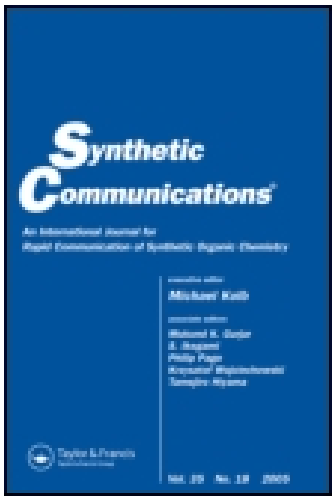

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PHASE TRANSFER CATALYTIC SYNTHESIS OF PHENYLACETYL ARYLTHIOUREAS UNDER MICROWAVE IRRADIATION CONDITIONS

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PHASE TRANSFER CATALYTIC SYNTHESIS OF PHENYLACETYL ARYLTHIOUREAS UNDER MICROWAVE IRRADIATION CONDITIONS

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ABSTRACT

A simple, rapid, and efficient method for the synthesis of phenylacetyl arylthioureas under microwave irradiation is reported. The effects of microwave irradiation power, times, and solvent on the reaction are investigated.

Acyl isothiocyanates have been known as important intermediates in organic synthesis for a long time.[1] Many methods have been described for the synthesis of both acyl and aroyl isothiocyanates.[2–7] However, long reaction times, expensive reagents and anhydrous conditions are often required for their preparation.[2] Reeves and coworkers[4,7] were the first to use phase transfer catalysis to prepare acyl isothiocyanates. They offered an attractive

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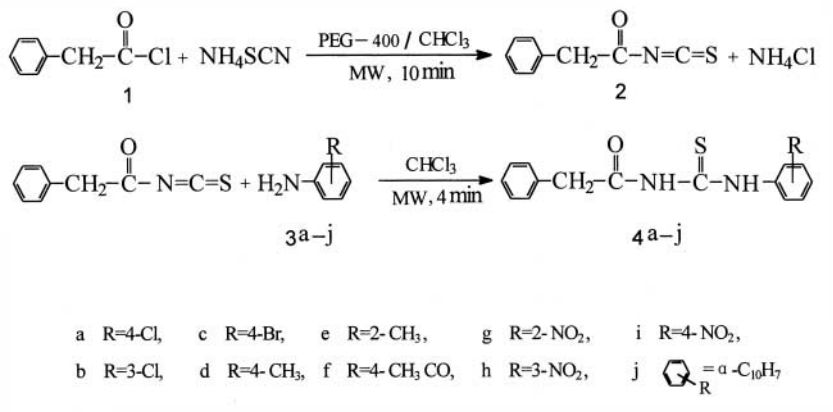
alternative for the preparation of both acyl and aroyl isothiocyanates. However, toxic potassium thiocyanate is part of the waste and the product obtained is low in yield. Recently Wei and Chen[8] improved Reeves' method, providing shorter reaction times, simple operation, and high yield. The isothiocyanates were converted to the acyl-*N*-phenylthioureas by treating with aniline for the purpose of characterization.[2,4]

The application of ultrasound in organic synthesis has been rapidly developed. Li and coworkers[9] have shown that phenylacetyl arylthioureas can be obtained from the corresponding acyl chlorides under ultrasound conditions. Using polyethylene glycol-400 as the phase transfer catalyst, the phenylacetyl arylthioureas can be obtained in high yield, but the reaction requires a long time.

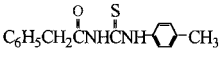
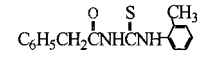
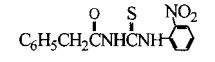
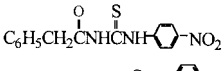
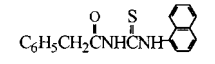
Microwave heating has been used for a wide variety of applications including the rapid synthesis of organic compounds and some important reviews have been published.[10] There are a variety of methods for carrying out microwave-assisted organic reactions using domestic or commercial ovens. We have reported the use of this technology in the synthesis of substituted glycerol selenide ethers,[11,12] chiral glycerol sulfide ethers[13], and 8-quinolinyl ethers.[14]

Recently, we have found that phenylacetyl arylthioureas **4** can be obtained from the reaction of phenylacetyl chloride 1 with first ammonium thiocyanate and then arylamines **3** in a solid–liquid system with polyethylene glycol-400 as a catalyst under microwave irradiation. This method is very simple, rapid, and affords good yields of phenylacetyl arylthioureas. The reactions are shown in the scheme and the results for the compounds prepared are listed in Table 1.



