Synthesis and antifungal activity of \( \omega-(1\text{-aryl-5-methyl-1,2,3-triazole-4-carboxyl})-\omega-(1H-1,2,4-triazol-1-yl)\)acetophenones

Chang-Hu Chu\(^1\), Xiao-Wen Sun\(^1\), Zi-Yi Zhang\(^1\), Zhi-Chun Li\(^2\) & Ren-An Liao\(^2\)

\(^1\)Department of Chemistry, National Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, P. R. China
\(^2\)State Key Laboratory of Elemento-Organic Chemistry, Naikai University, Tianjin 300071, P. R. China

Received 11 April 2000; accepted (revised) 15 September 2000

Several \( \omega-(1\text{-aryl-5-methyl-1,2,3-triazole-4-carboxyl})-\omega-(1H-1,2,4-triazol-1-yl)\)acetophenones \(3a-j\) have been synthesized. The structures of these compounds have been confirmed by elemental analyses and spectral data. The preliminary biological test results show that the representative compounds exhibit mild antifungal activities.

A number of \(1H-1,2,4\)-triazole derivatives were reported to show broad spectrum biological activities, some of which were commercialized as agrochemical fungicides, insecticides, herbicides and plant growth regulatory activities\(^1-^4\). Moreover, a lot of compounds containing 1,2,3-triazole ring were found to exhibit all kinds of biological activities similar to \(1H-1,2,4\)-triazole derivatives, such as antifungal, antibacterial, anti-inflammatory, herbicidal and insecticidal activities\(^5-^9\). In continuation of our work on heterocycles of biological interest and guided by the observation that many a time the combination of two or more heterocyclic nuclei in a molecule enhances the biological profile many-folds, we wish to synthesize ten new \(\omega-(1\text{-aryl-5-methyl-1,2,3-triazole-4-carboxyl})-\omega-(1H-1,2,4-triazol-1-yl)\)acetophenones in which \(1H-1,2,4\)-triazole and 1,2,3-triazole rings were incorporated into a single molecular framework.

The required \(1\text{-aryl-5-methyl-4-carboxyl-1,2,3-triazoles}\) \(1a-j\) were prepared by 1,3-dipolar cycloaddition reaction of aryl azides with ethyl acetocetate. The condensation of \(1a-j\) with \(\omega\)-bromo-\(\omega-(1H-1,2,4-triazol-1-yl)\)acetophenones \(2\) in the presence of triethylamine afforded the expected \(\omega-(1\text{-aryl-5-methyl-1,2,3-triazole-4-carboxyl})-\omega-(1H-1,2,4-triazol-1-yl)\)acetophenones \(3a-j\) (Scheme 1). The structure assignments of \(3a-j\) are based on elemental analyses and spectral data.

The \(1H\) NMR spectra of \(3a-j\) exhibited two singlet peaks at \(\delta 8.61-8.74\) and \(8.15-8.32\) ppm corresponding to the \(1H-1,2,4\)-triazole protons. A singlet at \(\delta 2.44-2.62\) ppm was assigned to 1,2,3-triazole methyl, whereas aromatic and \(CH\) protons displayed a multiplet at \(\delta 7.00-8.16\) ppm. Their IR spectra exhibited two strong absorptions around 1736 and 1709 cm\(^{-1}\) due to \(-CO-\) and \(PhCO-\) group, respectively. The band that appeared around 1592-1602 cm\(^{-1}\) was attributed to \(C=\text{N}\) function. By analyzing the mass spectra of \(3\), it was found that the fragmentation involved the expulsion of \(HC\text{COTr}\) moiety from the molecular ion. The base peak at \(m/z 105\) corresponded to \(Ph\text{CO}^+\).

Antifungal activities

The representative compounds \(3a, 3c, 3g\) and \(3j\) were screened for their fungicidal activity employing the agar diffusion technique. The preliminary results indicated that they exhibited mild inhibitory effect against plant pathogenetic fungi such as \(cercospora brown spot of penut, gray mold of cucumber, rhizoctonia rot of cotton\) and \(sclerotium blight of colza\) at a 50 ppm concentration. The degree of inhibition ranged from 0-43.7%.
Experimental Section

The melting points were determined on a kofler melting point apparatus and are uncorrected. Elemental analyses were carried out on a Yanaco CHN Corder MT-3 analyzer. IR spectra were recorded in KBr discs on a Nicolet FT-IR 170SX spectrometer; mass spectra on a HP-5988A spectrometer (El at 70 eV) and 1H NMR spectra (CDCl3) on a JEOL FX-90X instrument with TMS as an internal standard.

