A New Ring Contraction Rearrangement of 2,5- and 3,6-Di-*tert*-butyl-3*H*-azepines to Pyridine Derivatives

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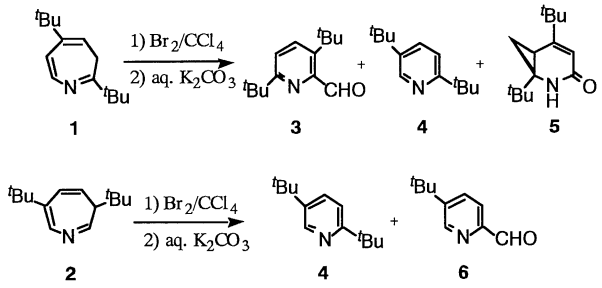
A new ring contraction reaction giving pyridine derivatives from 3,6- and 2,5-di-*tert*-butyl-3*H*-azepines was observed by a successive treatment with bromine and aqueous K_2CO_3. A plausible mechanism *via* azatropilium cation for the rearrangement was discussed based on the product's distribution from respective 3*H*-azepines.

Although, synthesis and reaction of 3*H*-azepines having a strongly electron donating substituent (*e.g.* dialkylamino[1-3] or alkoxy[4] group) at 2-position of the ring have been investigated extensively, seven-membered azatriene system without having any electron donating group on the ring were rarely explored. Syntheses of alkyl and/or aryl substituted 3*H*-azepines were developed by Hassner *et al.*[5] and Gökel *et al.*[6] by hetero-Diels-Alder reaction between highly reactive small-ring olefins and appropriate dienes. Nitta *et al.* have also reported the synthesis of 3-cyclohepta-2,4,6-trienyl-3*H*-azepine from the iron carbonyl complex of ethyl 1*H*-azepine-1-carboxylate.[7] Recently, we have developed a convenient procedure for the preparation of dialkyl 3*H*-azepines by a direct demethoxycarbonylation reaction of dialkyl 1*H*-azepine-1-carboxylate using 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU),[8] which has enabled the investigation of seven-membered azatriene system. We report here a new ring contraction reaction of 2,5- and 3,6-di-*tert*-butyl-3*H*-azepines giving pyridine derivatives under the bromination conditions.

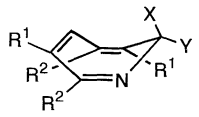
The reaction of 2,5-di-*tert*-butyl-3*H*-azepine **1** with an equimolar bromine in carbon tetrachloride at 0 °C gave an insoluble tarry brownish precipitates. The solvent was removed by decantation and the residual precipitate was dissolved into aqueous K_2CO_3 and extracted with ether. Chromatographic purification using silica-gel of the extract gave pyridines 3,6-di-*tert*-butyl-2-pyridinecarboxaldehyde **3**, 2,5-di-*tert*-butylpyridine **4**, and 1,2,4a,5a-tetrahydro-4,5a-di-*tert*-butylcyclopropa[*b*]pyrid-2-one **5** in 35, 16 and 6% yields, respectively. The presence of pyridine ring in **3** and **4** was indicated by the low field signals at δ7.38 (d, J = 8.0 Hz, 1H) and 7.76 (d, J = 8.0 Hz, 1H), and at δ7.23 (d, J = 8.5 Hz, 1H), 7.57 (dd, J = 8.5 and 2.5 Hz, 1H), and 8.59 (d, J = 2.5 Hz, 1H), respectively. In addition, compound **3** showed a signal for aldehyde proton at δ10.24 (s, 1H). The structure of cyclopropa[*b*]pyridine **5** was ascertained also by ^{1}H NMR spectrum. Condensed cyclopropane-ring protons were observed at δ0.17 (*pseudo* t, $^2J_{gem}$ and $^3J_{trans}$ = 5.0 Hz, 1H), δ1.46 (dd, $^3J_{cis}$ = 10.5 and $^2J_{gem}$ = 5.0 Hz, 1H) and δ1.69 (dd, $^3J_{cis}$ = 10.5 and $^3J_{trans}$ = 5.0 Hz, 1H). The signals at δ5.56 (s, 1H) and 5.79 (br s, 1H, a D_2O exchangeable) could be assigned to the olefinic and N-H protons, respectively. When the reaction was applied to 3,6-di-*tert*-butyl-3*H*-azepine **2** under similar conditions, 2,5-di-*tert*-butylpyridine **4** and 5-*tert*-butyl-2-pyridinecarboxaldehyde **6** were obtained by above described work up sequences in 50 and 8% yields, respectively. ^{1}H NMR spectrum of the compound **6** showed a *tert*-butyl group at δ1.38 (s, 9H), aromatic protons at δ7.84 (dd, J = 8.3 and 2.0 Hz, 1H), 7.89 (d, J = 8.3 Hz, 1H), and 8.81 (d, J = 2.0 Hz, 1H), and aldehyde proton at δ10.06 (s, 1H). All of the spectral and analytical data were consistent with the proposed structures of pyridines **3**, **4**, **5** and **6**.



