The preparation and fungicidal activity of a series of 1-[(3-arylisoxazolin- or isoxazol-5-yl)methyl]-1*H*-1, 2, 4-triazoles

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The synthesis and fungicidal activity of a novel series of 1-[(3-arylisoxazolin-5-yl)methyl]-1*H*-1, 2, 4-triazoles *V* and 1-[(3-arylisoxazol-5-yl)methyl]-1*H*-1, 2, 4-triazoles *VI* are discussed. The preparation of *V* and *VI* was straightforward and highlighted by a regiospecific 1, 3-dipolar cycloaddition of substituted benzonitrile oxides *II* with 1-allyl- (*III*) or 1-propargyl-1*H*-1, 2, 4-triazole (*IV*).

Dipolar cycloadditions of nitrile oxides with unsaturated compounds are of synthetic interest since the products isoxazolines and isoxazoles, respectively, are versatile intermediates for the synthesis of bifunctional compounds [1—3]. As a part of research on applications of the 1, 3-dipolar cycloadditions to the synthesis of biologically effective compounds, recently, we have reported the synthesis and biological activity of a novel class of antifungal isoxazolines, the preparation of which involved a cycloaddition of arylnitrile oxides with arylmaleinimides [4, 5]. Previous reports [6, 7] by a number of research laboratories indicated that introducing a 1*H*-1, 2, 4-triazole ring provided compounds having a more potent *in vivo* antifungal activity. The fact that compounds bearing a 1*H*-1, 2, 4-triazole group are of potential use in agrochemistry [8], coupled with better pharmacokinetic profile [9] made triazole derivatives attractive and promising targets as systemic antifungal agents. With a view to studying the influence of substituents on the fungicidal activity, reactions of some unsaturated compounds possessing a 1*H*-1, 2, 4-triazole ring with nitrile oxides have been investigated and the results together with the testing of fungicidal properties of the prepared compounds are reported in this paper.

1-Allyl- and 1-propargyl-1*H*-1, 2, 4-triazoles (*III* resp. *IV*) were prepared by established procedures [10] involving treatment of sodium salt of 1*H*-1, 2, 4-

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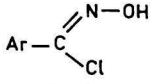
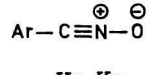
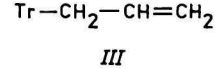
-triazole with allyl and propargyl bromide. The unstable substituted benzonitrile oxides *II* (Scheme 1) formed *in situ* from the corresponding *N*-hydroxybenzenecarboximidoyl chlorides *I* in the presence of potassium carbonate as acid receptor and one sterically stable nitrile oxide, *viz.* 2,4,6-trimethylbenzonitrile oxide (*IId*) were chosen for the reaction with *III* and *IV* The reactions were conducted in chloroform using equimolar amounts of reactants. In all cases, isoxazoline and isoxazole derivatives *V* resp. *VI*, were obtained as the solo products in very good yields. The results are summarized in Tables 1 and 2. Surprisingly, the classical method using triethylamine [11] as acid receptor gave lower yields of cycloadducts in comparison to potassium carbonate.



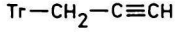
Ia–Iu



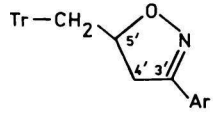
IIa–IIu



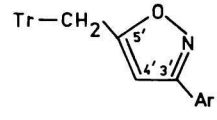
III



IV

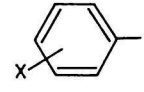


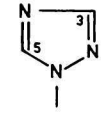
Va–Vu



VIa–VIu

For *I–VI*

Ar 

Tr 

X		X		X		X	
a	H	*f*	4-OCH_3	*k*	3-NO_2	*p*	3-Cl
b	3-CH_3	*g*	2,5-diOCH_3	*l*	4-NO_2	*r*	4-Cl
c	4-CH_3	*h*	3,4,5-triOCH_3	*m*	3-F	*s*	2,4-diCl
d	2,4,6-triCH_3		2-OCH_3-3,5-diCl	*n*	4-F	*t*	3,4-diCl
e	2-OCH_3	*j*	2-NO_2	*o*	2-Cl		4-Br

Scheme 1

The structure of the products was determined by ^1H and ^{13}C NMR spectra and elemental analyses. As expected [2, 3], the cycloadditions were highly regioselective, ^{13}C NMR spectroscopy showed the presence of a single isomer in all cases studied rather than a mixture of regioisomers. The regioselectivity observed in these cycloaddition reactions can be explained on the basis of the

Table 1

Characterization of the prepared 1-[(3-arylisoxazolin-5-yl)methyl]-1*H*-1,2,4-triazoles *V*

