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REACTION OF β,β-BIS(TRIFLUOROACETYL)VINYL ETHERS AND β-TRIFLUOROACETYLVINYL 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

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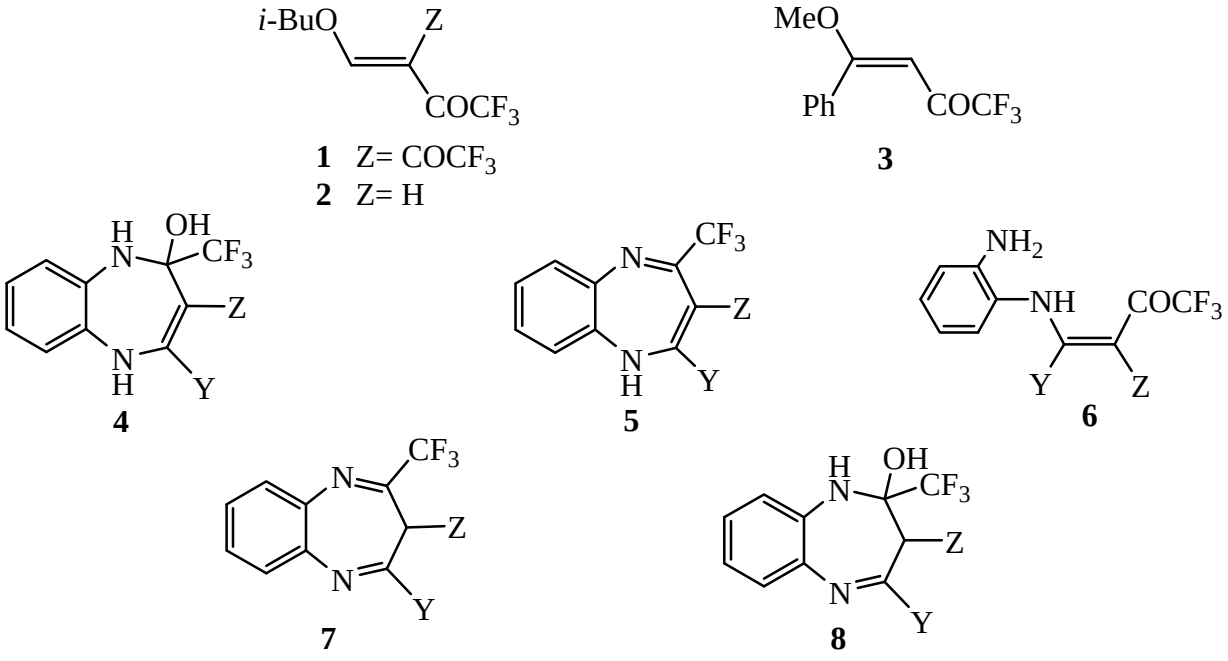
Abstract – β,β-Bis(trifluoroacetyl)vinyl ether (**1**) reacted with 1,2-phenylenediamine to give dihydrobenzodiazepinol (**4a**) selectively, whereas β-trifluoroacetylvinyl ether (**2**) and β-trifluoroacetyl-α-phenylvinyl ether (**3**) gave the corresponding *O*-*N* exchange products (**6b**, **c**) 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 activities[6] 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-

This paper is dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.

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.



