

**CYCLOADDITION OF ARYLNITRILE OXIDES TO
2H,5H-1,6-BENZODIOXOCINE AND RELATED COMPOUNDS***

Lubor FIŠERA^a, Libuše JAROŠKOVÁ^a, Werner SCHROTH^b, Michael GÄBLER^b
and Peter ORAVEC^a

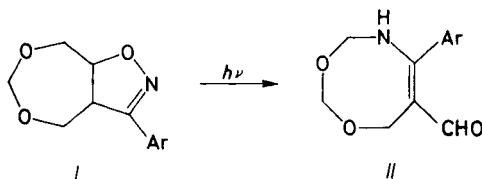
^a Department of Organic Chemistry,
Slovak Institute of Technology, 812 37 Bratislava, Czechoslovakia and

^b Department of Organic Chemistry,
Martin-Luther University, 4050 Halle-Wittenberg, G.D.R.

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3-Aryl-3a,4,11,11a-tetrahydroisoxazolo[5,4c]-1,6-benzodioxocines *VIII* were formed by a 1,3-dipolar cycloaddition of arynitrile oxides to 2H,5H-1,6-benzodioxocine (*III*). The heterocycle *VII* afforded monoadducts *IX*, whereas dipolarophiles *IV*–*VI* do not yield cycloaddition products with nitrile oxides under the same reaction conditions. Irradiation of isoxazolines *VIII*, *IX* with UV light led to tarry products.

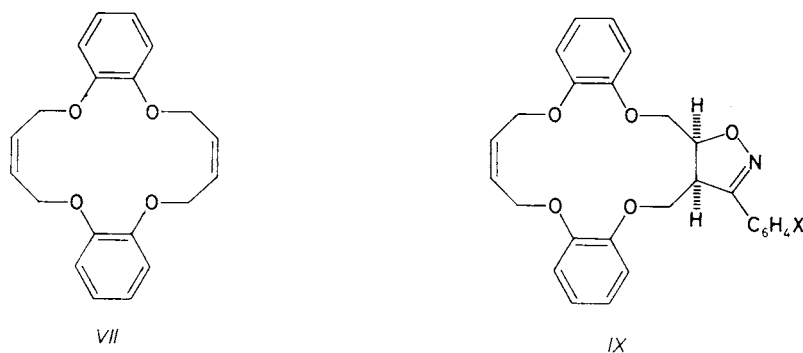
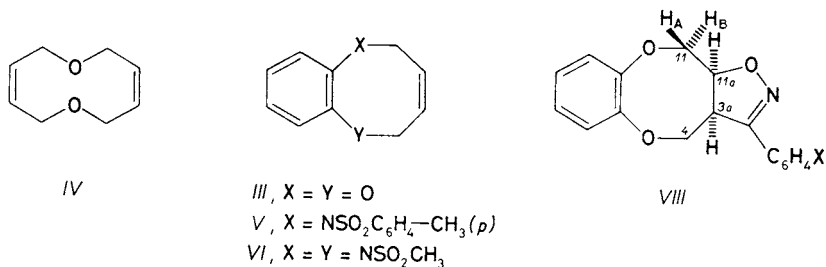
Isoxazolines are well suited precursors for the synthesis of β -hydroxyketones, β -hydroxynitriles, and γ -aminoalcohols¹. Recently, we reported^{2–5} that introduction of an oxygen atom to β -position with respect to the isoxazoline oxygen is associated with a highly selective photo-induced rearrangement to yield cyclic aminoaldehydes, e.g. *I* \rightarrow *II*. This new synthetic approach, i.e. the 1,3-dipolar cycloaddition of nitrile



oxides to n -membered oxygen-containing heterocycles followed by a photo-rearrangement leading to $(n + 1)$ -membered heterocycles was aimed to prepare 9-, 11- and 17-membered heterocycles. Starting materials for this project were the 8-membered heterocycles with a fused benzene ring *III* or *V*, the 10-membered *IV*, and the 16-membered *VII*. It is noteworthy that 1,3-cycloadditions of the above-mentioned dipolarophiles have not been mentioned as yet.

* Part XVIII in the series 1,3-Dipolar Cycloadditions to Heterocycles; Part XVII: Collect. Czech. Chem. Commun. 52, 1315 (1987).

