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A MOLECULAR ORBITAL CALCULATION STUDY ON RING-OPENING REACTIONS OF FLUORINE-CONTAINING 3,4-DIHYDRO-2*H*-PYRANS WITH AMINES AND THIOLS

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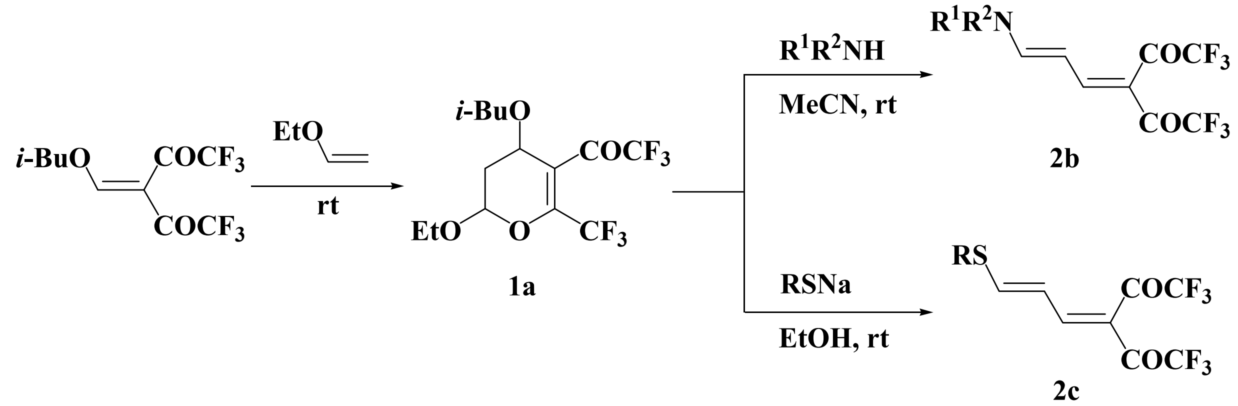
Abstract – The reactions of 5-trifluoroacetyl-6-trifluoromethyl-3,4-dihydro-2*H*-pyran (**1a**) with various amines and sodium thiolates gave the corresponding 4,4-bistrifluoroacetyl-1,3-butadienyl amines (**2b**) and sulfides (**2c**), respectively, in good yields. Our DFT calculations suggested that the elimination of isobutanol from **1a** and the subsequent electrocyclic ring-opening reaction on intermediate (**4a**) would proceed to afford 4,4-bistrifluoroacetyl-1,3-butadienyl ether (**2a**). Moreover, subsequent nucleophilic *O-N* and *O-S* exchange reactions on **2a** which gave **2b** and **2c**, respectively, were also predicted.

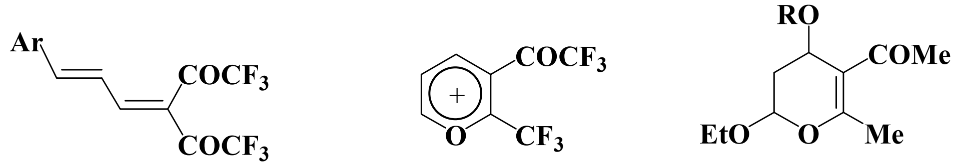
INTRODUCTION

It is well-known that various kinds of fluorine-containing heterocycles are assembled into new chemical entities given that these compounds are widely recognized as important organic materials that exhibit bioactive functions in modern drug discovery and development.[1-4] In the course of our continuous researches concerning syntheses and reactions of novel fluorine-containing heterocycles, we found that 2-ethoxy-4-isobutoxy-6-trifluoromethyl-3,4-dihydro-2*H*-pyran (**1a**) which could be easily obtained by hetero Diels-Alder reaction of 1,1,1,5,5,5-hexafluoro-3-(isobutoxyallylidene)pentane-2,4-dione with ethyl vinyl ether,[5] reacted with various amines and sodium thiolates under very mild conditions to give the corresponding 4,4-bistrifluoroacetyl-1,3-butadienyl amines (**2b**)[6] and sulfides (**2c**),[7] respectively, in good yields (Scheme 1). Both dienes, **2b** and **2c**, are versatile building blocks to access a variety of novel fluorine-containing heterocycles. Hence, these ring-opening reactions depicted in Scheme 1 are assumed to be the key steps to construct a wide range of novel fluorine-containing heterocyclic systems.



