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REACTION OF β-TRIFLUOROACETYLKETENE ACETALS AND β-TRIFLUOROACETYLVINYL ETHERS WITH 1,2-PHENYLENE-DIAMINES ACCESSING FLUORINE-CONTAINING BENZO-[*b*][1,4]DIAZEPINE DERIVATIVES: A MOLECULAR ORBITAL CALCULATION STUDY

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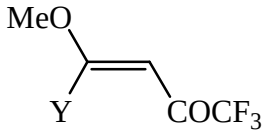
Abstract – β-Trifluoroacetylketene acetals (**1**) were found to react easily with 1,2-phenylenediamines to give dihydrobenzodiazepinols (**5a**) together with benzodiazepines (**6a**) under very mild conditions. In contrast, β-trifluoroacetyl-α-phenylvinyl ethers (**2**) and β-trifluoroacetylvinyl ethers (**3**) exclusively yielded *O*-*N* exchanged products (**9**) when they were reacted with 1,2-phenylenediamines. The factors determining product formation by the reaction of each of three similar substrates (**1**-**3**) with 1,2-phenylenediamine were elucidated on the basis of molecular orbital calculations. The dehydration processes converting dihydrobenzodiazepinols (**5** and **7**) to the corresponding benzodiazepines (**6** and **8**) are also discussed.

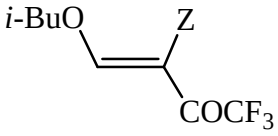
INTRODUCTION

Recently much attention has focused on developing new methodologies for the syntheses of many kinds of fluorine-containing heterocycles, as these compounds are now widely recognized as important organic materials showing specific functions and interesting biological activities.[1-4] In our preceding papers, we reported facile and convenient methods for synthesizing fluorine-containing dihydrobenzo[*b*][1,4]diazepinols and benzo[*b*][1,4]diazepines, which have remarkable anti-tumor activities,[5] from β-trifluoroacetylketene acetals[6] and β,β-bis(trifluoroacetyl)vinyl ethers.[7] In these

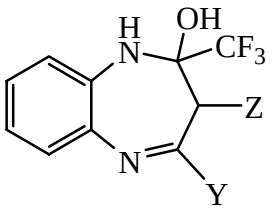
investigations, we found that β-trifluoroacetylketene dimethyl acetal (**1**) readily reacts with 1,2-phenylenediamine under very mild conditions to give 2,3-dihydro-1*H*-benzo[*b*][1,4]diazepin-2-ol (**5a**) as the major product and 3*H*-benzo[*b*][1,4]diazepine (**6a**) as the minor product. In contrast, only *O*-*N* exchanged products (**9**) were obtained by the reaction of β-trifluoroacetylvinyl *iso*-butyl ether (**3**) with 1,2-phenylenediamine. Bonacorso *et al*. reported that **9b** was the sole product of the reaction of β-trifluoroacetyl-α-phenylvinyl methyl ether (**2**) with 1,2-phenylenediamine.[8] In addition, it has been reported that 3*H*-benzo[*b*][1,4]diazepine (**6b**) is obtained by heating **2** with 1,2-phenylenediamine in the presence of acetic acid.[8] In contrast, neither heating nor acid catalysis is necessary for the reaction of **1** with 1,2-phenylenediamine to produce benzodiazepinol (**5a**) and benzodiazepine (**6a**).[6] However, no benzodiazepine derivatives were obtained even when **3** was heated with 1,2-phenylenediamine in the presence of an acid catalyst.



1 Y= MeO
2 Y= Ph



3 Z= H
4 Z= $COCF_3$



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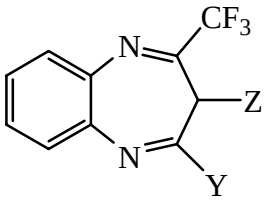

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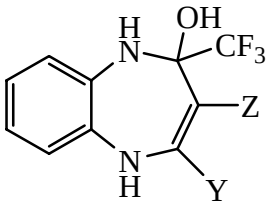

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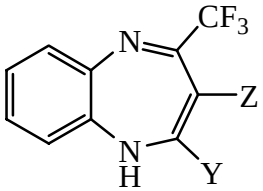

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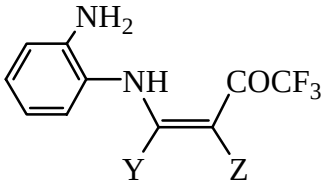


