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Synthesis of 5,7-Dimethyl-2-(5-Substituted-1,3,4-Oxadiazole-2-yl)-Methylenethio-1,2,4-Triazolo[1,5-a]Pyrimidines as Potential Fungicides

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Abstract: A series of diheterocyclic compounds containing 1,2,4-triazolo [1,5-a]pyrimidine and 1, 3,4-oxadiazole were designed and synthesized starting from 2-mercapto-5,7-dimethyl-1,2,4-triazolo [1,5-a] pyrimidine. The structure of all compounds prepared were confirmed by ^{1}H NMR spectroscopy and elemental analysis. The preliminary bioassay indicated that the title compounds displayed good fungicidal activity against *Rhizoctonia solani.*

Keywords: 1,2,4-Triazolo[1,5-a]pyrimidine, 1,3,4-oxadiazole, diheterocyclic compounds, synthesis, fungicides.

New challenging problems in plant protection technology have promoted research to discover more efficient pesticides. In recent years, many chemists have paid much attention to compounds bearing 1,2,4-triazolo [1,5-a] pyrimidine rings due to their broad spectrum of biological activities such as herbicidal and fungicidal effects[1-7]. Up to now, a great variety of these kinds of compounds have been synthesized, among which some commercially herbicides have been developed including metosulam, flumetsulam and TP4189. Moreover, 1,3,4-oxadiazole derivatives have been reported to possess antibacterial, anti-inflammatory and insecticidal properties[8-12]. The synthesis of heterocyclic compounds containing multi-structure in a molecule received much attention in recent years. The linked diheterocyclic compounds may enhance biological activity and enlarge the bioactive spectrum. In view of the above mentioned reason and as a proceeding of our research for new and better biologically active agents, we wish to describe herein the synthesis of a series of novel 1,2,4-triazolo [1,5-a] pyrimidine derivatives containing 1,3,4-oxadiazole nucleus as **4** and **6**, which were considered as interesting leading compounds for exploring potential pesticides.

The synthetic pathway for compounds **4a-c** and **6a-g** is outlined in **Scheme 1**. The structure of all compounds prepared were confirmed by ^{1}H NMR spectroscopy and elemental analysis. Preliminary fungicidal bioassay against four fungi, *Rhizoctonia solani, Fusarium oxysporum, Gibberella zeave* and *Phoma sparag*i was carried out. The results indicated that the title compounds were not active against *F oxysporum, G zeave* and *P sparag*i at the concentration of 100 ppm. But all products displayed good fungicidal activity against *R solani*. The further *in vivo* bioassay indicated that the

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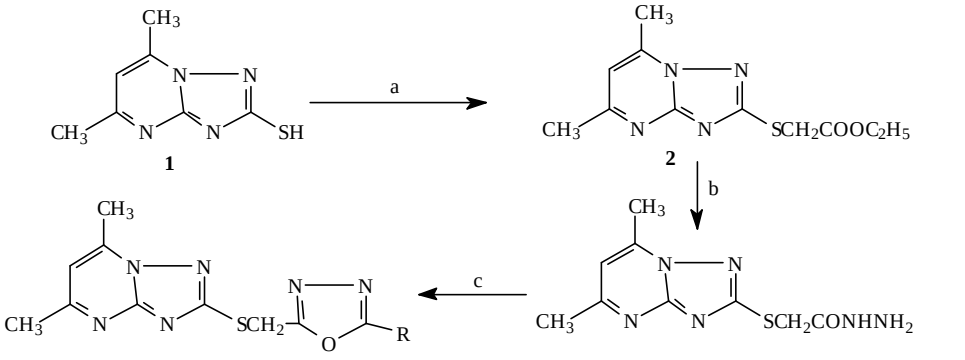
compound **6g** (R=4-$NO_2C_6H_4CH_2$) possesses better fungicidal activity against *R solani* (inhibition rate, 83.2%) at the concentration of 200 ppm than validamycin A (inhibition rate, 73.9%), which is well known for their good fungicidal activity against *R solani*. Although the 1,2,4-triazolo [1,5-a] pyrimidine derivatives have been reported to possess various biological activities, as far as we know there is no report on their fungicidal activity against *R solani*. Further studies on the structure activity relationships and structural modifications of these compounds are underway.

Scheme 1



1 **2** **3** **5** **6**

4a R = C_6H_5, **4b** R = 2-ClC_6H_4, **4c** R = 2-$CH_3C_6H_4$

6a R = CH_3, **6b** R = C_2H_5, **6c** R = $CH_2COOC_2H_5$
6d R = ClC_3H_6, **6e** R = $C_6H_5CH_2$, **6f** R = 4-$ClC_6H_4CH_2$
6g R = 4-$NO_2C_6H_4CH_2$

Reagents and conditions: a, $BrCH_2COOCH_2CH_3$, NaOH, H_2O, r.t.; b, $NH_2NH_2.H_2O$, EtOH, reflux; c, RCOOH, $POCl_3$, reflux; d, CS_2, KOH, EtOH, reflux; e, RX, NaOH, H_2O or DMF, r.t..

