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PLAUSIBLE MECHANISM FOR THE FORMATION OF 2-METHOXY-2*H*-AZEPINE DERIVATIVES FROM 3*H*-AZEPINES USING BROMINE AND NBS

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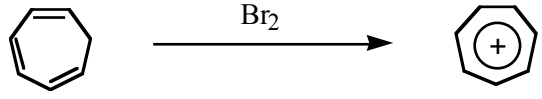
Abstract – Formation of 2-bromo-4-*t*-butyl-7-methoxy-2*H*-azepine and 4-*t*-butyl-7-methoxy-2-succinimidyl-2*H*-azepine by the respective reactions of 5-*t*-butyl-2-methoxy-3*H*-azepine with bromine and NBS suggests a plausible mechanism for the conversion of 3*H*-azepine to 2*H*-azepine as 1,4-addition of an electrophile and a consequent 1,2-dehydrobromination. Different from the case of cycloheptatriene, reaction of 3*H*-azepine with bromine did not give any delocalized ionic species.

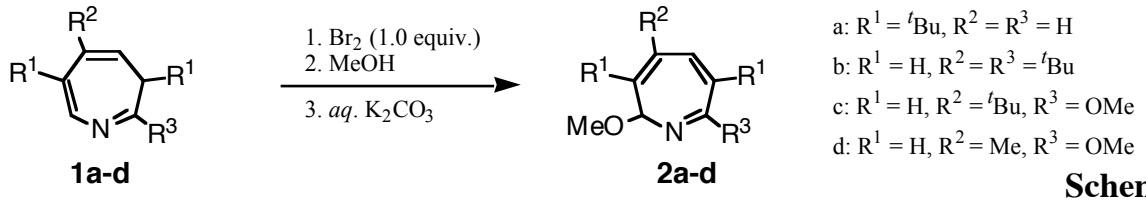
In the 1950's, 1,3,5-cycloheptatriene (CHT) was observed to react with an equivalent of bromine to give a stable delocalized aromatic tropylium bromide (*eq*. 1).[1] Tropylium bromide has been found to react with



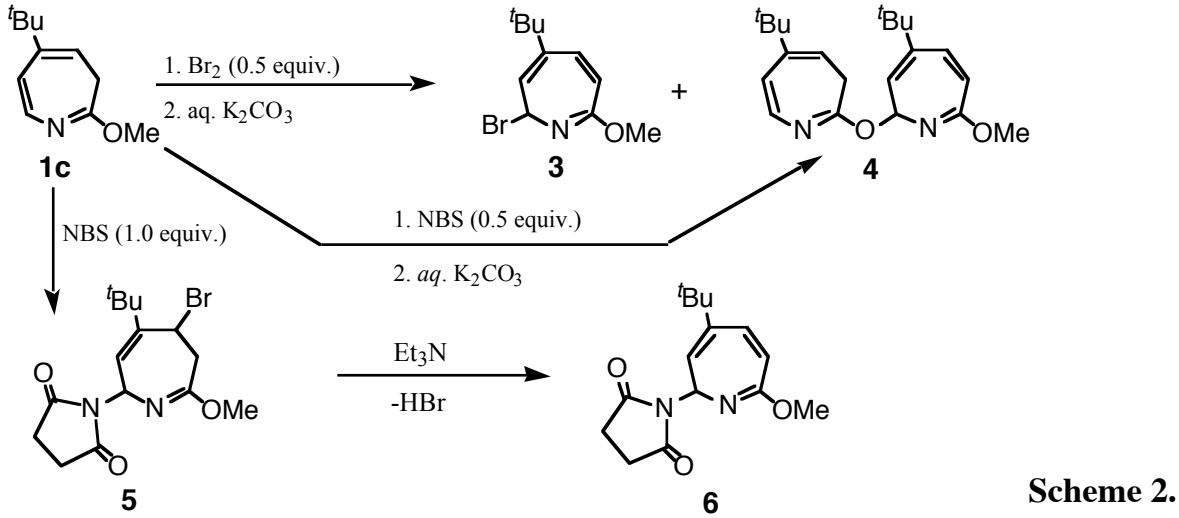
(*eq*. 1)

various nucleophiles to form the corresponding substituted CHT derivatives.[2] Recently, we reported the specific formation of 3,6- and 4,7-di-*t*-butyl-2-methoxy-2*H*-azepines (**2a** and **2b**) by adding excess methanol to the reaction mixture of 3,6- and 2,5-di-*t*-butyl-3*H*-azepines (**1a** and **1b**)[3,4] and bromine followed by work up with aqueous alkaline.[5] As the initial conditions of the reactions are similar to those of CHT and bromine, the formation of 2-methoxy-2*H*-azepine has been presumed to be a nucleophilic

