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Synthesis of 1,3-Benzenedicarbonyl Thiourea Derivatives under Phase Transfer Catalysis

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A series of 1,3-benzenedicarbonyl thiourea derivatives have been prepared in good to excellent yield under the conditions of solvent-free ground and phase transfer catalysis using polyethylene glycol-400 (PEG-400) as the catalyst at room temperature. The method has advantages of easy operations, good yields, mild reaction conditions and purification and environmental acceptability.

Key Words: 1,3-Benzenedicarbonyl thiourea, Solvent-free organic, Synthesis, Phase transfer catalysis.

INTRODUCTION

Thiourea derivatives have been found to possess many important biological activities[1]. Some thioureas are useful as herbicides[2], insecticides[3] and plant-growth regulators[4]. Moreover, thiourea derivatives and isothiocyanates are very valuable intermediates in the synthesis of medicines[5,6]. In recent years, thiourea derivatives play important roles in supramolecular chemistry. They have been used as excellent receptors for anions, such as fluoride, acetate and phosphate ions. The design, construction and anion recognition and sensing of thiourea-based receptors involving mainly multi hydrogen bonding interactions are widely reported[7-9]. Thiourea derivatives have been assembled using multifunctional organic ligands to link metals acting as node and supramolecular structures constructed from discrete coordination-type units[10,11].

Classical phase transfer catalysis synthesis of acyl isothiocyanates is under liquid-liquid phase transfer catalysis using tetrabutylammonium bromide as the catalyst, which after isolation reacted with aniline to give the corresponding thiourea derivatives. However, in presence of water, hydrolysis of the aroyl chloride may occur and the yield of the acyl isothiocyanate is decreased. Consequently, we have conducted our

reaction under solid-liquid phase transfer catalysis conditions using PEG-400 as the catalyst. It was found that the acyl chloride was quantitatively converted to the corresponding acyl isothiocyanate. This intermediate was then treated with various substituted aromatic amines to give the thiourea derivatives (**3**) in high yields.

In addition, the use of dry ground technology in organic chemistry has great-applied value and expensive prospects. It can simplify the reaction separation and enhance the chemical yield, even can increase reaction selectivity[12,13]. Moreover, in recent years, solvent-free organic synthesis under phase transfer catalysis condition has received considerable attention. In comparison with normal reaction, it has many advantages such as high efficiency and selectivity, easy separation and purification and environmental acceptability[14,15]. All these merits are in accord with the green chemistry's requirement of energy-saving, high efficiency and environmentally benign. In view of these and in continuation of our earlier work on the synthesis and activity of thiourea derivatives[16-20], we report herein a convenient and efficient method for the preparation of 1,3-benzenedicarbonyl thiourea derivatives (**3**) under the condition of solvent-free ground and phase transfer catalysis using polyethylene glycol-400 (PEG-400) as the catalyst at room temperature. Yield, melting points, elemental analytical, IR and ^{1}H NMR data of the compounds **3a-h** are given in Tables 1 and 2.

TABLE-1
PHYSICAL AND ELEMENTAL ANALYTICAL DATA OF COMPOUNDS **3a-h**

Compd.	Ar	Yield (%)	m.p. (ºC)	m.f.	Found (%) calcd.		
					C	H	N
3a	C_6H_5	99.6	197-198	$C_{22}H_{18}N_4O_2S_2$	60.78 (60.83)	4.20 (4.15)	12.94 (12.90)
3b	2-ClC_6H_4	99.3	200-201	$C_{22}H_{16}N_4O_2S_2Cl_2$	52.45 (52.48)	3.25 (3.20)	11.21 (11.13)
3c	4-ClC_6H_4	90.2	233-234	$C_{22}H_{16}N_4O_2S_2Cl_2$	52.52 (52.48)	3.22 (3.20)	11.16 (11.13)
3d	2-$OC_2H_5C_6H_4$	95.7	203-204	$C_{26}H_{26}N_4O_4S_2$	59.73 (59.77)	4.96 (4.98)	10.78 (10.73)
3e	4-$OC_2H_5C_6H_4$	99.8	195-196	$C_{26}H_{26}N_4O_4S_2$	59.73 (59.77)	4.96 (4.98)	10.78 (10.73)
3f	2-$OCH_3C_6H_4$	99.7	214-215	$C_{24}H_{22}N_4O_4S_2$	58.21 (58.27)	4.52 (4.49)	11.36 (11.33)
3g	2-$NO_2C_6H_4$	72.4	201-202	$C_{22}H_{16}N_6O_6S_2$	50.36 (50.38)	3.01 (3.05)	16.00 (16.03)
3h	1-Naphthyl	93.5	215-216	$C_{30}H_{22}N_4O_2S_2$	67.40 (67.42)	4.16 (4.12)	10.45 (10.49)

