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ADDITION OF NITRILE OXIDES TO ALLYL ESTERS OF ARYL-(HETARYL)CARBOXYLIC ACIDS*

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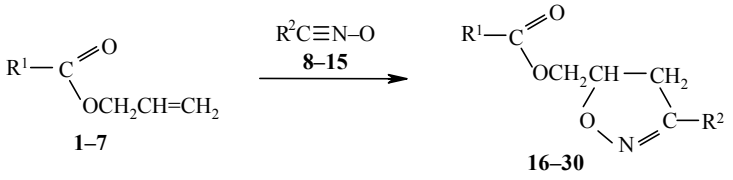
3,5-Disubstituted isoxazolines with an aryl(hetaryl) carboxymethyl group in position 5 have been synthesized. The addition reaction of nitrile oxides to allyl esters of aryl(hetaryl) carboxylic acids occurs regiospecifically with the formation of the 5-substituted isomer. Initial pharmacological screening showed that 5-(4-bromobenzoyloxy)methyl-3-(3,4-dimethoxyphenyl)isoxazoline possesses marked nootropic activity.

Keywords: isoxazolines, nitrile oxides, hydroxamic acid chlorides.

Isoxazolines are valuable synthons for obtaining various functionally substituted compounds (β-hydroxy ketones and acids, γ-amino alcohols, α,β-cyanohydrins, amino sugars, and complex heterocycles) [1-4], and also, thanks to the ability to interact with receptors, they possess marked biological activity [5-8].

One of the main methods of synthesis of these compounds is the [2 + 3] cycloaddition reaction of nitrile oxides or silyl nitronates to alkenes [**9-12**]. Derivatives of aryl(hetaryl) carboxylic acids **16-30**, containing an isoxazoline fragment in the ester group, have been synthesized by the addition of oxides of substituted aryl nitriles **8-15** to allyl esters of aryl(hetaryl) carboxylic acids **1-7**.



Compound	R^1	R^2	Compound	R^1	R^2
16	4-Br–C_6H_4–	C_6H_5–	**24**	2-Cl–C_6H_4–	4-CH_3O–C_6H_4–
17	4-Br–C_6H_4–	2-CH_3O–C_6H_4–	**25**	2-Cl–C_6H_4–	4-Cl–C_6H_4–
18	4-Br–C_6H_4–	3-CH_3O–C_6H_4–	**26**	2,4-Cl_2–C_6H_3–	4-CH_3O–C_6H_4–
19	4-Br–C_6H_4–	4-CH_3O–C_6H_4–	**27**	2,4-Cl_2–C_6H_3–	4-Cl–C_6H_4–
20	4-Br–C_6H_4–	3,4-$(CH_3O)_2$–C_6H_3–	**28**	2,4-Cl_2–C_6H_3–	4-O_2N–C_6H_4–
21	4-Br–C_6H_4–	2-Cl–C_6H_4–	**29**	5-Br–Furyl-	4-CH_3O–C_6H_4–
22	4-I–C_6H_4–	4-CH_3O–C_6H_4–	**30**	2-Quinolyl-	4-Cl–C_6H_4–
23	4-O_2N–C_6H_4–	4-CH_3O–C_6H_4–			

* Dedicated to Professor O. Neilands on the occasion of his Jubilee.

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The reaction was carried out in "one pot" sequentially by 1) conversion of a substituted aryl(hetaryl) oxime with N-chlorosuccinimide in chloroform to the corresponding arylhydroxamic acid chloride; 2) addition of the unsaturated compound, and 3) addition of triethylamine as dehydrohalogenating agent to generate the nitrile oxide.

The reaction proceeds regioselectively, only one regioisomer, the 5-substituted isoxazoline, is always formed.

Initial pharmacological screening for psychotropic activity showed that 5-(4-bromobenzoyloxy)methyl-3-(3,4-dimethoxyphenyl)isoxazoline (**20**) at a dose of 5 mg/kg possesses marked nootropic activity.

