

Article

Computational Study on the Acid Catalyzed Reactions of Fluorine-Containing 2,4-Dialkoxy-3,4-dihydro-2H-pyrans with Aromatic Compounds

Norio Ota ¹, Yasuhiro Kamitori ^{2,*}, Ryusuke Shirai ³, Mizuki Hatakenaka ² and Etsuji Okada ^{2,*}

¹ Graduate School of Science and Technology, Kobe University, Rokkodai-cho, Nada-ku, Kobe 657-8501, Japan; E-Mail: norio.ota@shionogi.co.jp

² Department of Chemical Science and Engineering, Graduate School of Engineering, Kobe University, Rokkodai-cho, Nada-ku, Kobe 657-8501, Japan; E-Mail: 119t453t@stu.kobe-u.ac.jp

³ Department of Chemical Science and Engineering, Faculty of Engineering, Kobe University, Rokkodai-cho, Nada-ku, Kobe 657-8501, Japan; shirai@s-micro.com

* Authors to whom correspondence should be addressed; E-Mails: kamitori@kobe-u.ac.jp (Y.K.); okaetsu@kobe-u.ac.jp (E.O.); Tel.: +81-78-803-6163; Fax: +81-78-803-6163.

Received: 14 January 2012; in revised form: 7 February 2012 / Accepted: 13 February 2012 /

Published: 24 February 2012

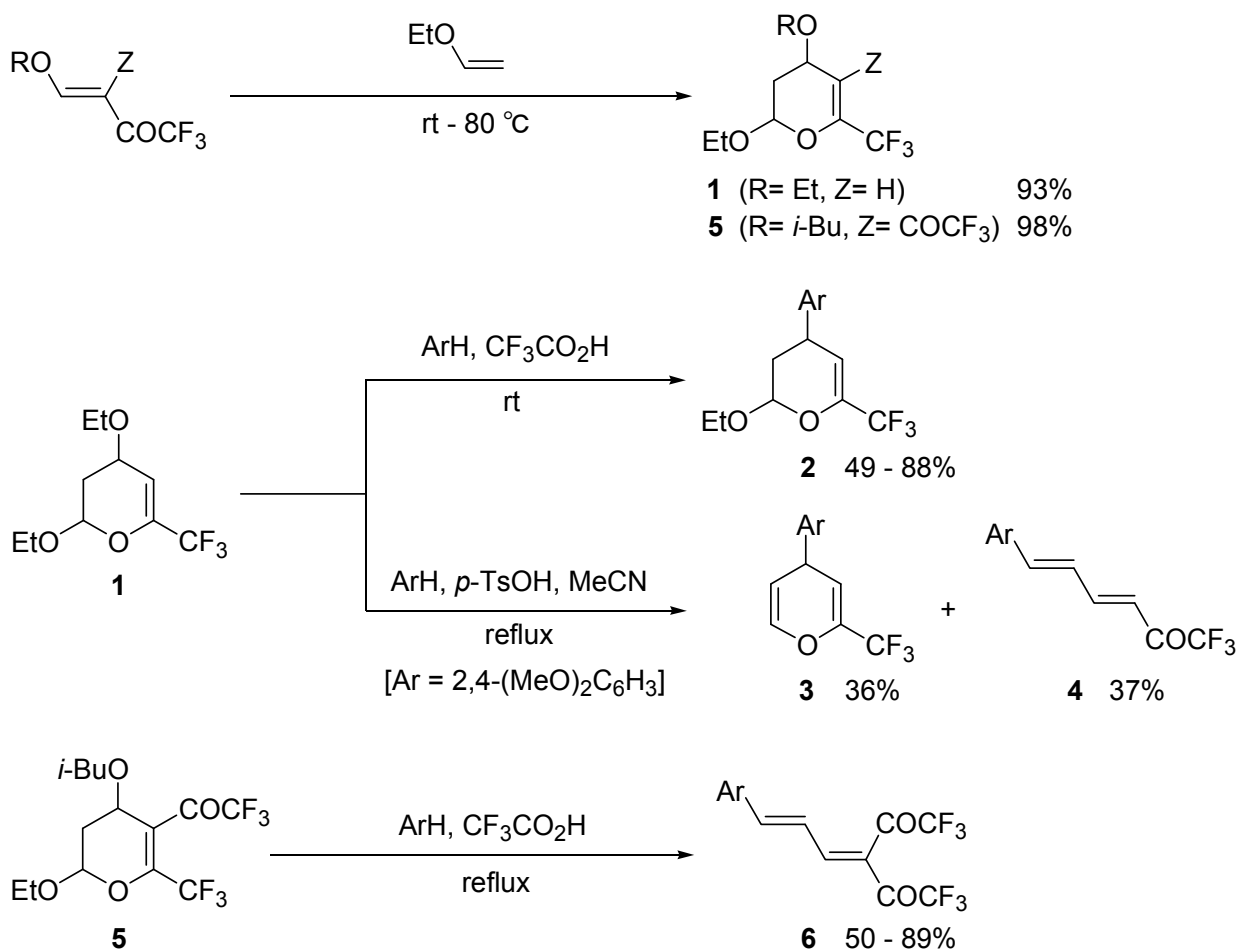
Abstract: The reaction of 2,4-diethoxy-6-trifluoromethyl-3,4-dihydro-2H-pyran (**1**) with aromatic compounds in refluxing acetonitrile in the presence of *p*-toluenesulfonic acid gave the mixture of 4-aryl-2-trifluoromethyl-4H-pyrans (**3**) and 6-aryl-1,1,1-trifluorohexa-3,5-dien-2-ones (**4**). In contrast, the same reaction carried out in trifluoroacetic acid at ambient temperature afforded 4-aryl-2-ethoxy-6-trifluoromethyl-3,4-dihydro-2H-pyrans (**2**) selectively. These two types of reactions giving quite different products under each condition were studied on the basis of DFT calculations. Moreover, the proposed mechanism for the reaction of 5-trifluoroacetyl-6-trifluoromethyl-3,4-dihydro-2H-pyran (**5**) with aromatic compounds affording butadiene derivatives (**6**) exclusively was also discussed based on the calculations and comparison with the reactivity of pyrylium intermediate (**7**).

