COMMUNICATION

Synthesis and characterization of 2-methoxy-2*H*-azepines: the first isolation of 2-azanorcaradiene, the valence isomer of 3*H*-azepine

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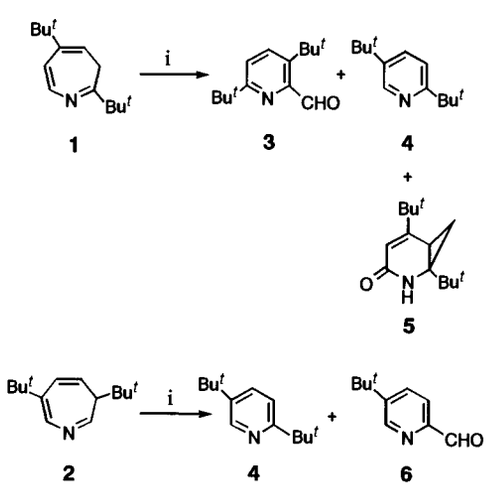
The selective formation of 2-methoxy-2*H*-azepine from 3*H*-azepines, *via* a likely azatropylium cation, is reported; the first isolation of 2-azanorcaradiene, which is considered to be the valence isomer of 3*H*-azepine, is also described.

Although the 2*H*-azepine system has been less explored compared to the more thermodynamically stable 3*H*-azepine system, naturally occurring 2*H*-azepine[1] and some synthesized substituted 2*H*-azepines are known.[2–4] We have reported the isolation of 3,6-di-*tert*-butyl-2*H*-azepine from a mixture obtained from the thermal distribution equilibrium of 3,6-di-*tert*-butyl-3*H*-azepine **2** at 140 °C due to a thermally allowed 1,5-hydrogen shift.[5] Steglich *et al.* have reported a noteworthy synthesis of a labile unsubstituted 2*H*-azepine.[6] We report here the formation of 2-methoxy-2*H*-azepine derivatives from 3*H*-azepines by regiospecific incorporation of a methoxy group in the seven-membered ring, by reaction of 3*H*-azepine and bromine and quenching with an excess of absolute methyl alcohol.

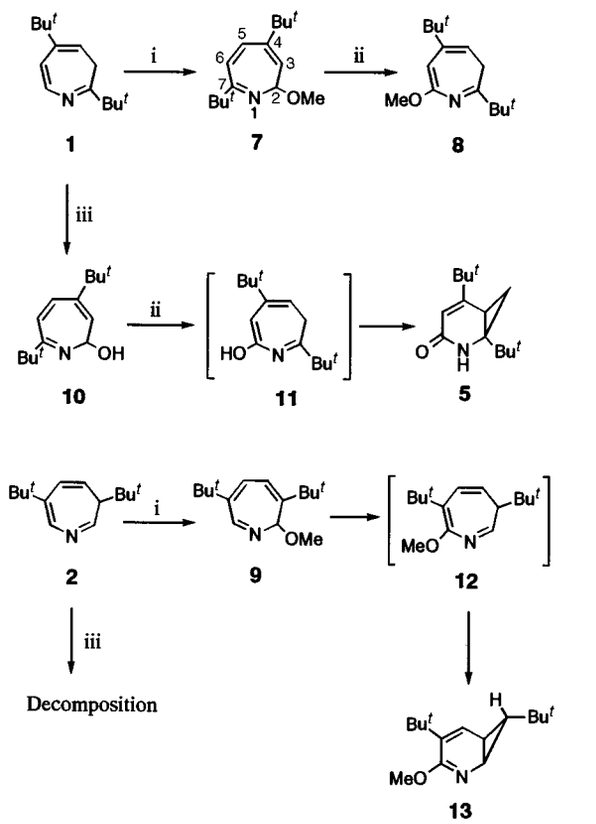
Recently, we have reported a new ring contraction reaction of 3*H*-azepines to pyridine derivatives under bromination conditions.[7] When a reaction mixture of 2,5- and 3,6-di-*tert*-butyl-3*H*-azepine (**1** and **2**) and bromine was treated with aqueous K_2CO_3, pyridines **3**–**5** and **4**, **6** were obtained, respectively (Scheme 1). The structure of the pyridines obtained led us to



Scheme 1 *Reagents and conditions:* i, (a) Br_2 (1 equiv.) in CCl_4, (b) aqueous K_2CO_3

speculate whether 2-hydroxy-2*H*-azepine was formed as an intermediate during the reaction. In order to confirm the identity of the intermediate, we quenched the reaction mixture with absolute methyl alcohol prior to treatment with alkaline solution.

