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THERMAL REACTION OF 5-ARYL-6-TRIFLUOROMETHYL-3,6-DIHYDRO-2*H*-[1,3,4]OXADIAZINES ACCESSING 5-TRIFLUOROMETHYLIMIDAZOLS

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Abstract – Thermal reaction of 5-aryl-6-trifluoromethyl-3,6-dihydro-2*H*-[1,3,4]oxadiazines (**2**) readily obtainable from 3-aryl-3-dimethylhydrazono-1,1,1-trifluoro-2-propanones (**1**) afforded 4-aryl-1-methyl-5-trifluoromethyl-imidazoles (**3**) in moderate to good yields. Mechanism for this thermal transformation reaction is also discussed.

INTRODUCTION

Fluorine-containing heterocycles are very attractive targets for synthetic organic chemists because of their potentially high physiological activities.[1-4] Previously we reported an acid catalyzed novel cyclization reaction of 3-aryl-3-dimethydrazono-1,1,1-trifluoro-2-propanones (**1**) affording 5-aryl-6-trifluoromethyl-3,6-dihydro-2*H*-[1,3,4]oxadiazines (**2**).[5,6] On the other hand, thermal reaction of hydrazones (**1**) in refluxing tetrachloromethane gave oxadiazines (**2**) together with small amounts of 4-aryl-1-methyl-5-trifluoromethylimidazoles (**3**).[7] In contrast, imidazoles (**3**) were obtained predominantly together with 5-aryl-1-methyl-4-trifluoromethylimidazoles (**4**) as minor products, when hydrazones (**1**) were heated in refluxing toluene.[8] Above results seem to suggest a possibility of reaction pathway from **1** to imidazoles (**3** and **4**) via oxadiazines (**2**). As a part of investigation about mechanisms for the reaction from hydrazones (**1**) to **3** and **4**, we elucidated in detail the thermal transformation of oxadiazines (**2**) to imidazoles (**3** and **4**).

RESULTS AND DISCUSSION

Thermal reaction was carried out for oxadizines (**2a** - **e**)[5,6] and are summarized in Table 1. In refluxing

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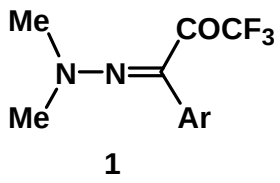
This Paper is dedicated to Professor Dr. Ekkhard Winterfeldt on the occasion of his 75th birthday.



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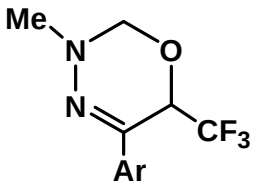

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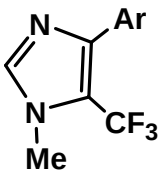

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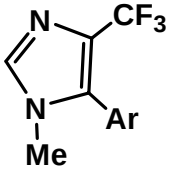


4

1 - 4	a	b	c	d	e
Ar	Ph	*p*-MeC_6H_4	*p*-$MeOC_6H_4$	*p*-ClC_6H_4	*p*-$O_2NC_6H_4$

tetrachloromethane, oxadiazine (**2b**) was remained intact and no imidazole was obtained even after 4 days (Entry 2). However, 83% of **2b** was converted to 5-trifluoromethylimidazole (**3b**) and no 4-trifluoromethylimidazole (**4b**) was detected in the reaction mixture when **2b** was heated for 2 days in refluxing toluene (Entry 3). To complete the reaction, prolonged reaction time (4 days) was required, and **3b** was obtained as a sole product (Entry 4).[8] No isomerization of **3b** to **4b** was observed even after 4 days in refluxing toluene. In contrast, hydrazone (**1b**) was completely converted to **3b** (major product) and **4b** (minor product) within 2 days in refluxing toluene.[8] Apparently, conversion of **2b** to **3b** proceeds more slowly than that of **1b** to **3b** or **4b**. These results indicate that oxadiazines (**2**) are not intermediates of the reaction from hydrazones (**1**) to imidazoles (**3** and **4**).