Keywords: fluorine-containing dihydropyrans; fluorine-containing 1,3-butadienes; acid catalyzed reaction; DFT calculation

1. Introduction

In recent years, a number of researches have been reported about the development of new methodologies for syntheses of various kinds of fluorine-containing heterocycles. These compounds have put emphasis on the interest of high biological activities especially in life-science fields due to the unique character that could contribute to the exploration of new active ingredients [1–4]. In the course of our researches concerning syntheses and reactions of novel fluorine-containing heterocycles, we found that 2,4-diethoxy-6-trifluoromethyl-3,4-dihydro-2*H*-pyran (**1**) prepared in a simple step of hetero-Diels–Alder reaction of 4-ethoxy-1,1,1-trifluorobut-3-en-2-one with ethyl vinyl ether [5] reacted with aromatic compounds in trifluoroacetic acid at ambient temperature to give 4-aryl-2-ethoxy-6-trifluoromethyl-3,4-dihydro-2*H*-pyrans (**2**) as a sole product (Scheme 1) [6]. In contrast to this, it was found that the reaction of **1** with 1,3-dimethoxybenzene in refluxing acetonitrile in the presence of catalytic amounts (0.3 equiv.) of *p*-toluenesulfonic acid afforded *ca.* 1:1 mixture of the corresponding 4-aryl-2-trifluoromethyl-4*H*-pyrans (**3**) and the ring-opening product, 6-aryl-1,1,1-trifluorohexa-3,5-dien-2-ones (**4**) [6]. Similar ring-opening reaction of fluorine-containing dihydro-2*H*-pyrans giving 6-aryl-1,1,1,5,5,5-hexafluoro-3-[(*E*)-3-propylidene]pentane-2,4-diones (**6**) was also found in the reaction of 2-ethoxy-4-isobutoxy-5-trifluoroacetyl-6-trifluoromethyl-3,4-dihydro-2*H*-pyran (**5**) [7] with aromatic compounds in refluxing trifluoroacetic acid [8].

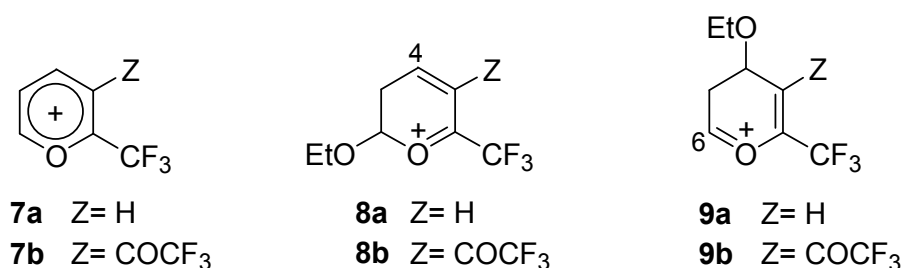
Scheme 1. Acid catalyzed reactions of 2,4-dialkoxy-3,4-dihydro-2*H*-pyrans with aromatic compounds.



Derivatives having the skeletons of dihydropyrans (**2**), 4*H*-pyrans (**3**), and 1,3-butadienes (**4** and **6**) have a high potential use as synthetic intermediates to access a variety of heterocycles [9–15]. Hence, highly important practices for the constructions of various kinds of novel fluorine-containing heterocyclic systems would be provided by the above reactions of dihydropyrans, **1** and **5**.

As we proposed in our previous report [16], the selective formation of dihydropyrans (**2**) from **1** and of butadiene derivatives (**6**) from **5** could be explained by the kinetically controlled reactions of pyrylium (**7a**) at C-4 and the thermodynamically controlled reaction of **7b** at C-6, respectively (Figure 1). Such pyryliums (**7a,b**) are assumed to form easily from **1** and **5** in the strong acid, trifluoroacetic acid. Moreover, the unexpected formation of **7a** in the course of the reaction of dihydropyran (**1**) giving 4*H*-pyrans (**3**) and butadiene derivatives (**4**) is also figured out under weaker acidic conditions such as the presence of catalytic *p*-toluenesulfonic acid in refluxing acetonitrile. In this case, it is probable that **3** and **4** are directly derived from 4-cation (**8a**) and 6-cation (**9a**), respectively, which are the precursors of pyrylium (**7a**).

Figure 1. Cations **7a,b**, **8a,b**, and **9a,b**.



