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Studies on Condensed Heterocyclic Compounds XVI. Synthesis of 3-Alkyl-6-(2,4-Dichlorophenoxymethyl)-s-Triazolo[3,4-b]-1,3,4-Thiadiazoles and 6,6′-Bis(3-Aryl-s-Triazolo[3,4-b]-1,3,4-Thiadiazoles)

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Several 3-alkyl-6-(2,4-dichlorophenoxymethyl)-s-triazolo[3,4-b]-1,3,4-thiadiazoles **3a-3e** and 6,6′-bis(3-aryl-s-triazolo[3,4-b]-1,3,4-thiadiazoles) **3f-3j** were synthesized. The structures of all the compounds synthesized were elucidated by elemental analyses and spectral data. The representative compounds **3a** and **3b** exhibited moderate biological activities.

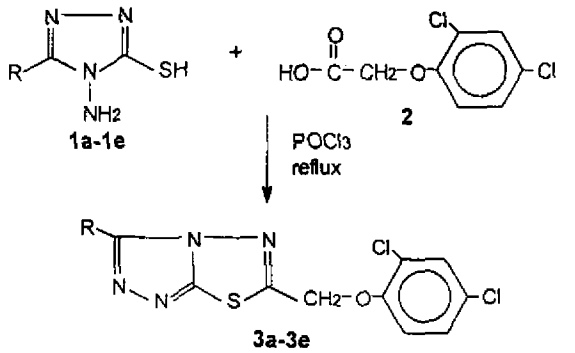
INTRODUCTION

Various 1,2,4-triazoles and 1,3,4-thiadiazoles have been reported to possess diverse biological activities such as antimicrobial, insecticidal, herbicidal, and plant growth regulative effects.[1-4] In addition to the above biological activities, s-triazolo[3,4-b]-1,3,4-thiadiazole derivatives obtained by coupling these two biolabile rings together had strong CNS depressant, mild hypocholesterolemic, and hypotensive properties.[5] The synthesis of this condensed heterocycle has received much attention during recent years. Our earlier work on the synthesis of 3,6-aryl/heterocyclyl-s-triazolo[3,4-b]-1,3,4-thiadiazoles revealed antibacterial and herbicidal activities for the compounds.[5-8] The introduction of alkyl groups or ether linkages in a heterocyclic nucleus may enhance its biological activities due to the improvement of its aliphatic solubility and hydrophilicity. Prompted by these observations and in continuation of our studies on condensed heterocycles, we describe in the present paper the condensation of 3-alkyl/aryl-4-amino-5-mercapto-1,2,4-triazoles **1a-1j** with 2,4-dichlorophenoxyacetic acid **2** in the presence of phosphorus oxychloride with the hope of achieving better farm insecticides.

RESULTS AND DISCUSSION

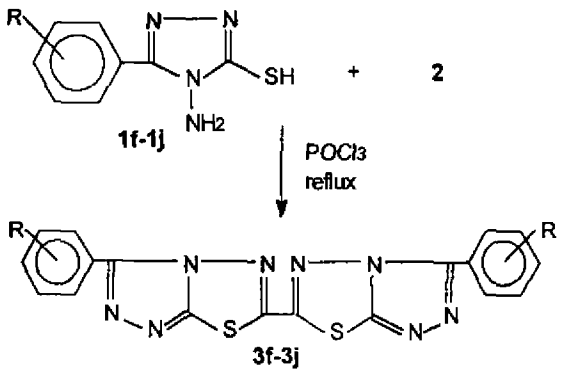
Prasad et al. reported that the reaction of 4-amino-5-mercapto-3-(3,4-methylenedioxyphenyl)-1,2,4-triazole with 2,4-dichlorophenoxyacetic acid in the presence of $POCl_3$ afforded the expected 6-(2,4-dichlorophenoxymethyl)-3-(3,4-methylenedioxyphenyl)-s-triazolo[3,4-b]-1,3,4-thiadiazole.[9] We have made a thorough investigation into the condensation of **1a-1j** with 2,4-dichlorophenoxyacetic acid and found that 3-alkyl-6-(2,4-dichlorophenoxymethyl)-s-triazolo[3,4-b]-1,3,4-thiadiazoles **3a-3e** were prepared successfully for 3-alkyl substituted 1,2,4-triazoles **1a-1e** (Scheme I); however, only high melting 6,6′-bis(3-aryl-s-triazolo[3,4-b]-1,3,4-thiadiazoles) **3f-3j** were isolated for 3-aryl substituted 1,2,4-triazoles **1f-1j** instead of the expected products (Scheme II). Compounds **3f-3j** could also be synthesized by virtue of the reaction of **1f-1j** with oxalic acid using $POCl_3$ as cyclising agent.[10-11] But the reaction of **1f-1j** with 2,4-dichlorophenoxyacetic acid to afford **3f-3j** in the present experimental conditions has not been reported up to now. It furnishes a novel method for preparing 6,6′-bis(s-triazolo[3,4-b]-1,3,4-thiadiazole) derivatives. It remains to be investigated whether the generation of **3f-3j** described in this paper is relevant to the formation of oxalic acid resulting from the decomposition of 2,4-dichlorophenoxyacetic acid and its subsequent condensation with **1f-1j**. The structures of **3a-3j** were established on the basis of their elemental analyses, IR, ^1H NMR, and mass spectral data.

