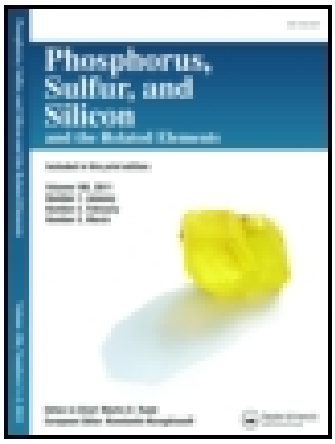

Phosphorus, Sulfur, and Silicon and the Related Elements

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PHASE TRANSFER CATALYZED SYNTHESIS OF THIOSEMICARBAZIDE AND bis-THIOSEMICARBAZIDE DERIVATIVES OF 2-ETHOXYBENZOIC ACID

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PHASE TRANSFER CATALYZED SYNTHESIS OF THIOSEMICARBAZIDE AND BIS-THIOSEMICARBAZIDE DERIVATIVES OF 2-ETHOXYBENZOIC ACID

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Reaction of aryloxyacetic acid hydrazide or arenedioxydiacetic acid hydrazide with 2-ethoxybenzoy chloride and ammonium thiocyanate under the condition of solid–liquid phase transfer catalysis using polyethylene glycol-400 (PEG-400) as the catalyst yielded the corresponding thiosemicarbazide or bisthiosemicarbazide derivatives of 2-ethoxybenzoic acid in good-to-excellent yield.

Keywords: Bis-thiosemicarbazide; phase transfer catalysis; thiosemicarbazide

INTRODUCTION

A series of 1,4-disubstituted thiosemicarbazide and their related heterocyclic compounds have been found to possess many important biological activities. Some thiosemicarbazides have been found to be useful as herbicides, insecticides and plant-growth regulators.[1] In view of these observations and in continuation of our earlier work on the synthesis of plant-growth regulators,[2–6] we now report a convenient and efficient method for the preparation of thiosemicarbazide and bisthiosemicarbazide derivatives of 2-ethoxybenzoic acid under the condition of solid–liquid phase transfer catalysis using polyethylene glycol-400 (PEG-400) as the catalyst.

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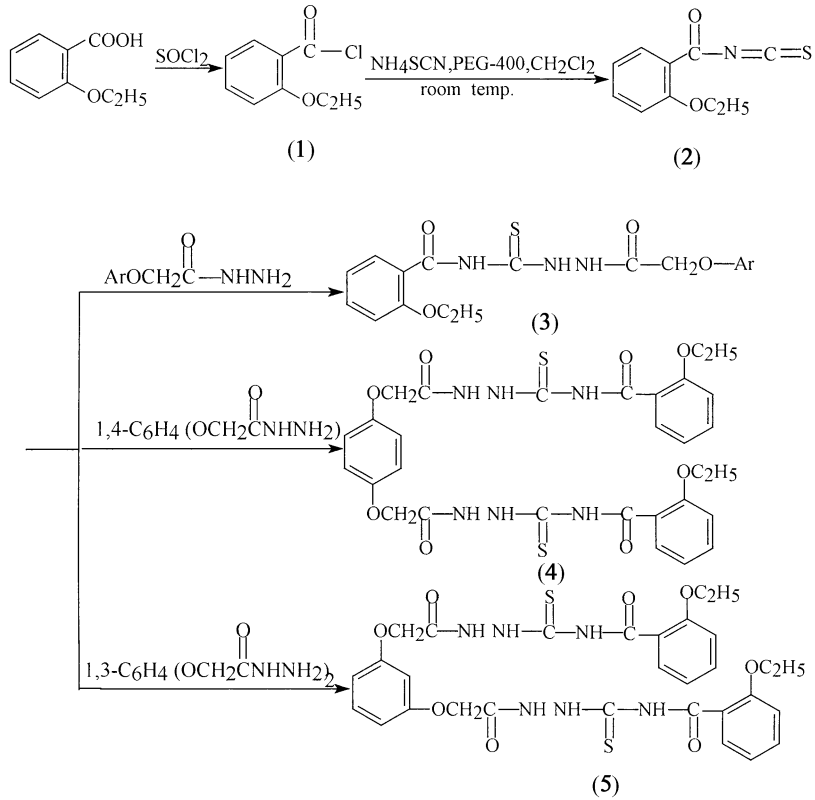
2-Ethoxybenzoyl chloride (**1**) is readily available by the reaction of 2-ethoxybenzoic acid with thionyl chloride. Its treatment with ammonium thiocyannte under the condition of solid–liquid phase transfer catalysis using 3% PEG-400 as the catalyst gave 2-ethoxybenzoyl isothiocyanate (**2**). This compound does not need to be isolated and reacts immediately with various aryloxyacetic acid hydrazide or arenedi-oxydiacetic acid hydrazide to afford the corresponding