Scheme 1

Recently, we reported a similar ring-opening reaction of **1a** with aromatic compounds in refluxing trifluoroacetic acid affording 4,4-bis(trifluoroacetyl)-1,3-butadienylated aromatic compounds (**2d**) selectively.[8] Formation of **2d** was reasonably explained by the mechanism including pyrylium (**3**) as a key intermediate which was afforded by the protonation on alkoxy oxygens of **1a** under strongly acidic conditions (Figure 1).[9] In contrast to this, it has been considered that **3** is not an inferred intermediate in the present reaction of **1a** giving **2b** and **2c** due to the strongly basic conditions.



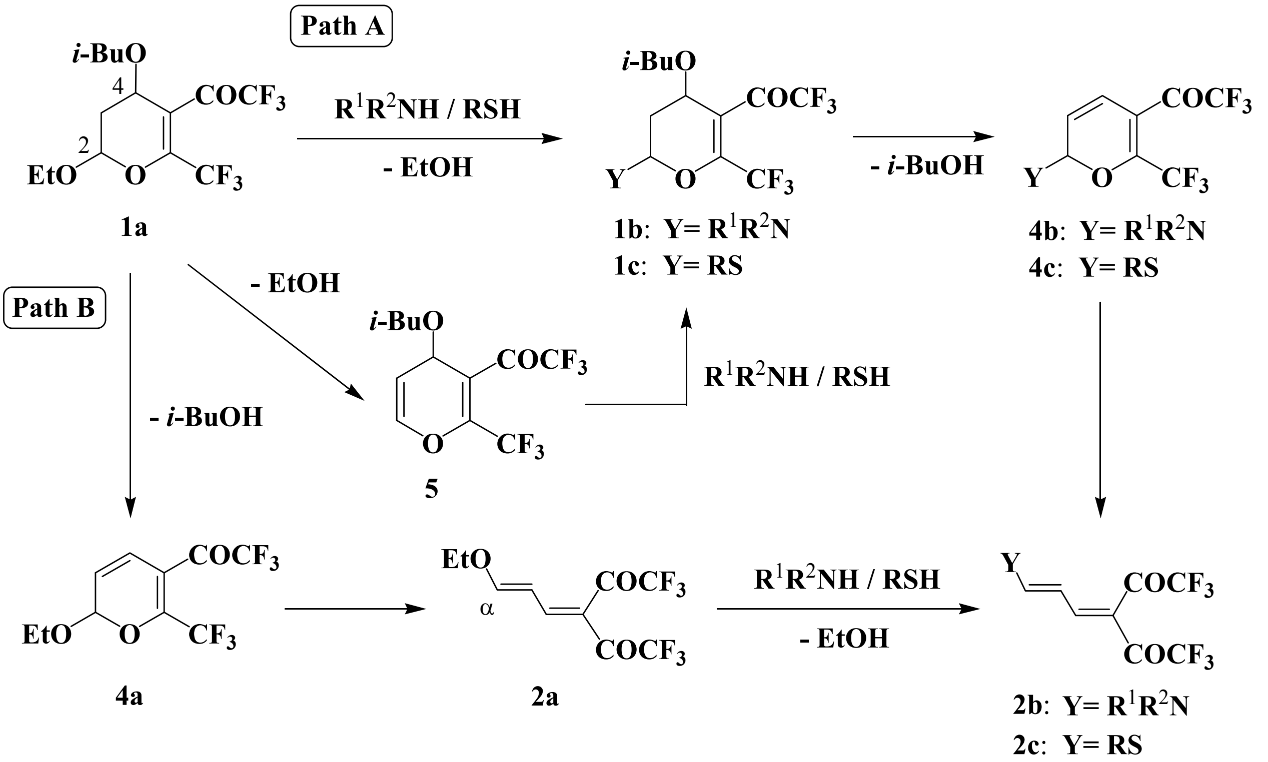
2d: **Ar= aromatic ucleus** **3** **1aa'**: **R= Et**
1ab': **R=** ***i*****-Bu**

