***SHORT PAPER***

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# A mild and efficient synthesis of N–aryl–N′–aroyl thioureas under phase transfer catalysis and solvent-free conditions

**Tai-Bao Wei, Qi Lin, You-Ming Zhang* and Wei Wei**

*Department of Chemistry, Northwest Normal University, Lanzhou, Gansu, 730070, P. R. China*

A series of *N*–aryl–*N*′–aroyl thioureas **3a-m** were synthesized in high yields (80.0-98.1%) by an environmentally benign, simple and efficient method under phase transfer catalysis and solvent-free conditions.

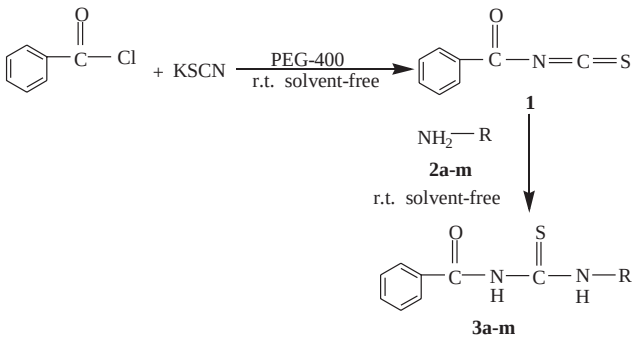
**Keywords:** solvent-free synthesis, *N*–aryl–*N*'–aroyl thioureas

Thiourea derivatives have been found to possess many important biological activites.[1] Some thioureas are useful as heribicides[2], insecticides[3] and plant-growth regulators.[4] Moreover, thiourea derivatives and isothiocyanates are very valuable intermediates in the synthesis of medicines.[5-8] For instance, *N*–aryl–*N*′–aroyl thioureas were employed as the key intermediates in the synthesis of antithrombotic agents.[5] Many methods have been described for the preparation of isothiocyanates,[9-13] which are important for the synthesis of thiourea derivatives. The reaction of an acyl chloride with ammonium thiocyanate under phase transfer catalysis is a good method for the preparation of acyl isothiocyanates, which react with aniline to afford the acyl phenyl thioureas. In our earlier work, we have reported the use of this method in the synthesis of a series of thiourea derivatives.[13-17]

In recent years the use of solvent-free technology in organic synthesis has received considerable attention. This technology has many advantages such as high efficiency and selectivity, easy separation and purification and environmental acceptability.[18-21] All these merits are in accord with green chemistry's requirements of energy-saving, high efficiency and environmental benevolence.

Classical phase transfer catalysis synthesis methods often need many organic solvents and the reaction procedure may be more complex than with solvent-free methods.[13-17] In addition, most solvent-free reactions use inorganic or organic solid supports, involving suitable chemical material such as silica gel or $Al_2O_3$ *etc*. as the solid support and need some operations to separate them after the reaction is complete.[18-20] Despite these shortcomings, phase transfer catalysis and solvent-free synthesis give an excellent method for synthesis acyl phenyl thioureas. In view of this and in continuation of our earlier work on the synthesis and activity of thiourea derivatives, we decided to try to synthesize the *N*–aryl–*N*′–aroyl thioureas by reacting benzoyl isothiocyanates **1** with aromatic amines **2** without solvent. **1** was prepared by reacting potassium thiocyanate with benzoyl chloride under phase transfer catalysis and solvent free conditions.

We first estimated the reactivity of a model reaction between benzoyl chloride (11mmol) and potassium thiocyanate (12mmol) under solvent-free conditions and phase transfer catalysis using polyethylene-glycol-400 (PEG-400) as phase transfer catalyst. The reaction mixture was intermittently stirred at room temperature for 5 hours. The intermediate **1** did not separate and the aromaticamine (10mmol) was slowly added to the reaction mixture with constant stirring. After the reaction mixture was intermittently stirred at room temperature for 5 hours again the reaction was completed. The separation and purification processes were very simple, owing to the products being almost insoluable in ethanol at room temperature whereas the isothiocyanates and aromatic amines soluble in ethanol. The reaction mixture was washed with 8 mL 75% ethanol three times and 10 ml water three times, the product **3a** being obtained in 98.0% yield. It must be emphasized that the first step does not occur significantly without the use of the phase transfer catalyst.




