

HETEROCYCLES, Vol. 77, No. 1, 2009, pp. 461 - 469. © The Japan Institute of Heterocyclic Chemistry
Received, 10th July, 2008, Accepted, 28th August, 2008, Published online, 1st September, 2008.
DOI: 10.3987/COM-08-S(F)43

REACTION OF β,β -BIS(TRIFLUOROACETYL)VINYL ETHERS AND β -TRIFLUOROACETYL VINYL ETHERS WITH 1,2-PHENYLENE-DIAMINES ACCESSING FLUORINE-CONTAINING BENZO[*b*][1,4]-DIAZEPINE DERIVATIVES – A STUDY ABOUT THE REACTION BASED ON MOLECULAR ORBITAL CALCULATIONS

Norio Ota,^a Yasuhiro Kamitori,^{b*} Takehisa Tomoda,^a Naoya Terai,^a and Etsuji Okada^{b*}

^aGraduate School of Science and Technology, Kobe University, Rokkodai-cho, Nada-ku, Kobe 657-8501, Japan

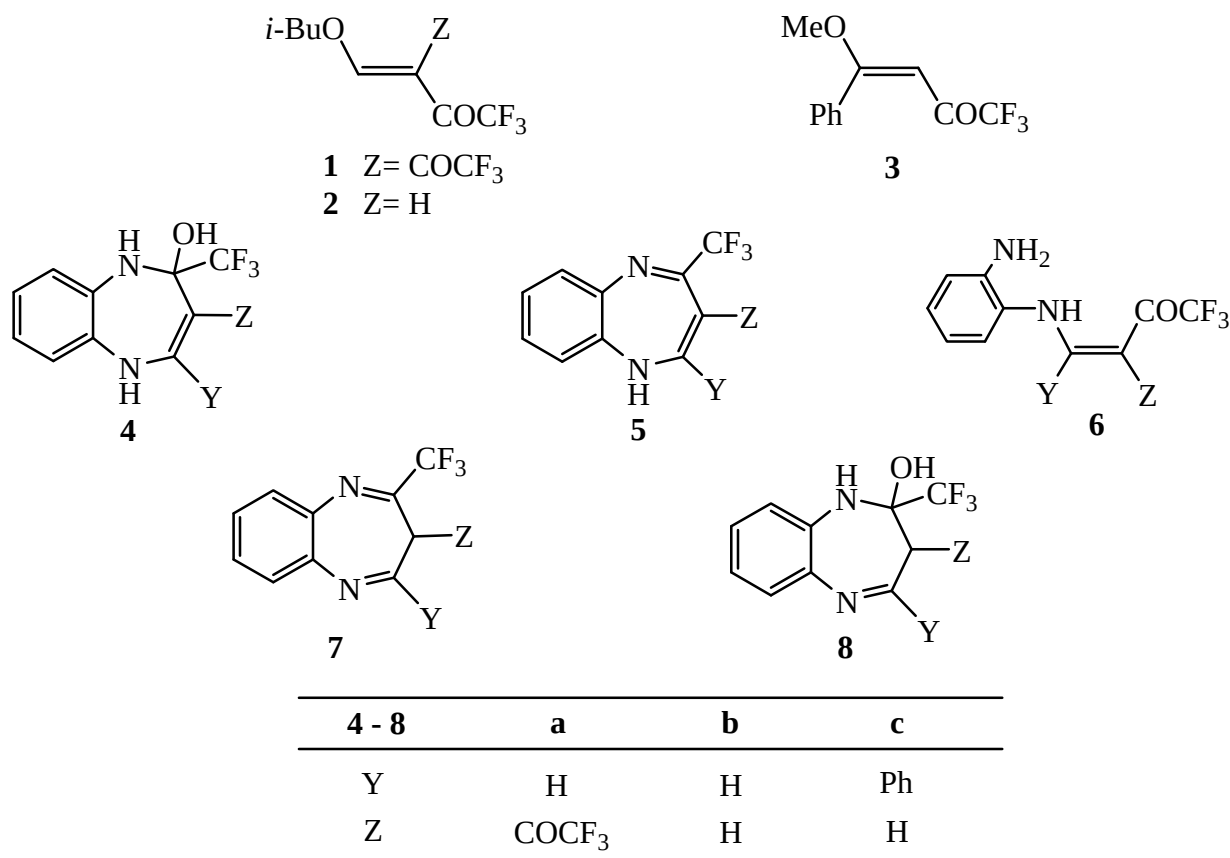
^bDepartment of Chemical Science and Engineering, Graduate School of Engineering, Kobe University, Rokkodai-cho, Nada-ku, Kobe 657-8501, Japan
Fax: +81(78)8036163; E-mail: kamitori@kobe-u.ac.jp