Here we wish to report our DFT calculation study for these acid catalyzed reactions of dihydropyrans, **1** and **5**, with aromatic compounds. The mechanisms giving 4*H*-pyrans (**3**) and 1,3-butadienes (**4**) from **1** in the presence of *p*-toluenesulfonic acid catalyst were elucidated by making use of benzene as a model of aromatic compounds. Additionally, the pathways via cations, **8a** and **9b**, for the reactions of **1** and **5** in trifluoroacetic acid giving dihydropyrans (**2**) and 1,3-butadienes (**6**), respectively, were also examined to support the proposed mechanisms via pyryliums [16] further.

2. Computational Method

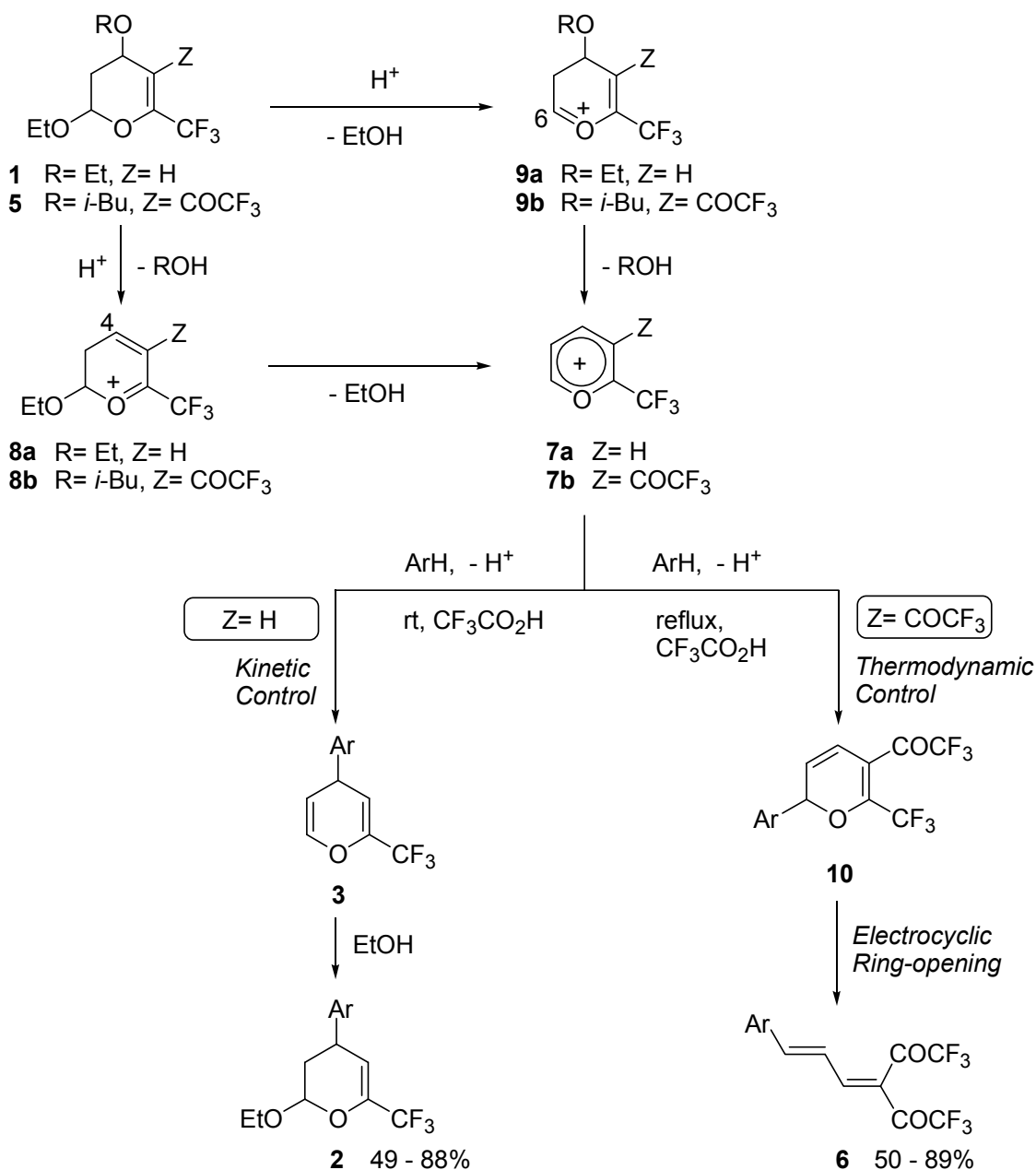
All calculations employed in this paper were accomplished by making use of the computer programs packages PC SPARTAN 02 and PC SPARTAN 04 [17]. All calculations for geometrical optimizations were performed with the 6-31G* basis set at B3LYP level [18]. The starting geometries employed for all optimizations were resulted from molecular mechanics using SYBYL [19] force field and subsequent semi-empirical PM3 [20] optimizations. The calculations for transition state geometries and their energies were also taken with the 6-31G* basis set at B3LYP level.

