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NUCLEOPHILIC SUBSTITUTION REACTION OF 5-*t*-BUTYL-2-METHOXY-3*H*-AZEPINE WITH ALKOXIDES AND ALKYLLITHIUM REAGENTS: A FORMATION OF BIS(5-*t*-BUTYL-3*H*-AZEPIN-2-YL)-METHANE HAVING A VINAMIDINE CONJUGATION

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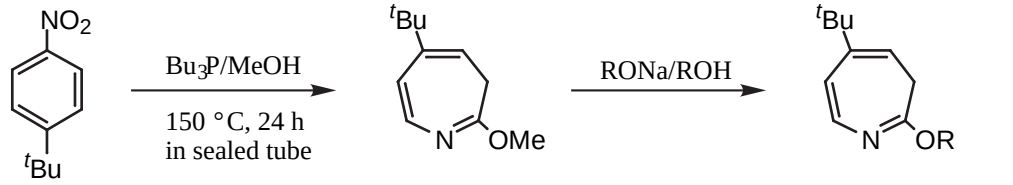
Abstract – Reaction of 5-*t*-butyl-2-methoxy-3*H*-azepine (**2**) with nuclephiles (alkoxides or *t*-butyllithium) gave respective substitution product at 2-position of the ring. Unexpectedly, when methyllithium was used as a nucleophile, bis(5-*t*-butyl-3*H*-azepin-2-yl)methane (**7**), the structure of which found to be tautomeric vinamidine (**7a,b**), was formed. Tautomerization between **7** and **7a,b** was characterized spectroscopically and theoretically based on the levels of B3LYP/6-31G(d).

Among the four possible azepine isomers (1*H*-, 2*H*-, 3*H*-, and 4*H*-azepine), 2-alkoxy- or 2-alkylamino-3*H*-azepines have been studied extensively,[1] because the synthesis of such 3*H*-azepines has been well explored.[2] In addition, these 3*H*-azepines were relatively stable making exploration of their reactivities

possible, although unsubstituted 3*H*-azepine has been reported to be a labile substance.[3] Nucleophilic substitution reactions at the 2-position of the ring with amines or active methylene compounds have been reported.[4] We report here alternative nuclephilic substitution reactions with alkoxide and alkyllithium reagents.

Ring expansion reaction of 4-*t*-butylnitrobenzene (**1**) was carried out by heating a methanol solution of **1** and tributylphosphine in a sealed tube at 150˚C for 24 h. Subsequent distillation under reduced pressure of the reaction mixture gave **2** in 74% yield.[5] In order to examine the nucleophilic substitution reaction by an alkoxide ion, an ethanol solution of **2** and excess of sodium ethoxide was refluxed for 24 h. An effective ether exchange reaction occurred to give 2-ethoxy-5-*t*-butyl-3*H*-azepine (**3a**) in 78% yield. Similar procedures for **2** using propanoxide, isopropanoxide, and triethylene monoglycoxide gave **3b** (74%), **3c** (62%), and **3d** (24%), respectively.[6]

