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Abstract - Mechanisms for the acid catalyzed cyclization reaction of 3- dialkylhydrazono-1,1,1-trifluoro-2-alkanones (1) to 6-trifluoromethyl-3,6-dihydro-2H-[1,3,4]oxadiazines (2) are discussed. The results indicate 1,5-sigmatropic shift of hydrogen atom from N-methyl group to carbonyl carbon center on protonated 1 to be a key step for this cyclization reaction.

INTRODUCTION
In the previous papers,\textsuperscript{1,2} we reported a novel cyclization reaction of 3-dimethylhydrazono-1,1,1-trifluoro-2-alkanones (1)\textsuperscript{3} affording 6-trifluoromethyl-3,6-dihydro-2H-[1,3,4]oxadiazines (2) under very mild conditions. This cyclization reaction proceeds in the presence of acid catalyst, such as acetic acid, trifluoroacetic acid (TFA), and silica gel. During the reaction, one of the N-methyl carbon atoms of hydrazone (1) that seems not to be so reactive in general, is easily incorporated into oxadiazine ring system of the products. These findings prompted us to study about the mechanism of this interesting cyclization reaction.

RESULTS AND DISCUSSION
Taking it in consideration that this cyclization reaction requires acid catalysis, we tried to estimate protonated structures of hydrazone (1) as an initial intermediate. On the basis of the 6-31G* level
density functional calculations (RB3LYP/6-31G*//RB3LYP/6-31G*), the estimations were carried out about 3-dimethylhydrazono-1,1,1-trifluoro-2-propanone (3) as a model compound for 1. In the presence of acid, reversible protonation should be possible at carbonyl oxygen, Schiff base nitrogen, dimethylamino nitrogen, and azomethine carbon atoms of hydrazone (3). In each case, the geometrically optimized structure (4a - d) as well as its energy were computed, and the results are summarized in Scheme 1 together with those for hydrazone (3). Among these mono cations, 4a derived from 3 by protonation at carbonyl oxygen atom was predicted to be most stable. The values in parentheses computed by RMP2/6-31G*//RMP2/6-31G* are also compatible with these predictions. These results suggest that considerable amounts of hydrazones (1) are converted to cations (4, Scheme 2) in the presence of acid catalyst. Dications (5) may be also possible in the presence of strong acid such as TFA.

On the basis of RMP2/6-31G*, Mulliken bond populations were calculated about hydrazone (3) and cation (4a). These are also indicated in Scheme 1. These data reveal exceeding multiple bonding characters on N-N and C-C bonds of cation (4a) in comparison with those of 3, i.e. considerable contribution of the canonical form B in Scheme 2. Similar situation should be true for hydrazones (1), and this suggests more enhanced azoolefinic character of 4 by protonation at carbonyl oxygen atom of 1.

On the basis of RB3LYP/6-31G*, estimated rotational barriers around central C-N bond are 19.4 Kcal/mol
and 11.9 Kcal/mol for cations (4a) and (4, R= Ph), respectively. Such azoolefinic character should be correlated with notable reactivity of 1 leading to several heterocyclic ring-formations. For instance, we reported TFA mediated hetero-Diels-Alder reaction of protonated hydrazone (6) affording pyridazine (7) in the previous report. These findings suggest the cation (4) to be the most reasonable precursor for the present cyclization reaction accessible oxadiazine (2).

Ionic as well as concerted processes are possible as a mechanism of the present cyclization reaction from cation (4) to oxadiazine (2). As for the mechanisms including only ionic processes, we can propose two possible pathways (Path A and Path B) illustrated in Scheme 3. Path A contains deprotonation process on N-methyl group of 4 affording betaines (8 and 8') as intermediates. Betaine (8) should be in equilibrium with 8'. The RB3LYP/6-31G* level calculations suggest that intermediate (8, R= H) in Path A is 28.1 Kcal/mol less stable than hydrazone (3, R= H). Betaine (8', R= H) is estimated to be 7.2 Kcal/mol less stable than 8 (R= H). Subsequent protonation at C4 of 8' affords cation (9) and intramolecular nucleophilic attack of hydroxyl oxygen atom toward terminal azomethine carbon atom on 9 followed by deprotonation should afford 2.