4 - 8	a	b	c
Y	H	H	Ph
Z	$COCF_3$	H	H

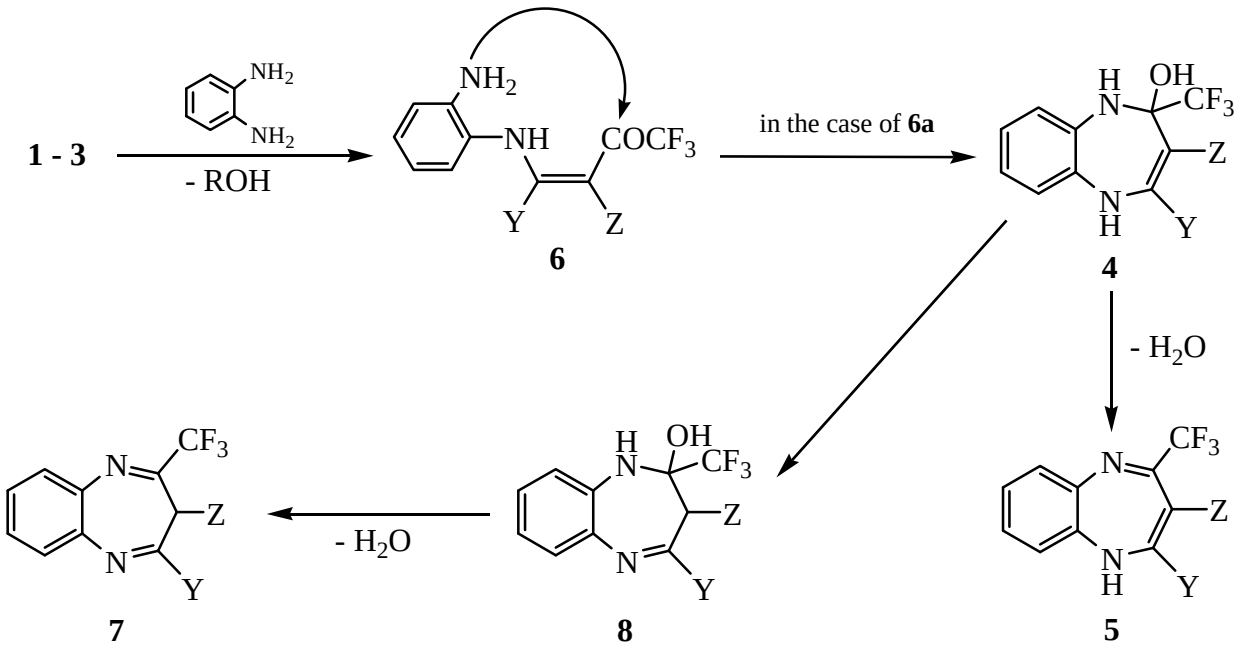
Scheme 1

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 dihydrobenzodiazepionol **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-phenylendiamine. 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 ethers[13] 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.

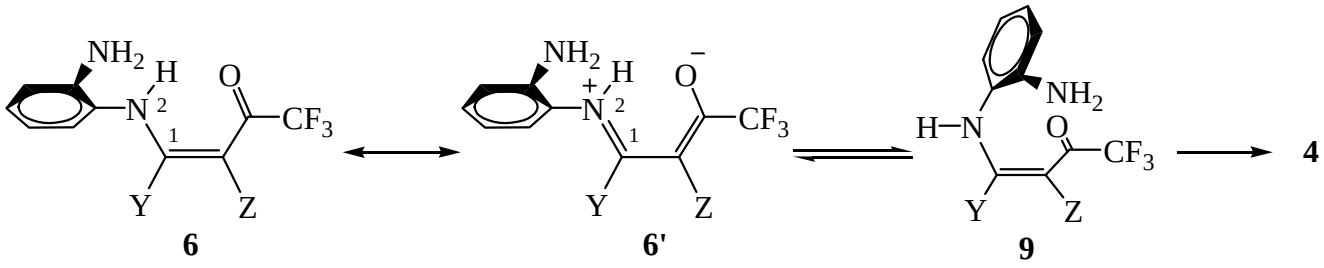


Scheme 2

If dehydration of dihydrobenzodiazepinols **4** is possible, 1*H*-benzo[*b*][1,4]diazepines (**5**) is obtained. If isomeric 2,3-dihydro-1*H*-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 orders[14] 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 $\underline{N}H_2$ and fr^{LUMO} at $\underline{C}OCF_3$ on **9a-c** were calculated and the results are shown together with C-N distances between $\underline{N}H_2$ and $\underline{C}OCF_3$ 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**.

