Strained Molecules

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Synthesis and Reactions of Highly Strained 2,3-Bridged 2*H*-Azirines[**]

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Strained compounds are of special interest because of their increased energy content and the enhanced reactivity that frequently results from this. The already considerable ring strain of simple cyclopropenes (ca. 54 kcal mol^{-1}) is significantly increased if the three-membered ring is incorporated into the bicyclic framework **1** (Scheme 1).[1] It should be possible to transfer this concept from the hydrocarbons **1** to the heterocycles **3**.[2,3] The 2,3-bridged azirine **3d**, which is easily obtainable from azide **2d** by photolysis or thermolysis, can be distilled in vacuo,[4] whereas the more unstable compound **4** could be characterized only in solution.[5] Until now, the even more strained azirine **3b** and many similar bridged azirines bearing a six-membered ring can be generated only in situ and detected by trapping reactions.[4a,6] Thus,

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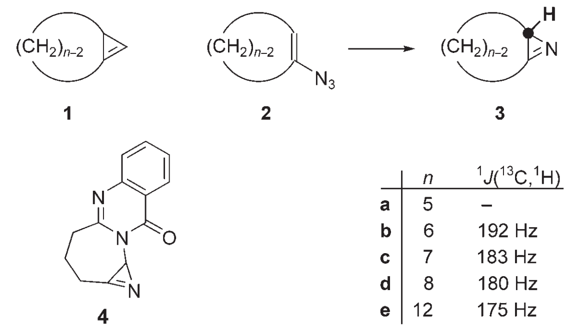
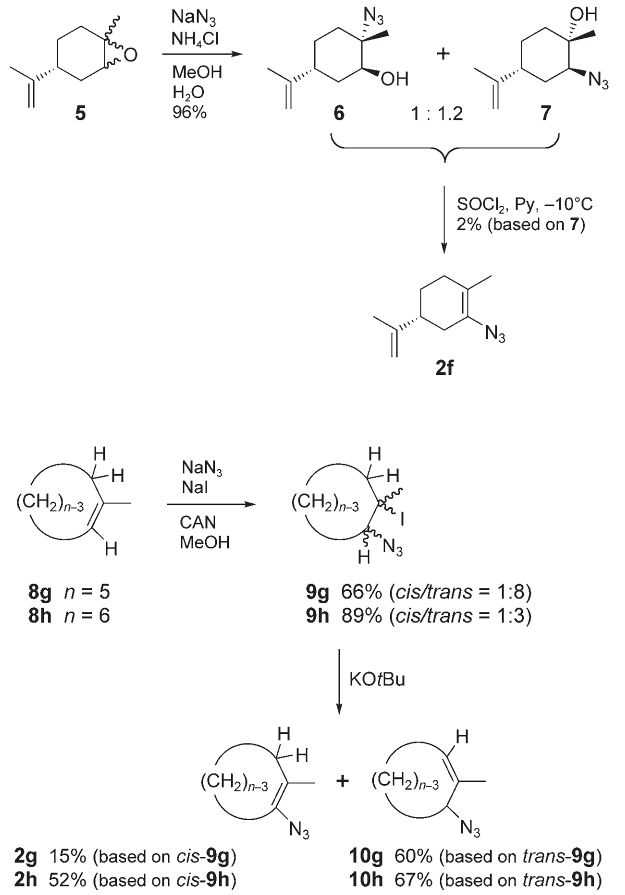


	n	$^1J(^{13}C,^1H)$
a	5	–
b	6	192 Hz
c	7	183 Hz
d	8	180 Hz
e	12	175 Hz

Scheme 1.



Scheme 2.

the prospect of spectroscopically characterizing **3b** in solution appears to be gloomy, especially as the ^{1}H NMR data of the analogous short-lived hydrocarbon **1b** were obtained even at −90 °C only partially.[7]

We now report the heterocycles **3b**, **3c**, **3e**, **3f**, and **3h–j** (Table 2), which have been analyzed spectroscopically for the first time, as well as some further 2,3-bridged azirines. The highly strained title compounds undergo several addition and cycloaddition reactions that are not possible for simple 2*H*-azirines.[2]