The selective transformation of oxadiazines (**2a** and **2c**) to the corresponding 5-trifluoromethylimidazoles (**3a** and **3c**) was also successful under the same conditions with **2b** (Entries 1 and 5). Oxadiazines bearing electron-withdrawing substituents on the benzene ring, **2d** and **2e**, were less reactive than **2a** - **c**. The reaction of *p*-chlorophenyl derivative (**2d**) in refluxing toluene proceeded more slowly and gave the mixture of two regioisomers (**3d** and **4d**) together with 11% recovery of **2d** (Entry 6). In the case of *p*-nitrophenyl derivative (**2e**), no reaction occurred with the whole recovery of **2e** (Entry 8).[8] The reaction of **2e** at 110 °C and at 125 °C without solvent afforded the mixture of **3e** and **4e** in the ratio of ca. 3 : 2 together with recovery of **2e** (Entries 9 and 10). Apparently, these results show that electron-withdrawing group at the *p*-position of aryl substituent hinders the present ring transformation reaction. Moreover, the reaction of oxadiazines having electron-withdrawing group on aryl substituent gave 4-trifluoromethylimidazoles (**4**) together with 5-trifluoromethylimidazoles (**3**).[9,10]

The use of *p*-xylene as a solvent having higher boiling point was found to be especially effective for **2d** and **2e**. The reactions of **2d** and **2e** for 4 - 6 days in refluxing *p*-xylene took place selectively to provide the single regioisomers (**3d** and **3e**) without any formation of the other ones (**4d** and **4e**) (Entries 7 and 11).

Table 1. Thermal reaction of oxadiazines (**2**) affording 5-trifluoromethylimidazoles (**3**). [a]

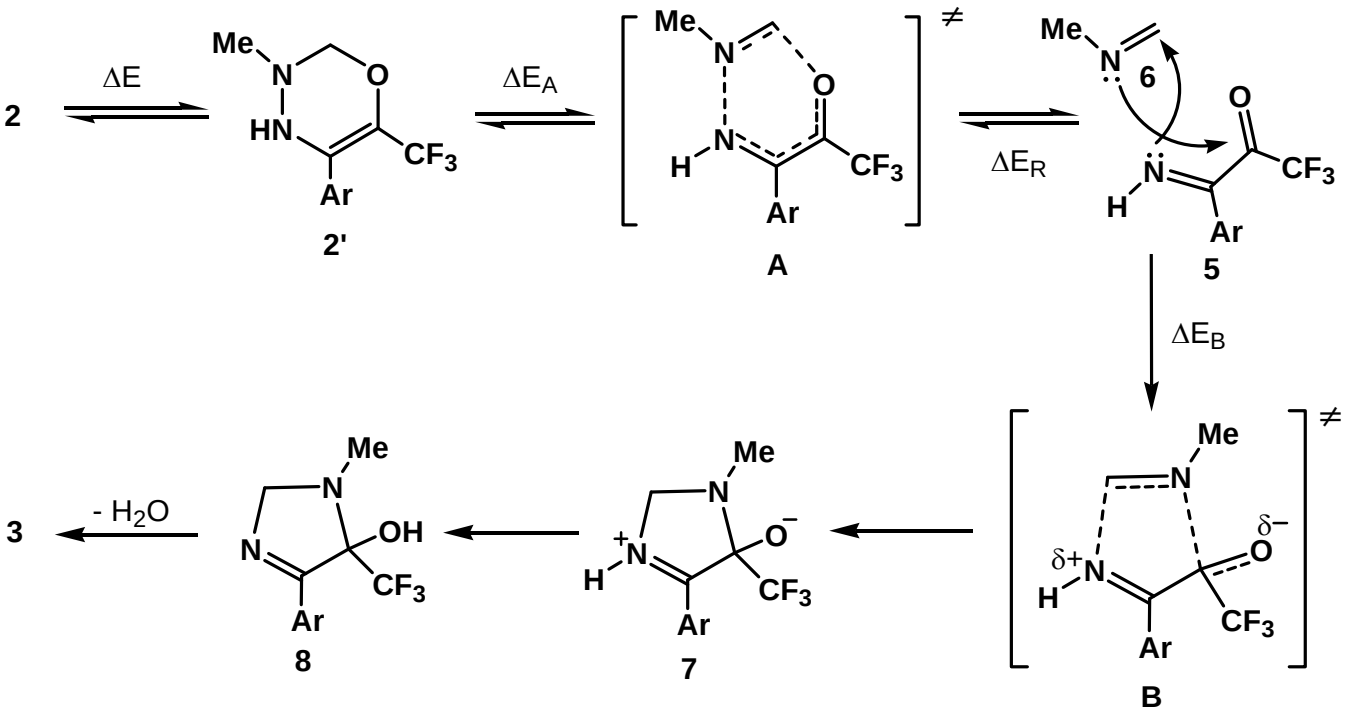
Entry	Substrate	Solvent	Time (d)	Product	Conversion[b] (%)	Yield[c] (%)
1	**2a**	toluene	4	**3a**	100	95[d]
2	**2b**	CCl_4	4	-	0[e]	-
3	**2b**	toluene	2	**3b**	83	65
4	**2b**	toluene	4	**3b**	100	86[d]
5	**2c**	toluene	4	**3c**	100	92[d]
6	**2d**	toluene	4	**3d**, **4d** (88 : 12)[b]	89	82[f]
7	**2d**	*p*-xylene	4	**3d**	100	91
8	**2e**	toluene	4	-	0[e]	-
9	**2e**	-	1 (110°C)[g]	**3e**, **4e** (61 : 39)[b]	66	59[f]
10	**2e**	-	1 (125°C)[g]	**3e**, **4e** (59 : 41)[b]	71	66[f]
11	**2e**	*p*-xylene	6	**3e**	100	57

