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Dihydro[*c*]benzazepin-3-ones via Conjugated Nitrone–Allene Precursors

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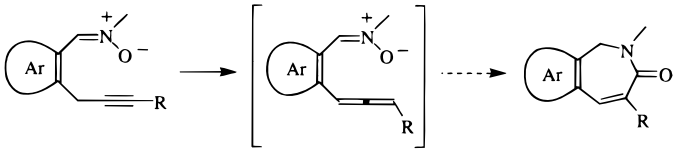
ABSTRACT

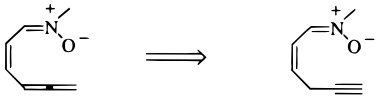


Treatment of *o*-propargylaryl nitrones with base provided 1,2-dihydro[*c*]benzazepin-3-ones in good yields. The straightforward transformation is explained on the basis of a multistep rearrangement involving conjugated allene–nitrones as precursors of a 1,7-dipolar electrocyclization process that is followed by further bond reorganizations.

The participation of an allene unit in pericyclic processes is amply documented in many [2 + 2] cycloadditions,[1] Diels−Alder reactions,[2] and the corresponding 1,3-dipolar methodology.[3] Much less common are examples involving electrocyclic ring closures of allene systems.[4] We have been engaged for some years in studies directed toward the application of 1,7-dipolar cyclization reactions[5] in order to develop new methods in heterocyclic synthesis. After the extensive use of dipoles bearing butadienyl and butenynyl groups as 4π-moieties, leading to a variety of new five-, six-, and seven-membered heterocycles,[6] we now report on results with nitrones derivatives of type **A** (Scheme 1).[7]

It was the intention of this work to generate the allene unit of **A** by base-catalyzed tautomerization of the corresponding propargyl derivative **B**. The experiments were performed with the benzannulated nitrone system **6**, which is available by the route sketched in Scheme 2.

Scheme 1



A **B**

Starting with the bromo aldehydes **1**, carbonyl protection and subsequent Grignard reaction gave compounds **2**, which after liberation of the aldehyde function, afforded the nitrones **6d**,**e**,**n** by treatment of the aldehydes **5** with methyl and phenyl hydroxylamine, respectively. The nitrones **6f**−**k**,**o** were made available from **2** by sequential hydrodesilylation (→ **3**), introduction of a terminal substituent (→ **4**) by the Sonogashira method[8] or *n*-butyllithium/methyl iodide treatment, deprotection (→ **5**), and nitrone formation. For the

(1) (a) Hopf, H. In *The Chemistry of Allenes*; Landor, S. R., Ed.; Academic Press: New York, 1982; Vol. 2, pp 525−562. (b) Pasto, D. J. *Tetrahedron* **1984**, *40*, 2805−2827.

(2) (a) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1990. (b) Larock, R. C. *Comprehensive Organic Transformations*; Wiley-VCH: Weinheim, 1999; p 541. See also ref 1a.

(3) For a recent review, see: Broggini, G.; Zecchi, G. *Gazz. Chim. Ital.* **1996**, *126*, 479−488.

(4) Hopf, H. In *The Chemistry of Allenes*; Landor, S. R., Ed.; Academic Press: New York, 1982; Vol. 2, pp 563−577.

(5) Reviews on 1,7-dipolar cyclizations: (a) Zecchi, G. *Synthesis* **1991**, 181−188. (b) Groundwater, P. W.; Nyerges, M. *Adv. Heterocycl. Chem.* **1999**, *73*, 97−129.

(6) (a) Eberbach, W.; Trostmann, U. *Chem. Ber.* **1985**, *118*, 4035−4058. (b) Eberbach, W.; Roser, J. *Tetrahedron* **1986**, *42*, 2221−2234. (c) Maier, W.; Eberbach, W.; Fritz, H. *Helv. Chim. Acta* **1991**, *74*, 1095−1101. (d) Bussenius, J.; Laber, N.; Müller, T.; Eberbach, W. *Chem. Ber.* **1994**, *127*, 247−259. (e) Lopez-Calle, E.; Höfler, J.; Eberbach, W. *Liebigs Ann. Chem.* **1996**, 1855−1866. (f) Marx, K.; Eberbach, W. *Chem. Eur. J.* **2000**, in press.

(7) Knobloch, K. Part of the forthcoming Dissertation, University Freiburg i. Br.

(8) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; pp 203−229.