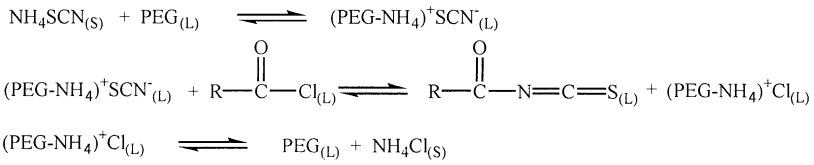
3	Ar	3	Ar
3a	2-Me Ph	**3e**	2-Cl Ph
3b	2-Me Ph	**3f**	4-NO_2 Ph
3c	2-Me Ph	**3g**	1-2Naphthyl
3d	4-Cl Ph	**3h**	2-Naphthyl

SCHEME 1

thiosemicarbazide and bis-thiosemicarbazide derivatives (**3**), (**4**), and (**5**) in good-to-excellent yields (Scheme 1).

Acyl isothiocyanates have been available under the condition of liquid–liquid phase transfer catalysis using tetrabutyl ammonium bromide as PTC (phase transfer catalyst); however, in the presence of water, hydrolysis of the acyl chloride may occur, and the yield of the acyl isothiocyanate may be decreased.[9] Harrison has also reported that polymer-supported thiocyanate reacting with benzoyl chloride in benzene yielded benzoyl isothiocyanate, but the preparation of the polymer-supported reagent required long reaction times and vacuum condition.[10] Therefore, the reaction was then operated under solid–liquid phase transfer catalysis condition using PEG-400 as PTC. It was found that 2-ethoxybenzoyl chloride was quantitatively converted to the corresponding acyl isocyanate (**2**). This intermediate reacts with aryloxyacetic acid hydrazides or arenedioxy diacetic acid hydrazides to give the title compounds (**3**), (**4**), and (**5**) in high yield.

According to our experiment resultes,[2–6] the production is a general method that may be applied to the preparation of most acylisothiocyanates by the reaction of different acyl chloride with ammonium thiocyanate. We tentatively propose the mechanism shown in Scheme 2.



S, Solid phase: L, Liquid phase.

SCHEME 2

In conclusion, this one-pot procedure is a facile and convenient method for the synthesis of 1,4-disubstituted thiosemicarbazide derivatives under solid–liquid phase transfer catalysis conditions, with the advantages of mild conditions, simple operation, short reaction times, and high yield. The catalyst PEG-400 is inexpensive, relatively nontoxic, highly stable, and easily available.

EXPERIMENTAL

Infrared (IR) spectra were recorded using KBr pellets on an Alpha Centauri Fourier Transform Infrared (FTIR) spectrophotometer and

^{1}H-NMR spectra on Brucke AC-80 instrument. DMSO-d_6 was used as solvent and TMS as internal standard. Elemental analyses were performed on a Perkin-Elmer-2400 CHN Element analyzer instrument. Melting points were observed in an open capillary tube and were uncorrected.

General Procedure for the Preparation of Compounds 3

Powdered ammonium thiocyanate (4.5 mmol) 2-ethoxybenzoyl chloride (3 mmol) 0.054 g PEG-400 (3% with respect to ammonium thiocyanate) and 15 ml of dichloro-methane were placed in a dried round-bottomed flask containing a magnetic stirret bar and stirred at room temperature for 1 h. Then aryloxyacetic acid hyddrazide (2.9 mmol) was added, and the mixture was stirred for 0.5 h. The corresponding thiosemicarbazide precipitates immediately. The product is filtered, wash with water to remove inorganic salts, dried, and recrystallized from DMF-EtOH-H_2O to give products (**3**).

Using 6 mmol 2-ethoxybenzoyl chloride, 9 mmol NH_4SCN, and 2.9 mmol 1.4-phenylenedioxydiacetic acid hydrazide or 1.3-phenylenedioxydiaceticacid hydrazide, compounds **4** and **5** were prepared similarly.

