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Synthesis of 2,7-Diazabicyclo[3.3.0]octane and 2,7-Diazabicyclo[3.3.0]oct-4-ene Derivatives via Cyclization Reaction and Julia Reaction

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SYNTHESIS OF 2,7-DIAZABICYCLO[3.3.0]OCTANE AND 2,7-DIAZA BICYCLO[3.3.0]OCT-4-ENE DERIVATIVES VIA CYCLIZATION REACTION AND JULIA REACTION

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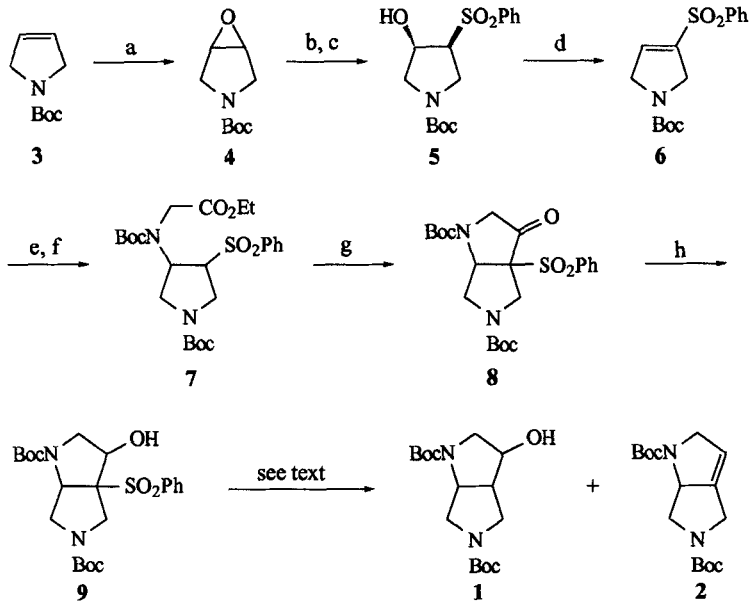
Abstract : 2,7-Diazabicyclo[3.3.0]octan-4-ol (**1**) and 2,7-diazabicyclo[3.3.0]oct-4-ene (**2**) are synthesized by the desulfonylation using Mg-$HgCl_2$(cat.) of β-hydroxy sulfone derivatives which have been prepared *via* cyclization of sulfone ester derivative.

Alkaloids that contain saturated five- and six-membered nitrogen heterocycles[1] and diazabicyclic compounds[2] have been popular synthetic targets due to the array of potent biological activities, the important component in many biologically active compounds, and the variety of structural challenges that are encounted in their construction. In connection with ongoing synthetic program to develop new methods for pyrrolidine ring system and diazabicyclic compounds,[3] we wish to report in this paper synthesis of 2,7-diazabicyclo[3.3.0]octan-4-ol (**1**)

Scheme 1[a]



[a]Reagents and Conditions : (a) MCPBA, CH_2Cl_2, 80 % ; (b) PhSH, NaH, MeCN, 85 % ; (c) H_2O_2, THF-AcOH, reflux, 80 % ; (d) MsCl, Et_3N, CH_2Cl_2, 83 % ; (e) $HCl{\cdot}H_2NCH_2CO_2Et$, Et_3N, EtOH, reflux, 70 % ; (f) $(Boc)_2O$, MeOH, 84 % ; (g) t-BuOK, THF, -70 ~ 0°C ; (h) $LiBH_4$, THF, 65 % in 2 steps.

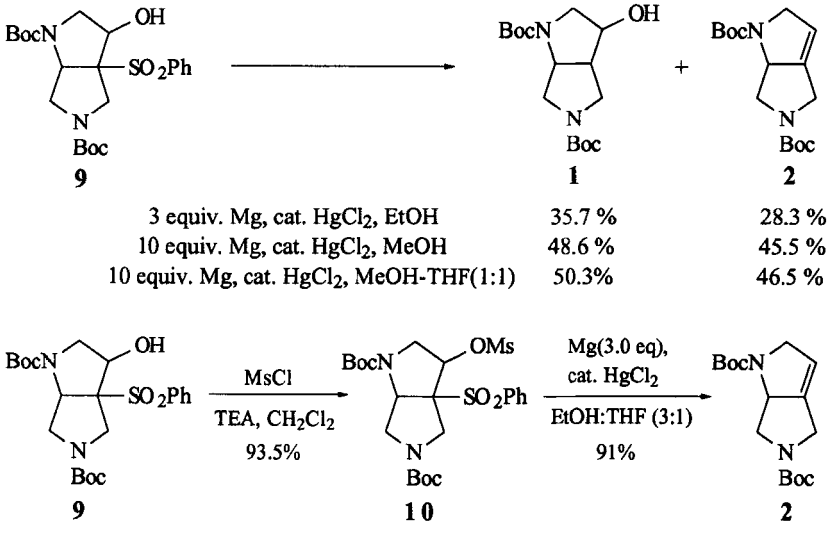
and 2,7-diazabicyclo[3.3.0]oct-4-ene (**2**) by novel reductive desulfonylation of β-hydroxy sulfone derivatives.

