

Synthesis and Bioactivity of Novel Aminomethyl-2- (1, 2, 4-triazol)-4, 4-dimethyl-3-pentanone (ol)

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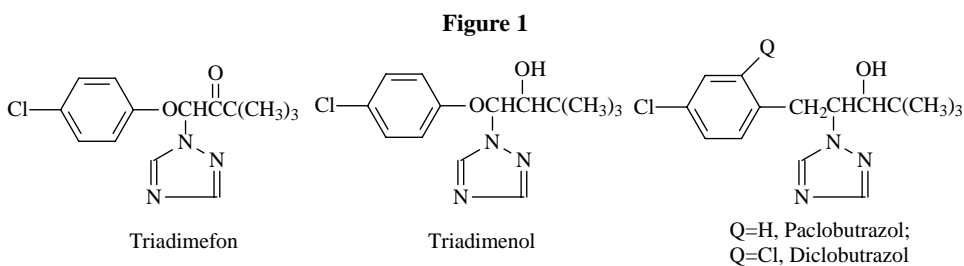
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Abstract: 3, 3-Dimethyl-1-(1, 2, 4-triazol)-2- butanone was treated with aqueous formaldehyde to give an additional product, and subsequent elimination by acetic anhydride yielded 4, 4-dimethyl-2-(1, 2, 4-triazol)-1-penten-3-one. Further addition with substituted amines provided a series of (1, 2, 4-triazol)-4, 4-dimethyl-3-pentanone, which were then reduced by KBH_4 to obtain a series of (1, 2, 4-triazol)-4, 4-dimethyl-3-pentanol. Their structures were confirmed by ^1H NMR and elemental analysis. The results of bioassay showed that the title products possess good fungicidal activities.

Keywords: (1, 2, 4-Triazol)-4, 4-dimethyl-3-pentanone, (1, 2, 4-triazol)-4, 4-dimethyl-3-pentanol, synthesis, fungicidal activities.

The 1, 2, 4-triazole derivatives represented a large group of systemic fungicides, which were the ergosterol biosynthesis inhibitors (EBIs). It is reported that these fungicides were powerful systemic, broad spectrum, high active and high selective fungic¹⁻⁴. The azolyl-alkane derivatives were an important class of this sort of compounds, such as triadimefon, which was a systemic fungicide developed by Bayer AG, as shown in **Figure 1**. Base on it, they discovered triadimenol, and diclobutrazol and paclobutrazol. Subsequently people studied mainly on the substitution of -C, bonded with 1, 2, 4-triazole. Substitution of alkyl, aryl and aryloxy at this position had been studied, whereas, aminomethyl substitution at this position was not reported.

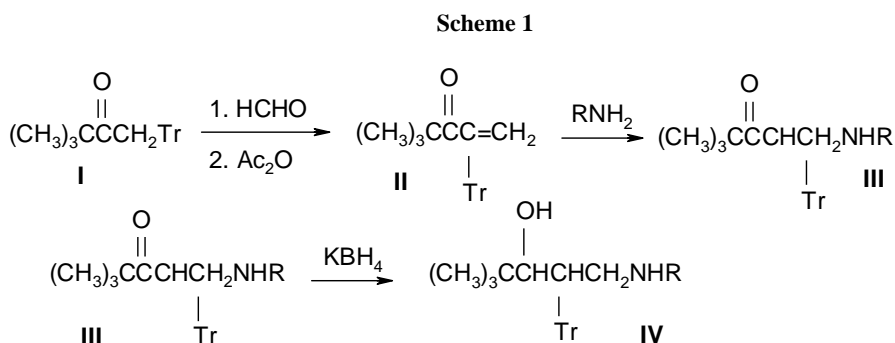
In this paper, we modified the structures of triadimefon group's fungicides to design and synthesize the title compounds **III** and **IV**. We introduced aminomethyl group to



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α -C instead of aryloxy or aryl and found that these compounds have very high fungicidal activities.

