Microwave promoted efficient synthesis of *N*–aryl–*N'*–ethoxycarbonyl thioureas under solvent-free and phase-transfer catalysis conditions

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A series of *N*–aryl–*N'*–ethoxycarbonyl thioureas **3a-j** were synthesised under microwave irradiation, phase transfer catalysis and solvent-free conditions.

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

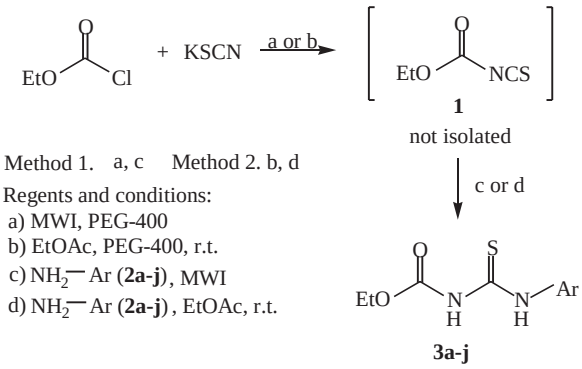
N–Aryl–*N'*–ethoxycarbonyl thioureas exhibit high antibacterial activity.[1] In addition, owing to their strong coordination ability, many *N*–substituted–*N'*– alkoxycarbonyl thioureas are extensively utilised as collectors for copper and precious metals in mining.[2-3] The reaction of an acyl chloride with ammonium thiocyanate under phase transfer catalysis is a good method for the preparation of acyl isothiocyanates, which react with aniline to afford the aroyl thioureas.[4]

As we know, microwave technology can enhance the chemical yield of reactions, and shorten the reaction time.[5] Moreover solvent-free organic synthesis has many advantages such as high efficiency and selectivity, easy separation and purification of products and environmental acceptability.[5, 6]

In view of these considerations and in continuation of our earlier work on the synthesis, biological activity and coordination behaviour of thiourea derivatives,[4,7-9] we have synthesised a series of *N*–aryl–*N'*–ethoxycarbonyl thioureas by reacting ethoxycarbonyl isothiocyanates **(1)** with a range of aromatic amines (**2a–j)** under microwave irradiation (MWI) and solvent-free conditions. Compound **1** was prepared by reacting potassium thiocyanate with ethyl chloroformate under MWI and solvent-free conditions using polyethyleneglycol-400 (PEG-400) as a phase transfer catalyst. The reactions are shown in Scheme 1 (method 1).

In order to make a comparison between this method and the classical phase transfer method (method 2),[4] we synthesised the **3a–j** using both two approaches (see Scheme 1). The results are listed in Table 1.

In conclusion, method 1 is an efficient and convenient method for the synthesis of *N*–aryl–*N'*– ethoxycarbonyl thioureas. All reactions were completed in minutes without using any solvents or any solid-supports, which gives many environmental benefits, *i.e.* no atmospheric pollution by escaping solvents, less waste produced and the catalyst is not noxious and is very inexpensive. In addition the experimental procedure is very simple, the intermediate does not require isolation and the product separation involves only a simple wash. For these reasons, this methodology represents an important improvement for the preparation of this kind of fine chemical following an environmentally benign procedure.



Scheme 1

Table 1 Synthesis **3a–j** using different methods

	Ar	Time[a]		Yields (%)	
		1[b]/min	2[c]/h	1[b]	2[c]
3a	C_6H_5	4	5	76	46
3b	3-$CH_3C_6H_4$	4	5	76	59
3c	4-$CH_3COC_6H_4$	5	7	75	51
3d	2-ClC_6H_4	5	8	64	45
3e	2, 4, 6 -triClC_6H_2	6	10	70	59
3f	2,4,6-triBrC_6H_2	6	10	86	84
3g	2-Thiazolyl	5	6	70	66
3h	1-Naphthyl	4	5	73	72
3i	2-Naphthyl	4	5	70	67
3j	4-$CH_3OC_6H_4$	4	5	75	70

[a]Reaction time of second step. [b]Method 1. [c]Method 2.

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}H NMR spectra on an FT-80A instrument using $CDCl_3$ as solvent and TMS as internal reference. Elemental analysis was determined on PE-2400 CHN instrument.

