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SYNTHESIS OF SUBSTITUTED 2-AZOLYL-1-PYRIDYLETHAN-1-OLS

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Through the reaction of (2-aryloxiran-2-yl)pyridines with triazole or imidazole a series of novel 2-azolyl-1-pyridylethan-1-ols has been synthesized with different positioning of the nitrogen atom in the pyridine fragment for pharmacological and agrochemical screening. The compounds prepared showed high fungicidal activity.

Keywords: 2-azolylethanols, 1-pyridylethanols, Corey-Chaykovsky reaction.

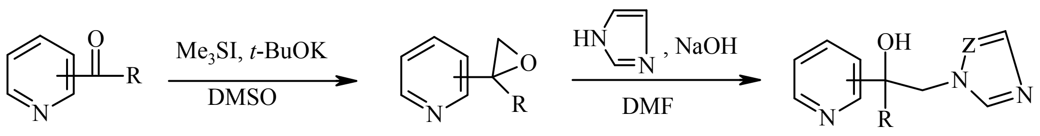
A large number of azolyl fungicides have been used successfully as chemical agents for plant protection and as medicinal preparations [1]. An important group amongst these are the substituted 2-azolylethanols and these show inhibition of lanosterol C-14 demethylase which is one of the key enzymes taking part in the construction of fungal pathogen cell membranes [2].

Recently, many compounds of the 2-azolylethanol series have been prepared with different alkyl and aryl substituents but pyridyl-substituted 2-azolylethanols have not been studied up to the present. Introduction of a pyridine fragment must increase the solubility of the compound in water and change the pK_a and systemic properties thus modifying the fungicidal activity spectrum.

We have obtained 1-aryl-2-azolyl-1-pyridylethanols and 2-azolyl-1-cyclohexyl-1-pyridylethanols.

In the first stage the 2-, 3-, and 4-benzoylpyridines, 2-(4-fluorobenzoyl)pyridine, and cyclohexyl 3-pyridyl ketone are epoxidated using the Corey-Chaykovsky reaction [3] by treatment with trimethylsulfonium iodide and potassium *tert*-butoxide. The oxiranes formed are unstable and rapidly isomerize at room temperature, hence they are used in the subsequent synthesis without purification. The oxiranes obtained are then treated with imidazole or triazole by heating with solid NaOH catalyst in DMF (Scheme 1).

Scheme 1



1–10

1, **2**, **7**, **8** Py-2, **3**, **4**, **9**, **10** Py-3, **5**, **6**, Py-4; **1–6** R = Ph, **7**, **8** R = 4-FC_6H_4,
9, **10** R = *c*-C_6H_{11}; **1**, **3**, **5**, **7**, **9** Z = N, **2, 4, 6**, **8**, **10** Z = CH

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TABLE 1. Physicochemical Characteristics of Compounds **1-10**

Compound	Ethanol	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
			C	H	N		
1	1-Phenyl-1-(2-pyridyl)-2-(1,2,4-triazol-1-yl)-	$C_{15}H_{14}N_4O$	67.51 67.65	5.38 5.30	20.97 21.04	105-107	54
2	2-(Imidazol-1-yl)-1-phenyl-1-(2-pyridyl)-	$C_{16}H_{15}N_3O$	72.35 72.43	5.76 5.70	15.76 15.84	150-152	65
3	1-Phenyl-1-(3-pyridyl)-2-(1,2,4-triazol-1-yl)-	$C_{15}H_{14}N_4O$	67.59 67.65	5.36 5.30	21.01 21.04	Oil	52
4	2-(Imidazol-1-yl)-1-phenyl-1-(3-pyridyl)-	$C_{16}H_{15}N_3O$	72.37 72.43	5.79 5.70	15.78 15.84	95-97	71
5	1-Phenyl-1-(4-pyridyl)-2-(1,2,4-triazol-1-yl)-	$C_{15}H_{14}N_4O$	67.61 67.65	5.33 5.30	21.07 21.04	153-155	65
6	2-(Imidazol-1-yl)-1-phenyl-1-(4-pyridyl)-	$C_{16}H_{15}N_3O$	72.35 72.43	5.75 5.70	15.76 15.84	87-89	77
7	1-(4-Fluorophenyl)-1-(2-pyridyl)-2-(1,2,4-triazol-1-yl)-	$C_{15}H_{13}FN_4O$	63.40 63.37	4.63 4.61	19.65 19.71	123-125	25
8	1-(4-Fluorophenyl)-2-(imidazol-1-yl)-1-(2-pyridyl)-	$C_{16}H_{14}FN_3O$	67.79 67.83	5.02 4.98	14.77 14.83	174-176	48
9	1-Cyclohexyl-1-(3-pyridyl)-2-(1,2,4-triazol-1-yl)-	$C_{15}H_{20}N_4O$	66.11 66.15	7.48 7.40	20.52 20.57	102-103	77
10	1-Cyclohexyl-2-(imidazol-1-yl)-1-(3-pyridyl)-	$C_{16}H_{21}N_3O$	70.75 70.82	7.83 7.80	15.41 15.49	89-91	94

