

A SYNTHESIS OF THE 6-AZA-BICYCLO(3,2,2)NONANE SKELETON

Claus Vogel* and Paul Delavier

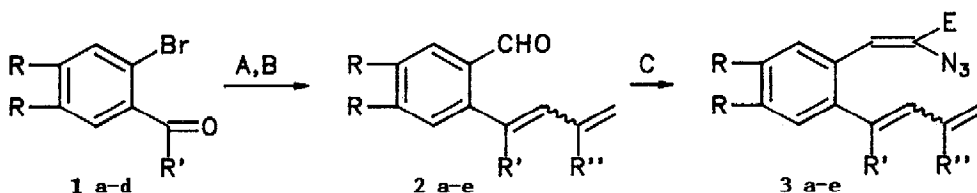
Institut für Organische Chemie, Hagenring 30,
 D-3300 Braunschweig, Federal Republic of Germany

Summary: The construction of the 6-aza-bicyclo(3,2,2)nonane skeleton by a new tandem aziridination/3-aza-Cope rearrangement sequence employing the intramolecular reaction of vinylazides with 1,3-dienes is reported.

The thermal decomposition of vinylazides, notably α -azidocinnamates (3-aryl,2-azidopropenoate esters), has been used for the construction of N-heterocycles like indoles, isoquinolines and benzazepines^{1,2}). The actual decomposition process, i.e. loss of N₂, was shown to involve the intermediacy of an azirine which is in equilibrium with the corresponding vinylnitrene³). The key step of N-heterocycle formation has been formulated as the reaction of the azide, azirine or vinylnitrene with an appropriate ortho substituent, e.g. an alkyl-, benzyl- or alkenylgroup or an ortho CH-bond^{2,3}). The intramolecular reaction with 1,3-dienes, i.e. azidocinnamates with ortho butadiene substituents, has on the other hand not been reported so far⁴). The additional vinyl group should give rise to an additional reaction pathway, leading to a new class of products.

In this communication we report on the intramolecular reaction of aryl-substituted and aliphatic vinylazides with 1,3-dienes. The required vinylazides 3 and 9 were prepared from the corresponding o-butadiene benzaldehydes 2 and the known heptadienal 8⁵), respectively, by condensation with methyl azidoacetate or ω -azido-p-chloroacetophenone analogous to procedures reported by HEMETSBERGER and KNITTEL^{2b,c}); see scheme 1 and 3.

Scheme 1



R, R', R'' see table 1

A: Ph₃P=CH-CR''=CH₂, THF, rt; B: 1. n-BuLi, THF, hexane, -78°C; 2. DMF, -78°C → rt
 3. NH₄Cl, H₂O; C: N₃CH₂COOMe, NaOMe, MeOH, 0°C → rt

Compounds 2 were prepared from the o-bromobenzaldehydes 1 a-c or o-bromoacetophenone 1 d by standard methods. Refluxing a solution of the vinylazides 3 in dry xylenes (0.03 M) for 30 min., removal of the solvent and separation of the products by column chromatography (silica gel, EtOAc - hexane 1:1) yields the compounds 5, 6 and 7 (see scheme 2 and table 1), as well as a mixture of polar products which could not be identified.

The separated products are each stable under the reaction conditions⁶⁾. The formation of the three types of products can be rationalized by assuming the *cis*- and *trans*-1,2-divinylaziridines **4** as intermediates. These would be formed by reaction of the azide or nitrene with the *ortho* double bond presumably in a stepwise nonspecific manner, so that the *cis*-divinylaziridine **4*** is formed also from the *trans*-butadiene derivative **3c** (see table 1, entry 4). Subsequent 1,2-H-shifts taking place at the aziridine result in the formation of a mixture of isoquinoline **5** and 3H-benzazepine **6**, analogous to cases which did not have the additional vinylgroup^{2d-f)}. The new 8,9-benzo-6-aza-bicyclo(3,2,2)nona-3,6,8-trienes **7** are most likely formed by a 3-aza Cope rearrangement of the *cis*-1,2-divinylaziridines **4***. 1,2-Divinylaziridines are known to undergo a rapid aza Cope

