Chinese Chemical Letters Vol. 10, No. 5, pp. 361–364, 1999

Synthesis and Biological Activities of ω-Heterocyclyl-ω-(1*H*-1,2,4-triazol-1-yl) Acetophenones

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Abstract: A series of ω-heterocyclyl-ω-(1*H*-1,2,4-triazol-1-yl) acetophenones have been synthesized. All the compounds were characterized by elemental analysis and spectral data. The preliminary biological test showed that some of them exhibited mild antifungal and plant growth regulative activities.

Keywords: 1*H*-1,2,4-triazole; heterocyclic group; biological activity.

In recent years, a great variety of heterocyclic compounds bearing 1*H*-1,2,4-triazole ring have been synthesized due to their broad spectrum biological activities including antiinflammatory, insecticidal, antiviral and antitumor activities[1-3], some of which have been developed into commercially antifungal agents such as triadimefon, triadimenol and diniconazole. We previously synthesized many kinds of heterocyclic compounds such as 1,3,4-oxadiazole, 1,2,4-triazole, 1,3,4-thiadiazole and 1,2,3-triazole derivatives which exhibited antibacterial, antitubercular and plant growth regulatory properties[4-6]. It is well known that the synthesis of heterocyclic compounds tends to contain multi-structure in a molecule. The biological activity of a heterocyclic compound may be improved by the promotion of its combination with the cell's microstructure and the accumulation of various biological activities resulting from the incorporation of different heterocyclic and non-heterocyclic nuclei in it. Prompted by the above mentioned facts and with a view to obtain new and better biologically active agents, we synthesized a series of ω-(1*H*-1,2,4-triazol-1-yl) acetophenone derivatives $\mathbf{2_{a\text{-}f}}$-$\mathbf{6_{a\text{-}f}}$ incorporating 1,3,4-oxadiazole, 1,2,4-triazole, 1,3,4-thiadiazole and 1,2,3-triazole rings starting from ω-bromo-ω-(1*H*-1,2,4-triazol-1-yl) acetophenone **1**[7].

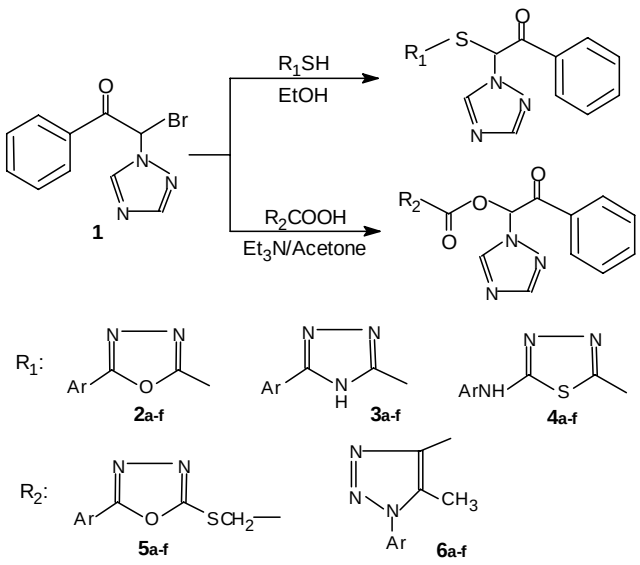
The reaction sequence for different compounds is outlined in **Scheme 1**. Structures of all the compounds were confirmed by their elemental analysis and IR, ^{1}H NMR and mass spectral data. The representative compounds $\mathbf{2_d}$, $\mathbf{3_b}$, $\mathbf{4_f}$, $\mathbf{5_d}$ and $\mathbf{6_d}$ were screened for their fungicidal activity employing the agar diffusion technique. The preliminary results indicated that they exhibited mild inhibitory activity against plant pathogenetic fungi such as *gray mold of cucumber*, *early blight of tomato*, *sclerotium*

blight of rape and *leaf spot of beet*. The degree of inhibition ranged from 7.6% to 44.4%. Moreover, compounds **2d** and **4f** displayed mild plant growth regulative effects. Further investigation on the biological activity of $\mathbf{2}_{\mathbf{a\text{-}f}}$-$\mathbf{6}_{\mathbf{a\text{-}f}}$ is in progress.

Experimental

The melting points were determined on a Kofler melting point apparatus and the thermometers were uncorrected. Elemental analysis were carried out on a Yanaco CHN Corder MT-3 analyzer. IR spectra were obtained in KBr discs on a Nicolet FT-IR 170SX spectrophotometer. Mass spectrum were performed on an HP-5988A spectrometer (EI at 70 eV). ^{1}H NMR spectra ($CDCl_3$) were recorded on a JEOL FX-90X instrument with TMS as an internal standard.

