

## A FACILE SYNTHESIS OF FLUORINE-CONTAINING BICYCLIC OXADIAZINES

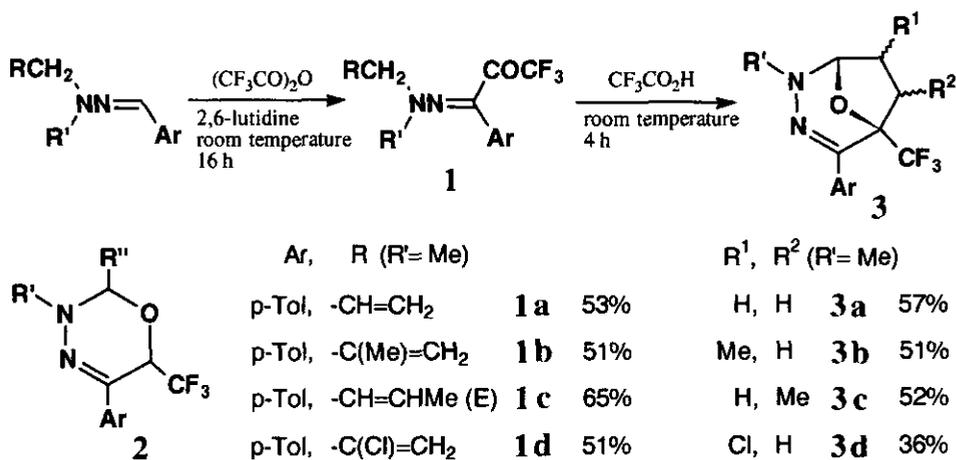
Yasuhiro Kamitori, Masaru Hojo,\* Ryoichi Masuda, Toru Numai,  
Katsumasa Yamamoto, and Isao Nakamura

Department of Industrial Chemistry, Faculty of Engineering,  
Kobe University, Kobe 657, Japan

**Abstract-** By treatment with trifluoroacetic acid fluorine-containing bicyclic oxadiazines (3) could be synthesized in satisfactory yields from hydrazones (1) which were prepared from aldehyde methylhydrazones bearing N-allylic group and trifluoroacetic anhydride.

Fluorine-containing heterocycles are one of the most fascinating target for many synthetic organic chemists because of their potentially high biological activity.<sup>1</sup> Recently we found an acid catalyzed novel cyclization reaction of hydrazones (1) which are easily obtainable from the corresponding aldehydes<sup>2,3</sup> to give 6-trifluoromethyl-3,6-dihydro-2H-1,3,4-oxadiazines (2).<sup>4,5</sup> In the course of our investigation in this field, we examined a reaction of hydrazones bearing N-allylic group in trifluoroacetic acid. Unexpectedly, "normal" cyclization product (2) was not detected in the crude products at all and a new fluorine-containing bicyclic oxadiazine derivative (3) was obtained as a main product. Now we wish to communicate the results.

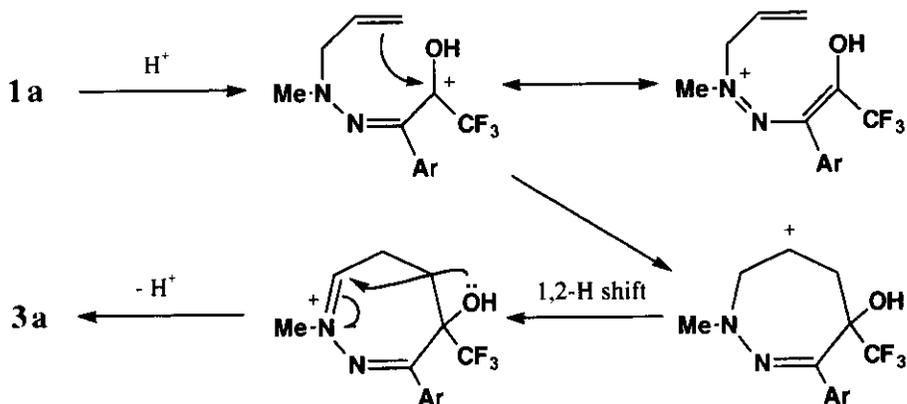
p-Tolualdehyde N-allyl-N-methylhydrazone prepared from p-tolualdehyde methylhydrazone and allyl bromide was acylated with two equiv. of trifluoroacetic anhydride in dry chloroform in the usual manner<sup>2,3</sup> to afford trifluoroacetylated hydrazone (1a) in 53% yields. This compound (1a, 1 mmol) was dissolved in trifluoroacetic acid (20 mmol) and stirred well for 4 h at room temperature. The reaction mixture was neutralized with 1N Na<sub>2</sub>CO<sub>3</sub> and successively extracted with CH<sub>2</sub>Cl<sub>2</sub>. The extract was washed with water and dried over Na<sub>2</sub>SO<sub>4</sub>. After removal of the solvent, the residue was submitted to silica gel column chromatography to give bicyclic oxadiazine (3a) in 57% yields. The structure



