Asian Journal of Chemistry Vol. 22, No. 2 (2010), 1503-1506

Synthesis and Fungicidal Activities of 1-(5-Methylisoxazoyl-4-carbonyl)-4-arylsulfonyl Thiosemicarbazides

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1-(5-Methylisoxazoyl-4-carbonyl)-4-arylsulfonyl thiosemicarbazides, which were prepared by treatment of arylsulfonyl hydrazine with 5-methyl-isoxazole-4-carbonyl isothiocyanate in good yields. The structures of all compounds were confirmed by ^{1}H NMR, MS and elemental analyses. The preliminary bioassays indicated that some compounds are comparable to the commercial fungicides. Some of these compounds also exhibit moderate fungicidal activities.

Key Words: Thiosemicarbazide, Synthesis, Fungicidal activities.

INTRODUCTION

The studies of the synthesis of heterocyclic compounds is an important developmental oriental in pesticide and medicine chemistry[1-4]. 5-Methylisoxazole-4-carboxylic acid is the mediate of Leflunomide which is a drug used for the treatment of rheumatoid arthritis, an illness that affects soft tissues and bones and can cause irreversible joint deformities and functional impairment[5]. Meanwhile, thiourea compounds exhibit excellent biological activities, such as herbicidal activity[6], insecticidal activity[7], fungicidal activity[8], *etc*.

Phase transfer catalysis (PTC) is a useful technique accomplishing a variety of reactions under mild conditions and efficient way. This technique has been widely used as an efficient synthetic tool and attracted much attention[9,10].

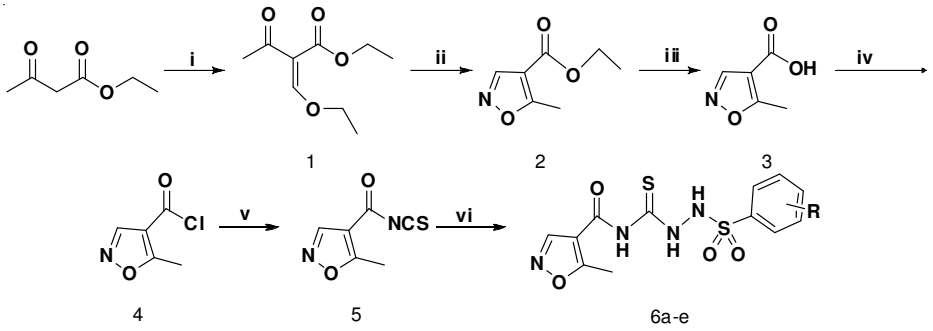
As part of our program aimed at developing potential bioactive compounds, the title compounds *i.e.*, 1-(5-methylisoxazoyl-4-carbonyl)-4-arylsulfonyl thiosemicarbazides were designed and synthesized under phase transfer catalysis condition. Their fungicidal activities were also evaluated.

EXPERIMENTAL

Melting points were determined using a X-4 apparatus and are uncorrected. ^{1}H NMR spectra were measured on a Varian Mercury VX 400 MHz instrument using TMS as an internal standard and DMSO-d_6 as solvent. Elemental analyses were performed on a Yanaco MT-3 CHN elemental analyzer.

All starting materials are commercial products of chemical or analytic grade purity. Ammonium thiocyanate was baked before use. Analytical TLC was performed on silica gel GF_{254}.

Synthesis: The route shown in **Scheme-I** was used for synthesizing 1-(5-methyl-isoxazoyl-4-carbonyl)-4-arylsulfonyl thiosemicarbazides.



i. $CH_3O(CH_2CH_3)_3$; ii. NH_2OH HCl; ii. HCl ; iv. $SOCl_2$, reflux; v. NH_4NCS, PEG-600, CH_2Cl_2; vi. NH_2NHSO_2Ar, r.t.

