1*H*-1,2,4-TRIAZOLE SUBSTITUTED β-AMINOENONES. β-DIONES AND PYRAZOLES AS POTENTIAL FUNGICIDES

Ivan SKAČÁNI[b], Ľubor FIŠERA[a,*], Margita BARTOVIČOVÁ[b], Štefan VARKONDA[b] and Oľga HÝBLOVÁ[b]

[a] *Department of Organic Chemistry, Slovak Technical University, 812 37 Bratislava*
[b] *Research Institute of Chemical Technology, 831 06 Bratislava*

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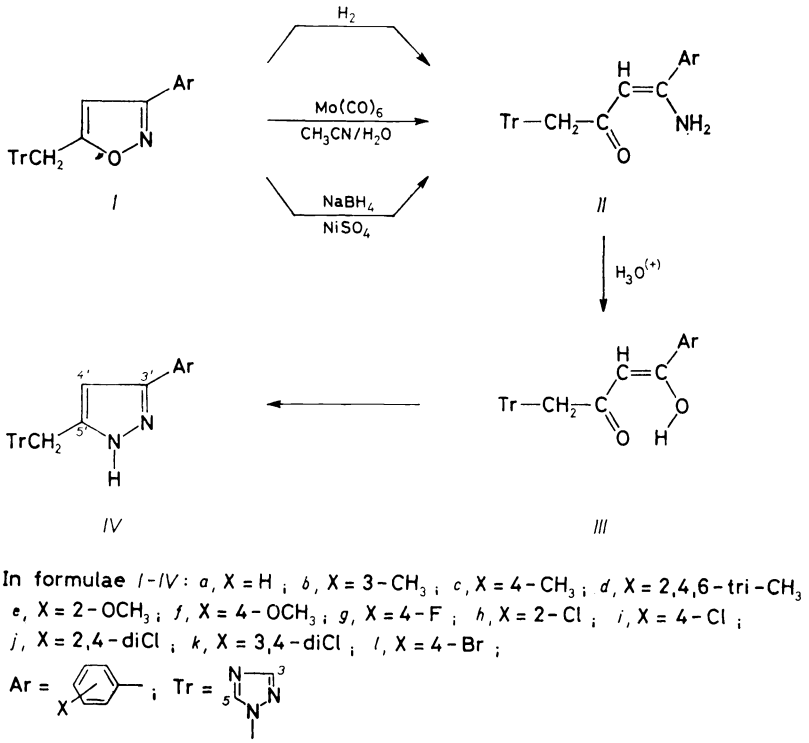
The 1-(1*H*-1,2,4-triazolyl)-4-amino-4-aryl-3-buten-2-ones *II* were synthesized from 1-((3-arylisoxazol-5-yl)methyl)-1*H*-1,2,4-triazoles *I* by alternative procedures involving treatment with molybdenum hexacarbonyl and water, or action of sodium hydridoborate in the presence of nickel disulfate, or hydrogenation. Hydrolysis of β-aminoenones *II* yielded β-diones *III*, which, on reaction with hydrazine afforded pyrazoles *IV*. All compounds were tested for their antifungal effect but none showed activity comparable with that of commercial preparations.

Introduction of a 1*H*-1,2,4-triazole ring into the molecule of an organic compound increases noticeably its in vivo antifungal activity[1,2] and improves its pharmacological profile[3]. Many compounds containing the 1*H*-1,2,4-triazole increment are commercial fungicides[4]. Recently, we reported[5] the preparation and antifungal properties of 1-((3-arylisoxazol-5-yl)methyl)-1*H*-1,2,4-triazoles *I* as a part of our programme on evaluation of 1,3-dipolar cycloadditions for the synthesis of biologically active compounds. Now, we wish to present the regiospecific derivatization of isoxazoles *I* aiming to prepare β-aminoenones, β-diones and pyrazoles containing the 1,2,4-triazole ring thus making use of isoxazolines described[6-8] as valuable precursors in the synthesis of bifunctional derivatives.