TABLE 2. ^{1}H NMR Spectra of Compounds **1-10**

Compound	Chemical shifts, δ, ppm. (J, Hz)
1	5.1-5.2 (2H, AB-system, $J_1 = 0.8$, $J_2 = 0.1$, CH$_2$); 6.45 (1H, s, OH); 7.27 (3H, m, 3H$_{\text{Ph}}$); 7.53 (4H, m, 3-H, 4-H$_{\text{Py}}$, 2H$_{\text{Ph}}$); 7.74 (2H, m, 5-H$_{\text{Py}}$, CH triazole); 8.18 (1H, s, CH triazole); 8.60 (1H, m, 6-H$_{\text{Py}}$)
2	4.80-4.95 (2H, AB-system, $J_1 = 4$, $J_2 = 0.8$, CH$_2$); 6.25 (1H, s, OH); 6.70 (1H, s, CH imidazole); 7.24 (5H, m, 3H$_{\text{Ph}}$, 3-H$_{\text{Py}}$, CH imidazole); 7.51 (2H, m, 2H$_{\text{Ph}}$); 7.58 (1H, d, $J = 0.5$, 4-H$_{\text{Py}}$); 7.74 (1H, t, $J = 0.33$, 5-H$_{\text{Py}}$); 8.60 (1H, d, $J = 0.1$, 6-H$_{\text{Py}}$)
3	5.03-5.20 (2H, AB-system, $J_1 = 3.5$, $J_2 = 0.7$, CH$_2$); 6.50 (1H, s, OH); 7.30 (4H, m, 4-H$_{\text{Py}}$, 3H$_{\text{Ph}}$); 7.52 (2H, m, 2H$_{\text{Ph}}$); 7.73 (1H, s, CH triazole); 7.80 (1H, d, $J = 0.4$, 5-H$_{\text{Py}}$); 8.25 (1H, s, CH triazole); 8.40 (1H, d, $J = 0.1$, 2-H$_{\text{Py}}$); 8.68 (1H, d, $J = 0.08$, 6-H$_{\text{Py}}$)
4	4.80-4.95 (2H, AB-system, $J_1 = 4.2$, $J_2 = 1.0$, CH$_2$); 6.41 (1H, s, OH); 6.25 (1H, s, CH imidazole); 6.82 (s, 1H, 4-H imidazole); 7.28 (5H, m, 3H$_{\text{Ph}}$, CH imidazole, 5-H$_{\text{Py}}$); 7.50 (2H, m, 2H$_{\text{Ph}}$); 7.80 (1H, d, $J = 0.4$, 4-H$_{\text{Py}}$); 8.40 (1H, d, $J = 0.2$, 2-H$_{\text{Py}}$); 8.65 (1H, d, $J = 0.1$, 6-H$_{\text{Py}}$)
5	5.0-5.2 (2H, AB-system, $J_1 = 4$, $J_2 = 0.9$, CH$_2$); 6.50 (1H, s, OH); 7.29 (3H, m, 3H$_{\text{Ph}}$); 7.50 (4H, m, 2 3-H$_{\text{Py}}$, 2H$_{\text{Ph}}$); 7.75 (1H, s, CH triazole); 8.28 (1H, s, 3-H triazole); 8.45 (2H, m, 2H-2 Py)