Experimental

Preparation of 2-ethoxycarboxylmethylenethio-5,7-dimethyl-1,2,4-triazolo [1,5-a] pyrimidine **2**

To a stirred mixture of 18 g (0.1 mol) of 2-mercapto-5,7-dimethyl-1,2,4-triazolo [1,5-a] -pyrimidine **1**,4 g (0.1 mol) of sodium hydroxide and 250 mL of water, a solution of 16.7 g (0.1 mol) ethyl bromoacetate in 50 mL of methanol was added dropwise at room temperature. The resulted mixture was stirred for 2 hours and filtered. The solid was recrystallized from methanol to afford 24 g of **2** as white needle crystal. Yield: 94%, mp 142-143°C. ^{1}H NMR ($CDCl_3$, δ ppm): 1.24 (t, 3H, J=7.10, CH_3), 2.57 (s, 3H,

5-CH_3), 2.67 (s, 3H, 7-CH_3), 4.07 (s, 2H, SCH_2), 4.16-4.19 (q, 2H, J=7.10, CH_2), 6.69 (s, 1H, 6-H). MS (*m/z*): 266 (M^+, 35), 221 (21), 220 (21), 194 (28), 193 (100), 180 (16), 149 (24), 148 (7), 108 (80), 107 (33), 67 (25). Anal. Calcd for $C_{11}H_{14}N_4O_2S$ (266.31): C, 49.49; H, 5.41; N, 21.27. Found: C, 49.62; H, 5.26; N, 21.05.

Ppreparation of intermediate **3**

A mixture of 13.3 g (0.05 mol) of intermediate **2** and 0.35 mol of hydrazine monohydrate in 200 mL of anhydrous ethanol were refluxed for 4 hours. After cooling to room temperature, the precipitate was filtered and washed with anhydrous ethanol twice. The solid was recrystallized from methanol to afford 11.7 g of white crystal. Yield: 93.2%. mp 202-203°C. ^{1}H NMR ($CDCl_3$, δ ppm): 2.55 (s, 3H, 5-CH_3), 2.65 (s, 3H, 7-CH_3), 3.95 (s, 2H, SCH_2), 4.35 (bs, 2H, NH_2), 7.10 (s, 1H, 6-H), 9.40 (s, 1H, NH). Anal. Calcd for $C_9H_{12}N_6OS$ (252.29): C, 42.86; H, 4.76; N, 33.33. Found: C, 42.63; H, 4.84; N, 33.46.

Procedure for the preparation of compounds **4a**

A mixture of 1 mmol of compound **3**, 1 mmol of benzoic acid and 5 mL of $POCl_3$ was refluxed for 6 hours. After cooled to room temperture, the mixture was poured into crushed ice and filtered. The solid was washed with sodium hydroxide solution (5%) and water for three times and recrystallized from EtOH to afford **4a** in yield of 65.6%, mp 171-173°C, ^{1}H NMR ($CDCl_3$, δ ppm): 2.64 (s, 3H, 5-CH_3), 2.73 (s, 3H, 7-CH_3), 4.82 (s, 2H, SCH_2), 6.76 (s, 1H, 6-H), 7.47-8.01 (m, 5H, Ar-H). Anal. Calcd for $C_{16}H_{14}N_6OS$: C, 56.80; H, 4.14; N, 24.85. Found: C, 57.13; H, 3.87; N, 24.69. **4b** and **4c** were synthesized in the same way as **4a**[13].

Preparation of intermediate **5**

To a solution of 1.34 g (0.024 mol) of potassium hydroxide and 160 mL of anhydrous ethanol, 5.04 g (0.02 mol) of **3** was added. To the vigorously stirred mixture, a solution of 2 g of carbon disulfide in 40 mL of anhydrous ethanol was added dropwise and then the reaction mixture was refluxed for 6 hours. The solvent was removed under reduced pressure, and the residue was dissolved in 100 mL of water. Then it was acidified to PH=5~6 with glacial acetic acid and filtered off to give the crude product, which was recrystallized from ethanol/petroleum ether to afford 5.51 g of pure **5** as white crystal. Yield: 93.7%. mp 203-204°C. ^{1}H NMR ($CDCl_3$, δ ppm): 2.50 (s, 1H, SH), 2.55 (s, 3H, 5-CH_3), 2.65 (s, 3H, 7-CH_3), 4.65 (s, 2H, SCH_2), 7.15 (s, 1H, 6-H). Anal. Calcd for $C_{10}H_{10}N_6OS_2$ (294.34): C, 40.82; H, 3.40; N, 28.57. Found: C, 40.67; H, 3.51; N, 28.68.

Preparation of compounds **6g**

To a stirred solution of 1.5 g (5.1 mmol) of **5** and 0.23 g (5.6 mmol) of sodium hydroxide

in 15 mL of water, a mixture of 5.6 mmol of *p*-nitrobenzyl chloride and 5 mL of methanol was added dropwise. The resulted mixture was stirred at room temperature for 2.5 hours. The precipitate was filtered and recrystallized from petroleum ether/acetone to give **6g** in yield of 56.3%, mp 132-133°C, ^{1}H NMR ($CDCl_3$, δ ppm): 2.58 (s, 3H, 5-CH_3), 2.65 (s, 3H, 7-CH_3), 4.41 (s, 2H, $CH_2C_6H_4$), 4.64 (s, 2H, SCH_2), 6.72 (s, 1H, 6-H), 7.51-8.08 (q, 4H, Ar-H). MS (*m/z*): 429 (M^+, 1), 293 (4), 262 (15), 261 (100), 221 (3), 219 (7), 193 (11), 180 (6), 149 (5), 148 (2), 136 (4), 108 (23), 107 (14). Anal. Calcd for $C_{17}H_{15}N_7O_3S_2$: C, 47.55; H, 3.50; N, 22.84. Found: C, 48.34; H, 3.96; N, 22.97. **6a-6f** were synthesized with the same method as **6g**[13].

Acknowledgments

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