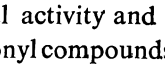
The starting 1-((3-arylisoxazol-5-yl)methyl)-1*H*-1,2,4-triazoles *I* were prepared by a 1,3-dipolar cycloaddition of substituted benzenenitrile oxides to 1-propargyl-1*H*-1,2,4-triazole[5]. The unstable benzenenitrile oxides were generated in situ from the corresponding benzenehydroximidoyl chlorides and potassium carbonate[6] except the 2,4,6-trimethylbenzenenitrile oxide, which is stable[9]. Three methods were employed to obtain the 1-(1*H*-1,2,4-triazolyl)-4-amino-4-aryl-3-buten-2-ones *II*. The orthodox catalytical hydrogenation of isoxazoles[10-13] (method *C*, cf. Experimental), affording the synthetically meaningful β-aminoenones – synthons for further synthe-

* To whom correspondence should be addressed.

ses[11-13], was found to be suitable for derivatives *IIa*–*IIf* only, because halogenaryl substituted derivatives *IIh*–*IIl* underwent also hydrogenolysis of the C—Hal bond. The more universal procedures were the action of molybdenum hexacarbonyl in acetonitrile in the presence of an equimolar amount of water[14-16] (method *A*), and reduction with sodium hydridoborate in the presence of nickel disulfate[17] (method *B*). The last-mentioned procedures proceeded under very mild conditions and the required β-aminoenones *II* could be obtained in good yields; these compounds are stable after a chromatographic purification (Scheme 1).



In formulae *I*–*IV*: *a*, X = H; *b*, X = 3-CH_3; *c*, X = 4-CH_3; *d*, X = 2,4,6-tri-CH_3; *e*, X = 2-OCH_3; *f*, X = 4-OCH_3; *g*, X = 4-F; *h*, X = 2-Cl; *i*, X = 4-Cl; *j*, X = 2,4-diCl; *k*, X = 3,4-diCl; *l*, X = 4-Br;

Ar =  ; Tr = 

SCHEME 1

β-Aminoenones are especially useful for the regiospecific synthesis of the corresponding pyrazole derivatives[18,19], which could be prepared on reaction with hydrazines. Many dicarbonyl compounds possessing a 1,2,4-triazole ring revealed antifungal activity and therefore, we synthesized the pyrazole derivatives *IV* from β-dicarbonyl compounds *III*. 1-Aryl-4-(1*H*-1,2,4-triazolyl)-1,3-butanediones *IIIa* to *IIIl* were obtained by acid hydrolysis[20] of β-aminoenones in very good yields (81–93%). Derivatives *III* appeared in the enol form as evidenced by ^{1}H and ^{13}C NMR spectra. Only the *o*-chlorophenyl derivative *IIIh* occured in two various enol forms (Tables V

and VIII). β-Diketones *III* furnished the expected 1-((3-arylpyrazol-5-yl)methyl)-1*H*-1,2,4-triazoles *IV* on treatment with hydrazine hydrate followed by chromatographic separation in good yields (75–84%).

The structural similarity of compounds prepared with some fungicidally active derivatives[1–4] prompted us to test their effect on phytopathogenic moulds. Compounds *IIe*, *IIf*, *IIh–IIi*, *IIIa*, *IIIc*, *IIIg–IIIk*, *IVa*, *IVh–IVk* showed activity against Erisyphe graminis and most of them also revealed a weak insecticide and acaricide effects. Nevertheless, none of them was of practical use.

EXPERIMENTAL

The melting points are uncorrected, the ^{1}H and ^{13}C NMR spectra of deuteriochloroform solutions containing tetramethylsilane as an internal reference were measured with a Varian VXR 300 spectrometer. The UV spectra of methanolic solutions were recorded with an M-40 (Zeiss, Jena) spectrophotometer in temperated cells (the tabulated ε values are expressed in $m^2\ mol^{-1}$). The reaction course and the purity of compounds were monitored by thin-layer chromatography on Silufol sheets (detection by UV_{254} light or with iodine vapours). Preparation of the substituted 1-((3-arylisoxazol-5-yl)methyl)-1*H*-1,2,4-triazoles *I* was reported in ref.[5]. Conditions for biological tests are presented in ref.[21].

1-(1*H*-1,2,4-Triazolyl)-4-amino-4-aryl-3-buten-2-ones *IIa–III*

Method A: A solution consisting of isoxazole *I* (20 mmol), water (20 mmol) and molybdenum hexacarbonyl (2·64 g, 10 mmol) in acetonitrile (60 ml) was refluxed for 2 h. The mixture was cooled, filtered, the solvent was evaporated under reduced pressure and the residue was chromatographed on a silica gel-packed column with chloroform as eluent.