To produce the corresponding azirines, we prepared first the necessary vinyl azides[8] **2c**,[9] **2d**,[4b,c] and **2e**[9] by using Hassner's method,[10] that is, by electrophilic addition of iodine azide, generated in situ, to cycloalkenes followed by base-induced elimination of hydrogen iodide. In the case of five- and six-membered rings, it is well-known[4b,c,11–13] that this method does not lead to vinyl azides, but rather to allyl azides. Thus, we switched over to Zbiral's[11b] sequence for the synthesis of **2a** and **2b**. Neither route was successful in the synthesis of 1-azido-2-methylcycloalkenes such as **2f**, **2g**, and **2h** (Scheme 2). The dehydration with thionyl chloride of a mixture of the regioisomeric azidoalcohols **6**[14] and **7**,[14] which could be easily synthesized from the inexpensive limonene oxide **5**, was problematic and led only to a very low yield of **2f**. However, the formal addition of iodine azide to 1-methylcycloalkenes **8g,h** assisted by cerium(IV) ammonium nitrate (CAN)[15] and the subsequent treatment of **9g,h** with potassium *tert*-butylate gave somewhat better yields of the desired vinyl azides **2g,h**.

When a solution of the azide **2b** in anhydrous $CDCl_3$ or [D$_8$]toluene was irradiated at −50 °C with a mercury high-pressure lamp, surprisingly the bridgehead azirine **3b** could be detected even at room temperature by its IR as well as ^{1}H NMR and ^{13}C NMR data (Table 1).[16] However, a rapid subsequent reaction led to the formation of the dimer **11b**, and this product was quickly oxidized to **12b** when oxygen was not excluded rigorously (Table 2).[17] Addition of tetrachloro-1,4-benzoquinone caused instantaneous transformation of **11b** to **12b**. If photolysis of **2b** is performed in $CDCl_3$ or [D$_8$]toluene saturated with water, the dimerization **3b**→**11b** is accelerated so strongly that the intermediate **3b** can no longer be observed by NMR spectroscopy. We assume that even traces of water act as a catalyst and initiate the reaction sequence shown in Scheme 3. The less strained bridgehead azirine **3c** dimerizes considerably slower than **3b** (3 months,

Table 1: Selected physical data of 2,3-bridged 2*H*-azirines **3b** and **3c**.[a]

3b: IR ($CDCl_3$): $\tilde{\nu}=1743$ cm^{-1} (C=N); ^{1}H-NMR ($CDCl_3$, −40 °C): $\delta=1.01$ (ddddd, $^2J=14.0$, $^3J=9.9$, 8.9, 4.7, 2.6 Hz, 1 H, 4-H$_{endo}$), 1.28 (ddddd, $^2J=14.7$, $^3J=5.5$, 4.7, $^4J=1.1$, $^3J=0.6$ Hz, 1 H, 5-H$_{endo}$), 1.41 (ddddd, $^2J=14.0$, $^3J=7.3$, 5.5, 5.0, 2.6 Hz, 1 H, 4-H$_{exo}$), 1.54 (dddddd, $^2J=12.6$, 7.3, 6.9, 5.0, 2.6, $^4J=1.1$ Hz, 1 H, 3-H$_{endo}$), 1.64 (dddd, $^2J=14.7$, $^3J=8.9$, 5.0, 3.8, 1 H, 5-H$_{exo}$), 1.82 (ddddd, $^2J=12.6$, $^3J=9.9$, 7.6, 7.1, 2.6 Hz, 1 H, 3-H$_{exo}$), 2.28 (dd, $^3J=3.8$, 0.6 Hz, 1 H, 6-H), 2.84 (ddd, $^2J=12.7$, $^3J=7.1$, 6.9 Hz, 1 H, 2-H$_{exo}$), 3.24 ppm (ddd, $^2J=12.7$, $^3J=7.6$, 5.0 Hz, 1 H, 2-H$_{endo}$); ^{13}C-NMR ($CDCl_3$, −40 °C): $\delta=21.39$ (t, C-4), 23.85 (t, C-3), 25.96 (d, $^1J_{C,H}\approx$ 192 Hz, C-6), 27.27 (t, C-2), 28.33 (t, C-5), 179.04 ppm (s, C-1).