TABLE-2
IR AND ^{1}HNMR SPECTRAL DATA OF COMPOUNDS **3a-h**

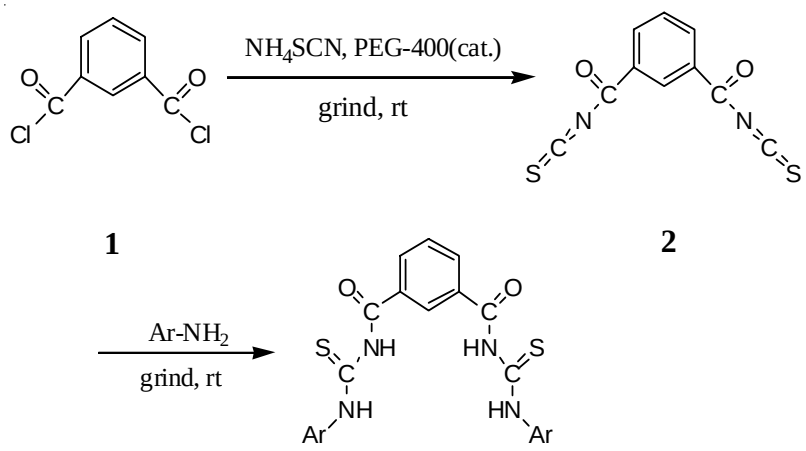
Compd.	IR (ν_{max}, cm^{-1})	^{1}H NMR (δ ppm)
3a	3298, 3223, 3173, 3033 (NH); 1700 (C=O), 1599, 1523 (C=C); 1348, 1246, 1145 (C=S)	12.56 (s, 2H, NHCO), 11.60 (s, 2H, NHAr), 7.28-8.58 (m, 14H, ArH)
3b	3221, 3159, 3067 (NH); 1675 (C=O), 1583, 1531 (C=C); 1243, 1158 (C=S)	12.63 (s, 2H, NHCO), 11.86 (s, 2H, NHAr), 7.34-8.66 (m, 12H, ArH)
3c	3205, 3149, 3025 (NH); 1673 (C=O), 1589, 1528 (C=C); 1252, 1157 (C=S)	12.50 (s, 2H, NHCO), 11.63 (s, 2H, NHAr), 7.43-8.57 (m, 12H, ArH)
3d	3242, 3034, 2981 (NH); 1680 (C=O), 1601, 1549 (C=C); 1231, 1150 (C=S)	12.98 (s, 2H, NHCO), 11.33 (s, 2H, NHAr), 7.24-8.56 (m, 12H, ArH), 4.18 (m, 4H, CH_2O), 1.41 (t, 6H, CH_3)
3e	3238, 3025 (NH); 1672 (C=O), 1598, 1556 (C=C); 1235, 1145 (C=S)	12.88 (s, 2H, NHCO), 11.36 (s, 2H, NHAr), 7.28-8.62 (m, 12H, ArH), 4.26 (m, 4H, CH_2O), 1.48 (t, 6H, CH_3)
3f	3243, 3171, 3150 (NH); 1679 (C=O), 1603, 1528 (C=C); 1243, 1141 (C=S)	12.98 (s, 2H, NHCO), 11.56 (s, 2H, NHAr), 7.00-8.60 (m, 12H, ArH), 3.87 (s, 6H, CH_3O)
3g	3179, 2998 (NH); 1727 (C=O); 1608, 1516 (C=C); 1242, 1182 (C=S); 851, 737 (C-N)	12.58 (s, 2H, NHCO), 11.58 (s, 2H, NHAr), 7.36-8.64 (m, 12H, ArH)
3h	3422, 3133 (NH); 1652 (C=O), 1532, 1280 (C=C), 1232, 1149 (C=S)	12.75 (s, 2H, NHCO), 11.68 (s, 2H, NHAr), 7.58-8.65 (m, 16H, ArH)

EXPERIMENTAL

Melting points were determined with an X-4 digital melting-point apparatus and are uncorrected. IR spectra were recorded in KBr on a Digilab FTS-3000 FT-IR spectrophotometer and ^{1}H NMR spectra on a Varian Mercury plus-400 MHz spectrometer using DMSO-d_6 as solvent and TMS as internal reference. Elemental analyses were determined on a PE-2400 CHN instrument.

Isophthalyl chloride (**1**) is readily available by the reaction for isophthalic acid with thionyl chloride and it is treated with ammonium thiocyanate under the conditions of solid-liquid phase transfer catalysis using 3 % polyethylene glycol-400 (PEG-400) as the catalyst and under solvent-free ground at room temperature to give isophthalyl isothiocyanate (**2**). This compound does not need to be isolated and reacts immediately with various substituted aromatic amines under solvent-free ground at room temperature to afford title compounds (**3**) in good to excellent yields. All products were characterized by IR, ^{1}H NMR spectra and elemental analysis.

General procedure for the preparation of 1,3-benzenedicarbonyl thioureas: The synthesis of 1,3-benzenedicarbonyl thioureas was carried out by adding powdered ammonium thiocyanate (15 mmol), isophthalyl chloride (5 mmol), PEG-400 (0.18g, 3 % with respect to ammonium thiocyanate) were ground up in a dried mortar at room temperature for 5-7 h, Aromatic amine (10 mmol) was then slowly added with constant stirring and the mixture was ground up at room temperature for 8-48 h. When the reaction completed, the reaction mixture was washed with ethanol three times and water three times to remove inorganic salts and filtered. The resulting solid was recrystallised from DMF-C_2H_5OH-H_2O to give pure compounds **3a-h**. The synthetic route of compounds **3a-h** is illustrated in **Scheme-I**.



Scheme-I

In conclusion, solvent-free ground is a facile and convenient method for the synthesis of 1,3-benzenedicarbonyl thiourea derivatives under solid-liquid phase transfer catalysis condition at room temperature. This technology has the advantages of mild reaction conditions, environmentally benign, energy-saving, high efficiency, simple operation and high yield. For these reasons, this methodology represents an important improvement for the preparation of this kind of fine convenient procedure.

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