Scheme.

Table 1. Phenylacetyl Arylthioureas **4a–j** Prepared[a]

Entry	Product	M.P. (°C)	Lit. M.P. (°C)[9]	Yield (%)
4a		157.7	155–156	94
4b		116.3	116–117	76
4c		175.2	174–175	87
4d		145.2	146–147	88
4e		142.4	141.5–142.5	83
4f		170.5	171	91
4g		153.2	151.5–152.5	62
4h		124.6	124	77
4i		157.7	156–157	67
4j		169.4	168.5–169	86

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

RESULTS AND DISCUSSION

Using the reaction of phenylacetyl chloride with NH_4SCN and *p*-$ClC_6H_4NH_2$ as an example, we investigated the effect of the power and time of microwave irradiation on the reaction. The results are summarized in Tables 2 and 3. The results show that the highest yield for compounds **4** can be obtained at 750 W with 14 min reaction time under microwave irradiation conditions.

The efficiency of various solvents on the formation of *N*-phenylacetyl-*N*′-4-chloro-arylthiourea **4a** was studied using PEG-400 as a phase transfer catalyst under microwave irradiation at 750 W for 14 min. $CHCl_3$ was found to be an effective solvent for the reaction. The effects of various solvents in the synthesis of *N*-phenylacetyl-*N*′-4-chloroarylthiourea **4a** are shown in Table 4.

The use of phase transfer catalysis for nucleophilic substitution reactions is well documented.[15,16] The mechanism of the synthesis of benzoyl

Table 2. Effect of the Power of Microwave Irradiation on the Formation of *N*-Phenylacetyl-*N*′-4-chloro-arylthiourea **4a**[a,b]

Power (W)	375	525	600	675	750	800	850
Yield (%)[c]	85	89	91	93	94	92	88

[a]Molar ratio: $PhCH_2COCl : NH_4SCN : p\text{-}ClC_6H_4NH_2 : PEG\text{-}400 = 1.2 : 1 : 1.8 : 0.1$.
[b]The time of microwave irradiation is 14 min.
[c]Yield of isolated product.

Table 3. Effect of the Time of Microwave Irradiation on the Formation of Phenylacetyl-Isothiocyanate **2** and *N*-Phenylacetyl-*N*′-4-chloro-arylthiourea **4a**[a,b]

Entry	Synthesis of **2** (min)	Synthesis of **4a** (min)	Yield[c] (%)
1	9	3	87
2	10	3	89
3	11	3	88
4	12	3	86
5	9	4	92
6	10	4	94
7	10	5	93
8	11	4	93
9	10	6	92

[a]Molar ratio: $PhCH_2COCl : NH_4SCN : p\text{-}ClC_6H_4NH_2 : PEG\text{-}400 = 1.2 : 1 : 1.8 : 0.1$.
[b]The time of microwave irradiation is 750 W.
[c]Isolated yield of the one-step transformation of compound **1** to **4a**.

Table 4. Effect of Solvents on the Synthesis of *N*-Phenylacetyl-*N*′-4-chloroarylthiourea **4a**

Solvents	C_6H_6	CH_2Cl_2	$CHCl_3$
Dielectric constant ($\varepsilon^{20^\circ C}$)	2.29	10.4	4.70
b.p. (°C)	80.1	40.2	61.2
Yield (%)	0	78	94

Table 5. Compare with Microwave Irradiation and Other Methods for Phenylacetyl Arylthioureas **4a** Preparation

Experimental	Conditions	Time	Yield (%)
MW-PTC	750 W	14 min	94
PTC[9]	10–30°C	2–6 h	92
Ultrasound-PTC[9]	10–30°C	1.5 h	95

isothiocyanate under phase transfer catalysis has been discussed. The heating effect utilized in microwave assisted organic transformation is due to the dielectric constant of solvent. The larger the dielectric constant, the greater the coupling with microwaves.[12,13,17] We found that with the microwave power at 750 W, a reaction time of 14 min and using $CHCl_3$ as solvent, which has large dielectric constant and high boiling point, the yield of the one-step transformation of compound 1 to phenylacetyl arylthiourea **4** is very good.