The synthesis of **III** and **IV** was shown in **Scheme 1**.



Tr is 1, 2, 4-triazol-1-yl, R = aryl, alkyl.

Table 1 Physical constants of compounds **III**

No.	R	Yield %	m.p.	elemental analysis (calcd.) %		
				C	H	N
III-1	2-Br-C ₆ H ₄	60.2	104~5	51.10 (51.28)	5.35 (5.46)	15.72 (15.95)
III-2	3-Br-C ₆ H ₄	83.4	132~4	51.26 (51.28)	5.51 (5.46)	15.90 (15.95)
III-3	2,4,5-Cl ₃ -C ₆ H ₂	17.7	140~2	47.98 (47.95)	4.50 (4.57)	14.69 (14.92)
III-4	3-CF ₃ -4-Cl-C ₆ H ₃	37.8	156~7	51.44 (51.27)	4.90 (4.85)	14.88 (14.95)

Table 2 Physical constants of compounds **IV**

No.	R	Yield %	m.p.	elemental analysis (calcd.) %		
				C	H	N
IV-1	2-Cl-C ₆ H ₄	76.3	98~100	58.13 (58.33)	6.83 (6.87)	18.18 (18.14)
IV-2	3-Cl-C ₆ H ₄	97.1	110~2	58.15 (58.33)	6.88 (6.87)	17.91 (18.14)
IV-3	2-Br-C ₆ H ₄	95.0	96~8	51.18 (50.99)	5.80 (6.00)	15.54 (15.86)
IV-4	3-Br-C ₆ H ₄	76.5	116~8	51.19 (50.99)	5.85 (6.00)	15.75 (15.86)
IV-5	4-Br-C ₆ H ₄	84.9	132~4	50.89 (50.99)	5.81 (6.00)	15.79 (15.86)
IV-6	2,3-Cl ₂ -C ₆ H ₃	96.4	158~60	52.19 (52.48)	5.77 (5.88)	16.05 (16.32)
IV-7	2,4-Cl ₂ -C ₆ H ₃	87.6	128~30	52.20 (52.48)	5.57 (5.88)	16.20 (16.32)
IV-8	2,5-Cl ₂ -C ₆ H ₃	36.4	107~8	52.42 (52.48)	5.91 (5.88)	16.35 (16.32)
IV-9	2,4,5-Cl ₃ -C ₆ H ₂	66.0	100~2	47.64 (47.69)	5.26 (5.08)	14.53 (14.84)
IV-10	3-CF ₃ -4-Cl-C ₆ H ₃	60.4	187~9	51.17 (50.99)	5.03 (5.36)	14.55 (14.87)
IV-11	CH(CH ₃) ₂	80.7	176~8	59.77 (59.95)	9.93 (10.08)	23.24 (23.31)
IV-12	(CH ₂) ₅	75.2	120~2	63.23 (63.11)	9.82 (9.86)	20.74 (21.03)

I was treated with aqueous formaldehyde (37%) to give an additional product, and subsequent elimination by acetic anhydride yielded **II**⁵. Further addition with substitut-

ed amines provided a series of novel (1, 2, 4-triazol)-4, 4-dimethyl-3-pentanone⁶ **III**, which were reduced by KBH_4 to obtain a series of novel (1, 2, 4-triazol)-4, 4-dimethyl-3-pentanol⁷ **IV**. If **I** was treated with aqueous formaldehyde in piperidine and methanol, many by-products were formed and could not be separated easily.

When the compounds **II** were treated with amines, to afford **III** we found that the position of substitution on the arylamino influenced the reactivity. Ortho substitution of arylamino decreased the reactivity, reaction with these amines needed longer time and higher temperature.

The structures of the title compounds were determined by ¹HNMR and elemental analysis. All products **III** were white solids.

