OXIDATIVE CYCLIZATION OF
TRIFLUOROACETYLATED ALDEHYDE DIMETHYLHYDRAZONES.
A NEW CONVENIENT SYNTHESIS OF
TRIFLUOROMETHYLATED OXADIAZINE DERIVATIVES

Yasuhiro Kamitori, Masaru Nojo, * Ryōichi Masuda,
Toshihiko Fujitani, and Katsumichi Sukegawa
Department of Industrial Chemistry, Faculty of Engineering,
Kobe University, Kobe 657, Japan

Abstract- Trifluoromethylated oxadiazine derivatives (2) were conveniently synthesized by NaIO₄-mediated cyclization of hydrazones (1) which are readily obtained by trifluoroacetylation of aldehyde dimethylhydrazones.

Oxadiazines, particularly their fluoro derivatives, have increasingly attracted attention in medicinal and agricultural fields because of their interesting potential biological activities.¹-³ However, little is known about their synthetic methodology. During our investigation on the reactions of 1,1,1-trifluoroalkane-2,3-dione 3-dialkylhydrazones which are readily obtainable by acylation of aldehyde dialkylhydrazones with trifluoroacetic anhydride, we found a novel cyclization reaction of 3-aryl-1,1,1-trifluoropropane-2,3-dione 3-dimethylhydrazones (1) affording new derivatives of oxadiazine, 6-trifluoromethyl-3,6-dihydro-2H-1,3,4-oxadiazines (2). This cyclization was effectively promoted by silica gel,⁴ trifluoroacetic acid,⁵ and hot acetic acid.⁵ In our continuous efforts to elucidate the mechanism of this cyclization reaction⁶ more in detail, we tried a number of reagents to mediate such a type of cyclization. After several trials,
we have found that NaIO4 induces a novel oxidative cyclization of 1 to give a similar type of oxadiazine derivative, 6-hydroxy-6-trifluoromethyl-3,6-dihydro-2H-1,3,4-oxadiazines (3) in satisfactory yields. We now wish to communicate the results.

Several 3-aryl-1,1,1-trifluoropropane-2,3-dione 3-dimethylhydrazones (1) were easily prepared from the corresponding arenecarbaldehyde according to the previously reported method. Treatment of 1 with NaIO4 in THF/H2O, in most cases at ambient temperature, afforded the corresponding oxadiazine (3) in satisfactory yields. We carried out the reaction under two different conditions where THF/H2O= 2/3 (Method A) and THF/H2O= 2/1 (Method B) were used as solvents. The reaction proceeded more rapidly in the former solvent. Although yields of 3 did not vary appreciably under these two conditions, considerable amounts of oxadiazine (3) was

Table. Cyclization of 1 to 3.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar Method</th>
<th>Yield</th>
<th>mp</th>
<th>H NMR δ, ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Method a</td>
<td>Yield</td>
<td>mp</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Ph A 120</td>
<td>63</td>
<td>2.97(s, 3H, Me), 3.00-3.67(br, 1H, OH), 4.14-4.71(ABq, J= 8 Hz, 2H, CH2, 7.12-7.33, 7.50-7.70(m, 5H, Ar)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>p-Tol B 119</td>
<td>72</td>
<td>2.32(s, 3H, p-Me), 2.95(s, 3H, NMe), 3.65-3.95(br, 2H, OH), 4.05-4.65(ABq, J= 8 Hz, 2H, CH2, 7.05, 7.54(d, J= 8 Hz, 4H, Ar)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>m-Tol B 110</td>
<td>63</td>
<td>2.33(s, 3H, m-Me), 2.57-2.95(br, 1H, OH), 2.98(s, 3H, NMe), 4.12-4.68(ABq, J= 8 Hz, 2H, CH2, 7.00-7.55(m, 4H, Ar)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>o-Tol C 119</td>
<td>65</td>
<td>2.36(s, 3H, o-Me), 2.94(s, 3H, NMe), 3.17-3.48(br, 1H, OH), 4.20-4.70(ABq, J= 8 Hz 2H, CH2, 6.97-7.51(m, 4H, Ar)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>p-MeOC6H4 B 124</td>
<td>52</td>
<td>2.97(s, 3H, NMe), 3.18-3.47(br, 1H, OH), 3.77(s, 3H, OMe), 4.10-4.67(ABq, J= 7 Hz, 2H, CH2, 6.77, 7.60(d, J= 9 Hz, 4H, Ar)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>p-ClC6H4 A 142</td>
<td>73</td>
<td>2.94(s, 3H, NMe), 2.70-3.00(br, 1H, OH), 4.12-4.72(ABq, J= 8 Hz, 2H, CH2, 7.20, 7.71(d, J= 8 Hz, 4H, Ar)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>p-O2NC6H4 A 154</td>
<td>71</td>
<td>2.90-3.10, 3.05(br and s, 4H, OH and NMe), 4.21-4.83 (ABq, J= 8 Hz, 2H, CH2, 7.38-8.20(q, J= 9 Hz, 4H, Ar)</td>
<td></td>
</tr>
</tbody>
</table>

Method A: room temperature, 2 d in THF/H2O= 2/3, Method B: room temperature, 5 d in THF/H2O= 2/1, Method C: 50°C, 3 d, in THF/H2O= 2/1. Isolated yields.

1H NMR spectra were recorded on a JEOL PMX 60SI spectrometer in CDCl3 solutions.