[a] The reaction was carried out under reflux conditions. [b] Calculated by ^{1}H NMR spectroscopy. [c] Isolated yield. [d] Ref. 8. [e] Substrate was recovered. [f] Combined yield of isomers (**3** and **4**). [g] The reaction was carried out in sealed tube without solvent at the indicated temperatures.

As for the reaction mechanism from oxadiazines (**2**) to 5-trifluoromethylimindazoles (**3**), the pathway containing reverse reaction process from **2** to hydrazones (**1**) followed by recyclization of **1** to **3** is unlikely, because thermal reaction of **1** to **3** does not proceed selectively and 4-trifluoromethyimidazoles (**4**) are always obtained as minor products.

Taking it into account that the ring construction reaction of oxadiazines (**2**) to imidazoles (**3**) is induced thermally and required no catalyst, and cleavage of both N-N and C-O bonds on **2** is included in the reaction, we proposed the most reasonable pathway illustrated in Scheme 1. Retro Diels-Alder reaction of tautomeric isomers (**2'**) of **2** affords 3-imino-1,1,1-trifluoro-2-propanones (**5**) and *N*-methyformimine (**6**). The subsequent cycloaddition of **5** with **6** gives betaines (**7**). Prototropy on **7** followed by dehydration affords 5-trifluoromethylimidazoles (**3**).

In order to confirm above mechanism, we computed, on the basis of the 6-31G* level density functional calculations (RB3LYP/6-31G*// RB3LYP/6-31G*), the optimized structures as well as the energies of **2** and intermediates (**2'**, **5** and **6**), in addition to the transition state structures (**A** and **B**) and the corresponding activation energies. The estimated transition state structures (**A** and **B**) were illustrated in Figure 1. Tautomer **2a'** (Ar= Ph) is 3.0 Kcal/mol less stable than oxadiazine (**2a**). Activation energy (ΔE_A) of



