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INTRAMOLECULAR REACTIONS OF α-AZIDOCINNAMATES WITH 4-SUBSTITUTED 1,3-DIENES

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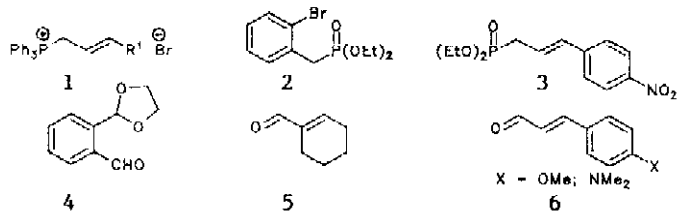
Summary: The synthesis of new 8,9-benzo-6-aza-bicyclo[3.2.2]nona-3,6,8-trienes **14** by intramolecular reaction of α-azidocinnamates **9** with alkyl- and phenylsubstituted ortho-butadienyl side chains is reported, as is the formation of the new 1-aza-2-carbomethoxy-7,8-benzo-tricyclo[4.30.0^{2,9}]nona-4,7-diene **15**.

Recently we reported intramolecular reactions of vinyl azides[1] with 1,3-dienes, forming the 6-aza-bicyclo[3.2.2]nonane skeleton.[2] In particular the thermal decomposition of α-azidocinnamates bearing an ortho-butadienyl side chain yields the 7-carbomethoxy-8,9-benzo-6-aza-bicyclo[3.2.2]nona-3,6,8-trienes (1,4-dihydro-1,4-propeno-isoquinoline carboxylic acid methyl esters) as major products; their structure is closely related to that of the isopavine alkaloids,[3] and the 6-aza-bicyclo[3.2.2]nonane skeleton is found as a structural subunit in some of the complex structures of the ajmaline and daphniphyllum alkaloids. 1-Allyl-3-carbomethoxy-isoquinolines and 2-vinyl-7-carbomethoxy-3H-benzazepines are also formed as minor products.

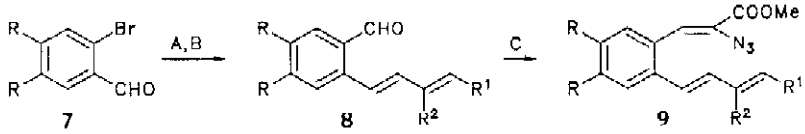
Here we report on the intramolecular reaction of α-azidocinnamates with 1,3-dienes bearing an alkyl- or phenyl substituent at the 4-position. The idea was to synthesize more complex 6-aza-bicyclo-[3.2.2]nonanes with an additional stereogenic center and to evaluate the influence of such substituents on the aforementioned product distribution. The required α-azidocinnamates (3-phenyl-2-azidopropenoate esters) **9** were prepared from the o-butadienyl benzaldehydes **8** by condensation with methyl azido-acetate, analogously to the procedure reported by Knittel;[4] see Scheme 2.

The aldehydes **8** were prepared from the o-bromo-benzaldehydes **7** and the building blocks **1** - **6** by standard methods; see Scheme 1 and 2.

Scheme 1

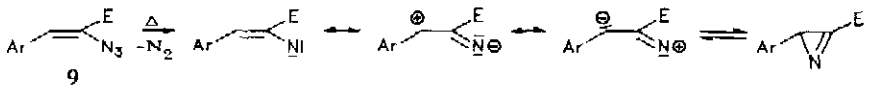


Scheme 2



R, R^1, R^2 see Table 1
A: $Ph_3P{=}CH{-}CR^2{=}CHR^1$, THF, rt; **B:** 1. n-BuLi,THF,hexane, -78°C; 2. DMF, -78°C → rt, 3. NH_4Cl,H_2O: **C:** N_3CH_2COOMe.NaOMe.MeOH, 0°C → rt.