Scheme I



R=CH_3(a), C_2H_5(b), n-C_3H_7(c), n-C_4H_9(d), n-C_5H_{11}(e)

Scheme II



R=H(f), 4-CH3(g), 4-F(h), 2-Cl(i), 4-Cl(j)

The synthesized compounds were screened for their biological activities. The preliminary results indicated that the representative compounds **3a** and **3b** exhibited moderate inhibitory effects against plant pathogenetic bacteria such as *cucumber grey mold, cotton damping-off, corn big speck, apple black rot, peanut foxiness*, and *wheat gibberella* at the concentration of 50 ppm. The average inhibitory percentage (AIP) was 50%.

EXPERIMENTAL SECTION

The melting points were determined on a Yanaco MP microscopic melting point apparatus and uncorrected. Elemental analyses were carried out on a Yanaco CHN Corder MT-3 analyzer. IR spectra were obtained in KBr discs on a Shimadzu IR-435 spectrometer. MS were performed on an HP-5988A spectrometer (EI at 70 eV or FAB). ^{1}H NMR spectra ($CDCl_3$ or CF_3COOD) were recorded on a JEOL FX-90Q instrument with TMS as an internal standard.

2,4-Dichlorophenoxyacetic acid **2** was recrystallized (m.p. 138 °C) and phosphorus oxychloride was redistilled (b.p. 105 °C). 3-Alkyl-4-amino-5-mercapto-1,2,4-triazoles **1a-1e** and 4-amino-3-aryl-5-mercapto-1,2,4-triazoles **1f-1j** were prepared following methods in the literature, respectively.[1,12]

General Procedure for the Preparation of 3-Alkyl-6-(2,4-Dichlorophenoxymethyl)-s-Triazolo[3,4-b]-1,3,4-Thiadiazoles 3a-3e

A mixture of **1a-1e** (1.5 mmol) and 2,4-dichlorophenoxyacetic acid (2 mmol) in the presence of $POCl_3$ (5 mL) was refluxed for 6 h. After removal of the excess of $POCl_3$ under reduced pressure, 40 mL of water was added to the residue. The resulting solid was filtered, treated with 10% aqueous sodium hydroxide, and then washed with water. The crude product thus obtained was purified through column chromatography under reduced pressure using ethyl acetate-methanol-triethylamine (96:2:3) as eluant, and the final pure sample was dried in vacuo.

6-(2,4-Dichlorophenoxymethyl)-3-methyl-s-triazolo[3,4-b]-1,3,4-thiadiazole 3a

Brown powder; yield 68%; mp 205-206 °C. IR ν_{max} (KBr) 3074 (m, ArH), 2920 (w, CH_3 or CH_2), 1590 (s, C=N), 1245 (s, N-N=C), 693 (m, C-S-C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.24 (m, 3H, ArH), 5.43 (s, 2H, OCH_2), 2.55 (s, 3H, CH_3); EI/MS *m/z* (%) 314 (M^+, 24), 161 (25), 153 (68), 84 (100); Anal. Calcd. for $C_{11}H_8Cl_2N_4OS$: C, 41.92; H, 2.56; N, 17.78; Found: C, 42.28; H, 2.60; N, 17.78.

