH_2)_2OH$	**3h**	4-$CH_3COC_6H_4$

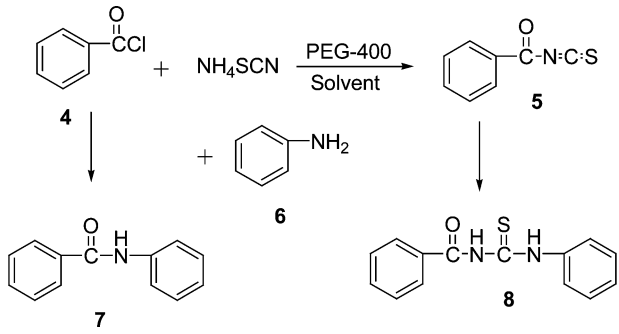
SCHEME 1

N-acylthioureas are classically prepared by acylating the reaction of *N*-arylthioueas with acyl chloride, but a long reaction time and high temperature are required.[10] Jirman et al.[11] have reported that substituted benzoyl chloride reacts with *N*-acetyl-*N*′-arylthioureas to give the corresponding acylthiourea derivatives; however, a long reaction time a high temperature, and the preparation of *N*-acetyl-*N*′-arylthiourea are also required. Reeves et al.[12] also reported that acyl chlorid reacted with KSCN and aniline under liquid-liquid phase-transfer catalysis using Bu_4NBr as the catalyst to give the corresponding *N*-aryl-*N*′-phenylthioureas. However, in the presence of water, the hydrolysis of acyl chloride occured, and the yield of the acyle isothiocyanate also decreased. Other methods[13] for the preparation of *N*-acylthioureas have been reported, but none of them was completely satisfactory for our purpose. Consequently, we have conducted our reaction under solid-liquid phase-transfer catalysis conditions using PEG-400 as the catalyst. It was found that *N*-aryl-*N*′-(4-ethyloxybenzoyl)-thioureas were prepared in a high yield.

Phase-transfer catalysis, for the advantages of simple experimental operations, mild reaction conditions, and inexpensive and environmentally benign reagents, has established its significance in organic synthesis as one of the most useful methods for the acceleration of heterogeneous reactions.[14–16] In this reaction, 4-Ethoxybenzoyl chloride

(1) is treated with potassium thiocyanate under the condition of solid-liquid phase-transfer catalysis using 3% PEG-400 as the catalyst. With the enhancement of the ion exchange between the inorganic salt and the organic solution, phase-transfer catalyst efficiently catalyzed this solid-liquid diphase reaction.

In searching for the best conditions, the condensation of benzoyl chloride (4) with ammonium thiocyanate in various solvents in the presence of PEG-400 was studied at r.t. in detail. Instead of the isolation of the formed benzoyl isothiocyanate (5), the reaction mixture was quenched by the addition of aniline (6) after 1 h. The added (6) gave rise to the formation of N-phenyl benzamide(7) and *N*-benzoyl- *N′*-phenylthiourea (8) from the starting benzoyl chloride 4 and the resulting benzoyl isothiocyanate (5), respectively (Scheme 2).



SCHEME 2

The results of Table I showed that CH_3CN, CH_2Cl_2, dioxane are good solvents for the preparation of 8. THF also led to a good yield, and other solvents were not effective. With the previously discussed results in hand, we have prepared eight *N*-aryl-*N′*-(4-ethyloxybenzoyl)-thioureas by the reaction of aromatic amines with 4-ethyloxybenzoyl chloride and ammonium thiocyanate under the condition of solid-liquid phase-transfer catalysis in the presence of catalystic amounts of PEG-400; dichloromethane was used as the solvent.

In conclusion, this one-pot procedure is a facile and convenient method for the synthesis of acyl-thiourea derivatives under solid-liquid phase-transfer catalysis conditions, with the advantages of mild conditions, a simple operation, short reaction times, and a high yield. The catalyst PEG-400 is inexpensive, relatively nontoxic, highly stable, and easily available.

TABLE I The Effect of Solvent on the Yield of 7 and 8

		100 ppm	
Run	Solvent	7[a]	8[b]
1	CH_3CN	—	98
2	CH_2Cl_2	—	98
3	THF	26	71
4		—	95
5		38	51
6	CCl_4	75	20
7		85	—
8	n-C_6H_{14}	88	—

[a]The m.p. of 7 is 162–163°C (Lit.[17] 163–164°C).
[b]The m.p. of 8 is 146–148°C (Lit.[12] 148°C).

BIOLOGICAL ACTIVITY

All of the synthesized compounds were investigated for plant-growth regulation activity. Here, we adopted the method of plate culture. The compounds were collected to the solution in concentrations of 100 ppm, 50 ppm, and 10 ppm, and coleseed were cultured in a 10-cm Petri dish with 10 mL of different solution and a circular filter paper. After growing at r.t. for 4 days, the root length was gained, and the percentage plant-growth activity was calculated according to the following equation:

$$\text{Percentage plant-growth activity} = (\text{N-N1})/\text{N1} \times 100\% \quad (1)$$

In Eq. 1, N is the root length cultured in compound solution and N1 is the root length cultured in the distilled water under the same condition. The data is shown in Table II.