Scheme 3



Scheme 4

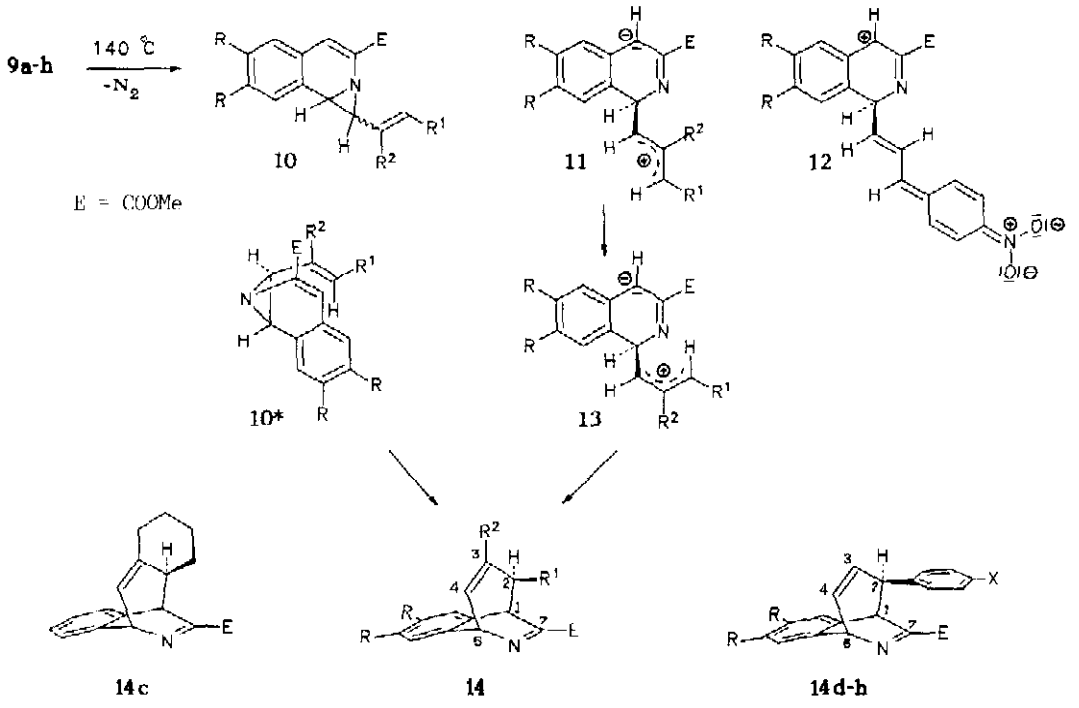


Table 1: Derivatives **9** - **14** and yield of products **14**

Entry	Derivative **9** - **14**	R	R^2	R^1	X	**14** Yield (%)
1	a	H	H	H		16[a]
2	b	OMe	H	Me		6[b]
3	c	H	$-(CH_2)_4-$			7
4	d	H	H	Ph	H	25
5	e	H	H	p-MeO-phenyl	OMe	38
6	f	H	H	p-NO_2-phenyl	NO_2	45
7	g	H	H	p-NMe_2-phenyl	NMe_2	60
8	h	OMe	H	Ph	H	53

[a] for the X-ray structure of **14a** see Scheme 5.

[b] in addition 1-(2-butenyl-)-3-carbomethoxy-6,7-dimethoxyisoquinoline is isolated in 3% yield.

A Wittig reaction of **7** with the phosphorane from **1** (treatment with n-BuLi) leads to a mixture of Z/E- and E/E-butadienes, which was converted into pure E/E-butadiene by treatment with a catalytic amount of iodine in toluene. Formylation then leads to o-butadienyl benzaldehydes **8**. Wittig-Horner reactions of deprotonated **2** (LDA) and aldehydes **5** and **6** yield E/E-butadienes, which were converted to the aldehydes **8**. A similar Wittig-Horner reaction of deprotonated **3** (NaH/THF) with **4**, followed by cleavage of the acetal ($THF/H_2O/HCl$) leads to the aldehyde **8f**.

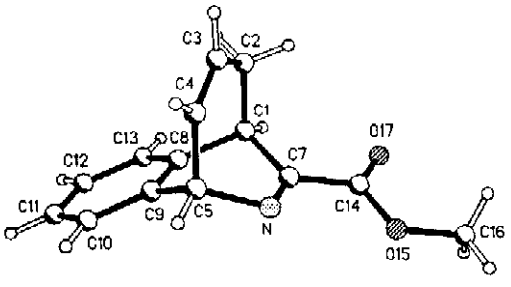
Refluxing a solution of vinylazides **9** in dry xylenes (0.03 M) for one hour, removal of the solvent and separation of the products by column chromatography (silica gel/EtOAc /hexanes) yields the new 7-carbomethoxy-8,9-benzo-6-aza-bicyclo[3.2.2]nona-3,6,8-trienes **14** ;[5] see Scheme 4, Table 1.

