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CYCLOADDITION OF BENZONITRILE OXIDE WITH SOME BUTADIENYLAMINES

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Abstract—A convenient and easy approach to the 4,5'-diisoxazole ring system, based on the cycloaddition of benzonitrile oxide to butadienylamines is described. Both mono- and bis-adducts are obtained, whose structures have been confirmed by spectral analysis and chemical transformations. Addition on the base substituted double bond occurs with inversion of the orientation with regard to butadiene.

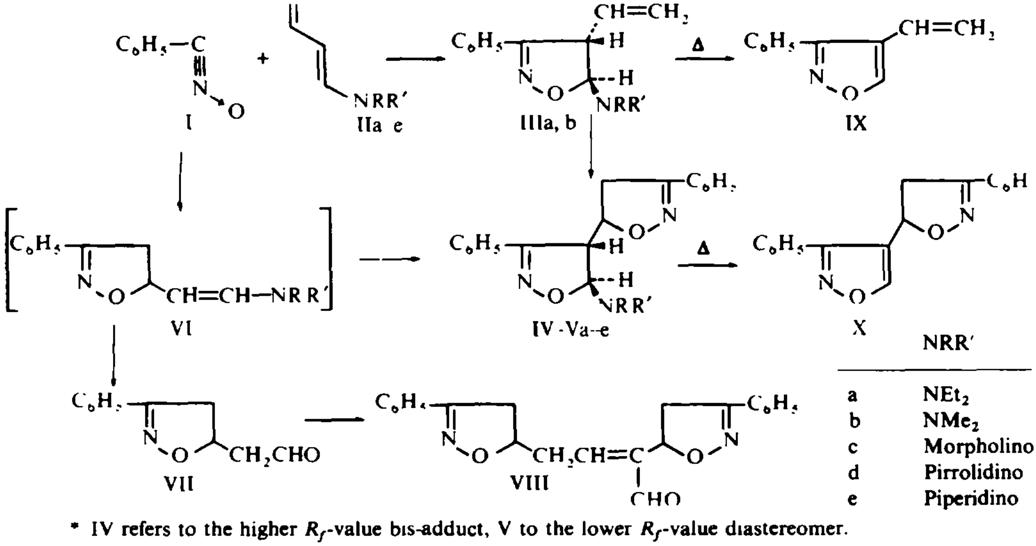
Pursuing our studies on 4,5'-diisoxazoles,[1-3] it was of interest to elaborate a one-step synthesis of the two heterocyclic rings. We studied the reaction of nitrile oxides with a suitable butadiene derivative.

The cycloaddition of two moles of benzonitrile oxide to butadiene yields the 3,3'-diphenyl-5,5'-di-Δ^2-isoxazoline.[4] Taking into account the orientation effect of an electron-releasing basic residue, inferred from the cycloaddition of nitrile oxides to enamines,[5] we studied the cycloaddition of benzonitrile oxide to butadienylamines.

Dienamines react as dienes[6] and give 2 + 2 cycloadditions with sulphenes.[7] In the latter case an initial exclusive attack on the terminal vinyl group has been reported. No systematic study on the 1,3-dipolarophilic activity of dienamines has been reported.

Reaction of benzonitrile oxide, either isolated in ethereal soln or prepared *in situ*, with an equimolar amount of 1-N,N-diethylaminobutadiene yielded six products: one mono-adduct, two aldehydes, two diasteomeric bis-adducts* and a minor by-product (see Chart I).

Chart I



	NRR'
a	NEt_2
b	NMe_2
c	Morpholino
d	Pirrolidino
e	Piperidino

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* IV refers to the higher R_f-value bis-adduct, V to the lower R_f-value diastereomer.