3c: Colorless liquid; IR ($CDCl_3$): $\tilde{\nu}=1764$ cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$): $\delta=0.87$ (m, 1 H), 1.27 (m, 1 H), 1.41 (m, 1 H), 1.54 (m, 1 H), 1.66–1.76 (m, 3 H), 2.07 (m, 1 H), 2.13 (m, 1 H), 2.79 (m, 1 H, 2-H), 3.00 ppm (m, 1 H, 2-H); ^{13}C NMR ($CDCl_3$): $\delta=26.37$ (t), 27.46 (t), 27.82 (t), 28.02 (t), 28.96 (d, $^1J_{C,H}=183$ Hz C-7), 31.53 (t), 175.35 ppm (s, C-1).

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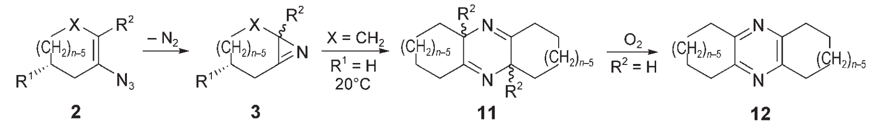
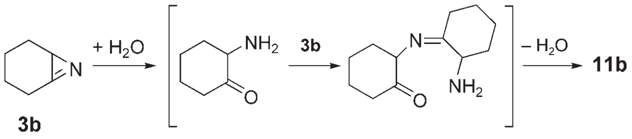
[a] The data of the other bridgehead azirines and those of other new compounds are summarized in the Supporting Information. ^{1}H NMR: 300 MHz, ^{13}C NMR: 75 MHz. The assignment of NMR signals and the measurement of coupling constants were performed with the help of ^{1}H,^{1}H double-resonance experiments, ^{1}H NMR NOE difference spectra, ^{1}H,^{1}H COSY experiments, ^{13}C,^{1}H shift correlations, DEPT135, GATED, and 2D *J*-resolved experiments, as well as spectrum simulation in the case of **3b**. The vicinal coupling constants found for **3b** correlate with the H-C-C-H torsion angles, which were calculated semiempirically (MOPAC), with the Karplus relationship.

Table 2: Generation and successive reactions of 2,3-bridged 2*H*-azirines **3**.



		Substrate **2**			Yield[a] of **3** [%] after photolysis	Yield[a] of **3** [%] after thermolysis	Yield of **11** [%]	Yield[a] of **12** [%]
	n	R¹	R²	X				
2a	5	H	H	CH_2	0 ($CDCl_2F$, −120 °C)	n.i.[b]	n.d.[b]	45[c]
2b	6	H	H	CH_2	83 ($CDCl_3$, −50 °C)	0 ($CDCl_3$, 80 °C)	n.m.[b]	49[d]
2c	7	H	H	CH_2	91 ($CDCl_3$, −50 °C)	85 ($CDCl_3$, 80 °C)	n.d.	54[d]
2e[e]	12	H	H	CH_2	100 ($CDCl_3$, −50 °C)	96 ($CDCl_3$, 80 °C)	0	0
2f	6	$CMe{=}CH_2$	Me	CH_2	94[f] ($CDCl_3$, −50 °C)	n.i.	n.i.	–
2g	5	H	Me	CH_2	0 (CD_2Cl_2, −80 °C)	n.i.	65[c,g,h]	–
2h	6	H	Me	CH_2	85 ($CDCl_3$, −50 °C)	n.i.	52[a,d,i]	–
2i	6	H	H	$C{=}O$	22[j] (CD_2Cl_2, −80 °C)	n.i.	0	0
2j	6	H	Me	$C{=}O$	65 ($CDCl_3$, −50 °C)	n.i.	0	–

[a] Yield based on ^{1}H NMR standard. [b] n.i. = reaction not investigated, n.d. = compound not detected because of rapid oxidation to **12**, n.m. = yield not measured. [c] Yield based on azide **2**. [d] Yield based on azirine **3**. [e] Mixture of (*Z*)-**2e**/(*E*)-**2e** = 2.5:1. [f] 1:1 mixture of diastereomers. [g] Yield based on isolated products. [h] Mixture of diastereomers (60:40). [i] Mixture of diastereomers (ca. 5:1). [j] 47% **2i** was recovered; prolonged irradiation led to destruction of **3i**.