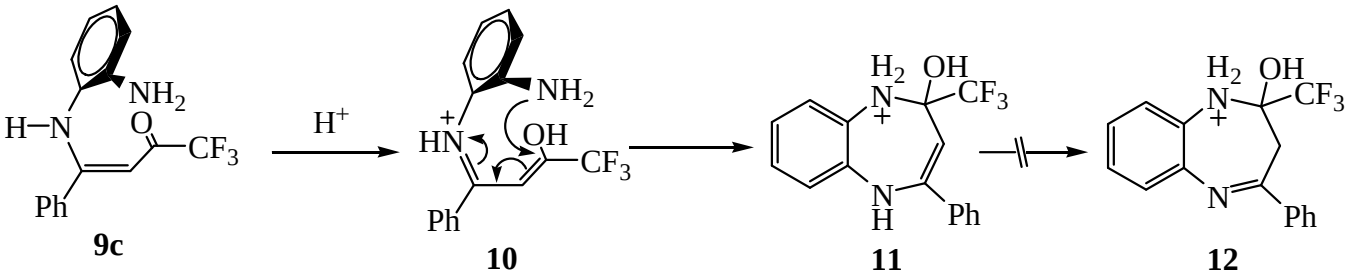
Table 2. Frontier electron densities, fr^{HOMO} at $\underline{N}H_2$ and fr^{LUMO} at $\underline{C}OCF_3$, and C-N distances (Å) between $\underline{N}H_2$ and $\underline{C}OCF_3$ on **9a-c**.

	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-phenylendiamine 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,

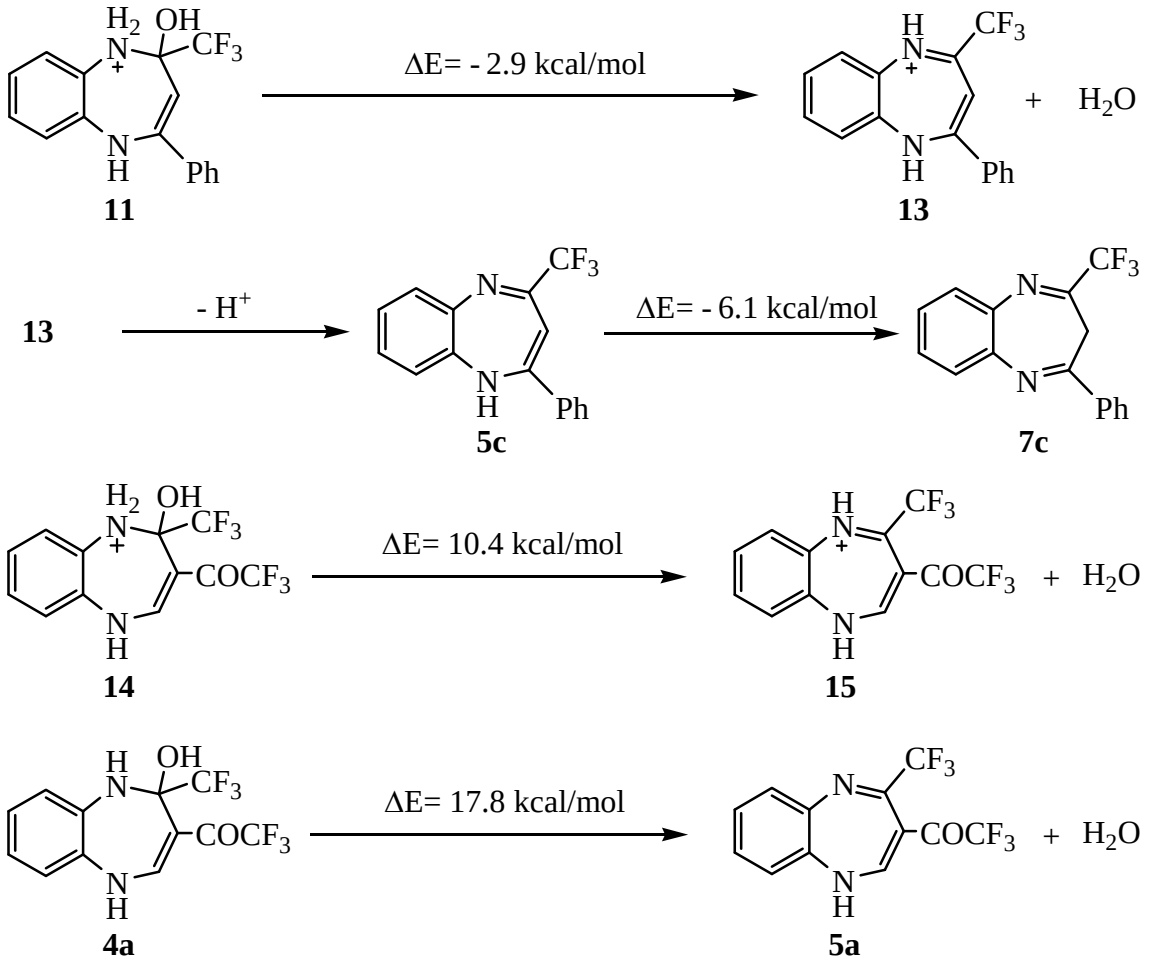
cyclization of **6c** would proceed via cation (**10**) produced by protonation on carbonyl oxygen of conformer (**9c**) in the presence of acid catalyst to produce 2-hydroxy-2,5-dihydro-1*H*-benzo[*b*][1,4]diazepin-1-ium cation (**11**). Cation (**11**) was estimated to be 0.52 kcal/mol more stable 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 5H-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**.

