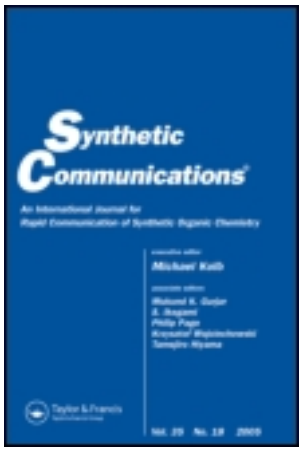

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SYNTHESIS OF BENZOYL-*N*-PHENYLTHIOUREAS UNDER MICROWAVE IRRADIATION AND PHASE TRANSFER CATALYSIS CONDITIONS

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ABSTRACT

A simple, rapid and efficient method for the synthesis of benzoyl-*N*-phenylthioureas under microwave irradiation is reported. The effect of microwave irradiation power, times and phase transfer catalyst on the reaction is investigated.

Many methods have been described for the preparation of both acyl and aroyl isothiocyanates,[1–7] which are important for the synthesis of acyl phenylthioureas. The reaction of acyl chloride with thiocyanate under phase transfer catalysis is a good method for the preparation of acyl isothiocyanates,[1,6,7] which react with aniline to afford the acyl phenylthioureas.[1,2]

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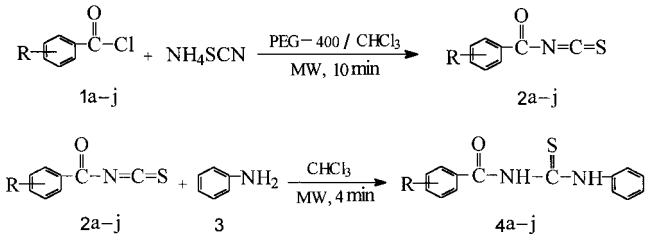
The applications of ultrasound in organic synthesis have been rapidly developed. Li and coworkers[8] have shown that phenylacetyl arylthioureas can be obtained from the corresponding acyl chlorides under ultrasound condition. Using polyethylene glycol-400 as phase transfer catalyst the phenylacetyl arylthioureas can produce high yield, but the reaction requires long time.

Microwave heating has been used for a wide variety of applications including the rapid synthesis of organic compounds and some important reviews have been published.[9] There are a variety of methods for carrying out microwave assisted organic reactions using domestic or commercial ovens. We have reported the use of this technology in the synthesis of the substituted glycerol selenide ethers,[10] diaryl diselenides,[11] chiral glycerol sulfide ethers[12] and 8-quinolinyl ethers.[13]

Recently, we have found that benzoy phenylthioureas 4 can be obtained from the reaction of substituted benzoyl chloride 1 with first ammonium thiocyanate and then aniline 3 in a two-phase system, at polyethylene glycol-400 as the catalyst under microwave irradiation condition. This method is very simple, rapid and affords good yields of benzoyl-*N*-phenylthioureas. The reactions are shown in the Scheme and the results for the compounds prepared are listed in Table 1. All products were characterized by ^{1}H NMR and IR spectra.



4a-f: R = H, 2-Cl, 3-CH_3, 4-CH_3, 4-OCH_3, 3,5-$(OCH_3)_2$

4g-j: PhR = C_6H_5CH=CH, $C_6H_5CH_2$, α - $C_{10}H_7$, β - $C_{10}H_7$

Scheme.

RESULTS AND DISCUSSION

Using the reaction of benzoyl chloride with NH_4SCN and $C_6H_5NH_2$ as an example, we investigated the effect of the power and time of

Table 1. Benzoyl-*N*-phenyl Thioureas 4a–j Prepared[a]

Entry	Product	M.P./°C	Lit. M.P./°C	Yield/%
3a	$C_6H_5CONHCSNHC_6H_5$	135.8	136[1]	92
3b	$2\text{-}ClC_6H_4CONHCSNHC_6H_5$	153.2	153[1]	85
3c	$3\text{-}CH_3C_6H_4CONHCSNHC_6H_5$	112.6	113[1]	86
3d	$4\text{-}CH_3C_6H_4CONHCSNHC_6H_5$	132.5	132–133[3]	84
3e	$4\text{-}OCH_3C_6H_4CONHCSNHC_6H_5$	84.4	84[1]	80
3f	$3,5\text{-}(OCH_3)_2C_6H_3CONHCSNHC_6H_5$	125.8	125.5[3]	72
3g	$C_6H_5CH{=}CHCONHCSNHC_6H_5$	163.6	163,[1] 163–164[3]	85
3h	$C_6H_5CH_2CONHCSNHC_6H_5$	108.4	107–108[3]	93
3i	$\alpha\text{-}C_{10}H_7CONHCSNHC_6H_5$	154.7	154[3]	66
3j	$\beta\text{-}C_{10}H_7CONHCSNHC_6H_5$	149.3	148,[1] 148.5[3]	65

[a]Time/Power: 14 min, 750 W.

microwave irradiation on the reaction. The results are summarized in Table 2 and Table 3. The result shown that the highest yield for compounds 4 can be obtained at 750 W power with 14 min reaction time under microwave irradiation conditions.

