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

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

Abstruct- Trifluoromethylated oxadiazine derivatives (3) were conveniently synthesized by $NaIO_4$-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 reaction[6] more in detail, we tried a number of reagents to mediate such a type of cyclization. After several trials,

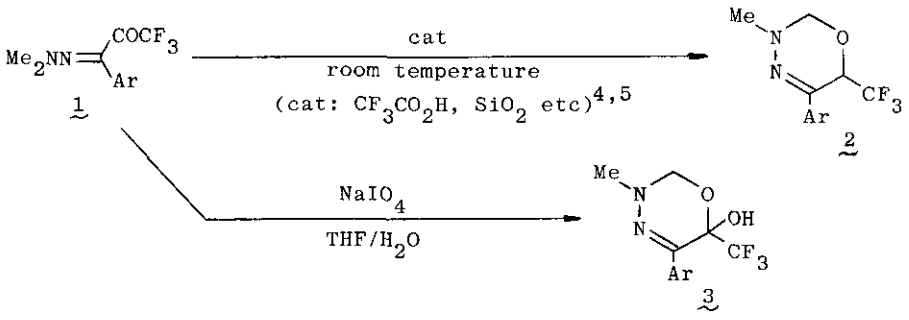


Table. Cyclization of 1 to 3.

Entry	Ar	Method[a]	Yield[b] %	mp °C	^{1}H nmr[c] δ, ppm
1	Ph	A	63	120 (CCl_4)	2.97(s, 3H, Me), 3.00-3.67(br, 1H, OH), 4.14-4.71(ABq, J= 8 Hz, 2H, CH_2), 7.12-7.33, 7.50-7.70(m, 5H, Ar)
2	p-Tol	B	72	119 (CCl_4)	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, CH_2), 7.05, 7.54(d, J= 8 Hz, 4H, Ar)
3	m-Tol	B	63	110 (c-C_6H_{12})	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, CH_2), 7.00-7.55(m, 4H, Ar)
4	o-Tol	C	65	119 (c-C_6H_{12})	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, CH_2), 6.97-7.51(m, 4H, Ar)
5	p-$MeOC_6H_4$	B	52	124 (c-C_6H_{12})	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, CH_2), 6.77, 7.60(d, J= 9 Hz, 4H, Ar)
6	p-ClC_6H_4	A	73	142 ($CHCl_3$)	2.94(s, 3H, NMe), 2.70-3.00(br, 1H, OH), 4.12-4.72(ABq, J= 8 Hz, 2H, CH_2), 7.20, 7.71 (d, J= 8 Hz, 4H, Ar)
7	p-$O_2NC_6H_4$	A	71	154 ($CHCl_3$)	2.90-3.10, 3.05(br and s, 4H, OH and NMe), 4.21-4.83 (ABq, J= 8 Hz, 2H, CH_2), 7.78-8.20 (q, J= 9 Hz, 4H, Ar)

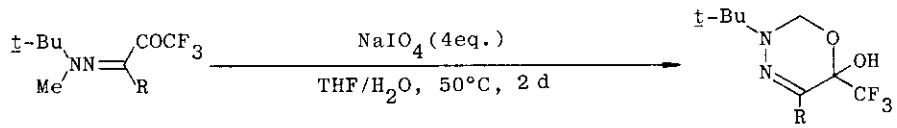
[a] Method A: room temperature, 2 d in THF/H_2O= 2/3, Method B: room temperature, 5 d in THF/H_2O= 2/1, Method C: 50°C, 3 d, in THF/H_2O= 2/1. [b] Isolated yields. [c] ^{1}H Nmr spectra were recorded on a JEOL PMX 60SI spectrometer in $CDCl_3$ solutions.

we have found that $NaIO_4$ 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.[7,8] Treatment of 1 with $NaIO_4$ in THF/H_2O, 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/H_2O= 2/3 (Method A) and THF/H_2O= 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 (2) was

obtained together with 3 under the condition of Method B in the cases of entries 1, 6 and 7. In contrast, undesirable hydrolysis of 3 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_2O we also examined several alcoholic solvents to result in lower yields of 3. 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 3. However, 1 bearing sterically hindered aryl group (entry 4) needed heating at 50°C (Method C) for efficient conversion of 1 to 3.