Scheme-I: Synthetic route of title compounds

Aryl acylhydrazine and 5-methyl-isoxazolecarboxylic acid: All the substituted benzenesulfonohydrazide and 5-methyl-isoxazolecarboxylic acid were prepared according to reference[5,11] . The physical data are according with the reference.

1-(5-Methylisoxazoyl-4-carbonyl)-4-arylthiosemicarbazides: Powdered ammonium thiocyanate (1.14 g, 15 mmol), 5-methylisoxazole-4-carbonyl chloride (1.41 g, 10 mmol), PEG-600 (0.18 g, 3 % with respect to ammonium thiocyanate) and methylene dichloride (25 mL) were placed in a dried round-bottomed flask containing a magnetic stirrer bar and stirred at room temperature for 1.5 h. Then substituted benzenesulfonohydrazide (4.5 mmol) in methylene dichloride (10 mL) were added dropwise over 0.5 h and the mixture was stirred for 5 h. The corresponding products precipitated immediately. The product was filtered, washed with water to remove inorganic salts, dried. Title compounds were recrystallized from DMF-EtOH-H_2O, dried on the infrared lamp.

N-(2-(Phenylsulfonyl)hydrazinecarbonothioyl)-5-methyl-isoxazole-4-carboxamide (6a): Light yellow crystal, yield 88.6 %, m.p. 183-184 ºC; ^{1}H NMR (DMSO-d_6) δ: 2.64 (s, 3H, Me), 7.18-7.89 (m, 5H, Ar), 8.88 (s, 1H, H-isoxazole), 10.32 (s, 1H, NH), 11.23 (s, 1H, NH), 11.78 (s, 1H, NH); ESI-MS: 339; Elemental analysis for $C_{12}H_{12}N_4O_4S_2$: found (%) C 43.73, H 3.48, N 16.67; calcd. (%) C, 42.34; H, 3.55; N, 16.46.

N-(2-Tosylhydrazinecarbonothioyl)-5-methyl-isoxazole-4-carboxamide (6b): Light yellow crystal, yield 87.4 %, m.p. 182-183 ºC; ^{1}H NMR (DMSO-d_6) δ: 2.64 (s, 3H, Me), 2.66 (s, 3H, Me), 7.86 (d, J = 8.01 Hz, 2H, Ar), 7.89 (d, J = 8.01 Hz, 2H, Ar), 8.96 (s, 1H, H-isoxazole), 10.16 (s, 1H, NH), 10.68 (s, 1H, NH), 11.98 (s, 1H, NH); ESI-MS: 353; Elemental analysis for $C_{13}H_{14}N_4O_4S_2$: found (%) C 43.89, H 3.68, N 15.98; calcd. (%) C, 44.06; H, 3.98; N, 15.81.

N-(2-(4-Chlorophenylsulfonyl)hydrazinecarbonothioyl)-5-methylisoxazole-4-carboxamide (6c): Light yellow crystal, yield 84.3 %, m.p. 227-229 ºC; ^{1}H NMR (DMSO-d_6) δ: 2.48 (s, 3H, Me), 7.20-7.67 (m, 4H, Ar), 9.23 (s, 1H, H-isoxazole), 10.29 (s, 1H, NH), 11.46 (s, 1H, NH), 12.11 (s, 1H, NH); ESI-MS: 373; Elemental analysis for $C_{12}H_{11}ClN_4O_4S_2$: found (%) C 38.55, H 2.89, N 15.23; calcd. (%) C, 38.45; H, 2.96; N, 14.95.

N-(2-(4-Bromophenylsulfonyl)hydrazinecarbonothioyl)-5-methylisoxazole-4-carboxamide (6d): Light yellow crystal, yield 83.5 %, m.p. 162-163 ºC; ^{1}H NMR (DMSO-d_6) δ: 2.64 (s, 3H, Me), 7.76 (d, J = 8.62 Hz, 2H, Ar), 7.78 (d, J = 8.62 Hz, 2H, Ar), 9.14 (s, 1H, H-isoxazole), 10.56 (s, 1H, NH), 11.57 (s, 1H, NH), 11.96 (s, 1H, NH); ESI-MS: 418; Elemental analysis for $C_{12}H_{11}BrN_4O_4S_2$: found (%) C 34.77, H 2.34, N 13.65; calcd. (%) C, 34.38; H, 2.64; N, 13.36.