On the other hand, Path B includes the formation of dication (5) and subsequent deprotonation process on N-methyl group of 5 affording cationic intermediates (10 and 10'). Cyclization mediated by nucleophilic attack of hydroxyl oxygen atom toward terminal azomethine carbon atom on 10' and subsequent deprotonation afford oxadiazine (11), i.e. a tautomer of 2.

Also, protonation at Schiff base nitrogen atom of 8' in Path A can give intermediate (10'), and consequently, oxadiazine (2) via 11.
As a mechanism including concerted process as a key step, the reaction path shown in Scheme 4 is possible. There, 1,5-sigmatropic shift of N-methyl hydrogen atom to C4 on 4′ affords intermediate (9) directly. The cyclization of 9 as is seen in Scheme 3 leads to oxadiazine (2).

If the cyclization reaction proceeds via 1,5-sigmatropic shift, a methine hydrogen atom bound to C6 of oxadiazines (2) is derived from N-methyl hydrogen atoms of hydrazones (1). In contrast, if the cyclization occurs according to ionic mechanism shown in Scheme 3, the proton from acid catalyst must be incorporated into oxadiazine (2) as the methine hydrogen atom. In order to clarify whether this
methine hydrogen atom is derived from acid or not, we examined the cyclization reaction of hydrazone (1, R= p-Tol) in trifluoroacetic acid-\textit{d}. The reaction was monitored by $^1$H NMR spectrometer.

![Scheme 4](image)

During the reaction, no signal assignable as the methine proton at C6 of 2 (R= p-Tol) appeared in the spectra, and the methine hydrogen atom of obtained oxadiazine after workup was completely replaced with a deuterium atom. Pseudo-first-order rate constant for this cyclization reaction was roughly estimated as $1.9 \times 10^{-4}$ s$^{-1}$ by $^1$H NMR spectral measurement. These facts seem to suggest that this cyclization reaction proceeds according to ionic manner (Path A or Path B). However, we found that H-D exchange reaction also occurs at C6 of oxadiazines (2) in trifluoroacetic acid-\textit{d}. To elucidate a possibility of such H-D exchange reaction on 2, we examined monitoring experiments about oxadiazine (2, R= p-Tol) in trifluoroacetic acid-\textit{d} by means of $^1$H NMR spectroscopy. The signal intensity of methine proton of 2 (R= p-Tol) decreased smoothly in trifluoroacetic acid-\textit{d}. The pseudo-first-order rate constant for this exchange reaction was calculated as ca. $2.0 \times 10^{-3}$ s$^{-1}$. This rate of H-D exchange reaction is over 10 times higher than that of cyclization reaction from hydrazone (1, R= p-Tol) to oxadiazine (2, R= p-Tol) described above. Such H-D exchange on 2 is thought to occur along with enamine-imine tautomerization as is shown in Scheme 5.

From above results, it seems to be difficult to decide whether the cyclization reaction proceeds according to ionic manner or concerted one. However it is necessary to take in account that H-D exchange occurred neither on N-methyl nor methylene groups of deuteriooxadiazine (2', R= p-Tol). Both Path A and Path B in Scheme 3 contain a deprotonation process from N-methyl groups of the starting cations (4 or 4'), or dication (5). In addition, these processes need to proceed in the presence of strong acid, i.e. trifluoroacetic acid. There should be rapid equilibrium between cations (4, 4') and betains (8, 8') in the
case of Path A, and that between dication (5) and cation (10) in the case of Path B. These equilibriums in the presence of trifluoroacetic acid-d should mediate rapid H-D exchange reaction at N-methyl

\[
1 (R= p\text{-Tol}) \quad \text{CF}_3\text{CO}_2\text{D} \quad k \approx 1.9 \times 10^{-4}
\]

\[
2 (R= p\text{-Tol}) \quad \text{CF}_3\text{CO}_2\text{D} \quad k_{\text{H-D}} \approx 2.0 \times 10^{-3}
\]

\[
\begin{array}{c}
\text{CH}_3 \quad \text{N} \quad \text{O} \\
\quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad 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Computed energy of this transition state structure was -679.219960 a.u., and activation energy (\(\Delta E\)) from 4' (R= H) to C was calculated as 38.1 Kcal/mol. Estimated rotational barrier between cations 4a and 4' (R=H) was 19.4 Kcal/mol. These values can be correlated with required energy for the process from cation (4a) to intermediate (9, R= H). We also carried out the estimation of energies using RHF/6-31G* and RMP2/6-31G* level calculations. The results are summarized in Table 1.