Compound 3a

85% Yield; m.p., 128–130°C; IR (KBr, cm^{-1}): 3450, 3287, 334, 3143 (N—H), 2980, 2866 (CH_2, CH_3), 1671, 1684 (C=O), 1163 (C=S), 1617, 1599, 1515, 1473 (C=C), 1251, 1030 (Ar—O—); ^{1}H-NMR (80MH_2, DMSO-d_6): 1.48 (t, 3H, CH_3), 2.23 (s, 3H, CH_3), 4,39 (q, 2H, CH_2), 4.67 ($ArOCH_2$), 6.64–7.98 (m, 8H, Ar—H), 11.01 (s, 1H, N—H), 11.36 (s, 1H, N—H), 12.35 (s, 1H, N—H); Anal. Calc. for $C_{19}H_{21}N_3O_4S$: C, 58.80, H, 5.46; N, 10.84. Found: C, 58.94; H, 5.37; N, 10.89.

Compound 3b

80% yield; m.p., 154–156°C; IR (KB_r, cm^{-1}): 3290, 3143 (N—H), 2980, 2856 (CH_3, CH_2); 1679, 1686 (C=O), 1159 (C=S), 1600, 1587, 1486 (C=C), 1257, 1013 (A_r—o—); ^{1}H-NMR (80MH_z, DMSO-d_6): 1.49 (t, 3H, CH_3), 2.28 (S, 3H, CH_3), 4.31 (q, 2H, CH_2), 4.69 (S, 2H, $ArOCH_2$), 6.75–7.98 (m, 8H, Ar—H), 11.02 (S, 1H, N—H), 11.38 (S, 1H, N—H), 12.27 (S, 1H, N—H); Anal. Calc. for $C_{19}H_{21}N_3O_4S$: C, 58.80; H, 5.46; N, 10.84. Found: C, 58.77; H, 5.49; N, 10.81.

Compound 3c

86% yield; m.p., 178–180°C; IR (KB_r, cm^{-1}): 3295, 3150 (N–H), 2989, 2890 (CH_3, CH_2); 1650, 1686 (C=O), 1163 (C=S), 1599, 1560, 1487

(C=C), 1033, 1249 (A_r–O–); ^{1}H-NMR (80MH$_2$, DMSO-d$_6$): 1.48 (t, 3H, CH_3), 2.24 (S, 3H, CH_3), 4.31 (q, 2H, CH_2), 4.74 (S, 2H, ArOCH_2), 6.77–7.99 (m, 8H, Ar–H), 10.96 (S, 1H, N–H), 11.38 (S, 1H, N–H), 12.41 (S, 1H, N–H); Anal. Calc. for $C_{19}H_{21}N_3O_4S$: C, 58.80; H, 5.46; N, 10.84. Found: C, 58.89; H, 5.40; N, 10.93.

Compound 3d

88% Yield; m.p., 158–160°C; IR (KBr, cm^{-1}): 3273, 3134, 3132 (N–H), 2904, 2853 (CH2, CH3), 1664, 1684 (C=O), 1163 (C=S), 1601, 1559, 1469 (C=C), 1248, 1038 (ArO–); ^{1}H-NMR (80MH2, DMSO-d6): 1.48 (t, 3H, CH3), 4.31 (q, 2H, CH2), 4.73 (S, 2H, ArOCH2), 6.97–7.97 (m, 8H, ArH), 11.06 (S, 1H, N–H), 11.36 (S, 1H, N–H), 12.24 (S, 1H, N–H); Anal Calc. for $C_{18}H_{18}ClN_3O_4S$: C, 53.00; H, 4.48; N, 10.30. Found: C, 53.21; H, 4.49; N, 10.28.

Compound 3e

93% Yield; m.p., 202–204°C; IR (KBr, cm^{-1}): 3297, 3148 (N–H), 2980, 2929, 2890, 2853 (CH_2CH_3), 1656, 1694 (C=O), 1157 (C=S), 1600, 1577, 1487 (C=C), 1263, 1036 (ArO–); ^{1}H-NMR (80MH2, DMSO-d$_6$): 1.48 (t, 2H, CH_3), 4.20–4.28 (q, 2H, CH_2), 4.86 (S, 2H, ArOCH_2), 7.20–7.97 (m, 8H, Ar–H), 11.08 (S, 1H, N–H), 11.35 (S, 1H, N–H) 12.43 (S, 1H, N–H); Anal Calc. for $C_{18}H_{18}ClN_3O_4S$: C, 53.00; H, 4.48; N, 10.30. Found: C, 53.26; H, 4.47; N, 10.21.