6-(2,4-Dichlorophenoxymethyl)-3-ethyl-s-triazolo[3,4-b]-1,3,4-thiadiazole 3b

Brown powder; yield 56%; mp 148-149 °C. IR ν_{max} (KBr) 3078 (w, ArH), 2921 (w, CH_3 or CH_2), 1590 (m, C=N), 1243 (s, N-N=C), 712 (m, C-S-C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.52-6.72 (m, 3H, ArH), 5.38 (s, 2H, OCH_2), 3.15 (q, J = 7.2 Hz, 2H, CH_2), 1.48 (t, J = 7.2 Hz, 3H, CH_3); EI/MS *m/z* (%) 328 (M^+, 20), 161 (21), 133 (31), 84 (100); Anal. Calcd. for $C_{12}H_{10}Cl_2N_4OS$: C, 43.78; H, 3.06; N, 17.02; Found: C, 43.76; H, 2.95; N, 17.03.

6-(2,4-Dichlorophenoxymethyl)-3-n-propyl-s-triazolo[3,4-b]-1,3,4-thiadiazole 3c

Pale brown powder; yield 42%; mp 128-129 °C. IR ν_{max} (KBr) 3071 (w, ArH), 2949 (m, CH_3 or CH_2), 1581 (m, C=N), 1259 (s, N-N=C), 698 (w, C-S-C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.60-6.90 (m, 3H, ArH), 5.41 (s, 2H, OCH_2), 3.10 (t, J = 7.1 Hz, 2H, CH_2), 1.94 (m, 2H, CH_2), 1.08 (t, J = 7.2 Hz, 3H, CH_3); EI/MS *m/z* (%) 342 (M^+, 3), 161 (21), 153 (38), 133 (24), 99 (4), 98 (10), 84 (100), 63 (13), 58 (15); Anal. Calcd. for $C_{13}H_{12}Cl_2N_4OS$: C, 45.48; H, 3.49; N, 16.33; Found: C, 45.67; H, 3.69; N, 16.32.

6-(2,4-Dichlorophenoxymethyl)-3-n-butyl-s-triazolo[3,4-b]-1,3,4-thiadiazole 3d

Pale yellow powder; yield 43%; mp 99-100 °C. IR ν_{max} (KBr) 3075 (w, ArH), 2942 (m, CH_3 or CH_2), 1590 (m, C=N), 1287 (m. N-N=C), 706 (m, C-S-C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.60-6.94 (m, 3H, ArH), 5.42 (s, 2H, OCH_2), 3.14 (t, J = 7.0 Hz, 2H, CH_2), 2.20-1.00 (m, 7H, C_3H_7); EI/MS *m/z* (%) 161 (28), 153 (64), 133 (25), 98 (9), 86 (4), 84 (100), 63 (18); Anal. Calcd. for $C_{14}H_{14}Cl_2N_4OS$: C, 47.07;

H, 3.95; N, 15.63; Found: C, 47.06; H, 3.95; N, 15.62.

6-(2,4-Dichlorophenoxymethyl)-3-n-pentyl-s-triazolo[3,4-b]-1,3,4-thiadiazole 3e

Yellow powder; yield 53%; mp 100-101 °C. IR ν_{max} (KBr) 3079 (w, ArH), 2959 (m, CH_3 or CH_2), 1595 (m, C=N), 1242 (s, N-N=C), 680 (m, C-S-C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.56-6.84 (m, 3H, ArH), 5.36 (s, 2H, OCH_2), 3.08 (t, J = 7.0 Hz, 2H, CH_2), 2.14-0.62 (m, 9H, C_4H_9); Anal. Calcd. for $C_{15}H_{16}Cl_2N_4OS$: C, 48.52; H, 4.34; N, 15.09; Found: C, 48.50; H, 4.33; N, 15.10.