To a dry CH_2Cl_2 solution of 3*H*-azepine **1** (50 mg, 0.21 mmol), was added one equivalent of bromine solution in CH_2Cl_2 and the mixture was stirred for 3 h at 23 °C. After adding an excess of absolute methyl alcohol to the reaction mixture, volatile solvents were removed under reduced pressure. The tarry brownish residue obtained was treated with saturated aqueous $NaHCO_3$ and extracted with diethyl ether. Chromatographic treatment of the extract on silica gel (hexane–ethyl acetate, 8:2 v/v) gave 4,7-di-*tert*-butyl-2-methoxy-2*H*-azepine **7** in 52% yield as a pale yellow oil (Scheme 2). 3*H*-Azepine **2** (50 mg,



Scheme 2 *Reagents and conditions:* i, (a) Br_2 (1 equiv.) in CH_2Cl_2, (b) absolute MeOH; ii, $CHCl_3$, 25 °C; iii, (a) NBS (1 equiv.) in CH_2Cl_2, (b) aqueous $NaHCO_3$

0.21 mmol) gave 3,6-di-*tert*-butyl-2-methoxy-2*H*-azepine **9** as a pale yellow oil in 43% yield under similar conditions. ^{1}H NMR (200 MHz, $CDCl_3$) data of the ring protons and the substituents for **7** and **9** are listed and assigned in Table 1, along with the reported data for unsubstituted 2*H*-azepine[6] for comparison. A coincidental chemical shift meant that the coupling constant between 5-H and 6-H could not be observed even when using a higher magnetic field (500 MHz) apparatus. The 2*H*-azepine structure of **7** and **9** was further confirmed from the similarities of their electronic spectra with that of the reported 3,6-di-*tert*-butyl-2*H*-azepine[5] (Fig. 1).

Further effort into obtaining the speculative 2-hydroxy-2*H*-azepine intermediate was carried out by changing the conditions of bromination. When a mixture of one equivalent of *N*-

Table 1 ^{1}H NMR data (200 MHz, $CDCl_3$) for 2*H*-azepine and substituted 2*H*-azepines (**7**, **9** and **10**)

	δ_H							
2*H*-Azepine	2-H	3-H	4-H	5-H	6-H	7-H	*J*/Hz	δ_H of substituents
2*H*-Azepine	3.61	5.69	6.35	6.74	6.60	7.84		
7	3.79	5.70	—	7.00	7.00	—	$J_{2,3}$ 4.2	Bu^t: 1.08, 1.14; Me: 3.47
9	3.90	—	6.05	6.66	—	7.87	$J_{4,5}$ 6.4, $J_{5,7}$ 1.8	Bu^t: 1.24, 1.26; Me: 3.35
10	4.51	5.94	—	6.98	6.94	—	$J_{2,3}$ 4.2, $J_{5,6}$ 12.6, $J_{3,5}$ *ca.* 1	Bu^t: 1.07, 1.09

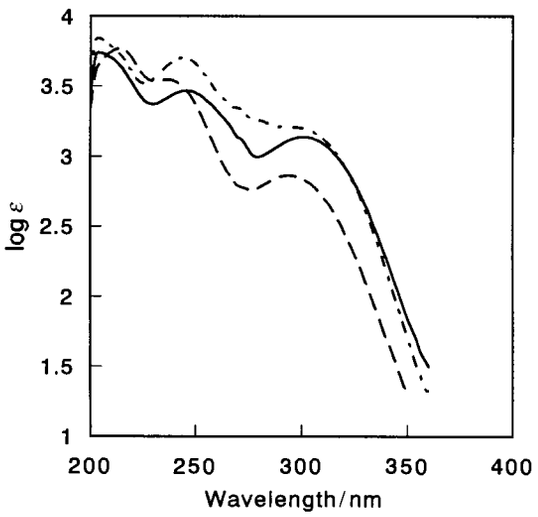


Fig. 1 Electronic spectra of **7** (– – –), **9** (– · –) and 3,6-di-*tert*-butyl-2*H*-azepine (——) in EtOH

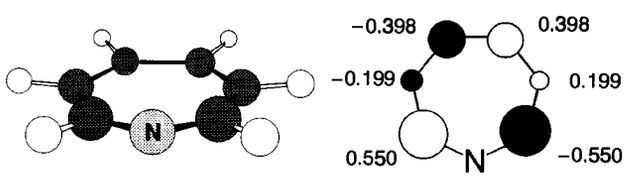
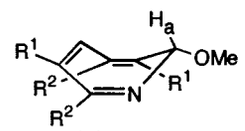


Fig. 2 AM1[10] calculated structure (left) and an orbital profile of π_{LUMO} (right) for an azatropylium cation

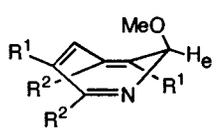
bromosuccinimide (NBS) and **1** in CH_2Cl_2 was stirred at 20 °C for 1 h and then treated with aqueous $NaHCO_3$, 4,7-di-*tert*-butyl-2-hydroxy-2*H*-azepine **10** was obtained as colourless prisms (mp 177–178 °C) in 15% yield together with ring contracted 3,6-di-*tert*-butylpyridine-2-carbaldehyde **3**, whereas **2** did not give identifiable products under similar conditions. While **10** isomerized to 4,5a-di-*tert*-butyl-2,4a,5,5a-tetrahydro-1*H*-cyclopropa[*b*]pyridin-2-one **5** in $CDCl_3$ solution completely at room temperature, presumably *via* intermediate 7-hydroxy-3*H*-azepine **11**, a rapid ^{1}H NMR measurement revealed the presence of 2-hydroxy-2*H*-azepine. In this case, an AB pattern (*J* 12.6 Hz) was observed for 5-H and 6-H, and a small W coupling (≈1 Hz) between 3-H and 5-H could be estimated from the broadening and decreased intensity of the lower field part of the AB pattern signal. The assigned spectral data for **10** are listed in Table 1 although the 2-hydroxy proton could not be detected under the measurement conditions.