addition of methanol to an azatropylium ion. In order to confirm the reaction mechanism, attempts were made to determine the structure of any reaction products without adding methanol to the reaction mixture. An analogous reaction sequence was applied to 5-*t*-butyl- and 5-methyl-2-methoxy-3*H*-azepine (**1c** and **1d**),[6] from which formation of 4-*t*-butyl- and 4-methyl-2,7-dimethoxy-2*H*-azepines (**2c** and **2d**) was observed in 52 and 30% yields, respectively (Scheme 1). The structure of **2c** and **2d** was confirmed by a similar coupling pattern to that of previously obtained **2b** in the ^{1}H-NMR spectrum.[7,8] At this point our interest was focused on the reaction mechanism for the formation of 2*H*-azepine from 3*H*-azepine. The intermediate formation of delocalized azepinium ion, as in the case of CHT, is a reasonable consideration to explain the specific formation of the products but no attributable peaks to an azepinium ion were detected by careful ^{1}H-NMR spectral observation of a mixture of 3*H*-azepine and bromine. We next investigated the reaction of **1c** with bromine under similar conditions except no methanol was introduced before treatment with aqueous alkaline. A half equivalent of bromine was used for the reaction because only decomposition products were obtained when a full equivalent of bromine reacted. The compounds formed were separated by chromatography (hexane : ethyl acetate = 3 : 2 *v*/*v*) on silica gel at 0°C and structures assigned to labile 2-bromo-4-*t*-butyl-7-methoxy-*2H*-azepine (**3**) in 12% yield and 5-*t*-butyl-*3H*-azepin-2-yl 4-*t*-butyl-7-methoxy-*2H*-azepin-2-yl ether (**4**) in 82% yield. The structure of **3** has proven not to be an azatropylium bromide but 2-bromo-2*H*-azepine (**3**) based on the NMR spectral observation of



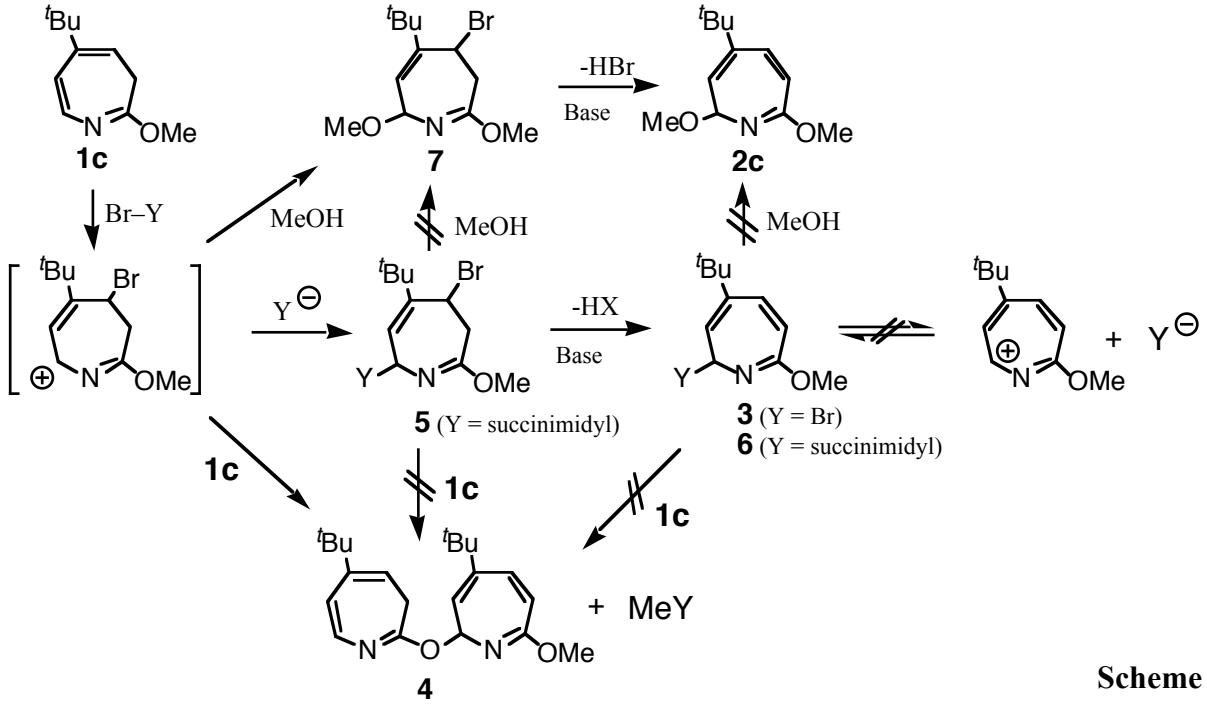
Scheme 1.



