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Substituted-nicotinyl thiourea derivatives bearing pyrimidine moiety: synthesis and biological evaluation

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Abstract A series of substituted-nicotinyl thiourea derivatives containing pyrimidine ring were synthesized in good to excellent yield using PEG-400 as solid–liquid phase transfer catalyst under ultrasonic irradiation. The structures of all newly synthesized compounds were elucidated and confirmed by IR, ^{1}H NMR and elemental analysis. The preliminary biological tests show that some of the target compounds present good inhibitory activities against the root and stalk of dicotyledon plants and are safe for monocotyledon plants.

Keywords Nicotinyl thiourea · PTC · Synthesis · Bioactivity

Introduction

Nitrogen heterocycles are extremely versatile building blocks for the manufacture of active compounds such as antimicrobial, antibacterial, herbicides, fungicides, and insecticides in the pharmaceutical drug design and agrochemical industries [1–7]. Among these, substituted nicotinic acid and its derivatives such as agricultural and pharmaceutical intermediates are well established [8–11]. Moreover, acylthiourea derivatives are well-known scaffolds for a wide range of biological activities such as antioxidant, bactericidal, herbicidal, insecticidal and regulating activities for plant growth [12–18].

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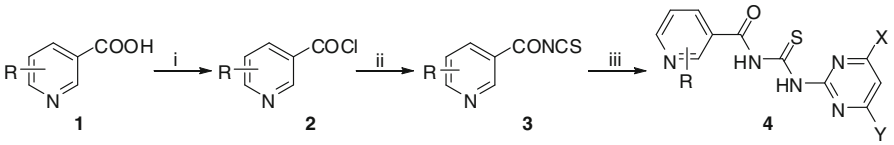

a. R = 2-Cl, X = Y = OMe
b. R = 2-Cl, X = Y = Me
c. R = 2-Cl, X = Y = OEt
d. R = 2-Cl, X = Cl, Y = OMe
e. R = 2-Cl, X = Cl, Y = OEt
f. R = 2-Cl, X = Y = Cl
g. R = 6-Cl, X = Y = OMe
h. R = 6-Cl, X = Y = OEt
i. R = 6-Cl, X = Cl, Y = OMe
j. R = 5,6-Cl_2, X = Y = OMe
k. R = 5,6-Cl_2, X = Y = OEt
l. R = 5,6-Cl_2, X = Cl, Y = OMe

Scheme 1 General synthetic route for substituted-nicotinyl thiourea **4a–l**. Reagents and conditions: *I* $SOCl_2$; *II* KSCN, PEG-400, MeCN, USI; *III* substituted-pyrimidine, MeCN, USI

On the other hand, the phase transfer catalysis reaction technique has been widely recognized as an efficient synthetic tool and has attracted much attention [19–23]. In addition, the ultrasonic wave has been utilized in organic synthesis for its lower reaction temperature and simple operation as compared with conventional heating methods. A survey of the literature shows that many organic reactions have recently been accelerated by ultrasonic irradiation [24–28]. In view of these observations, a series of substituted-nicotinyl thiourea derivatives containing the pyrimidine ring were synthesized (Scheme 1) and tested for their biological activity. In this paper, we have conducted our reactions using PEG-400 as the solid–liquid phase transfer catalyst under ultrasonic irradiation, which is an easy and convenient method for access to nicotinyl-thiourea derivatives. Under ultrasonic irradiation, the intermediate acyl isothiocyanate undergoes a rapid reaction with an added amino pyrimidine to give the corresponding target compounds in good yields. Our ultrasonic irradiation method apparently improves the efficiency of the synthetic process with a good yield and a shorter processing time: this modified method shortened the reaction time from 5–6 to 1–1.5 h and yielded acylthiourea derivatives in greater quantities compared with conventional methods.

