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COMPUTATIONAL STUDY FOR 1,5-SIGMATROPIC HYDROGEN SHIFT ON TRIFLUOROMETHYLAZADIENE DERIVATIVES - THE KEY STEP IN THE SYNTHESIS OF FLUORINE-CONTAINING OXAZINES -

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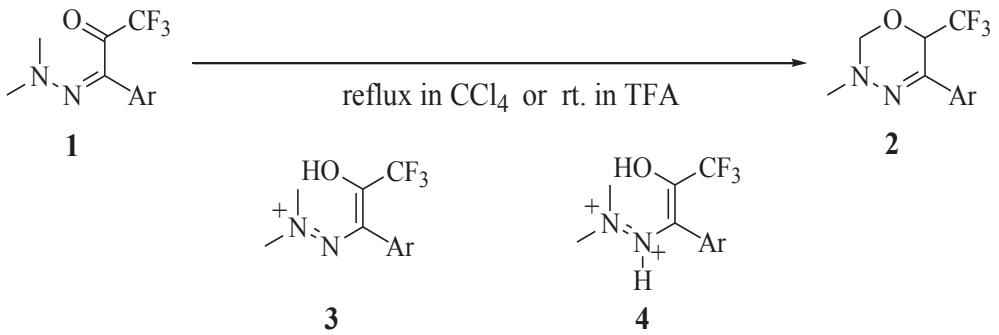
Abstract – 1,5-Sigmatropic hydrogen shifts on two types of azadiene systems, *O*-protonated β-trifluoroacetylenamines **9** and 3,3,3-trifluoro-1-alkylideneaminopropen-2-ols **10**, are elucidated on the basis of DFT calculations to develop new synthetic methodologies accessing novel fluorine-containing heterocycles. These results suggest that the 1,5-hydrogen shift on **9** and **10** requires slightly further enhanced conditions compared with the corresponding step on diazadiene systems, *O*-protonated 1,1,1-trifluoro-3-hydrazono-2-alkanones **3**, which results in the derivation of oxadiazines **2**.

INTRODUCTION

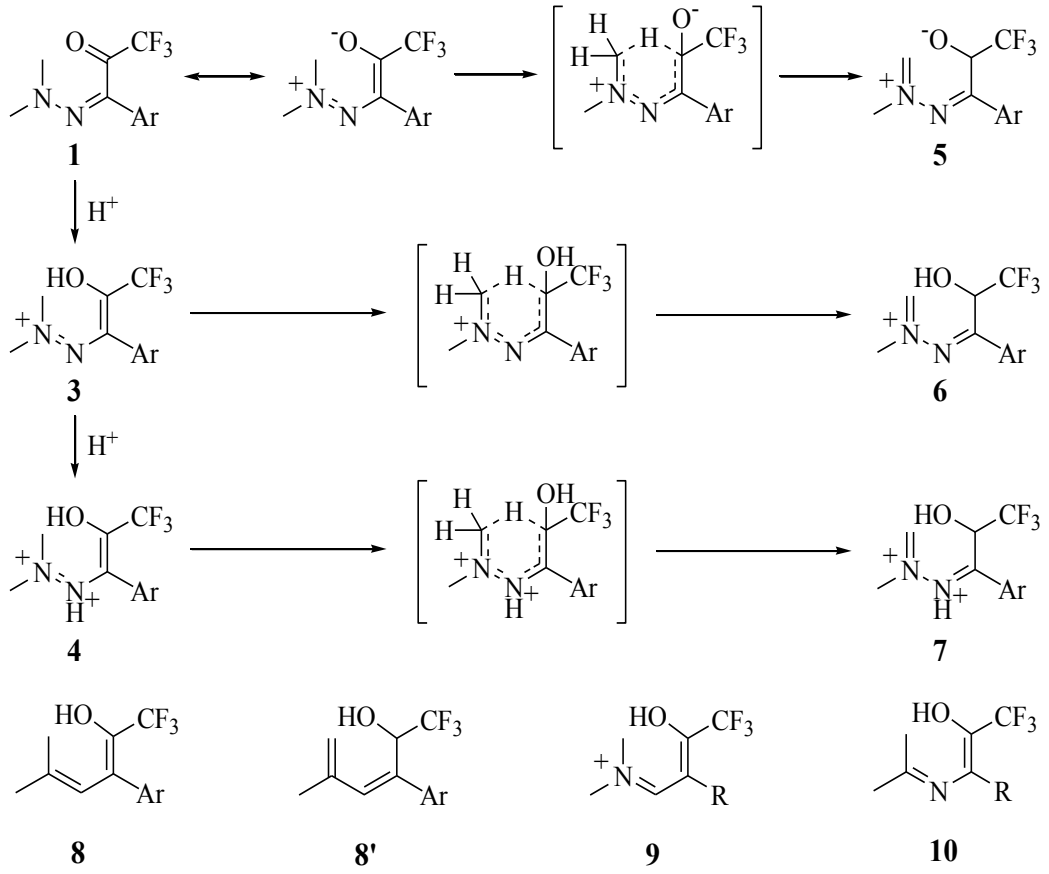
In recent years, a number of researchers have reported about the development of new synthetic methodologies for various kinds of fluorine-containing heterocycles because their potentially high biological activities can contribute to the investigation of unique pharmacological and agrochemical ingredients.[1-4] Previously, our research group has developed simple and effective synthetic method