Abstract – β,β -Bis(trifluoroacetyl)vinyl ether (**1**) reacted with 1,2-phenylenediamine to give dihydrobenzodiazepinol (**4a**) selectively, whereas β -trifluoroacetylvinyl ether (**2**) and β -trifluoroacetyl- α -phenylvinyl ether (**3**) gave the corresponding *O-N* exchange products (**6b**, **c**) when reacted with 1,2-phenylenediamine. The factors determining the reaction products of the reaction of three substrates **1-3** having similar structures with 1,2-phenylenediamine were elucidated on the basis of molecular orbital calculations. The dehydration processes from dihydrobenzodiazepinols (**4** and **8**) to benzodiazepines (**5** and **7**) are also discussed.

INTRODUCTION

In recent years, much attention has been focused on the development of new methodologies for the syntheses of many kinds of fluorine-containing heterocycles, since these compounds are now widely recognized as important organic materials showing specific functions as well as interesting biological activities.¹⁻⁴ In our previous paper,⁵ we reported an efficient and convenient synthetic method accessing fluorine-containing dihydrobenzo[*b*][1,4]diazepinols which have remarkable anti-tumor activities⁶ from β,β -bis(perfluoroalkanoyl)vinyl ethers. During the investigations, we found that the reaction of β,β -bis(trifluoroacetyl)vinyl *iso*-butyl ether (**1**) with 1,2-phenylenediamine gave 2,5-dihydro-3-

trifluoroacetyl-2-trifluoromethyl-1*H*-benzo[*b*][1,4]diazepin-2-ol (**4a**) selectively under very mild conditions without microwave irradiation. Our results showed clear contrast with Reddy's reports of obtaining 1*H*-benzo[*b*][1,4]diazepine (**5a**) by the reaction of **1** with 1,2-phenylenediamine carried out under microwave irradiation.^{7,8} We also found that the reaction of β -trifluoroacetylvinyl *iso*-butyl ether (**2**) with 1,2-phenylenediamine produced only *O*-*N* exchange product (**6b**). A similar *O*-*N* exchange product was seen in Bonacorso's work in which **6c** was obtained as the sole product of the reaction of β -trifluoroacetyl- α -phenylvinyl methyl ether (**3**) with 1,2-phenylenediamine.⁹ Moreover, it has been reported that **6c** was converted to the corresponding 3*H*-benzo[*b*][1,4]diazepine (**7c**) by heating **6c** in the presence of acetic acid.⁹ In contrast, **6b** did not give any benzodiazepines or dihydrobenzodiazepinols, even in the presence of acid catalyst.