N-(2-(2-Nitrophenylsulfonyl)hydrazinecarbonothioyl)-5-methyl-isoxazole-4-carboxamide (6e): Light yellow crystal, yield 86.3 %, m.p. 172-173 ºC; ^{1}H NMR (DMSO-d_6) δ: 2.66 (s, 3H, Me), 7.86-8.10 (m, 4H, Ar), 9.16 (s, 1H, H-isoxazole), 10.87 (s, 1H, NH), 11.67 (s, 1H, NH), 12.07 (s, 1H, NH); ESI-MS: 384; Elemental analysis for $C_{12}H_{11}N_5O_6S_2$: found (%) C 37.60, H 2.48, N 18.05; calcd. (%) C, 37.40; H, 2.88; N, 18.17.

Bioassay of fungicidal activities: Fungicidal activities of all the thiosemicarbazides compounds against *Corynespora cassiicola, Pseudomonas syringae* pv. *Lachrymans*, *Ascochyta citrullina Smith, Pseudoperonospora cubensis* and *Sclerotinia sclerotiorum* were evaluated according to reference[11]. The culture plates were cultivated at 24 ± 1 ºC. 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

The synthesis of the starting isoxazole derivative was attempted as shown in **Scheme-I**. The acid was obtained according the reference. Substituted benzene sulfonohydrazides were synthesized according the reference. In this process, the reaction must under ice-water condition.

We have conducted our reaction using PEG-600 as solid-liquid phase transfer catalyst, this is a facile and convenient method for the synthesis of title compounds (**Scheme-I**), PEG-600 as a phase transfer catalyst is indispensable for these reactions. It can easily react with NH_4SCN to form complex [PEG-600-NH_4^+]SCN^-, which makes it possible for SCN^- to readily react with 5-methylisoxazoyl chloride. In addition, the ultrasonic irradiation method distinctly improves the efficiency of the synthetic process and shorten there action time. The catalyst PEG-600 is inexpensive, relatively nontoxic, highly stable and easily available[5,10].

Biological activities: The fungicidal activities of title compounds were listed in Table-1. As shown in Table-1, the title compounds exhibited good fungicidal activities against *Corynespora cassiicola* and *Seudomonas syringae* pv. *Lachrymans*. For example, Compounds **6a** have fair to good fungicidal activity with the commercial fungicide dimethomorph against *Corynespora cassiicola*. The compounds display moderate activity against *Pseudomonas syringae* pv. *Lachrymans* and *Pseudoperonospora cubensis*. Title compounds did not display obvious fungicidal activities against *Ascochyta citrullina* Smith and *Sclerotinia sclerotiorum*.

TABLE-1
FUNGICIDAL ACTIVITIES OF TITLE COMPOUNDS AT 500 ppm

Compd. No.	R	A	B	C	D	E
6a	C_6H_5	92.77	58.22	48.17	53.13	-10.26
6b	*p*-$CH_3C_6H_4$	43.41	49.01	29.70	41.11	6.56
6c	*p*-ClC_6H_4	65.11	34.34	4.88	56.81	-9.54
6d	*p*-BrC_6H_5	13.57	3.53	24.69	42.99	13.15
6e	*o*-$NO_2C_6H_4$	50.22	49.08	42.10	66.03	47.44
	Dimethomorph	95.31	13.98	98.35	83.75	98.35

A = *Corynespora cassiicola*; B = *Pseudomonas syringae* pv. *Lachrymans*; C = *Ascochyta citrullina* Smith; D = *Pseudoperonospora cubensis*; E = *Sclerotinia sclerotiorum*

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(*Received*: 14 June 2009; *Accepted*: 31 October 2009) AJC-8008