1,3-Dipolar cycloaddition of substituted benzenitrile oxides ($X = \text{H}$, 4- OCH_3 , 4- CH_3 , 4- Cl , 4- NO_2 , 4- Br , 4- F , and 3- Cl) to 2H, 5H-1,6-benzodioxocine (*III*) furnished 3-aryl-3a,4,11,11a-tetrahydroisoxazolo[5,4-c]-1,6-benzodioxocines *VIII* in 29–65% yields. The corresponding aromatic nitrile oxides were generated both



In formulae *VIII*, *IX*: *a*, $X = \text{H}$ *b*, $X = 4\text{-OCH}_3$ *c*, $X = 4\text{-CH}_3$ *d*, $X = 4\text{-Cl}$
 e, $X = 4\text{-NO}_2$ *f*, $X = 4\text{-Br}$ *g*, $X = 4\text{-F}$ *h*, $X = 3\text{-Cl}$

from benzenehydroxamic acid chlorides (method *A*) and from the corresponding benzenealdoximes treated with sodium hypochlorite under catalysis of triethylamine (method *B*). Both methods yielded, in addition to products *VIII*, also the unreacted starting compound *III* and dimers of nitrile oxides⁶. When subtracting the recovery of *III* the yields ranged within 60 and 80% (see Table I).

The structure *VIII* was deduced from the ^1H and ^{13}C NMR data (Tables II and III). The ^1H NMR spectrum of 3-phenyl-3a,4,11,11a-tetrahydroisoxazolo[5,4-c]-1,6-benzodioxocine showed multiplets of four protons δ 4.02–4.53 (H-3a , $2 \times \text{H-4}$ and $\text{H}_\text{B}\text{-11}$) and two protons at δ 4.75–5.02 (H-11a , $\text{H}_\text{A}\text{-11}$). This assignment is consistent with signals of the ^{13}C NMR spectrum with a singlet at δ 157.44 (the isoxazoline $\text{C}=\text{N}$ atom), triplets at δ 67.81 and 69.21 (C-4 and C-11) and doublets at δ 48.21 and 81.21 (C-3 and C-11a). Signal for the C-11a atom is downfield shifted

due to shielding of the isoxazoline oxygen atom. The spectra of derivatives *VIIIb* to *VIIIh* are very close and their chemical shifts differ only slightly in relation to the respective substituent (Tables II, III).

Isoxazolines *IXa*, *IXd*, *IXe*, *IXh* were obtained under the same conditions as derivatives *VIII* using the symmetric dipolarophile *VII* (Table I). Analogously, also dimers of nitrile oxides and the starting *VIII* were isolated. The presence of possible

TABLE I
Physicochemical data of fused 3-aryl-4,5-dihydroisoxazoles *VIII* and *IX*

Compound	Formula (M_r)	M.p., °C method (yield, %)	Calculated/found			λ_{\max} , nm (log ϵ)
			% C	% H	% N	
<i>VIIIa</i>	$C_{17}H_{15}NO_3$ (281.3)	155–157	72.58	5.37	4.98	268
		<i>A</i> (63), <i>B</i> (29)	72.24	5.45	5.13	(3.03)
<i>VIIIb</i>	$C_{18}H_{17}NO_4$ (311.3)	144–146	69.44	5.50	4.50	275
		<i>B</i> (40)	69.71	5.38	4.34	(3.13)
<i>VIIIc</i>	$C_{18}H_{16}NO_3$ (295.3)	145–147	73.20	5.80	4.74	270
		<i>A</i> (48)	73.08	5.91	4.93	(3.13)
<i>VIIId</i>	$C_{17}H_{14}ClNO_3$ (315.8)	191–192	64.65	4.46	4.43	284 ^a
		<i>A</i> (51)	64.90	4.45	4.82	(2.94)
<i>VIIIe</i>	$C_{17}H_{14}N_2O_5$ (326.5)	222–224	62.57	4.32	8.59	308
		<i>A</i> (65)	62.23	4.38	8.68	(3.15)
<i>VIIIf</i>	$C_{17}H_{14}BrNO_3$ (360.2)	153–155	56.68	3.91	3.88	— ^b
		<i>A</i> (33)	59.87	4.12	4.07	
<i>VIIIg</i>	$C_{17}H_{14}FNO_3$ (299.3)	163–164	68.22	4.71	4.67	267
		<i>A</i> (53)	68.33	4.79	4.91	(2.99)
<i>VIIIh</i>	$C_{17}H_{14}ClNO_3$ (315.8)	159–160	64.65	4.46	4.43	265
		<i>A</i> (38)	64.81	4.33	4.67	(3.19)
<i>IXa</i>	$C_{27}H_{25}NO_5$ (443.5)	178–180	73.12	5.68	3.15	269
		<i>A</i> (72)	73.17	5.87	3.27	(2.92)
<i>IXd</i>	$C_{27}H_{24}ClNO_5$ (477.9)	218–220	67.85	5.06	2.93	274
		<i>A</i> (67)	68.04	5.21	3.18	(2.60)
<i>IXe</i>	$C_{27}H_{24}N_2O_7$ (488.5)	213–215	66.38	4.95	5.73	307
		<i>A</i> (53)	66.57	4.83	6.00	(2.57)
<i>IXh</i>	$C_{27}H_{24}ClNO_5$ (477.9)	144–145	67.85	5.06	2.93	274
		<i>A</i> (42)	67.63	4.91	3.12	(2.52)