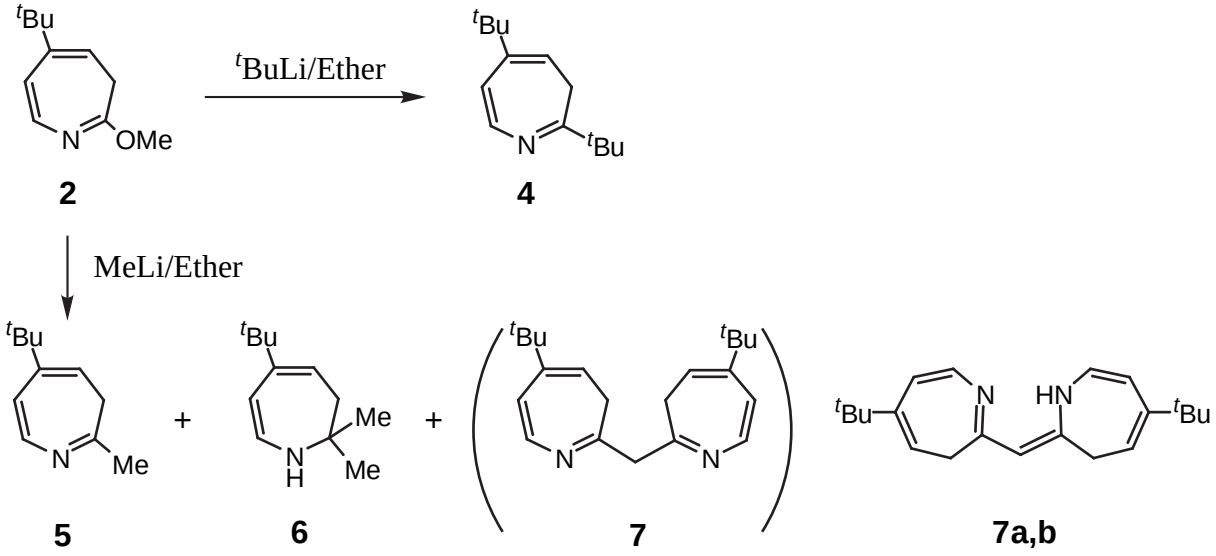


1 **2** **3a-d**

a: R = Et
b: R = Pr
c: R = ^{i}Pr
d: R = $(CH_2CH_2O)_3H$

We next examined the possibility for the synthesis of 2,5-dialkyl-3*H*-azepines by nucleophilic alkyl substitution reaction. Previously, we have reported the synthesis of 2,5-dialkyl-3*H*-azepines by means of a demethoxycarbonylation reaction of methyl 2,5-dialkyl 1*H*-azepine-1-carboxylate.[7] To inspect an alternative and effective synthetic method of 2,5-di-*t*-butyl-3*H*-azepine (**4**), *t*-butyllithium was used as a nucleophile. To a dry ether solution of **2**, excess of *t*-butyllithium ether solution was added at room temperature with stirring. After quenching the reaction mixture with water, di-*t*-butyl derivative (**4**) was obtained from the organic layer in 44% yield. On the other hand, when methyllithium was used as a nucleophile under similar conditions, the reaction gave not only the expected 2-methyl-5-*t*-butyl-3*H*-azepine (**5**) in 12% yield, but also 2,3-dihydro-2,2-dimethyl-5-*t*-butyl-1*H*-azepine (**6**) and bis(5-*t*-butyl-

3*H*-azepin-2-yl)methane (**7**) in 37 and 25% yields. Structures for **4** and **5** were confirmed by comparing the spectral data with those of previously reported.[7] The formation of **6** is presumed to doubly occurred nucleophilic attacks of methylide on **2**, because the reaction of **5** with methyllithium also gave **6**. The enamine structure of **6** was supported by $\nu_{N\text{-}H}$ band at 3295 cm^{-1} and three olefinic proton signals at δ4.63 (dd, *J* = 10.0, 1.7 Hz, 1H), 5.37 (dt, *J* = 6.8, 1.7 Hz, 1H), and 6.12 (d, *J* = 10.0 Hz, 1H) ppm in the IR and ^{1}H NMR spectra, respectively.[8]



Another sequential nucleophilic reaction between **2** and the carbanion from **5** gave **7** which showed m/z 311.2483 [$(M+H)^+$ calcd for $C_{21}H_{31}N_2$: 311.2487] in HRMS (FAB). The NMR spectral signals could not be assigned to **7** due to an ^{1}H NMR signal of olefinic methyne at δ4.42 (s, 1H) ppm and an acidic proton at δ12.0 (br, 1H) ppm and the ^{13}C NMR signal at δ93.9 (d) ppm.[9] Reasonable assignment for the NMR spectra was made possible by considering the tautomers (**7a**,**b**), which are considered to be promoted by intramolecular hydrogen bond. As well, the stretching band for N-H at 3046 cm^{-1} indicates the existence of an effective hydrogen bond. D_2O exchange experiment showed instant disappearance of the signal at δ12.0 ppm (N-H) and then gradually decreasing of the signal intensity at δ4.42 ppm (central =CH–) with a half-life period by 81 min at 22˚C. The observed independent rates for D_2O exchange suggest the interconversion between **7a** and **7b** is not only attributed to 1,3-prototropy but mainly attributed to a degenerate 1,5-hydrogen shift between both rings with lower activation energy (Ea).