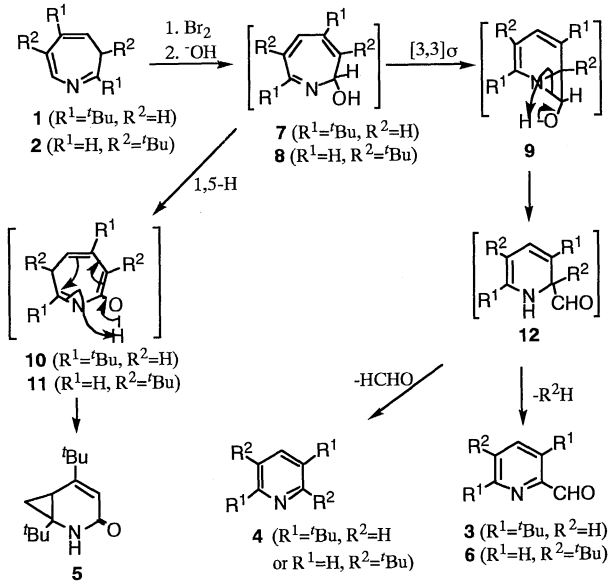
It has been known that the 1*H*-azepine derivatives easily isomerize to aniline derivative in the presence of catalytic amount of acid.[9] Also in the case of 3*H*-azepines, ring contraction occurred to give aniline derivatives both under the acidic[10] or electrophilic[1,2] conditions. We have also confirmed the isomerization reaction of 3*H*-azepines giving aniline derivatives when they were heated up to 300 °C using an apparatus for differential scanning calorimetry (DSC).[11] Previously reported ring contraction reaction from 3*H*-azepines to pyridines is only in the case of the system containing at C-3 the C(=O)-R (R = OMe, C_6H_5) group.[12] The reaction presented here is an alternative example for the 3*H*-azepine ring contraction reaction without extruding the nitrogen atom from the seven-membered ring.

The key intermediate of here present reactions would be a 2-hydroxy-2*H*-azepine (**7** or **8**) on the basis of giving analogous pyridines in both cases. The intermediate **7** is converted to final products *via* competitive two paths; that is, the major one is a [3,3] sigmatropic path leading to hydroxyazanorcaradiene intermediate **9** and the other is a path of 1,5-hydrogen shift which leads to 7-hydroxy-2,5-di-*tert*-butyl-3*H*-azepine intermediate **10**. A C-N bond cleavage of the three-membered ring of **9** occurred to form dihydropyridine intermediate **12** which aromatizes competitively to 3,6-di-*tert*-butylpyridine-2-carboxaldehyde **3** by dehydrogenation and to 2,5-di-*tert*-butylpyridine **4** by an elimination of formaldehyde. The formation of cyclopropa[*b*]pyridine **5** would be explained by the valence isomerization of the intermediate **10**. On the other hand, in the case of the intermediate **8**, it is considered that only a [3,3] sigmatropic path occurs to form the dihydropyridine **12**. It also aromatizes competitively to **4** by the elimination of formaldehyde and to 5-*tert*-butylpyridine-2-carbaldehyde **6** by the elimination of 2-methylpropane. Owing to clarify the defference of the reactivity for 1,5-hydrogen shift between intermediate **7** and **8**, a conformational analysis for the conformers **7a**, **7e**, **8a** and **8e** was performed by optimization calculation using PM3[13] method (Table 1). The result shows that a predominant conformer for **7** is **7e** whose 2-hydroxy group located in equatorial position and that of **8** is axial one **8a**. Thus, in the case of intermediate **8**, thermally allowed *supra-supra* 1,5-hydrogen shift leading to **11** would be depressed compared with in the case of intermediate **7**.

Table 1. Calculated ΔH_f values for conformational isomers of 2-hydroxy-2*H*-azepines (**7a**, **7e**, **8a** and **8e**) by PM3[13] method



Confomers	Substituents				ΔH_f
	R^1	R^2	X	Y	(kJ/mol)
7a	^{t}Bu	H	OH	H	-151.38
7e	^{t}Bu	H	H	OH	-162.91
8a	H	^{t}Bu	OH	H	-161.96
8e	H	^{t}Bu	H	OH	-152.28



A selective formation of the key intermediate (**7** or **8**) from a corresponding 3*H*-azepine (**1** or **2**) can be explained by referring to Doering's proposal for the bromination of cycloheptatriene leading to an aromatic tropylium cation.[14] When the cyclic azatriene reported here is converted to azatropylium cation [A] (see Figure 1) by the action of bromine, a selective nucleophilic hydroxylation would be promised by the frontier molecular orbital theory (Figure 2). Recently, Gomper *et al.* reported that the salts of the aromatic azaztropylium cation are expected to be fairly stable, although a nitrogen atom in this cation destabilizes the π-electron system compared to that of tropylium cation on the basis of HMO charge

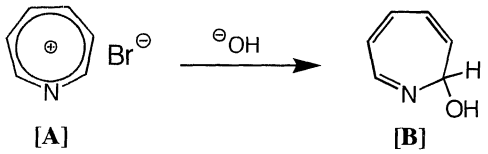


Figure 1. Elucidative route to a 2-hydroxy-2*H*-azepine [**B**] *via* an azatropylium cation [**A**].

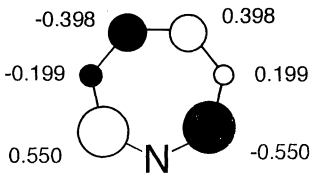


Figure 2. AM1[15] calculated π_{LUMO} of an azatropylium cation.

density analysis.[16] We are still under investigation for a direct observation or trapping of the azatropylium cation.

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