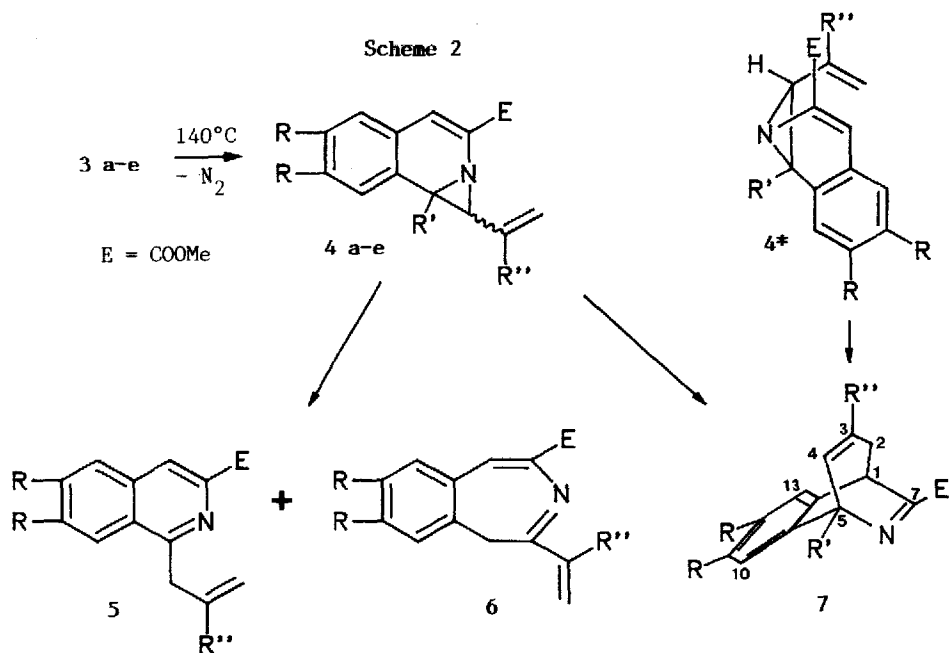


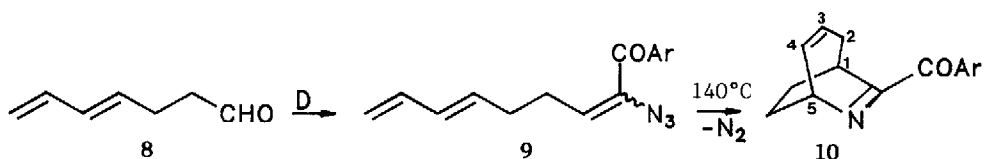
Table 1

Entry	Derivative	R			E/Z-Ratio of Butadiene 3	Yield %		
		R	R'	R''		5	6	7
1	a	H	H	H	6:4	8	trace	16
2	b	-OCH ₂ O-	H	H	6:4	11	18	16
3	c	OMe	H	H	6:4	20	16	35
4	c	OMe	H	H	E	12	16	40
5	c	OMe	H	H	Z	13	4	28
6	d	OMe	H	Me	1:1	11	8	22
7	e	H	Me	H	1:1	0	0	20

rearrangement even at temperatures as low as -20°C ⁷⁾. In our case the nitrogen is locked in a rigid structure, which prevents N-inversion, and thus only the 2,3-cis-aziridines (or cis H, methyl for entry 7, table 1) can adopt the boat-like conformation 4*, required for that rearrangement. Since the 3-aza Cope rearrangement should be a fast process, once the cis-1,2-divinylaziridine is formed, one might speculate that products 7 result from 4*, and products 5 and 6 result from 1,2-H-shifts at the trans-divinylaziridine.

When the vinylazide 9 (1:1 mixture of E/Z-isomers) was subjected to the same reaction conditions, the new 6-aza-bicyclo(3,2,2)nona-3,6-diene 10 could be isolated from the reaction mixture in poor yield (5%); the residue being a mixture of unidentified polar decomposition products.

Scheme 3



D: $p\text{-Cl-C}_6\text{H}_4\text{-COCH}_2\text{N}_3$, piperidine, HOAc, EtOH, rt; Ar = $p\text{-Cl-phenyl}$

We ascribe the low yield of 10 mainly to the less defined decomposition pathway of α -benzoylvinylazides^{3a)}. The p -chlorobenzoyl group was chosen here to synthesize the vinylazide by the condensation route; see scheme 3. A similar mechanism as described above for compounds 7 would account for the formation of 10. Although the yields of the new products 7 and 10 are presently low to moderate, we consider their formation to be an interesting new contribution to vinylazide chemistry. These structures constitute the characteristic part of the general skeleton of the isopavine alkaloids⁸⁾. They display sufficiently different functionalities for further transformations. An application of the novel tandem aziridination/3-aza Cope rearrangement sequence for the synthesis of isopavine alkaloids is in progress in our laboratory.

Acknowledgement: Financial support of this work by the Deutsche Forschungsgemeinschaft is gratefully acknowledged.