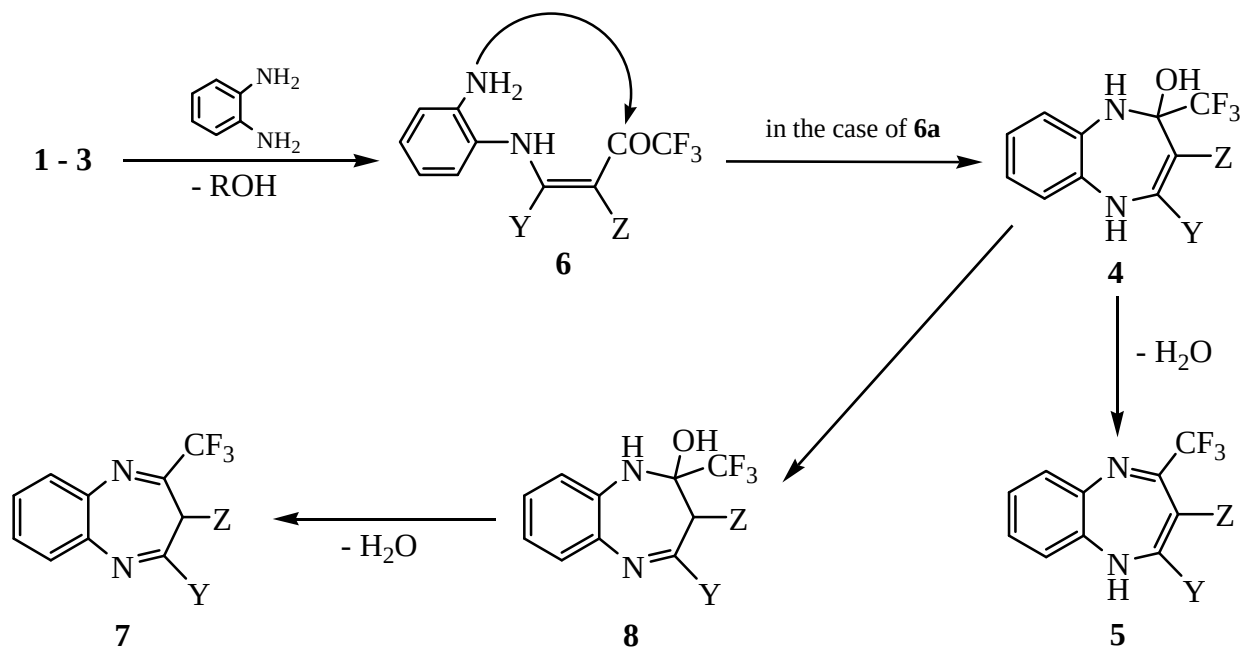
Scheme 1

The finding that the conversion of *O*-*N* exchange product **6c** to benzodiazepine **7c** occurred in the presence of acid catalyst suggests that dehydration on dihydrobenzodiazepinol **4c** or **8c**, which is thought to be the precursor of **7c**, proceeded smoothly by acid catalysis. However, acid-catalyzed dehydration of dihydrobenzodiazepinol **4a** was not successful and the corresponding benzodiazepine **5a** was not obtained at all.⁵

We here present the most reasonable interpretation on the basis of molecular orbital calculations for these interesting differences in reactivity among three substrates **1-3** in the reaction with 1,2-phenylenediamine. Moreover, dehydration processes of dihydrobenzodiazepinols **4** and **8** to benzodiazepines **5** and **7** are also discussed.

RESULTS AND DISCUSSION

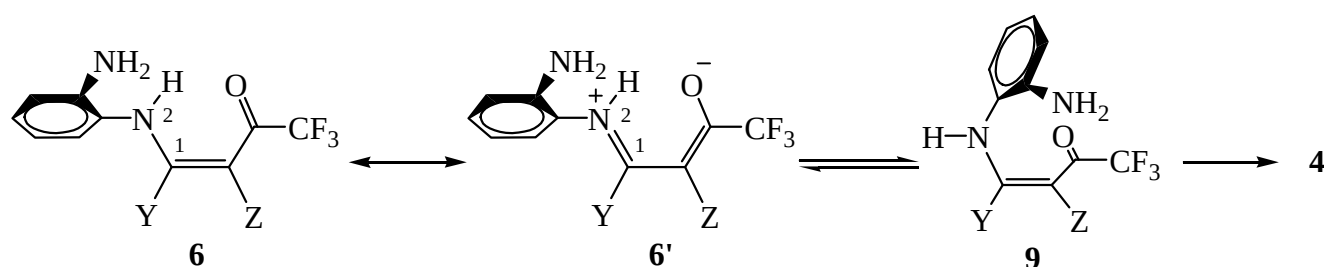
Derivatives of β -trifluoroacetylated vinyl ethers such as β -trifluoroacetylketene acetals,¹⁰ β,β -bis(trifluoroacetyl)vinyl ethers,¹¹ β -trifluoroacetyl- α -phenylvinyl ethers,¹² and β -trifluoroacetylvinyl ethers¹³ readily undergo nucleophilic *O-N* exchange reactions at olefinic carbons with various aliphatic and aromatic amines to give the corresponding β -trifluoroacetylated ketene *O,N*-acetals, β,β -bis(trifluoroacetyl)enamines, β -trifluoroacetyl- α -phenylenamines, and β -trifluoroacetylenamines. Consequently, *O-N* exchange products **6a-c** were supposed to be the initial intermediates in the reaction of three substrates **1-3** with 1,2-phenylenediamine (Scheme 1). In the cases of β -trifluoroacetylvinyl *iso*-butyl ether (**2**) and β -trifluoroacetyl- α -phenylvinyl methyl ether (**3**), the reaction stops at this stage. In contrast, the subsequent intramolecular nucleophilic addition of the remaining aromatic NH_2 group to trifluoroacetyl carbonyl group in **6** (**6a**) proceeds to give dihydrobenzodiazepinol **4** (**4a**) in the case of bis(trifluoroacetyl)vinyl *iso*-butyl ether (**1**) as illustrated in Scheme 2.