^a 247 (3.22); ^b methanol insoluble.

bis-adducts was not proved by ^1H and ^{13}C NMR measurements either in the crude reaction mixtures, or in mother liquors after filtration. This phenomenon can be rationalized by the insolubility of the mono-adducts in the medium, which precipitate during the reaction; consequently, the subsequent 1,3-dipolar cycloaddition leading to bis-adducts was prevented. The ^1H NMR spectra (Table IV) of mono-adducts *IX* displayed multiplets, which were ascribed by analogy with compounds *VIII*. Thus, e.g. the multiplet at δ 3.97–4.75 of *IXa* embodies nine protons (H-3a, $2 \times$ H-4, $2 \times$ H-7, $2 \times$ H-10, and $2 \times$ H-13). The multiplet at δ 4.96 was ascribed to H-13a in the neighbourhood of the isoxazoline oxygen atom. The presence of a multiplet at δ 6.00–6.25, assigned to two vinylic protons, evidences the formation of a monoadduct. Its ^{13}C NMR spectrum (Table V) is characteristic of the singlet at δ 157.58 (C=N), triplets at δ 69.80 (C-13) and doublets at δ 47.91 (C-3a) and 82.13 (C-13a). Spectra of other isoxazolines *IX* are analogous.

Related isoxazoline derivatives were attempted to prepare by cycloaddition of aryl nitrile oxides to dipolarophiles *IV–VI* employing methods *A* and *B*. Nevertheless, only unreacted *IV–VI* and dimers of the respective aryl nitrile oxides ($\sim 100\%$)

TABLE II

^1H NMR chemical shifts of 3-aryl-3a,4,11,11a-tetrahydroisoxazolo[5,4-c]-1,6-benzodioxocines *VIII*

Compound	δ , ppm			
	H-arom.	H-11a, H _A -11	H _B -11, H-4, H-3a	Others
<i>VIIIa</i>	6.90–7.72	4.75–5.02 m	4.02–4.53 m	
<i>VIIIb</i>	6.85–7.32 7.62–7.80	4.72–5.05 m	4.07–4.52 m	3.85 s, 3 H (OCH ₃)
<i>VIIIc</i>	6.82–7.30 7.50–7.72	4.75–5.05 m	4.00–4.50 m	2.38 s, 3 H (CH ₃)
<i>VIII d</i>	6.85–7.76	4.75–5.02 m	4.00–4.50 m	
<i>VIII e</i>	6.82–6.93 7.86–8.26	4.65–5.00 m	4.00–4.56 m	
<i>VIII f</i>	6.87–7.26 7.50–7.75	4.72–5.00 m	3.96–4.50 m	
<i>VIII g</i>	6.82–7.25 7.57–7.82	4.70–5.00 m	3.97–4.47 m	
<i>VIII h</i>	6.82–7.02 7.40–7.82	4.61–4.97 m	4.17–4.50 m	

were isolated from the reaction. The failure to react *V* and *VI* might be due to electron-accepting N-tosyl or N-mesyl groups. The ability of *IV*, having the same —O—CH₂—CH=CH₂—O— sequence as *III*, to react can be explained by steric effects only, in other words by an unsuitable conformation for the 1,3-dipolar cycloaddition.

