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Phase Transfer-Catalyzed, One-Pot Synthesis of Some Novel N-Pyrimidinyl-N'-nicotinyl Thiourea Derivatives

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PHASE TRANSFER-CATALYZED, ONE-POT SYNTHESIS OF SOME NOVEL *N*-PYRIMIDINYL-*N'*-NICOTINYL THIOUREA DERIVATIVES

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GRAPHICAL ABSTRACT



Abstract A new series of acyl thiourea derivatives were synthesized in one-pot using PEG-600 as the phase transfer catalyst (PTC). The structures of title compounds were characterized by ${}^{1}H$ NMR, IR, MS, and elemental analysis. In addition, the fungicidal activity of the acyl thiourea derivatives were tested, which showed that most of them exhibit moderate activity.

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Keywords Acyl thiourea; fungicidal activity; one-pot synthesis; phase transfer catalysis

INTRODUCTION

The synthesisand bioactivity study of heterocyclic compounds is an important research area in pesticidal and medicinal chemistry.^{1–5} Nicotinic acid, pyrimidine, and their derivatives are well-known heterocyclic compounds due to their excellent biological activities. Thus, numerous pyridine and pyrimidine derivatives have been used in the synthesis of natural compounds, drugs, and agrochemicals. For example, milirinone⁶ is a phosphodiesterase 3 inhibitor, which is useful in the treatment of heart diseases. Sulfonylurea herbicides⁷ containing a pyrimidine ring have been wildly used in agriculture. Imidacloprid,⁸ developed by Bayer Company, is a neonieotinoid insecticide. In the bioactive compounds

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research area, there is another type of molecules, namely thioureas, which are also extensively used in medicinal chemistry and agrochemistry due to their superior biological activities. As far as their applications in the agrotechnology area are concerned, thiourea and its derivatives, especially acyl-thiourea compounds, exhibit a variety of herbicidal,⁹ fungicidal,¹⁰ and insecticidal activities.¹¹ In view of their superior features, we believe that the rational combination of pyridine/pyrimidine and thiourea should be promising in the development of novel bioactive compounds. In this article, we report the design and synthesis of a new group of thiourea compounds (**3a–j**) incorporated with pyrimidine rings. Their structures were characterized by ¹H NMR, IR, MS, and elemental analysis. The preliminary biological tests showed that these compounds have moderate fungicidal activities.

Regarding the synthesis of the title compounds, phase transfer catalysis (PTC) proved to be an effective tool. In recent years, this method has been widely used in numerous organic syntheses, and has become a powerful and efficient technique that can promote a variety of reactions under mild conditions.^{12–14} Harrison and Hodge¹⁵ reported the successful preparation of benzoyl isothiocyanate by treating benzoyl chloride and polymer-supported thiocyanate in benzene. However, the preparation of such polymer-supported reagents requires long reaction time and vacuum conditions. Later, as shown in Scheme 1, Wei et al.¹⁶ proposed the reaction mechanism of a PEG-catalyzed procedure.

NH₄SCN (S) + PEG (L) (PEG-NH₄)⁺SCN⁻

(PEG-NH ₄) ⁺ SCN ⁻	(L) +	RCOCI (L)		RCONCS(L	-) +	(PEG-NH ₄) ⁺ CI ⁻ (L)
	(PEG	-NH₄)⁺CI⁻(L)		PEG(L) +	NH₄C	I(S)

S: Solid phase; L: Liquid phase

Scheme 1 The proposed mechanism by PEG catalysis.

RESULTS AND DISCUSSION

The preferable reaction temperature for preparing 4-chloropyrimidin-2-amine should be below 90°C, because the higher temperature will lower the yield. When treating 4chloropyrimidin-2-amine with NaOMe in MeOH to synthesize 4-methoxypyrimidin-2amine, a large amount of inorganic salt NaCl was formed, which resulted in a highly viscous suspension. Thus, in order to get a better yield, the reaction mixture was filtered while hot when working up.

In this article, we report the successful synthesis of the title acyl thiourea derivatives using PEG-600 as solid–liquid phase transfer catalyst (Scheme 2). The catalyst PEG-600 is indispensable for these reactions. This procedure is facile and convenient. In addition, PEG-600 is inexpensive, relatively nontoxic, highly stable, and ready available.

In the infrared spectrum (FT-IR) of compound **3**, N–H stretching absorption signal appears at 3436–3125 cm⁻¹, and the characteristic stretching vibration signals of ν (C=O) and ν (C=S) appears at 1700–1720 cm⁻¹ and 1258–1264 cm⁻¹, respectively. In the ¹H NMR spectrum of **3**, the -NH proton signals were observed at δ 8.13~13.98 ppm as a singlet.



Scheme 2 Synthetic route for the title compounds.