of **3a** was confirmed by ir, and <sup>1</sup>H and <sup>13</sup>C nmr spectra and microcombustion analysis.<sup>6</sup> Particularly, <sup>13</sup>C nmr spectra provided diagnostic informations for structure of **3a**: (ppm in CDCl<sub>3</sub>) 21.1 (p-Me), 31.0 (CHCH<sub>2</sub>), 36.7 (CF<sub>3</sub>CCH<sub>2</sub>), 41.1 (NMe), 80.7 (<sup>2</sup>J<sub>CF</sub> = 30.9 Hz, CF<sub>3</sub>C), 89.3 (OCH), 123.4 (<sup>1</sup>J<sub>CF</sub> = 282 Hz, CF<sub>3</sub>), 128.0, 128.6, 132.6, 138.0 (Ar), 145.9 (N=C).

Quite similarly, **3b** and **3c** could be obtained from **1b** and **1c**, respectively, in satisfactory yields. Column chromatography of crude **3b** afforded endo **3b** in 40% and exo **3b** in 11% yield. In the case of **3c**, exo isomer was obtained in 52% yield, but endo isomer which probably occurred together with exo **3c** could not be isolated from the reaction mixtures. In <sup>1</sup>H nmr spectra a bridge-head proton of endo **3b** appears as doublet at 4.81 ppm with vicinal coupling of 4.0 Hz, and that of exo **3b** as singlet at 4.68 ppm because of minimized vicinal H-H coupling of this configuration. Apparent through-space H-F coupling (ca. 1.9 Hz) was observed for bridge methyl protons of exo **3c**. Under the same reaction conditions, however, **1c** afforded a monocyclic oxadiazines (**2**) (R' = CH<sub>2</sub>C(Cl)=CH<sub>2</sub> and R'' = H, 35%) together with expected bicyclic oxadiazines (**3d**) (exo 19% and endo 17%).

Although both **2** and **3** have a common oxadiazine skeleton, **3** should not be derived from **2** (R' = Me, R'' = C(R<sup>1</sup>)=CHR<sup>2</sup>) initially formed from **1**, because cyclization of **2** leading to **3** includes intramolecular cycloaddition of C-H part to C=C bond which probably requires



high energy and therefore hardly occurs under the present conditions. In fact, none of species such as **2** could be detected in any stage of the reaction of **1a-c** to **3a-c**, and conversion of **2** ( $R^1 = CH_2C(Cl)=CH_2$ ,  $R'' = H$ ) dissolved in trifluoroacetic acid to **3d** could not be observed at all even after 24 h. In addition, under non-acidic conditions conversion of **1** ( $R = Me$ ) to **2** ( $R^1 = Me$ ,  $R'' = H$ ) proceeds by simple heating<sup>2</sup> whereas neither **3a** nor **2** was obtained from **1a** under the same conditions. These suggest cyclization mechanism of **1** to **3** is quite different from that of **1** to **2**.<sup>7</sup> At present, an ionic mechanism illustrated in the above Scheme seems to be the most reasonable for the cyclization reaction of **1** to **3**. Relatively low yield of **3d** as well as formation of **2** ( $R^1 = CH_2C(Cl)=CH_2$ ,  $R'' = H$ ) instead of **3d** seen in the reaction of **1d** bearing electron deficient chlorinated olefine are well compatible with above mechanism. Detailed mechanistic studies are now in progress in this laboratory.