The isoxazolines *VIII*, *IX* were attempted to transform into heterocyclic enaminoaldehydes *X* in methanol, acetonitrile, benzene, and ether using a monochromatic irradiation of λ_{\max} 254 nm, similarly as in the preceding papers²⁻⁵. The photolysis

TABLE III
¹³C NMR chemical shifts of 3-aryl-3a,4,11,11a-tetrahydroisoxazolo[5,4-c]-1,6-benzodioxocines *VIII*

Com- pound	δ , ppm					
	C-3	C-3a	C-4	C-11	C-11a	C-arom.
<i>VIIIa</i>	157.44	48.21	67.81	69.21	81.21	121.28 122.34 123.33 123.86 126.84 128.48 129.06 130.29 149.83 150.01
<i>VIIIb^a</i>	156.91	48.39	67.93	69.21	80.97	114.50 120.81 121.28 122.34 134.27 123.84 123.42 139.82 140.03 160.71
<i>VIIIc^b</i>	157.19	48.24	67.85	69.21	81.03	121.22 122.20 123.23 123.75 175.63 126.67 127.19 129.53 139.99 149.21 149.73 149.92
<i>VIII^d</i>	156.54	48.05	67.65	69.15	81.42	121.22 122.26 123.30 123.82 127.33 128.56 129.08 134.79 149.73 149.92
<i>VIII^e</i>	156.21	47.80	67.34	69.04	81.91	120.93 121.98 123.10 123.53 123.74 127.78 134.50 147.96 149.48 149.66
<i>VIII^f</i>	156.54	48.24	67.72	69.15	81.29	115.32 116.74 121.22 122.26 123.30 123.82 124.92 125.12 128.88 129.47 149.73 149.92
<i>VIII^g</i>	156.67	47.98	67.15	69.15	81.48	121.22 122.26 123.30 123.56 123.82 124.53 127.66 128.75 132.00 149.73 149.92
<i>VIII^h</i>	156.54	47.92	67.65	69.15	81.55	121.22 122.26 123.30 123.82 125.51 126.28 130.05 130.57 130.90 133.75

^a 55.29 q (OCH₃); ^b 20.90 q (CH₃).

led to tarry products even though the experiment was carried out in an inert atmosphere. The UV-monitoring of photolyses of *VIII* and *IX* at a low concentration (0.1 mmol l^{-1}) showed only a hypochromic shift of the band at λ 285 nm (the isoxazoline chromophore). Also monitoring by HPL-chromatography indicated a decrease of the starting *VIII* or *IX* in relation to time, and an appearance of a mixture consisting of more than 8 peaks, which disappeared during further irradiation. The ^1H NMR spectrum of the crude reaction mixture after irradiation contained only signals indicative of aromatic protons. This and some of the preceding results allow to conclude that the fused benzene ring exerts an unfavourable effect on the photochemical reaction of isoxazolines. Analogous results were obtained with two

TABLE IV
 ^1H NMR chemical shifts of *IX*

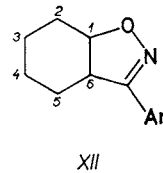
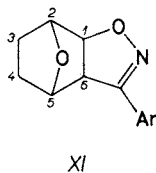
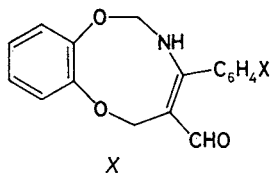
Compound	δ , ppm			
	H-arom	H-vinyl	H-13a	H-3a, H-4, H-10, H-13, H-7
<i>IXa</i>	6.66–7.90	6.00–6.25 m	4.96 m	3.97–4.75 m
<i>IXd</i>	6.76–7.00 7.32–7.80	5.92–6.17 m	4.91 m	3.87–4.62 m
<i>IXe</i>	6.62–7.00 7.90–8.28	5.85–6.21 m	4.89 m	3.87–4.67 m
<i>IXh</i>	6.75–8.15	5.62–6.16 m	5.00 m	3.88–4.75 m

TABLE V
 ^{13}C NMR chemical shifts of *IX*

Compound	δ , ppm						
	C-3	C-3a	C-4	C-7	C-10	C-13	C-13a
<i>IXa</i> ^a	157.58	47.91	63.50	63.89	64.67	69.80	82.13
<i>IXd</i> ^b	156.62	47.69	63.42	64.01	64.77	69.10	82.79

