Convenient and Facile Syntheses of 6-Trifluoromethyl-3,6-dihydro-2*H*-1,3,4-oxadiazines

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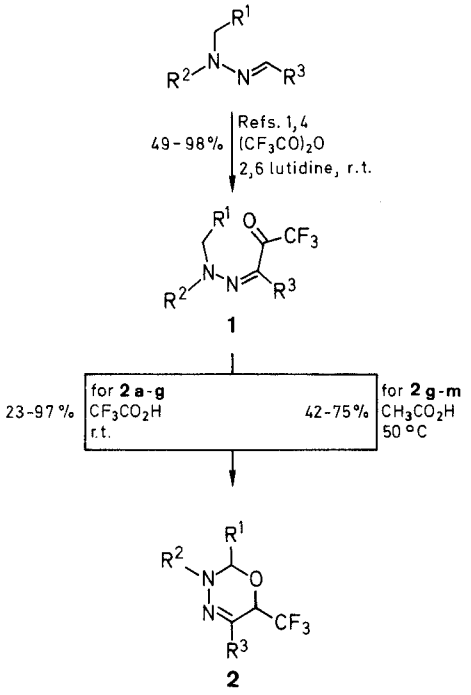
Several 6-trifluoromethyl-3,6-dihydro-2*H*-1,3,4-oxadiazines **2** were synthesized in good yields by treatment of trifluoroacetylated hydrazones **1**, prepared from substituted benzaldehyde and alkanal dialkylhydrazones and trifluoroacetic anhydride, with trifluoroacetic acid at 25 °C or acetic acid at 50 °C. This is an improved method for the synthesis of **2** compared to previous methods developed in this laboratory.

In previous papers,[1,2] we reported the synthesis of 5-aryl-6-trifluoromethyl-3,6-dihydro-2*H*-1,3,4-oxadiazines **2**, which have potential biological activities.[3] This key step was a novel silica gel catalyzed cyclization[2] of *C*-trifluoroacetylated hydrazones prepared from various aldehyde dialkylhydrazones.[1,4] The synthetic procedure is simple and the cyclization proceeds quite efficiently. However, the disadvantage to this method is the long reaction time (8–20 days). This prompted us to develop a more convenient synthetic method for the preparation of **2** from **1**.



1, 2	R^1	R^2	R^3
a	H	Me	Ph
b	H	Me	4-MeC_6H_4
c	H	Me	4-$MeOC_6H_4$
d	H	Me	4-ClC_6H_4
e	H	Me	4-$O_2NC_6H_4$
f	Me	Et	4-MeC_6H_4
g	H	*t*-Bu	4-MeC_6H_4
h	H	*t*-Bu	Et
i	H	*t*-Bu	*i*-Pr
j	H	*t*-Bu	*i*-Bu
k	H	*t*-Bu	*n*-C_6H_{13}
l	H	*t*-Bu	$(CH_3)_2C{=}CH(CH_2)_2CH(CH_3)CH_2$
m	H	*t*-Bu	$PhCH_2$
n	H	H	4-MeC_6H_4

Among the several acid catalysts examined in place of silica gel for the conversion of **1b** to **2b**, we found trifluoroacetic acid (TFA) to be particularly suitable. In TFA the reaction was complete within 6 hours and **2b** was obtained in 89% yield, which is comparable to the previous method.[2] Thus, a series of dimethylhydrazones **1a–e** in TFA (Method A) were converted successfully to the corresponding oxadiazines **2a–e** within 15 hours (Table 1). In the case of *tert*-butyl(methyl)hydrazone **1g**, its conversion to **2g** using silica gel as catalyst the yield was only 60% even after a period of 20 days.[2] In contrast, the reaction of **1g** in TFA was complete within 4 days, however, de-*tert*-butylation, which was not observed in the method using silica gel, occurred concurrently and **2g** was obtained in only 23% yield together with undesired **1n**. In the case of diethylhydrazone **1f**, the cylization proceeded very cleanly in TFA to afford **2f** in almost quantitative yield. The latter compound could not be obtained by the method using silica gel.

In contrast to the above results for 3-aryl-3-dialkylhydrazono-1,1,1-trifluoro-2-alkanones **1a–g** using TFA, attempted synthesis of **2h–m** from 3-*tert*-butyl-(methyl)hydrazono-1,1,1-trifluoro-2-alkanones **1h–m**[5] and TFA were not successful. For example, the reaction of **1h** in TFA proceeded very slowly, and even after 4 days only trace amounts of **2h** could be observed in the ^{1}H-NMR spectra of the crude product. Most of the starting material **1h** was recovered unchanged. Much longer reaction time resulted in the formation of complicated mixtures.