1-Aryl-5-methyl-4-carboxyl-1,2,3-triazoles 1a-j and o-bromo-o-(1H-1,2,4-triazol-1-yl)acetophenones were prepared following the literature procedure.10-11

General procedure for preparation o-(1-aryl-5-methyl-1, 2, 3-triazole-4-carboxyl)-o-(1H-1,2,4-triazol-1-yl)acetophenones 3a-j. A mixture of 1a-j (2 mmol) and triethylamine (2 mmol) in 15 mL anhydrous acetonitrile was added dropwise with stirring to a solution of 2 (2 mmol) also in 20 mL anhydrous acetonitrile at 0 °C. After an hour, the mixture was stirred at room temperature overnight. The formed salts were filtered and the solvent was evaporated. The crude product was chromatographed on silica gel using petroleum-acetone (5:1) as eluent. It was then recrystallized from 95% ethanol to afford pure 3a-j.

o-[1-(4-Chlorophenyl)-5-methyl-1,2,3-triazole-4-carboxyl]-o-(1H-1, 2, 4-triazol-1-yl)acetophenone 3a: Yield 89%, m.p. 166-67 °C (Found: C, 56.73; H, 3.30; N, 19.71. C20H15ClN5O3 requires C, 56.81; H, 3.58; N, 19.88%). IR (KBr): 1730 (-C=O), 1714 (C=O), 1599 cm⁻¹ (C=N); 1H NMR: δ 8.62 (s, 1H, TrH), 8.20 (s, 1H, TrH), 8.07-7.29 (m, 10H, ArH, CHTr), 2.62 (s, 3H, CH3); MS: m/z 422 (M⁺, 4), 325 (4), 220 (5), 192 (9), 164 (4), 152 (9), 138 (19), 105 (100).

o-[1-(3-Bromomethyl)-5-methyl-1,2,3-triazole-4-carboxyl]-o-(1H-1, 2, 4-triazol-1-yl)acetophenone 3b: Yield 88%, m.p. 131-32°C (Found: C, 51.28; H, 2.97; N, 17.99. C20H15BrN5O3 requires C, 51.41; H, 3.23; N, 17.98%). IR (KBr): 1731 (-C=O), 1714 (C=O), 1592 cm⁻¹ (C=N); 1H NMR: δ 8.61 (s, 1H, TrH), 8.16 (s, 1H, TrH), 8.06-7.28 (m, 10H, ArH, CHTr), 2.60 (s, 3H, CH3).

o-[1-(2-Chlorophenyl)-5-methyl-1,2,3-triazole-4-carboxyl]-o-(1H-1, 2, 4-triazol-1-yl)acetophenone 3c: Yield 90%, m.p. 154-55°C (Found: C, 57.06; H, 3.48; N, 19.43. C20H15ClN5O3 requires C, 56.81; H, 3.58; N, 19.88%). IR (KBr): 1743 (-C=O), 1701 (C=O), 1597 cm⁻¹ (C=N); 1H NMR: δ 8.64 (s, 1H, TrH), 8.22 (s, 1H, TrH), 8.10-7.47 (m, 10H, ArH, CHTr), 2.46 (s, 3H, CH3).

o-[1-(4-Methylphenyl)-5-methyl-1, 2, 3-triazole-4-carboxyl]-o-(1H-1,2,4-triazol-1-yl)acetophenone 3d: Yield, 85%, mp 174-75°C (Found: C, 62.97; H, 4.30; N, 20.88. C20H16N6O3 requires C, 62.68; H, 4.51; N, 20.94%). IR (KBr): 1730 (-C=O), 1709 (C=O), 1599 cm⁻¹ (C=N); 1H NMR: δ 8.65 (s, 1H, TrH), 8.21 (s, 1H, TrH), 8.06-7.30 (m, 10H, ArH, CHTr), 2.60 (s, 3H, CH3), 2.48 (s, 3H, ArCH3); MS: m/z 402 (M⁺, 2), 305 (18), 276 (2), 200 (37), 172 (57), 158 (6), 144 (32), 105 (100).

o-[1-(3-Methylphenyl)-5-methyl-1, 2, 3-triazole-4-carboxyl]-o-(1H-1,2,4-triazol-1-yl)acetophenone 3e: Yield 91%, mp 143-44°C (Found: C, 62.49; H, 4.27; N, 20.54. C20H16N6O3 requires C, 62.68; H, 4.51; N, 20.94%). IR (KBr): 1739 (-C=O), 1705 (C=O), 1598 cm⁻¹ (C=N); 1H NMR: δ 8.65 (s, 1H, TrH), 8.21 (s, 1H, TrH), 8.05-7.16 (m, 10H, ArH, CHTr), 2.61 (s, 3H, CH3), 2.47 (s, 3H, ArCH3).

