A Convenient Synthesis of 5-Aryl-6-trifluoromethyl-3,6-dihydro-2*H*-1,3,4-oxadiazines. A Silica Gel Catalyzed Novel Cyclization Reaction

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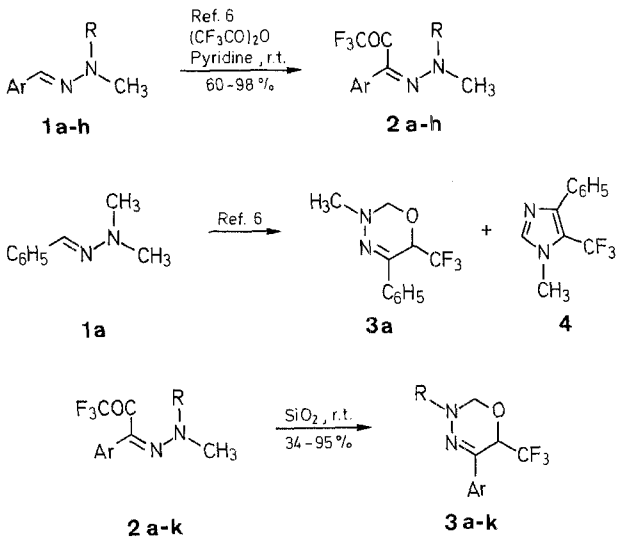
Arenecarbaldehyde dimethylhydrazones were successfully acylated by trifluoroacetic anhydride to afford trifluoroacetylated hydrazones **2**. Several 5-Aryl-6-trifluoromethyl-3,6-dihydro-2*H*-1,3,4-oxadiazines **3** were synthesized in good yields by novel cyclization of **2**, thus obtained, using silica gel as an effective catalyst. Hydrolytic ring cleavage of **3** afforded α-hydroxyketones **5** bearing the trifluoromethyl group in high yields.

There have been several reports concerning biological interest for dihydro-1,3,4-oxadiazine and its derivatives. Some of these compounds are known to have activities such as cardiotonics,[1] antibactericidals,[2] plant growth regulators[3] and other useful properties.[4] 5-Aryl-6-trifluoromethyl-3,6-dihydro-2*H*-1,3,4-oxadiazines **3** belong to this class of compounds and can be expected to have medicinal activities. However, the synthesis of these fluorine containing heterocycles has not been reported so far.[5]

Recently we found an interesting cyclization reaction of trifluoroacetylated hydrazone **2a**, which can be readily prepared from dimethylhydrazone **1a** and trifluoroacetic anhydride, to afford **3a** together with the imidazole **4**.[6] This finding prompted us to investigate the cyclization in more detail and to make it more selective and efficient as a new convenient synthesis of **3a**. After some examination, we have found that silica gel can be used as a very effective catalyst for the transformation of **1a** to **3a**. We now wish to communicate the synthesis of **3a–k**.



1–3	R	Ar	1–3	R	Ar
a	CH_3	C_6H_5	**g**	CH_3	2-$O_2NC_6H_4$
b	CH_3	4-$CH_3C_6H_5$	**h**	CH_3	4-$CH_3OC_6H_4$
c	CH_3	4-ClC_6H_4	**i**	CH_3	1-Naphthyl
d	CH_3	2-ClC_6H_4	**j**	C_2H_5	4-$CH_3C_6H_4$
e	CH_3	4-$O_2NC_6H_4$	**k**	*t*-C_4H_9	4-$CH_3C_6H_4$
f	CH_3	3-$O_2NC_6H_4$			