The use of phase transfer catalysis for nucleophilic substitution reaction is well documented.[14,15] The mechanism of synthesis of benzoyl isothiocyanate under phase transfer catalysis has been discussed.[7] We studied the effect of different phase transfer catalyst on the reaction. It was found that the activities of the catalysts are in the following sequence: PEG-400 > PEG-600 > Bu_4NBr > $C_6H_5CH_2N(CH_3)_3Cl$ > Bu_4NI. The results shown in Table 4.

The heating effect utilized in microwave assisted organic transformations is due to the dielectric constant of solvent. The larger the dielectric constant, the greater the coupling with microwaves.[10–13] We found when power at 750 W, a reaction time of 14 min and using $CHCl_3$ which has large dielectric constant and high boiling point, as solvent, the yield of the one-step transformation of compound 1 to benzoyl phenylthiourea 4 is very good.

The quantity of dimethylformamide is very important in the reaction. When a small amount of dimethylformamide is added to the heterogeneous reaction mixture, rapid reaction occurs between dimethylformamide and NH_4SCN to produce dimethylformamide ammonium ion pairs, $(CH_3)_2NCHO^-NH_4^+$, which is distributed into the chloroform layer. Which eventually facilitates the nuoleophilic displacement reaction.[15] Experiment results showed that 2 drops dimethylformamide was added into the heterogeneous mixture, the efficiency were very good. In the absence of

Table 2. Effect of the Time of Microwave Irradiation on the Formation of Benzoyl Isothiocyanate 2a and Benzoyl-*N*-phenyl Thiourea 4a[a,b]

Entry	Synthesis of 2a (min)	Synthesis of 4a (min)	Yield[c] (%)
1	9	3	78
2	10	3	80
3	11	3	82
4	12	3	84
5	8	4	83
6	9	4	87
7	10	4	92
8	10	5	90
9	11	4	91
10	10	6	88

[a]Molar ratio: $C_6H_5COCl : NH_4SCN : p\text{-}ClC_6H_4NH_2 :$ PEG-400 = 1.2 : 1 : 1.8 : 0.1.
[b]The power of microwave irradiation is 750 W.
[c]Isolated yield of the one-step transformation of compound 1a to 4a.

Table 3. Effect of the Power of Microwave Irradiation on the Formation of Benzoyl-*N*-phenyl Thiourea 4a[a,b]

Power (W)	375	525	600	675	750	800	850
Yield (%)[c]	80	82	86	90	92	90	87

[a]Molar ratio: $C_6H_5COCl : NH_4SCN : C_6N_5NH_2$: PEG-400 = 1.2 : 1 : 1.8 : 0.1.
[b]The time of microwave irradiation is 14 min.
[c]Yield of isolated product.

Table 4. Effect of the Phase Transfer Catalyst on the Formation of Benzoyl-*N*-phenyl Thiourea 4a[a,b]

Power (W)	PEG-400	PEG-600	Bu_4NBr	Bu_4NI	$C_6H_5CH_2N(CH_3)_3Cl$
Yield (%)[c]	92	87	84	76	80

[a]Molar ratio: $C_6H_5COCl : NH_4SCN : C_6H_5NH_2$: PEG-400 = 1.2 : 1 : 1.8 : 0.1.
[b]Time/Power: 14 min, 750 W.
[c]Yield of isolated product.

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dimethylformamide the reaction of C_6H_5COCl with SCN^- will require long time.

EXPERIMENTAL

The melting points were determined on a WRS-1A digital melting point apparatus. IR spectra were measured for KBr discs using an Alpha Centauri FT-IR spectrophotometer. ^1H NMR spectra (80 MHz) were recorded in $CDCl_3$ using a FT-80 spectrometer. *J* values are given in Hz. Microwave irradiation is carried out with an improved reflux Galanz WP 750B commercial microwave oven at 2450 MHz.

General Procedure

In a typical experiment, the ammonium thiocyanate (4.5 mmol), benzoyl chloride (3 mmol), PEG-400 (0.25 mmol), DMF (2 drops) and trichloromethane (20 mL) were added in a bottle (50 mL), and refluxed under microwave irradiation at 750 W for 10 min. Then a mixture of aniline (2.5 mmol) and trichloromethane (5 mL) was added dropwise over a period of 2 min and irradiated continued for 2 min. After cooling to room temperature and water (15 mL) was added. The organic layer was separated, the aqueous phase was washed with trichloromethane (2×5 mL). The combined trichloromethane layer was dried over anhydrous $MgSO_4$. The solvent was removed by evaporation under reduced pressure to afford the benzoyl-*N*-phenylthiourea 4. Recrystallization from ethanol gave the analytically pure product.

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