From the results summarized in Table II, compared with heteroauxing, most of the compounds exhibited root elongation activity, while they showed weak root elongation or inhibition activities at the high concentration of 100 ppm and remarkable enhancing root elongation activities at the low concentration of 50 ppm and 10 ppm. It is evident from the results that this series of compounds show good plant-growth regulation activity.

EXPERIMENTAL

Melting points were measured on a X-4 digital melting point apparatus and were uncorrected. Infrared spectra were performed on a Digilab

TABLE II Plant-Growth Regulating Activity Data

	% Plant Growth Activity [a]		
Compounds	100 ppm	50 ppm	10 ppm
3a	13.6	15.3	32.7
3b	6.0	17.0	44.5
3c	−3.6	23.1	36.9
3d	6.2	23.4	36.0
3e	−4.76	−3.5	15.8
3f	7.7	30.1	33.3
3g	−6.04	11.8	16.5
3h	−3.7	16.27	22.3
Heteroauxing	−81.7	−63.1	−30.9

[a]The solution was prepared in the proportion of H_2O:DMF = 99.5:0.5, and 0.1 g Tween-80 was added to promote the compound to be dissolved.

FTS-3000 FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury plus-400 MHz spectrometer.

General Procedure for the Preparation of Compounds 3

Powdered potassium thiocyanate (7.5 mmol) 2-ethoxybenzoyl chloride (5 mmol), PEG-400 (3% with respect to ammonium thiocyanate), and 20 mL of dichloro-methane were placed in a dried round-bottomed flask containing a magnetic stirrer bar and were stirred at r.t. for 1 h then aromatic amine (5 mmol) was added, and the mixture was stirred for an additional 0.5 h. The corresponding thiosemicarbazide precipitated immediately. The product was filtered, washed with water to remove inorganic salts, dried, and recrystallized from DMF-EtOH-H_2O to give products (3).

Compound 3a

85% Yield; m.p. 179–181°C; ^{1}H NMR (DMSO-d6, 400MHz) δ: 12.82 (s, 1H, NH), 11.57(s, H, NH), 7.04 ~8.78(m, 8H, ArH), 4.13(dd 2H, CH_2), 1.37(t, 3H, CH_3); ^{13}C NMR (DMSO-d6, 400MHz) δ: 14.53, 63.69, 113.12, 114.22 (2C), 118.93, 120.81, 123.31, 130.01, 131.02, 131.14, 139.12, 147.51, 162.70, 167.61, 178.80; IR (KBr,cm-1)υ: 3301, 3104 (NH), 2984, 2941 (CH), 1560, 1535, 1500 (Ar), 1668 (C═O), 1157 (C═S); 1259(-O-); Anal. calcd. for $C_{16}H_{15}N_3SO_4$: C, 55.64; H, 4.38; N, 12.17; Found: C, 55.61: H, 4.32; N, 12.11.

Compound 3b

80% yield; m.p. 137–141°C; ^{1}H NMR(DMSO-d6, 400MHz) δ: 12.87 (s, 1H, NH), 11.58(s, H, NH), 7.04 ~8.83(m, 8H, ArH), 4.13(dd 2H, CH_2),

1.38(t, 3H, CH_3), 1.39 (s, 3H, CH_3); ^{13}C NMR (DMSO-d6, 400MHz) δ: 14.51, 56.02, 63.64, 111.27, 114.13(2C), 119.77, 123.32, 123.52, 126.61, 126.95, 131.07(2C), 150.68, 162.58, 167.62, 178.14; IR (KBr, cm-1) υ: 3222, 3066 (NH), 2984, 2943 (CH), 1602, 1536, 1501 (Ar), 1668 (C=O), 1148 (C=S); 1256(-O-); Anal. calcd. for $C_{17}H_{18}N_2SO_3$: C, 61.80; H, 5.49; N, 8.48; Found C, 62.01; H, 5.42; N: 8.71.

Compound 3c

76% yield; m.p. 128–130°C; ^1H NMR (DMSO-d6, 400MHz) δ: 12.68 (s, 1H, NH), 11.37 (s, 1H, NH), 7.02 ~8.02 (m, 8H, ArH), 3.98 (t, 2H, CH_2), 4.15 (dd, 2H, CH_2), 1.36 (t, 3H, CH_3), 2.332 (s, 3H, CH_3);^{13}C NMR (DMSO-d6, 400MHz) δ: 14.52, 20.97, 63.64, 114.15(2C), 121.16, 123.56, 124.49, 126.93, 128.51, 130.52(2C), 137.94, 138.13, 162.59, 167.64, 179.08; IR (KBr, cm-1) υ. 3308, 3009 (NH), 2977, 2929 (CH) 1669 (C=O), 1602, 1566, 1535 (Ar), 1186 (C=S), 1254(-O-); Anal. calcd. for $C_{17}H_{18}N_2SO_2$: C, 64.94; H, 5.77; N, 8.91; Found: C, 64.89; H, 5.71; N, 8.95.