Scheme 1



Ar = C_6H_5(a), *o*-ClC_6H_4(b), *m*-ClC_6H_4(c), *p*-ClC_6H_4(d), *m*-$CH_3C_6H_4$(e), *o*-$CH_3OC_6H_4$(f)

ω-(5-Aryl-1,3,4-oxadiazol-2-thiol)-ω-(1*H*-1,2,4-triazol-1-yl) acetophenones $\mathbf{2}_{\mathbf{a\text{-}f}}$. A solution of 5-aryl-1,3,4-oxadiazol-2-thiol (2 mmol) in 20 mL anhydrous ethanol was added dropwise to a solution of **1** (2 mmol) in 20 mL anhydrous ethanol. The mixture was stirred at room temperature for 3-5 h and the solvent was evaporated. The resultant precipitate was filtered, dried and then recrystallized from 95% ethanol. Compound $\mathbf{2}_{\mathbf{a}}$, m.p. 162-163℃, yield 90%; IR (KBr): 1680 (C=O), 1607 (C=N), 1124 cm^{-1} (C-O-C); ^{1}H NMR ($CDCl_3$): δ 8.59 (s, 1H, TrH), 8.14 (s, 1H, TrH), 8.06-7.30 (m, 11H, ArH and CHTr); MS: *m/z* 363 (M^+, 3), 294 (5), 258 (11), 187 (2), 178 (5), 105 (100), 103 (4), 77 (20); Anal. Calcd. for $C_{18}H_{13}N_5O_2S$: C, 59.49; H, 3.61; N, 19.27; Found: C, 59.32; H, 3.17; N, 19.45. Compound $\mathbf{2}_{\mathbf{b}}$, m.p. 154-155℃, yield 85%; IR (KBr): 1684 (C=O), 1594 (C=N), 1126 cm^{-1} (C-O-C); ^{1}H NMR ($CDCl_3$): δ 8.82 (s, 1H, TrH), 8.08 (s, 1H, TrH), 8.02-7.36 (m, 10H, ArH and CHTr); MS: *m/z* 397 (M^+, 2), 328 (3), 292 (5), 212

(9), 187 (5), 139 (17), 137 (11), 105 (100); Anal. Calcd. for $C_{18}H_{12}ClN_5O_2S$: C, 54.34; H, 3.04; N, 17.60; Found: C, 53.97; H, 2.92; N, 17.20.

The synthesis of ω-(5-aryl-1,2,4-triazol-2-thiol)-ω-(1*H*-1,2,4-triazol-1-yl) aceto-phenones $\mathbf{3_{a-f}}$ and ω-(5-arylamino-1,3,4-thiadiazol-2-thiol)-ω-(1*H*-1,2,4-triazol-1-yl) acetophenones $\mathbf{4_{a-f}}$ was similar to $\mathbf{2_{a-f}}$. Compound $\mathbf{3_a}$, m.p. 171-172℃, yield 85%; IR (KBr): 3385 (N-H), 1680 (C=O), 1588 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 8.88 (s, 1H, TrH), 8.20 (s, 1H, TrH), 8.12-7.40 (m, 11H, ArH and CHTr); MS: *m/z* 362 (M^+, 2), 293 (8), 257 (22), 187 (4), 176 (12), 118 (3), 105 (100); Anal. Calcd. for $C_{18}H_{14}N_6OS$: C, 59.66; H, 3.89; N, 23.19; Found: C, 59.63; H, 3.94; N, 22.72. Compound $\mathbf{3_d}$, m.p. 187-188℃, yield 90%; IR (KBr): 3127 (N-H), 1693 (C=O), 1598 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 8.90 (s, 1H, TrH), 8.22 (s, 1H, TrH), 8.08-7.40 (m, 10H, ArH and CHTr); MS: *m/z* 396 (M^+, 3), 327 (10), 291 (2), 223 (4), 185 (8), 158 (18), 137 (48), 105 (100); Anal. Calcd. for $C_{18}H_{13}ClN_6OS$: C, 54.48; H, 3.30; N, 21.18; Found: C, 54.67; H, 3.55; N, 20.62. Compound $\mathbf{4_a}$, m.p. 184-185℃, yield 78%; IR (KBr): 3240 (N-H), 1689 (C=O), 1597 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 8.90 (s, 1H, TrH), 8.22 (s, 1H, TrH), 8.16-7.14 (m, 11H, ArH and CHTr); MS: *m/z* 394 (M^+, 3), 325 (1), 289 (8), 221 (5), 209 (15), 187 (10), 135 (8), 118 (16), 105 (100); Anal. Calcd. for $C_{18}H_{14}N_6OS_2$: C, 54.81; H, 3.58; N, 21.30; Found: C, 54.91; H, 3.95; N, 20.91. Compound $\mathbf{4_f}$, m.p. 171-172℃, yield 89%; IR (KBr): 3303 (N-H), 1684 (C=O), 1601 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 8.92 (s, 1H, TrH), 8.24 (s, 1H, TrH), 8.18-7.08 (m, 10H, ArH and CHTr), 3.98 (s, 3H, OCH_3); MS: *m/z* 424 (M^+, 3), 319 (4), 239 (11), 208 (4), 187 (5), 166 (8), 133 (3), 105 (100); Anal. Calcd. for $C_{19}H_{16}N_6O_2S_2$: C, 53.76; H, 3.80; N, 19.80; Found: C, 53.80; H, 4.11; N, 19.34.