Scheme 2.

C2-H at δ_H 4.96 (d, J = 4.0 Hz, 1H) and C2 at δ_C 82.2 (d).[9] The covalent structure of **3** shows an essential difference between the azatropylium and tropylium ions. Additionally, methanol solution of **3** was found to give no methanolysis product such as **2c** even at elevated temperature. Unexpected formation of bisazepinyl ether (**4**) was substantiated by MS (FAB) spectrum m/z 343 $(M+H)^+$. The structures of each ring linked by an oxygen atom were determined to be a 5-*t*-butyl-3*H*-azepin-2-yl and a 4-*t*-butyl-7-methoxy-2*H*- group based on the ^{1}H-NMR spectrum, which showed nearly superimposable signals to those of **1c** and **2c** in the region of olefinic ring protons.[10]

Similar to the case of CHT,[11] an alternative attempt to investigate the behavior of **1c** using NBS was performed. Bisazepinyl ether (**4**) was obtained in 86% yield by the reaction of **1c** with 0.5 molar equivalents of NBS in dichloromethane at 25°C. When an equivalent of NBS was added into the dichloromethane solution of **1c** at -98 °C, 1,4-addition at the 4- and 7-positions of the ring occurred to give 5-bromo-4-*t*-butyl-5,6-dihydro-7-methoxy-2-succinimidyl-2*H*-azepine (**5**)[12] in quantitative yield. Compound **5** is the first isolated 1,4-addition product of NBS to a conjugated system. Succinimidyl group and its position of **5** were confirmed by $\delta_{C=O}$ band at 1692 and 1711 cm^{-1} and the anisotropic deshielding effect by the imido carbonyl group on the C2-H which observed at δ 6.97, respectively. A quantitative conversion of **5** into 4-*t*-butyl-7-methoxy-2-succinimidyl-2*H*-azepine (**6**)[13] was accomplished by treatment with triethylamine. Unfortunately, a 1,4-adduct of **1c** with bromine could not be isolated although the results reported here suggest a plausible mechanism for the formation of 2,7-dimethoxy-2*H*-



Scheme 3

azepine by the action of Br_2 and a subsequent treatment of methanol as illustrated in Scheme 3. Analogous to the reported reaction of NBS on a diene in the presence of methanol,[14] the reaction of **1c** gave 5-bromo-4-*t*-butyl-5,6-dihydro-2,7-dimethoxy-2*H*-azepine (**7**) which was found to be the precursor of **2c**, formed quantitatively. Structure of **7** was estimated by ^{1}H- and ^{13}C-NMR spectra without isolation because of its instability.[15]

The ionic form of tropylium bromide is a reflection of the high degree of resonance stabilization in the cyclic aromatic cation.[1] In contrast, **3** is a covalent isomer of azatropylium bromide, and this covalent nature may illustrate the degree of conjugation in the electronegative sp^2 nitrogen atom in the ring, howener, the aromatic conjugation was expected by a theoretical consideration of the azepinium ion.[16]

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7. Selected data for **2c**; colorless prisms mp 37–37.5°C; ^{1}H-NMR (200 MHz, $CDCl_3$) □ 1.10 (s, 9H), 3.48 (s, 3H), 3.71 (s, 3H), 4.23 (d, *J* = 3.8 Hz, 1H), 5.77 (dd, *J* = 3.8, 1.2 Hz, 1H), 6.46 (d, *J* = 12.4 Hz, 1H), 6.94 (dd, *J* = 12.4, 1.2 Hz, 1H); IR (KBr) $\square_{max}$ 2962, 1640, 1448, 1261, 1199, 1112 cm^{-1}.
8. Selected data for **2d**; colorless prisms mp 31-34°C; ^{1}H-NMR (300 MHz, $CDCl_3$) □ 1.86 (s, 3H), 3.45 (s, 3H), 3.71 (s, 3H), 4.28 (br d, *J* = 4.8 Hz), 5.71 (br d, *J* = 4.8 Hz, 1H), 6.40 (d, *J* = 11.7 Hz), 6.63 (d, *J* = 11.7 Hz); IR (KBr) $\square_{max}$ 2948, 1638, 1444, 1249, 1133, 1094 cm^{-1}; MS (FAB) m/z 168

$(M+H)^+$.

