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Microwave Assisted Synthesis and Biological Activity of *N*-Aryl-*N*'-nicotinoyl Thiourea

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A series of *N*-aryl-*N*'-nicotinoyl thiourea derivatives were synthesized using microwave irradiation. The synthesized compounds were characterized by ^{1}H NMR, IR, MS and elemental analysis. Fungicidal activity of the compounds were evaluated through *G. zeae* Petch, *B. cinerea* Pers, *Phytophthora infestans* (Mont.) de Bary, *Botryosphaeria berengeriana* f. sp. *piricola* (Nose) koganezawa et Sakuma, *Fusarium oxysporum* f. sp. *cucumerinum* and *Cercospora arachidicola*. tests, their activity are moderate.

Key Words: Microwave irradiation, Acyl thiourea, Nicotinic acid, Fungicidal activity.

INTRODUCTION

Research on the synthesis and biological activity of heterocyclic compounds is an important developmental oriental in pesticide and medicine chemistry[1]. It is well known that nicotinic acid and their derivatives exhibit excellent biological activity. Novel pyridine and related derivatives[2] are attractive molecules because their structure is present in several natural compounds, drugs or argochemicals. Additionally, various types of acyl-thiourea derivatives had comprehensive bioactivities, due to they held amide group[3] and thioamide group.

Microwave technique, meanwhile, has been widely used for a variety of organic reactions, such as Claisen, heterocyclic synthesis, oxidation, hydrolysis, esterification, etherification and so on. Many reports[4] have been published in favour of its considerable accelerations of the reaction rates and satisfactory yields.

In order to search for new compounds with good biological activity, ten thiourea derivatives (**3a-j**) were synthesized under microwave irradiation. Their structures are confirmed by ^{1}H NMR, IR, MS and elemental analysis. The preliminary biological tests show that these compounds had moderate fungicidal activity.

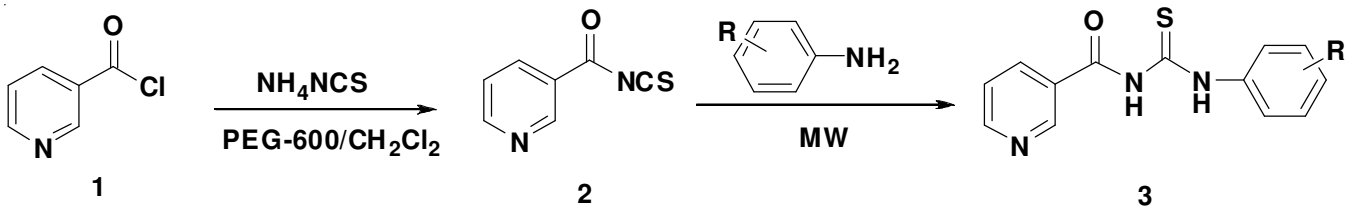
EXPERIMENTAL

Nicotinic acid, substituted aniline were commercially available. Melting points were determined using a X-4 melting apparatus and were uncorrected. Infrared spectra were recorded on a Bruker Equinox55 spectrophotometer as potassium bromide tablets. ^{1}H NMR spectra were measured on a Bruker AC-P500 instrument (300 MHz) using tetramethyl-silane as an internal standard and deuterochloroform as solvent. Mass spectra were recorded on a Thermo Finnigan LCQ Advantage LC/mass detector instrument. Elemental analyses were performed on a Yanaco MT-3CHN elemental analyzer.

Preparation of *N*-aryl-*N*'-nicotinoyl thiourea: Nicotinic acid (5 g, 40 mmol) was added thionyl chloride 10 mL and the mixture was refluxed for 3 h to give 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 were placed in a dried round-bottomed flask containing a magnetic stirrer bar and stirred at room temperature for 1 h. Then substituted substituted aniline (4.5 mmol) in methylene dichloride (10 mL) was added drop wise over 0.5 h and the mixture was stirred for 15 min under microwave irradiation. The corresponding thiourea precipitated immediately. The product was filtered and recrystallized from DMF-EtOH-H_2O, afforded a light yellow solid (**Scheme-I**).