Results and discussion

Synthesis for substituted-nicotinylthiourea derivatives 4a–l

The intermediate substituted-nicotinyl chloride **1** obtained by the reaction of substituted-nicotinic acid with thionyl chloride was treated with potassium thiocyanate using PEG-400 as the phase transfer catalyst under ultrasonic irradiation to give substituted-nicotinyl isothiocyanate **2**. It was found that the acyl chloride was quantitatively converted to the corresponding acyl isothiocyanate. This intermediate was then treated with 4,6-disubstituted-2-amino pyrimidine **3** to give the desired substituted-nicotinyl thiourea derivatives **4** in good yields.

We know that the use of ultrasonic irradiation as a method of agitating a heterogeneous reaction system is gaining recognition. In our search to improve methods of preparing acylthiourea by reacting acyl isothiocyanates with nucleophiles, we have found that the ultrasonic vibration of a mixture of acyl chloride, potassium thiocyanate and 3% PEG-400 in acetonitrile can obtain acyl isothiocyanates in good yields. In this

Table 1 Physical constants of compounds **4a–l**

Compound	Molecular formula Formula weight	Appearance	M.P. (°C)	Yield (%)	Analytical data calculated (%) (found)		
					C	H	N
4a	$C_{13}H_{12}ClN_5O_3S$ 353.5	Light yellow powder	260–262	90	44.13 (44.02)	3.39 (3.47)	19.80 (19.92)
4b	$C_{13}H_{12}ClN_5OS$ 321.5	Yellow powder	258–259	84	48.52 (48.61)	3.73 (3.65)	21.77 (21.63)
4c	$C_{15}H_{16}ClN_5O_3S$ 381.5	Light yellow crystal	172–174	86	47.18 (47.26)	4.19 (4.25)	18.35 (18.24)
4d	$C_{12}H_9Cl_2N_5O_2S$ 358	Light yellow powder	265–267	88	40.22 (40.16)	2.51 (2.59)	19.55 (19.63)
4e	$C_{13}H_{11}Cl_2N_5O_2S$ 372	Light yellow powder	205–207	82	41.94 (41.86)	2.96 (2.82)	18.82 (18.91)
4f	$C_{11}H_6Cl_3N_5OS$ 362.5	Yellow powder	>270	78	36.41 (36.35)	1.66 (1.72)	19.31 (19.24)
4g	$C_{13}H_{12}ClN_5O_3S$ 353.5	Light yellow powder	254–256	88	44.13 (44.21)	3.39 (3.42)	19.80 (19.71)
4h	$C_{15}H_{16}ClN_5O_3S$ 381.5	Light yellow powder	176–178	87	47.18 (47.26)	4.19 (4.12)	18.35 (18.46)
4i	$C_{12}H_9Cl_2N_5O_2S$ 358	Yellow powder	>260	82	40.22 (40.28)	2.51 (2.60)	19.55 (19.43)
4j	$C_{13}H_{11}Cl_2N_5O_3S$ 388	Yellow powder	>260	85	40.21 (40.27)	2.84 (2.75)	18.04 (17.96)
4k	$C_{15}H_{15}Cl_2N_5O_3S$ 416	Light yellow powder	173–174	86	43.27 (43.35)	3.61 (3.68)	16.83 (16.75)
4l	$C_{12}H_8Cl_3N_5O_2S$ 392.5	Light yellow powder	>260	80	36.69 (36.58)	2.04 (2.12)	17.83 (17.76)

paper, we have conducted our reaction using PEG-400 as the solid–liquid phase transfer catalyst under ultrasonic irradiation, which is an easy and convenient method for the synthesis of nicotinyl thiourea derivatives, with the advantages of simple operation, short reaction times and high yields over the typical method.