TABLE 1. Characteristics of Isoxazoline Derivatives **16-30**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
16	$C_{17}H_{14}BrNO_3$	56.59 / 56.69	3.84 / 3.92	3.85 / 3.89	146	70
17	$C_{18}H_{16}BrNO_4$	55.45 / 55.40	4.13 / 4.13	3.54 / 3.59	105	68
18	$C_{18}H_{16}BrNO_4$	55.26 / 55.40	4.12 / 4.13	3.60 / 3.59	87	69
19	$C_{18}H_{16}BrNO_4$	55.40 / 55.40	4.09 / 4.13	3.60 / 3.59	140	72
20	$C_{19}H_{18}BrNO_5$	54.38 / 54.30	4.25 / 4.32	3.27 / 3.33	134	69
21	$C_{17}H_{13}BrClNO_3$	51.56 / 51.74	3.29 / 3.32	3.56 / 3.55	72	71
22	$C_{18}H_{16}INO_4$	49.61 / 49.45	3.71 / 3.69	3.13 / 3.20	146	70
23	$C_{18}H_{16}N_2O_6$	60.42 / 60.67	4.53 / 4.53	7.77 / 7.86	185	67
24	$C_{18}H_{16}ClNO_4$	62.57 / 62.52	4.64 / 4.66	4.02 / 4.05	62	69
25	$C_{17}H_{13}Cl_2NO_3$	58.39 / 58.31	3.76 / 3.74	4.02 / 4.00	76	68
26	$C_{18}H_{15}Cl_2NO_4$	56.91 / 56.86	3.99 / 3.97	3.62 / 3.68	125	65
27	$C_{17}H_{12}Cl_3NO_3$	52.92 / 53.08	3.16 / 3.14	3.63 / 3.64	104	67
28	$C_{17}H_{12}Cl_2N_2O_5$	51.69 / 51.67	3.09 / 3.06	7.14 / 7.09	136	51
29	$C_{16}H_{14}BrNO_5$	50.51 / 50.55	3.70 / 3.71	3.70 / 3.68	143	50
30	$C_{20}H_{15}ClN_2O_3$	65.37 / 65.49	4.14 / 4.12	7.68 / 7.64	146	52

TABLE 2. ^{1}H NMR Spectra of Isoxazolines **16-30**

Compound	Chemical shifts, δ, ppm, coupling constants, *J* (Hz)
1	2
16	3.23 (1H, dd, *J* = 6.5, *J* = 15.8, CH); 3.54 (1H, dd, *J* = 9.8, *J* = 15.8, CH); 4.49 (2H, m, OCH_2); 5.12 (1H, m, CH); 7.36-7.78 (7H, m, H arom); 7.89 (2H, d, *J* = 7.9, H arom)
17	3.34 (1H, dd, *J* = 6.3, *J* = 16.7, CH); 3.67 (1H, dd, *J* = 9.8, *J* = 16.7, CH); 3.81 (3H, s, OCH_3); 4.48 (2H, m, OCH_2); 5.08 (1H, m, CH); 6.84-7.07 (2H, m, H arom); 7.41 (1H, dd, *J* =1.5, *J* = 7.5, H arom), 7.56 (2H, d, *J* = 8.2, H arom), 7.78 (1H, dd., *J* = 1.5, *J* = 7.5, H arom), 7.94 (2H, d, *J* = 8.2, H arom)
18	3.21 (1H, dd, *J* = 6.8, *J* = 15.9, CH); 3.54 (1H, dd, *J* = 9.4, *J* = 15.9, CH); 3.85 (3H, s, OCH_3); 4.43 (1H, dd, *J* = 5.2, *J* = 10.9, OCH_2); 4.52 (1H, dd, *J* = 3.2, *J* = 10.9, OCH_2); 5.11 (1H, m, CH); 6.92-7.18 (1H, m, H arom); 7.25-7.33 (3H, m, H arom); 7.58 (2H, d, *J* = 8.4, H arom); 7.87 (2H, d, *J* = 8.4, H arom)

TABLE 2 (continued)