In order to investigate an energy profile for a diimine (**7**), tautomers (**7a,b**) and the transition structure of 1,5-hydrogen shift ($\mathbf{7}_{TS}$), an *ab initio* energy analysis was carried out using GAUSSIAN98 program.[10] Theoretical levels of B3LYP/6-31G(d)[11] were applied and zero-point-energy correction was made on all calculations.[12] Calculated energy for **7**, **7a,b**, and $\mathbf{7}_{TS}$ were -927.2880, -927.2971, and -927.2909 Hartrees, respectively. The vibrational analysis for the optimized $\mathbf{7}_{TS}$ showed only one imaginary frequency by -1431.1 cm^{-1}. The six central hexagonally arranged atoms of **7a,b** and $\mathbf{7}_{TS}$ are on a plane; each of them corresponds to the classical and nonclassical expression for a vinamidine conjugation,[13] respectively. Calculated internuclear distances between central hydrogen and both sides of nitrogen of **7a,b** are 1.03 and 1.88 Å. In the case of $\mathbf{7}_{TS}$, the location of the hydrogen is on a C_2 symmetry axis of the molecule with an internuclear distance of 1.28 Å. Both the transition structure ($\mathbf{7}_{TS}$) and the diimine (**7**) are less stable than **7a,b** by 3.9 and 5.7 kcal/mol, respectively. This explains that the D_2O exchange rates for N–H proton and central C–H proton are attributed to the degenerate 1,5-hydrogen shift (calcd Ea = 3.8 kcal/mol) and 1,3-prototropy (calcd Ea > 5.7 kcal/mol), respectively (Figure 1).

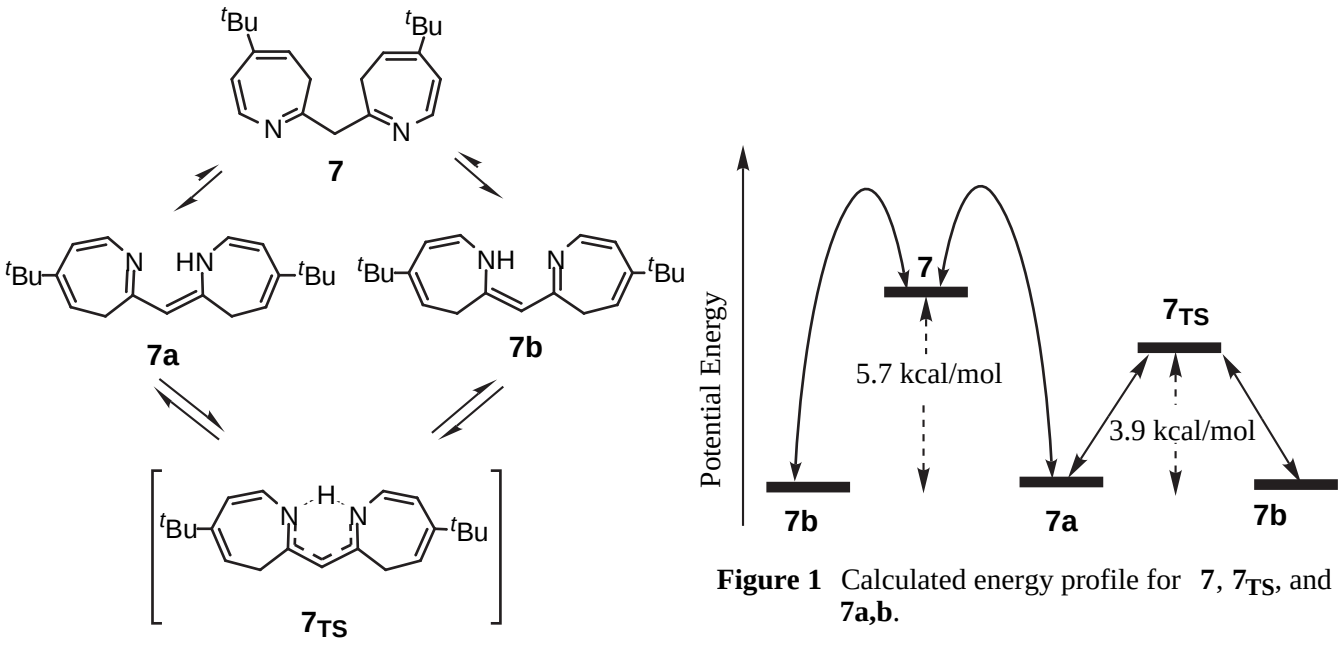


Figure 1 Calculated energy profile for **7**, $\mathbf{7}_{TS}$, and **7a,b**.

We are interested in the character of the unique vinamidine conjugation proposed here, which is incorporated in a seven-membered conjugated olefinic system. Further investigation for the chemistry of bisazepinylmethane is underway.