## REFERENCES AND NOTES

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6. 3a: mp 57°C;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ , 250 MHz)  $\delta$  2.33, 2.15–2.41, 2.65–2.80 (s, m and m, 7H,  $\underline{p}$ -Me and  $\text{CH}_2$ ), 2.94 (s, 3H, NMe), 5.13 (d,  $J$  = 5.2 Hz, 1H, CH), 7.00–7.30 (q,  $J$  = 7.9 Hz, 4H, ArH); ir (KBr) 1513 (m), 1453 (s), 1353 (s), 1250 (s), 1160 (s), 1092 (m), 1049 (s), 1017 (m), 942 (s), 896 (s)  $\text{cm}^{-1}$ . Anal. Calcd for  $\text{C}_{14}\text{H}_{15}\text{N}_2\text{OF}_3$ : C, 59.15; H, 5.32; N, 9.85; F, 20.05. Found C, 59.09; H, 5.19; N, 9.87; F, 20.09. 3b (exo): 130°C/4 torr (oven temperature of Kugelrohr distillation);  $^1\text{H}$  nmr ( $\text{CDCl}_3$ , 250 MHz)  $\delta$  1.18 (d,  $J$  = 7.0 Hz, 3H,  $\underline{\text{CHMe}}$ ), 1.89 (dd,  $J$  = 11.8 and 5.4 Hz, 1H,  $\text{CH}_2$ ), 2.32 (s, 3H,  $\underline{p}$ -Me), 2.60–2.90 (m, 1H,  $\underline{\text{CHMe}}$ ), 2.90–3.00, 2.97 (m and s, 4H,  $\text{CH}_2$  and NMe), 4.68 (s, 1H, OCH), 7.05–7.30 (q,  $J$  = 8.2 Hz, 4H, ArH). 3b (endo): 160°C/4 torr (oven temperature of Kugelrohr distillation);  $^1\text{H}$  nmr ( $\text{CDCl}_3$ , 250 MHz)  $\delta$  1.05 (d,  $J$  = 6.2 Hz, 3H,  $\underline{\text{CHMe}}$ ), 2.04 (d,  $J$  = 7.5 Hz, 1H,  $\text{CH}_2$ ), 2.31 (s, 3H,  $\underline{p}$ -Me), 2.40–2.60 (m, 2H,  $\text{CH}_2$  and  $\underline{\text{CHMe}}$ ), 2.99 (s, 3H, NMe), 4.81 (d,  $J$  = 4.0 Hz, 1H, OCH), 7.00–7.26 (q,  $J$  = 7.9 Hz, 4H, ArH). 3c (exo): mp 82°C;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ , 250 MHz)  $\delta$  1.08–1.18 (dq,  $J$  = 7.0 and 1.9 Hz, 3H,  $\underline{\text{CHMe}}$ ), 1.67–1.79 (m, 1H,  $\text{CH}_2$ ), 2.30 (s, 3H,  $\underline{p}$ -Me), 2.49–2.60 (dd,  $J$  = 13.5 and 8.3 Hz, 1H,  $\text{CH}_2$ ), 2.87 (s, 3H, NMe), 3.15–3.29 (m, 1H,  $\underline{\text{CHMe}}$ ), 5.10 (d,  $J$  = 6.3 Hz, 1H, OCH), 7.08–7.32 (q,  $J$  = 7.9 Hz, 4H, ArH). 3d (exo): mp 155.0°C;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ , 60 MHz)  $\delta$  2.31 (s, 3H,  $\underline{p}$ -Me), 2.40–2.77 (m, 1H,  $\text{CH}_2$ ), 3.03, 3.02–3.45 (s and dd,  $J$  = 14.0 and 8.0 Hz, 4H, NMe and  $\text{CH}_2$ ), 4.58 (dd,  $J$  = 7.4 and 3.6 Hz, 1H, ClCH), 5.03 (s, 1H, OCH), 7.08 (s, 4H, ArH). 3d (endo): mp 90.5°C;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ , 60 MHz)  $\delta$  2.32 (s, 3H,  $\underline{p}$ -Me), 2.38–3.00 (m, 2H,  $\text{CH}_2$ ), 3.11 (s, 3H, NMe), 4.33 (quint,  $J$  = 4.6 Hz, 1H, ClCH), 4.91 (d,  $J$  = 4.6 Hz, 1H, OCH), 6.93–7.31 (br s, 4H, ArH). 2 ( $\text{R}' = \text{CH}_2\text{C}(\text{Cl})=\text{CH}_2$ ,  $\text{R}'' = \text{H}$ ): 132°C/5 torr (oven temperature of Kugelrohr distillation);  $^1\text{H}$  nmr ( $\text{CDCl}_3$ , 60 MHz)  $\delta$  2.68 (s, 3H,  $\underline{p}$ -Me), 3.90 (s, 2H, NCH<sub>2</sub>), 4.15–4.63 (ABq,  $J$  = 7.6 Hz, 2H, OCH<sub>2</sub>), 4.93 (q,  $J$  = 6.6 Hz, 1H, CH), 5.26, 5.36 (d,  $J$  = 1.0 Hz, 2H, =CH<sub>2</sub>), 6.80–7.35 (q,  $J$  = 8.0 Hz, 4H, ArH).
7. A mechanism including 1,5-sigmatropic rearrangement of  $\underline{\text{N}}$ -alkyl hydrogen atom ( $-\text{NCH}-$ ) to carbonyl carbon center as a key step seems to be most suitable for the reaction of 1 to 2. Detailed mechanism will be reported in near future.

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