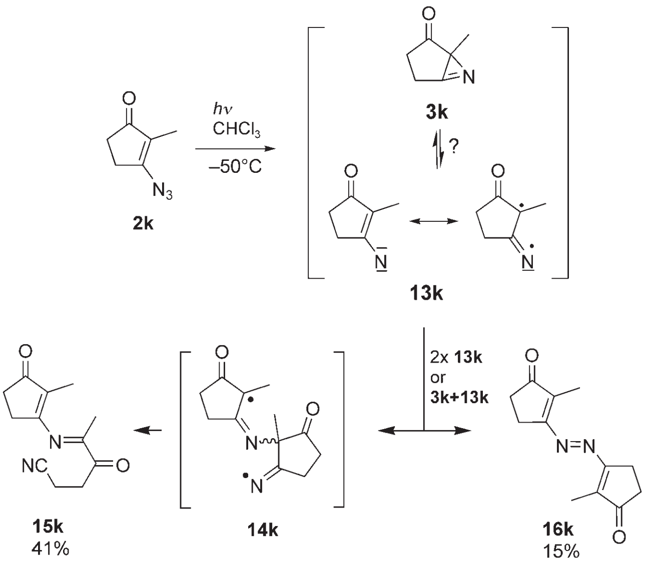
Scheme 3.

20 °C, 54% yield of **12c**). Moreover, we were not able to observe the corresponding reaction of **3e**. The azirines **3i**,**j** generated from azides **2i**,**j**[6f,g] did not form pyrazines analogous to **11** and **12**, but decomposed by unknown subsequent reactions.

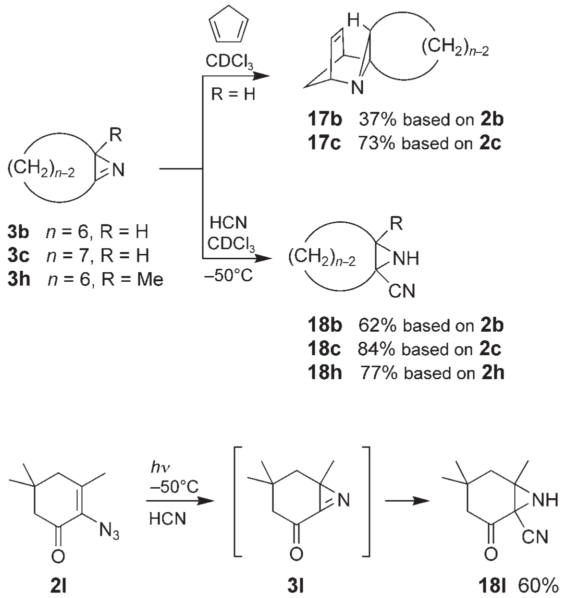
The significantly increased ring strain for **3b** relative to **3c** is demonstrated by the $^1J(^{13}C,^1H)$ NMR coupling constants of the C–H unit at the bridgehead (Scheme 1). Consequently, **3b** is distinctly more reactive than the azirine **3c**, which can also be observed, similarly to **3e**, after thermolysis in solution (Table 2) and which can be isolated after flash vacuum pyrolysis (300 °C, 2×10^{-4} Torr) in 78% yield. In contrast, it was not possible to remove the solvent from a solution of photochemically generated **3b** without complete destruction. Furthermore, no trace of **3b** could be detected by monitoring the thermolysis of a solution of **2b** in chloroform or cyclohexane by NMR spectroscopy,[16] whereas flash vacuum pyrolysis led to low yields of **3b**. Comparison of the properties of **3b** with those of **3h** and of **3i** with those of **3j** shows that an additional methyl group at the bridgehead increases the kinetical stability of the azirines significantly.

Our attempts to detect azirines bridged by a five-membered ring, such as **3a**, **3g**, or **3k**, by spectroscopy directly led at best to strongly broadened NMR signals of the starting materials even after irradiation and measurement at low temperatures (Table 2 and Scheme 4). Nevertheless, the photolyzed solutions yielded definite products after thawing. The azides **2a** and **2g** gave the pyrazine derivatives **12a** and **11g**, respectively (Table 2), and we were able to isolate the nitrile **15k** as well as the azo compound **16k** after photolysis of **2k** and workup by chromatography (Scheme 4). The diradical intermediates shown in Scheme 4 could possibly play a role in the formation of **15k** and **16k**; thus, the difficulties in detecting azirine **3k** by NMR spectroscopy may result not only from its short lifetime.