3. Results and Discussion

In trifluoroacetic acid, pyryliums (**7a,b**) are assumed to form from **1** and **5** via 4-cations (**8a,b**) or 6-cations (**9a,b**) as illustrated in Scheme 2. As we proposed in previous report [16], the selective formation of dihydropyrans (**2**) from **1** and of butadiene derivatives (**6**) from **5** could be reasonably

explained by the kinetically controlled reaction of pyrylium (**7a**) with aromatic compounds giving the precursor, 4*H*-pyrans (**3**) and the thermodynamically controlled reaction of **7b** with aromatic compounds affording the intermediate, 2*H*-pyrans (**10**), respectively (Scheme 2).

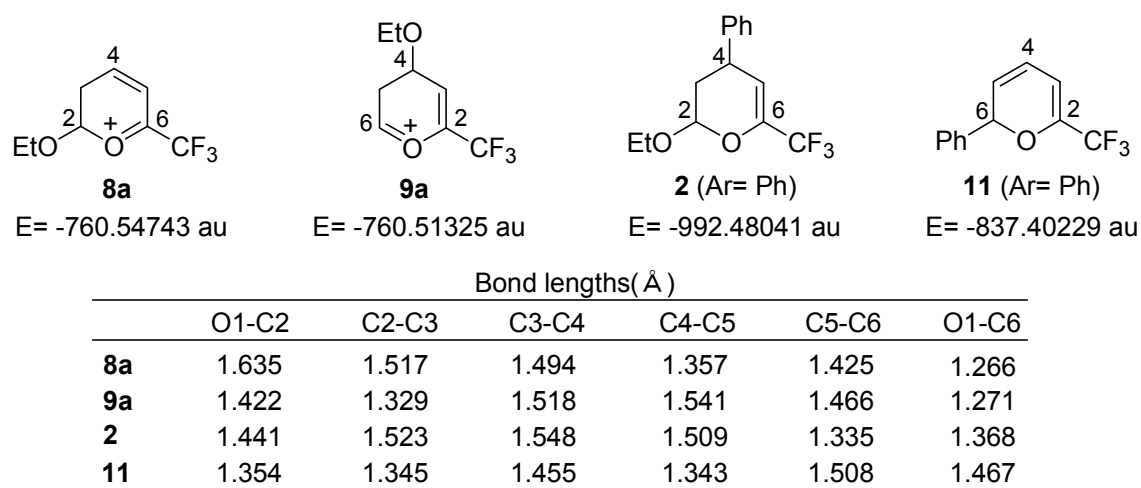
Scheme 2. Proposed reaction paths for the acid catalyzed reactions of dihydropyrans (**1** and **5**) with aromatic compounds.



Meanwhile, the formation of pyrylium (**7a**) was hardly considered to occur in the reaction of dihydropyran (**1**) with aromatic compounds giving 4*H*-pyrans (**3**) and butadiene derivatives (**4**) under weaker acidic conditions such as the presence of catalytic *p*-toluenesulfonic acid in acetonitrile. In this case, the alternative pathways in which **3** and **4** are directly derived from 4-cation (**8a**) and 6-cation (**9a**), respectively, are possible. We figured out the optimized structures of **8a** and **9a** using RB3LYP/6-31G* as depicted in Figure 2 together with the result for dihydropyran (**2**) to confirm these reaction pathways.

The results exhibit that 4-cation (**8a**) is *ca.* 21 kcal/mol more stable than 6-cation (**9a**). This value accounts for the exclusive formation of **8a** in the presence of acid catalyst, which suggest that 1,3-butadienes (**4**) are not derived from **9a**. On the other hand, the reaction of **8a** with aromatic compounds giving **2** followed by the elimination of ethanol from **2** can afford 4*H*-pyrans (**3**). According to the energy value for **2** (Ar = Ph) and our previous calculation results for **3** (Ar = Ph) [16,21], the latter elimination process from **2** to **3** is estimated to be an endothermic step with *ca.* 27 kcal/mol, which would negatively affect the conversion of **2** to **3** even if the reaction is carried out in refluxing acetonitrile. Though the de-ethanolization on 4-cation (**8a**) giving pyrylium (**7a**) [22] is also computed to be an endothermic process, the required external energy is no more than 11.3 kcal/mol. It means this elimination reaction is presumed to proceed readily in refluxing acetonitrile. Therefore, the above results strongly suggest the formation of 1,3-butadienes (**4**) and 4*H*-pyrans (**3**) via pyrylium (**7a**). The conversion from **1** to pyrylium (**7a**) is noteworthy in spite of the conditions using only a catalytic amount of *p*-toluenesulfonic acid.

Figure 2. Optimized structures and energy values of intermediates (**8a,b**, **2**, and **11**).