Method B: A fine-powdered $NaBH_4$ (15·5 g, 40 mmol) was added to a stirred and to −30°C cooled solution of isoxazole *I* and $NiSO_4.7\ H_2O$ (12·2 g, 40 mmol) in methanol (500 ml) during 30 min. The temperature was than allowed to rise to 20°C at which 26%-ammonia (2 300 ml) was added. The mixture was stirred for 1 h, the product was extracted with chloroform and worked up as given with method *A*.

Method C: Palladium on charcoal (10%, 0·2 g) was introduced into the solution of an isoxazole *I* (5 mmol) in ethanol (60 ml) and the content was hydrogenated with vigorous stirring at room temperature. The clear solution obained by filtration was concentrated and worked up as with method *A*.

Characteristic data for compounds *II* are listed in Tables I, IV and VII.

1-Aryl-4-(1*H*-1,2,4-triazolyl)-1,3-butanediones *III*

The respective aminoenone *II* (3 mmol) dissolved in water (40 ml) and concentrated hydrochloric acid (13 ml) was refluxed for 1 h and cooled. A saturated aqueous solution of sodium acetate (11 g) was added and the product was extracted with chloroform. The organic layer was washed with water, dried and concentrated under diminished pressure; the residue was chromatographically purified on a silica gel-packed column with chloroform as eluent. Characteristic data for compounds *III* are tabulated in Tables II, V and VIII.

1-((3-Arylpyrazol-5-yl)methyl)-1*H*-1,2,4-triazoles *IV*

A solution of a 1,3-dione *III* (10 mmol) and hydrazine hydrate (80%, 0·7 g, 11 mmol) in ethanol (40 ml) was refluxed for 2 h. The cooled mixture was poured into cold water (20 ml), the precipitate being formed was filtered off, washed with water, dried and chromatographically purified on a silica gel-packed column with chloroform–methanol 98 : 2 as eluent. Characteristic data for compounds *IV* are presented in Tables III and VI.

TABLE I

Charac teristic data for substituted β-aminoenones *II*

Compound	Formula (M.w.)	M.p., °C (Yield, %; method)	Calculated/Found			λ_{max}, nm (log ε)
			% C	% H	% N	
IIa	$C_{12}H_{12}N_4O$ (228·2)	153–154 (85; *C*)	63·14 63·21	5·30 5·45	24·55 24·71	325 (3·59)
IIb	$C_{13}H_{14}N_4O$ (242·3)	129–131 (65; *B*)	64·44 64·31	5·82 5·72	23·12 23·35	304 (3·30)
IIc	$C_{13}H_{14}N_4O$ (242·3)	118–120 (64; *B*)	64·44 64·31	5·82 5·71	23·12 23·30	328 (3·68)
IId	$C_{15}H_{18}N_4O$ (270·3)	111–113 (60; *B*)	66·64 66·38	6·71 6·61	20·73 20·85	304 (3·32)
IIe	$C_{13}H_{14}N_4O_2$ (258·3)	97–99 (83; *B*)	60·45 60·60	5·46 5·39	21·69 21·78	321 (3·55)
IIf	$C_{13}H_{14}N_4O_2$ (258·3)	161–163 (62; *A*)	60·45 60·28	5·46 5·30	21·69 21·81	331 (3·69)
IIg	$C_{12}H_{11}FN_4O$ (246·2)	128–129 (65; *A*)	58·53 58·40	4·50 4·41	22·75 22·90	324 (3·61)
IIh	$C_{12}H_{11}ClN_4O$ (262·7)	118–120 (60; *A*)	54·86 54·71	4·22 4·10	21·33 21·50	317 (3·51)
IIi	$C_{12}H_{11}ClN_4O$ (262·7)	161–163 (70; *B*)	54·86 54·70	4·22 4·11	21·33 21·45	326 (3·52)
IIj	$C_{12}H_{10}Cl_2N_4O$ (297·1)	171–173 (64; *A*)	48·50 48·63	3·39 3·27	18·85 18·90	309 (3·27)
IIk	$C_{12}H_{10}Cl_2N_4O$ (297·1)	149–151 (66; *A*)	48·50 48·66	3·39 3·25	18·85 19·00	327 (3·28)
III	$C_{12}H_{11}BrN_4O$ (307·1)	176–178 (68; *A*)	46·92 46·80	3·61 3·50	18·24 18·40	327 (3·59)