ω-(5-Aryl-1,3,4-oxadiazol-2-thiolacetoxyl)-ω-(1*H*-1,2,4-triazol-1-yl) acetophenones $\mathbf{5_{a-f}}$. A mixture of 5-aryl-1,3,4-oxadiazol-2-thiolacetic acid (2 mmol) and triethylamine (2 mmol) in 20 mL anhydrous acetone was added dropwise with stirring to a solution of **1** in 20 mL anhydrous acetone at 0℃. After an hour, the mixture was stirred at room temperature over night, the formed salt was filtered and the solvent was evaporated. The precipitate was filtered and then recrystallized from 95% ethanol. Compound $\mathbf{5_c}$, m.p. 129-130℃, yield 81%; IR (KBr): 1758 (-CO_2-), 1692 (C=O), 1588 (C=N), 1147 cm^{-1} (C-O-C); ^1H NMR ($CDCl_3$): δ 8.43 (s, 1H, TrH), 7.96 (s, 1H, TrH), 7.90-7.22 (m, 10H, ArH and CHTr), 4.20 (s, 2H, CH_2); MS: *m/z* 455 (M^+, 1), 316 (9), 253 (35), 219 (60), 159 (29), 145 (29), 105 (100), 77 (19); Anal. Calcd. for $C_{20}H_{14}ClN_5O_4S$: C, 52.69; H, 3.09; N, 15.36; Found: C, 52.89; H, 3.35; N, 15.08. Compound $\mathbf{5_d}$, m.p. 165-166℃, yield 84%; IR (KBr): 1754 (-CO_2-), 1694 (C=O), 1600 (C=N), 1147 cm^{-1} (C-O-C); ^1H NMR ($CDCl_3$): δ 8.43 (s, 1H, TrH), 7.98 (s, 1H, TrH), 7.88-7.42 (m, 10H, ArH and CHTr), 4.22 (s, 2H, CH_2); Anal. Calcd. for $C_{20}H_{14}ClN_5O_4S$: C, 52.69; H, 3.09; N, 15.36; Found: C, 52.80; H, 3.01; N, 14.91.

The synthesis of ω-(1-aryl-5-methyl-1,2,3-triazol-4-carboxyl)-ω-(1*H*-1,2,4-triazol-1-yl) acetophenones $\mathbf{6_{a-f}}$ was similar to $\mathbf{5_{a-f}}$. Compound $\mathbf{6_d}$, m.p. 166-167℃, yield 89%; IR (KBr): 1730 (-CO_2-), 1714 (C=O), 1599 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 8.62 (s, 1H, TrH), 8.20 (s, 1H, TrH), 8.07-7.29 (m, 10H, ArH and CHTr), 2.62 (s, 3H, CH_3); MS: *m/z* 422 (M^+, 43), 325 (37), 220 (53), 192 (92), 164 (43), 152 (94), 105 (100); Anal. Calcd. for $C_{20}H_{15}ClN_6O_3$: C,

56.81; H, 3.58; N, 19.88; Found: C, 56.73; H, 3.30; N, 19.71. Compound **6_e**, m.p. 143-144℃, yield 91%; IR (KBr): 1739 (-CO_2-), 1705 (C=O), 1598 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$): δ 8.65 (s, 1H, TrH), 8.21 (s, 1H, TrH), 8.05-7.16 (m, 10H, ArH and CHTr), 2.61 (s, 3H, CH_3), 2.47 (s, 3H, $ArCH_3$). Anal. Calcd. for $C_{21}H_{18}N_6O_3$: C, 62.68; H, 4.51; N, 20.88; Found: C, 62.49; H, 4.27; N, 20.54.

Acknowledgments

Financial support from the State Key Laboratory of Elemento-Organic Chemistry of Nankai University is gratefully acknowledged.

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Received 7 December 1998