9

5 - 9	**a**	**b**	**c**	**d**
Y	MeO	Ph	H	H
Z	H	H	H	$COCF_3$

Scheme 1

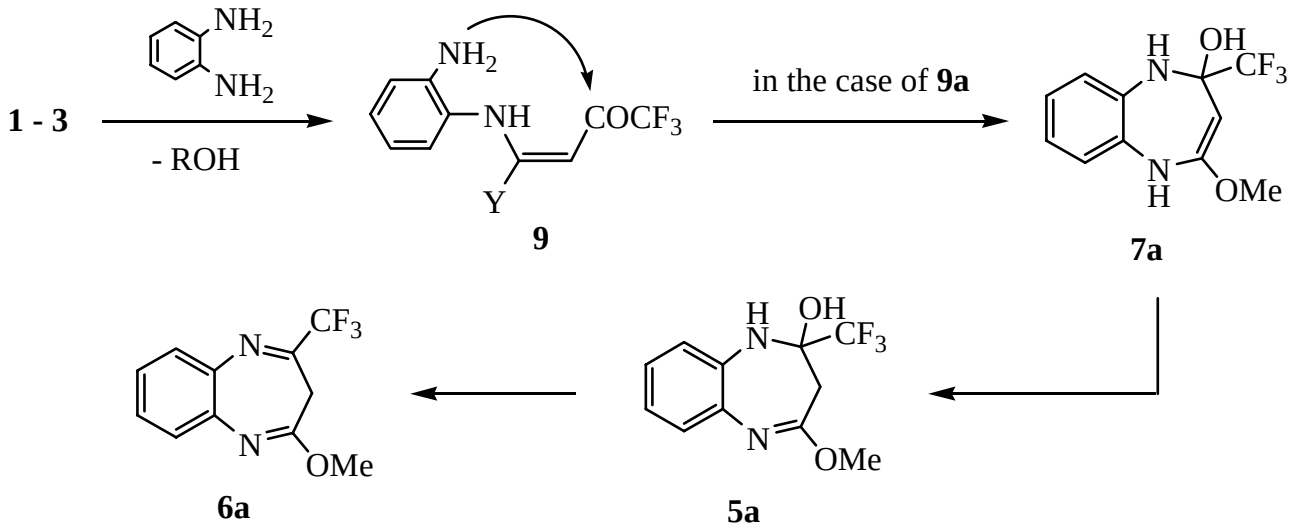
We also found that β,β-bis(trifluoroacetyl)vinyl ether (**4**) reacts with 1,2-phenylenediamine under very

mild conditions to give 2,5-dihydro-1*H*-benzo[*b*][1,4]diazepin-2-ol (**7d**).[7] Moreover, it was reported that the reaction of **4** with 1,2-phenylenediamine under microwave irradiation afforded 1*H*-benzo[*b*][1,4]diazepine (**8d**).[9] When **1** was reacted with 1,2-phenylenediamine, only **5a** and **6a** were obtained, with no formation of benzodiazepinol (**7a**) or benzodiazepine (**8a**).

Using molecular orbital calculations, we previously elucidated the reaction of β,β-bis(trifluoroacetyl)vinyl ether (**4**) with 1,2-phenylenediamine, affording benzodiazepinol (**7a**).[10] In the present report, the factors determining the products obtained by the reaction of each of three similar substrates (**1**-**3**) with 1,2-phenylenediamine are clarified using molecular orbital calculations. Also, the dehydration of dihydrobenzodiazepinols (**5** and **7**) to benzodiazepines (**6** and **8**) is discussed.

RESULTS AND DISCUSSION

Similar to β,β-bis(trifluoroacetyl)vinyl ethers,[11] β-trifluoroacetyl-α-phenylvinyl ethers,[12] and β-trifluoroacetylvinyl ethers,[13] β-trifluoroacetylketene acetals 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.[14] Consequently, the *O*-*N* exchanged product (**9a**) depicted in Scheme 1 was thought to be the initial intermediate in the reaction of β-trifluoroacetylketene dimethyl acetal (**1**) with 1,2-phenylenediamine. The theory was similar to the cases of **9b**-**d** which were supposed to be the initial intermediates in the reaction of β-trifluoroacetyl-α-phenylvinyl methyl ether (**2**), β-trifluoroacetylvinyl *iso*-butyl ethers (**3**), and β,β-bis(trifluoroacetyl)vinyl *iso*-butyl ether (**4**), respectively, with 1,2-phenylenediamine.[10]