N-2,4,5-trichlorophenyl-N'-nicotinoyl thiourea (3a): The compound was obtained in 67.1 % yield as a yellow crystal; m.p. 199-200 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 12.44 (s, NH, 1H), 11.90 (s, NH, 1H), 7.09-8.26 (m, ArH and Py, 6H). IR (KBr, ν_{max}, cm^{-1}): 3321, 3104 (NH), 1670 (C=O), 1151 (C=S). MS (ESI), *m/z*: 359 (M -1). Elemental anal. (%), calculated: C, 43.29; H, 2.24; N, 11.65; found: C, 43.50; H, 2.41; N, 11.51.

***N*-2,5-dichlorophenyl-*N*'-nicotinoyl thiourea (3b):** The compound was obtained in 67.1 % yield as a yellow crystal;



Scheme-I: Synthesis route for the title compounds

m.p. 206-207 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 11.98 (s, NH, 1H), 11.78 (s, NH, 1H), 7.23-8.14 (m, ArH and Py, 7H). IR (KBr, ν_{max}, cm^{-1}): 3301, 3112 (NH), 1668 (C=O), 1157 (C=S). MS (ESI), *m/z* : 325 (M-1). Elemental anal. (%), calculated: C, 47.87; H, 2.78; N, 12.88; found: C, 47.99; H, 2.44; N, 12.85.

N-3-methylphenyl-*N'*-nicotinoyl thiourea (3c): The compound was obtained in 67.1 % yield as a yellow crystal; m.p. 106-107 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 11.98 (s, NH, 1H), 11.81 (s, NH, 1H), 7.12-8.66 (m, ArH and Py, 8H), 2.55 (s, CH_3, 3H). IR (KBr, ν_{max}, cm^{-1}): 3221, 3089 (NH), 1672 (C=O), 1151 (C=S). MS (ESI), *m/z*: 270 (M-1). Elemental anal. (%), calculated: C, 61.97; H, 4.83; N, 15.49; found: C, 61.89; H, 4.65; N, 15.45.

N-3-chlorophenyl-*N'*-nicotinoyl thiourea (3d): The compound was obtained in 67.1 % yield as a yellow crystal; m.p. 153-154 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 12.32 (s, NH, 1H), 11.78 (s, NH, 1H), 7.33-8.34 (m, ArH and Py, 8H). IR (KBr, ν_{max}, cm^{-1}): 3345, 3132 (NH), 1665 (C=O), 1147 (C=S). MS (ESI), *m/z*: 291 (M -1). Elemental anal. (%), calculated: C, 53.52; H, 3.45; N, 14.40; found: C, 53.88; H, 3.47; N, 14.56.

***N*-2-chlorophenyl-*N'*-nicotinoyl thiourea (3e):** The compound was obtained in 67.1 % yield as a yellow crystal; m.p. 210-211 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 12.12 (s, NH, 1H), 11.98 (s, NH, 1H), 7.21-8.25 (m, ArH and Py, 8H). IR (KBr, ν_{max}, cm^{-1}): 3341, 3189 (NH), 1669 (C=O), 1158 (C=S). MS (ESI), *m/z*: 291 (M-1). Elemental anal. (%), calculated: C, 53.52; H, 3.45; N, 14.40; found: C, 53.77; H, 3.33; N, 14.51.

***N*-3-trifluoromethylphenyl-*N'*-nicotinoyl thiourea (3f) :** The compound was obtained in 67.1% yield as a yellow crystal; m.p. > 250 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 11.95 (s, NH, 1H), 11.67 (s, NH, 1H), 7.14-8.33 (m, ArH and Py, 8H). IR (KBr, ν_{max}, cm^{-1}): 3245, 3111 (NH), 1665 (C=O), 1144 (C=S). MS (ESI), *m/z* : 324 (M-1). Elemental anal. (%), calculated: C, 51.69; H, 3.10; N, 12.92; found: C, 51.80; H, 3.48; N, 12.64.

N-2-iodophenyl-N'-nicotinoyl thiourea (3g): The compound was obtained in 67.1 % yield as a yellow crystal; m.p. 238-240 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 12.11 (s, NH, 1H), 11.99 (s, NH, 1H), 7.05-8.23 (m, ArH and Py, 8H). IR (KBr, ν_{max}, cm^{-1}): 3334, 3144 (NH), 1668 (C=O), 1161 (C=S). MS (ESI), *m/z*: 382 (M-1). Elemental anal. (%), calculated: C, 40.75; H, 2.63; N, 10.97; found: C, 40.45; H, 2.41; N, 10.57.