1	2
19	3.21 (1H, dd, J = 6.4, J = 16.1, CH); 3.56 (1H, dd, J = 9.7, J = 16.1, CH); 3.85 (3H, s, OCH_3); 4.47 (2H, m, OCH_2); 5.09 (1H, m, CH); 6.96 (2H, d, J = 8.2, H arom), 7.56 (2H, d, J = 7.8, H arom); 7.67 (2H, d, J = 8.2, H arom); 7.92 (2H, d, J = 7.8, H arom)
20	3.21 (1H, dd, J = 6.7, J = 16.2, CH); 3.54 (1H, dd, J = 9.8, J = 16.2, CH); 3.92 (6H, s, $2 \times OCH_3$); 4.47 (2H, m, OCH_2); 5.12 (1H, m, CH); 6.89-7.12 (2H, m, H arom); 7.36-7.58 (3H, m, H arom); 7.89 (2H, d, J = 7.8, H arom)
21	3.38 (1H, dd, J = 6.6, J = 16.0, CH); 3.69 (1H, dd, J = 9.8, J = 16.0, CH); 4.47 (2H, m, OCH_2); 5.09 (1H, m, CH); 7.27-7.65 (4H, m, H arom); 7.52 (2H, d, J = 7.5, H arom); 7.89 (2H, d, J = 7.5, H arom)
22	3.18 (1H, dd, J = 6.3, J = 15.5, CH); 3.52 (1H, dd, J = 9.8, J = 15.5, CH); 3.85 (3H, s, OCH_3); 4.47 (2H, m, OCH_2); 5.08 (1H, m, CH); 6.96 (2H, d, J = 8.2, H arom); 7.65 (2H, d, J = 8.2, H arom); 7.76 (4H, s, H arom)
23	3.21 (1H, dd, J = 6.6, J = 15.9, CH); 3.56 (1H, dd, J = 9.6, J = 15.9, CH); 3.89 (3H, s, OCH_3); 4.52 (2H, m, OCH_2); 5.12 (1H, m, CH); 6.98 (2H, d, J = 8.2, H arom); 7.67 (2H, d, J = 8.2, H arom); 8.27 (4H, s, H arom)
24	3.25 (1H, dd, J = 7.2, J = 16.0, CH); 3.54 (1H, dd, J = 9.9, J = 16.0, CH); 3.83 (3H, s, OCH_3); 4.52 (2H, d, J = 4.4, OCH_2); 5.09 (1H, m, CH); 6.96 (2H, d, J = 8.2, H arom); 7.21–7.47 (3H, m, H arom); 7.65 (2H, d, J = 8.2, H arom); 7.87 (1H, dd, J = 0.5, H arom, = 5.9, H arom)
25	3.25 (1H, dd, J = 6.9, J = 15.9, CH); 3.52 (1H, dd, J = 9.6, J = 15.9, CH); 4.47 (1H, dd, J = 4.2, J = 9.6, OCH_2); 4.56 (1H, dd, J = 3.4, J = 9.6, OCH_2); 5.13 (1H, m, CH); 7.18-7.47 (5H, m, H arom); 7.65 (2H, d, J = 8.1, H arom); 7.78-7.92 (1H, m, H arom)
26	3.23 (1H, dd, J = 7.2, J = 16.5, CH); 3.54 (1H, dd, J = 10.1, J = 16.5, CH); 3.87 (3H, s, OCH_3); 4.43 (1H, dd, J = 4.4, J = 10.7, OCH_2); 4.56 (1H, dd, J = 2.8, J = 10.7, OCH_2); 5.11 (1H, m, CH); 6.98 (2H, d, J = 8.7, H arom); 7.24 (1H, dd, J = 1.5, J = 7.2, H arom); 7.52 (1H, d, J = 1.5, H arom); 7.67 (2H, d, J = 8.7, H arom); 7.87 (1H, d, J = 7.2, H arom)
27	3.25 (1H, dd, J = 7.5, J = 15.9, CH); 3.54 (1H, dd, J = 9.8, J = 15.9, CH); 4.45 (1H, dd, J = 4.6, J = 10.1, OCH_2); 4.58 (1H, dd, J =3.8, J = 10.1, OCH_2); 5.16 (1H, m, CH); 7.21-7.34 (2H, m, H arom); 7.43 (2H, d, J = 8.0, H arom); 7.65 (2H, d, J = 8.0, H arom); 7.85 (1H, d, J = 7.9, H arom)
28	3.34 (1H, dd, J = 7.1, J = 15.2, CH); 3.61 (1H, dd, J = 10.2, J = 15.2, CH); 4.47 (1H, dd, J = 4.1, J = 10.1, OCH_2); 4.67 (1H, dd, J =3.2, J = 10.1, OCH_2); 5.24 (1H, m, CH); 7.23-7.49 (2H, m, H arom); 7.87 (2H, d, J = 8.2, H arom); 8.21-8.41 (1H, m, H arom); 8.32 (2H, d, J = 8.2, H arom)
29	3.18 (1H, dd, J = 6.6, J = 15.9, CH); 3.49 (1H, dd, J = 9.7, J = 15.9, CH); 3.83 (3H, s, OCH_3); 4.45 (2H, m, OCH_2); 5.08 (1H, m, CH); 6.47 (1H, d, J =3.1, H fur.); 6.96 (2H, d, J = 8.2, H arom); 7.14 (1H, d, J =3.1, H fur.); 7.65 (2H, d, J = 8.2, H arom)
30	3.32 (1H, dd, J = 6.2, J = 15.9, CH); 3.58 (1H, dd, J = 9.7, J = 15.9, CH); 4.67 (2H, d, J = 4.1, OCH_2); 5.24 (1H, m, CH); 7.43 (2H, d, J = 8.3, H arom) 7.69 (2H, d, J = 8.3, H arom); 7.81-7.96 (3H, m, H arom); 8.12-8.38 (3H, m, H arom)

EXPERIMENTAL

The ^{1}H NMR spectra of the synthesized compounds were recorded on a Bruker WP 90 (90.1 MHz) in deuterochloroform, internal standard was TMS.

General Procedure for Obtaining Isoxazolines 16-30 [13]. Oxime (10 mmol) was added in one portion to a suspension of N-chlorosuccinimide (10 mmol) in dry chloroform (20 ml). After this as the N-chlorosuccinimide passed into solution (end of chlorination), the olefin (5 mmol) was added. Triethylamine (11 mmol) in chloroform (11 ml) was added dropwise to the solution during 30 min. The reaction mixture was maintained at room temperature a further 30 min, and then washed with water (2 × 21 ml). The organic layer was dried with anhydrous sodium sulfate, and evaporated in vacuum. The isoxazolines were purified by crystallization from acetonitrile or by column chromatography (SiO_2, hexane–ethyl acetate, 20%).

The characteristics of the compounds obtained are given in Tables 1 and 2.

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