Compound	Formula M_r	w_i(calc.)/% w_i(found)/%			Yield	M. p.	λ_{max}/nm
		C	H	N	%	°C	log ε
Va	$C_{12}H_{12}N_4O$	63.14	5.30	24.54	82	104—106	260
	228.25	63.25	5.44	24.38			3.15
Vd	$C_{15}H_{18}N_4O$	66.64	6.71	20.72	89	71—73	234 sh
	270.32	66.81	6.55	20.81			2.38
Vg	$C_{14}H_{16}N_4O_3$	58.32	5.59	19.43	80	110—112	262, 323
	288.30	58.44	5.41	19.30			2.82, 2.60
Vj	$C_{12}H_{11}N_5O_3$	52.74	4.05	25.63	90	104—106	241 sh
	273.25	52.63	3.99	25.42			2.75
Vk	$C_{12}H_{11}N_5O_3$	52.74	4.05	25.63	88	150—152	257
	273.25	52.60	3.89	25.48			3.20
Vl	$C_{12}H_{11}N_5O_3$	52.74	4.05	25.63	74	169—171	304
	273.25	52.55	4.00	25.48			3.05
Vn	$C_{12}H_{11}FN_4O$	58.52	4.50	22.75	85	97—99	259
	246.24	58.38	4.30	22.91			3.02
Vo	$C_{12}H_{11}ClN_4O$	54.86	4.22	21.32	87	Oil	253
	262.69	54.71	4.49	21.01			2.75
Vp	$C_{12}H_{11}ClN_4O$	54.86	4.22	21.32	82	130—132	263
	262.69	54.62	4.01	21.43			3.04
Vr	$C_{12}H_{11}ClN_4O$	54.86	4.22	21.32	78	123—125	265
	262.69	54.72	4.31	21.22			3.21
Vs	$C_{12}H_{10}Cl_2N_4O$	48.50	3.39	18.85	79	130—132	262
	297.14	48.33	3.41	18.66			2.64
Vt	$C_{12}H_{10}Cl_2N_4O$	48.50	3.39	18.85	66	126—128	265
	297.14	48.41	3.42	18.91			3.18
Vu	$C_{12}H_{11}BrN_4O$	46.92	3.61	18.24	72	136—137	267
	307.15	46.86	3.73	18.31			3.23

model proposed by *Houk* for HOMO—LUMO interactions between the reacting species [12, 13].

The structure of the products 1-[(3-arylisoxazolin-5-yl)methyl]-1*H*-1,2,4-triazole *V* obtained by the reaction of nitrile oxides *II* with compound *III* was determined on the basis of the comparable chemical shifts of 5-methine and 4-methylene protons and carbons with those (Tables 3 and 5) of analogues reported in the literature [14].

The chemical shift of the angular methine signal shows undoubtedly that the orientation of the addition reactions is such as indicated in Scheme 1. Similarly, the oxides *II* readily underwent the 1,3-dipolar cycloaddition with *IV* This

Table 2

Characterization of the prepared 1-[(3-arylisoxazol-5-yl)methyl]-1*H*-1,2,4-triazoles *VI*