The mono adduct, isolated in 16% yield, is an oil, whose IR spectrum shows vinyl absorption at 1637 cm^{-1} and 990, 922 cm^{-1}. An attempted vacuum distillation led to loss of diethylamine and isolation of the known 3-phenyl-4-vinyl-isoxazole (IX)[2]. The NMR spectrum confirmed that the mono-adduct was a single product and was consistent with the structure of *trans*-3-phenyl-4-vinyl-5-N,N-diethylamino-Δ^2-isoxazoline (IIIa). The *trans*-configuration was indicated by the coupling constant of the ring protons of 3·6 c/s,[8] and was supported by the easy thermal *cis*-elimination of diethylamine as well as by the *trans*-configuration of the starting 1-N,N-diethylamino butadiene, whose NMR spectrum shows a $J_{1,2}$ of 13·7 c/s. The cycloaddition is therefore completely stereospecific.

Of the two aldehydes, only one could be isolated in pure form as a colourless solid, m.p. 139–143°, whereas the second was obtained as an impure oil. The former compound has a molecular formula $C_{22}H_{20}O_3N_2$ and shows IR absorption of an α,β-unsaturated aldehyde at 1687 cm^{-1}, 1641 cm^{-1} and 2745 cm^{-1}. NMR data support the structure of 2,4-di-(3-phenyl-5-Δ^2-isoxazolinyl)-2-butenal (VIII): a singlet at 0·59 τ (1 H, aldehydic proton), a triplet at 3·24 τ (1 H, olefinic proton, $J = 7{\cdot}7$ c/s), multiplets at 4·40, 5·08 (2 H, isoxazoline 5-protons) and 6·05–7·3 τ (6 H, methylene protons), besides the multiplet of the aromatic protons (10 H).

The oily aldehyde shows IR absorptions at 1721 cm^{-1} and 2725 cm^{-1} (CHO) besides those of a monosubstituted phenyl group. The NMR spectrum shows, besides the aromatic protons signal, a triplet at 0·18 τ ($J = 1{\cdot}5$ c/s), a multiplet centred at 4·84 τ (C-5 ring proton) and a complex absorption between 6·1 and 7·2 τ. Taking into account its spectral properties and the fact that after standing at room temp for some weeks the carbonyl absorption of VIII appears in the IR spectrum, the product was assigned the structure of (3-phenyl-5-isoxazolyl)-acetaldehyde (VII).

The bis-adducts, m.p. 153–154° resp. m.p. 146° dec, were obtained in better yields when the reaction was carried out with 2·5 equiv of benzonitrile oxide and could be easily isolated owing to their low solubility in isopropyl ether. They are easily distinguishable by TLC analysis (IVa R_f 0·6, Va R_f 0·4).

Both compounds, having analytical values corresponding to the molecular formula $C_{22}H_{25}O_2N_3$ were assigned the diastereomeric structures of *trans*-3-phenyl-4-(3'-phenyl-5'-Δ^2-isoxazolinyl)-5-diethylamino-Δ^2-isoxazoline (IVa and Va) on the basis of following evidence:

(i) By thermolysis at 160° or by vacuum distillation diethylamine split off and the known 3-phenyl-5-(3'-phenyl-4'-isoxazolyl)-Δ^2-isoxazoline (X)[2] was obtained. The same compound was also present as a by-product in the cycloaddition reaction mixture.

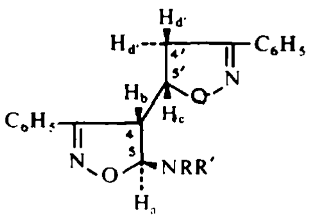
(ii) Cycloaddition of IIIa with I gave 20% and 40% yields of the bis-adducts IVa and Va respectively.

(iii) Spectroscopic data (NMR, UV, IR) are consistent with the assigned structures. The coupling constants of the trisubstituted isoxazoline ring protons, equal to 3 and 4 c/s for IVa and Va respectively, as well as the easy *cis*-elimination of diethylamine, confirm the *trans* stereochemistry.