6	4.80-4.95 (2H, AB-system, $J_1 = 4.1$, $J_2 = 0.9$, CH$_2$); 6.43 (1H, s, OH); 6.65 (1H, s, CH imidazole); 6.83 (1H, s, CH imidazole); 7.28 (4H, m, 3H$_{\text{Ph}}$, CH imidazole); 7.50 (4H, m, 2H-3 Py, 2H$_{\text{Ph}}$); 8.50 (2H, m, 2H-2 Py)
7	5.08-5.14 (2H, AB-system, $J_1 = 7.4$, $J_2 = 0.7$, CH$_2$); 6.55 (1H, s, OH); 7.07 (2H, m, 2H$_{\text{Ph}}$); 7.27 (1H, m, 4-H$_{\text{Py}}$); 7.50 (2H, m, 2H$_{\text{Ph}}$); 7.57 (1H, m, 3-H$_{\text{Py}}$); 7.72 (1H, s, CH triazole); 7.76 (1H, m, 5-H$_{\text{Py}}$); 8.20 (1H, s, CH triazole); 8.58 (1H, m, 6-H$_{\text{Py}}$)
8	4.81-4.89 (2H, AB-system, $J_1 = 8.8$, $J_2 = 1.1$, CH$_2$); 6.49 (1H, s, OH); 6.64 (1H, s, CH imidazole); 6.77 (1H, c, CH imidazole); 7.09 (2H, m, 2H$_{\text{Ph}}$); 7.27 (2H, m, 4-H$_{\text{Py}}$, CH imidazole); 7.53 (2H, m, 2H$_{\text{Ph}}$); 7.58 (1H, m, 3-H$_{\text{Py}}$); 7.75 (1H, t, $J = 0.3$, 5-H$_{\text{Py}}$); 8.58 (1H, d, $J = 0.1$, 6-H$_{\text{Py}}$)
9	0.80-1.95 (11H, m, CH cyclohexane); 4.68–5.87 (2H, AB-system, $J = 14.2$, CH$_2$); 4.68 (1H, s, OH); 7.26 (1H, dd, $J_1 = 0.38$, $J_2 = 0.3$, 5-H$_{\text{Py}}$); 7.69 (1H, dt, $J_1 = 0.38$, $J_2 = 0.07$, 4-H$_{\text{Py}}$); 7.76 (1 H, s, CH triazole); 8.00 (1H, s, CH triazole); 8.37 (1H, dd, $J_1 = 0{,}2$, $J_2 = 0{,}07$, 6-H$_{\text{Py}}$); 8.54 (1H, d, $J = 0.07$, 2-H$_{\text{Py}}$)
10	0.80-1.95 (11H, m, CH cyclohexane); 4.45 (2H, AB-system, $J = 1.89$, CH$_2$); 5.31 (1H, s, OH); 6.63 and 6.82 (2H, both s, each 1H, CH imidazole); 7.25 (1H, dd, $J_1 = 0.42$, $J_2 = 0.28$, 5-H$_{\text{Py}}$); 7.32 (1H, s, CH imidazole); 7.72 (1H, d, $J = 0.42$, 4-H$_{\text{Py}}$); 8.36 (1H, d, $J = 0.28$, 6-H$_{\text{Py}}$); 8.56 (1H, s, 2-H$_{\text{Py}}$)