Compound	Formula M_r	w_i(calc.)/% w_i(found)/%			Yield	M. p.	λ_{max}/nm
		C	H	N	%	°C	log ε
VIa	$C_{12}H_{10}N_4O$	63.70	4.45	24.76	92	108—109	242
	226.22	63.51	4.40	24.82			2.79
VIb	$C_{13}H_{12}N_4O$	64.98	5.03	23.32	82	81—83	245
	240.25	64.73	5.11	23.18			2.70
VIc	$C_{13}H_{12}N_4O$	64.98	5.03	23.32	78	102—103	248
	240.25	64.80	5.16	23.14			2.83
VId	$C_{15}H_{16}N_4O$	67.14	6.01	20.88	88	94—95	232 sh
	268.30	67.03	6.12	20.67			2.45
VIe	$C_{13}H_{12}N_4O_2$	60.92	4.72	21.86	71	101—103	245, 294
	256.26	60.79	4.81	21.73			2.68, 2.30
VIf	$C_{13}H_{12}N_4O_2$	60.92	4.72	21.86	78	113—114	261
	256.26	60.80	4.65	21.78			2.89
VIg	$C_{14}H_{14}N_3O_3$	58.73	4.92	19.57	82	122—124	246 sh, 318
	286.28	58.64	4.85	19.65			2.56, 2.34
VIh	$C_{15}H_{16}N_4O_4$	56.95	5.09	17.71	65	142—144	266
	316.31	56.82	5.14	17.65			2.68
VIi	$C_{13}H_{10}Cl_2N_4O_2$	48.01	3.10	17.23	72	96—97	244 sh
	325.15	47.91	3.00	17.01			2.62
VIj	$C_{12}H_9N_5O_3$	53.13	3.34	25.82	92	86—88	244 sh
	271.23	53.25	3.18	25.94			2.81
VIk	$C_{12}H_9N_5O_3$	53.13	3.34	25.82	88	109—111	232, 264 sh
	271.23	53.00	3.24	25.69			3.26, 2.78
VIl	$C_{12}H_9N_5O_3$	53.13	3.34	25.82	91	136—138	277
	271.23	53.21	3.41	25.93			2.81
VIm	$C_{12}H_9FN_4O$	59.01	3.71	22.94	62	99—100	242
	244.22	58.89	3.83	22.78			2.81
VIn	$C_{12}H_9FN_4O$	59.01	3.71	22.94	70	86—88	243
	244.22	59.14	3.79	23.05			2.76
VIo	$C_{12}H_9ClN_4O$	55.28	3.48	21.49	72	65—67	237
	260.67	55.41	3.58	21.61			2.85
VIp	$C_{12}H_9ClN_4O$	55.28	3.48	21.49	76	91—93	243
	260.67	55.11	3.58	21.33			2.73
VIr	$C_{12}H_9ClN_4O$	55.28	3.48	21.49	70	90—92	247
	260.67	55.15	3.60	21.58			2.86
VIs	$C_{12}H_8Cl_2N_4O$	48.83	2.73	18.98	75	115—117	243
	295.15	48.71	2.90	19.10			2.76
VIt	$C_{12}H_8Cl_2N_4O$	48.83	2.73	18.98	80	107—109	249
	295.15	48.72	2.58	18.75			2.88
VIu	$C_{12}H_9BrN_4O$	47.07	2.96	18.30	88	96—97	252
	305.13	47.20	2.82	18.45			2.93

Table 3

^{1}H NMR spectral data of 1-[(3-arylisoxazolin-5-yl)methyl]-1*H*-1,2,4-triazoles *V*

Compound	δ						
	H-3 s	H-5 s	H-5′ m	H_A-4′ dd	H_B-4′ dd	CH_2 d	H_{arom}
Va	7.91	8.23	5.10	3.53	3.29	4.42	7.41—7.67
Vd[a]	7.99	8.39	5.12	3.30	3.07	4.52	6.87
Vg[b]	7.93	8.26	5.07	3.62	3.34	4.40	6.84—7.26
Vj[c]	8.00	8.55	5.17	3.56	3.00	4.45	7.62—8.03
Vk	7.89	8.36	5.21	3.55	3.42	4.49	7.57—8.36
Vl	7.89	8.25	5.21	3.53	3.40	4.49	7.74—8.26
Vn	7.95	8.39	5.14	3.49	3.30	4.47	7.06—7.61
Vp	7.93	8.30	5.14	3.48	3.31	4.46	7.25—7.58
Vr	7.90	8.24	5.13	3.47	3.29	4.44	7.35—7.54
Vs	7.91	8.25	5.15	3.66	3.44	4.44	7.24—7.43
Vt	7.95	8.38	5.16	3.47	3.31	4.47	7.45—7.66
Vu	7.89	8.23	5.13	3.47	3.29	4.44	7.22—7.54

a) 2.27 (s, 3H, CH_3), 2.11 (s, 3H, CH_3); *b*) 3.79 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3); *c*) CD_3SOCD_3.

reaction gave exclusively 1-[(3-arylisoxazol-5-yl)methyl]-1*H*-1,2,4-triazole *VI* in excellent yields (Tables 2, 4, 6); the alternative 1,3-addition product described in the reaction of benzonitrile oxide with phenylacetylene [15] was not detected at all.

The structural resemblance between the products obtained and some of the reported biologically active 1*H*-1,2,4-triazole derivatives [6—9] led us to test fungicidal properties of our products. The compounds *V* and *VI* were evaluated for control of the phytopathogenic fungi *Phytophthora infestans*, *Alternaria species*, *Botrytis cinerea*, and *Fusarium nivale* in *in vitro* tests and *Erysiphe graminis* on barley in *in vivo* test [4, 5]. From the isoxazoline series *V* only the chloro- and nitro-substituted derivatives showed fungicidal activity in both *in vitro* and *in vivo* testing. For example, *Vt* efficiently controls *Erysiphe graminis* on barley, however, not sufficiently as to justify its commercializations. The isoxazole series *VI* shows a large dependence between the fungicidal activity and structure. No activity has been found with the methoxy- and bromo-substituted derivatives *VI*, nitro and methyl derivatives show only moderate fungicidal effects. The parent derivative *VIa* is active only *in vitro* and the fluoro--substituted derivatives *in vivo*. The only minor exceptions are the chloro--substituted derivatives *VI*, which exhibit fungicidal activity both *in vitro* and *in vivo*. But none of the compounds screened showed antifungal activity, as in the case with the reference compounds.