General spectroscopy for substituted-nicotinylthiourea derivatives 4a–l

All the structures of the newly synthesized compounds **4** were assigned on the basis of their elemental analyses (Table 1) and spectroscopic data, IR and ^{1}H NMR (Table 2). The IR (KBr) spectrum displayed absorptions at about 3,280, 1,635 and 1,280 cm^{-1}, which are assigned to N–H, C=O and C=S functions, respectively. The

Table 2 IR and ^{1}H NMR data of compounds **4a–4l**

Compound	IR (ν_{max}/cm^{-1}, KBr)			^{1}H NMR (δ, ppm)					
	N–H	C=O	C=S	Pyridine–H	Py–H	N–H	N′–H	CH_3/OCH_3	CH_2
4a	3,285	1,620	1,285	7.50–8.60 (m, 3H)	6.54 (s, 1H)	11.25 (s, 1H)	11.94 (s, 1H)	3.75 (s, 6H)	–
4b	3,271	1,635	1,290	7.60–8.82 (m, 3H)	6.18 (s, 1H)	11.28 (s, 1H)	12.10 (s, 1H)	2.38 (s, 6H)	–
4c	3,275	1,625	1,288	7.42–8.65 (m, 3H)	6.26 (s, 1H)	11.15 (s, 1H)	11.82 (s, 1H)	1.52 (t, 3H)	4.21 (q, 2H)
4d	3,280	1,642	1,282	7.48–8.75 (m, 3H)	6.35 (s, 1H)	11.20 (s, 1H)	11.90 (s, 1H)	3.84 (s, 3H)	–
4e	3,288	1,632	1,278	7.35–8.58 (m, 3H)	6.48 (s, 1H)	11.24 (s, 1H)	11.86 (s, 1H)	1.58 (t, 3H)	4.34 (q, 2H)
4f	3,290	1,638	1,275	7.50–8.62 (m, 3H)	6.15 (s, 1H)	11.30 (s, 1H)	12.02 (s, 1H)	–	–
4g	3,284	1,640	1,286	7.62–8.85 (m, 3H)	6.08 (s, 1H)	11.26 (s, 1H)	11.82 (s, 1H)	3.87 (s, 6H)	–
4h	3,285	1,637	1,280	7.48–8.70 (m, 3H)	6.05 (s, 1H)	11.20 (s, 1H)	11.95 (s, 1H)	1.46 (t, 3H)	4.15 (q, 2H)
4i	3,282	1,633	1,274	7.65–8.90 (m, 3H)	6.15 (s, 1H)	11.32 (s, 1H)	12.10 (s, 1H)	3.81 (s, 3H)	–
4j	3,292	1,643	1,280	8.28–8.75 (m, 2H)	6.25 (s, 1H)	12.05 (s, 1H)	12.68 (s, 1H)	3.78 (s, 6H)	–
4k	3,286	1,637	1,279	8.40–8.95 (m, 2H)	6.02 (s, 1H)	12.20 (s, 1H)	12.92 (s, 1H)	1.32 (t, 3H)	4.28 (q, 2H)
4l	3,289	1,640	1,282	8.33–8.80 (m, 2H)	6.12 (s, 1H)	12.15 (s, 1H)	12.84 (s, 1H)	3.85 (s, 3H)	–

s singlet, *t* triplet, *q* quadruplet, *m* multiplet, *Py* pyrimidine

Table 3 The inhibition percentage of some target compounds to kinds of plants

Compound	Concentration (μg/mL)	Inhibition (%)	*Digitaria sanguinalis* (L) Scop	*E. crusgallis* L.	*Chenopodium serotinum* L.	*Amaranthus retroflexus* L.
4b	100	Stalk	90	90	100	90
		Root	90	10	100	90
	50	Stalk	80	0	80	85
		Root	90	80	80	90
4f	100	Stalk	20	80	20	90
		Root	20	30	30	100
	50	Stalk	20	50	20	0
		Root	20	30	30	0
4g	100	Stalk	0	10	90	90
		Root	0	0	90	80
	50	Stalk	0	10	90	90
		Root	0	0	90	30
4k	100	Stalk	70	30	100	20
		Root	80	80	100	20
	50	Stalk	60	0	20	20
		Root	70	20	20	20