The yields of the azolylpyridylethanols depend on the nature of the radical in the oxiranylpyridine ring and the nature of the azole and increase from 25% for 1-(4-fluorophenyl)-1-(2-pyridyl)-2-(1,2,4-triazol-1-yl)ethanol (**7**) to 94% for 1-cyclohexyl-2-(imidazol-1-yl)-1-(3-pyridyl)ethanol (**10**). It was a characteristic that the yield was higher for the imidazole derivative than the triazole for the same oxirane and the compound with an alicyclic radical gave a higher yield than did an aromatic (Table 1).

All of the compounds obtained showed high fungicidal activity.

EXPERIMENTAL

^{1}H NMR spectra were obtained on a Bruker AC-400 instrument (400 MHz) using DMSO-d$_6$ solvent.

2-, 3-, and 4-Benzoylpyridines are commercially available, **2-(4-fluorobenzoyl)pyridine** was prepared by acylation of fluorobenzene using 2-pyridinecarboxylic acid chloride [5].

Cyclohexyl 3-Pyridyl Ketone. BuLi (15%, 65 ml, 100 mmol) was added with stirring to a solution of 3-bromopyridine (15.8 g, 100 mmol) in absolute ether (60 ml) cooled to -70°C. The reaction product was then stirred for 10 min and a solution of cyclohexanecarboxylic acid dimethylamide (15.5 g, 100 mmol) in absolute

THF (100 ml) was added dropwise with stirring. Cooling was stopped and the mixture was left overnight. The mixture was evaporated in vacuo, a saturated solution of NH_4Cl (50 ml) was added, and the product was extracted with ether (3 × 100 ml). The ether extract was washed with saturated salt solution, dried over $MgSO_4$, solvent was distilled off, and the residue was distilled in vacuo to give cyclohexyl 3-pyridyl ketone (13.7 g, 72%); bp 140-155°C (1 mm Hg) (bp 141-142°C at 1 mm Hg [6]).

2-(2-Phenyloxiran-2-yl)pyridine. A solution of potassium *tert*-butoxide (4.63 g, 63 mmol) in DMSO (31 ml) was added dropwise over 30 min to a mixture of 2-benzoylpyridine (9.15 g, 50 mmol), trimethylsulfonium iodide (14.28 g, 70 mmol), and DMSO (31 ml) cooled to 0°C. Stirring was continued for 15 min, the product was cooled in ice and salt, water (150 ml) was added dropwise over 30 min, and then extracted with $CHCl_3$ (3 × 30 ml). The extract was washed with water (3 × 30 ml) and saturated salt solution (20 ml). The solution was dried over $MgSO_4$ and solvent was removed in vacuo to give the 2-(2-oxiranyl-2-phenyl)pyridine (6.3 g, 64%) as a reddish oil. ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.26-3.45 (2H, AB-system, $J_1 = 3.8$, $J_2 = 0.3$, CH_2); 7.40 (7H, m, $2H_{Py}$, $5H_{Ph}$); 7.83 (1H, t, $J = 0.3$, 4-H_{Py}); 8.60 (1H, m, 6-H_{Py}).

3-(2-Phenyloxiran-2-yl)pyridine. Yield 68%. Oil. ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.35-3.39 (2H, AB-system, $J = 0.93$, CH_2); 7.37 (6H, m, 3-H_{Py}, $5H_{Ph}$); 7.73 (1H, m, 4-H_{Py}); 8.55 (2H, m, 2-, 6-H_{Py}).

4-(2-Phenyloxiran-2-yl)pyridine. Yield 85%. Oil. ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.28-3.42 (2H, AB-system, $J_1 = 3$, $J_2 = 0.3$, CH_2); 7.24 (2H, m, $2H_{Ph}$); 7.40 (5H, m, 3-H_{Py}, $3H_{Ph}$); 8.55 (2H, m, 2-H_{Py}).

3-(2-Cyclohexyloxiran-2-yl)pyridine. Yield 85%. Oil. ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.75-1.75 (11H, m, CH cyclohexane); 2.70-3.10 (2H, AB-system, $J = 8$, CH_2); 7.38 (1H, dd, $J_1 = 0.42$, $J_2 = 0.21$, 5-H_{Py}); 7.66 (1H, dt, $J_1 = 0.42$, $J_2 = 0.1$, 4-H_{Py}); 8.45 (1H, dd, $J_1 = 0.21$, $J_2 = 0.1$, 2-H_{Py}); 8.47 (1H, d, $J = 0.1$, 6-H_{Py}).

The analysis of the **2-[2-(4-fluorophenyl)oxiran-2-yl]pyridine** by ^1H NMR spectroscopy gave unsatisfactory results due to its instability.

1-Phenyl-1-(2-pyridyl)-2-(1,2,4-triazol-1-yl)ethanol (1). Water (0.033 ml) and sodium hydroxide (0.11 g) were added to a solution of 2-(2-oxiranyl-2-phenyl)pyridine (1.65 g, 8.3 mmol) and triazole (0.57 g, 8.3 mmol) in DMF (5.63 ml). The product was stirred for 4 h at 120°C, cooled, and poured into water (40 ml). The precipitated crystals were filtered off, washed with water, and recrystallized from toluene to give compound **1** (1.2 g, 54%); mp 105-107°C.

The remaining azolylpyridylethanols were prepared similarly.

1-Phenyl-1-(3-pyridyl)-2-(1,2,4-triazol-1-yl)ethanol (3) separated as an oil and was purified by reprecipitation from toluene.

The yields, melting points, and elemental analytical data for the azolylpyridylethanols prepared are given in Table 1 and ^1H NMR spectroscopic data in Table 2.

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