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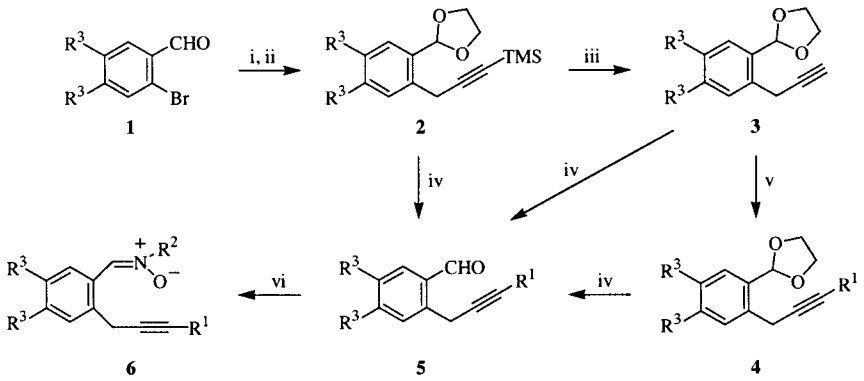
Scheme 2



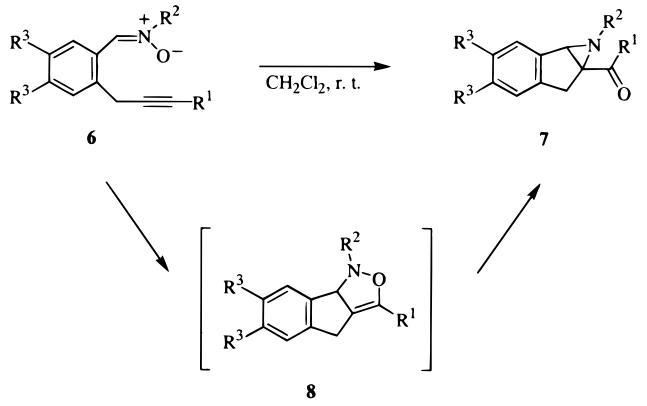
i: $HOCH_2CH_2OH$, PTSA; 91-98%.- ii: a) *n*-BuLi; b) $MgBr_2$; c) Br-CH_2-C≡C-TMS; 64-89%.- iii: NBu_4HSO_4, NH_4Cl, KF; 82-93%.- iv: PTSA, acetone/water; 84-95%.- v: ArI, $PdCl_2(PPh_3)_2$, CuI, NEt_3, or a) *n*-BuLi, b) CH_3I, 66-82%.- vi: $CH_3NHOH{\cdot}HCl$, NaOAc or PhNHOH, CH_2Cl_2; 53-86%.

	a	b	c	d	e	f	g	h	i	j	k	l	m	n	o
R^1	H	H	H	TMS	TMS	Me	Me	Ph	Ph	Ph	pMePh	H	H	TMS	pMePh
R^2	Me	Ph	CMe_3	Me	Ph	Me	Ph	Me	Ph	CMe_3	Me	Me	Ph	Me	Me
R^3	H	H	H	H	H	H	H	H	H	H	H	OMe	OMe	OMe	OMe

synthesis of **6a**−**c**,**l**,**m** direct deprotection of **3** (→ **5**) was followed by reaction with the corresponding hydroxylamines (see Scheme 2).

In some cases the ^{1}H NMR spectra of the crude products containing the nitrones **6** as major component showed additional signals of a product that turned out to belong to the epimino indenes **7**. The formation of **7** is explained by a known pathway involving a 1,3-dipolar cycloaddition reaction affording the isoxazolines **8**, which are subsequently transformed into the aziridines **7** (Scheme 3).[9,10] It must be

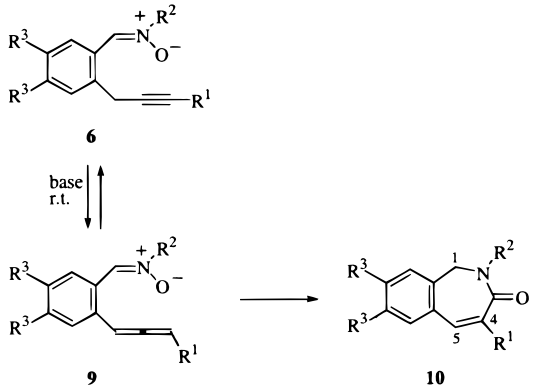
Scheme 3



due to the particular annulation of the isoxazolines that no direct evidence for **8** was obtained. However, control experiments with **6a**,**d**,**e**,**i** revealed that on standing or on heating in boiling benzene the nitrones are indeed transformed into the bicyclic systems **7**.

