A FACILE SYNTHESIS OF FLUORINE-CONTAINING BICYCLIC OXADIAZINES

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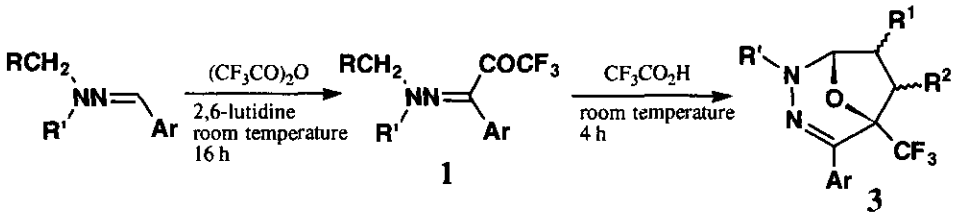
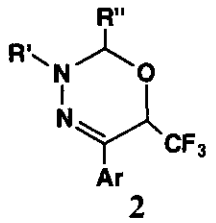
Abstract- By treatment with trifluoroacetic acid fluorine-containing bicyclic oxadiazines (3) could be synthesized in satisfactory yields from hydrazones (1) which were prepared from aldehyde methylhydrazones bearing N-allylic group and trifluoroacetic anhydride.

Fluorine-containing heterocycles are one of the most fascinating target for many synthetic organic chemists because of their potentially high biological activity.[1] Recently we found an acid catalyzed novel cyclization reaction of hydrazones (1) which are easily obtainable from the corresponding aldehydes[2,3] to give 6-trifluoromethyl-3,6-dihydro-2H-1,3,4-oxadiazines (2).[4,5] 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[2,3] 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_2CO_3 and successively extracted with CH_2Cl_2. The extract was washed with water and dried over Na_2SO_4. After removal of the solvent, the residue was submitted to silica gel column chromatography to give bicyclic oxadiazine (3a) in 57% yields. The structure



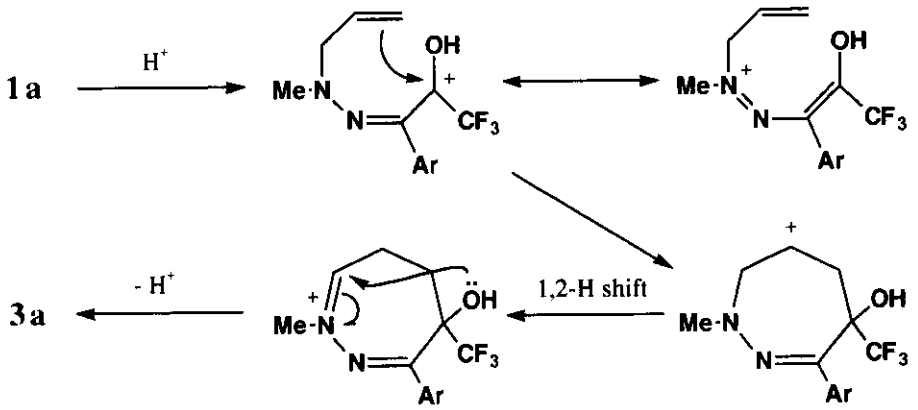


Ar, R (R'= Me)			R^1, R^2 (R'= Me)		
p-Tol, -CH=CH_2	**1a**	53%	H, H	**3a**	57%
p-Tol, -C(Me)=CH_2	**1b**	51%	Me, H	**3b**	51%
p-Tol, -CH=CHMe (E)	**1c**	65%	H, Me	**3c**	52%
p-Tol, -C(Cl)=CH_2	**1d**	51%	Cl, H	**3d**	36%

of 3a was confirmed by ir, and ^1H and ^{13}C nmr spectra and microcombustion analysis.[6] Particularly, ^{13}C nmr spectra provided diagnostic informations for structure of 3a: (ppm in $CDCl_3$) 21.1 (p-Me), 31.0 ($CHCH_2$), 36.7 (CF_3CCH_2), 41.1 (NMe), 80.7 ($^2J_{CF}$= 30.9 Hz, CF_3C), 89.3 (OCH), 123.4 ($^1J_{CF}$= 282 Hz, CF_3), 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 ^1H 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'= $CH_2C(Cl)=CH_2$ 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''= $C(R^1)=CHR^2$) 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'= $CH_2C(Cl)=CH_2$, 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'= Me, R"= H) proceeds by simple heating[2] 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.[7] 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'= $CH_2C(Cl)=CH_2$, 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.

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6. 3a: mp 57°C; ^{1}H nmr ($CDCl_3$, 250 MHz) δ 2.33, 2.15-2.41, 2.65-2.80 (s, m and m, 7H, p-Me and 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) cm^{-1}. Anal. Calcd for $C_{14}H_{15}N_2OF_3$: 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}H nmr ($CDCl_3$, 250 MHz) δ 1.18 (d, J= 7.0 Hz, 3H, CHMe), 1.89 (dd, J= 11.8 and 5.4 Hz, 1H, CH_2), 2.32 (s, 3H, p-Me), 2.60-2.90 (m, 1H, CHMe), 2.90-3.00, 2.97 (m and s, 4H, 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}H nmr ($CDCl_3$, 250 MHz) δ 1.05 (d, J= 6.2 Hz, 3H, CHMe), 2.04 (d, J= 7.5 Hz, 1H, CH_2), 2.31 (s, 3H, p-Me), 2.40-2.60 (m, 2H, CH_2 and 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}H nmr ($CDCl_3$, 250 MHz) δ 1.08-1.18 (dq, J= 7.0 and 1.9 Hz, 3H, CHMe), 1.67-1.79 (m, 1H, CH_2), 2.30 (s, 3H, p-Me), 2.49-2.60 (dd, J= 13.5 and 8.3 Hz, 1H, CH_2), 2.87 (s, 3H, NMe), 3.15-3.29 (m, 1H, 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}H nmr ($CDCl_3$, 60 MHz) δ 2.31 (s, 3H, p-Me), 2.40-2.77 (m, 1H, CH_2), 3.03, 3.02-3.45 (s and dd, J= 14.0 and 8.0 Hz, 4H, NMe and 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}H nmr ($CDCl_3$, 60 MHz) δ 2.32 (s, 3H, p-Me), 2.38-3.00 (m, 2H, 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 (R'= $CH_2C(Cl)=CH_2$, R"= H): 132°C/$_5$ torr (oven temperature of Kugelrohr distillation); ^{1}H nmr ($CDCl_3$, 60 MHz) δ 2.68 (s, 3H, p-Me), 3.90 (s, 2H, NCH_2), 4.15-4.63 (ABq, J= 7.6 Hz, 2H, OCH_2), 4.93 (q, J= 6.6 Hz, 1H, CH), 5.26, 5.36 (d, J= 1.0 Hz, 2H, $=CH_2$), 6.80-7.35 (q, J= 8.0 Hz, 4H, ArH).

7. A mechanism including 1,5-sigmatropic rearrangement of N-alkyl hydrogen atom (-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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