Dimethylformamide can dissolve many organic substrates and inorganic salts. When a small amount of DMF is added to the heterogeneous reaction mixture, rapid reaction occurs between DMF and NH_4SCN to produce the dimethylformamide ammonium ion pairs, $(CH_3)_2NCHO^-NH_4^+$, which is distributed into the chloroform layer and eventually facilitates the nucleophilic displacement reactions.[18]

The quantity of DMF in the reaction mixture is very important. Experimental results showed that with two drops of DMF in the heterogeneous mixture, the efficiency was very good. In the absence of DMF the reaction of $PhCH_2COCl$ with SCN^- will not occur.

Compared with other methods for the synthesis of phenylacetyl arylthioureas, using microwave irradiation conditions has the advantages of short reaction times and high product yield. Table 5 shows the results for different reaction conditions.

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. ^{1}H-NMR spectra (80 MHz) were recorded in $CDCl_3$ using a FT-80 spectrometer. J values were given in Hz. Microwave irradiation was carried out with an improved reflux Galanz WP 750B commercial microwave oven at 2450 MHz.

General Procedure

In a typical experiment, ammonium thiocyanate (0.34 g, 4.5 mmol), phenylacetyl chloride (0.46 g, 3 mmol), PEG-400 (0.1 g, 0.25 mmol), DMF (two 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 substituted aniline (2.5 mmol) and trichloromethane (5 ml) was added dropwise over a period of 2 min and irradiation continued for 2 min. After cooling to room temperature, water (15 ml) was added. The organic layer was separated and 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 phenylacetyl arylthioureas **4**. Recrystallization from ethanol gave the analytically pure products.

4a: IR ν (KBr): 1692, 1607, 1598, 1495, 1152, 3241. ^{1}H-NMR ($CDCl_3$): δ 3.75 (2H, s, CH_2), 7.25–7.67 (9H, m, ArH), 9.05 (1H, s, S=CNH), 12.31 (1H, s, O=CNH).

4b: IR ν (KBr): 1682, 1609, 1597, 1494, 1149, 3221. ^{1}H-NMR ($CDCl_3$): δ 3.75 (2H, s, CH_2), 7.21–7.77 (9H, m, ArH), 8.80 (1H, s, S=CNH), 12.36 (1H, s, O=CNH).

4c: IR ν (KBr): 1689, 1596, 1587, 1482, 1152, 3241. ^{1}H-NMR ($CDCl_3$): δ 3.75 (2H, s, CH_2), 7.28–7.50 (9H, m, ArH), 8.92 (1H, s, S=CNH), 12.35 (1H, s, O=CNH).

4d: IR ν (KBr): 1687, 1598, 1497, 1148, 3234. ^{1}H-NMR ($CDCl_3$): δ 2.38 (3H, s, CH_3), 3.75 (2H, s, CH_2), 7.14–7.51 (9H, m, ArH), 9.17 (1H, s, S=CNH), 12.27 (1H, s, O=CNH).

4e: IR ν (KBr): 1678, 1452, 1178, 3247. ^{1}H-NMR ($CDCl_3$): δ 2.30 (3H, s, CH_3), 3.75 (2H, s, CH_2), 7.14–7.68 (9H, m, ArH), 9.51 (1H, s, S=CNH), 12.02 (1H, s, O=CNH).