9. Selected data for **3**; colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.10 (s, 9H), 3.63 (s, 3H), 4.96 (d, *J* = 4.0 Hz, 1H), 5.95 (dd, *J* = 4.0, 1.0 Hz, 1H), 6.43 (d, *J* = 12.0 Hz, 1H), 6.94 (dd, *J* = 1.0, 12.0 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 29.5 (q), 34.5 (s), 53.6 (q), 82.2 (d), 124.3 (d), 128.9 (d), 139.4 (d), 144.6 (s), 158.6 (s); IR (neat) ν_{max} 1634, 1444, 1255, 1207, 1112 cm^{-1}.
10. Selected data for **4**; colorless plates mp 115-116°C; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 1.04 (s, 9H), 1.13 (s, 9H), 2.62 (dd, *J* = 12.2, 6.1 Hz, 1H), 3.16 (dd, *J* = 12.2, 7.9 Hz, 1H), 3.67 (s, 3H), 5.29 (d, *J* = 4.9 Hz, 1H), 5.53 (dd, *J* = 7.9, 6.1 Hz, 1H), 5.72 (d, *J* = 4.9 Hz, 1H), 6.23 (d, *J* = 9.3 Hz, 1H), 6.47 (d, *J* = 12.0 Hz, 1H), 6.93 (d, *J* = 12.0 Hz, 1H), 7.03 (d, *J* = 9.3 Hz, 1H); IR (KBr) ν_{max} 1678, 1630 cm^{-1}; MS (m/z, FAB) 343 $(M+1)^+$.
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12. Selected data for **5**; colorless solid mp 140–141°C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.09 (s, 9H), 2.76 (s, 4H), 3.04 (ddd, *J* = 18.6, 3.7, 2.8 Hz, 1H), 3.14 (ddd, *J* = 18.6, 4.0, 2.8 Hz, 1H), 3.50 (s, 3H), 4.84 (ddd, *J* = 4.0, 3.7, 2.1 Hz, 1H), 5.83 (dd, *J* = 3.4, 2.1 Hz, 1H), 6.97 (dt, *J* = 3.4, 2.8 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 28.0 (q), 28.3 (t), 37.1 (s), 39.7 (t), 41.9 (d), 52.7 (q), 60.5 (d), 129.2 (d), 149.1 (s), 158.4 (s), 176.2 (s); IR (KBr) ν_{max} 1711, 1692, 1400, 1373. 1187 cm^{-1}; MS (m/z, FAB) 357 $(M+1)^+$.
13. Selected data for **6**; colorless solid mp 121–122°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.06 (s, 9H), 2.75 (s, 4H), 3.58 (s, 3H), 5.21 (d, *J* = 5.2 Hz, 1H), 5.95 (d, *J* = 5.2 Hz, 1H), 6.47 (d, *J* = 11.8 Hz, 1H), 6.93 (d, *J* = 11.8 Hz, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 27.4 (t), 28.6 (q), 33.9 (s), 52.9 (q), 62.3 (d), 122.9 (d), 124.3 (d), 138.1 (d), 146.5 (s), 160.4 (s), 176.1 (s); IR (KBr) ν_{max} 1705, 1644, 1404, 1251, 1187 cm^{-1}; MS (m/z, FAB) 277 $(M+1)^+$.
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15. NMR data for **7**; ^{1}H-NMR (500 MHz, CD_2Cl_2) δ 1.09 (s, 9H), 3.03 (ddd, *J* = 18.9, 3.7, 2.7 Hz, 1H), 3.09 (ddd, *J* = 18.9, 4.0, 2.4 Hz, 1H), 3.48 (s, 3H), 3.62 (s, 3H), 4.86 (ddd, *J* = 4.0, 3.7, 2.1 Hz, 1H), 5.75 (ddd, *J* = 3.1, 2.7, 2.4 Hz, 1H), 5.86 (dd, *J* = 3.1, 2.1 Hz, 1H); ^{13}C-NMR (125 MHz, CD_2Cl_2) δ 28.2 (q), 37.0 (s), 40.3 (t), 43.1 (d), 52.5 (q), 54.6 (q), 84.8 (d), 133.4 (d), 147.9 (s), 162.1 (s).
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