1 **2** **3** **4**

Scheme 1

accessing fluorine-containing 1,3,4-oxadiazine derivatives **2**.[5-7] The method includes thermally induced[5] or acid catalyzed[6,7] cyclization of hydrazonoalkanones **1**. For instance, the thermal reaction of **1** in refluxing tetrachloromethane gave **2** in moderate yields,[5] while the cyclization of **1** in trifluoroacetic acid (TFA) occurred at ambient temperature to afford **2** in high yields (Scheme 1).[7]



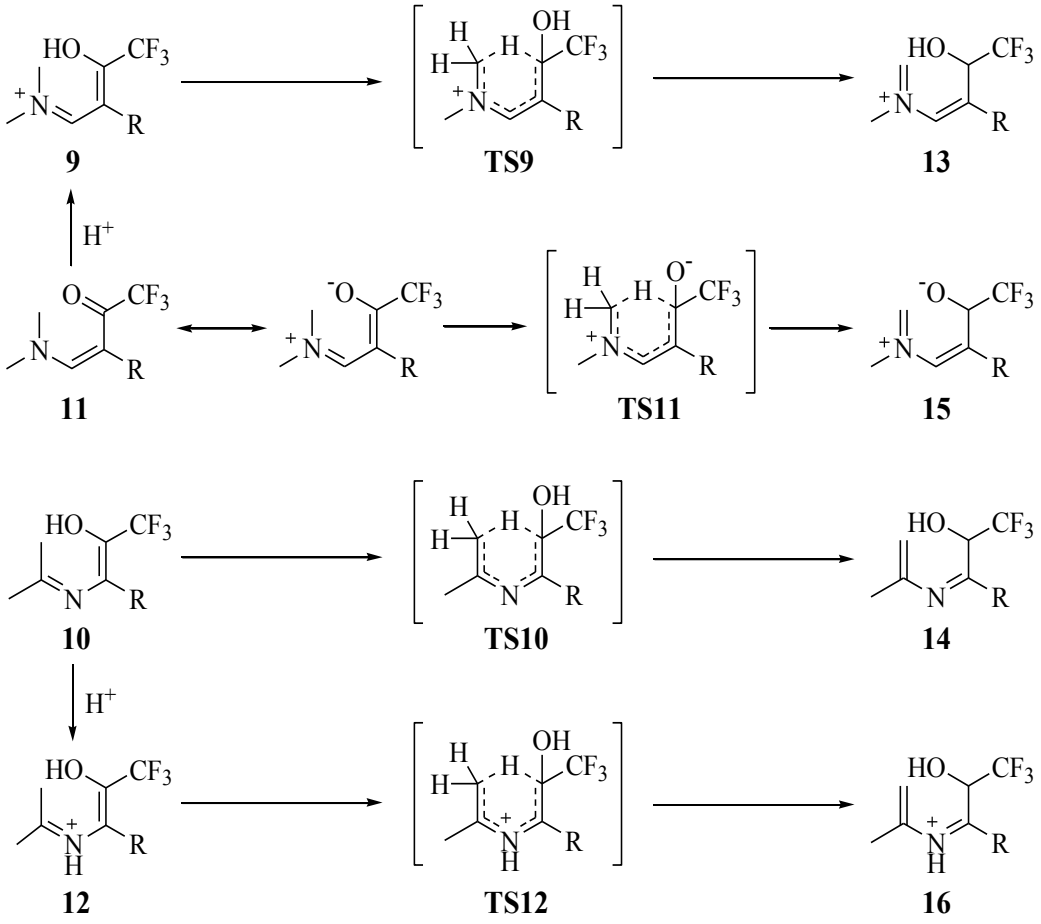
Scheme 2

Our subsequent work has showed the key step of this interesting cyclization step which comprises 1,5-sigmatropic hydrogen shift on **1** or the protonated and diprotonated cations **3**, **4** affording the corresponding intermediates **5**-**7** (Scheme 2).[8,9] We also found that the activation energy of 1,5-hydrogen shift decreases considerably on diazadiene system **3** compared to the corresponding hydrogen shift on parent 1,3-diene system **8**. These findings prompted us to elucidate the 1,5-hydrogen shift on analogous azadiene systems **9** and **10** to explore new synthetic methodologies accessing novel fluorine-containing heterocycles incorporating oxazine systems.