Bátori *et al.* reported that the salts of the aromatic azatropylium cation are expected to be fairly stable, although a nitrogen atom in this cation destabilizes the π-electron system compared to that of the tropylium cation on the basis of HMO charge density analysis.[8] The azatropylium cation was suggested as an intermediate in the reaction of 1,3-dimethoxybenzene with phthalimidonitrene, because the reaction did not give *N*-phtalimido-1*H*-azepine but 2-phthalimido-2*H*-azepine.[3] The intermediate of the present reaction also seems to be the azatropylium cation by reference to Doering's results on the formation of tropylium cations from the reaction of

Table 2 Calculated ΔH_f values for conformational isomers of 2-methoxy-2*H*-azepines (**7a**, **7e**, **9a** and **9e**) by the PM3[11] method



axial-type



equatorial-type

	Substituents		
Conformers	R^1	R^2	ΔH_f/kcal mol^{-1}
7a	Bu^t	H	−32.43
7e	Bu^t	H	−29.78
9a	H	Bu^t	−25.90
9e	H	Bu^t	−31.28

cycloheptatriene with bromine.[9] Regiospecific attack by the methoxy group at the C-2 position of an azepine ring could be well explained by a frontier molecular orbital (FMO) consideration of the mutual interaction between a nucleophile and the delocalized azatropylium cation whose AM1[10] optimized structure is a charge distributed planar molecule (Fig. 2). The most important orbital for the reaction is considered to be the π_{LUMO} of the cation, the orbital profile of which is illustrated in Fig. 2. Thus the selective formation of 2-methoxy-2*H*-azepine can be interpreted by nucleophilic attack occurring on C-2 or C-7 which have the largest orbital coefficients in the π_{LUMO} orbital.

The likely tendency for the rearrangement from 2*H*-azepine **7** to 2,5-di-*tert*-butyl-7-methoxy-3*H*-azepine **8** is recognized as being time-dependent by observation of the change in the 200 MHz ^{1}H NMR spectrum in $CDCl_3$ solution at room temperature. The 3*H*-azepine **8** was isolated as a pale yellow oil by chromatographic treatment. The methylene protons at C-3 for the structure **8** were observed at δ 1.1 and 3.6 as broad signals. The half life for isomerization from **7** to **8** was determined as 78 min at 55 °C in $CDCl_3$ by measuring the reduction in the peak area for the methoxy group of **7**. In contrast, the 1,5-hydrogen shift could not be observed for the 2*H*-azepine **9** because the process occurred so rapidly. The difference in the tendency of **7** and **9** to undergo a 1,5-hydrogen shift can be explained by an analysis of the heat of formations (ΔH_f) obtained using the PM3[11] molecular orbital method (Table 2). Calculated results suggested that the axial (**7**) and equatorial (**9**) conformations (**7a** and **9e**) were the most stable for **7** and **9**, respectively. Thus the predicted axial conformation for **7** is more amenable to a thermally allowed concerted 1,5-hydrogen shift from 2-H to 5-H. Kinetic parameters obtained from an Arrhenius plot from 200 MHz ^{1}H NMR measurements at different temperatures (E_a 23.3 kcal mol^{-1}, ln A = 27, $\Delta H^{\ddagger}$ = 22.9 kcal mol^{-1}, $\Delta S^{\ddagger}$ = −7.0 cal K^{-1} mol^{-1}) correlate well with those reported for the concerted hydrogen shift in cycloheptatriene[12] and the 2*H*-azepine derivative.[4] Isomerization of **9**, whose preferable conformer is predicted as **9e**, was found to be slower than for **7**. After four days at room temperature a $CDCl_3$ solution of **9** had been changed into a 1:1 mixture of **9** and an isomerized compound. Chromatographic treatment of the mixture gave the purified isomer as a pale yellow oil. Characteristic signals assigned for the three protons on the condensed cyclopropane ring (5-H, 4a-H, 5a-H) and the olefinic proton 4-H were observed at

δ 0.20 (dd, 1 H, *J* 4.4 and 3.5 Hz), 1.83 (ddd, 1 H, *J* 6.2, 5.4 and 4.4 Hz), 3.47 (dd, 1 H, *J* 5.4 and 3.5 Hz) and 6.58 (d, 1 H, *J* 6.2 Hz), respectively. Thus the structure of the isomer was not the expected 3*H*-azepine **12** but 2-azanorcaradiene, 5,5a-dihydro-3,5-di-*tert*-butyl-2-methoxy-4a*H*-cyclopropa[*b*]pyridine **13**. This is the first example of the valence isomerization between 2-azanorcaradiene and 3*H*-azepine, though the latter could not be detected.[13] The isolated compound **13** did not revert into valence isomer **12** or 2*H*-azepine **9** at room temperature.

Acknowledgements

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