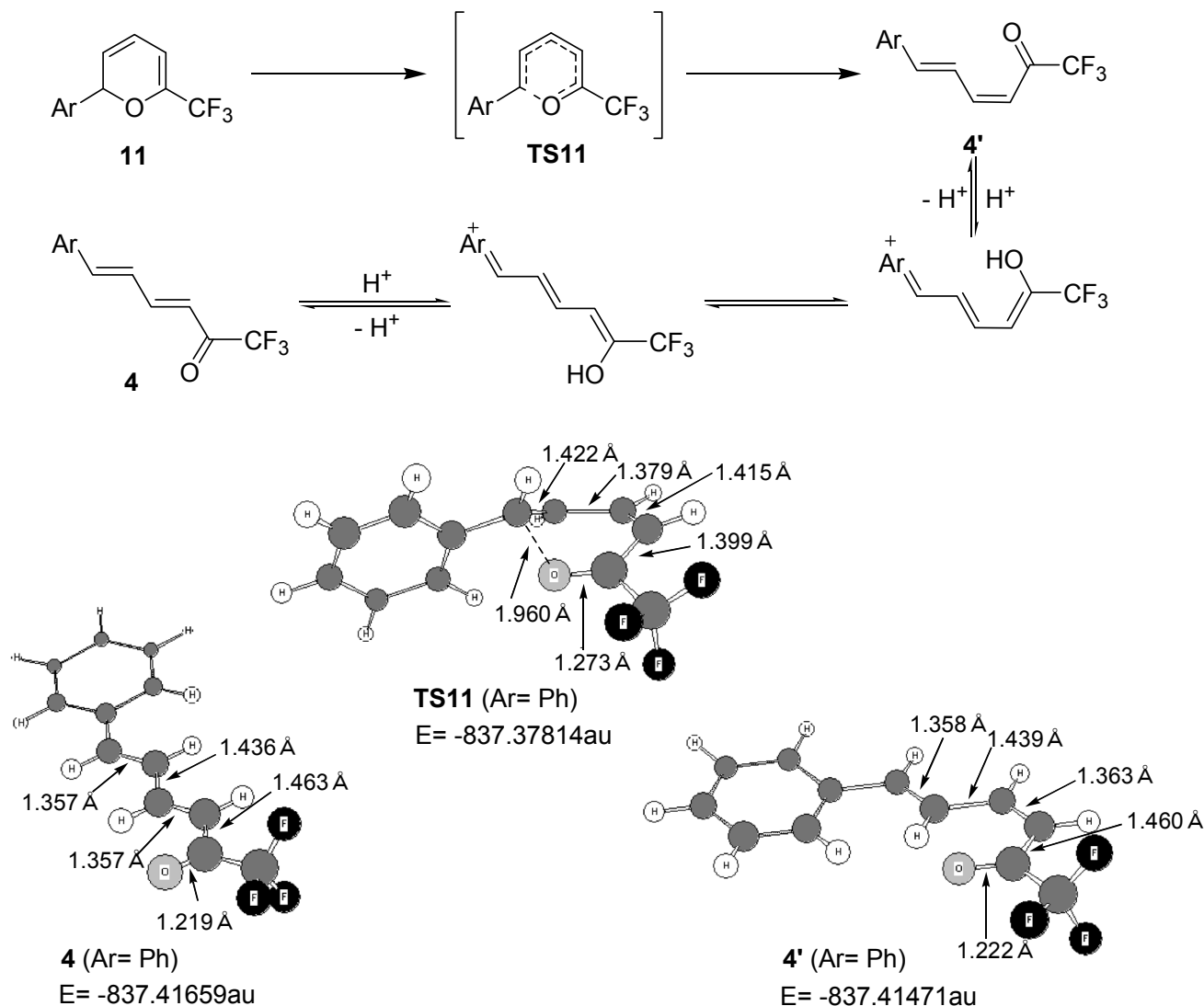


As is described in previous report [16], the kinetically controlled reaction of **7a** with aromatic compounds is predicted to proceed selectively at C-4 to give 4*H*-pyrans (**3**) because the frontier electron density (LUMO of **7a**) at C-4 is considerably larger than that at C-6 [23]. In contrast, the energy of 4*H*-pyrans (**3**) is very close to 2*H*-pyrans (**11**) [24] which are the precursors of 1,3-butadienes (**4**) shown in Figure 2 to attribute the preparation of both **3** and **11** to the thermodynamically controlled reaction of **7a** with aromatic compounds. Relatively high temperature (the temperature of refluxing acetonitrile) required for the reaction of **1** giving **3** and **4** is consistent with the thermodynamically controlled reaction of pyrylium (**7a**) with aromatic compounds.

Next, we estimated the activation energy for the ring-opening process from 2*H*-pyrans (**11**) resulted by the reaction of pyrylium (**7a**) with aromatic compounds at 6-position (Figure 3). The optimized transition state structure (**TS11**; Ar = Ph) [25] and the most stable structure of **4** (Ar = Ph) are illustrated together with their energies. The energy difference between **11** (Ar = Ph) [16] and **TS11** (Ar = Ph) is estimated to be *ca.* 15 kcal/mol, which corresponds to the activation energy of this process. The (*E,Z*)-dienes (**4'**) given by ring-opening of **11** readily isomerize to thermodynamically more stable (*E,E*)-dienes (**4**) via protonation and deprotonation processes (Figure 3). The dienes **4'**

(Ar = Ph) and **4** (Ar = Ph) are calculated to be *ca.* 8 kcal/mol and *ca.* 9 kcal/mol more stable than **11** (Ar = Ph), respectively. The above results suggest that the irreversible ring-opening of the intermediates (**11**) will easily occur at acetonitrile reflux temperature to afford **4**.