Figure 1

Here we wish to report the molecular orbital calculation study for these ring-opening reactions of dihydropyran (**1a**) with amines and thiols. Probable pathways from **1a** to the dienes, **2b** and **2c**, were examined on the basis of DFT calculations to clarify the mechanism of this reaction. Moreover, the contrastive reactivity of non-fluorinated dihydropyran (**1aa'**) with amines under the similar conditions resulted in the complete recovery of **1aa'**[6] was also elucidated (Figure 1).

RESULTS AND DISCUSSION

The present reaction of dihydropyran (**1a**) providing dienes is assumed to propose two routes as shown in Scheme 2. In Path A, direct nucleophilic substitution by amines and thiols at C-2 of **1a** or elimination-addition processes via 4*H*-pyran (**5**) gives the corresponding intermediates, **1b** and **1c**, respectively. The following elimination of isobutanol from **1b** and **1c**, and subsequent electrocyclic ring-opening reaction on 2*H*-pyrans (**4b**,**c**) affords the dienes, **2b** and **2c**, respectively. On the other hand, a preceding elimination of isobutanol from **1a** gives 2*H*-pyran (**4a**), which undergoes electrocyclic ring-opening to afford butadienyl ether (**2a**) in Path B. The nucleophilic *O-N* and *O-S* exchange reactions occur at α-position of **2a** successively to afford **2b** and **2c**, respectively.



Scheme 2

First, we carried out structural optimization of the substrate, **1a**, and the intermediate, **5**, using RB3LYP/6-31G* as for the Path A. The results are summarized in Figure 2 where the lengths of C-C bond comprising the each pyran rings of **1a** and **5** are indicated together with their energy values. The frontier electron densities of LUMO (f_r^N) on some ring carbons of **1a** and **5**, and the LUMO levels of these two pyrans are also described in Figure 2. Extremely small f_r^N (0.011) at C-2 less than that (0.061) at C-4 on **1a** indicates that nucleophiles hardly attack **1a** at C-2. As for the energy profiles of the substitution at C-4 and C-2 of **1a,** which are giving **1b'**, **1c'**, and **1ba**, **1ca**, respectively, the results of model calculations employing dimethylamine and methanethiol are shown in Scheme 3.[10] All of these