The cycloaddition has been extended to several other 1-dialkylaminobutadienes IIb–e (see Chart I). Starting from IIb and excess I, we isolated and identified both the mono-adduct IIIb and the two diastereomeric bis-adducts (IVb and Vb).

When IIc–e reacted with two equivs of I, an approximate 20% yield of the bis-

TABLE 1. NMR DATA* OF THE HIGHER R_f-VALUE BIS-ADDUCTS IV



Compound	H_a	H_b	H_c	H_d and $H_{d'}$	J_{ab}	J_{bc}	J_{cd}
IVa	4·53 d	6·06 t	4·83 sx	6·82 d	3	5·3	10
IVb	4·74 d	6·09 q	4·87 sx	6·83 d	2·2	5	9·7
IVc	4·80 d	—	4·81 sx	6·78 d	2·7	5·3	10
IVd	4·47 d	6·01 q	4·90 sx	6·81 d	2·5	5·6	10
IVe	4·79 d	6·07 q	4·88 sx	6·85 d	2·4	5·5	10

TABLE 2. NMR DATA* OF THE LOWER R_f-VALUE BIS-ADDUCTS V

Compound	H_a	H_b	H_c	H_d†	$H_{d'}$†	J_{ab}	J_{bc}	J_{cd}†	$J_{d'c}$†	$J_{dd'}$†
Va	4·55 d	6·23 t	4·92m	6·69	6·85	4	4	10·5	8·6	−17
Vb	4·67 d	6·21 q	4·94m	6·67	6·88	3	4·5	10·3	8·6	−17
Vc	4·84 d	6·20 q	5·01m	6·70	6·92	2·7	5·5	10·2	8	−17
Vd	4·50 d	6·18 q	4·99m	6·69	6·91	3	5	10·4	8·3	−17
Ve	4·80 d	6·20 q	4·97m	6·69	6·90	2·7	4·6	10·4	8·3	−17

* Chemical shifts in τ-values, coupling constants in c/s; s = singlet, d = doublet, t = triplet, q = quartet, sx = sextet, m = multiplet

† Calculated according to P. Diehl, *Helv. Chim. Acta* 47, 1 (1964)

adducts Vc–e could be directly separated by taking up the oily reaction mixture in a suitable solvent, whilst isolation of the bis-adducts IVc–e could usually be achieved by column chromatography.

In Tables 1 and 2 the essential NMR data of all bis-adducts (IV and V) are given. The lower R_f-value compounds Va–e always show 8 lines for the C-4' ring protons, the C-4' ring H *cis* to the C-5' ring H absorbing regularly at *c.* 0·20 ppm at lower field as the *trans*-proton. Bis adducts IVa–e on the contrary show only a doublet for the C-4' ring protons. Similar observations have been reported for isoxazolines carrying an electron-withdrawing substituent in the 5-position.[9]

Since the aldehydes VII and VIII were isolated only in the reaction between equimolecular amounts of the reactants and were absent when two or more equivalents of benzonitrile oxide were used, they can exclusively originate from the hitherto non-isolated mono-adduct VI. Our results demonstrate that both double bonds of butadienylamines are reactive in the 1,3 dipolar cycloaddition to nitrile oxides and the orientation of the addition to the amino-substituted double bond is the reverse of that to the other double bond (and to that with butadiene[4]). Although no quantitative study has been undertaken so far, the 1,3-dipolarophilic activities of the two different double bonds are comparable, the terminal vinyl group being perhaps slightly more reactive, thus testing an efficient transmission of the activation effect of the amino group through the diene system.

Since the isoxazolyl-isoxazoline X is known to oxidize easily to 3,3′-diphenyl-4,5′-diisoxazole,[2] the cycloaddition of nitrile oxides to dieneamines may represent a convenient route of general applicability to 4,5′-diisoxazoles.