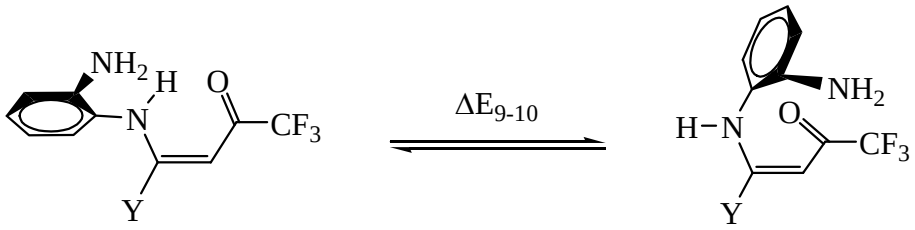


Scheme 2

The subsequent intramolecular nucleophilic addition of the aromatic NH_2 group to the trifluoroacetyl

carbonyl group in **9a** would proceed to give dihydrobenzodiazepinol **7a**, whereas a similar cyclization reaction would not take place in **9b** and **9c**. Dehydrobenzodiazepinol (**5a**) and benzodiazepine (**6a**) are thought to derive from **7a**, if the isomerization of **7a** to **5a** and the dehydration of **5a** to **6a** are possible, as shown in Scheme 2.

As an initial step to elucidate the difference in reactivity of **9a-c**, we computed the most stable structures of **9a-c** and their energies (E_9) using RB3LYP/6-31G*//RB3LYP/6-31G*. As illustrated in Scheme 3, transformation from the most stable conformers (**9**) to **10**, which are suitable for subsequent cyclization, would be required for the conversion of **9** to the corresponding dihydrobenzodiazepinols (**7**). We presumed that the ease of cyclization of **9** to **7** would be correlated with the energy difference between **9** and **10**. Structural optimization was performed for conformers (**10a-c**), and $\Delta E_{9\text{-}10}$ (E_{10}-E_9) values were calculated. Table 1 summarizes the values of $\Delta E_{9\text{-}10,}$ together with the energies of **9a-c** (E_9) and **10a-c** (E_{10}).



9 **10**

Scheme 3

Table 1. The values of E_9, E_{10} (au) and $\Delta E_{9\text{-}10}$ (kcal/mol) for **9** and **10**

9, **10**	Y	E_9	E_{10}	$\Delta E_{9\text{-}10}$
a	MeO	-985.25765	-985.23508	14.2
b	Ph	-1101.78062	-1101.76393	10.5
c	H	-870.72864	-870.70436	15.2

The largest $\Delta E_{9\text{-}10}$ was estimated for the transformation of **9c** to **10c**. This result seems to explain the extremely slow cyclization of *O-N* exchanged product **9c** to dihydrobenzodiazepinol **7c**, resulting in the reaction of β-trifluoroacetylvinyl *iso*-butyl ether (**3**) with 1,2-phenylenediamine to afford **9c** as the sole product. However, the difference in $\Delta E_{9\text{-}10}$ between **9a** and **9c** was estimated to be no more than 1 kcal/mol. Moreover, $\Delta E_{9\text{-}10}$ for **9b** is smaller than that for **9a**. These results are incompatible with the

experimental results, where **9a** cyclized easily to give dihydrobenzodiazepinol (**5a**) and benzodiazepine (**6a**) *via* **7a**,[6] while **9b** and **9c** did not cyclize to any benzodiazepine derivative under similar conditions. Therefore, the conformational change required to convert **9** to **10** is not so important energetically for the overall cyclization process from **9** to **7**. This means that the cyclization process from conformers (**10**) to dihydrobenzodiazepinols (**7**) is a key step determining whether *O-N* exchanged products **9** are converted to **7** or not.

As a second step, we tried to elucidate the transition state for the cyclization reaction from **10** to **7**. Our attempts to compute the transition state structures for the cyclization reactions of **10a-c** resulted in failure. Therefore, we focused on intramolecular frontier orbital interactions, i.e., the interactions between the nitrogen in the NH_2 group (HOMO) and the carbonyl carbon in the $COCF_3$ group (LUMO) for conformers (**10a-c**). Frontier electron densities, fr^{HOMO} at $\underline{\mathbf{N}}H_2$ and fr^{LUMO} at $\underline{\mathbf{C}}OCF_3$ for **10a-c** are shown in Table 2.