The cyclization experiments were typically carried out at room temperature by stirring solutions of the nitrones **6** in methanol in the presence of 0.5−1 equiv of sodium methylate or potassium hydroxide. In the case of the *N*-methyl derivative **6a** total conversion was reached after 0.5 h, resulting in a reaction mixture which, after aqueous workup and flash chromatographic purification, gave a single monomeric product in 84% yield. The structural identification of the compound as the dihydrobenzazepin-3-one **10a** (Scheme 4) is based on the elemental analysis and the MS

Scheme 4



and other spectroscopic data. In the IR spectrum there is a strong band at 1650 cm^{-1} indicating a carbonyl group; the ^{1}H

(9) The ring transformation of type **8** → **7** can be brought about either by thermal or photochemical activation of 4-isoxazolines; in the latter case the isolation of intermediate azomethine ylides was successfully accomplished: Lopez-Calle, E.; Eberbach, W. *J. Chem. Soc., Chem. Commun.* **1994**, 301−302.

(10) For thermal tranformations of type **8** → **7**, see: (a) Huisgen, R.; Niklas, K. *Heterocycles* **1984**, *22*, 21−26. (b) Padwa, A.; Wong, G. S. K. *J. Org. Chem.* **1986**, *51*, 3125−3133. (c) Mullen, G. B.; Bennet, G. A.; Georgiev, V. St. *Liebigs Ann. Chem.* **1990**, 109−110.

NMR spectrum shows, besides signals in the aromatic region and the singlet for the *N*-methyl group, a singlet for the methylene protons at C-1 and an AB pattern ascribed to the olefinic protons H-4 and H-5 (see Table 1). The final proof of structure **6a** came from the results of an X-ray analysis.[11]

Table 1. Yields and Selected ^{1}H NMR Data for Azepinones **10**[a]

		^{1}H NMR data			
	yield (%)	δ_{1-H}	δ_{4-H}	δ_{5-H}	$J_{4,5}$ (Hz)
a	84[b]	4.24	6.41	7.08	12.2
b	84[c]	4.66	6.55	7.20	12.2
c	85[c]	4.27	6.36	6.98	12.1
d	24[b,d]	4.12		7.20	
e	68[c,e]	4.55		~7.2[f]	
f	86[b,g]	4.10		6.89	
g	46[b,g]	4.57		7.06	
h	75[b]	4.50		~7.4[f]	
i	40[b]	4.72		~7.4[f]	
j	77[b]	4.24/4.53[h]		7.20	
k	64[c]	4.28		7.28	
l	77[b]	4.18	6.33	6.99	12.2
m	93[c]	4.58	6.44	7.09	12.2
n	25[c,i]	4.08		7.13	
o	76[c]	4.22		7.21	

[a] Reaction conditions: 0.2 molar in MeOH, 0.5−1 equiv of base, 0.5−5 h (**f**, 24 h; **g**, 20 h), rt. [b] Base: NaOMe. [c] Base: KOH. [d] +29% **a**. [e] +26% **b**. [f] Partially covered by signals of Ar-H. [g] Solvent: CH_2Cl_2. [h] $J_{1a,1b}$= 15.3 Hz. [i] +43% **l**.

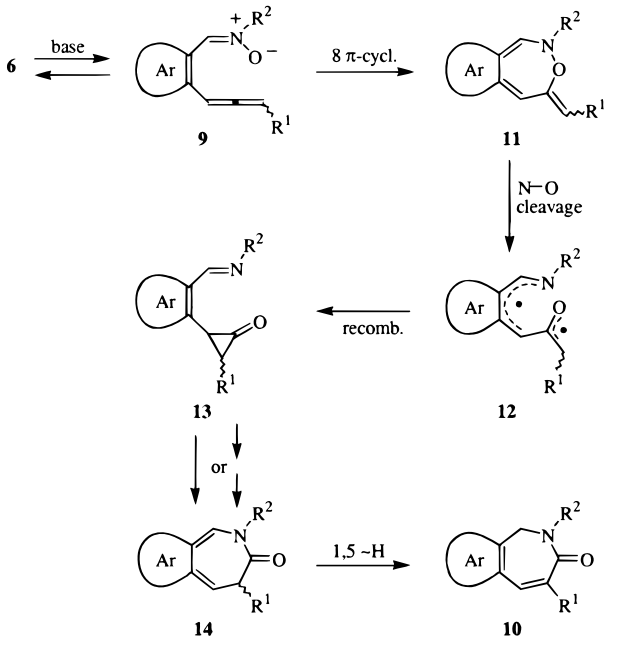
The conversion of type **6** → **10** turned out to be quite general and was successfully accomplished for many different derivatives. Thus, under analogous conditions the nitrones **6b**−**o** afforded the corresponding benzazepinones **10b**−**o** with yields up to 93%. As a result of partial hydrodesilylation during the reaction of **6d**,**e**,**n** the additional amount of **10a, 10b** and **10l**, respectively, has to be added to the yields given in the table.