Scheme 2

If dehydration of dihydrobenzodiazepinols **4** is possible, 1H-benzo[b][1,4]diazepines (**5**) is obtained. If isomeric 2,3-dihydro-1H-benzo[b][1,4]diazepin-2-ols (**8**) are thermodynamically more stable than 2,5-

dihydro-1*H*-benzo[*b*][1,4]diazepin-2-ols (**4**), 3*H*-benzo[*b*][1,4]diazepines (**7**) are produced from **4** via **8**. As an initial step to clarify the reason why cyclization of *O*-*N* exchange products **6** to dihydrobenzodiazepinols **4** did not occur in the cases of **6b** and **6c** whereas it proceeded smoothly in the case of **6a**, we computed the most stable structures of **6a-c** and their energies (E_6) using RB3LYP/6-31G*/RB3LYP/6-31G*. As depicted in Scheme 3, the transformation from the most stable conformers **6** to **9** suitable for subsequent cyclization would be necessary to convert **6** to dihydrobenzodiazepinols (**4**). We presumed that the facility of the transformation from **6** to **9** would be correlated with multiple bonding characters on C(1)-N(2) bond of **6** owing to the push-pull type canonical contribution of **6'**. Thus, we calculated Mulliken bond orders¹⁴ on C(1)-N(2) bond of **6a-c** and performed structural optimization for conformers (**9a-c**). In Table 1, the values of bond order P_{CN} for **6a-c** are listed together with the energies of **6a-c** (E_6) and **9a-c** (E_9).



Scheme 3

Table 1. The values of Mulliken bond order P_{CN} for **6** and the energies E_5 , E_9 (au) for **6** and **9**.

6, 6', 9, 4	Y	Z	P_{CN}	E_6	E_9
a	H	COCF ₃	1.303	-1321.07586	-1321.05816
b	H	H	1.267	-870.72864	-870.70436
c	Ph	H	1.233	-1101.78062	-1101.76393

P_{CN} of **6a** is apparently larger than those of **6b** and **6c** indicating enhanced multiple bonding character on C(1)-N(2) bond of **6a** compared to those of **6b** and **6c**. Enhanced multiple bonding character would prevent the rotation around C(1)-N(2) bond on conformer (**6a**) and, consequently, the transformation from **6a** to conformer (**9a**). Therefore, the above results are incompatible with the experimental results in which cyclization of intermediate (**6a**) occurred easily to give dihydrobenzodiazepinol (**4a**),⁵ while **6b** and **6c** did not cyclize to **4b** and **4c**, respectively. Therefore, the conformation change process from **6** to **9** is not important for the overall cyclization process from **6** to **4**, showing that the cyclization process from conformers (**9**) to dihydrobenzodiazepinols (**4**) is a key step in determining whether *O*-*N* exchange products (**6**) are converted to **4**.

We focused on intramolecular frontier orbital interactions, i.e. the interactions between nitrogen in aromatic NH_2 group (HOMO) and carbonyl carbon in COCF_3 group (LUMO) on conformers (**9a-c**). Thus, frontier electron densities, fr^{HOMO} at $\underline{\text{N}}\text{H}_2$ and fr^{LUMO} at $\underline{\text{C}}\text{OCF}_3$ on **9a-c** were calculated and the results are shown together with C-N distances between $\underline{\text{N}}\text{H}_2$ and $\underline{\text{C}}\text{OCF}_3$ in Table 2. In the case of **9a** bearing two trifluoroacetyl groups, frontier electron density on LUMO is concentrated at carbonyl carbon of the other trifluoroacetyl group, which is not a reaction center of the present cyclization reaction. Therefore, we used the electron density on the 2nd LUMO, which has a slightly higher energy level (ca. 0.65 eV) than LUMO on **9a**.