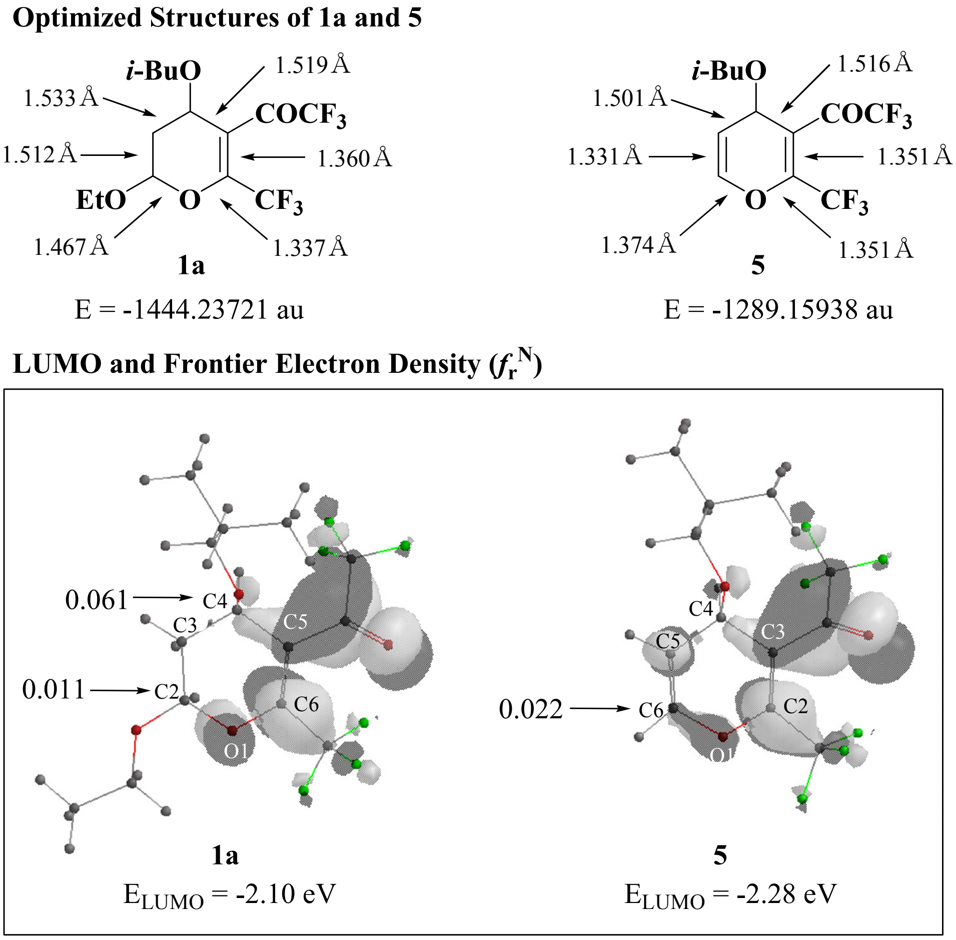
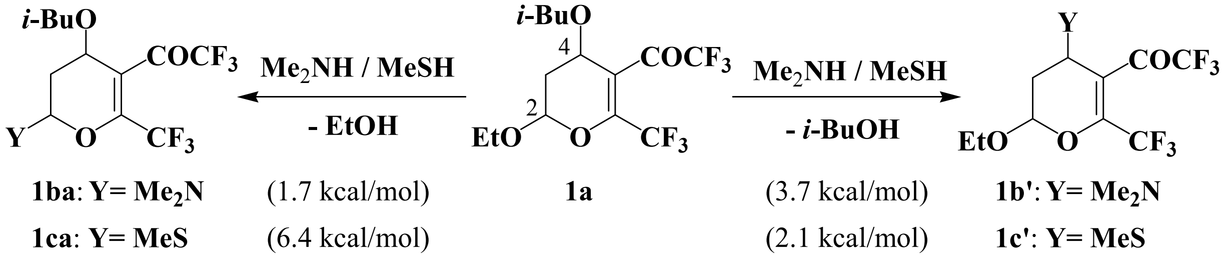


Figure 2

substitutions are predicted to be endothermic processes demanding external energy exhibited in parenthesis. These energy values suggest the probability of substitutions at C-4 in addition to C-2 and, especially in the case of the reaction of **1a** with methanethiol, the C-4 substitution giving **1c'** proceeds preferentially over the C-2 substitution affording **1ca**, even if the direct substitution at C-2 on **1a** affording **1ca** is possible. However the products corresponding to **1b'**, **1c'** and any products derived from them could not be detected in the crude materials of the reaction of **1a** with amines and thiols. Hence, the above results indicate that the direct substitution on **1a** giving **1b** and **1c** would be disallowed.



Scheme 3

Two kinds of courses are regarded as tentative dealcoholization step of **1a**. One is the ethanol elimination affording 4*H*-pyran (**5**) and the other is the isobutanol elimination affording 2*H*-pyran (**4a**). To clarify which type of the elimination occurred preferentially, we also carried out calculations as for **4a** (Figure 3).

The results indicate that the elimination reactions from **1a** to **5** and **4a** take place endothermically to absorb 27.3 kcal/mol and 19.3 kcal/mol, respectively. Thus the energy difference of ca. 8 kcal/mol between these two processes suggests that the elimination of isobutanol from **1a** giving 2*H*-pyran (**4a**) would proceed exclusively. Moreover, f_r^N no more than 0.022 at C-6 on **5** (Figure 2) predicts that nucleophilic addition to **5** affording **1b** and **1c** hardly occurs even if **5** formed to some extent. Therefore, elimination-addition route via **5** is also considered to be impossible process. Based on the above results, we can conclude that the reactions of **1a** giving **2b** and **2c** do not proceed along Path A.