Table 4

^{13}C NMR chemical shifts of 1-[(3-arylisoxazolin-5-yl)methyl]-1*H*-1,2,4-triazoles *V*

Compound	δ							
	C-3′	C-4′	C-5′	C-3	C-5	CH_2	C_{arom}	
Va	156.65	37.79	78.40	152.10	144.21	52.28	130.50,	128.81,
							126.77	
Vd[a]	157.64	41.27	77.73	151.61	144.33	52.00	139.12,	136.33,
							128.55,	125.26
Vg[b]	156.25	40.19	78.43	151.92	144.12	52.47	153.50,	118.13,
							113.22,	112.91
Vj[c]	154.87	37.55	78.83	151.61	144.91	51.45	147.94,	133.23,
							131.26,	131.60,
							124.30,	122.94
Vk	155.03	37.24	79.16	152.22	148.46	52.07	132.21,	130.53,
							129.94,	124.96,
							121.59	
Vl	155.14	37.12	79.30	152.20	143.81	52.13	134.66,	127.51,
							124.06	
Vn	155.66	37.80	78.37	151.45	144.31	52.44	165.66,	128.82,
							124.93,	116.17
Vp	155.60	37.48	78.62	151.90	144.02	52.29	134.84,	130.48,
							130.39,	130.05,
							126.76,	124.78
Vr	155.73	37.56	78.59	152.03	144.30	52.23	136.56,	129.10,
							127.97,	127.18
Vs	155.73	39.71	79.06	152.10	144.38	52.17	136.73,	133.45,
							131.30,	130.43,
							127.52,	126.74
Vt	154.90	37.60	78.78	151.93	144.45	52.34	134.71,	133.24,
							130.87,	128.60,
							125.75,	128.50
Vu	155.82	37.50	78.62	152.10	144.18	52.30	129.10,	127.96,
							127.61,	124.88

a) 21.05 (q, CH_3), 19.58 (q, CH_3); *b*) 56.10 (q, OCH_3), 55.85 (q, OCH_3); *c*) CD_3SOCD_3.

Experimental

Melting points were determined with a Kofler apparatus. ^{1}H and ^{13}C NMR spectra were obtained from deuterochloroform solutions, relative to tetramethylsilane, on a Varian VX 300 instrument (300 MHz). Ultraviolet spectra were obtained on a spectrometer M-40 (Zeiss, Jena) in methanol. Values of ε are given in $m^2 mol^{-1}$ The progress of the reaction was followed by thin-layer chromatography (TLC) on silica gel plates.

Table 5

^{1}H NMR spectral data of 1-[(3-arylisoxazol-5-yl)methyl]-1*H*-1,2,4-triazoles *VI*

Compound	δ					
	H-4′	H-3	H-5	CH_2	H_{arom}	CH_3
VIa	6.57	8.02	8.26	5.54	7.44—7.87	—
VIb	6.55	8.02	8.29	5.54	7.25—7.59	2.39
VIc[a]	6.99	8.05	8.72	5.73	7.29—7.75	2.49
VId	6.21	8.02	8.31	5.57	6.92	2.10—2.30
VIf	6.51	8.02	8.29	5.53	6.96, 7.71	3.85
VIg[a]	6.89	8.05	8.72	5.74	7.07—7.26	3.80, 3.73
VIh[a]	7.06	8.05	8.71	5.73	7.13	3.84, 3.71
VIi[a]	6.97	8.06	8.73	5.79	7.75—7.84	3.72
VIj	6.42	8.03	8.36	5.58	7.26—8.04	—
VIk	6.67	8.04	8.30	5.59	7.64—8.61	—
VIm[a]	7.09	8.06	8.72	5.76	7.35—7.73	—
VIn[a]	7.04	8.05	8.72	5.75	7.31—7.94	—
VIo	6.74	8.00	8.27	5.55	7.26—7.70	—
VIp[a]	7.12	8.06	8.73	5.76	7.54—7.93	—
VIr[a]	7.08	8.05	8.72	5.75	7.56—7.90	—
VIs[a]	6.95	8.06	8.79	5.79	7.55—7.84	—
VIu[a]	7.06	8.06	8.73	5.76	7.69—7.83	—

a) CD_3SOCD_3.