Scheme 1

retro Diels-Alder reaction from **2a'** (Ar= Ph) to ketoimine (**5**; Ar= Ph) and formimine (**6**) was calculated as 35.9 Kcal/mol. The second activation energy (ΔE_B) of cycloaddition reaction from **5** (Ar= Ph) and **6** affording betaines (**7**; Ar= Ph) was estimated as 6.9 Kcal/mol. This value is much smaller than that of first activation energy (ΔE_A). In addition, activation energy (ΔE_R) of reverse reaction (Diels-Alder reaction) from **5** (Ar= Ph) and **6** to **2a'** (Ar= Ph) is calculated as 28.7 Kcal/mol, which is much larger than the value of ΔE_B but ca. 7 Kcal/mol smaller than that of ΔE_A. These results indicate that, under the reaction conditions, there is an equilibrium state between **2'** and intermediates (**5** and **6**) and once **5** and **6** are produced by retro Diels-Alder reaction of **2'**, they are quickly consumed to yield betaines (**7**). Retro Diels-Alder reaction of **2'** would be a key step of overall reaction processes from oxadiazines (**2**) to imidazoles (**3**). The energy value (35.9 Kcal/mol) of ΔE_A for **2a'** (Ar= Ph) is compatible with the reaction conditions from **2a** to **3a** (Table 1).

We also calculated ΔE, ΔE_A, and ΔE_B for the ring transformation of oxadiazine (**2e**) bearing nitro group on the benzene ring to the corresponding imidazole (**3e**), which required higher temperature to complete the reaction. Unexpectedly, estimated activation energies, ΔE_A (34.9 Kcal/mol) and ΔE_B (6.0 Kcal/mol) are slightly lower than the corresponding ΔE_A (35.9 Kcal/mol) and ΔE_B (6.9 Kcal/mol), respectively, on the reaction of **2a** to **3a**. On the other hand, tautomer (**2e'**; Ar= *p*-$O_2NC_6H_4$) is ca. 7 Kcal/mol less stable than oxadiazine (**2e**), whereas **2a'** (Ar= Ph) is only 3 Kcal/mol less stable than **2a**. Instability of **2e'** (Ar= *p*-$O_2NC_6H_4$) relative to **2a'** (Ar= Ph) is unfavorable for the reaction of **2e** to **3e**. In addition, ΔE_R (25.1

Kcal/mol) in the case of **2e** being 3.6 Kcal/mol lower than ΔE_R (28.7 Kcal/mol) in the case of **2a** means that the reverse reaction of **5** with **6** to **2'** proceeds more rapidly in the case of **2e** than in the case of **2a**. Relatively rapid reverse reaction (Diels-Alder reaction of **5** with **6**) is unprofitable for conversion of oxadiazine (**2e**) to imidazole (**3e**).