As a result of their increased ring strain, 2,3-bridged azirines such as **3b**, **3c**, and **3h** can undergo addition and cycloaddition reactions that are not possible for simple 2*H*-azirines. Whereas alkyl- or aryl-substituted azirines do not react with cyclopentadiene,[2b] the corresponding Diels–Alder reactions of **3b** and **3c** were successful under mild conditions (1 h, −50 °C for **17b** and 4 days, 20 °C for **17c**, Scheme 5). Of the four imaginable diastereomeric [4+2] cycloadducts (*exo,exo*; *endo,exo*; *exo,endo*; *endo,endo*), we isolated always the *exo,endo* stereoisomer **17**, which has the cyclopentadiene added to the *exo* side of the bridgehead azirine to form a 5-azanorbornene with an attached three-membered ring in the *endo* position. The addition of hydrogen cyanide to the highly strained azirines takes place already at −50 °C and leads to good yields of the aziridines **18b**,**c**,**h**. The less strained 2,3-bridged heterocycle **3e** does not undergo addition of hydrogen cyanide even after 7 days at 90 °C.[18] However, the photolysis of the azide **2l**[19] in the presence of hydrogen cyanide can be used to gain evidence for the highly strained



Scheme 4.

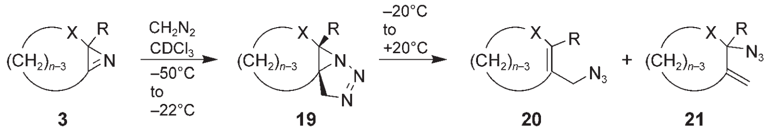


Scheme 5.

bridgehead azirine **3l**, which is not detectable by NMR spectroscopy. The trapping product **18l** proves the particularly short-lived intermediate **3l**, in which the azirine unit is further destabilized by the electron-withdrawing carbonyl group.

The reaction of simple 2*H*-azirines with diazo compounds to give allyl azides via 1,2,3-triazabicyclo[3.1.0]hex-2-enes (compared with **19** in Table 3) has been known for more than forty years.[20] The 1,3-dipolar cycloaddition of the starting materials proceeds relatively slowly at room temperature relative to the fragmentation of the postulated intermediate to yield the final products. Hence, short-lived 1,2,3-triazabicyclo[3.1.0]hex-2-enes, which were also discussed as intermediates of the rearrangement of allyl azides,[21] could not be proved spectroscopically until now.

Table 3: Treatment of 2,3-bridged 2*H*-azirines with diazomethane.



Substrate 3				Max. yield[a] of **19** [%]	Yield[a,b] of **20**+**21** [%]	Initial ratio **20**/**21**[c]	**20**/**21** after equilibration
	n	R	X				
3b	6	H	CH_2	89	89	4:1 (−20°C)	4:1
3c	7	H	CH_2	97	84 (62)[d]	1:1 (−20°C)	2:1
3d	8	H	CH_2	<8	96 (78)[d]	2:1 (0°C)	5:1
3j	6	Me	C=O	86	85 (37)[d]	1:0 (−20°C)	1:0

[a] Yield based on ^{1}H NMR standard. [b] Yield based on **3**. [c] At low temperature. [d] Values in brackets correspond to the yields of isolated products **20**+**21** based on the precursor **2**.

At −50 °C, the highly strained bridgehead azirines **3b** and **3j** react instantaneously with diazomethane by *exo* addition to give the tricyclic compounds **19b** and **19j**, respectively (Table 3). These tricyclic compounds, as well as **19c**, could be characterized by their ^{1}H and ^{13}C NMR data. The analogous transformations of **3c** or the less reactive azirine **3d** required 1 h at −40 °C and 4 days at −22 °C, respectively. The intermediates **19** decomposed already at −20 °C to yield the allyl azides[22] **20** and **21**, hence **19d** especially was always present only in small proportions. We observed that at low temperatures, at which the rearrangement of allyl azides (equilibration of **20** and **21**) had not yet begun, **20b–d** as well as **21b–d** formed from **19b–d**. Consequently, **19** reacts not only by cleavage of the two C−N bonds of the three-membered ring, but also by cycloreversion of the five-membered ring.

Highly strained 2,3-bridged 2*H*-azirines can also be converted in the presence of ketenes, acyl isocyanates, or nitrile oxides. We will report on these remarkable reactions elsewhere.

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