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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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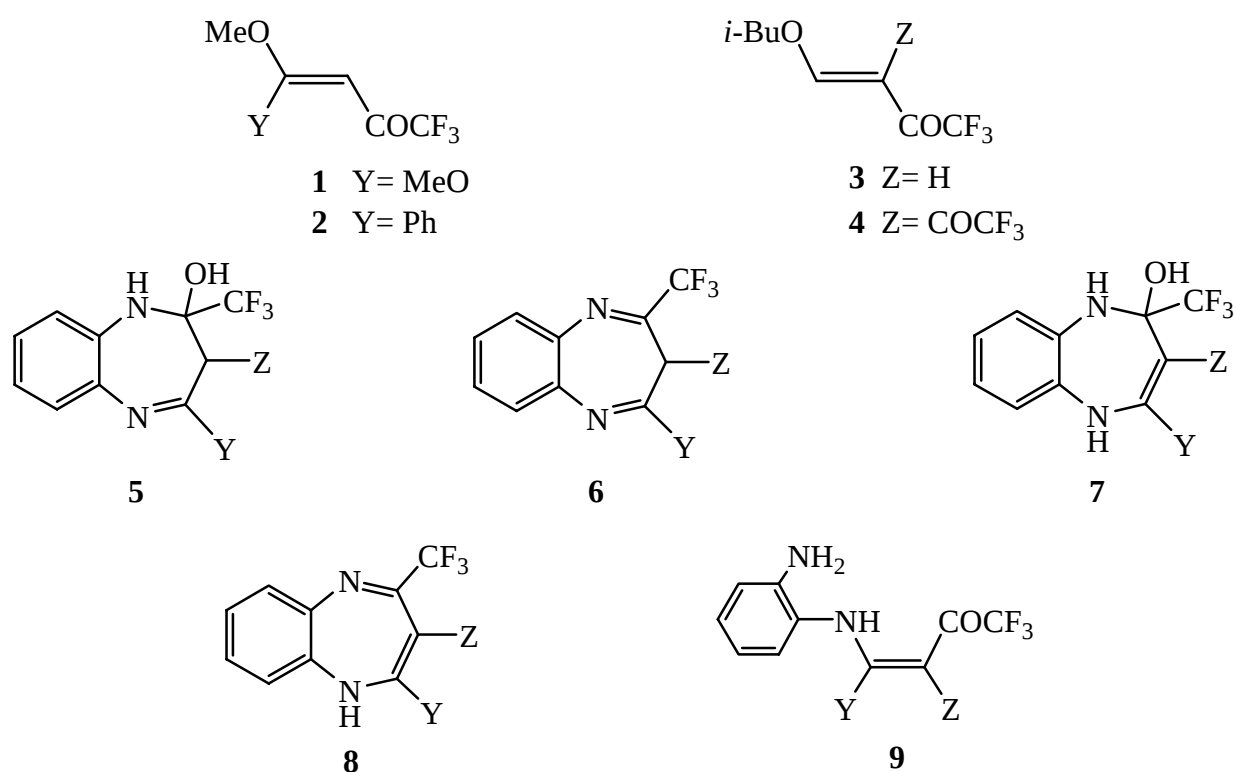
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Abstract – β -Trifluoroacetylketene acetals (**1**) were found to react easily with 1,2-phenylenediamines to give dihydrobenzodiazepinols (**5a**) together with benzodiazepines (**6a**) under very mild conditions. In contrast, β -trifluoroacetyl- α -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 acetals⁶ 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.