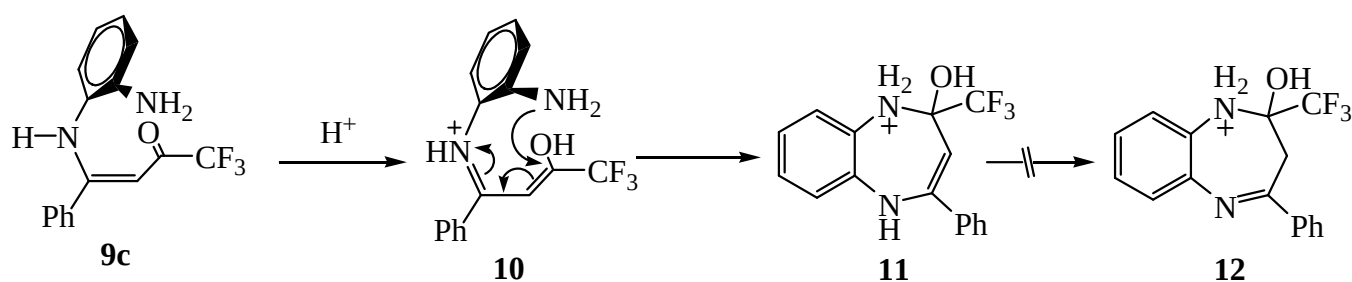
Table 2. Frontier electron densities, fr^{HOMO} at $\underline{\text{N}}\text{H}_2$ and fr^{LUMO} at $\underline{\text{C}}\text{OCF}_3$, and C-N distances (Å) between $\underline{\text{N}}\text{H}_2$ and $\underline{\text{C}}\text{OCF}_3$ on **9a-c**.

	9a	9b	9c
fr^{HOMO}	0.393	0.386	0.371
fr^{LUMO}	0.597 ^a	0.391	0.215
C-N distance	2.756	3.041	3.025

^a Electron density on 2nd LUMO.

Both values of fr^{HOMO} and fr^{LUMO} on **9a** are apparently larger than those on **9b** and **9c**. These values of frontier electron density indicate that the intramolecular frontier orbital interaction on **9a** would be considerably greater than those on **9b** and **9c**. In addition, the C-N distance on **9a** being ca. 0.3 Å shorter than those on **9b** and **9c** would also assist the intramolecular frontier orbital interaction on **9a** to a greater extent. The strong intramolecular frontier orbital interaction would promote the cyclization of **9a** to dihydrobenzodiazepinol (**4a**) under very mild reaction conditions. In contrast, the intramolecular HOMO-LUMO interaction on **9b** and **9c** would not be strong enough to mediate cyclization of **9b** and **9c** to the corresponding dihydrobenzodiazepinols (**4b** and **4c**), respectively, under similar reaction conditions. To clarify the relative stability of dihydrobenzodiazepinols (**4** and **8**) depicted in Scheme 2, we computed the optimized structures of **4a,c** and **8a,c** together with their energies. Our results indicate that **8a** is ca. 4.5 kcal/mol less stable than **4a**, whereas **8c** is ca. 10 kcal/mol more stable than **4c**. Therefore, the isomerization process from **4a** to **8a** is thought to be inhibited. This would be a reason why the reaction of β -bis(trifluoroacetyl)vinyl *iso*-butyl ether (**1**) with 1,2-phenyldiamine produced dihydrobenzodiazepinol (**4a**) (not **8a**) as a sole product. On the other hand, **4c** is thought to isomerize immediately to more stable **8c** when **4c** is able to form by cyclization of **6c**. However, it is necessary to take in account that acid catalyst was necessary for cyclization of **6c**.⁹ As illustrated in Scheme 4,