In our pathway approaching to the compounds (**1**) and (**2**), *N-tert* -butoxycarbonyl(Boc)-3-pyrroline (**3**) was chosen as a starting material, and its epoxidation with MCPBA proceeded to give a pyrrolidine epoxide (**4**) (Scheme 1). The reaction of epoxide (**4**) with benzenethiol under NaH, followed by the oxidation with hydrogen peroxide afforded compound (**5**). The reaction of β-hydroxy sulfone (**5**) with methanesulfonyl chloride in the presence of excess

triethylamine gave *N*-Boc-3-phenylsulfonyl-3-pyrroline (**6**).[4, 5] The sulfone ester (**7**) was easily obtained by the addition[6] of glycine ethyl ester to vinyl sulfone (**6**), followed by *N*-Boc protection of amine using $(Boc)_2O$. The stereochemistry of sulfone ester (**7**) is trans which was supported by the X-ray crystallography.[7]

Fortunately,[8] sulfone ester (**7**) was successfully converted into desired β-hydroxy sulfone (**9**) by cyclization using *t*-BuOK in THF, followed by the reduction of β-keto sulfone (**8**) with $LiBH_4$. On the other hand, cyclization of **7** and *in situ* reduction reaction proceeded to give **9** in good yield. While this type of ring closure has previously been used for the construction of five-, six-, and eight-membered carbocycles,[9] it has not found application in occurrence of five-membered nitrogen heterocycle. The reductive desulfonylation reaction of β-hydroxy sulfones and derivatives thereof(Julia reaction) has long been recognized as a useful synthetic transformation.[10] Therefore, we tried to conduct the desulfonylation[11] of β-hydroxy sulfone (**9**). When the β-hydroxy sulfone (**9**) was subjected to react with 3.0 equiv. of magnesium(powder, 50 mesh, Aldrich®) in ethanol in the presence of catalytic amount of mercuric chloride,[12] the desired alcohol (**1**)[13] and alkene (**2**)[13] were isolated in 35.7 % yield and 28.3 % yield, respectively, and starting material was recovered. In an attempt to consume the starting material, less reactive ethanol was substituted for methanol or methanol-THF(1:1) and 10 equiv. of magnesium was used. Reaction proceeded to consume completely starting material in the presence of mercuric chloride. In the absence of mercuric chloride, the reaction was not completed. To our knowlege, it is the first example to apply Julia reaction to the heterocyclic compound.

The reductive elimination reaction of the β-mesyloxy sulfone (**10**) prepared by mesylation of **9** was also attempted for comparison. In this case, the reaction underwent cleanly to give the corresponding alkene (**2**) under 3.0 equiv. of Mg



and cat. $HgCl_2$ in EtOH-THF(3:1). The structure for *N,N'*-di-*tert*-butoxycarbonyl-2,7-diazabicyclo[3.3.0]oct-4-ene (**2**) was completely confirmed by spectroscopic data[13] and the X-ray crystallography[7](Figure 1).

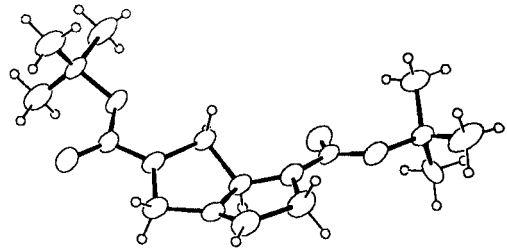


Figure 1. X-ray structure of compound (**2**)

In summary, the 2,7-diazabicyclo[3.3.0]octane derivatives (**1**, **8**, and **9**) and 2,7-diazabicyclo[3.3.0]oct-4-ene (**2**) were synthesized from the strategy of the cyclization of sulfone ester derivative and the reductive desulfonylation. Also, it

has been developed the new method for the Julia alkenylation using Mg-$HgCl_2$ system.

Acknowledgement

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13. **1** : mp 140~142°C ; ^{1}Hnmr (80 MHz, $CDCl_3$) δ 1.45(s, 9H), 1.47(s, 9H), 2.26(br, 1H), 2.75~3.02(m, 1H), 3.17~3.33(m, 1H), 3.44~3.76(m, 5H), 4.17(m, 1H), 4.38(m, 1H). **2** : mp 96~100°C ; ^{1}Hnmr (80 MHz, $CDCl_3$) δ 1.47(s, 18H), 2.87(dd, J=9.87 Hz ; J=8.72 Hz, 1H), 3.89(br, 2H), 4.11(m, 1H), 4.34(br, 2H), 4.67(m, 1H), 5.61(br, 1H) ; ir(υ, cm^{-1}) 1106, 1129, 1152, 1174, 1333, 1365, 1402, 1477, 1676, 1697, 2876, 2978 ; ms(m/z) 57(100), 80(73.2),

153(39.9), 197(42.8), 253(M^+ - 57, loss of t-Bu, 5.1). **9** : mp 174~176°C ; ^{1}Hnmr (80 MHz, $CDCl_3$) δ 1.41(s, 9H), 1.48(s, 9H), 3.12~4.22(m. 7H), 4.94(m, 1H), 7.53~7.75(m, 3H), 7.98~8.10(m, 2H) ; ir(υ, cm^{-1}) 1149, 1169, 1251, 1308, 1368, 1408, 1680, 1697, 3399.

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