In contrast to examples reported earlier,[2] the thermolysis of the new vinylazides **9**, with 4-substituted o-butadienyl side chains, does not give isoquinolines and 3H-benzazepines in isolable yield, except for **9b**; see Table 1, entry 2. The alkyl-substituted derivatives **9b,c** react to **14** in only poor yield. Other products could not be identified. The yield of the desired product **14** increases when substituents such as phenyl, p-MeO-phenyl-, p-NMe_2-phenyl or p-NO_2-phenyl, which can stabilize a positive or negative charge, are placed in the 4-position of the butadiene side chain; see entry 4 - 8. This can be explained by assuming that the formation of **14** involves the dipolar intermediates **11**, **12** and **13**, rather than divinyl-aziridine **10**. Products **14** could be formed from the 2,3-cis-divinyl-aziridine part of **10** by 3-aza Cope rearrangement through the boat-like transition state **10***. But intermediate **10** would also give rise to the formation of 1-allyl-isoquinolines and 2-vinyl-3H-benzazepines by a 1,2-H-shift.[1c,2] Since this is not observed for derivatives **9d - h**, we assume that the vinylnitrene, formed from the vinylazide by thermolytic loss of N_2, adds to the ortho double bond through one of its 1,3-dipolar resonance structures, to give the dipolar intermediates **11** or **12** stabilized by the p-X-phenyl substituent. The fact that derivative **9g** with the more polarisable p-NMe_2-phenyl group gives a higher yield of **14** than the p-MeO-phenyl derivative **9e** is in accord with this assumption.

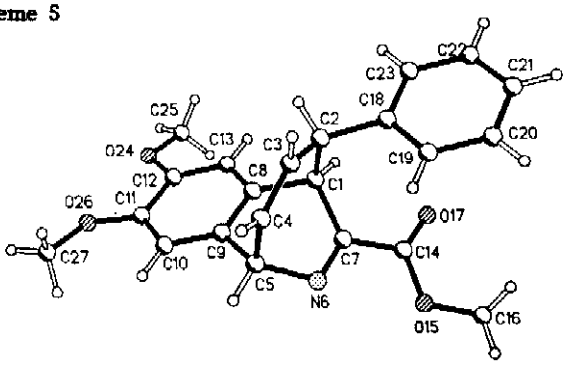
The yield of product **14** increases markedly when methoxy substituents are present on the aromatic ring of the azidocinnamate; see entry 8 and ref. 2. Whether this is due to the para-MeO group stabilizing the vinylazide/vinylnitrene, or the other para-MeO group that makes the diene side chain more electron rich and attractive to the electrophilic vinylnitrene, will be investigated further.

The configuration at C-2 of the 2-phenyl derivatives **14d - h** has been assigned, as shown in Scheme 4, on the observation that the ^1H nmr signal of the ester-OMe group is shifted upfield by 0.8 ppm, which suggests that the phenyl group is placed above the ester group. This assignment has been confirmed by X-ray structure analysis of derivative **14 h**; see Scheme 5.[6] A likely reaction pathway to those structures is shown in Scheme 4.

Scheme 5



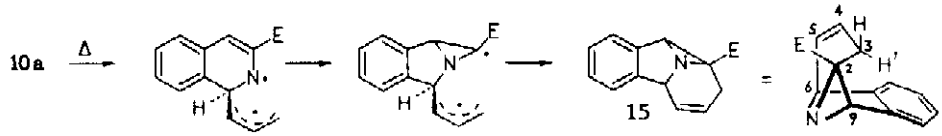
X-ray structure of **14a**



X-ray structure of **14h**

The parent o-butadienyl α-azidocinnamate **9a**, having no additional substituent, gives, under the same reaction conditions, a mixture of four separable products. In addition to 1-allyl-3-carbomethoxy-isoquinoline (7%), formed from **10a** by a 1,2-H-shift, and product **14a** (16%, see also ref. 2), 3-carbomethoxy-isoquinoline (2%), possibly from intermediate **11** by cleaving the 3-carbon side chain, and product **15** (9%) are isolated. This new 1-aza 2 carbomethoxy 7,8 benzo tricyclo[4.3.0.$0^{2,9}$]nona 4,7 diene **15** is possibly formed from **10a** by a radical pathway, as shown in Scheme 6.