EXPERIMENTAL

Nicotinic acid, iso-nicotinic acid, 2-chloro nicotinic acid, and PEG-600 were commercially available. The mono-substituted pyrimidines were synthesized according to the procedure reported in the literature.¹⁷ Melting points were determined using an X-4 apparatus without calibration. Infrared spectra (FT-IR) were recorded on a Bruker Equinox 55 spectrophotometer using potassium bromide tablets. ¹H NMR spectra were measured on a Bruker AC-P500 instrument (300 MHz) using TMS as the internal standard and DMSO- d_6 as solvent. Mass spectra (ESI-MS) were recorded on a Thermo Finnigan LCQ Advantage LC/mass detector instrument. Elemental analyses were performed on a Vario EL elemental analyzer.

General Procedure for the Preparation of Acyl Thiourea

Thionyl chloride (15 mL) was added into nicotinic acid (5 g, 40 mmol), and the mixture was refluxed for 3 h. Next, the excessive thionyl chloride was distilled off under reduced pressure. Then, the resulting residue was re-dissolved in toluene (20 mL) and again concentrated using a rotary evaporator to afford nicotinic acid chloride hydrochloride (6.81 g, 95%) as a solid. Nicotinic acid chloride hydrochloride (6.81g, 38 mmol) was added into a solution of triethylamine (28 mL, 38 mmol) in THF (30 mL) and then stirred at room temperature for 2 h. Afterward, the reaction was quenched with water (50 mL) and extracted with CH_2Cl_2 . The combined organic layer was dried over sodium sulfate, filtered, and concentrated on a rotary evaporator to give the desired acid chloride.

Powdered ammonium thiocyanate (1.14 g, 15 mmol), acid chloride (1.04 g, 10 mmol), PEG-600 (0.18 g, 3% with respect to ammonium thiocyanate), methylene

chloride (25 mL), and pyridine(0.5 mL) were charged into a dry round-bottomed flask equipped with a magnetic stirrer bar and stirred at room temperature for 1 h. Then the solution of substituted 2-amino-pyrimidine (4.5 mmol) in methylene dichloride (10 mL) was added dropwise into the flask over 0.5 h. During this course, the corresponding acyl thiourea precipitated immediately. The reaction was stirred for a further $1\sim2$ h with TLC monitoring. When the reaction was complete, the product was filtered, washed with water to remove inorganic salts, dried, and recrystallized from DMF/EtOH/H₂O. Finally, the acyl thiourea was obtained as a light yellow solid.

N-(Pyrimidin-2-ylcarbamothioyl)nicotinamide 3a

Yellow crystal, yield 42.3%, mp 185–186°C; ¹H NMR (DMSO- d_6) δ : 7.21–9.06 (m, 6H, Py and ph), 12.26 (s, 1H, NH), 13.36(s, 1H, NH); IR/cm⁻¹: 3420 (N–H), 3167 (N–H), 1718 (C=O), 1554, 1452 (Ar), 1263 (C=S); ESI-MS: 258[M-1]⁻; Elemental analysis for C₁₁H₉N₅OS: found C 50.60, H 3.48, N 27.05; calc. C, 50.95; H, 3.50; N, 27.01.

N-(4-Methylpyrimidin-2-ylcarbamothioyl)nicotinamide 3b

Yellow crystal, yield 55.83%, mp 192–194°C; ¹H NMR (DMSO- d_6) δ : 2.43 (s, 3H, CH₃), 7.22–9.15 (m, 6H, Py and ph), 11.88 (s, 1H, NH),13.98 (s, 1H, NH); IR/cm⁻¹: 3417 (N–H), 3125 (N–H), 1703 (C=O), 1550, 1450 (Ar), 1261 (C=S); ESI-MS: 272[M-1]⁻; Elemental analysis for C₁₂H₁₁N₅OS: found C 52.64, H 4.08, N 25.31; calc. C, 52.73; H, 4.06; N, 25.62.

2-Chloro-N-(pyrimidin-2-ylcarbamothioyl)nicotinamide 3c

Yellow crystal, yield 65.87%, mp 190–191°C; ¹H NMR (DMSO- d_6) δ : 7.22–8.98 (m, 6H, Py–H and ArH), 12.34 (s, 1H, NH),13.21 (s, 1H, NH); IR/cm⁻¹: 3425 (N–H), 3157 (N–H), 1720 (C=O), 1548, 1450 (Ar), 1264 (C=S); ESI-MS: 292[M-1]⁻; Elemental analysis for C₁₁H₈ClN₅OS: found C 44.95, H 2.84, N 23.76; calc. C, 44.98; H, 2.75; N, 23.84. The ¹H NMR spectrum of **3c** is shown as Figure S 1 (Supplemental Materials, available online).