General Procedure for the Preparation of 6,6′-Bis(3-Aryl-s-Triazolo[3,4-b]-1,3,4-Thiadiazoles) 3f-3j

A mixture of **1f-1j** (2 mmol) and 2,4-dichlorophenoxyacetic acid (2 mmol) in $POCl_3$ (5 mL) was refluxed over oil-bath for 5-8 h. When the color of the reaction mixture gradually changed to yellow or dark brown, the reaction was stopped. After removal of the excess of $POCl_3$ under reduced pressure, a little water was added to the residue. The resulting solid was filtered, successively washed with 10% aqueous sodium hydroxide and water, and finally recrystallized 3-4 times from DMF or glacial acetic acid to analytical purity.

6,6′-Bis(3-phenyl-s-triazolo[3,4-b]-1,3,4-thiadiazole) 3f

Brown powder; yield 60%; mp > 320 °C. IR ν_{max} (KBr) 3050 (w, ArH), 1599 (s, C=N), 1266 (m, N-N=C), 710 (s, C-S-C) cm^{-1}; ^1H NMR (CF_3COOD) δ 8.33-7.80 (m, 10H, ArH); FAB/MS *m/z* (%) 403 (M+1, 25); Anal. Calcd. for $C_{18}H_{10}N_8S_2$: C, 53.72; H, 2.50; N, 27.84; Found: C, 53.41; H, 2.37; N, 27.51.

6,6′-Bis(3-(4-methylphenyl)-s-triazolo[3,4-b]-1,3,4-thiadiazole) 3g

Brown powder; yield 65%; mp 316-317 °C. IR ν_{max} (KBr) 3049 (w, ArH), 1598 (s, C=N), 1260 (m, N-N=C), 710 (s, C-S-C) cm^{-1}; ^1H NMR (CF_3COOD) δ 8.31-7.67 (m, 8H, ArH), 2.98 (s, 6H, $2CH_3$); Anal. Calcd. for $C_{20}H_{14}N_8S_2$: C, 55.80; H, 3.28; N, 26.03; Found: C, 55.60; H, 3.31; N, 25.81.

6,6′-Bis(3-(4-fluorophenyl)-s-triazolo[3,4-b]-1,3,4-thiadiazole) 3h

Brown powder; yield 71%; mp > 320 °C. IR ν_{max} (KBr) 3036 (w, ArH), 1602, 1526, 1446 (s, Ar), 1602 (s, C=N), 1272 (m, N-N=C), 707 (m, C-S-C) cm^{-1}; ^1H NMR (CF_3COOD) δ 8.26-7.70 (m, 8H, ArH); FAB/MS *m/z* (%) 439 (M+1, 8); Anal. Calcd. for $C_{18}H_8N_8S_2F_2$: C, 49.32; H, 1.83; N, 25.57; Found: C, 49.01; H, 1.76; N, 25.32.

6,6′-Bis(3-(2-chlorophenyl)-s-triazolo[3,4-b]-1,3,4-thiadiazole) 3i

Brown powder; yield 70%; mp > 300 °C. IR ν_{max} (KBr) 3042 (w, ArH), 1602, 1561, 1447 (s, Ar), 1602 (s, C=N), 1272 (s, N-N=C), 708 (m, C-S-C) cm^{-1}; ^1H NMR (CF_3COOD) δ 8.19-7.71 (m, 8H, ArH); FAB/MS *m/z* (%) 471 (M+1, 4); Anal. Calcd. for $C_{18}H_8N_8S_2Cl_2$: C, 45.86; H, 1.70; N, 23.78; Found: C, 45.76; H, 1.69; N, 23.70.

6,6′-Bis(3-(4-chlorophenyl)-s-triazolo[3,4-b]-1,3,4-thiadiazole) 3j

Brown powder; yield 75%; mp > 320 °C. IR ν_{max} (KBr) 3040 (w, ArH), 1602, 1549, 1440 (s, Ar), 1602 (s, C=N), 1270 (s, N-N=C), 708 (m, C-S-C) cm^{-1}; ^1H NMR (CF_3COOD) δ 8.28-7.80 (m, 8H, ArH); Anal. Calcd. for $C_{18}H_8N_8S_2Cl_2$: C, 45.86; H, 1.70; N, 23.78; Found: C, 45.80; H, 1.69; N, 23.66.

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Key Words

s-Triazolothiadiazoles; Biological activities.

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