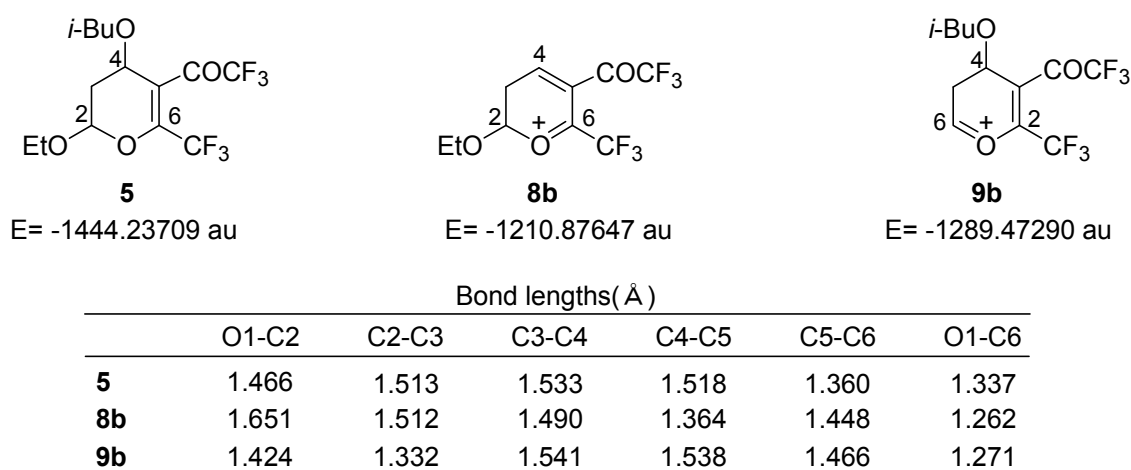
Figure 3. Ring-opening process from 2*H*-pyrans (**11**) to (*E,E*)-dienes (**4**).



In addition, we examined the process from 4-cation (**8a**) to pyrylium (**7a**) to support the mechanism presented in our previous report [16] for the reaction of dihydropyran (**1**) with aromatic compounds in trifluoroacetic acid at ambient temperature giving dihydro-4*H*-pyrans (**2**) solely (Scheme 1). As is mentioned before, this elimination is an endothermic reaction requiring the external energy of 11.3 kcal/mol [22]. Therefore, this result predicts that the reaction of the first intermediate, 4-cation (**8a**), with aromatic compounds directly affording dihydro-4*H*-pyrans (**2**) have precedence over the course via 4*H*-pyrans (**3**) comprised of the reaction of pyrylium (**7a**) with aromatic compounds given that the dihydropyran (**1**) would undergo the reaction at ambient temperature. Even though 4*H*-pyrans (**3**) was given by the *p*-toluenesulfonic acid catalyzed reaction, the reaction of **1** carried out in trifluoroacetic acid with aromatic compounds [6] resulted in the failure of the formation of **3**. These experimental evidences provide us with compatible conclusion as to the above calculated prediction.

Finally, we examined the reaction of dihydropyran (**5**) with aromatic compounds giving butadiene derivatives (**6**) shown in Scheme 1. As for this reaction, an alternative pathway including the reaction of 6-cation (**9b**) with aromatic compounds directly affording 2*H*-pyrans (**10**) is possible in addition to the pathway via pyrylium (**7b**) illustrated in Scheme 2. To elucidate such alternative pathway, we considered as to figuring out dihydropyran (**5**), 4-cation (**8b**), and 6-cation (**9b**). The results are summarized in Figure 4.

Figure 4. Optimized structures and energy values of dihydropyran (**5**), and cations (**8b** and **9b**).

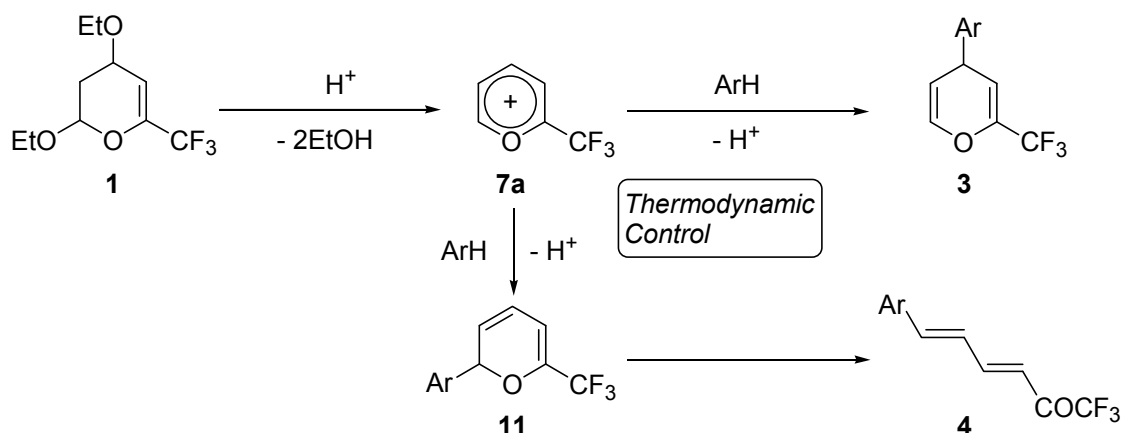


Based on the energy values for **5**, **8b**, and **9b**, the ionization process from **5** to 6-cation (**9b**) is estimated to require *ca.* 20 kcal/mol more energy [26] compared with such ionization to 4-cation (**8b**). The exclusive formation of **8b** from **5** in trifluoroacetic acid is attributed to this value. Hence, the reaction of **5** with aromatic compounds giving **6** does not proceed along the pathway via **9b**. In other words, butadiene derivatives (**6**) are assumed to be derived from pyrylium (**7b**) which formed via 4-cation (**8b**) along the pathway shown in Scheme 2 as we reported previously [16,27]. This de-alcoholization step from **8b** to **7b** is an endothermic process, however the required external energy no more than 13 kcal/mol suggests that **8b** is easily converted to **7b** in refluxing trifluoroacetic acid.