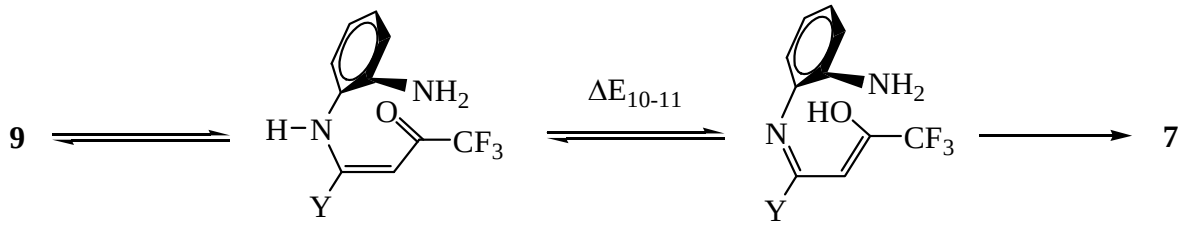
Table 2. Frontier electron densities, fr^{HOMO} at $\underline{\mathbf{N}}H_2$ and fr^{LUMO} at $\underline{\mathbf{C}}OCF_3$ on **10a-c**

	10a	**10b**	**10c**
fr^{HOMO}	0.427	0.371	0.386
fr^{LUMO}	0.341	0.215	0.391

Both fr^{HOMO} and fr^{LUMO} in **10a** are larger than those in **10b**. These results suggest that the intramolecular HOMO-LUMO interaction in **10a** is considerably greater than that in **10b**. Strong intramolecular frontier orbital interaction is expected to promote the cyclization of **10a** to **7a** under very mild reaction conditions. In contrast, intramolecular HOMO-LUMO interaction in **10b** would not be large enough to mediate the cyclization to **7b**. On the other hand, the values of fr^{HOMO} and fr^{LUMO} in **10c** are considerably larger than those in **10b**, indicating that the intramolecular HOMO-LUMO interaction in **10c** would be comparable with that in **10a**. Therefore, these data are in conflict with our experimental results where *O-N* exchanged product (**9c**) did not cyclize to dihydrobenzodiazepinol (**7c**).

It is necessary to take into account steric factors in enamine (**9**) to explain the lack of cyclization of **9c**. Steric repulsion between the methoxy group and the 2-aminophenylamino group in **9a** would assist the transformation from **9a** to **10a**. In contrast, steric repulsion promoting the conformational change from **9c**, which bears no α-substituent, to **10c** is unlikely. Difficulty in forming **10c** from **9c** is a likely reason why **9c** could not be converted to dihydrobenzodiazepinol (**7c**).

As shown in Scheme 4, an alternative reaction to go from **9** to **7** *via* enol type intermediates (**11**) is also possible. In order to estimate the relative stability of **11** compared to **10**, we computed the optimized structures of **11a-c**, and calculated the energy difference ($\Delta E_{10\text{-}11}$) between **10a-c** and the corresponding **11a-c**. The results are summarized in Table 3. In all cases, enol type intermediates (**11**) are ca. 13 - 15 kcal/mol more unstable compared with **10**. These results indicate that the cyclization of *O-N* exchanged products (**9**) to dihydrobenzodiazepinols (**7**) proceeds predominantly along the direct reaction pathway (Scheme 2).