Compound 3d

88% m.p. 163–165°C; ^1H NMR (DMSO-d6, 400MHz) δ: 11.81 (s, 1H, NH), 11.14 (s, 1H, NH), 9.92 (s, 1H, OH), 7.00 ~7.94 (m, 4H, ArH), 4.12 (t, 2H, CH_2), 1.36 (t, 3H, CH_3); ^{13}C NMR (DMSO-d6, 400MHz) δ: 14.53, 47.51, 58.38, 63.62, 114.13(2C), 123.84, 130.83(2C), 162.42, 167.39, 180.43; IR (KBr, cm-1) υ: 3273, 3073 (NH), 3224 (OH), 2942, 2889 (CH) 1668 (C=O), 1609, 1575, 1527 (Ar), 1186 (C=S), 1255(-O-); Anal. calcd. for $C_{12}H_{16}N_2SO_3$: C, 53.71; H, 6.01; N, 10.44; Found: C, 53.98; H, 5.81; N, 10.28.

Compound 3e

82% Yield; m.p. 180–182°C; ^1H NMR (DMSO-d6, 400MHz) δ: 13.04 (s, 1H, NH), 11.29 (s, 1H, NH), 10.25 (s, 1H, OH), 6.82 ~8.56 (m, 8H, ArH), 4.21 (dd, 2H, CH_2), 1.36 (t, 3H, CH_3); ^{13}C NMR (DMSO-d6, 400MHz) δ: 14.51, 63.63, 114.15(2C), 115.12, 118.28, 123.23, 123.69, 126.03, 126.37, 131.02(2C), 148.94, 162.52, 167.45, 177.64; IR (KBr, cm-1) υ. 3310, 3043 (NH), 3219 (OH), 2982, 2932 (CH), 1655 (C=O), 1603, 1548, 1501 (Ar), 1184 (C=S), 1254(-O-); Anal. calcd. for $C_{16}H_{16}N_2SO_3$: C, 60.74; H, 5.10; N, 8.85; Found C, 60.74; H, 5.28; N, 8.99.

Compound 3f

81% Yield; m.p. 195–197°C; ^1H NMR (DMSO-d6, 400MHz) δ: 12.71 (s, 1H, NH), 11.33 (s, 1H, NH), 9.67 (s, 1H, OH), 6.67 ~8.01 (m, 8H, ArH), 4.14 (dd, 2H, CH_2), 1.36 (t, 3H, CH_3); ^{13}C NMR (DMSO-d6, 400MHz)

δ: 14.53, 63.66, 110.88, 113.33, 114.41(2C), 114.56, 124.05, 129.50, 131.04(2C), 138.31, 157.54, 162.60, 167.81, 179.20; IR (KBr, cm-1) υ. 3383, 3053 (NH), 3223 (OH), 2980, 2935 (CH), 1668 (C=O), 1604, 1557, 1502 (Ar), 1190 (C=S), 1251(-O-); Anal. calcd. for $C_{16}H_{16}N_2SO_3$: C, 60.74; H, 5.10; N, 8.85; Found C, 60.51; H, 5.31; N, 8.96.

Compound 3g

75% Yield; m.p. 179–181°C; ^{1}H NMR (DMSO-d6, 400MHz) δ: 12.56 (s, 1H, NH), 11.28 (s, 1H, NH), 9.62 (s, 1H, OH), 6.80 ~8.01 (m, 8H, ArH), 4.12 (dd, 2H, CH_2), 1.35 (t, 3H, CH_3);^{13}C NMR (DMSO-d6, 400MHz) δ: 14.55, 63.66, 114.17(2C), 115.14(2C), 123.74, 125.94(2C), 129.45, 131.00(2C), 155.79, 162.55, 167.58, 179.16; IR (KBr, cm-1) υ: 3333, 3073 (NH), 3156 (OH), 2981, 2936 (CH), 1680 (C=O), 1603, 1542, 1512 (Ar), 1176 (C=S), 1254(-O-); Anal. calcd. for $C_{16}H_{16}N_2SO_3$: C, 60.74; H, 5.10; N, 8.85; Found: C, 60.71; H, 5.19; N, 8.72.

Compound 3h

83% Yield; m.p. 165–167°C; 1H NMR (DMSO-d6, 400MHz) δ: 12.98 (s, 1H, NH), 11.50 (s, 1H, NH), 7.04 ~8.02 (m, 8H, ArH), 4.13 (dd, 2H, CH_2), 2.59 (s, 3H, CH_3), 1.37 (t, 3H, CH_3); ^{13}C NMR (DMSO-d6, 400MHz) δ: 14.40, 26.66, 63.62, 114.13(2C), 123.29(2C), 123.47, 128.90(2C), 131.07(2C), 134.04, 142.17, 162.63, 167.52, 179.07, 196.76; IR (KBr, cm-1) υ: 3429, 3055 (NH), 2977, 2960 (CH), 1596 (C=O), 1596, 1539, 1500 (Ar), 1176 (C=S), 1256(-O-); Anal. calcd. for $C_{16}H_{16}N_2SO_3$: C: 63.14; H, 5.30; N, 8.18; Found: C, 63.23; H, 5.18; N, 8.01.

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