EXPERIMENTAL

All m.ps are uncorrected. UV spectra: abs ethanolic soln, Hilger-Watts Ultrascan spectrophotometer. IR spectra: Nujol mulls, Perkin Elmer Infracord spectrophotometer. Microanalyses by Dr. Lucia Maggi Dacrema. NMR spectra: $CDCl_3$ soln, TMS as internal standard, Varian DP 60 spectrometer (temp 25°). Column and thin-layer chromatography: silicagel H plates, eluant cyclohexane: AcOEt = 70/30, unless otherwise specified.

The butadienylamines were prepared according to known procedures.[6a, b, 10] The 1-pyrrolidino-butadiene, hitherto unknown was prepared by the method of Hünig in 40% yield: colourless oil, b.p. 95°/22 mm, $\nu_{C=C}$ 1640 cm^{-1} (Found: C, 78·08; H, 10·19; N, 11·44. Calc. for $C_8H_{13}N$: C, 77·99; H, 10·64; N, 11·37%).

Cycloaddition of benzonitrile oxide to 1-N,N-*diethylamino*-1,3-*butadiene*

A. An ethereal soln of I (2·0 g, 22 mmoles), prepared by standard method from 5·0 g of benzhydroximic acid chloride,[11] and IIa (1·38 g, 11 mmoles) was refluxed for 1 hr, then left overnight at room temp. After evaporation of the solvent, the oily residue (3·65 g) showed by TLC analysis the presence of two compounds, besides traces of all the other compounds obtained by procedure C (see below). When the oil was taken up in isopropyl ether, a crystalline mixture, m.p. 85–90°, of IVa and Va separated out (1·9 g, 47·5% yield). The two compounds were readily separated by column chromatography on silicagel H: (i) 19% of IVa as colourless crystals from isopropyl ether; (ii) 17% of Va as colourless flakes. The characterization data are reported in Table 3.

B. To a well stirred and ice-cooled soln of freshly distilled IIa (1·25 g, 10 mmoles) and triethylamine (5·5 g, 50 mmoles) in abs ether (20 ml), an ethereal soln of benzhydroximic acid chloride (3·9 g, 25 mmoles) was slowly added. The mixture was further stirred for 2 hr at room temp and kept overnight. The triethylamine chlorhydrate (94% yield) was filtered off and the filtrate after solvent removal and treatment of the oily residue with isopropyl ether, afforded a solid mixture, m.p. 92–97°, of IVa and Va (1·9 g 52%). Column chromatography separated the two components in 18 and 17% yields respectively.

C. The condensation of I (7·75 mmoles), generated *in situ* as under (B), with IIa (8 mmoles) afforded, after filtration of the triethylamine chlorhydrate (94% yield), an oily mixture of four components (1·5 g), as shown by TLC analysis. Column chromatography on silicagel H separated four fractions:

(i) The mono-adduct IIIa (300 mg; 16%) as a slightly red oil: IR: $\nu_{C=C}$ 1637 cm^{-1}. $\delta_{CH=CH}$, 990. 922 cm^{-1}. The NMR spectrum showed a single product: 8·90 τ (t, J = 7 c/s, 6 H), 7·26 τ (q, J = 7 c/s, 4 H), 6·07 τ (q, J = 7·9 c/s and 3·6 c/s, 1 H), 4·66 τ (d, J = 3·6 c/s, 1 H), 4·04 τ (sx, J = 7·9 c/s, 1 H), 4·5–4·95 τ (m, 2 H), 2–2·8 τ (m, 5 H).

(ii) A mixture (350 mg) c 2:1 of IVa and X (TLC analysis in $CHCl_3$: $R_f = 0·3$ and 0·6 respectively). Crystallization from MeOH gave 177 mg (12·5%) of IVa, whereas concentration of the mother liquor afforded X, m.p. 82–83°, identical with an authentic sample.[2]

(iii) The bis-adduct Va (250 mg; 18%).