medium-strong $\nu_{C=O}$ band in the IR spectra of all the compounds appears at about 1,635 cm^{-1}, apparently decreasing in wave-number compared with the ordinary carbonyl absorption (1,710 cm^{-1}), which is due to interaction and hydrogen bonding between the N–H and C=O groups. The ^1H NMR (DMSO-d_6) spectrum exhibited two broad absorption bands in the low-field region that were attributed to the protons of N–H. In addition, the singlet and multiplet signals at about δ 6.00–6.60 and δ 7.20–9.00 were assigned to pyrimidine–CH and pyridine–CH protons, respectively. All the compounds can be dissolved in DMF, DMSO and other nonprotonic solvents, but were insoluble in chloroform and dichloromethane.

Biological activity evaluation

The preliminary biological activities of compounds **4a–l** have been determined by the flat-utensil method according to the standard bioactivity test procedures. Compounds **4b**, **4f**, **4g**, **4k**, etc. showed inhibitory activities against the root and stalk of dicotyledon plants (such as *Chenopodium Serotinum* L.) and monoctyledon plants (such as *Echinochloa crusgallis* L.). The inhibition percentages of some active compounds are shown in Table 3.

Conclusions

In conclusion, we have described a molecular diversity-oriented convenient process for the assembly of substituted-nicotinic core and acylthiourea scaffold that are

potential agrochemical agents. In the above-described experimental conditions, the reaction reached completion with a very simple disposal, good yield and mild reaction conditions compared to the conventional methods. The preliminary biological tests show that some of the target compounds have better inhibitory activities against root and stalk of dicotyledons and are safe for monocotyledon plants.

Experimental

Instrumentation and chemicals

The melting points were determined on an XT4A micro digital melting point apparatus and are uncorrected. The isolated compounds **4** were characterized by elemental microanalyses. The C, H and N analyses were repeated twice. IR spectra were obtained on a Nicolet5DX FT-IR spectrophotometer in the region 4,000–400 cm^{-1} KBr discs. ^1H NMR spectra were recorded on a Varian-300-54 spectrometer with DMSO-d_6 as the solvent. Chemical shift values are reported in ppm (δ) relative to TMS as internal standard. Thin layer chromatography (TLC) analyses were carried out on 5 × 20 cm plates coated with silica gel GF_{254} type 60 (50–250 mesh) using a ethyl acetate–petroleum ether mixture as solvent. Ultrasonic irradiation was performed within a CQ-250S ultrasonic cleaner (35 ± 5% kHz, 250 W, made in Shanghai J and L ultrasonic Ltd., Shanghai, P. R. China). All starting materials are commercial products of chemical or analytic grade purity. Sulfuric chloride was distillated before use and potassium thiocyanate was baked before use. All the substituted-pyrimidine intermediates were prepared by the literature method [29].

General synthetic procedures for the target compounds 4a–l

Substituted-nicotinic acid (0.05 mol), 10 mL of toluene and sulfuric chloride (15 mL) were placed in a dried round-bottomed flask containing a magnetic stirrer bar and stirred at about 50 °C for 2 h. Then the excessive sulfuric chloride was removed under reduced pressure to give a clear solution of substituted-nicotinyl chloride **1**.

To a solution of potassium thiocyanate (0.15 mol) in 10 mL of acetonitrile, the clear solution of substituted-nicotinyl chloride **1** and 3% PEG-400 were added. The flask with the reaction mixture was immersed into the water bath of an ultrasonic cleaner at refluxed temperature for about 0.5 h and then the reaction mixture was filtered off to yield an orange-red solution **2**. Then equimolar quantity of 4,6-disubstituted-2-amino pyrimidine **3** was added and under ultrasonic irradiation for about 15–20 min and the reaction was monitored by TLC. At the end of the reaction, the resulting precipitate was collected by filtration and recrystallized from EtOH to yield compound **4**. All the physico-chemical properties for the target compounds are given in Tables 2 and 3, respectively.

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