2-Chloro-N-(4-methylpyrimidin-2-ylcarbamothioyl)nicotinamide 3d

Yellow crystal, yield 65.44%, mp 195–196°C; ¹H NMR (DMSO- d_6) δ : 2.46 (s, 3H, CH₃), 7.20–8.99 (m, 5H, Py–H and Ar–H), 12.01 (s, 1H, NH), 13.65 (s, 1H, NH); IR/cm⁻¹: 3423 (N–H), 3168 (N–H), 1717 (C=O), 1550, 1452 (Ar), 1265 (C=S); ESI-MS: 306[M-1]⁻; Elemental analysis for C₁₂H₁₀ClN₅OS: found C 46.95, H 3.08, N 22.61; calc. C, 46.83; H, 3.28; N, 22.76.

N-(Pyrimidin-2-ylcarbamothioyl)isonicotinamide 3e

Yellow crystal, yield 54.13%, mp 194–195°C; ¹H NMR (DMSO- d_6) δ : 7.31–8.98 (m, 7H, Py–H and ArH,), 12.15 (s, 1H, NH),13.75 (s, 1H, NH); IR/cm⁻¹: 3423 (N–H), 3166 (N–H), 1714 (C=O), 1550, 1452 (Ar), 1264 (C=S); ESI-MS: 258[M-1]⁻; Elemental analysis for C₁₁H₉N₅OS: found C 51.01, H 3.55, N 27.15; calc. C, 50.95; H, 3.50; N, 27.01.

N-(4-Methylpyrimidin-2-ylcarbamothioyl)isonicotinamide 3f

Yellow crystal, yield 45.66%, mp 202–204°C; ¹H NMR (DMSO- d_6) δ : 2.40 (s, 3H, CH₃), 7.15–8.86 (m, 6H, Py–H and Ar–H), 11.92 (s, 1H, NH), 13.83 (s, 1H, NH); IR/cm⁻¹: 3424 (N–H), 3159 (N–H), 1701 (C=O), 1549, 1450 (Ar), 1260 (C=S); ESI-MS: 272[M-1]⁻; Elemental analysis for C₁₂H₁₁N₅OS: found C 52.84, H 4.18, N 25.55; calc. C, 52.73; H, 4.06; N, 25.62.

N-(4-Methoxylpyrimidin-2-ylcarbamothioyl)nicotinamide 3g

Yellow crystal, yield 55.15%, mp 203–204°C; ¹H NMR (DMSO- d_6) δ : 3.94 (s, 3H, OCH₃), 7.16–7.41 (m, 6H, Py–H), 8.13 (s, 1H, NH), 8.14 (s, 1H, NH); IR/cm⁻¹: 3423 (N–H), 3156 (N–H), 1703 (C=O), 1545, 1451 (Ar), 1261 (C=S); ESI-MS: 288[M-1]⁻; Elemental analysis for C₁₂H₁₁N₅O₂S: found C 49.79, H 3.95, N 24.55; calc. C 49.82; H 3.83; N 24.21.

N-(4-Chloropyrimidin-2-ylcarbamothioyl)nicotinamide 3h

Yellow crystal, yield 54.38%, mp 200–201°C; ¹H NMR (DMSO- d_6) δ : 7.21–7.66 (m, 6H, Py–H and Ar–H), 9.08 (s, 1H, NH), 9.85 (s, 1H, NH); IR/cm⁻¹: 3425 (N–H), 3149 (N–H), 1698 (C=O), 1550, 1450 (Ar), 1261 (C=S); ESI-MS: 292[M-1]⁻; Elemental analysis for C₁₁H₈ClN₅OS: found C 52.84, H 4.18, N 25.55; calc. C 44.98, H 2.75, N 23.84.

N-(4-Methoxylpyrimidin-2-ylcarbamothioyl)isonicotinamide 3i

Yellow crystal, yield 65.21%, mp 199–200°C; ¹H NMR (DMSO- d_6) δ : 7.15–8.86 (m, 5H, Py–H and Ar–H), 8.75 (s, 1H, NH), 10.33 (s, 1H, NH); IR/cm⁻¹: 3434 (N–H), 3159 (N–H), 1700 (C=O), 1545, 1450 (Ar), 1259 (C=S); ESI-MS: 288[M-1]⁻; Elemental analysis for C₁₂H₁₁N₅OS: found C 52.84, H 4.18, N 25.55; calc. C, 52.73; H, 4.06; N, 25.62.

N-(4-Chloropyrimidin-2-ylcarbamothioyl)isonicotinamide 3j

Yellow crystal, yield 49.98%, mp 206–207°C; ¹H NMR (DMSO- d_6) δ : 7.15–8.86 (m, 6H, Py–H and Ar–H), 9.73 (s, 1H, NH), 12.17 (s, 1H, NH); IR/cm⁻¹: 3436 (N–H), 3160 (N–H), 1708 (C=O), 1552, 1450 (Ar), 1258 (C=S); ESI-MS: 292[M-1]⁻; Elemental analysis for C₁₁H₈ClN₅OS: found C 52.84, H 4.18, N 25.55; calc. C 52.77, H 4.33, N 25.45.

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