The energy values more than 35 Kcal/mol seem to be too large in the case of the TFA mediating reaction of hydrazone (1) affording oxadiazines (2), because the conversion from 1 to 2 proceeds smoothly at room temperature. We also carried out calculations about 4 (R= Ph, Table 1). Computed activation energies are 5 – 10 Kcal/mol lower than those for 4a. However, even in these cases, the energy values are a little large for the reaction proceeding at room temperature.

<table>
<thead>
<tr>
<th></th>
<th>Calculation</th>
<th>Rotational Barrier from 4 to 4' (Kcal/mol)</th>
<th>(\Delta E) from 4 to Transition State (Kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R= H</td>
<td>RB3LYP/6-31G*</td>
<td>19.4</td>
<td>38.1</td>
</tr>
<tr>
<td>(4a)</td>
<td>RHF/6-31G*</td>
<td>13.4</td>
<td>53.2</td>
</tr>
<tr>
<td></td>
<td>RMP2/6-31G*</td>
<td>15.7</td>
<td>35.7</td>
</tr>
<tr>
<td>R= Ph</td>
<td>RB3LYP/6-31G*</td>
<td>11.9</td>
<td>28.6</td>
</tr>
<tr>
<td></td>
<td>RHF/6-31G*</td>
<td>5.0</td>
<td>47.6</td>
</tr>
<tr>
<td></td>
<td>RMP2/6-31G*</td>
<td>9.2</td>
<td>26.6</td>
</tr>
</tbody>
</table>
Taking these results in account, we focused on the possibility of second protonation on cation (4') in the presence of strong acid such as TFA. We calculated activation energy for 1,5-sigmatropic hydrogen shift on dication (5', R=Ph) affording 12 (R= Ph). Required energy from 5' (R= Ph) to transition state D (R= Ph) was estimated as 13.7 Kcal/mol (RHF/6-31G*) and 18.1 Kcal/mol (RB3LYP/6-31G*). These values are consistent with the fact that the reaction from hydrazones (1) to oxadiazines (2) proceeds even at room temperature in the presence of TFA. Thus TFA catalyzed reaction should proceed mainly along with the second protonation assisted mechanism via 5' as is illustrated in Scheme 6. On the other hand, acetic acid catalyzed reaction of hydrazones (1) requires heating, and prolonged reaction time is necessary for conversion of 1 to oxadiazines (2) under the catalysis of silica gel. In the presence of such relatively weak acid catalysts, the reaction is thought to proceed mainly along with the reaction path via mono cations (4', Scheme 4).

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>ΔE (Kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C</td>
<td>CH</td>
<td>H</td>
<td>40.9</td>
</tr>
<tr>
<td>2</td>
<td>C</td>
<td>CH</td>
<td>F</td>
<td>37.1</td>
</tr>
<tr>
<td>3</td>
<td>N⁺</td>
<td>N</td>
<td>H</td>
<td>30.9</td>
</tr>
<tr>
<td>4</td>
<td>N⁺</td>
<td>N</td>
<td>F</td>
<td>28.6</td>
</tr>
</tbody>
</table>
It is known that rates of thermal pericyclic reactions are affected by properties as well as positions of substituents on a substrate, and these substituent effects vary with a type of pericyclic reaction itself. In Scheme 7, estimated activation energies (RB3LYP/6-31G*) about 1,5-sigmatropic hydrogen shift for related compounds of cation (4', R= Ph) are listed. Entry 1 is corresponding to the parent system for the present 1,5-sigmatropic shift (Entry 4). When one methyl group of 5-methyl-2,4-hexadien-2-ol is replaced with trifluoromethyl group (Entry 2), ΔE decreases in the rage of 3 – 4 Kcal/mol. On the other hand, a replacement of two carbon atoms of 5-methyl-3-phenyl-2,4-hexadien-2-ol with nitrogen atoms (Entry 3) reduces ΔE in the range of ca.10 Kcal/mol. In the case of 4' (R= Ph, Entry 4), these two factors reduce activation energy additively, and the lowest ΔE is resulted among these four systems in Scheme 7.