Method A: room temperature, 2 d in THF/H2O= 2/3, Method B: room temperature, 5 d in THF/H2O= 2/1, Method C: 50°C, 3 d, in THF/H2O= 2/1. Isolated yields. 1H NMR spectra were recorded on a JEOL PMX 60SI spectrometer in CDCl3 solutions.
obtained together with \( \mathcal{J} \) under the condition of Method B in the cases of entries 1, 6 and 7. In contrast, undesirable hydrolysis of \( \mathcal{J} \) to 3-aryl-1,1,1-trifluoropropane-2,3-dione was not negligible under the condition of Method A, particularly in the cases of entries 2, 3 and 5. In place of THF/H\(_2\)O we also examined several alcoholic solvents to result in lower yields of \( \mathcal{J} \). Except for the case of entry 3 the reaction at higher temperature afforded considerable amounts of 3-aryl-1,1,1-trifluoropropane-2,3-dione as a major by-product together with \( \mathcal{J} \). However, \( \mathcal{J} \) bearing sterically hindered aryl group (entry 4) needed heating at 50°C (Method C) for efficient conversion of \( \mathcal{J} \) to \( \mathcal{J} \).

We also tried the cyclization of 3-((t-butyllmethyl)hydrazones of 3-(p-tolyl)-1,1,1-trifluoropropane-2,3-dione (4a) and 1,1,1-trifluorodecane-2,3-dione (4b)\(^9\) to the corresponding oxadiazines. In these cases too, expected products (5a)\(^10\) and (5b)\(^10\) were successfully obtained by Method C, but unfortunately, their yields were lower than those of \( \mathcal{J} \) from \( \mathcal{J} \).

\[
\begin{align*}
&\quad \text{Me}^+ \quad \text{COCF}_3^- \quad \text{NaIO}_4(4\text{eq.}) \quad \text{THF/H}_2\text{O, 50°C, 2 d} \quad \text{R} \quad \text{O} \quad \text{CF}_3^- \\
&\quad \text{R: p-Tol 4a} \quad 5\% \quad 32\% \\
&\quad \text{H-C}_6\text{H}_5 \quad 4b \quad 5b \quad 38\%
\end{align*}
\]

It is obvious that \( \mathcal{J} \) is not derived by oxidation of initially formed \( \mathcal{J} \), because \( \mathcal{J} \) remained strictly unchanged by both Method A and B which can converted \( \mathcal{J} \) (Ar= p-Tol) to the corresponding \( \mathcal{J} \) completely. Therefore \( \mathcal{J} \) is thought to be formed directly from \( \mathcal{J} \) by a mechanism quite different from that for \( \mathcal{J} \) from \( \mathcal{J} \). Detailed mechanistic studies for this cyclization reaction are now under investigation.

**Typical Procedures** (Method A): To a solution of NaIO\(_4\) (856 mg, 4 mmol) in water (15 ml) was added a solution of \( \mathcal{J} \) (Ar= Ph, 244 mg, 1 mmol) in THF (10 ml) and the mixture was well stirred for 2 days at room temperature. The reaction mixture was poured into water (100 ml), extracted with CH\(_2\)Cl\(_2\) (50 ml X 2). The organic layer was washed with 0.1N NaHCO\(_3\) solution (100 ml), dried over MgSO\(_4\), and the solvent was removed to afford \( \mathcal{J} \) (Ar= Ph, 165 mg, 63%) as pale yellow crystals.\(^11\)

**REFERENCES AND NOTES**


6. Formation of \( \mathcal{Z} \) was also observed when \( \mathcal{I} \) was heated or dissolved in polar solvents. See ref 7.


9. Unfortunately 1,1,1-trifluoroalkane-2,3-dione 3-dimethylhydrazones can not be obtained as yet. All our attempts about trifluoroacetylation of alkanecarbaldehyde dimethylhydrazones accessible to them resulted in failure in spite of any our efforts. See ref. 8.

10. 5a: 120°C/5.5 torr (oven temperature of Kugelrohr distillation); \(^1\)H nmr (CDCl\(_3\)) \( \delta \) 1.27 (s, 9H, \( \text{t-Bu} \)), 2.31 (s, 3H, \( \text{p-Me} \)), 2.95-3.30 (br, 1H, \( \text{OH} \)), 4.11-4.96 (ABq, \( J = 8 \text{ Hz} \), 2H, CH\(_2\)), 7.00, 7.57 (d, \( J = 8 \text{ Hz} \), 4H, Ar); ir (KBr) 3040-3480 (m, br), 2950 (s), 1450 (m), 1047 (s), 936 (m), 1823 (m) cm\(^{-1}\). 

11. \( \mathcal{Z} \) (Ar= Ph);ir (KBr) 3600-2600 (m, br), 1190 (s), 1180 (m), 1170 (s), 765 (s), 690 (m) cm\(^{-1}\); \(^1^3\)C nmr (CDCl\(_3\)) \( \delta \) 40.7 (CH\(_3\)), 74.1 (C-2, \(^1^J_{\text{CH}} = 157 \text{ Hz} \)), 89.0 (C-6, \(^2^J_{\text{CF}} = 35.8 \text{ Hz} \)), 121.8 (CF\(_3\)), \(^1^J_{\text{CF}} = 288 \text{ Hz} \), 128.0, 128.6, 135.1 (Ar), 140.0 (C-4).

Received, 12th June, 1991