Alternatively the conversion of **1h** to **2h** can be performed effectively by heating **1h** in acetic acid (Method B). Thus **1h** was heated at 50 °C for 48 hours in acetic acid to afford **2h** in 53% yield. Higher reaction temperatures gave

Table 1. Synthesis of 3,6-Dihydro-2*H*-1,3,4-oxadiazines **2** from Hydrazones **1** using Trifluoroacetic Acid

Product	Time (h)	Yield[a,b] (%)	mp (°C) or bp (°C)/mbar[c]	Molecular Formula or Lit.[2] mp (°C) or bp (°C)/mbar[c]
2a	6.5	83	160/3	165/4
2b	6	89	49	49
2c	6	88	140/1	150/3
2d	6.5	88	140/3	120/0.7
2e	15	72	108.5	108
2f	2	97	100/2	$C_{14}H_{17}F_3N_2O$[e] (286.3)
2g	96	23[d]	100/1	100/1.33

[a] Yield refer to pure isolated compounds.
[b] Products, except the new compound **2f**, are identified by comparison of their ^{1}H-NMR spectra with those of authentic samples prepared by literature method.[2]
[c] Oven temperature of Kugelrohr distillation.
[d] Together with **2g**, hydrazone **1n** is obtained in 29% yield.
[e] See experimental for C,H-values and ^{1}H-NMR spectrum.

Table 2. Synthesis of 3,6-Dihydro-2*H*-1,3,4-oxadiazines **2f**, **h–m** from Hydrazones **1** Using Acetic Acid at 50 °C

Product	Yield[a] (%)	bp (°C)/ mbar	Molecular Formula[c] or Lit. bp (°C)/mbar	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)
2g	68	100/1	100/1.33[2]	–
2h	53	120/60	$C_{10}H_{17}F_3N_2O$ (238.3)	1.12, 1.20 (t and s, 12H, J = 7.2), 2.29 (q, 2H, J = 7.2), 4.00–4.54, 4.22 (q and ABq, 3H, J_{HF} = 7.8)
2i	61	120/60	$C_{11}H_{19}F_3N_2O$ (252.3)	1.14, 1.20 (d and s, 15H, J = 6.8), 2.56 (heptet, 1H, J = 6.8), 4.08–4.50, 4.34 (q and ABq, 3H, J_{HF} = 7.8)
2j	48	80/20	$C_{12}H_{21}F_3N_2O$ (266.3)	0.83–1.06 (m, 6H), 1.20 (s, 9H), 1.50–2.03 (m, 1H), 2.12 (br, 2H), 4.11–4.54, 4.22 (q and ABq, 3H, J_{HF} = 7.8)
2k	42	130/3	$C_{14}H_{25}F_3N_2O$ (294.4)	0.67–1.96, 1.19 (m and s, 20H), 2.10–2.46 (m, 2H), 4.05–4.54, 4.20 (q and ABq, 3H, J_{HF} = 7.6)
2l	54	135/3	$C_{17}H_{29}F_3N_2O$ (334.4)	0.80–2.36, 1.20, 1.58, 1.67 (m, s, s and s, 24H), 4.10–4.53, 4.22 (q and ABq, 3H, J_{HF} = 7.8), 5.03 (t, 1H)
2m	75	120/1	$C_{15}H_{19}F_3N_2O$ (300.3)	1.22 (s, 9H), 3.60 (s, 2H), 4.11–4.52, 4.12 (q and ABq, 3H, J_{HF} = 7.6), 7.10 (s, 5H)

[a] Yield refer to pure isolated compounds.
[b] Oven temperature of Kugelrohr distillation.
[c] Satisfactory microanalyses obtained: C ±0.27, H ±0.26, F ±0.24, N ±0.25.

1-(*tert*-butyl)-4-ethyl-5-trifluoromethylimidazole[6] together with **2h**. As shown in Table 2, several hydrazono-2-alkanones **1i–m** afforded the corresponding oxadiazines **2i–m** in satisfactory yields. This method is also effective for the conversion of 3-aryl derivatives. For example, **2g** was obtained in 68% yield from **1g**. The yields are higher than those when TFA (Method A, 23%) or silica gel (34%) is used as the catalyst. The reaction time, with acetic acid (Method B) is also shorter than the other two methods. In contrast, for the conversion of dimethylhydrazones **1a–e** diethylhydrazone **1f** to **2a–e,f** Method A is superior to Method B; in the case of **1b** the latter method afforded byproducts whilst **1f** did not give **2f**.