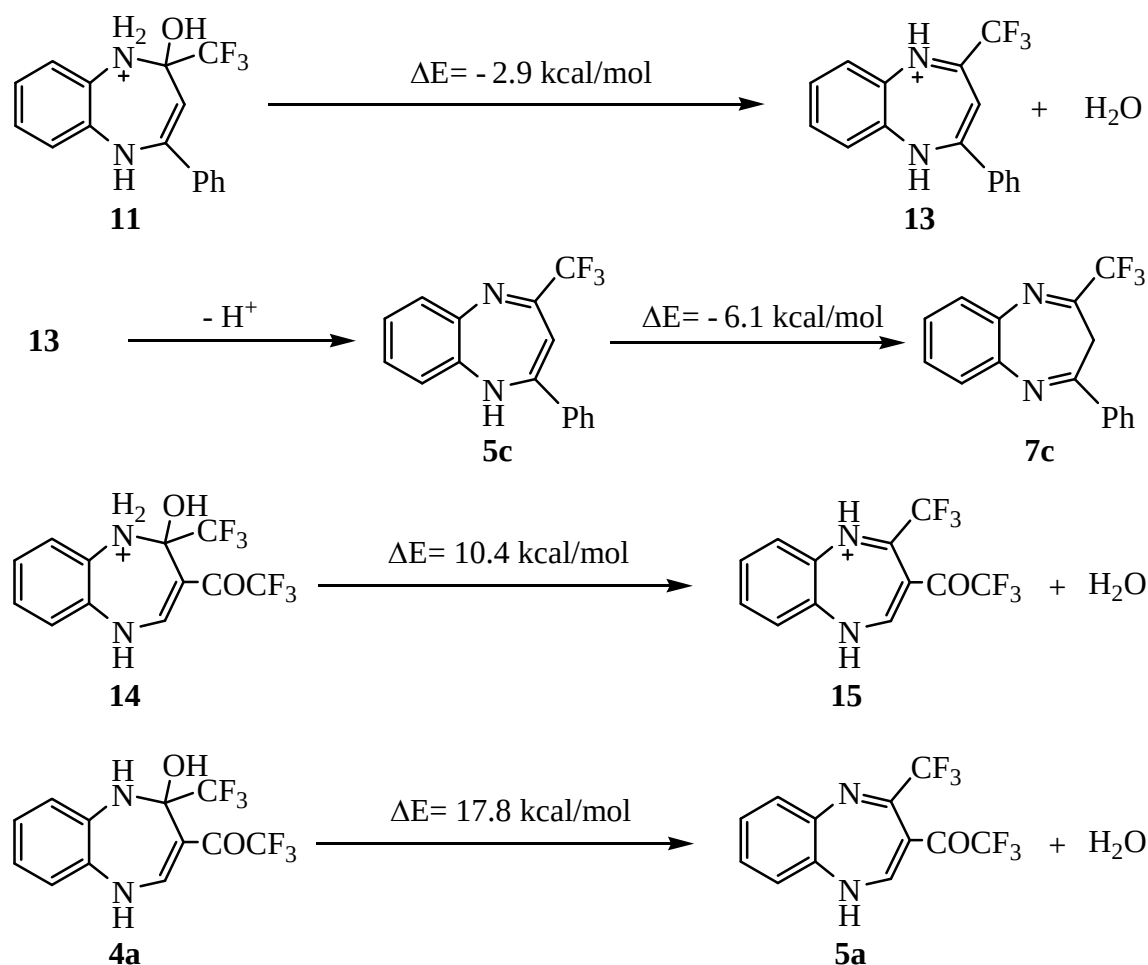
cyclization of **6c** would proceed via cation (**10**) produced by protonation on carbonyl oxygen of conformer (**9c**) in the presence of acid catalyst to produce 2-hydroxy-2,5-dihydro-1*H*-benzo[*b*][1,4]diazepin-1-ium cation (**11**). Cation (**11**) was estimated to be 0.52 kcal/mol more stable than isomeric 2-hydroxy-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepin-1-ium cation (**12**). Thus, isomerization from **11** to **12** would not be an energetically favorable process and, therefore, subsequent dehydration is thought to proceed predominantly from **11**.



Scheme 4

As for the dehydration processes from dihydrobenzodiazepinol (**4a**) to benzodiazepine (**5a**) in the presence of acid catalyst, we can postulate the most reasonable model reactions, as shown in Scheme 5. Cation (**14**) was employed as the most suitable precursor for acid-catalyzed dehydration of **4a**. Dehydration of **14** gives 5*H*-benzo[*b*][1,4]diazepin-1-ium cation (**15**). On the other hand, cation (**13**) would be formed by dehydration of cation (**11**). Deprotonation of **13** gives 1*H*-benzo[*b*][1,4]diazepine (**5c**) which would isomerize to 3*H*-benzo[*b*][1,4]diazepine (**7c**) because **7c** was estimated to be 6.1 kcal/mol more stable than **5c**.