Table 1. Compounds **3** Prepared

Product	Yield (%)	Time (days)	mp (°C) (solvent) or bp (°C)/mbar[a]	Molecular Formula[b]	^{1}H-NMR ($CDCl_3$/TMS)[c] δ, *J*(Hz)
3a	95	10	165/4	$C_{11}H_{11}F_3N_2O$ (244.2)	2.90 (s, 3H, CH_3); 4.07–4.59 (ABq, 2H, J = 6, CH_2); 5.20 (q, 1H, J_{HF} = 7, CH); 7.10–7.40 (m, 5H, H_{arom})
3b	93	8	49 (CCl_4)	$C_{12}H_{13}F_3N_2O$ (258.2)	2.30 (s, 3H, CH_3); 2.90 (s, 3H, NCH_3); 4.05–4.45 (ABq, 2H, J = 7, CH_2); 5.04 (q, 1H, J_{HF} = 7, CH); 6.93–7.41 (q, 4H, H_{arom})
3c	88	8	120/0.7	$C_{11}H_{10}ClF_3N_2O$ (278.7)	2.87 (s, 3H, CH_3); 4.10–4.43 (ABq, 2H, J = 8, CH_2); 4.92 (q, 1H, J_{HF} = 7, CH); 6.93–7.47 (q, 4H, H_{arom})
3d	71	19	170/3	$C_{11}H_{10}ClF_3N_2O$ (278.7)	2.90 (s, 3H, CH_3); 4.36 (s, 2H, CH_2); 5.13 (q, 1H, J_{HF} = 7, CH); 6.90–7.40 (m, 4H, H_{arom})
3e	76	11	108 (MeOH)	$C_{11}H_{10}F_3N_3O_3$ (289.2)	2.97 (s, 3H, CH_3); 4.07–4.51 (ABq, 2H, J = 8, CH_2); 4.97 (q, 1H, J_{HF} = 7, CH); 7.42, 7.93 (d, 4H, H_{arom})
3f	84	10	180/3	$C_{11}H_{10}F_3N_3O_3$ (289.2)	3.00 (s, 3H, CH_3); 4.20–4.58 (ABq, 2H, J = 7, CH_2); 5.17 (q, 1H, J_{HF} = 7, CH); 7.13–8.33 (m, 4H, H_{arom})
3g	53	16	75/4	$C_{11}H_{10}F_3N_3O_3$ (289.2)	2.87 (s, 3H, CH_3); 4.37 (s, 2H, CH_2); 4.92 (q, J_{HF} = 7, 1H, CH); 7.12–7.60 (m, 3H, H_{arom}); 7.80–8.30 (m, 4H, H_{arom})
3h	68	10	150/3	$C_{12}H_{13}F_3N_2O_2$ (274.2)	2.84 (s, 3H, CH_3); 3.70 (s, 3H, OCH_3); 3.92–4.38 (ABq, 2H, J = 7, CH_2); 4.91 (q, 1H, J_{HF} = 7, CH); 6.64, 7.25 (d, 4H, H_{arom})
3i	63	19	oil[d]	$C_{15}H_{13}F_3N_2O$ (294.3)	2.84 (s, 3H, CH_3); 4.10–4.47 (ABq, 2H, J = 8, CH_2); 4.84 (q, 1H, J_{HF} = 7, CH); 7.16–8.10 (m, 7H, H_{arom})
3j	84	8	120/1.33	$C_{13}H_{15}F_3N_2O$ (272.3)	1.24 (t, 3H, CH_2CH_3); 2.30 (s, 3H, CH_3); 3.08 (q, 2H, CH_2CH_3); 4.00–4.49 (ABq, 2H, J = 8, CH_2); 4.92 (q, 1H, J_{HF} = 7, CH); 6.80–7.53 (q, 4H, H_{arom})
3j'	4	8	150/1.33	$C_{13}H_{15}F_2N_2O$ (272.3)	1.41 (d, 3H, CH_3); 2.31 (s, 3H, CH_3); 2.91 (s, 3H, NCH_3); 4.19 (q, 1H, J = 6, CH); 4.84 (q, J_{HF} = 7, 1H, CH); 6.80–7.30 (q, 4H, H_{arom})
3k	34	20	100/1.33	$C_{15}H_{19}F_3N_2O$ (300.3)	1.29 (s, 9H, t-C_4H_9); 2.32 (s, 3H, CH_3); 4.48 (s, 2H, CH_2); 5.01 (q, 1H, J_{HF} = 7, CH); 6.90–7.44 (q, 4H, H_{arom})

[a] Oven temperature of Kugelrohr distillation.

[b] The microanalyses were in satisfactory agreement with the calculated values: C ±0.19, H ±0.24, Cl ±0.26, F ±0.29, N ±0.29.

[c] ^{1}H-NMR spectra were recorded at 60 MHz on JEOL PMX 60SI.

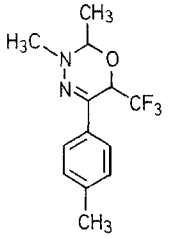
[d] This compound was purified by silica gel column chromatography (benzene).

Table 2. Ring Cleavage of **3** to **5**

Substrate	Product	Yield (%)	mp (°C) or bp (°C)/mbar[a]	Molecular Formula[b]	^{1}H-NMR[c] ($CDCl_3$/TMS) δ, J(Hz)
3a	**5a**	84	87[d]	$C_9H_7F_3O_2$ (204.1)	4.17–4.83 (br, 1H, OH); 5.42 (q, 1H, J_{HF} = 6, CH); 7.83–8.33 (m, 5H, H_{arom})
3b	**5b**	88	101[d]	$C_{10}H_9F_3O_2$ (218.2)	2.43 (s, 3H, CH_3); 4.13–4.30 (br, 1H, OH); 5.29 (q, 1H, J_{HF} = 6, CH); 7.28, 7.75 (d, 4H, H_{arom})
3g	**5g**	88	80/1.33	$C_9H_6F_3NO_4$ (249.1)	3.33–4.10 (br, 1H, CH); 4.85 (q, 1H, J_{HF} = 7, CH); 7.10–8.17 (m, 4H, H_{arom})

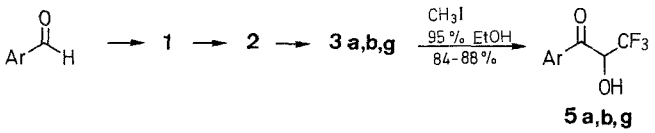
[a] Oven temperature of Kugelrohr distillation.
[b] Microanalyses were satisfactory agreement with the calculated values: C ±0.26, H ±0.40, F ±0.24, N ±0.02.
[c] ^{1}H-NMR spectra were recorded at 60 MHz on JEOL PMX 60SI.
[d] These compounds were purified by Kugelrohr distillation (oven temperature; **5a**: 150 °C/3 mbar, **5b**: 200 °C/3 mbar).