4f: IR ν (KBr): 1691, 1659, 1597, 1458, 1162, 3243. ^{1}H-NMR ($CDCl_3$): δ 2.61 (3H, s, $COCH_3$), 3.75 (2H, s, CH_2), 7.28–7.40 (5H, m, ArH), 7.78–8.04 (4H, m, ArH), 8.86 (1H, s, S=CNH), 12.58 (1H, s, O=CNH).

4g: IR ν (KBr): 1678, 1607, 1584, 1462, 1157, 3251. ^{1}H-NMR ($CDCl_3$): δ 3.75 (2H, s, CH_2), 7.26–8.39 (9H, m, ArH), 8.91 (1H, s, S=CNH), 13.05 (1H, s, O=CNH).

4h: IR ν (KBr): 1688, 1587, 1486, 1456, 1174, 3197. ^{1}H-NMR ($CDCl_3$): δ 3.75 (2H, s, CH_2), 7.28–8.69 (9H, m, ArH), 9.12 (1H, s, S=CNH), 12.65 (1H, s, O=CNH).

4i: IR ν (KBr): 1708, 1612, 1594, 1454, 1187, 3184. ^{1}H-NMR ($CDCl_3$): δ 3.75 (2H, s, CH_2), 7.28–7.48 (5H, m, ArH), 7.90–8.34 (4H, m, ArH), 8.72 (1H, s, S=CNH), 12.76 (1H, s, O=CNH).

4j: IR ν (KBr): 1689, 1600, 1456, 1175, 3198. ^{1}H-NMR ($CDCl_3$): δ 3.75 (2H, s, CH_2), 7.22–8.01 (12H, m, ArH), 9.20 (1H, s, S=CNH), 12.48 (1H, s, O=CNH).

REFERENCES

1. Dixo, A.E.; Taylor, J. J. Chem. Soc. **1908**, *93*, 648.
2. Smith, P.A.S.; Kan, R.O. J. Org. Chem. **1964**, *29*, 2261–2265.
3. Cainelli, G.; Manescalchi, F. Synthesis **1979**, 141–144.
4. Reeves, W.P.; Simmons, A.Jr., et al. Synth. Commun. **1981**, *11*(10), 781–785.
5. Lipp, M.; Dallacker, F.; Koenen, G. Chem. Ber. **1958**, *91*, 1660.
6. Ivanovz, Zh.M.; Kirsanova, N.A.; Derkach, C.I. Zh. Organ. Khim. **1965**, *1*(12), 2186; CA, **1966**, *64*, 11123c.
7. Reeves, W.P.; Simmons, A., et al. Synth. Commun. **1980**, *10*(8), 633.
8. Taibao Wei; Jichou Chen. Pesticides (Chinese) **1995**, *34*(2), 12–14.
9. Li, Y.; Guo, W.; Xu, Y., et al. Chin. J. Appl. Chem. **1998**, *15*(1), 95–97.
10. (a) Caddick, K. Tetrahedron **1995**, *51*, 10403–10432. (b) Strauss, C.R.; Trainor, R.W. Australian J. Chem. **1995**, *48*, 1665–1692. (c) Galema, S.A. Chem. Soc. Rev. **1997**, *26*, 233–238.
11. Wang, J.-X.; Wu, X.; Hu, Y., et al. J. Chem. Research(S) **1999**, 688–689; J. Chem. Research(M) **1999**, 688–689.
12. Wang, J.-X.; Xi, Y.; Wu, X.; Hu, Y.; Du, Z. Synth. Commun. **1998**, *28*(24), 4916–4627.
13. Wang, J.-X.; Zhang, Y.; Huang, D.; Hu, Y. J. Chem. Res. (S) **1998**, 216–217.
14. Wang, J.-X.; Zhang, M.; Hu, Y. Synth. Commun. **1998**, *28*(13), 2407–2413.
15. Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*. Academic Press: New York, 1978.
16. Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis*. Springer Verlag: New York, 1977.
17. Wang, J.-X.; Bai, L.; Li, W., et al. Synth. Commun. **2000**, *30*(2), 325–332.
18. Hongwen Hu. *Organic Chemistry*, 2nd Ed.; Higher Education Press: Beijing, 1990; 545–546.

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