5 - 9	a	b	c	d
Y	MeO	Ph	H	H
Z	H	H	H	COCF ₃

Scheme 1

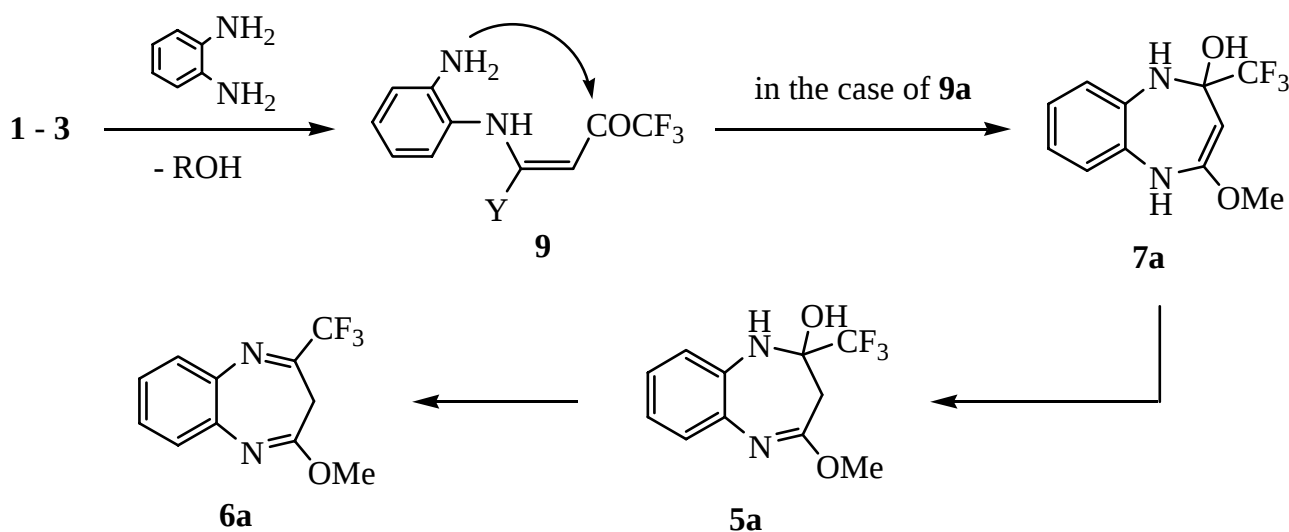
We also found that β,β -bis(trifluoroacetyl)vinyl ether (**4**) reacts with 1,2-phenylenediamine under very

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

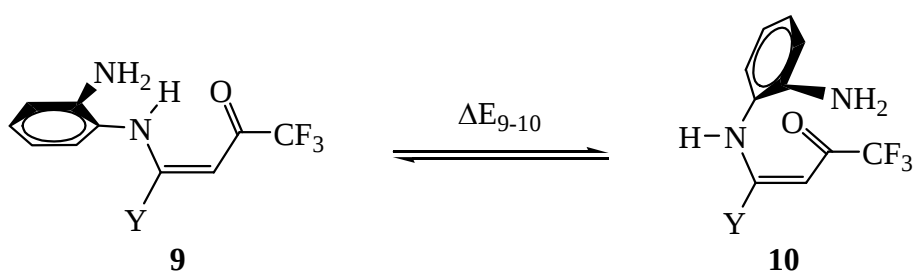


Scheme 2

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 ΔE_{9-10} ($E_{10}-E_9$) values were calculated. Table 1 summarizes the values of ΔE_{9-10} , together with the energies of **9a-c** (E_9) and **10a-c** (E_{10}).



Scheme 3

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

9, 10	Y	E_9	E_{10}	ΔE_{9-10}
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 ΔE_{9-10} 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 ΔE_{9-10} between **9a** and **9c** was estimated to be no more than 1 kcal/mol. Moreover, ΔE_{9-10} 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 NH₂ group (HOMO) and the carbonyl carbon in the COCF₃ group (LUMO) for conformers (**10a-c**). Frontier electron densities, fr^{HOMO} at NH₂ and fr^{LUMO} at COCF₃ for **10a-c** are shown in Table 2.

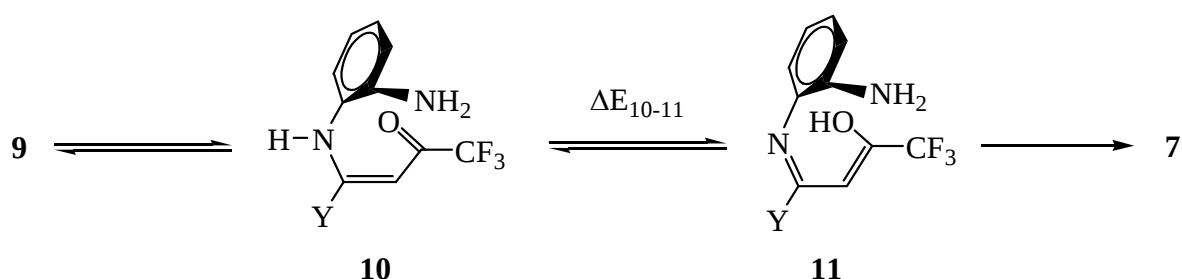
Table 2. Frontier electron densities, fr^{HOMO} at NH₂ and fr^{LUMO} at COCF₃ on **10a-c**

	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 (ΔE_{10-11}) 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).