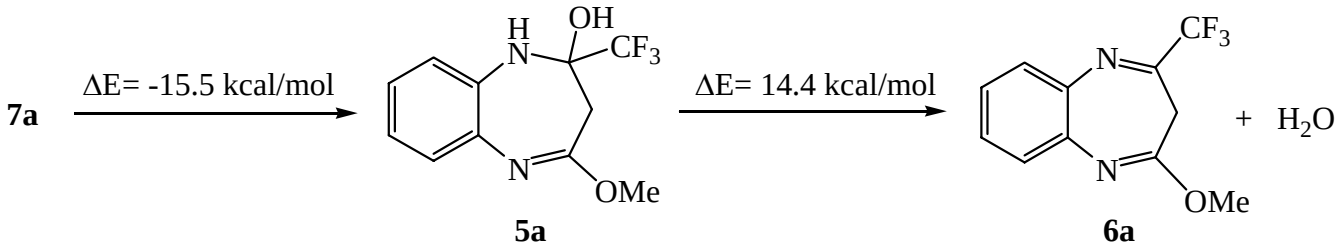
10 **11**

Scheme 4

Table 3. The values of $\Delta E_{10\text{-}11}$ (kcal/mol) and frontier electron densities, fr^{HOMO} at **N**H_2 and fr^{LUMO} at **C**$(OH)CF_3$ for **11a-c**

11	Y	Z	$\Delta E_{10\text{-}11}$ (E_{11}-E_{10})	fr^{HOMO}	fr^{LUMO}
a	MeO	H	14.4	0.408	0.725
b	Ph	H	13.4	0.407	0.320
c	H	H	14.9	0.359	0.527

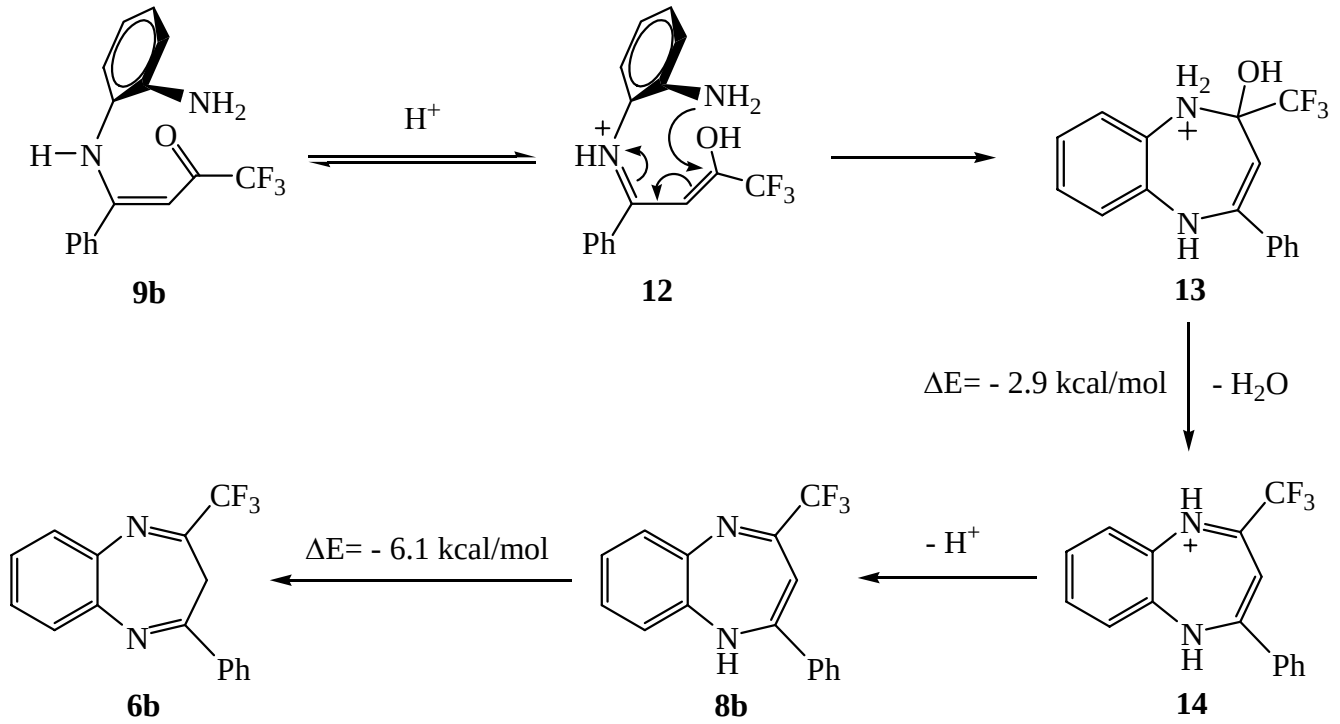
Frontier electron densities, fr^{HOMO} at **N**H_2 and fr^{LUMO} at **C**$(OH)CF_3$ for **11a-c** are listed in Table 3. It appears that intramolecular HOMO-LUMO interaction in **11a** is rather larger than that in **11b**. Thus, the trend in the intramolecular frontier orbital interaction for **11a-c** is similar to that for **10a-c**, and is compatible with the experimental results described above, even if the reaction from *O-N* exchanged products (**9**) to dihydrobenzodiazepinols (**7**) occurs partially along the reaction pathway *via* **11** (Scheme 4).