With regard to the conformational mobility of the annulated azepinone system, only the *N*-*tert*-butyl 4-phenyl compound **10j** has some rigidity under ambient conditions. According to the ^{1}H NMR spectra the methylene protons at C-1 are not equivalent and therefore give rise to a pair of doublets (J = 15.3 Hz).

From the inspection of the structural differences of the starting and final products, **6** and **10**, it becomes clear that there is no simple connection between the nitrone and azepinone compounds. The most striking feature concerns the interchange of the terminal and central positions of the allene unit of **9**, i.e., the carbon atom connected to R^1 ends up at C-4 of **10**, which is now flanked by both former allene carbons. A possible but still tentative mechanism for the observed transformation includes the sequence outlined in Scheme 5: (i) propargyl−allene tautomerization (**6** → **9**),[12]

(11) Knobloch, K.; Keller, M.; Eberbach, W. paper in preparation.
(12) (a) Taylor, D. R. *Chem. Rev.* **1967**, *67*, 317−359. Grimaldi, J., Bertrand, M. *Bull. Soc. Chim. Fr.* **1971**, 947−957; 4316−4320.

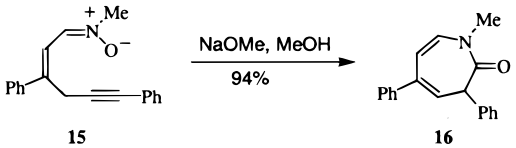
Scheme 5



(ii) 8π-cyclization **9** → **11**,[5,6] (iii) N−O cleavage (**11** → **12**),[6d,e,13] (iv) diradical recombination (**12** → **13**), (v) one- or two-step cyclization of the azadienyl cyclopropanone **13** to **14**, and finally, (vi) 1,5-H shift **14** → **10**. There is precedent at least for the first three steps of this pathway (see references).

The transformation **6** → **10** is not restricted to benzannulated derivatives. Preliminary work has shown that the same reaction takes place with alkenoannulated compounds and also with simple linear derivatives. For instance, treatment of the diphenyl nitrone **15** with NaOMe/MeOH produces the corresponding azepinone **16** in 94% yield; in this case there is no final H-migration (Scheme 6).

Scheme 6



Despite the structural simplicity of 1,2-dihydro[*c*]benzazepin-3-ones **10**, there are only a few synthetic methods available, mostly used for the synthesis of further annulated compounds,[14] which frequently possess biological activity.[15] The parent compound of **6** (**6a**, NH instead of NMe) has

(13) (a) Eberbach, W.; Roser, J. *Tetrahedron Lett.* **1987**, *28*, 2689−2692. (b) Eberbach, W.; Laber, N. *Tetrahedron Lett.* **1992**, *33*, 61−64.
(14) (a) Gschwend, H. W.; Hamdan, A. *J. Org. Chem.* **1982**, *47*, 3652−3657. (b) Röhrkasten, R.; Kreher, R. P. *Chem. Ber.* **1991**, *124*, 2085−2090. (c) Kai, H.; Yamauchi, M.; Murai, S. *Tetrahedron Lett.* **1997**, *38*, 9027−9030.

been synthesized in modest yield by irradiation of β-azidonaphthalene in methanol and subsequent hydrolysis of the iminoether.[16] The novel access to **10** described in this paper is a useful and widely applicable method for simple and more complex derivatives of this heterocyclic system.[17]

Acknowledgment. This work was supported by the Fonds der Chemischen Industrie.

Supporting Information Available: Full characterization data of compounds **7a**,**d**,**e**,**i**, **10a**−**o**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) (a) Hawthorne, J. O.; Mihelic, E. L. U.S. Patent 3,668,232, 1972; *Chem. Abstr.* **1972**, *77*, P101199s; U.S. Patent 3,551,414v, 1970; *Chem. Abstr*. **1971**, *74*, P125484. (b) Gorshkova, V. K.; Saratikov, A. S.; Tignibidina, L. G. *Pharm. Chem. J. (Engl. Transl.)* **1994**, *28*, 158−162.

(16) Rigaudy, J.; Igier, C.; Barcelo, J. *Tetrahedron Lett.* **1975**, *16*, 3845−3848.

(17) **Typical procedure**, exemplified for **10a**, is as follows. The solution of **6a** (100 mg, 0.58 mmol) and sodium methylate (16 mg, 0.29 mmol) in 4 mL of dry methanol was stirred at room temp. After complete conversion (0.5 h, monitored by TLC) the solution was diluted with water (10 mL) and then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was washed successively with saturated NH_4Cl and NaCl solutions, dried, and concentrated. Flash chromatography of the residue (SiO_2, cyclohexane/ethyl acetate 1:1, 1:2) gave **10a** (84 mg, 84%) as a white solid; mp 132−133 °C (ethanol).