^a Aromatic and vinyl shifts: 113.62, 114.92, 116.67, 120.83, 121.35, 121.35, 121.94, 123.82, 126.87, 128.43, 128.95, 129.60, 130.12, 147.78, 148.56, 149.27, 150.25; ^b aromatic and vinyl shifts: 114.73, 115.14, 115.38, 116.52, 119.78, 121.16, 121.69, 123.37, 123.62, 127.95, 129.06, 130.17, 134.24, 147.84, 148.13, 149.17.

preceding experiments. Thus, e.g. irradiation of derivatives *XI* and *XII* led to cyclic enaminoaldehydes^{2,7}, whilst their 3,4-benzo derivatives afforded only unidentified products^{8,9}. This anomalous behaviour could not relevantly be rationalized as yet.



EXPERIMENTAL

The melting points are uncorrected, the ¹H and ¹³C NMR spectra of deuteriodimethyl sulfoxide solutions were measured with Tesla 487 C and JEOL spectrometers, respectively, tetramethylsilane being the internal reference. The UV spectra of methanolic solutions were recorded in tempered cells with a Perkin-Elmer, model 323, spectrophotometer; the ε values are given in m² mol⁻¹. The IR spectra of chloroform solutions were taken with a Unicam SP apparatus. The reaction course was monitored by thin-layer chromatography (Silufol sheets), detection by UV light (254 nm) or by iodine vapours.

The respective benzenehydroxamic acid chlorides were prepared by chlorination of the corresponding benzaldoximes according to literature¹⁰, the photochemical process and the synthesis of dipolarophiles *III* to *VII* were already described in ref.¹² and ref.¹³, respectively.

Isoxazolines *VIII* and *IX*

Method A: Triethylamine (13 mmol) in ether (30 ml) was added to a stirred solution of the benzenehydroxamic acid chloride (10 mmol) and the dipolarophile (10 mmol) in ether at 0–5°C within 1 h. The mixture was stirred overnight at room temperature, the separated triethylammonium chloride was filtered off, removed by dissolving in water and the organic material was evaporated under diminished pressure, dried, triturated with a suitable solvent or separated by chromatography on a silica gel column, and purified by crystallization.

Method B: Sodium hypochlorite¹¹ (8 ml, 12%) was added during 30 min to a stirred solution of the respective benzaldoxime (10 mmol), triethylamine (0.15 ml) and the dipolarophile (10 mmol) in dichloromethane (20 ml) at 0°C. The mixture was stirred overnight at an ambient temperature and extracted with dichloromethane (3 × 15 ml). The combined extracts were dried with magnesium sulfate, the solvent was evaporated under reduced pressure and the residue was worked up as with method *A*.

REFERENCES

1. Kozikowski A. P.: *Acc. Chem. Res.* **17**, 410 (1984).
2. Fišera E., Laudár S., Timpe H.-J., Zálupský P., Štibrány L.: *Collect. Czech. Chem. Commun.* **49**, 1193 (1984).
3. Fišera E., Štibrány L., Máfušová A., Oremus V., Timpe H.-J.: *Tetrahedron Lett.* **25**, 2731 (1984).

4. Fišera L., Oremus V., Štibrányi L., Timpe H.-J., Mátušová A.: *Collect. Czech. Chem. Commun.* **51**, 2158 (1986).
5. Fišera L., Oravec P., Štibrányi L., Kozhina N. D., Badovskaya L. A.: *Synthesis* **1986**, 565.
6. Caramella P. in the book: *1,3-Dipolar Cycloaddition Chemistry* (A. Padwa, Ed.), p. 291. Wiley, New York 1984.
7. Mukai T., Kumagai T., Seshimoto O.: *Pure Appl. Chem.* **49**, 287 (1977).
8. Fišera L., Oravkin J.: *Chem. Papers* **39**, 783 (1985).
9. Štibrányi L., Fišera L., Hubová K.: *Chem. Papers* **42**, 59 (1988).
10. Werner A., Buss H.: *Ber. Dtsch. Chem. Ges.* **27**, 2193 (1948).
11. Lee G. A.: *Synthesis* **1982**, 508.
12. Oremus V., Fišera L., Štibrányi L.: *Collect. Czech. Chem. Commun.* **52**, 1773 (1987).
13. Schroth W.: *Wiss. Z. Univ. Halle* **30 M. H. 1**, 97 (1981).

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