Scheme 5

To clarify the relative stability of dihydrobenzodiazepinols **5** and **7**, we computed optimized structures of **5a**,**b** and **7a**,**b** together with their energies. Our results indicate that **5a** is ca. 16 kcal/mol more stable than **7a** and, therefore, **7a** generated by cyclization of **9a** would immediately isomerize to the more stable **5a** (Scheme 5). This could explain why the reaction of β-trifluoroacetylketene dimethyl acetal (**1**) with 1,2-phenylenediamine gives dihydrobenzodiazepinol (**5a**).

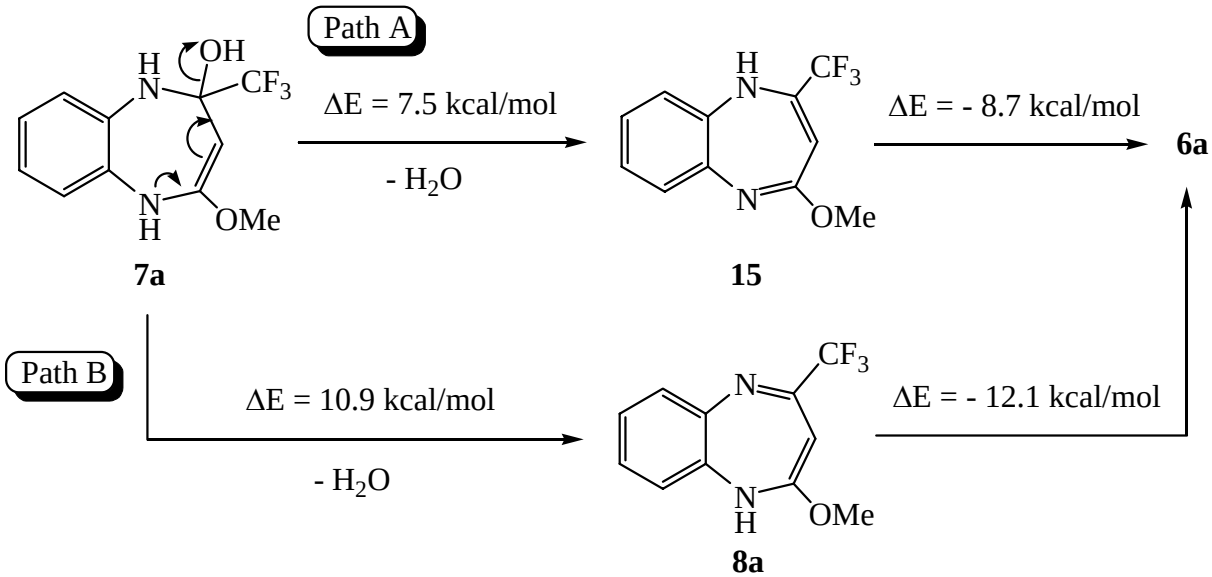
Similar to the case of **5a**, **5b** was estimated to be ca. 10 kcal/mol more stable than **7b**. Therefore, isomerization from **7b** to **5b** is thought to occur easily, and subsequent dehydration of **5b** would give **6b**, if cyclization of **9b** to **7b** is possible. However the cyclization reaction of **9b** to afford **6b** requires acid catalysis.[8] As discussed previously,[10] benzodiazepine (**6b**) would be formed from **9b** along the reaction pathway illustrated in Scheme 6. Two exothermic processes, i.e., the dehydration from cation (**13**) to **14** and the isomerization from **8b** to **6b,** are thought to be key steps in the reaction of β-trifluoroacetylvinyl ether (**2**) with 1,2-phenylenediamine affording benzodiazepine (**6b**).[8]



Scheme 6

Dehydration of dihydrobenzodiazepinol (**5a**) to benzodiazepine (**6a**) was estimated to be an endothermic reaction (14.4 kcal/mol; Scheme 5). This result is compatible with our experimental result where dehydration of **5a** to **6a** required heating (ca. 120 °C) under reduced pressure (ca. 2.5 Torr).[6] Obviously, **6a** obtained by the reaction of β-trifluoroacetylketene dimethyl acetal (**1**) with 1,2-phenylenediamine did not derive from **5a** as shown in Scheme 2, because the reaction of **1** with 1,2-phenylenediamine proceeded at ambient temperature to give **6a** together with **5a**.