Scheme 6



In conclusion we have synthesised new 8,9 benzo-6-aza-bicyclo[3,2,2]nonatrienes that are structurally related to the isopavine alkaloids and may also be of interest, after ester hydrolysis and reduction of the CN double bond, as amino acids.

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References and Notes

1. (a) Scriven, E.F.V. (Ed.) -Azides and Nitrenes- Academic Press 1984; (b) Scriven, E.F.V.; Turnbull, K., Chem. Rev. **1988**, 88, 297; (c) Moody, C.J. in -Studies in Natural Products Chemistry- A. Rahman (Ed.), Elsevier 1988, Vol. 1, pp 163 - 185.
2. C. Vogel; P. Delavier, Tetrahedron Lett. **1989**, 30, 1789.
3. Gözler, B. in: -The Alkaloids- A. Brossi (Ed.), Academic Press 1987, Vol. 31, p 317.
4. Knittel, D., Synthesis, **1985**, 186 and references therein.
5. All new compounds were fully characterized by spectroscopic means.
   Data for compound **15**: m.p. 93 °C, IR (CCl_4) ν_{max}: 3030, 2941, 2849, 1740, 1720, 1474, 1440, 1379, 1362, 1271 cm^{-1}; UV (MeOH): λ_{max}: 208 (15770), 232 sh (5500), 261 (1320) nm (ε); ^{1}H-nmr (400 MHz, $CDCl_3$) δ(ppm): 7.34 (d, J=6.8 Hz, 1 H), 7.25 (t, J=7.3 Hz, 1 H), 7.19 (t, J=7.3 Hz, 1 H), 6.98 (d, J=7.3 Hz, 1H), 6.44 (ddd, J=8.5 Hz, 7.9 Hz, 1.2 Hz, 1 H, H^5), 5.96 (ddd, J=8.5 Hz, 6.3 Hz, 2 Hz, 1 H, H^4), 4.59 (d, J=7.9 Hz, 1 H, H^6), 3.91 (s, 1 H, H^9), 3.85 (dd, J=16.3 Hz, 6.3 Hz, 1 H, 1 H^3), 3.77 (s, 3 H), 2.22 (ddd, J=16.1 Hz, 6.1 Hz, 1.2 Hz, 1 H, $H^{3'}$); ^{13}C-nmr (100.6 MHz, $CDCl_3$) δ(ppm): 171.6, 143.7, 137.2, 129.9, 128.9, 128.0, 126.6, 124.8, 124.7, 53.4, 53.1, 52.6, 42.6, 39.2; MS (70 eV) m/e (%): 227 (11, M^+), 196 (3), 169 (14), 168 (100), 141 (14) 115 (14), 97 (5); Elemental analysis: $C_{14}H_{13}NO_2$: calculated: C 73.99, H 5.77, N 6.16; found: C 73.61, H 5.70, N 6.19;
6. Crystal Data for compound **14a** at -95 °C: $C_{14}H_{13}NO_2$, M = 227.3, monoclinic, $P2_1/n$, a = 614.4(2), b = 2388.1(9), c = 809.4(3) pm, β = 99,95(2)°, V = 1.1697 nm^3, Z = 4, D_X = 1.290 Mg m^{-3}, λ(Mo Kα) = 71.069 pm, μ = 0.08 mm^{-1}, R = 0.037 for 1506 reflections > 4σ(F). Crystal data for compound **14h** at -95 °C: $C_{22}H_{21}NO_4 \cdot CHCl_3$, M = 482.38 monoclinic, $P2_1/n$, a = 1608.4(5), b = 646.1(2), c = 2283.6(7) pm, β = 106.21(2)°, V = 2.279 nm^3, Z = 4, D_X = 1.407 Mg m^{-3}, μ = 0.43 mm^{-1}, R = 0.037 for 3353 reflections > 4σ(F). Full details of the structure determinations have been deposited at the Fachinformationszentrum Karlsruhe, Gesellschaft für Wissenschaftlich-technische Information mbH, D-7514 Eggenstein-Leopoldshafen 2, Federal Republic of Germany. Any request for this material should quote a full literature citation and the reference number CSD 55051.

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