Next, an examination about Path B should be discussed. As mentioned in the preceding investigation for Path A, the first elimination step from dihydropyran (**1a**) to 2*H*-pyran (**4a**) would occur predominantly instead of the forming of **5**. In order to elucidate the second step, we estimated the transition state structure on the electrocyclic ring-opening from **4a** to **2a**. In Figure 3, the optimized transition state structure (**TS4a**) and its energy are illustrated together with the optimized structures of butadienyl ether (**2a**) and 2*H*-pyran (**4a**) with their energies. Additionally, the steric structures of **4a**, **TS4a** and **2a** also provided on the results of IRC calculations of transition state (**TS4a**) obviously shows the formation of *trans*-isomer of **2a** (*s-cis* form) via **TS4a** (Figure 4).[11] According to these data, activation energy of this ring-opening is estimated to be 12.2 kcal/mol, and it is also predicted that this ring-opening to **2a** (*s-trans* as a final form) takes place exothermically to release 0.2 kcal/mol. This activation energy is regarded as

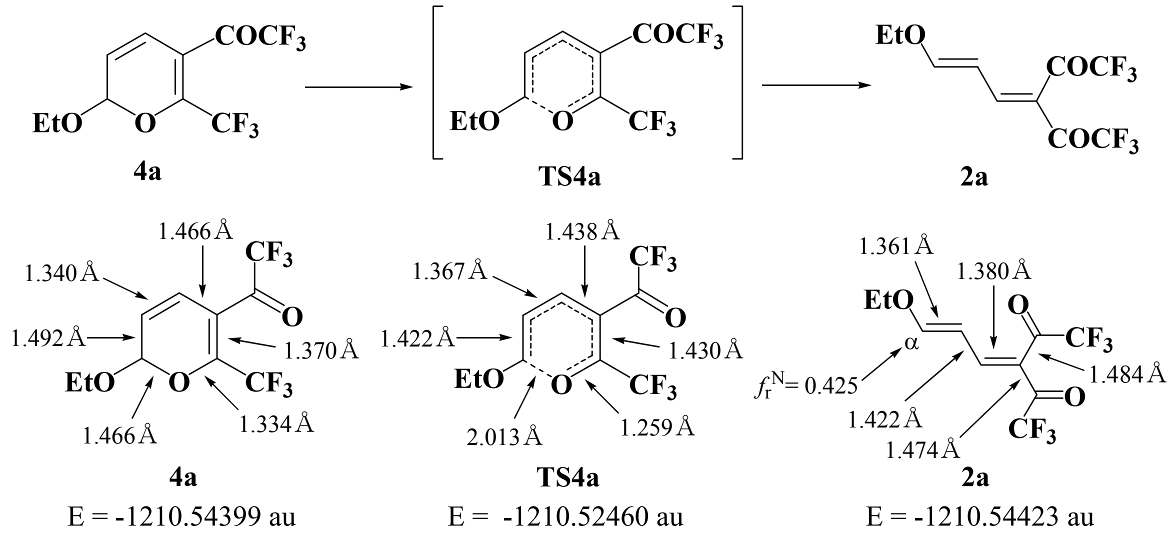


Figure 3

relatively low, which suggests that this ring-opening reaction would occur smoothly under the very mild conditions as shown in Scheme 1.