General procedure

Method 1: The syntheses of **3a–3j** were carried out by taking powdered KSCN (12 mmol), ethyl chloroformate (11 mmol) and PEG-400 (0.1 mol) in a dried test tube. The reaction mixture was subjected to microwave irradiation (500W) for 0.5 min periods up to a total of 5 min irradiation (the interval between each irradiation was 0.5–1 min and the progress of the reaction was monitored by TLC). After the reaction was complete, the reaction mixture was cooled to room temperature and the aromatic amine (10 mmol) was slowly added to the reaction mixture with constant stirring over 5 min. Then, the reaction mixture was subjected to microwave irradiation (500 W) for 0.5 min periods up to a total of 4–6 min irradiation as above. Then, the reaction was complete. Owing to the fact that the products were not soluble in ethanol at room temperature whereas the isothiocyanates and aromatic amines were soluble, the reaction mixture was washed with 75% ethanol (3 × 8 ml) and water (3 × 10 ml) and then, the product was obtained. Recrystallisation from ethanol gave the pure product.

Method 2: Powdered KSCN (12 mmol), ethyl chloroformate (11 mmol), PEG-400 (0.1 mol) and EtOAc (20 ml) were taken in a dried test tube. The reaction mixture was stirred at room temperature for 5 h. After the reaction was completed, the aromatic amine (10 mmol) was added to the reaction mixture with constant stirring. Then, the reaction mixture was stirred at room temperature for 5–10 h when, the reaction was complete. After evaporation of the solvent *in vacuum*, the isolation of the products was similar to that of method 1.

N-Phenyl-N'-ethoxycarbonylthiourea (**3a**)*:* Colourless needles, m.p. 125–126 °C. IR: ν = 3416, 3220, 1712, 1596, 1534, 1449, 1237cm^{-1}. ^{1}H NMR: δ_H = 11.48(s, 1H, NH), 8.29 (s, 1H, NH), 7.34–7.70 (m, 5H, ArH), 4.36 (q, 2H, *J*=7.1 Hz, CH_2), 1.36, (t, 3H, *J*=7.1 Hz, CH_3). Anal. Calcd. for $C_{10}H_{12}N_2O_2S$: C, 53.55; H, 5.39; N, 12.49. Found (%): C, 53.55; H, 5.40; N, 12.54.

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N-(3-Methylphenyl)-N'-ethoxycarbonylthiourea (**3b**)*:* Colourless needles, m.p. 102–103 °C. IR: ν = 3422, 3212, 1714, 1603, 1538, 1474, 1242. ^{1}H NMR: δ_H = 11.43 (s, 1H, NH), 8.30 (s, 1H, NH), 7.05–7.51 (m, 4H, ArH), 4.35 (q, 2H, *J*=7.2 Hz, CH_2), 2.40 (s, 3H, CH_3), 1.36, (t, *J*=7.2 Hz, 3H, CH_3). Anal. Calcd. for $C_{11}H_{14}N_2O_2S$: C, 55.44; H, 5.92; N, 11.76. Found: C, 55.41; H, 5.92; N, 11.78.

N-Acetylphenyl-N'-ethoxycarbonylthiourea (**3c**)*:* Colourless needles, m.p. 177–178°C. IR: ν = 3174, 3061, 1728, 1681, 1618, 1598, 1537, 1249. ^{1}H NMR: δ_H = 11.76 (s, 1H, NH), 8.43 (s, 1H, NH), 7.96 (q, 4H, *J*=8.7 Hz, ArH), 4.35 (q, 2H, *J*=7.0 Hz, CH_2), 2.61 (s, 3H, CH_3), 1.36 (t, 3H, *J*=7.0 Hz, CH_3). Anal. Calcd. for $C_{12}H_{14}N_2O_3S$: C, 54.12; H, 5.30; N, 10.52. Found: C, 54.04; H, 5.57; N, 10.80.

N-(2-Chlorophenyl)-N'-ethoxycarbonylthiourea (**3d**)*:* Colourless needles, m.p. 126–128 °C. IR: ν = 3415, 3166, 1723, 1559, 1539, 1477, 1246. ^{1}H NMR: δ_H = 11.65 (s, 1H, NH), 8.29 (s, 1H, NH), 7.20–8.38 (m, 4H, ArH), 4.38 (q, 2H, *J*=7.1 Hz, CH_2), 1.38 (t, 3H, *J*=7.1 Hz, CH_3). Anal. Calcd. for $C_{10}H_{11}N_2O_2SCl$: C, 46.42; H, 4.29; N, 10.83. Found: C, 46.27; H, 4.30; N, 10.79.