The bioactivity data of **IV** were listed in **Table 3**. From the data, we found that these compounds had good fungicidal activity, especially compound **IV**. At the same time we found that the fungicidal activity of **IV** was higher than **III**. From the data, we concluded that when R was alkyl group (**IV-11**) the fungicidal activity disappeared.

Table 3 Bioactivity* data of **IV**

No.	R	Inhibitory rate (%)				
		Dosage ppm	Alternaria solani	Phoma asparagi	Physalospora	Cercospora arachidicola
III-1	2-Br-C ₆ H ₄	50	27.8	42.9	38.9	36.4
III-2	3-Br-C ₆ H ₄	50	26.1	47.0	16.7	45.5
IV-2	3-Cl-C ₆ H ₄	50	97.1	93.7	95.7	94.4
IV-5	4-Br-C ₆ H ₄	50	94.1	93.7	95.7	94.4
IV-6	2, 3-Cl ₂ -C ₆ H ₃	50	76.5	93.7	95.7	94.4
IV-7	2, 4-Cl ₂ -C ₆ H ₃	50	70.6	93.7	93.5	94.4
IV-11	CH(CH ₃) ₂	50	6.5	5.9	8.7	0

*The test method is rape test.

References and Notes

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5. 4, 4-Dimethyl-2-(1, 2, 4-triazol)-1-penten-3-one: The mixture of 90.0 g. of 3, 3-dimethyl-1-(1, 2, 4-triazol)-2-butanone **I** (0.5 mole) and 130 mL of aqueous formaldehyde (37~40%) in 30 mL water was refluxed for 4 hours. After cooling the white solid was formed, collected and dried. 42.8 g. of above solid (0.2 mole) was mixed with 150 mL of acetic anhydride, stirred in 106~109 °C for 3 hours, then the acetic anhydride was removed and distilled in reduced pressure, and collected the portion of 90~2°C/0.2 mmHg (31.2 g) in yield 36%.
6. 1-(2-Bromophenyl amino)-4, 4-dimethyl-2-(1, 2, 4-triazol)-3-pentanone: To 1.8 g. of 4, 4-dimethyl-2-(1, 2, 4-triazol)-1-pentene-3-one (0.01 mole) in 30 mL of toluene was added 2.2 g. 2-bromophenyl amine (0.012 mole). The mixture was stirred at 60°C for 18 hours, then the solvent was removed. The precipitate compound **III-1** was filtrated and washed with ether, yielding 4.2 g. of white solid (60.2%), m. p. 104~5°C. ¹HNMR: 1.10 (s, 9H, Bu^t), 3.86 (dq,

- 2H, $J=7$, CH₂), 4.48 (s, 1H, NH), 5.78 (t, 1H, $J=7$, CHTr), 6.61~7.41 (m, 4H, PhH), 7.96 (s, 1H, TrH), 8.32 (s, 1H, TrH).
7. 1-(2-Bromophenyl amino)-4,4-dimethyl-2-(1, 2, 4-triazol)-3-pentanol (**IV-3**): 0.5 g. of KBH₄ was added to 2.2 g. of 1-(2-bromophenylamino)-4, 4-dimethyl-2-(1, 2, 4-triazol)-3-pentanone (0.006 mole) in 20 mL of methanol, in cooling below -5°C . After the addition, stirring continued below -5°C for 30 min and 12 hours at room temperature. The solvent was removed, the water was added to the residue, the precipitate product was formed, filtrated and washed with petroleum ether, collected 2.0 g., yield 95.0%, m. p. $96\sim 8^{\circ}\text{C}$. ¹HNMR: 0.70 (s, 9H, Bu^t), 3.62 (s, 1H, CHOH), 3.80 (dd, 2H, $J=7$, CH₂), 4.09 (s, 2H, NH&OH), 4.74 (t, 1H, $J=7$, CHTr), 6.60~7.37 (m, 4H, PhH), 8.00 (s, 1H, TrH), 8.14 (s, 1H, TrH).

Received 2 February, 2003