Relatively small difference (ΔΔE<3 Kcal/mol) between the cases of Entry 3 and 4 suggests that the cyclization reaction accessible the corresponding oxadiazines may be possible for hydrazones bearing no trifluoromethyl group if the reaction is carried out under appropriate conditions. However our all attempts to obtain oxadiazine (15) from hydrazone (13) resulted in failure. Intermediate (19) resulted by 1,5-sigmatropic hydrogen shift on 18 (Entry 3) is calculated as 6.9 Kcal/mol less stable than 18, whereas intermediate (9, R= Ph, Entry 4) is estimated as 5.9 Kcal/mol more stable than 4' (R= Ph). This should be one of the reasons why the conversion of 13 to the corresponding oxadiazine (15) was unsuccessful contrary to the case of hydrazones (1). We also examined the cyclization reaction about hydrazones (14) under several conditions. Similarly, all of these attempts were unsuccessful except for only the following case. When 14 was treated with hot diluted acetic acid, oxadiazine (17), the tautomer of 16, was obtained, though the yield was no more than 5%.
CONCLUSION
In conclusion, we can present the most reasonable mechanism for the cyclization reaction from 3-dimethyldrazono-1,1,1-trifluoro-2-alkanones (1) to 6-trifluoromethyl-3,6-dihydro-2H-[1,3,4]oxadiazines (2). Molecular orbital calculations and H-D exchange experiments suggest a concerted 1,5-sigmatropic shift of N-methyl hydrogen to carbonyl carbon on protonated or diprotonated hydrazones to be a key step in the overall reaction processes. An extension of this cyclization reaction to general α-hydrazonoketone systems is under investigation.

COMPUTATIONAL METHODS
All calculations employed in this paper were accomplished using the computer programs packages SPARTAN and PC SPARTAN 02. All calculations for geometrical optimizations were performed with the 6-31G* basis set at B3LYP and MP2 level. The starting geometries employed for all optimizations were resulted from molecular mechanics using SYBYL force field and subsequent semi-empirical PM3 optimizations. The calculations for energy of intermediates as well as transition states were also taken with ab initio calculations using the 6-31G* basis set at HF and MP2 level together with density functional B3LYP.

EXPERIMENTAL
1H and 13C NMR spectra were recorded at 60 MHz on a JEOL PMX60SI and at 59.5 MHz on a Bruker AC250, respectively.

Monitoring Experiments for the Cyclization of 3-Dimethylhydrazono-3-(p-tolyl)-1,1,1-trifluoro-2-propanone (1, R= p-Tol) and the H-D Exchange Reaction of 3-Methyl-5-(p-tolyl)-6-trifluoromethyl-3,6-dihydro-2H-[1,3,4]oxadiazine (2, R= p-Tol)
To 1 (R= p-Tol) or 2 (R= p-Tol, 77.5 mg, 0.300 mmol) in φ5 NMR glass tube was added trifluoroacetic acid-d (0.45 mL, 5.84 mmol). The well-mixed solution was immediately monitored at 35°C using 1H NMR spectroscopy. The rate for the cyclization reaction of 1 (R= p-Tol) was measured by monitoring the appearance of methylene protons of 2’ (R= p-Tol), and that for H-D exchange reaction of 2 (R= p-Tol) was done by following the disappearance of methine proton of 2 (R= p-Tol). The rates were measured in duplicate.

