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PHASE-TRANSFER-CATALYZED SYNTHESIS OF N-ARYL-N'-(2-CHLOROBENZOYL)-THIOUREA DERIVATIVES

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Abstract Reaction of aromatic amines with 2-chlorobenzoyl chloride and ammonium thiocyanate under the condition of solid-liquid phase-transfer catalysis using polyethylene glycol-400(PEG-400) as the catalyst yielded N-aryl-N'-(2-chlorobenzoyl)thioureas 3a—3j in good to excellent yield.

A series of 1, 3-disubstituted thiourea derivatives have been found to possess many important biological activities[1]. Some thioureas have been found to be useful as herbicides[2], insecticides[3] and plant-growth regulators[4].

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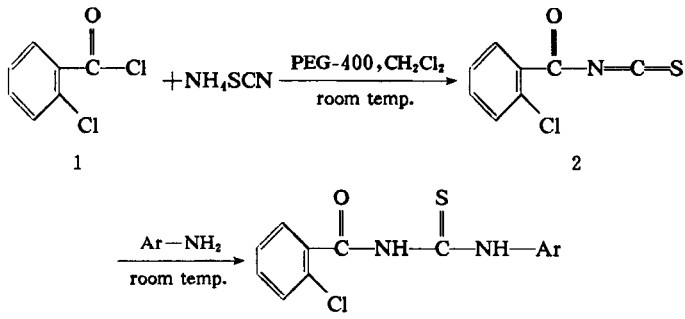
In view of these and in continuation of our earlier work on the synthesis and biological activity of thiourea derivatives[5-7], we now report a convenient and efficient method for the preparation of N-aryl-N'-(2-chlorobenzoyl) thiourea derivatives under the condition of solid-liquid phase-transfer catalysis using PEG-400 as the catalyst.

2-Chlorobenzoyl chloride(1) is readily available by the reaction 2-chlorobenzoic-acid with thionyl chloride. Its treatment with ammonium thiocyanate under the condition of solid-liquid phase-transfer catalysis using 3% PEG-400 as the catalyst gave 2-chlorobenzoyl isothiocyanate (2). This compound does not need to be isolated and reacts immediately with various sustituted aromatic amines to afford N-aryl-N'-(2-chlorobenzoyl) thiourea derivatives (3) in good to excellent yields (Scheme 1).



	Ar		Ar
a	C_6H_5	f	$C_6H_4CH_3$-4
b	C_6H_4OH-2	g	C_6H_4Br-4
c	C_6H_4Cl-4	h	$C_6H_4OCH_3$-4
d	$C_6H_4NO_2$-4	i	$C_6H_4COCH_3$-4
e	C_6H_4I-4	j	$C_6H_4CF_3$-4

Scheme 1

Acyl isothiocyanates have been prepared under liquid-liquid phasetransfer catalysis using tetrabutylammonium bromide as the catalyst, which after isolation reacted

with aniline to give the corresponding thiourea derivatives[8]. However, in the presence of water, hydrolysis of the acyl chloride may occur, and the yield of the acyl isothiocyanate is decreased. Meshkatalsadat has also reported that acyl chloride reacted with different phenylthioureas to yield N-aryl-N′-acylthioureas, but long reaction times and high temperature are required[9]. 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 aromatic amines to give the thiourea derivatives 3 in high yield.

We have investigated the catalytic effet of phase-transfer catalyst on the yield of N-Phenyl-N′-(2-chlorobenzoyl)thiourea(3a). It was found that the phase-transfer catalyst, such as PEG-400, PEG-600, PEG-2000 and PEG-6000, has an obvious catalytic effects. Tetrabutylammonium bromide and 18-crown-6 can also be used as PTC. Other quaternary ammonium salts tested and 15-crown-5 are no effective. The results are summarized in Table 1.

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

Experimental Procedures

IR spectra were recorded using KBr pellets on an Alpha Centauri FT-IR spectrophotometer and ^{1}H NMR spectra on a FT-80A instrument, DMSO-d_6 was used as solvent and Me_4Si as internal standard. Elemental analyses were performed on a Carlo-Erba 1106 Elemental Analysis instrument. Mps were observed in an open capillary

Table 1 Catalytic effect of PTC on the yield of N-Phenyl-N′-(2-chlorobenzoyl) thiourea(3a)

Entry[a]	PTC	Yield[b](%)
1	PEG-400	98
2	PEG-600	96
3	PEG-2000	92
4	PEG-6000	90
5	18-crown-6	77
6	15-crown-5	—
7	Bu_4NBr	82
8	$PhCH_2NBu_3Cl$	—
9	$PhCH_2NEt_3Cl$	—
10	$PhCH_2NMe_3Cl$	—
11	$PhCH_2NMe_3NO_3$	—
12	Me_4NCl	—
13	$C_{16}H_{33}NMe_3Cl$	—
14	no PTC	—

[a]For Entry 6,8,9,10,11,12,13,and14,only N-Phenyl-2-chlorobenzamide was abtained. [b]Based on aniline.