Compound 3f

80% Yield; m.p., 208–210°C; IR (KBr, cm^{-1}): 3325, 3301, 3162, 3123 (N–H), 2988, 2998, 2849 (CH_3, CH_2), 1654, 1697 (C=O), 1163 (C=S), 1611, 1594, 1484 (C=C), 1535, 1358 (NO2), 1036, 1251 (ArO–); ^{1}H-NMR (80MH2, DMSO-d$_6$): 1.48 (t, 3H, CH_3), 4.29 (q, 2H, CH_2), 4.91 (S, 2H, ArOCH_2), 7.02–8.26 (m8H, Ar–H), 11.20 (S, 1H, N–H), 11.35 (S, 1H, N–H), 12.24 (S, 1H, N–H); Anal Calc. for $C_{18}H_{18}N_4O_6S$: C, 51.67; H, 4.34; N, 13.39. Found: C, 51.82; H, 4.33; N, 13.47.

Compound 3g

74% Yield; m.p., 216–218°C; IR (KBr, cm^{-1}): 3317, 3291, 3160, 3137 (N–H), 2986, 2951, 2867 (CH2, CH_3), 1654, 1697 (C=O), 1159 (C=S), 1613, 1598, 1508, 1487 (C=C), 1033, 1250 (Ar–O–); ^{1}H-NMR (80MH2, DMSO-d$_6$): 1.49 (t, 3H, CH_3), 4.23 (q, 2H, CH_2), 4.85 (S, 2H, ArOCH_2) 6.96–8.37 (m, 11H, Ar–H) 11.12 (S, 1H, N–H), 11.36 (S, 1H, N–H) 12.40 (S, 1H, N–H); Anal Calc. for $C_{22}H_{21}N_3O_4S$: C, 62.39; H, 5.00; N, 9.92. Found: C, 62.45; H 4.97; N, 9.78.

Compound 3h

95% Yield; m.p., 206–208°C; IR (KBr, cm^{-1}) 3447, 3155, 3134 (N—H), 2986, 2873 (CH_2CH_3), 1656, 1696 (C=O), 1163 (C=S), 1600, 1514, 1485 (C=C), 1037, 1257 (ArO—); ^{1}H-NMR (80MH2, DMSO-d_6): 1.47 (t, 3H, CH_3), 4.27 (q, 2H, CH_2), 4.86 (S, 2H, $ArOCH_2$), 7.03–7.89 (m, 11H, Ar—H), 11.15 (S, 1H, N—H), 11.38 (S, 1H, N—H), 12.28 (S, 1H, N—H); Anal Calc. for $C_{22}H_{21}N_3O_4S$: C, 62.39; H, 5.00; N, 9.92. Found: C, 62.33; H, 5.07; N, 9.95.

Compound 4

65% Yield; m.p., 229–230°C; IR (KBr, cm^{-1}): 3313, 3211, 3133 (N—H), 2980, 2912, 2829 (CH3, CH2), 1658, 1684 (C=O), 1159 (C=S), 1599, 1576, 1485 (C=C), 1031, 1251 (ArO—); ^{1}H-NMR (80MH2, DMSO-d_6): 1.49 (t, 6H, $2CH_3$), 4.41 (q, 4H, $2CH_2$), 4.65 (S, 4H, $ArO2CH_2$), 6.91–8.04 (m, 12H, Ar—H), 11.09 (S, 2H, N—H_2), 11.37 (S, 2H, N—H_2), 12.16 (S, 2H, N—H_2); Anal Calc. for $C_{30}H_{32}N_6O_8S_2$: C, 53.88; H, 4.82; N, 12.57. Found: C, 53.97; H, 4.78; N, 12.61.

Compound 5

60% Yield; m.p., 221–222°C; IR (KBr, cm^{-1}): 3363, 3149 (N—H), 2985, 2939 (CH_3, CH_2), 1658, 1689 (C=O), 1160 (C=S), 1600, 1559, 1486 (C=C), 1033, 1251 (ArO—); ^{1}H-NMR (80MH2, DMSO-d_6): 1.49 (t, 6H, 2 CH_3), 4.23 (q, 4H, $2CH_2$) 4.73 (S, 4H, $ArO2CH_2$), 6.69–7.98 (m, 12H, Ar—H), 11.07 (S, 2H, N—H_2) 11.34 (S, 2H, N—H_2), 12.21 (S, 2H, N—H_2). Anal Calc for $C_{30}H_{32}N_6O_8S_2$: C, 53.88; H, 4.82; N, 12.57. Found: C, 53.93; H, 4.86; N, 12.64.

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