TABLE II

Characteristic data for substituted β-dicarbonyl derivatives *III*

Compound	Formula (M.w.)	M.p., °C (Yield, %)	Calculated/Found			λ_{max}, nm (log ε)
			% C	% H	% N	
IIIa	$C_{12}H_{11}N_3O_2$ (229·2)	79—80 (90)	62·87 62·61	4·83 4·70	18·33 18·50	315 (3·47)
IIIc	$C_{13}H_{13}N_3O_2$ (243·2)	91—93 (88)	64·18 64·01	5·38 5·26	17·27 17·41	320 (3·56)
IIId	$C_{15}H_{17}N_3O_2$ (271·3)	114—116 (81)	66·40 66·61	6·31 6·27	15·48 15·62	307 (3·30)
IIIg	$C_{12}H_{10}FN_3O_2$ (247·2)	75—77 (85)	58·29 58·13	4·07 3·90	16·99 16·75	314 (3·51)
IIIh	$C_{12}H_{10}ClN_3O_2$ (263·7)	62—64 (90)	54·65 54·78	3·82 3·71	15·93 16·18	304 (3·33)
IIIi	$C_{12}H_{10}ClN_3O_2$ (263·7)	94—96 (93)	54·65 54·48	3·82 3·71	15·93 15·75	318 (3·45)
IIIk	$C_{12}H_9Cl_2N_3O_2$ (298·1)	97—99 (89)	48·34 48·21	3·04 2·89	14·09 14·22	317 (3·54)
IIIl	$C_{12}H_{10}BrN_3O_2$ (308·1)	125—127 (90)	46·77 46·91	3·27 3·10	13·63 13·80	319 (3·60)

TABLE III

Characteristic data for substituted pyrazoles *IV*

Compound	Formula (M.w.)	M.p., °C (Yield, %)	Calculated/Found			λ_{max}, nm (log ε)
			% C	% H	% N	
IVa	$C_{12}H_{11}N_5$ (225·2)	157—159 (82)	63·98 63·71	4·92 4·80	31·09 31·20	253 (3·34)
IVb	$C_{13}H_{13}N_5$ (239·3)	115—117 (80)	65·25 65·40	5·47 5·31	29·27 29·41	256 (3·26)
IVc	$C_{13}H_{13}N_5$ (239·3)	190—192 (78)	65·25 65·09	5·47 5·32	29·27 29·41	257 (3·33)
IVg	$C_{12}H_{10}FN_5$ (243·2)	187—189 (75)	59·25 59·41	4·14 4·01	28·79 28·96	252 (3·23)
IVh	$C_{12}H_{10}ClN_5$ (259·7)	161—163 (80)	55·49 55·62	3·88 3·73	26·96 27·11	250 (3·13)
IVi	$C_{12}H_{10}ClN_5$ (259·7)	189—191 (84)	55·49 55·31	3·88 3·74	26·96 26·75	260 (3·34)
IVk	$C_{12}H_9Cl_2N_5$ (294·1)	151—153 (79)	48·99 49·14	3·08 2·81	23·81 23·65	261 (3·40)
IVl	$C_{12}H_{10}BrN_5$ (304·1)	156—158 (83)	47·38 47·21	3·31 3·20	23·03 23·20	253 (3·38)

TABLE IV

^{1}H NMR chemical shift data of substituted β-aminoenones *II*

Compound	δ, ppm					
	H-3	H-5	H-vinyl	CH_2	NH	H-arom
IIa	7·99	8·21	5·25	4·97	5·73; 10·01	7·46—7·51
IIc[a]	8·02	8·27	5·26	4·98	5·58; 10·05	7·23—7·41
IId[b]	7·95	8·20	4·87	4·93	5·38; 9·92	6·87—7·26
IIe[c]	8·00	8·27	5·18	4·96	6·45; 10·34	6·96—7·42
IIf[d]	8·01	8·24	5·23	4·97	5·57; 10·05	6·92—7·47
IIg	7·99	8·21	5·20	4·97	5·63; 9·99	7·09—7·52
IIh	7·90	8·15	5·21	4·91	5·92; 9·93	7·26—7·49
IIi	8·01	8·21	5·22	4·99	5·48; 9·91	7·34—7·60
IIj	7·98	8·22	5·18	4·98	5·45; 9·92	7·29—7·47
IIk	8·00	8·22	5·22	4·98	5·51; 9·97	7·26—7·43
III	8·00	8·22	5·22	4·97	5·52; 9·94	7·38—7·59

[a] 2·40 s (CH_3); [b] 2·22 s and 2·28 s (CH_3); [c] 3·87 s (OCH_3); [d] 3·85 s (OCH_3).

