

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

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Abstract- 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 reaction⁶ more in detail, we tried a number of reagents to mediate such a type of cyclization. After several trials,

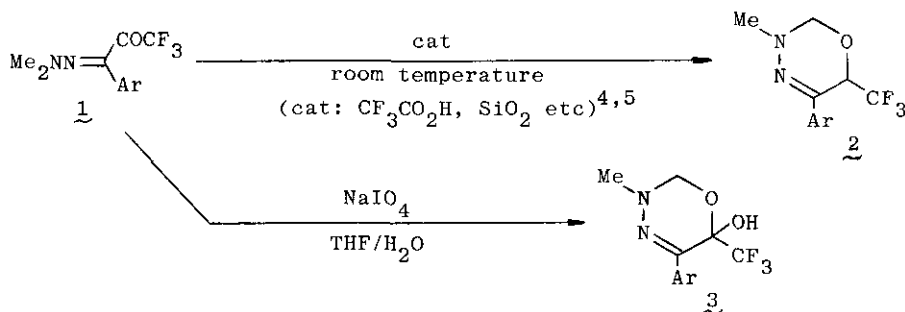


Table. Cyclization of 1 to 3.

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 ₆ H 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 ₆ H 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 ₆ H ₄	B	52	124 (c-C ₆ H 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 ₆ H 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 ₂ NC ₆ H 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/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. ^b Isolated yields.

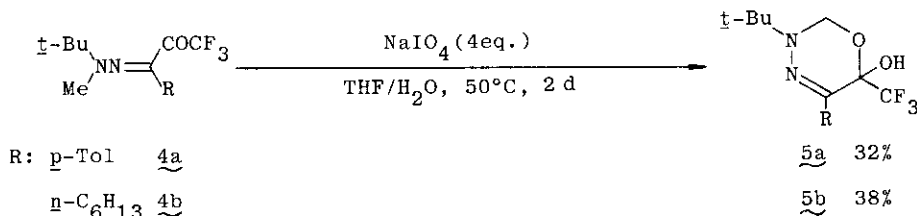
^c ¹H Nmr spectra were recorded on a JEOL PMX 60SI spectrometer in CDCl₃ solutions.

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.^{7,8} 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 (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/H₂O 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.



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 NaIO₄ (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 CH₂Cl₂ (50 ml X 2). The organic layer was washed with 0.1N NaHCO₃ solution (100 ml), dried over MgSO₄, and the solvent was removed to afford 3 (Ar= Ph, 165 mg, 63%) as pale yellow crystals.¹¹

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6. Formation of 2 was also observed when 1 was heated or dissolved in polar solvents. See ref 7.
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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 alkane-carbaldehyde 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); ¹H nmr (CDCl₃) 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, CH₂), 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); ¹H nmr (CDCl₃) δ 0.65-2.55, 1.20 (m and s, 22H, n-C₆H₁₃ and t-Bu), 2.68-3.17 (br, 1H, OH), 3.85-4.82 (ABq, J= 7 Hz, 2H, CH₂); ir (KBr) 3060-3570 (br, m), 2910 (s), 1183 (s), 1090 (m), 1063 (m), 1018 (m) cm⁻¹. Anal. Calcd for C₁₄H₂₅N₂O₂F₃: 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; ¹³C nmr (CDCl₃) δ 40.7 (CH₃), 74.1 (C-2, ¹J_{CH}= 157 Hz), 89.0 (C-6, ²J_{CF}= 35.8 Hz), 121.8 (CF₃, ¹J_{CF}= 288 Hz), 128.0, 128.6, 135.1 (Ar), 140.0 (C-4). Anal. Calcd for C₁₁H₁₁N₂O₂F₃: 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.

Received, 12th June, 1991