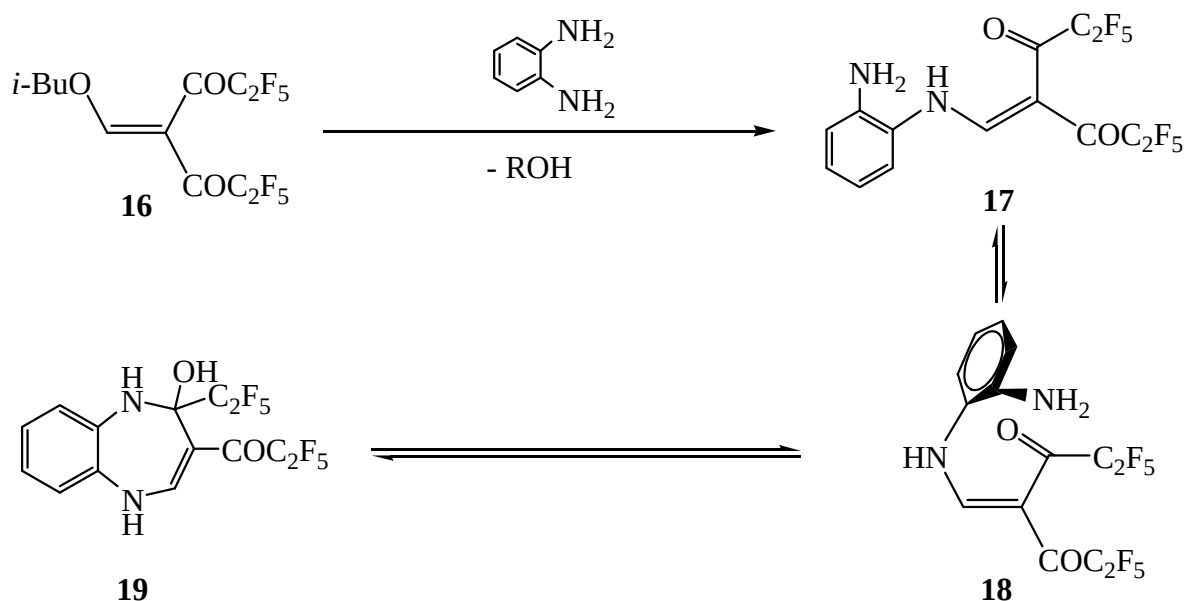
We compared the energies of cations (**11** and **14**) with the total energies of cations (**13** and **15**), respectively, and water. The process from **11** to **13** was predicted to be an exothermic reaction with a heat of reaction of -2.9 kcal/mol, while that from **14** to **15** was predicted to be endothermic with 10.4 kcal/mol. These results suggest that dehydration of cation (**11**) readily occurs to give **13**, whereas that of cation (**14**) producing **15** in an energetically unfavorable process. Since cation (**11**) is produced by acid-catalyzed cyclization of **6c** (Scheme 4) and deprotonation of cation (**13**), benzodiazepine (**7c**) is easily produced via **5c** (Scheme 5), and the overall reaction from **6c** to **7c** is predicted to proceed smoothly by acid catalysis. However, acid-catalyzed dehydration of **4a** to **5a** via **14** is estimated to be difficult. These predictions are quite compatible with the experimental results^{5,9} where the *O-N* exchange product (**6c**) could be converted to the corresponding benzodiazepine (**7c**) by heating **6c** in the presence of acetic acid, while acid-catalyzed dehydration of dihydrobenzodiazepinol (**4a**) to the corresponding benzodiazepine (**5a**) was unsuccessful.



Scheme 5

We also carried out calculations about the dehydration process from dihydrobenzodiazepinol (**4a**) to benzodiazepine (**5a**) in the absence of an acid catalyst. The process from **4a** to **5a** and water was estimated to be an endothermic reaction with 17.8 kcal/mol (Scheme 5), suggesting that dehydration of **4a** to **5a** requires high external energy. It is likely that microwaves merely assisted the endothermic dehydration of dihydrobenzodiazepinols (**4**) to benzodiazepines (**5**) as an effective external energy in Reddy's work^{7,8} because we found **4** could be readily obtained by the reaction of β,β -bis(trifluoroacetyl)vinyl *iso*-butyl ether (**1**) with 1,2-phenylenediamines without microwave irradiation under very mild conditions.⁵ In contrast with the case of **5c**, **5a** was estimated to be 3.6 kcal/mol more stable than **7a**, which explains why the isomerization from **5a** to **7a** was not observed.^{7,8}

Finally, we made calculations about the reaction of β,β -bis(pentafluoropropionyl)vinyl *iso*-butyl ether (**16**) with 1,2-phenylenediamine. This reaction was found to give a mixture of *O-N* exchange product (**17**) and dihydrobenzodiazepinol (**19**), and the complete conversion from **17** to **19** could not be achieved by prolonging reaction time (in Scheme 6).⁵



Scheme 6

The cyclization process from conformer (**18**) to dihydrobenzodiazepinol (**19**) was estimated to be an endothermic reaction with a heat of reaction of 1.7 kcal/mol whereas that from conformer (**9a**) to dihydrobenzodiazepinol (**4a**) was predicted to be exothermic with -1.5 kcal/mol. In the case of the reaction of **16** with 1,2-phenylenediamine, the relative instability of **19** compared to **18** and possible equilibrium between **18** and **19** are thought to prevent the complete conversion from *O*-*N* exchange product (**17**) to dihydrobenzodiazepinol (**19**).