References and Notes

- (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;
- (a) Isomura, K.; Kobayashi, S.; Taniguchi, H., *Tetrahedron Lett.* **1968**, 3499; (b) Hemetsberger, H.; Knittel, D., *Monatsh. f. Chem.* **1972**, *103*, pp 194, 205;

- (c) Knittel, D., Synthesis, **1985**, 186; (d) Hickey, D.; Moody, C.J.; Rees, C.W. J. Chem. Soc. Chem. Commun., **1982**, 3; (e) Moody, C.J.; Warreilow, G.J., J. Chem. Soc. Perkin Trans. 1, **1986**, 1123; (f) Moody, C.J.; Warreilow, G.J., Tetrahedron Lett. **1987**, 28, 6089
3. (a) Hassner, A.; Wiegand, N.H.; Gottlieb, H.E., J. Org. Chem., **1986**, 51, 3176;
 (b) Isomura, K.; Ayabe, G.-I.; Hatano, . S.; Taniguchi, H., J. Chem. Soc. Chem. Commun., **1980**, 1252;
4. For the intramolecular reaction of alkylazides and azidoquinones with dienes, leading to fused 3-pyrrolines, see: (a) Hudlicky, T.; Frazier, J.O.; Seoane, G.; Tiedje, M.; Seoane, A.; Kwart, L.; Beal, C., J. Am. Chem. Soc., **1986**, 108, 3755;
 (b) Naruta, Y.; Nagai, N.; Arita, Y.; Maruyama, K., J. Org. Chem. **1987**, 52, 3956
5. Reed, S.F. jr., J. Org. Chem. **1965**, 30, 1663
6. All new compounds were fully characterized by spectroscopic means.
 Data for Compound **7c**: m.p. 143°C (dec.); IR (CCl₄) $\tilde{\nu}_{\max}$: 3030, 3000, 2950, 2830, 1725 (Ester-CO), 1510, 1265, 1115, 1095 cm⁻¹; UV (MeOH) λ_{\max} : 209 (22000), 237 (5600), 284 (3600) nm (ϵ); ¹H-NMR (400 MHz, CDCl₃) δ (ppm): 6.87 (s, 1H_{arom.}, C¹³-H), 6.79 (s, 1H_{arom.}, C¹⁰-H), 6.22 (m, 1H, C⁴-H), 5.3 (d, J=7.5 Hz, 1H, C⁵-H), 5.17 (dtr, J= 10.7 Hz, 3.4 Hz, 1H, C³-H), 4.4 (tr, J=3.4 Hz, 1H, C¹-H), 2.4 (m, 2H, (C²)H₂), 3.9, 3.88, 3.87 (s each, 3H each, three OMe); ¹³C-NMR (100.6 MHz, CDCl₃) δ (ppm): 166.0, 164.1, 148.1, 147.6, 135.5, 129.8, 127.8, 109.98, 107.4, 61.4 (C⁵), 56.2 (-OCH₃), 56.1 (-OCH₃), 53.0 (-OCH₃), 40.0 (C¹), 28.2 (C²), 127.1; MS (70 eV) m/e (%): 287 (100, M⁺), 272 (6), 228 (42), 202 (96), 187 (24), 171 (33), 115 (19); Elemental analysis, C₁₆H₁₇NO₄, Calcd: C 66.89, H 5.96, N 4.88; Found: C 66.79, H 5.89, N 4.93;
 Data for compound **10**: IR (CCl₄) $\tilde{\nu}_{\max}$: 3020, 2940, 2900, 2880, 1665, 1635, 1585, 1480, 1400, 1270, 1170, 1090, 1010, 920, 840, 700; UV (MeOH), λ_{\max} : 205 (13500), 268 (11800) nm (ϵ); ¹H-NMR (400 MHz, CDCl₃) δ (ppm): 8.01 (d, J=8.5 Hz, 2H_{arom.}), 7.41 (d, J=8.5 Hz, 2H_{arom.}), 5.97 (m, 1H, C⁴-H), 5.53 (dtr, J=10.8 Hz, 2.9 Hz, 1H, C³-H), 4.54 (tr, J=4.6 Hz, 1H, C⁵-H), 3.42 (tr, J=3.7 Hz, 1H, C¹-H), 2.38 (m, 2H, (C²)H₂), 2.21 (m, 1H) 2.04 (m, 2H), 1.78 (m, 1H); ¹³C-NMR (100.6 MHz, CDCl₃) δ (ppm): 191.6 (C=O), 172.9 (C=N), 139.5, 133.8, 132.3, 129.8, 129.6, 128.4, 55.4, 33.4, 30.8, 29.3 (C²), 23.7; MS (70eV) m/e (%): 259 (43, M⁺), 233 (10), 231 (30), 224 (13), 120 (20), 111 (51);
7. Cases of structures which allowed N-inversion: (a) Stogryn, E.L.; Brois, S.J., J. Am. Chem. Soc. **1967**, 89, 605; (b) Hassner, A.; D'Costa, R., Tetrahedron Lett. **1981**, 22, 3691; (c) Calcagno, M.A.; Schweizer, E.E., J. Org. Chem. **1978**, 43, 4207; (d) Hasenrueck, K.; Martin, H.D., Synthesis **1988**, 569
8. (a) Gözler, B. in: -The Alkaloids- Brossi, A. (Ed.), Academic Press 1987, Vol. 31, p 317 ff; (b) Jung, M.E.; Miller, S.J., J. Am. Chem. Soc. **1981**, 103, 1984

(Received in Germany 1 February 1989)