RESULTS AND DISCUSSION

In the previous studies, it was found that the activation energy of 1,5-hydrogen shift (Scheme 2) decreases in the order of hydrazonoalkanones **1** > protonated hydrazonoalkanones **3** > diprotonated hydrazono-

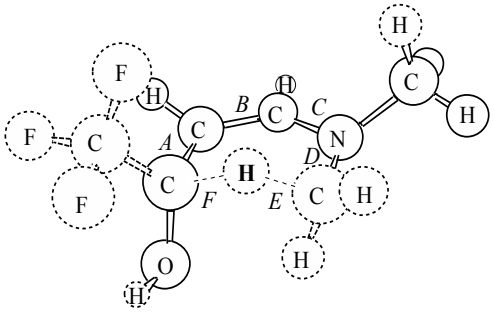
alkanones **4**.[9] These findings are consistent with the experimental results in which acid catalyst accelerates the formation of oxadiazine from **1**, and even more stronger acid takes part in such reaction getting further acceleration.[5-7] In the presence of TFA, the conversion of **1** to **2** (via **4**) has completed within 15 h at ambient temperature, whereas the heat condition (>70 °C) is essential for the reaction progress of **1** in tetrachloromethane.[7] When acetic acid[7] or silica gel[6] was used instead of TFA, it was



9-12, 13-16, TS9-TS12	a	b	c
R	H	Me	Ph

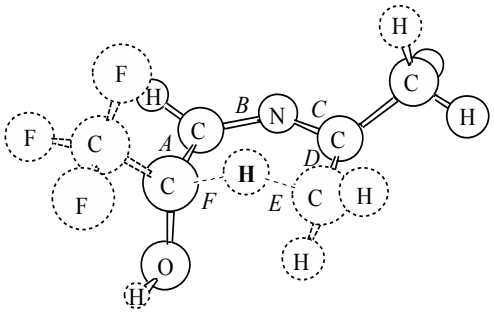
Scheme 3

required that heating (50 °C) or extension of time (>8 days) was employed to the reaction completion (via **3**). Taking above findings on diazadiene systems, **1**, **3** and **4,** in consideration, we elucidated 1,5-hydrogen shift on two types of azadiene system, **9** and **10**, together with β-trifluoroacetylated enamines, **11** and **12** (Scheme 3). The cations, **9** and **12**, are respectively *O*-protonated **11** and *N*-protonated **10**.[10, 11] On the basis of 6-31G* level DFT calculations (RB3LYP/6-31G*//RB3LYP/6-31G*), we estimated the transition state structure, **TS9** and **TS10**,[12] for 1,5-hydrogen shift from **9** and **10** to the corresponding



TS9a

Length	Å
A	1.461
B	1.362
C	1.379
D	1.365
E	1.393
F	1.365



TS10a

Length	Å
A	1.442
B	1.327
C	1.347
D	1.418
E	1.420
F	1.408

Figure 1

products, **13** and **14**. Calculations were performed for the substrates, **9a-c** and **10a-c**, in which it assumed the model of H, Me, and Ph as substituent R. The results for **TS9a** and **TS10a** are illustrated in Figure 1 as representative cases. The activation energy E_a for 1,5-hydrogen shift from **9a** to **13a** was estimated to be 42.6 kcal/mol and the same one from **10a** to **14a** was 45.8 kcal/mol. Quite similarly, E_a for the reaction of other substrates, **9b**,**c**, **10b**,**c**, **11a-c**, and **12a-c**, were also evaluated. Table 1 shows E_a values for **9c-12c** together with the corresponding 1,3-diene **8** (Ar= Ph) and diazadiene **3** (Ar= Ph). As for azadiene **9c**, E_a is ca. 9 kcal/mol higher than that for diazadiene **3** (Ar= Ph) and almost equal to that for 1,3-diene **8** (Ar= Ph).

Table 1. Energy values (kcal/mol) of 1,5-hydrogen shift on azadienes **9c-12c** (R= Ph)

Substrate	Product	E_a	ΔE^a
9c	**13c**	37.3	12.0
10c	**14c**	40.9	5.2
11c	**15c**	58.0	26.8
12c	**16c**	32.4	2.2
8 (Ar= Ph)	**8'** (Ar= Ph)	37.1[b]	5.8
3 (Ar= Ph)	**6** (Ar= Ph)	28.6[b]	-6.2

a) E(Product) – E(Substrate) . b) Reported values in ref. 8.