(iv) A mixture (370 mg) of VII and VIII. From the last fractions almost pure VIII (200 mg; 14%) could be separated, which crystallized from MeOH in colourless crystals, m.p. 139–143°. (Found: C, 73·27; H, 5·59; N, 7·49. Calc. for $C_{22}H_{20}O_3N_2$: C, 73·31; H, 5·59; N, 7·77%). From the first fractions 170 mg (12%) of VII was separated as an oil, IR absorption at 1721 and 2725 cm^{-1}. The NMR spectrum showed the compound to be impure; after the oily product had been left aside for some weeks the carbonyl absorption of VIII increased appreciably in intensity.

Cycloaddition of benzonitrile oxide to IIIa

To a well stirred and ice-cooled soln of IIIa (183 mg; 0·75 mmoles) and triethylamine (1 ml; 7 mmoles) in abs ether (30 ml), an ethereal soln of benzhydroximic acid chloride (465 mg; 3 mmoles) was slowly

TABLE 3. CHARACTERIZATION DATA OF BIS-ADDUCTS

Compound	M.p. (°C)	Recrystallization solvent	Molecular formula	Analysis % Found C	H	N	Calc. C	H	N	UV Spectrum λ_{max}	log ε
IVa	153–154	isopr. ether	$C_{22}H_{25}O_2N_3$	72·63	7·08	11·65	72·70	6·93	11·56	264	4·42
Va	146 dec	isopr. ether	$C_{22}H_{25}O_2N_3$	72·99	6·85	11·55	72·70	6·93	11·56	264	4·42
IVb	128–130	n-heptane	$C_{20}H_{21}O_2N_3$	72·05	6·36	12·54	71·62	6·31	12·53	263	4·40
Vb	133	isopr. ether	$C_{20}H_{21}O_2N_3$	71·92	6·33	12·38	71·62	6·31	12·53	263·5	4·39
IVc	158–160	ethanol	$C_{22}H_{23}O_3N_3 \cdot \frac{1}{2}H_2O$	68·46	6·55	10·62	68·37	6·25	10·88	264	4·41
Vc	139–142	ethanol	$C_{22}H_{23}O_3N_3 \cdot \frac{1}{2}H_2O$	68·24	6·17	10·77	68·37	6·25	10·88	264	4·37
IVd	109 110	petr. ether	$C_{22}H_{23}O_2N_3$	72·56	6·31	11·50	73·10	6·41	11·63	265	4·39
Vd	139–140	isopr. ether	$C_{22}H_{23}O_2N_3$	73·12	6·46	11·93	73·10	6·41	11·63	264	4·40
IVe	145–146	isopr. ether	$C_{23}H_{25}O_2N_3$	73·91	6·77	11·24	73·57	6·71	11·19	264	4·40
Ve	173–174	ethanol	$C_{23}H_{25}O_2N_3$	73·56	6·73	11·13	73·57	6·71	11·19	264	4·41

added. Operating in the usual way 370 mg of triethylamine chlorhydrate (90%) and 511 mg of an oily mixture were obtained. Column chromatography on Silicagel H afforded besides diphenylfuroxane: (i) 89 mg of a mixture of IVa (20%) and X c 2:1 (TLC analysis, eluant $CHCl_3$). Crystallization from EtOH gave the pure IVa; (ii) 110 mg (40%) of Va.

Thermolysis of the bis-adducts IVa *and* Va

A. Compound IVa or Va (20 ml) was heated in a test tube for 1 hr at 160°. The oily residue, on treatment with MeOH, gave in both cases a solid (m.p. 79–80°) identical in every respect with X (mixed m.p., superimposable IR spectra, same R_f value).

B. Compound IVa (130 ml) was heated under vacuum and distilled at 200–220° (bath)/0·3 mm collecting 72 mg (58%) of a yellowish oil which, treated with EtOH, solidified (m.p. 82–83°, identical with X). Va gave analogous results.

Thermolysis of mono-adduct IIIa

Compound IIIa (104 ml) was heated under reduced pressure; at 150–170° (bath)/25 mm, 55 mg (73%) of an oily fraction was collected, which solidified m.p. 44–45°, identical with IX (mixed m.p., superimposable IR spectra, same R_f value).