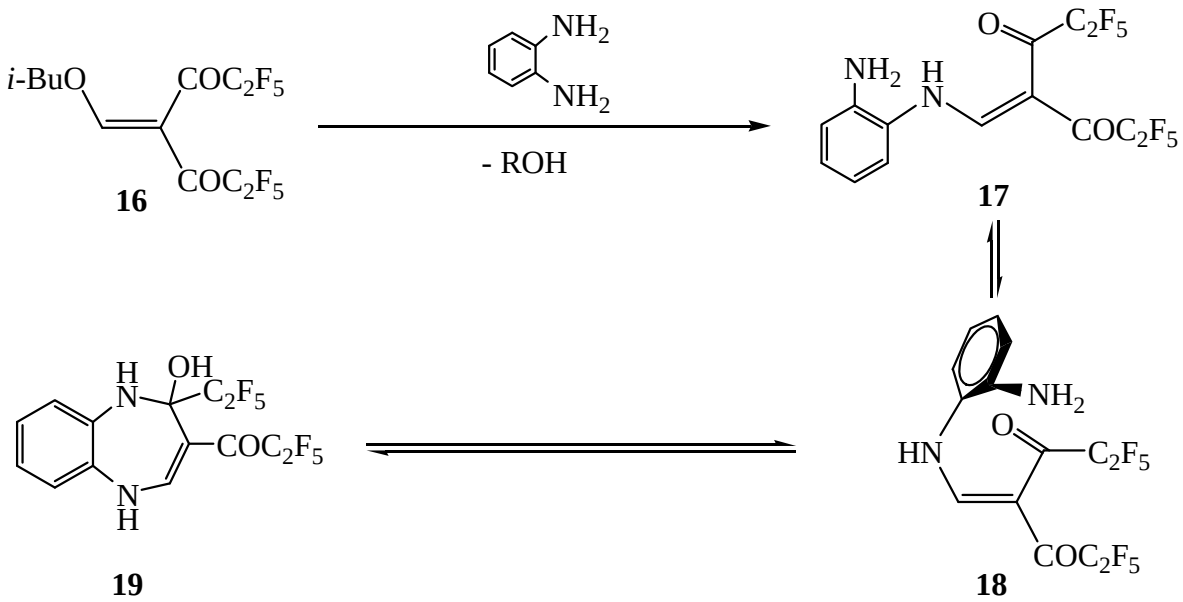
We compared the energies of cations (**11** and **14**) with the total energies of cations (**13** and **15**), respectively, and water. The process from **11** to **13** was predicted to be an exothermic reaction with a heat of reaction of -2.9 kcal/mol, while that from **14** to **15** was predicted 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 dihydrobenzodiazepionol (**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 B3LYP[16] level. The starting geometries employed for all optimizations were resulted from molecular mechanics using SYBYL[17] force field and subsequent semi-empirical

PM3[18] optimizations. The calculations for energy of intermediates were also taken with the 6-31G* basis set at B3LYP level.

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