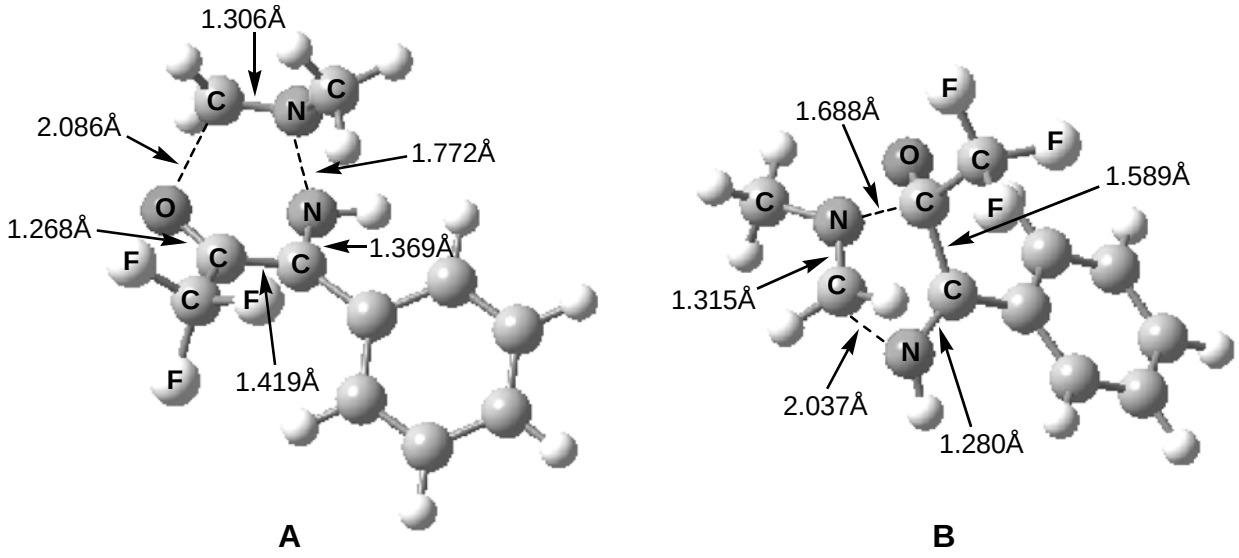


Figure 1

CONCLUSION

Thermal reaction of oxadiazines (**2**) in refluxing toluene or *p*-xylene gave 5-trifluoromethylimidazoles (**3**) selectively. Molecular orbital calculations suggest that key steps of the reaction processes from **2** to **3** would be retro Diels-Alder reaction of tautomers (**2'**) and subsequent cycloaddition of resulted ketoimines (**5**) and formimine (**6**). The tandem transformations hydrazones (**1**) → **2** → **3** would be superior method to prepare 5-trifluoromethylimidazoles (**3**) selectively. Selective synthesis of 4-trifluoromethylimidazoles (**4**) from hydrazones (**1**) was reported previously,[11] so we established selective synthetic methods suitable for each 5-trifluoromethylimidazoles (**3**) and 4-trifluoromethylimidazoles (**4**) starting from common hydrazones (**1**) readily obtainable from various arylaldehydes.[7]

COMPUTATIONAL METHODS

All calculations employed in this paper were accomplished using the computer programs packages PC SPARTAN 02.[12] All calculations for geometrical optimizations were performed with the 6-31G* basis set at B3LYP[13] levels. The starting geometries employed for all optimizations were resulted from semi-empirical PM3[14] optimizations. The calculations for energy of intermediates as well as transition

states were also taken with density functional calculations using the 6-31G* basis set at B3LYP levels.

EXPERIMENTAL

Thermal reaction of 5-aryl-6-trifluoromethyl-3,6-dihydro-2*H*-[1,3,4]oxadiazines (**2a** - **e**) with the use of solvents was carried out according to literature manner.[8] The products were analyzed by ^{1}H NMR spectroscopy. Conversion and product ratio were calculated from signal intensities of the corresponding NMe protons of **2**, **3**, and **4**.[5,6,8]

Thermal reaction of 5-(*p*-nitrophenyl)-6-trifluoromethyl-3,6-dihydro-2*H*-[1,3,4]oxadiazine (2e) without solvent

In a nitrogen replaced Φ6 mm glass sealed tube, **2e** (0.18 mmol, 50.8 mg) was heated for 24 h at 110 °C or 125 °C (oil bath temperature). Crude materials were analyzed by ^{1}H NMR spectroscopy. Yields and ratios (**2e** : **3e** : **4e**) are as follows - 47.4 mg, 17 : 20 : 13 (110 °C); 44.8 mg, 29 : 42 : 29 (125 °C).

Identification of **3a** - **e** and **4d** - **e** were pursued by comparing ^{1}H NMR spectra of them with those of authentic samples.[7,8]

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9. When 4-trifluoromethyimidazole (**4e**) was heated for 6 d in refluxing *p*-xylene (the conditions for Entry 11), no isomerization to 5-trifluoromethylimidazole (**3e**) occurred with the whole recovery of **4e**.
10. Although the reaction mechanism from **2e** (or **2d**) to **4e** (or **4d**) is still unknown, the reverse reaction from oxadiazines (**2**) to hydrazones (**1**) followed by recyclization of **1** to **4** (and **3**)[8] would be one of possible pathways from **2e** (or **2d**) to **4e** (or **4d**).
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