o-[1-(4-Methoxyphenyl)-5-methyl-1,2,3-triazole-4-carboxyl]-o-(1H-1,2,4-triazol-1-yl)acetophenone 3f: Yield 90%, mp 154-55°C (Found: C, 60.08; H, 4.04; N, 19.87. C20H16N6O4 requires C, 60.28; H, 4.34; N, 20.08%). IR (KBr): 1733 (-C=O), 1703 (C=O), 1599 cm⁻¹ (C=N); 1H NMR: δ 8.61 (s, 1H, TrH), 8.15 (s, 1H, TrH), 8.05-7.00 (m, 10H, ArH, CHTr), 3.88 (s, 3H, OCH3), 2.54 (s, 3H, CH3); MS: m/z 418 (M⁺, 4), 321 (5), 292 (1), 216 (10), 188 (52), 174 (2), 160 (98), 148 (18), 105 (92), 92 (21), 77 (100).

o-[1-(3-Methoxyphenyl)-5-methyl-1,2,3-triazole-4-carboxyl]-o-(1H-1,2,4-triazol-1-yl)acetophenone 3g: Yield 90%, mp 180-81°C (Found: C, 60.09; H, 4.26; N, 19.86. C20H16N6O4 requires C, 60.28; H, 4.34; N, 20.08%). IR (KBr): 1742 (-C=O), 1709 (C=O), 1602 cm⁻¹ (C=N); 1H NMR: δ 8.74 (s, 1H, TrH), 8.32 (s, 1H, TrH), 8.16-7.16 (m, 10H, ArH, CHTr), 3.86 (s, 3H, OCH3), 2.48 (s, 3H, CH3).

o-[1-(2-Methylphenyl)-5-methyl-1, 2, 3-triazole-4-carboxyl]-o-(1H-1,2,4-triazol-1-yl)acetophenone 3h: Yield 86%, mp 147-48°C (Found: C, 62.55; H, 4.54; N, 20.42. C20H16N6O3 requires C, 62.68; H, 4.51; N, 20.94%). IR (KBr): 1738 (-C=O), 1705 (C=O), 1598 cm⁻¹ (C=N); 1H NMR: δ 8.72 (s, 1H, TrH), 8.28 (s, 1H, TrH), 8.12-7.42 (m, 10H, ArH, CHTr), 2.44 (s, 3H, CH3), 2.04 (s, 3H, ArCH3).

o-(1-Phenyl-5-methyl-1,2,3-triazole-4-carboxyl)-o-(1H-1,2,4-triazol-1-yl)acetophenone 3i: Yield 88%, mp 149-50°C (Found: C, 62.06; H, 3.89; N, 21.09. C20H16N6O3 requires C, 61.85; H, 4.15; N,
21.63%); IR (KBr) : 1728 (-CO\textsubscript{2}⁻), 1716 (C=O), 1598 cm\(^{-1}\) (C=N); \(^1\)H NMR : δ 8.63 (s, 1H, TrH), 8.19 (s, 1H, TrH), 8.08-7.30 (m, 11H, ArH, CHTr), 2.59 (s, 3H, CH\(_3\)); MS : m/z 388 (M\(^+\), 1), 291 (12), 255 (2), 186 (23), 158 (27), 130 (17), 118 (47), 105 (76), 77 (100).

\[ \text{co-[1-} (4-\text{Bromophenyl})-5\text{-methyl-1,2,3-triazole-4-carboxyl]-co-(1H-1,2,4-triazol-1-yl)acetophenone} \]

3j: Yield 85%, mp 170-71°C (Found: C, 51.15; H, 2.76; N, 17.58. C\(_{20}\)H\(_{16}\)BrN\(_4\)O\(_3\) requires C, 51.41; H, 3.23; N, 17.98%); IR (KBr) : 1729 (-CO\textsubscript{2}⁻), 1705 (C=O), 1597 cm\(^{-1}\) (C=N); \(^1\)H NMR : δ 8.62 (s, 1H, TrH), 8.19 (s, 1H, TrH), 8.09-7.30 (m, 10H, ArH, CHTr), 2.60 (s, 3H, CH\(_3\)); MS : m/z 371 (M\(^+\)-97, 3), 369 (3), 264 (6), 237 (4), 196 (13), 157 (25), 155 (10), 129 (9), 105 (100).

Acknowledgement
This work was financially supported by the State Key Laboratory of Elemento-Organic Chemistry of Nankai University.

References