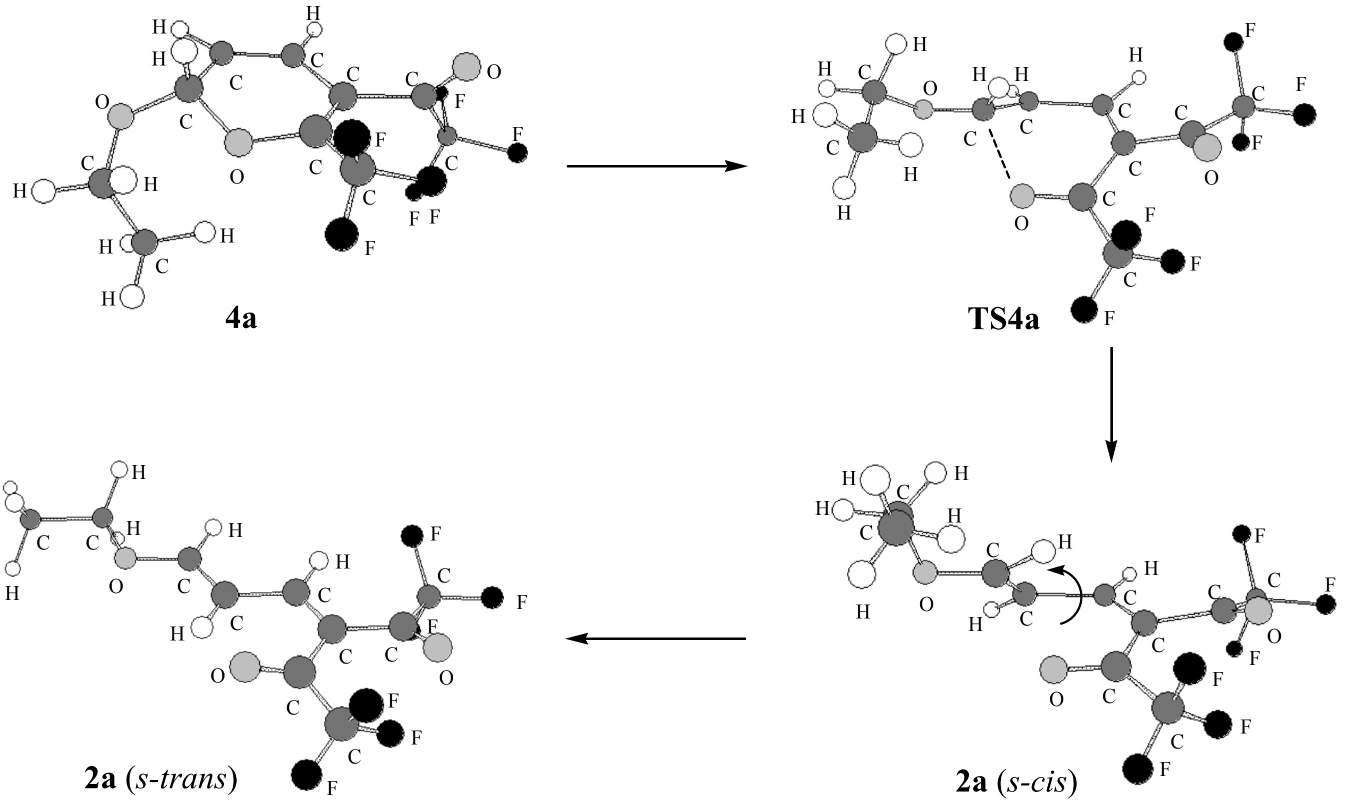
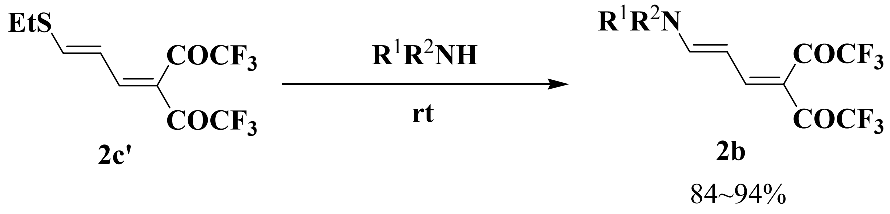


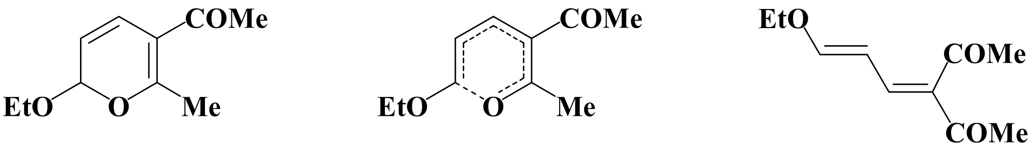
Figure 4

The subsequent substitution from butadienyl ether (**2a**) to the corresponding amine (**2b**) and sulfide (**2c**) are assumed to be easily achievable since f_r^N on C-α of **2a** is calculated as 0.425 which is enough large value to promote the nucleophilic attack of amines and thiols to that position. Additionally, the analogous successful substitution (*S-N* exchange reaction) on ethyl butadienyl sulfide (**2c'**)[12] under the mild conditions is also consistent with an implication of the calculational study on this simple processes from **2a** to **2b** and **2c** (Scheme 4).[13] Consequently, Path B is concluded to be a reasonable mechanism for the present reaction of dihydropyran (**1a**) giving the corresponding butadienyl amines (**2b**) and sulfides (**2c**).