Dimethylhydrazones of arenecarbaldehydes **1a–k** afforded on treatment with trifluoroacetic anhydride, the corresponding trifluoroacetylated products **2a–k** in high yields.[6] Compounds **2a–k**, without any purification, were adsorbed on silica gel and allowed to stand for several days. As shown in Table 1, the reaction proceeded cleanly in all cases and **3a–k** were obtained in fair yields simply by extraction with ether. In the absence of solvent this reaction proceeded very cleanly at room temperature. Heating to facilitate the reaction resulted in the formation of appreciable amounts of imidazoles together with **3**. *ortho*-Substituted aryl groups (**2d** and **2g**) and the 1-naphthyl group (**2i**) retarded the reaction and prolonged standing was needed for complete conversion. The cyclization of **2k** to **3k** occurred most slowly, and 40% of **2k** were recovered unchanged even after 20 days. Steric hindrance is probably responsible for the sluggish reaction. It is of interest to note that although the ring closure of **2j** occurred selectively between the methyl and the carbonyl groups, a small amount of the other possible isomer **3j'** was also obtained as a result of the reaction between the methylene of the ethyl group and the carbonyl group.



3j'

Treatment of **3a** with excess iodomethane in 95% aqueous ethyl alcohol easily led to the α-hydroxyketone **5a**. Similarly **3b** and **3g** were converted to **5b** and **5g** respectively, in high yields (Table 2). These series of transformations can be used as a convenient synthetic method to substitute formyl hydrogen by 1-hydroxy-2,2,2-trifluoromethyl group as in **5**.



5a,b,g

The mechanisms for the cyclization reaction and the formation of α-hydroxyketones are now under investigation and will be discussed elsewhere. The biological activity of **3a–k** is also under study.

Trifluoroacetyl hydrazones **2a–k** were prepared according to literature.[6] The physical and spectral data of **2a–h** have been already reported,[6] those of the new compounds **2i–k** are given below.

2i; yield: 60%; m.p. 137 °C (cyclohexane).

$C_{15}H_{13}F_3N_2O$ (294.3)	calc.	C 61.22	H 4.45	F 19.37	N 9.52
	found	61.40	4.38	19.45	9.52

^{1}H-NMR ($CDCl_3$/TMS): δ = 2.87 (s, 6H, CH_3); 7.07–7.92 (m, 7H_{arom}).

2j; yield: 89%; m.p. 85 °C (*n*-hexane).

$C_{13}H_{15}F_3N_2O$ (272.3)	calc.	C 57.40	H 5.55	F 20.93	N 10.29
	found	57.47	5.53	21.19	10.28

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.20 (t, 3H, $CH_2\underline{CH_3}$); 2.31 (s, 3H, Ar-$\underline{CH_3}$); 2.65 (s, 3H, NCH_3); 3.42 (q, 2H, $\underline{CH_2}CH_3$); 6.95 (s, 4H_{arom}).

2k; yield: 95%; m.p. 86 °C (cyclohexane).

$C_{15}H_{19}F_3N_2O$ (300.3)	calc.	C 59.99	H 6.38	F 18.98	N 9.33
	found	60.10	6.46	19.13	9.27

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.37 (s, 9H, *t*-C_4H_9); 2.33 (s, 3H, Ar-$\underline{CH_3}$); 2.56 (s, 3H, NCH_3); 6.97 (s, 4H_{arom}).

5-Aryl-6-trifluoromethyl-3,6-dihydro-2*H*-1,3,4-oxadiazines 3; General Procedure:

To a solution of **2** (5 mmol) in benzene (5 mL) is added silica gel (wakogel C 300 for column chromatography, 1.5 g). The mixture is well stirred for 30 min and evaporated to dryness under reduced pressure. The powder is introduced into a flask flashed with nitrogen and allowed to stand for 10 days in the closed flask. To this mixture is added ether (50 mL) and the mixture is well stirred. Silica gel is filtered off and washed with ether (2 × 10 mL). Removal of the solvent and Kugelrohr distillation of the residual oil afford pure product **3** (Table 1).

Ring cleavage of 3a,b,g to 5a,b,g; General Procedure:

To a solution of **3** (1 mmol) in 95% EtOH (150 mL) is added iodomethane (35 g, 247 mmol). The mixture is stirred for 16 h at 78 °C. After removal of the solvent and remaining iodomethane, CH_2Cl_2 (20 mL) is added and the mixture is washed successively with a 5% aqueous solution of sodium dithionite and sat. brine. The organic layer is dried (Na_2SO_4), the solvent evaporated and the residue is purified by Kugelrohr distillation (Table 2).

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