Two reaction pathways from dihydrobenzodiazepinol (**7a**) to benzodiazepine (**6a**) are possible (Scheme 7). Path A requires dehydration of **7a** to benzodiazepine (**15**) and subsequent isomerization of **15** to **6a**. Path B requires conversion of **7a** to **6a** *via* benzodiazepine (**8a**). The first dehydration process in both Path A and Path B is endothermic. However, ΔE (7.5 kcal/mol) between **7a** and **15** is about 3 kcal/mol less than that between **7a** and **8a** (10.9 kcal/mol), and about 7 kcal/mol smaller than that between **5a** and **6a** (14.4 kcal/mol; Scheme 5). Dehydration of dihydrobenzodiazepinol (**7a**) arising from cyclization of **9a** to **15** would proceed partially before the isomerization of **7a** to **5a** occurs. This is a possible reason why the reaction of **1** with 1,2-phenylenediamine gives **6a** as a minor product together with **5a** under very mild conditions.



Scheme 7

CONCLUSION

On the basis of molecular orbital calculations, we can explain reasonably the preferred products formed by the individual reaction of β-trifluoroacetylketene dimethyl acetal (**1**), β-trifluoroacetyl-α-phenylvinyl methyl ether (**2**), and β-bis(trifluoroacetyl)vinyl *iso*-butyl ether (**3**) with 1,2-phenylenediamine. Intramolecular frontier orbital interaction in *O*-*N* exchanged products (**10**) formed as intermediates in the

above reactions would be a key factor determining whether the subsequent cyclization yielding dihydrobenzodiazepinols (**7**) proceeds or not. Major formation of product (**5a**) as a result of the reaction of **1** with 1,2-phenylenediamine could be rationalized by isomerization of **7a** to **5a** because of the relative thermodynamic stability of 2,3-dihydro-1*H*-benzo[*b*][1,4]diazepin-2-ol (**5a**) compared to 2,5-dihydro-1*H*-benzo[*b*][1,4]diazepin-2-ol (**7a**). The minor product (**6a**) would not derive from **5a** but would be produced from **7a** *via* 1*H*-benzo[*b*][1,4]diazepine (**15**).

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.

REFERENCES

1. R. Filler and Y. Kobayashi, 'Biomedicinal 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. E. Okada, N. Ota, T. Tomoda, M. Fujimoto, and H. Takenaka, Jpn. Kokai Tokkyo Koho, 2006-273844, 2006.
6. N. Ota, E. Okada, N. Terai, T. Miyamura, D. Shibata, and T. Sakata, *Heterocycles*, 2009, **77**, 983.
7. N. Ota, T. Tomoda, N. Terai, Y. Kamitori, D. Shibata, M. Médebielle, and E. Okada, *Heterocycles*, 2008, **76**, 1205.
8. H. B. Bonacorso, L. M. L. Marques, N. Zanatta, and M. A. P. Martins, *Synth. Commun*., 2002, **32**, 3225.
9. A. C. S. Reddy, P. S. Rao, and R. V. Venkataratnam, *Tetrahedron Lett*., 1996, **37**, 2845; A. C. S. Reddy, P. S. Rao, and R. V. Venkataratnam, *Tetrahedron*, 1997, **53**, 5847.
10. N. Ota, Y. Kamitori, T. Tomoda, N. Terai, and E. Okada, *Heterocycles*, 2009, **77**, 461.
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. M. Hojo, R. Masuda, E. Okada, H. Yamamoto, K. Morimoto, and K. Okada, *Synthesis*, 1990, 195.
15. Wavefunction, Inc.
16. A. D. Becke, *J. Chem. Phys*., 1993, **98**, 5648.
17. M. Clark, R. D. Cramer III, and N. van Opdensch, *J. Computational Chem.*, 1989, **10**, 982.
18. J. J. P. Stewart, *J. Computer Aided Molecular Design*, 1992, **6**, 69.