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5. Selected data for **2**; colorless oil (bp 105–109˚C); ^{1}H NMR (200 MHz, $CDCl_3$) δ1.10 (s, 9H), 2.59 (d, *J* = 6.8 Hz, 2H), 3.71 (s, 3H), 5.15 (dt, *J* = 6.8, 1.0 Hz, 1H), 6.15 (dd, J = 8.8, 1.0 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ30.0 (q), 32.5 (t), 34.5 (s), 54.4 (q), 110.1 (d), 115.5 (d), 137.4 (d), 148.6 (s), 154.8 (s); IR (neat) ν_{max} 1628 cm^{-1} (C=N); UV-Vis λ_{max} (EtOH) 254 nm (*log* ε = 3.61).
6. Selected data for **3a**; ^{1}H NMR (200 MHz, $CDCl_3$) δ1.10 (s, 9H), 1.26 (t, *J* = 7.2 Hz, 3H), 2.54 (d, *J* = 6.8 Hz, 2H), 4.12 (q, *J* = 7.2 Hz, 2H), 5.15 (dt, *J* = 6.8, 1.4 Hz, 1H), 6.13 (dd, *J* = 8.6 Hz, 1.4 Hz, 1H), 6.92 (d, *J* = 8.6 Hz, 1H); IR ν_{max} (neat) 1626 cm^{-1} (C=N); UV-Vis λ_{max} (EtOH) 254 nm (*log* ε = 3.77); **3b**; ^{1}H NMR (200 MHz, $CDCl_3$) δ0.89 (t, *J* = 7.2 Hz, 3H), 1.06 (s, 9H), 1.61 (dq, *J* = 7.2, 6.8 Hz, 2H), 2.50 (d, *J* = 6.7 Hz, 2H), 3.98 (t, *J* = 6.8 Hz, 2H), 5.11 (dt, *J* = 6.7, 1.4 Hz, 1H), 6.09 (dd, *J* = 8.8, 1.4 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 1H); IR ν_{max} (neat) 1624 cm^{-1} (C=N); UV-Vis λ_{max} (EtOH) 254 nm (*log* ε = 3.70); **3c**; ^{1}H NMR (200 MHz, $CDCl_3$) δ1.10 (s, 9H), 1.19 (d, *J* = 6.3 Hz, 6H), 2.51 (d, *J* = 7.4 Hz, 2H), 4.99 (hept, *J* = 6.3 Hz, 1H), 5.12 (dt, *J* = 7.4, 1.2 Hz, 1H), 6.12 (dd, *J* = 8.8, 1.2 Hz, 1H), 6.92 (d, *J* = 8.8, 1H); IR ν_{max} (neat) 1620 cm^{-1} (C=N); UV-Vis λ_{max} (EtOH) 254 nm (*log* ε = 3.44); **3d**; ^{1}H NMR (200 MHz, $CDCl_3$) δ1.10 (s, 9H), 2.58 (d, *J* = 6.6 Hz, 2H), 3.66-3.75 (m, 10H), 4.25 (t, *J* =

4.7 Hz, 2H), 5.15 (t, *J* = 6.6 Hz, 1H), 6.15 (d, *J* = 8.6 Hz, 1H), 6.90 (d, *J* = 8.6 Hz, 1H); IR λ_{max} (neat) 1624 cm^{-1} (C=N); UV-Vis λ_{max} (EtOH) 254 nm (*log* ε = 3.52).

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8. Selected data for **6**; ^{1}H NMR (200 MHz, $CDCl_3$) δ1.07 (s, 6H), 1.09 (s, 9H), 2.08 (d, *J* = 6.8 Hz, 2H), 3.80 (br s, 1H), 4.63 (dd, *J* = 10.0, 1.7 Hz, 1H), 5.37 (dt, *J* = 6.8, 1.7 Hz, 1H), 6.12 (d, *J* = 10.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ29.9 (q), 30.0 (q), 35.2 (s), 42.6 (t), 55.7 (s), 94.5 (d), 113.0 (d), 132.0 (d), 148.3 (s); IR ν_{max} (neat) 3295 cm^{-1} (NH).
9. Selected data for **7**; yellow needles (mp 145-146˚C); ^{1}H NMR (200 MHz, $CDCl_3$) δ1.09 (s, 18H), 2.63 (d, *J* = 6.8 Hz, 4H), 4.42 (s, 1H), 5.24 (dt, *J* = 6.8, 1.2 Hz, 2H), 5.85 (dd, *J* = 9.0, 1.2 Hz, 2H), 6.83 (d, *J* = 9.0 Hz, 2H), 12.0 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ29.9 (q), 34.7 (s), 36.2 (t), 93.9 (d), 113.4 (d), 114.1 (d), 134.8 (d), 148.6 (s), 155.4 (s); IR ν_{max} (KBr) 3046 cm^{-1} (NH); UV-Vis λ_{max} (EtOH) 380 nm (*log* ε = 4.40).
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