TABLE V

^{1}H NMR chemical shift data of substituted β-diketones *III*

Compound	δ, ppm				
	H-3	H-5	H-vinyl	CH_2	H-arom
IIIa	8·05	8·25	5·99	5·07	7·42—7·82
IIIc[a]	8·05	8·26	5·97	5·06	7·23—7·72
IIIg	8·06	8·27	5·95	5·07	7·10—7·86
IIIh	8·05	8·27	6·00	5·00	7·42—7·82
	8·04	8·26	5·94		
IIIi	8·05	8·24	5·96	5·07	7·40—7·76
IIIk	8·06	8·26	5·97	5·09	7·50—7·90
IIIl	8·07	8·28	5·97	5·08	7·57—7·69

[a] 2·40 s (CH_3).

TABLE VI

^{1}H NMR chemical shift data of substituted pyrazoles *IV*

Compound	δ, ppm				
	H-3	H-5	H'-4	CH_2	H-arom
IVa	7·99	8·21	6·54	5·42	7·35—7·59
IVc[a]	8·00	8·23	6·52	5·43	7·21—7·47
IVg	8·07	8·23	6·62	5·42	7·14—7·84
IVh	8·01	8·25	6·65	5·46	7·29—7·61
IVi	8·01	8·27	6·54	5·46	7·39—7·55
IVk	8·08	8·28	6·62	5·49	7·51—7·77

[a] 2·37 s (CH_3).

TABLE VII
^{13}C NMR chemical shifts of *II*

Compound	δ, ppm					
	C=O	C-3	C-5	CH_2	C-vinyl	C-arom
IIa	189·05	151·95	144·51	56·79	90·76, 164·15	136·23, 131·29 129·14, 126·28
IIc[a]	188·73	152·05	144·13	56·90	90·46, 164·17	141·93, 133·23 129·84, 126·15
IId[b]	189·18	151·78	144·21	56·70	92·84, 165·20	138·84, 134·78 133·73, 128·38
IIe[c]	188·31	151·80	144·50	56·92	91·30, 163·30	157·14, 132·22 129·53, 123·60 121·26, 111·88
IIf[d]	188·62	151·92	144·30	56·86	90·12, 163·78	162·19, 128·15 127·81, 114·49
IIg	189·13	152·00	144·25	56·80	90·84, 166·14	162·90, 132·37 128·43, 116·31
IIh[e]	189·32	151·85	144·44	56·74	90·68, 164·24	136·20, 131·41 131·09, 129·66 127·16
IIi	189·64	152·13	144·31	56·82	91·30, 161·21	136·19, 131·24 128·30, 125·49
IIk	189·34	152·01	144·10	56·80	90·96, 162·70	137·49, 134·67 129·45, 127·61
III	189·38	152·09	144·42	56·83	90·95, 162·74	135·15, 132·42 127·80, 125·75

[a] 21·41 q (CH_3); [b] 21·04 q and 19·24 q (CH_3); [c] 55·86 q (OCH_3); [d] 55·49 q (OCH_3); [e] 189·32, 162·28, 151·83, 144·48, 135·48, 131·27, 131·09, 130·41, 129·10, 126·33, 93·04, 56·69.

TABLE VIII
^{13}C NMR chemical shifts of *III*

Compound	δ, ppm					
	C=O	C-3	C-5	CH_2	C-vinyl	C-arom
IIIa	189·50	152·51	144·62	54·77	93·88, 182·85	133·38, 133·18 128·86, 127·23
IIIc[a]	189·12	152·74	144·48	54·96	93·77, 183·46	130·92, 129·99 129·85, 127·58
IIIg	188·97	152·76	144·50	54·87	93·95, 182·54	162·10, 130·11 116·23
IIIh[b]	189·40	152·52	144·42	54·56	93·82, 182·94	133·78, 133·13 132·08, 130·25 127·18
IIIi	189·45	152·56	144·61	54·64	93·80, 181·64	139·51, 131·78 129·36, 128·80
IIIk	189·73	152·59	144·57	54·63	94·13, 180·22	137·51, 133·53 133·23, 130·87 129·02, 126·09
IIIl	189·60	152·50	144·31	55·06	94·14, 181·37	135·25, 132·12 128·14, 125·70

[a] 22·02 q (CH_3); [b] 188·86, 182·90, 152·52, 144·50, 133·32, 132·30, 130·93, 128·80, 127·05, 99·31, 54·76.

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