In conclusion both the methods, Method A using TFA at room temperature and Method B using acetic acid at 50 °C, achieved speedy conversion of trifluoroacetylated hydrazones **1** to 6-trifluoromethyl-3,6-dihydro-2*H*-1,3,4-oxadiazines **2** in excellent yields. These two methods are superior alternatives to the use silica gel as a catalyst, unless substrate **1** is labile and decomposes in acidic media.

^{1}H-NMR spectra were recorded at 60 MHz on a JEOL PMX 60 SI spectrometer.

Trifluoroacetylated hydrazones **1a–m** were prepared according to literature.[1,2,4,7,8] The physical and spectral data of the new compounds **1f** and **1j–l** are given below.

1f; Yield: 55%; mp 72 °C (EtOH/H_2O).

$C_{14}H_{17}F_3N_2O$ (286.3) calc. C 58.73 H 5.98 F 19.91 N 9.78
found 58.44 5.95 20.11 9.68

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.04 (t, 6H, J = 6.8 Hz), 2.33 (s, 3H), 3.30 (q, 4H, J = 6.8 Hz), 7.03 (s, 4H).

1j; Yield: 61%; this compound is purified by column chromatography on silica gel (hexane/benzene, 9:1).

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.87 (d, 6H, J = 6.2 Hz), 1.37, 1.30–2.02 (s and m, 10H), 2.57 (d, 2H, J = 7.0 Hz), 3.14 (s, 3H).

1k; Yield: 81%; 135 °C/2 mbar (oven temperature of Kugelrohr distillation).

$C_{14}H_{25}F_3N_2O$ (294.4) calc. C 57.13 H 8.56 N 9.52
found 57.06 8.71 9.49

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.67–1.50, 1.33 (m and s, 20H), 2.17–2.50 (m, 2H), 3.17 (s, 3H).

1l; Yield: 60%; this compound is purified by column chromatography on silica gel (hexane/benzene, 9:1).

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.73–2.35, 1.31, 1.57, 1.65 (m, s, s and s, 24H), 2.57 (d, 2H, J = 7.0 Hz), 3.10 (s, 3H), 4.97 (t, 1H, J = 7.2 Hz).

3,6-Dihydro-6-trifluoromethyl-2*H*-1,3,4-oxadiazines 2; General Procedure:

Method A, *for* **2a–g**: To the appropriate hydrazone **1a–g** (5 mmol) cooled in an ice bath is added dropwise TFA (3.85 mL, 50 mmol). The mixture is stirred for 2–96 h at 25 °C and then poured into a large excess of aq Na_2CO_3 solution. The organic layer is extracted with CH_2Cl_2 (2 × 60 mL), dried ($NaSO_4$), and the solvent is evaporated. Residual material is essentially pure **2**. In the case of **2g**, crude product is fractionated by silica gel column chromatography, affording **2g**; yield: 345 mg (23%) (eluent: hexane/benzene, 2:3) and **1n**; yield: 354 mg (29%) (eluent: benzene) (Table 1).

1n; Yield: 29%; mp 81 °C (cyclohexane).

$C_{11}H_{11}F_3N_2O$ (244.2) calc. C 54.10 H 4.54 F 23.34 N 11.47
found 54.38 4.37 23.28 11.47

^{1}H-NMR ($CDCl_3$/TMS): δ = 2.33 (s, 3H), 3.20 (d, 3H, J = 4.0 Hz), 6.92 (d, 2H, J = 7.9 Hz), 7.17 (d, 2H, J = 7.9 Hz).

2f; Yield: 97%; 100 °C/2 mbar (oven temperature of Kugelrohr distillation).

$C_{14}H_{17}F_3N_2O$ (286.3) calc. C 58.73 H 5.98 F 19.91 N 9.78
found 58.67 5.96 19.85 9.87

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.20 (t, 3H, J = 7.0 Hz), 1.45 (d, 3H, J = 5.4 Hz), 2.32 (s, 3H), 3.00–3.60 (m, 2H), 4.43 (q, 1H, J = 5.4 Hz), 4.93 (q, 1H, J = 5.4 Hz), 7.03 (d, 2H, J = 8.2 Hz), 7.26 (d, 2H, J = 8.2 Hz).

Method B, *for* **2g–m**: To the appropriate hydrazone **1g–m** (5 mmol) is added HOAc (5.77 mL, 100 mmol), and the mixture is stirred for 48 h at 50 °C. After cooling to r.t., the mixture is poured into a large excess of aq Na_2CO_3 solution and the organic layer is extracted with CH_2Cl_2 (2 × 60 mL). The extract is dried ($NaSO_4$), the solvent is evaporated, and the residue is purified by Kugelrohr distillation (Table 2).

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