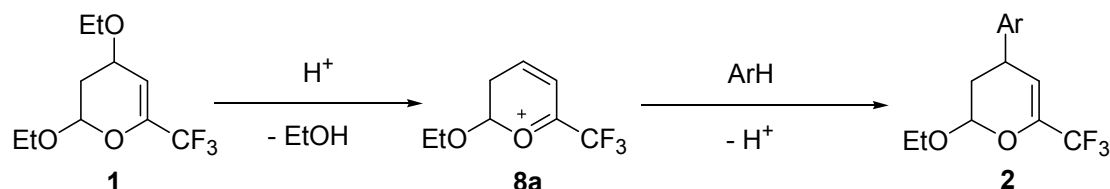
The proposed most reasonable and interesting mechanisms based on our DFT calculations for the acid catalyzed reactions of dihydropyrans (**1** and **5**) with aromatic compounds are summarized in Scheme 3.

Scheme 3. Proposed most reasonable mechanisms for the acid catalyzed reactions of dihydropyrans (**1** and **5**) with aromatic compounds.

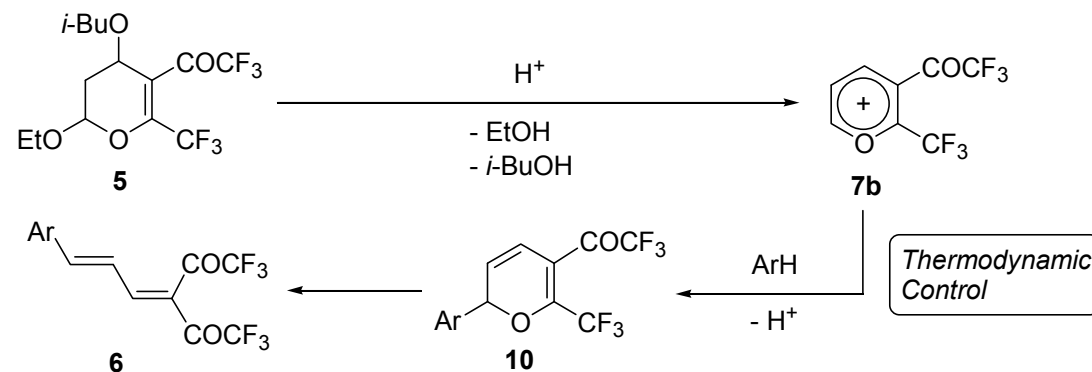
Reaction of 1 in refluxing acetonitrile in the presence of *p*-toluenesulfonic acid



Reaction of 1 in trifluoroacetic acid at ambient temperature



Reaction of 5 in refluxing trifluoroacetic acid



4. Conclusions

On the basis of DFT calculation results, we have achieved a comprehensive explanation regarding the mechanisms for the reactions of dihydropyran (**1**) with aromatic compounds under different acidic reaction conditions. The reaction in the presence of *p*-toluenesulfonic acid giving 4*H*-pyrans (**3**) and butadiene derivatives (**4**) proceeding in refluxing acetonitrile is reasonably explained by the thermodynamically controlled reaction of pyrylium (**7a**) with aromatic compounds. Meanwhile, the reaction in trifluoroacetic acid affording dihydropyrans (**2**) at ambient temperature can be interpreted as a result of the reaction of 4-cation (**8a**) with aromatic compounds. Our study also illustrated the selective formation of butadiene derivatives (**6**) from dihydropyran (**5**) by the reaction in refluxing trifluoroacetic acid in which the thermodynamically controlled attack of aromatic compounds to pyrylium (**7b**) was comprised.