Table 2 Physical and analytical data for compounds 3a—j

Compound	m. p. (T/℃)	Yield (%)	Molecular formula	Found(required)(%)		
				C	H	N
3a	158—159	98	$C_{14}H_{11}ClN_2OS$	57.64 (57.82)	3.73 (3.82)	9.85 (9.64)
3b	155—156	86	$C_{14}H_{11}ClN_2O_2S$	54.85 (54.81)	3.74 (3.62)	9.06 (9.13)
3c	184—185	94	$C_{14}H_{10}Cl_2N_2OS$	51.47 (51.68)	3.15 (3.10)	8.82 (8.62)
3d	192—193	90	$C_{14}H_{10}ClN_3O_3S$	50.01 (50.07)	2.96 (3.00)	12.65 (12.52)
3e	180—181	92	$C_{14}H_{10}ClN_2OS$	40.58 (40.34)	2.33 (2.42)	6.56 (6.72)
3f	164—165	95	$C_{15}H_{13}ClN_2OS$	58.93 (59.10)	4.55 (4.30)	9.07 (9.19)
3g	178—179	89	$C_{14}H_{10}BrClN_2OS$	45.64 (45.47)	2.92 (2.73)	7.46 (7.58)
3h	158—159	93	$C_{15}H_{13}ClN_2O_2S$	56.01 (56.15)	4.18 (4.09)	8.92 (8.73)
3i	212—213	85	$C_{16}H_{13}ClN_2O_2S$	57.58 (57.73)	3.77 (3.94)	8.56 (8.42)
3j	194—195	90	$C_{15}H_{10}ClF_3N_2OS$	50.41 (50.20)	2.62 (2.81)	7.96 (7.81)

Table 3 IR and ^{1}HNMR spectral data for compounds 3a—j

Compound	IR(ν_{max}/cm^{-1})			^{1}H NMR(ppm)
	NH	C=O	C=S	
3a	3238	1668	1174	12.83(1 H,s,NH),11.34(1 H,s,NH),7.03—8.11(9 H,m,arom.)
3b	3318	1672	1168	12.76(1 H,s,NH),11.45(1 H,s,NH),10.21(1 H,s,OH),6.89—8.52(8 H,m,arom.)
3c	3305	1671	1163	12.85(1 H,s,NH),11.51(1 H,s,NH),6.91—8.15(8 H,s,arom.)
3d	3277	1675	1169	12.95(1 H,s,NH),11.68(1 H,s,NH),7.21—8.59(8 H,m,arom.)
3e	3317	1670	1172	12.77(1 H,s,NH),11.42(1 H,s,NH),7.05—8.14(8 H,m,arom.)
3f	3329	1669	1173	12.58(1 H,s,NH),11.31(1 H,s,NH),6.93—8.23(8 H,m,arom.),2.33(3H,s,CH_3)
3g	3268	1671	1168	12.73(1 H,s,NH),11.38(1 H,s,NH),7.02—8.14(8 H,m,arom.)
3h	3334	1671	1175	12.59(1 H,s,NH),11.31(1 H,s,NH),6.87—8.15(8 H,m,arom.),3.47(3 H,s,CH_3)
3i	3327	1674	1169	12.74(1 H,s,NH),11.52(1 H,s,NH),7.35—8.45(8 H,m,arom.),2.55(3 H,s,CH_3)
3j	3274	1669	1174	12.83(1 H,s,NH),11.66(1 H,s,NH),7.12—8.58(8 H,m,arom.)

tube and are uncorrected. 2-Chlorobenzoyl chloride was prepared in 96% yield by refluxing 2-chlorobenzoic acid and an excess of thionyl chloride.

General procedure—— Powdered ammonium thiocyanate (15 mmol), 2-chlorobenzoyl chloride(10 mmol),PEG-400(0.18 g,3% with respect to ammonium thiocyanate) and methylene dichloride(25 ml)were placed in a dried round-bottomed flask containing a magnetic stirrer bar and stirred at room temperature for 1 h,then the aromatic amine(9.5 mmol) was added,and the mixture was stirred for 0.5 h. The mixture was filtered off to remove inorganic salts and the solvent distilled off. The resulting solid was recrystallised from anhydrous ethanol to give compound 3. Yields,mps,analytical,IR and H NMR data of the product are given in Tables 2～3.

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