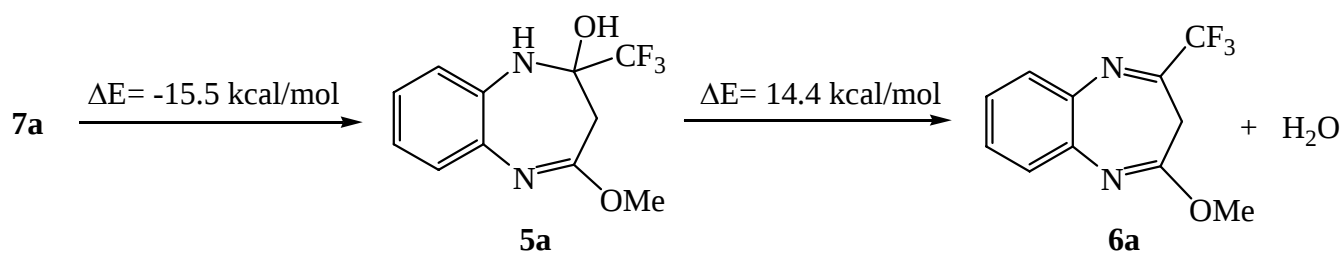


Scheme 4

Table 3. The values of ΔE_{10-11} (kcal/mol) and frontier electron densities, fr^{HOMO} at $\underline{\text{N}}\text{H}_2$ and fr^{LUMO} at $\underline{\text{C}}(\text{OH})\text{CF}_3$ for **11a-c**

11	Y	Z	ΔE_{10-11} ($E_{11}-E_{10}$)	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

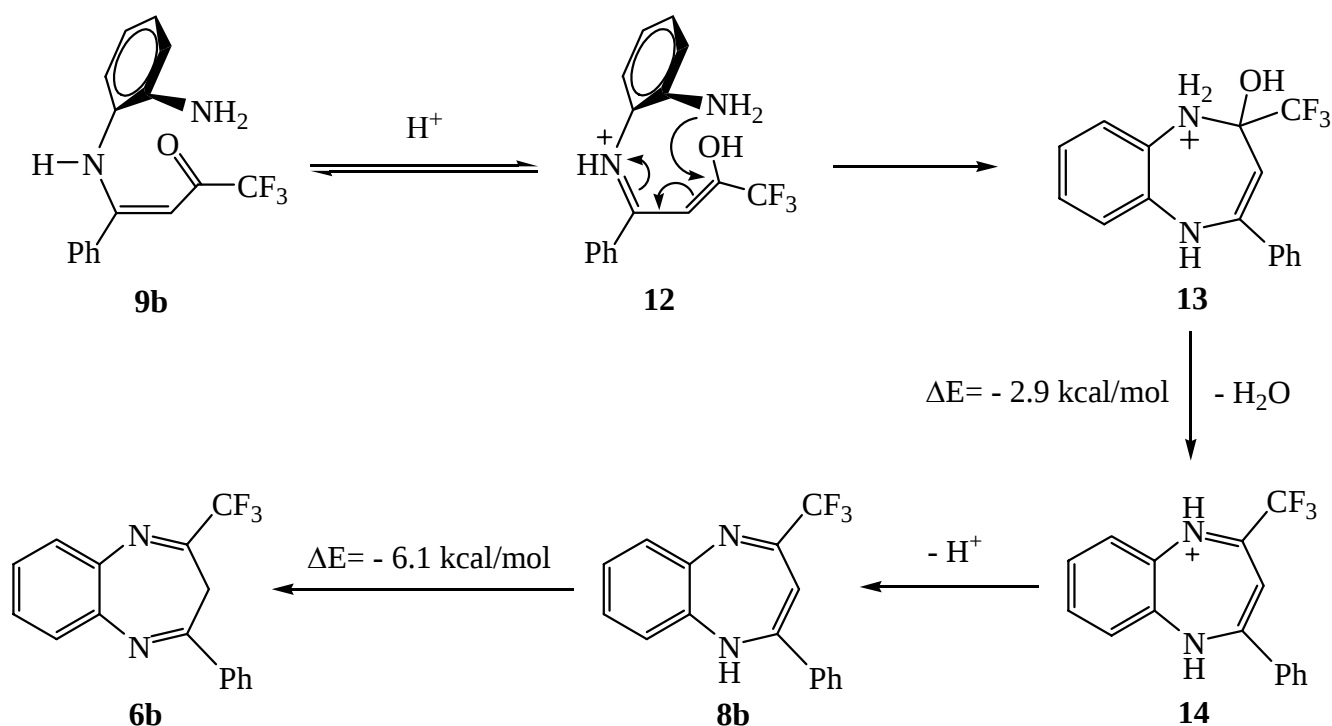
Frontier electron densities, fr^{HOMO} at $\underline{\text{N}}\text{H}_2$ and fr^{LUMO} at $\underline{\text{C}}(\text{OH})\text{CF}_3$ for **11a-c** are listed in Table 3. It appears that intramolecular HOMO-LUMO interaction in **11a** is rather larger than that in **11b**. Thus, the trend in the intramolecular 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**).