Compounds *III* and *IV* were prepared according to [10]. *N*-Hydroxybenzenecarboximidoyl chlorides *I* were prepared by chlorination of the corresponding benzal oximes in chloroform according to [16], *N*-hydroxymethoxybenzenecarboximidoyl chlorides were obtained by treatment of oxime with nitrosyl chloride [17], *IId* was synthesized according to [18].

Antifungal screening assay was described in [4].

Triazoles Va—Vu and VIa—VIu

III (5.5 g; 0.05 mol) or *IV* (5.4 g; 0.05 mol) was dissolved in chloroform (50 cm^3) and mixed with an aqueous solution (20 cm^3) of potassium carbonate (3.8 g; 0.0275 mol). The stirred mixture was kept at 0 °C for 10 min, and *N*-hydroxybenzenecarboximidoyl chlorides (0.05 mol) were added during 1 h. The reaction mixture was then stirred at 0 °C for 1 h and at room temperature for 5 h. Organic layer was separated and combined with chloroform extracts (2×20 cm^3) of the aqueous layer, dried over Na_2SO_4 and evaporated. Products were isolated by column chromatography (silica gel/chloroform).

The cycloadditions of *IId* were performed by the following way: The nitrile oxide (0.05 mol) and dipolarophile *III* or *IV* (0.05 mol) in dry benzene (30 cm^3) were heated to 80 °C for 4 h. After cooling, the mixture was concentrated and worked up as described above.

Table 6

^{13}C NMR chemical shifts of 1-[(3-arylisoxazol-5-yl)methyl]-1*H*-1, 2, 4-triazoles *VI*

Compound	δ							
	C-3′	C-4′	C-5′	C-3	C-5	CH_2	C_{arom}	
VIa	162.87	102.15	165.48	152.68	143.62	44.87	130.42, 128.25,	129.02, 126.84
VIb[a]	162.97	102.21	165.35	152.57	138.81	44.91	131.18, 128.11, 123.98	128.90, 127.42,
VIc[b,h]	162.02	101.81	167.18	152.04	144.82	43.88	140.14, 126.53,	129.126, 125.31
VId[c]	162.60	105.50	164.78	152.43	143.59	44.95	139.17, 128.46,	137.07, 125.18
VIf[d]	162.46	101.95	165.12	152.50	143.60	44.95	161.31, 120.73,	128.27, 114.43
VIg[e,h]	159.57	104.98	166.23	152.03	144.81	43.74	153.06, 117.18, 113.69,	151.16, 117.11, 113.47
VIh[f,h]	162.12	102.12	167.27	152.07	144.82	43.95	153.32, 123.55,	139.11, 104.07
VIi[g,h]	158.19	104.30	167.50	152.08	144.88	43.75	152.71, 129.39, 127.75,	131.57, 129.04, 125.17
VIj	160.40	104.53	165.32	152.73	143.41	44.75	148.41, 131.72, 124.72,	133.20, 131.02, 123.64
VIk	161.04	102.09	166.63	152.79	143.67	44.80	132.50, 130.07, 121.87	130.22, 125.00,
VIm[h]	164.29	102.15	167.75	152.09	144.86	43.89	164.03, 130.39, 117.39,	131.40, 122.81, 113.37
VIn[h]	164.91	101.93	167.50	152.05	144.83	43.88	161.62, 124.71,	129.08, 116.33
VIo	161.46	105.39	164.68	152.60	143.63	44.79	132.86, 130.94, 127.52,	131.23, 130.46, 127.20
VIp[h]	161.35	102.32	168.05	152.32	145.10	44.17	134.16, 130.51, 126.89,	131.35, 130.39, 125.50
VIr[h]	161.25	101.99	167.70	152.13	144.10	43.89	135.11, 128.47,	129.27, 127.00
VIs[h]	159.99	104.81	167.00	152.11	144.20	43.72	135.61, 132.28, 128.00,	132.85, 129.97, 126.38
VIu[h]	161.57	102.19	167.95	152.32	145.09	44.14	132.40, 127.60,	128.91, 124.10

a) 21.36 (q, CH_3); *b*) 20.94 (q, CH_3); *c*) 21.11, 20.24 (q, CH_3); *d*) 55.38 (q, OCH_3); *e*) 56.20, 55.53 (q, OCH_3); *f*) 60.09, 56.07 (q, OCH_3); *g*) 61.40 (q, OCH_3); *h*) CD_3SOCD_3.

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