Short Communication

Fused Heterocycles, Triazolotriazole-1,3(2*H*)-diones as New Potential FungicidesYUZURU SANEMITSU, YOSHINORI NAKAYAMA
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Recently, hydrazones have been intensively modified because of some of their biological activities, *e.g.*, fungicidal activity,¹⁾ and antiviral properties.²⁾ Novel double addition reaction of hydrazones with isocyanates provided a facile route to new fused heterocycles, 1*H*,5*H*-[1,2,4]triazolo [1,2-*a*][1,2,4] triazole-1,3(2*H*)-diones (**4a~e**).³⁾ 2-*t*-Butyl-1*H*,5*H*-[1,2,4]triazolo [1,2-*a*][1,2,4] triazole-1,3(2*H*)-diones (**4c**) demonstrated excellent systemic activity at low concentrations for the control of rice blast disease caused by the fungus *Pyricularia oryzae*. Here we report the synthesis of 1*H*,5*H*-[1,2,4]triazolo [1,2-*a*][1,2,4]

triazole-1,3(2*H*)-diones, and also describe the results of their biological evaluation.

Synthesis routes are given in Fig. 1 with some products exemplified in Table I. 1-Isopropylidene-4- (methoxycarbonyl)-3-methylthiosemicarbazide (**1**) was used as a suitable synthon for preparing the fused heterocycles. The starting material (**1**), mp 54~55°C, was easily prepared in 50% yield by the reaction of 1-isopropylidene-3-methylthiosemicarbazide⁴⁾ with methyl chloroformate in the presence of triethylamine in refluxing chloroform. Treatment of compound (**1**) with methylisocyanate in anhydrous tetrahydrofuran at room temperature overnight afforded a cyclized product, 1-(methylcarbamoyl)-4²-1,2,4-triazoline (**2a**), mp 133°C, in 88% yield. The structure of compound (**2a**) was determined on the basis of spectroscopic data. The IR absorption at 3,300 cm⁻¹ and the ¹H NMR signal of a doublet peak at δ2.78 ppm suggested the presence of a methylcarbamoyl substituent. Instead of two singlets (δ1.96 and 2.06) due to an isopropylidene group of compound (**1**), the ¹H NMR spectrum of compound (**2a**) exhibited one singlet (δ1.94) whose chemical shift was similar to that (δ1.69) of a cyclic compound, 3,5,5-trimethyl-1,3,4-thiadiazolidine-2-thione.⁵⁾ As shown in Fig. 1, the formation of

FIG. 1.

Δ^2 -1,2,4-triazoline (**2a**) from compound (**1**) is assumed to be a two-step reaction consisting of the first attack of an isocyanate to the C=N bond and the second intramolecular addition of a nitrogen atom. The reaction of compound (**2a**) with 10% aqueous methanol solution of sodium hydroxide gave Δ^3 -1,2,4-triazoline (**3a**), mp 146°C, in a quantitative yield. Demethoxycarbonylation was verified by the disappearance of an ester group in the IR and ^1H NMR spectra. Transformation of compound (**3a**) into a fused heterocycle, 2-methyl-1*H*,5*H*-[1,2,4]triazolo [1,2-*a*][1,2,4]triazole-1,3(2*H*)-dione (**4a**), mp 104°C, was achieved through the cyclization reaction with 1,1'-carbonyldiimidazole at 120°C for 1 hr in 86% yield. The structure of compound (**4a**) was assigned on the basis of the spectroscopic data (^1H - and ^{13}C -NMR, IR and MS) and elemental analysis. To examine the effect of the substituent at the 2-position on biological activity, 1*H*,5*H*-[1,2,4]triazolo [1,2-*a*][1,2,4] triazole-1,3(2*H*)-diones (**4b**~**d**) were also prepared under similar condition as described above.

The *in vivo* fungicidal activities of 1*H*,5*H*-[1,2,4]triazolo [1,2-*a*][1,2,4]triazole-1,3(2*H*)-diones are shown in Table I. In the systemic activities of the title compounds by soil treatment in pot tests, compounds (**4a**~**c**) showed considerable antifungal activities against rice blast disease. Substitution of the bulky alkyl group at the 2-position of the fused heterocycle increased the fungicidal activity (Table I). In particular, 2-*t*-butyl-1*H*,5*H*-[1,2,4]triazolo

TABLE I. SOME PROPERTIES OF 1*H*, 5*H*-[1,2,4]-TRIAZOLO-[1,2-*a*][1,2,4]TRIAZOLE-1,3(2*H*)-DIONES

Compound	Yield (%)	mp (°C)	Disease-control activity (%) ^a
			Concentration (50 µg/ml)
4a	86	104	60
4b	81	78	80
4c	87	99	100
4d	84	115	0
4e	90	140	20

^a Systemic activities by soil treatment.

[1,2-*a*][1,2,4] triazole-1,3(2*H*)-dione (**4c**) completely controlled the disease at low concentrations above 12.5 µg/ml. On the other hand, curative treatment was not effective in controlling the disease even at concentrations as high as 500 µg/ml.

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