Cycloaddition of benzonitrile oxide to 1-N,N-*dimethylamino*-1,3-*butadiene*

To a well stirred and ice-cooled soln of freshly distilled IIb (2 g, 20·6 mmoles) and triethylamine (9 ml, 64 mmoles) in abs ether (30 ml), an ethereal soln of benzhydroximic acid chloride (5 g, 32 mmoles) was slowly added. The mixture was then kept overnight at room temp. The triethylamine chlorhydrate was filtered off and the filtrate was evaporated. Treatment of the oily residue with isopropyl ether afforded Vb (1·4 g 26%). The mother liquors were evaporated and column chromatography on silicagel H yielded two fractions: (i) the mono-adduct IIIb (340 mg, 7·6%) as an oil; IR: $\nu_{C=C}$ 1639 cm^{-1}, $\delta_{CH=CH_2}$ 990, 910 cm^{-1}; NMR spectrum showed a single product: 7·65 τ (s, 6 H), 6·09 τ (q, J = 3 c/s and 7·6 c/s, 1 H), 4·85 τ (d, J = 3 c/s, 1 H), 4·5 5 τ (m, 2 H), 4·07 τ (sx, 1 H), 2·1–2·8 τ (m, 10 H). (ii) the bis-adduct IVb (1·05 g, 20%).

Cycloaddition of benzonitrile oxide to IIIb

An ethereal soln of 2 mmoles of I[11] and IIIb (87 mg, 0·4 mmoles) was refluxed for 1·5 hr, then left overnight at room temp. After evaporation of the solvent, preparative TLC of the residue afforded, besides some diphenylfuroxane: (i) a mixture (22 mg) c 2:1 of IVb and X according to TLC analysis. Crystallization from cyclohexane gave IVb. (ii) Vb (21 mg; 16%).

Thermolysis of bis-adducts IVb *and* Vb

(a) Compound IVb (70 mg) after heating for 1 hr at 180° under reduced pressure, gave after vacuum distillation 51 mg (84%) of an oil, b.p. 210–230° (bath)/0·2 mm, which, after treatment with MeOH, solidified, m.p. 79–80°, identical with X (mixed m.p. superimposable IR spectra, same R_f value).

(b) Similarly Vb afforded X in 94% yield.

Thermolysis of mono-adduct IIIb

(a) Compound IIIb (27 mg) was heated under reduced pressure. At 140–170° (bath)/25 mm, 20 mg of an oily mixture of IIIb and IX (according to TLC) was collected;

(b) Compound IIIb (35 mg) heated at 200–250° (bath), gave on distillation at normal pressure 10 mg of an oil, which showed the same R_f value of IX and superimposable IR spectra.

Cycloaddition of benzonitrile oxide to 1-*morpholino*-1,3-*butadiene*

An ethereal soln of I (7·3 mmoles)[11] and IIc (0·40 g, 2·87 mmoles) was refluxed for 1 hr. After being kept overnight, Vc (0·30 g, 27%) separated. Concentration of the ethereal mother liquors afforded IVc (0·20 g 18%).

Cycloaddition of benzonitrile oxide to 1-*pyrrolidino and* 1-*piperidino*-1,3-*butadiene*

Operating in the usual way as described for the cycloaddition of I to IIa (procedure B), bis-adducts Vd and Ve were easily separated by treatment of the oily residue with isopropyl ether in 19% and 21% yields. Column chromatography afforded IVd and IVe in 10% and 16% yields respectively.

Thermolysis of the bis-adducts IVc–e *and* Vc–e

The bis-adducts were heated for 1 hr at 220° under reduced press, then distilled under vacuum. At 200–230° (bath)/0·2 mm 90–98 % yields of oily products were collected, which solidified on treatment with MeOH. All the products were identical to X.

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