***N*-4-trifluoromethylphenyl-*N'*-nicotinoyl thiourea (3h):** The compound was obtained in 67.1 % yield as a yellow crystal; m.p. 121-123 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 12.05 (s, NH, 1H), 11.99 (s, NH, 1H), 7.16-8.39 (m, ArH and Py, 8H). IR (KBr, ν_{max}, cm^{-1}): 3318, 3096 (NH), 1650 (C=O), 1145 (C=S). MS (ESI), *m/z*: 324 (M-1). Elemental anal. (%), calculated: C, 51.69; H, 3.10; N, 12.92; found: C, 51.45; H, 3.09; N, 13.05.

***N*-4-chlorophenyl-*N'*-nicotinoyl thiourea (3i):** The compound was obtained in 67.1 % yield as a yellow crystal; m.p. 232-234 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 12.12 (s, NH, 1H), 11.88(s, NH, 1H), 7.22-8.25 (m, ArH and Py, 8H). IR (KBr, ν_{max}, cm^{-1}): 3352, 3156 (NH), 1669 (C=O), 1154 (C=S). MS (ESI), *m/z*: 291 (M-1). Elemental anal. (%), calculated: C, 53.52; H, 3.45; N, 14.40; found: C, 53.48; H, 3.65; N, 14.12.

***N*-2-trifluoromethylphenyl-*N'*-nicotinoyl thiourea (3j):** The compound was obtained in 67.1 % yield as a yellow crystal; m.p. 203-204 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 12.15 (s, NH, 1H), 12.03 (s, NH, 1H), 7.19-8.26 (m, ArH and Py, 8H). IR (KBr, ν_{max}, cm^{-1}): 3291, 3144 (NH), 1670 (C=O), 1155 (C=S). MS (ESI), *m/z*: 324 (M-1). Elemental anal. (%), calculated: C, 51.69; H, 3.10; N, 12.92; found: C, 51.45; H, 3.43; N, 13.21.

Bioassay of fungicidal activities: The method for testing the primary biological activities was performed in an isolated culture. Under a sterile condition, 1 mL of sample was added to the culture plates, followed by the addition of 9 mL of culture medium. The final mass concentration was 50 μg/mL. The blank assay was performed with 1 mL of sterile water. Circle mycelium with a diameter of 4 mm was cut using a drill. The culture plates were cultivated at (24 ±1) ºC. The extended diameters of the circle mycelium were measured after 72 h. The relative inhibition rate of the circle mycelium compared to blank assay was calculated via the following equation:

$$\text{Relative inhibition rate (\%)} = \frac{d_{ex} - d_{ex}'}{d_{ex}} \times 100\%$$

where d_{ex} is the extended diameter of the circle mycelium during the blank assay; and d'_{ex}, is the extended diameter of the circle mycelium during testing.

RESULTS AND DISCUSSION

Biological activities: Fungicidal activities of compounds **3a, 3c, 3e, 4a, 4c, 4e** against G. zeae Petch, *Phytophthora infestans* (Mont.) de Bary, *Botryosphaeria berengeriana* f. sp. piricola (Nose*) koganezawa et Sakuma*, *Fusarium oxysporum* f.sp. cucumerinum and *Cercospora arachidicola*. The fungicidal activities of the title compounds were determined. The results were shown in Table-1. It was also found that some of these compounds displayed moderate fungicidal activity.

TABLE-1
FUNGICIDAL ACTIVITY OF TESTED COMPOUNDS AT 50 ppm

No	*G. zeae* Petch	*Phytophthora infestans* (Mont.) de Bary	*Botryosphaeria berengeriana* f. sp. *piricola* (Nose) koganezawa et Sakuma	*Fusarium oxysporum* f.sp. *cucumerinum*	*Cercospora arachidicola*
3a	10	23	57	26	0
3b	25	34	45	32	65
3c	5	40	21	45	45
3d	28	0	49	38	0
3e	51	21	8	62	15
3f	0	35	41	55	8
3g	42	34	51	24	24
3h	15	18	28	25	33
3i	48	36	27	25	34
3j	34	35	36	48	15

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