N-(2,4,6-Trichlorophenyl)-N'-ethoxycarbonylthiourea (**3e**). White needles, m.p. 177–178 °C. IR: ν = 3432, 3194, 1728, 1554, 1514, 1242. ^{1}H NMR: δ_H = 10.92 (s, 1H, NH), 8.55 (s, 1H, NH), 7.45 (s, 2H, ArH), 4.369 (q, 2H, *J*=7.2 Hz, CH_2), 1.371 (t, 3H, *J*=7.2 Hz, CH_3). Anal. Calcd. for $C_{10}H_9Cl_3N_2O_2S$: C, 36.66; H, 2.77; N, 8.55. Found: C, 36.66; H, 3.77; N, 8.24.

N-(2,4,6-Tribromophenyl)-N'-ethoxycarbonylthiourea (**3f**). White needles, m.p. 196–198 °C. IR: ν = 3430, 3175, 1724, 1514, 1442, 1247. ^{1}H NMR: δ_H = 10.95 (s, 1H, NH), 8.65 (s, 1H, NH), 7.80 (s, 2H, ArH), 4.37 (q, 2H, *J*=7.2 Hz, CH_2), 1.37 (t, 3H, *J*=7.2 Hz, CH_3). Anal. Calcd. for $C_{10}H_9N_2O_2SBr_3$: C, 26.06; H, 1.97; N, 6.08. Found: C, 26.07; H, 1.96; N, 6.11.

N-(2-Thiazolyl)-N'-ethoxycarbonylthiourea (**3g**): Yellow needles, m.p. 166–167 °C. IR: ν = 3434, 3169, 1725, 1568, 1510, 1244. ^{1}H NMR: δ_H = 9.71 (s, 1H, NH), 8.35 (s, 1H, NH), 7.06–7.58 (m, 2H, ArH), 4.39 (q, 2H, *J*=7.1 Hz CH_2), 1.37 (t, 3H, *J*=7.1 Hz, CH_3). Anal. Calcd. for $C_7H_9N_3O_2S_2$: C,36.35; H, 3.92; N, 18.17. Found: C, 36.55; H, 3.68; N, 18.39.

N-(1-Naphthyl)-N'-ethoxycarbonylthiourea (**3h**): White needles, m.p. 106–108 °C. IR: ν = 3426, 3259, 1720, 1597, 1521, 1478, 1241. ^{1}H NMR: δ_H = 11.65 (s, 1H, NH), 8.50 (s, 1H, NH), 7.45–8.03 (m, 7H, ArH), 4.39 (q, 2H, *J*=7.1 Hz, CH_2), 1.39 (t, 3H, *J*=7.1 Hz, CH_3). Anal. Calcd. for $C_{14}H_{14}N_2O_2S$: C, 61.29; H, 5.14; N, 10.21. Found: C, 61.51; H, 5.20; N, 10.27.

N-(2-Naphthyl)-N'-ethoxycarbonylthiourea (**3i**)*:* White needles, m.p. 159–160 °C. IR: ν = 3416, 3161, 1711, 1599, 1531, 1472, 1247. ^{1}H NMR: δ_H = 11.67 (s, 1H, NH), 8.44 (s, 1H, NH), 7.45–9.27 (m, 7H, ArH), 4.37 (q, 2H, *J*=7.2 Hz, CH_2), 1.37 (t, 3H, *J*=7.2 Hz, CH_3). Anal. Calcd. for $C_{14}H_{14}N_2O_2S$: C, 61.29; H, 5.14; N, 10.21. Found: C, 61.17; H, 5.20; N, 10.30.

N-(4-Methoxyphenyl)-N'-ethoxycarbonylthiourea (**3j**): Colourless needles, m.p. 137–138 °C. IR: ν = 3431, 3132, 1724, 1564, 1538, 1492, 125. ^{1}H NMR: δ_H = 11.29 (s, 1H, NH), 8.26 (s, 1H, NH), 6.99–7.55 (m, 4H, ArH), 4.34 (q, 2H, *J*=7.1 Hz, CH_2), 3.83 (s, 3H, CH_3) 1.36 (t, 3H, *J*=7.1 Hz, CH_3). Anal. Calcd. for $C_{11}H_{14}N_2O_3S$: C, 51.95; H, 5.55; N, 11.02. Found: C, 51.93; H, 5.49; N, 11.06.

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