Scheme 4

Lastly, we also examined by conducting calculations as to the non-fluorinated dihydropyrans (**1aa'**,**ab'**), 2*H*-pyran (**4a'**), transition state (**TS4a'**), and butadienyl ether (**2a'**) to emphasize the uniqueness about the reaction of the fluorinated dihydropyran (**1a**) (Figure 5). The both elimination reactions on **1aa'** and **1ab'** affording **4a'** were estimated to be endothermic processes with 17.4 kcal/mol and 17.7 kcal/mol, respectively. Thus these eliminations are assumed to proceed readily similar to the corresponding step of **1a** (19.3 kcal/mol).[14] However, the required energy of activation for the step of the ring-opening of 2*H*-pyran (**4a'**) giving butadienyl ether (**2a'**) is calculated as 16.8 kcal/mol, which is ca. 4 kcal/mol higher than the corresponding reaction of **4a**. Moreover, **2a'** was calculated to be 4.0 kcal/mol less stable than **4a'**. In spite of the adoption of the same conditions which promotes the successful conversion of **1a** to **2b**, these unfavorable factors would be believed to be the significant reasons for the failure on the reaction of **1aa'** with amines.



4a' E= -615.135574 au

TS4a' E= -615.110344 au

2a' E= -615.129121 au

Figure 5

CONCLUSION

On the basis of our DFT calculation results, we could have presented the reasonable mechanism for the ring-opening on the reaction of dihydropyran (**1a**) affording the corresponding butadienyl amines (**2b**) and sulfides (**2c**). Our study shows that the elimination of isobutanol from **1a** and the subsequent electrocyclic ring-opening on intermediate (**4a**) give 4,4-bistrifluoroacetyl-1,3-butadienyl ether (**2a**) initially, and the following nucleophilic *O-N* and *O-S* exchange reactions on α-carbon of **2a** afford **2b** and **2c**, respectively. In contrast, the endothermic ring-opening of **4a'** to **2a'** requires relatively high activation energy, which would be the important factor why non-fluorinated dihydropyran (**1aa'**) did not afford the corresponding butadienyl amines.

Based on the novel knowledge given by a series of our studies regarding **1a**, further works are under progress on the syntheses of novel fluorine-containing heterocycles, especially, using butadienyl amines (**2b**) and sulfides (**2c**) as building blocks.

COMPUTATIONAL METHODS

All calculations employed in this paper were accomplished using the computer programs packages PC

SPARTAN 02 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 transition state geometries and their energies were also taken with the 6-31G* basis set at B3LYP level.

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10. The energies of **1ba**, **1b'**, **1ca**, and **1c'** were calculated as followings; **1ba**: -1424.36316 au; **1b'**: -1345.73141 au; **1ca**: -1727.89121 au; **1c'**: -1649.26950 au.
11. Since the ring-opening process from **4a** to **2a** (*s-cis* form) and the rotation process from **2a** (*s-cis* form) to **2a** (*s-trans* form) are independent to each other, IRC calculation on **TS4a** could not reproduce the latter rotation process.
12. Frontier electron density (f_r^N) at α-position of this compound was calculated as 0.456.
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14. Similar to the case of **1a**, the preceding substitutions at C-2 of **1aa'** and **1ab'** (Path A type) were predicted to be disallowed [f_r^N at C-2 are 0.023 (**1aa'**) and 0.022 (**1ab'**), and the 2*H*-pyran (**4a'**) formation is ca. 7 kcal/mol less endothermic than the corresponding 4*H*-pyran formation].
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