**Scheme 1**

In a second series of experiments we explored the general validity of the present methodology; different *N*–aryl–*N*′–aroyl thioureas **3b**–**3m** were synthesised in 80.0–98.1% yield. The reactions are shown in the scheme 1 and the results for the compounds prepared are listed in Table 1. All products were characterised by $^1$HNMR, IR spectra and elemental analysis.

In conclusion, we have found that *N*–aryl–*N*′–aroyl thioureas can be synthesised in high yield under phase transfer catalysis and solvent-free conditions. All reaction were completed at room temperature and solvent-free conditions which give many environmental benefits, *i.e.* no atmospheric pollution by escaping solvents, no energy use for heating the reaction, less waste produced and the catalyst is innocuous and very inexpensive. In addition the experimental procedure is very simple, the intermediate need not be separated and the product separation involves only a simple washing. For these reasons, this methodology represents an important improvement for the preparation of this kind of fine chemical following an environmentally benign procedure.

## Experimental

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded in KBr on an Alpha Centauri FT-IR spectrophotometer and $^1$HNMR spectra on an FT-80A instrument using $CDCl_3$ as solvent and TMS as internal reference. Elemental analyses were determined on a PE-2400 CHN instrument.

* To receive any correspondence. E-mail: kejichu@nwnu.edu.cn

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**Table 1** *N*-aryl-*N*′-aroylthioureas **3a–m** prepared

| Entry | R | M.p./°C | Lit. M.P./°C | Yield/% |
|---|---|---|---|---|
| **3a** | $C_6H_5$ | 147–148 | 148[12] | 98.0 |
| **3b** | 3-$CH_3C_6H_4$ | 127–128 | 128[12] | 92.9 |
| **3c** | 4-$CH_3C_6H_4$ | 158–159 | 157[12] | 89.9 |
| **3d** | 2-$NO_2C_6H_4$ | 140–141 | 139[13] | 86.4 |
| **3e** | 3-$NO_2C_6H_4$ | 164–165 | 164[13] | 83.1 |
| **3f** | 2-$ClC_6H_4$ | 143–144 | 144[12] | 95.0 |
| **3g** | 4-$ClC_6H_4$ | 139–140 | 140.5[12] | 98.1 |
| **3h** | 4-$BrC_6H_4$ | 149–150 | 150[12] | 95.8 |
| **3i** | 4-$FC_6H_4$ | 127–128 | 128–129.5[12] | 97.1 |
| **3j** | 1-Naphthyl | 168–170 | 171[22] | 94.8 |
| **3k** | 2-Naphthyl | 171–172 | 173[22] | 80.1 |
| **3l** | 2-$CH_3C_6H_4$ | 116–117 | 117[12] | 92.6 |
| **3m** | 4-$CH_3OC_6H_4$ | 154–155 | 154.4–155[12] | 90.9 |

The synthesis of *N*–aryl–*N*′–aroyl thioureas was carried out by adding powdered KSCN (12mmol), benzoyl chloride (11mmol) and PEG-400 (0.1ml) to a dried agate mortar. The reaction mixture was mixed thoroughly and intermittently stirred at room temperature for 5 hours. Then the aromatic amine (10mmol) was slowly added to the reaction mixture with constant stirring. The reaction mixture was intermittently stirred at room temperature for 5 hours again after which it was mixed thoroughly. When the reaction was completed, the products were obtained from washing the reaction mixture with 8ml 75% ethanol three times and 10mL $H_2O$ three times. If necessary, recrystallisation from ethanol gave the pure product.

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