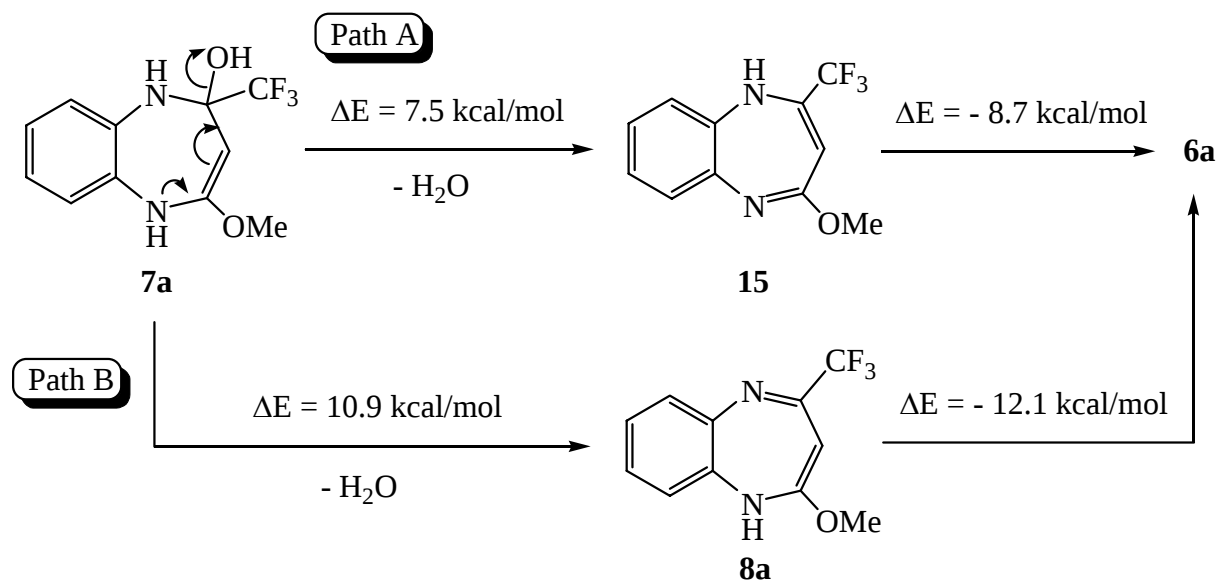
Similar to the case of **5a**, **5b** was estimated to be ca. 10 kcal/mol more stable than **7b**. Therefore, isomerization from **7b** to **5b** is thought to occur easily, and subsequent dehydration of **5b** would give **6b**, if cyclization of **9b** to **7b** is possible. However the cyclization 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 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.

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