CONCLUSION

Based on molecular orbital calculations, we can rationalize the difference of products resulting from the reactions of β,β -bis(trifluoroacetyl)vinyl *iso*-butyl ether (**1**), β -trifluoroacetylvinyl *iso*-butyl ether (**2**), and β -trifluoroacetyl- α -phenylvinyl methyl ether (**3**) with 1,2-phenylenediamine. Intramolecular frontier orbital interaction on *O*-*N* exchange products (**6**) (conformers **9**) as intermediates of the above reactions would be a key factor in determining whether the subsequent cyclization reactions yielding dihydrobenzodiazepinols (**4**) take place. Unsuccessful dehydration of dihydrobenzodiazepinol (**4a**) to benzodiazepine (**5a**) in the presence of acid catalyst is attributed to the endothermic dehydration process from protonated dihydrobenzodiazepinol (**14**) to protonated benzodiazepinol (**15**) requiring high energy.

COMPUTATIONAL METHODS

All calculations employed in this paper were accomplished using the computer programs packages SPARTAN and PC SPARTAN 04.¹⁵ All calculations for geometrical optimizations were performed with the 6-31G* basis set at B3LYP¹⁶ level. The starting geometries employed for all optimizations were resulted from molecular mechanics using SYBYL¹⁷ force field and subsequent semi-empirical

PM3¹⁸ optimizations. The calculations for energy of intermediates were also taken with the 6-31G* basis set at B3LYP level.

REFERENCES

1. R. Filler and Y. Kobayashi, '*Biomedical Aspects of Fluorine Chemistry*,' Kodansha & Elsevier Biomedical, Tokyo, 1982.
2. R. Filler, '*Organofluorine Chemicals and Their Industrial Applications*,' Ellis Horwood, London, 1979.
3. J. T. Welch, *Tetrahedron*, 1987, **43**, 3123.
4. R. Filler, Y. Kobayashi, and L. M. Yagupolskii, '*Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*,' Elsevier, Amsterdam, 1993.
5. N Ota, T. Tomoda, N. Terai, Y. Kamitori, D. Shibata, M. Médebielle, and E. Okada, *Heterocycles*, 2008, **76**, 1205.
6. E. Okada, N. Ota, T. Tomoda, M. Fujimoto, and H. Takenaka, Jpn. Kokai Tokkyo Koho 2006-273844, 2006.
7. A. C. S. Reddy, P. S. Rao, and R. V. Venkataratnam, *Tetrahedron Lett.*, 1996, **37**, 2845.
8. A. C. S. Reddy, P. S. Rao, and R. V. Venkataratnam, *Tetrahedron*, 1997, **53**, 5847.
9. H. B. Bonacorso, L. M. L. Marques, N. Zanatta, and M. A. P. Martins, *Synth. Commun.*, 2002, **32**, 3225.
10. M. Hojo, R. Masuda, E. Okada, H. Yamamoto, K. Morimoto, and K. Okada, *Synthesis*, 1990, 195.
11. M. Hojo, R. Masuda, E. Okada, and Y. Mochizuki, *Synthesis*, 1992, 455.
12. M. Hojo, R. Masuda, and E. Okada, *Synthesis*, 1986, 1013.
13. M. Hojo, R. Masuda, E. Okada, S. Sakaguchi, H. Narumiya, and K. Morimoto, *Tetrahedron Lett.*, 1989, **30**, 6173.
14. R. S. Mulliken, *J. Chem. Phys.*, 1955, **23**, 1833, 1841, 2338, 2343.
15. Wavefunction, Inc.
16. A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648.
17. M. Clark, R. D. Cramer III, and N. van Opdensh, *J. Computational Chem.*, 1989, **10**, 982.
18. J. J. P. Stewart, *J. Computer Aided Molecular Design*, 1992, **6**, 69.