References and Notes

1. Filler, R.; Kobayashi, Y. *Biomedical Aspects of Fluorine Chemistry*; Kodansha & Elsevier Biomedical: Tokyo, Japan, 1982.
2. Filler, R. *Organofluorine Chemicals and Their Industrial Applications*; Ellis Horwood: London, UK, 1979.
3. Welch, J.T. Advances in the preparation of biologically active organofluorine compounds. *Tetrahedron* **1987**, *43*, 3123–3197.
4. Filler, R.; Kobayashi, Y.; Yagupolskii, L.M. *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Elsevier: Amsterdam, The Netherlands, 1993.
5. Hojo, M.; Masuda, R.; Okada, E. A facile synthesis of 2,4-dialkoxy-, 2-alkoxy-4-phenoxy-, and 2,4-diphenoxy-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyrans. Hetero Diels-Alder reactions of trans- β -(trifluoroacetyl)vinyl ethers with various vinyl ethers. *Synthesis* **1989**, vol? 215–217.
6. Ota, N.; Okada, E.; Shibata, D.; Adachi, S.; Saikawa, S. A facile synthesis of 4-aryl-1,1,1-trifluorobut-3-en-2-ones via 4-aryl substituted CF₃-containing dihydropyran derivatives: A versatile method for the introduction of fluorine-containing C₄- and C₆- unit to aromatic compounds. *Heterocycles* **2010**, *80*, 515–525.
7. Hojo, M.; Masuda, R.; Okada, E. A convenient synthetic route to functionalized 5-(trifluoroacetyl)-3,4-dihydro-2*H*-pyrans: hetero-Diels-Alder reaction of β,β -bis(trifluoroacetyl)vinyl ethers with electron-rich alkenes. *Synthesis* **1990**, vol? 347–350.
8. Ota, N.; Okada, E.; Sonoda, A.; Muro, N.; Shibata, D.; Médebielle, M. One step introduction of 4,4-bis(trifluoroacetyl)-1,3-butadiene system to aromatic rings using fluorine-containing 3,4-dihydro-2*H*-pyrans. A facile synthetic method for 1,1,1,5,5,5-hexafluoro-3-[(*E*)-3-arylallylidene]pentane-2,4-diones. *Heterocycles* **2008**, *76*, 215–219.
9. Zanatta, N.; Fernandes, L.S.; Nachtigall, F.M.; Coelho, H.S.; Amaral, S.S.; Flores, A.F.C.; Bonacorso, H.G.; Martins, M.A.P. Highly chemoselective synthesis of 6-alkoxy-1-alkyl(aryl)-3-trifluoroacetyl-1,4,5,6-tetrahydropyridines and 1-alkyl(aryl)-6-amino-3-trifluoroacetyl-1,4,5,6-tetrahydropyridines. *Eur. J. Org. Chem.* **2009**, vol? 1435–1444.
10. Shimizu, M.; Oishi, A.; Taguchi, Y.; Sano, T.; Gama, Y.; Shibuya, I. Quinoline ring formation by cycloaddition of *N*-arylketenimines with enol ethers under high pressure. *Heterocycles* **2001**, *55*, 1971–1980.
11. Caramella, P.; Invernizzi, A.G.; Pastormelo, E.; Quadrelli, P.; Corsaro, A. A pericyclic cascade in the addition of diphenyl nitrile imine to pyridine. *Heterocycles* **1995**, *40*, 515–520.
12. Oinuma, H.; Dan, S.; Kakisawa, H. Stereoselective syntheses of α -isosparteine. *J. Chem. Soc. Perkin Trans.* **1990**, vol? 2593–2597.
13. Wendelin, W.; Schramm, H.-W.; Blasi-Rabassa, A. Reactions of guanidine and thiourea with $\alpha,\beta,\gamma,\delta$ -unsaturated ketones. *Monatsh. Chem.* **1985**, *116*, 385–400.
14. Mohammed, F.K. Synthesis of some new benzo[*b*]carbazole-6,11-diones. *Egypt. J. Chem.* **2006**, *49*, 139–147.
15. Rubinov, D.B.; Rubinova, I.L.; Lakhvich, F.A. Synthesis of exo- and endocyclic enamino derivatives of 2-(3-arylprop-2-enoyl)cyclohexane-1,3-diones. *Russ. J. Org. Chem.* **2011**, *47*, 319–330.

16. Ota, N.; Kamitori, Y.; Nishiguchi, E.; Ishii, M.; Okada, E. A molecular orbital calculation study on the interesting reactivity of fluorine-containing 3,4-dihydro-2*H*-pyrans with aromatic compounds in the presence of trifluoroacetic acid. *Heterocycles* **2011**, *82*, 1337–1343.
17. Wavefunction, Inc. Irvine, CA, USA. Available online: <http://www.wavefun.com> (accessed on 20 February 2012).
18. Becke, A.D. Density-functional thermochemistry. III. The role of exact exchange. *J. Chem. Phys.* **1993**, *98*, 5648–5652.
19. Clark, M.; Cramer, R.D., III.; van Opdenesch, N. Validation of the general purpose Tripos 5.2 force field. *J. Comput. Chem.* **1989**, *10*, 982–1012.
20. Stewart, J.J.P. Optimization of parameters for semiempirical methods. I. Method. *J. Comput. Chem.* **1989**, *10*, 209–220.
21. The previously calculated energy value (−837.40329 au: see ref. 16) was used for **3** (Ar= Ph). The energy of ethanol was calculated as −155.06425 au (this work).
22. The previously calculated energy value (−605.49511 au: see ref. 16) was used for **7a**.
23. The frontier electron densities (LUMO) at C-4 and C-6 of **7a** were calculated as 0.582 and 0.341, respectively: see ref. 16.
24. The energy difference between **3** and **11** was estimated to be less than 1 kcal/mol: see ref. 16.
25. Our calculations for vibrational frequencies of **TS11** showed only one imaginary frequency at −416.3 cm^{−1} having the vibrational mode corresponding to the bond formation and cleavage between C6 and O1.
26. The previously calculated energy value (−1055.82147 au: see ref. 16) was used for **7b**. The energy of isobutanol was calculated as −233.66241 au (this work).
27. It was predicted that the reaction of pyrylium (**7b**) with aromatic compounds occurs at C-4 under kinetically controlled conditions and that proceeds at C-6 under thermodynamically controlled conditions: see ref. 16. In addition, the steric hindrance due to trifluoroacetyl group at C-5 would prevent the attack to C-4 on **7b**.