Preparation of 2-τ-Butylmethyldrazono-1,2-diphenylethanone (14)
To a mixture of diphenylethanedione (4.205 g, 20 mmol) and tert-BuNHNH2·HCl (3.735 g, 30 mmol) dissolved in MeOH (200 mL) was added NaOAc (2.461 g, 30 mmol), and the mixture was stirred for 4
days at ambient temperature. The reaction mixture was poured into saturated aq. Na₂CO₃ (100 mL) and the organic layer was extracted with CH₂Cl₂ (2 x 100 mL). The extract was dried over Na₂SO₄ and the solvent was removed in vacuo. The residue was dissolved in DMF (48.9 mL), then KOH (1.614 g, 24.5 mmol) was added, and the mixture was stirred for 30 min at 40°C. After cooling to ambient temperature, MeI (10.2 mL, 163 mmol) was added and the mixture was stirred for 24 h. The mixture was poured into 1N HCl (100 mL) and the organic layer was extracted with CH₂Cl₂ (2 x 100 mL). The extract was washed with 1N aq. NaHCO₃ (100 mL) and dried over Na₂SO₄. Removal of the solvent followed by fractionation of the residual materials by silica gel column chromatography (benzene) gave 3.438 g (58%) of 14. Without further purification this was used in the following experiment.

**Cyclization Reaction of 2-tert-Butylmethylhydrazono-1,2-diphenylethanone (14)**

To 14 (320 mg, 1.1 mmol) dissolved in AcOH (2.2 mL, 38.1 mmol) was added water (0.75 mL, 41.7 mmol). After stirring for 20 h at 70°C, the mixture was poured into 0.5N aq. Na₂CO₃ (100 mL) and the organic layer was extracted with CH₂Cl₂ (2 x 50 mL). The extract was dried over Na₂SO₄ and the solvent was evaporated. Fractionation of the residual materials by preparative TLC (benzene) afforded 14 mg (5%, Rf= 0.1) of 3-tert-butyl-5,6-diphenyl- 3,4-dihydro-2H-[1,3,4]oxadiazine (17) as pale yellow crystals, mp 97-99°C (cyclohexane): ^13^C NMR (CDCl₃) δ 27.8 (CH₃), 59.1 (CCH₃), 59.3 (CH₂, JCH= 149.6 Hz), 126.9, 127.1, 127.9, 128.0, 129.3, 129.4, 136.2, 137.0 (C₆H₅), 140.8 (NC=), 158.4 (OC=); ^1^H NMR (CDCl₃) δ 1.40 (s, 9H, tert-Bu), 4.33 (s, 2H, CH₂), 6.91-7.49 (m, 11H, C₆H₅ and NH); IR (KBr) ν 2980 (m), 1600 (m), 1570 (m), 1440 (m), 1370 (m), 1205 (s), 1150 (s), 1040 (m), 960 (m) cm⁻¹.

**REFERENCES AND NOTES**


6. On the basis of our calculations (RMP2/6-31G*), oxadiazine tautomer (9) is estimated as 15.0 Kcal/mol less stable than 2 (R= H). Such tautomer like 9 could not be detected in any experiment we examined so far using hydrazones (1).

8. The difference of $\Delta H$ between the reaction from 18 to 19 and that from 4' to 9 is thought to be mainly owing to the instability of 4' compared to 18. Electron-withdrawing CF$_3$ group is directly attached to the cation conjugate system on 4', whereas CH$_3$ hyperconjugation should stabilize cation (18) effectively. The following proton exchange reaction is 8.1 Kcal/mol exothermic (RB3LYP/6-31G*//RB3LYP/6-31G*).

\[
4' (R= \text{Ph}) + \begin{array}{c} \text{N} \\ \text{N} \\ \text{CH}_3 \\ \text{CH}_3 \\ \text{Ph} \end{array} \rightleftharpoons \begin{array}{c} \text{N} \\ \text{N} \\ \text{CH}_3 \\ \text{CH}_3 \\ \text{Ph} \end{array} + 18
\]

Such substituent effects should be insignificant for intermediates 9 and 13.

9. Larger resonance energy expected in oxadiazine (17) in comparison with 16 should be the main reason why 16 could not be isolated at all. Semi-empirical PM3 calculations suggest that 17 is about 0.8 Kcal/mol more stable than 16.

10. Wavefunction, Inc.


15. $^1$H NMR (CDCl$_3$) $\delta$ 1.13 (s, 9H, tert-Bu), 2.45 (s, 3H, NCH$_3$), 6.97-7.87 (m, 10H, C$_6$H$_5$).