Next, we examined the substituent effect of R for the 1,5-hydrogen shift on azadienes **9-12**. Activation energies E_a for **9-12** (R= H, Me, Ph) are summarized in Table 2. The introduction of substituent R decreases E_a of 1,5-hydrogen-shift on **9-12** except for the postulated structure having Me group in protonated azadiene **12b**. Obviously, Ph substituent (**9c-12c**) decreases E_a more effectively than Me substituent (**9b-12b**).[13] These results suggest that the introduction of aromatic group at olefinic carbon makes it easy to achieve the reactions via 1,5-hydrogen shift on both azadienes **9** and **10** (**12**).

In conclusion, our study brings out the explanation in which the 1,5-sigmatropic hydrogen shift on azadiene systems, β-trifluoroacetylenamines **11** and 3,3,3-trifluoro-1-alkylideneaminopropen-2-ols **10**, demands further enhanced conditions compared with the corresponding step on diazadiene systems, *O*-protonated 1,1,1-trifluoro-3-hydrazono-2-alkanones **3**. However, this 1,5-sigmatropic hydrogen shift can be accelerated by acid-catalyzed transformation from **11** and **10** to **9** and **12**, respectively. It was also demonstrated that the introduction of aromatic substituent at olefinic carbon of azadienes **9-12** facilitates the progress of 1,5-hydrogen shift giving the corresponding products **13-16**.

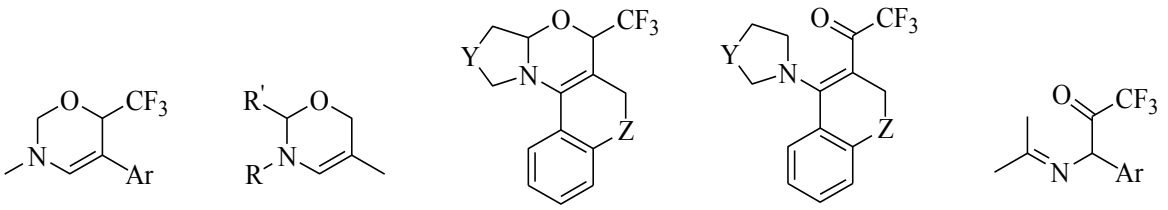
These findings strongly indicate the possibility of acid catalyzed reactions affording fluorine-containing oxadiazines **17** (Scheme 4) from β-trifluoroacetylenamines **11** via intermediates **9** and **13**. As for 3,6-dihydro-2*H*-1,3-oxazines, it has been reported that **18** (Scheme 4) is accessible by adopting

Table 2. Energy values (kcal/mol) of 1,5-hydrogen shift on azadienes **9-12**

Substrate	Product	R	E_a	ΔE^a
9a	**13a**	H	42.6	16.1
9b	**13b**	Me	40.5	12.3
9c	**13c**	Ph	37.3	12.0
10a	**14a**	H	45.8	6.5
10b	**14b**	Me	43.2	4.3
10c	**14c**	Ph	40.9	5.2
11a	**15a**	H	65.2	3.6
11b	**15b**	Me	58.0	25.0
11c	**15c**	Ph	58.0	26.8
12a	**16a**	H	44.2	17.1
12b	**16b**	Me	45.2	14.1
12c	**16c**	Ph	32.4	2.2

a) E(Product) – E(Substrate) .

cycloaddition of divinylamines with aliphatic aldehydes in the presence of phosphoric acid.[14] However, fluorine-containing oxazines such as **17** are hardly synthesized by this method. Only ring-fused type oxazines **19** (Scheme 4) have been synthesized by acid catalyzed reaction of **20** (Scheme 4).[15] This cyclization reaction can be reasonably explained by the present 1,5-sigmatropic hydrogen shift as a key



17 **18** **19** **20** **21**

Y, Z= CH_2, CH_2CH_2

Scheme 4

step. Meanwhile, there have been no reports for the syntheses of enamine derivatives **14** and **16**. We are now going to investigate the synthesis of 6-trifluoromethyl-3,6-dihydro-2*H*-1,3-oxazines **17** from β-trifluoroacetylenamines **11** (R= Ar) via intermediates **9** (R= Ar) and **13** (R= Ar), and novel heterocycles from aminoketone derivatives **21** (Scheme 4) via intermediates **12** (R= Ar) and **16** (R= Ar).

COMPUTATIONAL METHODS

All calculations employed in this paper were accomplished using the computer programs packages PC SPARTAN 02 and PC SPARTAN 04.[16] All calculations for geometrical optimizations were performed with the 6-31G* basis set at B3LYP[17] level. The starting geometries employed for all optimizations were resulted from molecular mechanics using SYBYL[18] force field and subsequent semi-empirical PM3[19] optimizations. The calculations for transition state geometries and their energies were also taken with the 6-31G* basis set at B3LYP level.[20]

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