We also tried the cyclization of 3-(t-butyl)methylhydrazones 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 3 from 1.



R: p-Tol 4a — 5a 32%

n-C_6H_{13} 4b — 5b 38%

It is obvious that 3 is not derived by oxidation of initially formed 2, because 2 remained strictly unchanged by both Method A and B which can converted 1 (Ar= p-Tol) to the corresponding 3 completely. Therefore 3 is thought to be formed directly from 1 by a mechanism quite different from that for 2 from 1. 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 1 (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_2Cl_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 3 (Ar= Ph, 165 mg, 63%) as pale yellow crystals.[11]

REFERENCES AND NOTES

1. R. B. Hargreaves, B. J. McLoughlin, and S. D. Mills, European Patent 85227 (1983) (Chem. Abstr., 1984, 100, 6561). I. Sircar, M. H. Cain, and J. G.

Topliss, U.S. Patent 4508718 (1984) (Chem. Abstr., 1985, 103, 6373).

2. Japanese Patent 58,131,973 (1983), Imperial Chemical Industries PLC. (Chem. Abstr., 1983, 100, 6567). Japanese Patent 59,062,578 (1984), Mitsui Toatsu Chemicals Inc. (Chem. Abstr., 1983, 101, 72767).
3. K. Suhasin, T. V. P. Rao, and V. Thirupathaiah, Curr. Sci., 1983, 52, 1133 (Chem. Abstr., 1984, 100, 156574).
4. Y. Kamitori, M. Hojo, R. Masuda, T. Fujitani, S. Ohara, and T. Yokoyama, Synthesis, 1988, 208.
5. Y. Kamitori, M. Hojo, R. Masuda, S. Ohara, K. Kawasaki, and Y. Kawamura, Synthesis, 1990, 493.
6. Formation of 2 was also observed when 1 was heated or dissolved in polar solvents. See ref 7.
7. Y. Kamitori, M. Hojo, R. Masuda, T. Fujitani, S. Ohara, and T. Yokoyama, J. Org. Chem., 1988, 53, 129.
8. Y. Kamitori, M. Hojo, R. Masuda, T. Yoshida, S. Ohara, and N. Yoshikawa, J. Org. Chem., 1988, 53, 519.
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 ($CDCl_3$) δ 1.27 (s, 9H, t-Bu), 2.31 (s, 3H, p-Me), 2.95-3.30 (br, 1H, OH), 4.11-4.96 (ABq, J= 8 Hz, 2H, CH_2), 7.00, 7.57 (d, J= 8 Hz, 4H, Ar); ir (KBr) 3040-3480 (m, br), 2950 (s), 1261 (m), 1195(s), 1111 (s), 1047 (m), 936 (m), 823 (m) cm^{-1}. 5b: 68°C/$_5$ torr (oven temperature of Kugelrohr distillation); ^{1}H nmr ($CDCl_3$) δ 0.65-2.55, 1.20 (m and s, 22H, n-C_6H_{13} and t-Bu), 2.68-3.17 (br, 1H, OH), 3.85-4.82 (ABq, J= 7 Hz, 2H, CH_2); ir (KBr) 3060-3570 (br, m), 2910 (s), 1183 (s), 1090 (m), 1063 (m), 1018 (m) cm^{-1}. Anal. Calcd for $C_{14}H_{25}N_2O_2F_3$: C, 54.18; H, 8.12; N, 9.03; F, 18.37. Found C, 54.55; H, 8.33; N, 8.85; F, 18.11.
11. 3 (Ar= Ph);ir (KBr) 3600-2600 (m, br), 1190 (s), 1180 (m), 1170 (s), 765 (s), 690 (m) cm^{-1}; ^{13}C nmr ($CDCl_3$) δ 40.7 (CH_3), 74.1 (C-2, $^1J_{CH}$= 157 Hz), 89.0 (C-6, $^2J_{CF}$= 35.8 Hz), 121.8 (CF_3, $^1J_{CF}$= 288 Hz), 128.0, 128.6, 135.1 (Ar), 140.0 (C-4). Anal. Calcd for $C_{11}H_{11}N_2O_2F_3$: C, 50.77; H, 4.26; N, 10.77; F, 21.90. Found C, 50.74; H, 4.23; N, 10.81; F, 22.17.

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