A Convenient Synthesis of 3-Alkyl-6-trifluoromethyl-3,6-dihydro-2*H*-1,3,4-thiadiazines

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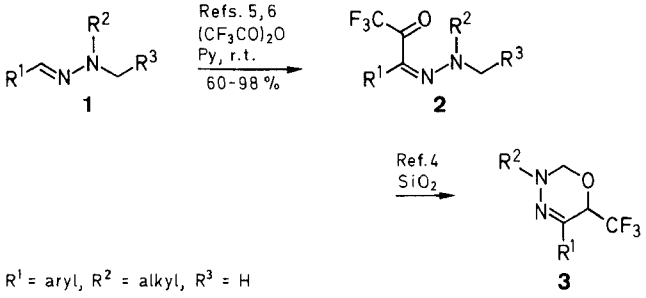
3-Dialkylhydrazono-1,1,1-trifluoro-2-alkanones **2**, readily obtainable from the reaction of substituted benzaldehyde, propanal and formaldehyde dialkylhydrazones with trifluoroacetic anhydride, afford title compounds **5** in satisfactory yields on treatment with Lawesson reagent in refluxing benzene.

Oxadiazine derivatives are of special interest due to their potentially high pharmacological properties applicable to cardiotonics, antihypertensives etc.[1-3] For similar reasons the sulfur analogues of oxadiazines, thiadiazines, are also synthetically very attractive compounds.

We reported earlier on the synthesis of 6-trifluoromethyl-3,6-dihydro-1,3,4-oxadiazines (**3**) by a silica gel catalyzed novel cyclization reaction[4] of 3-dialkylhydrazono-1,1,1-trifluoro-2-alkanones **2**, which were prepared by our established method from substituted benzaldehyde dialkylhydrazones **1** and trifluoroacetic anhydride (TFAA).[5,6] Compounds **3** can also be obtained together with 5-trifluoromethylimidazole by heating **2** in refluxing carbon tetrachloride.[5]

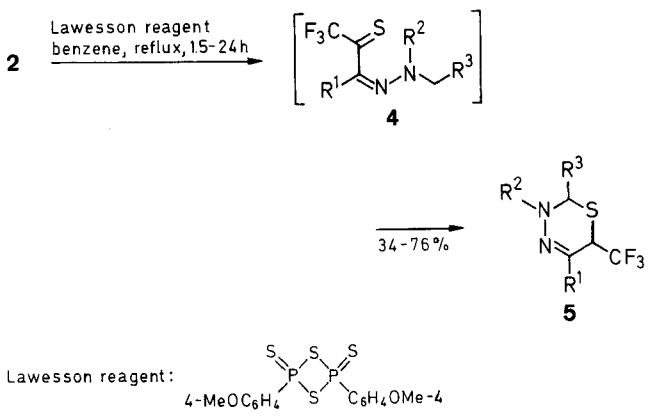


1 **2** **3**

A possible route to the thia-analogues 6-trifluoromethyl-3,6-dihydro-2*H*-1,3,4-thiadiazines (**5**), via cyclization of the corresponding thiocarbonyl analogues **4** to **5**, a simple extension of the above cyclization of **2** to **3**, prompted us to study the reaction of **2** with 2,4-bis(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4-dithiadiphosphetane (Lawesson reagent).

We examined the reaction of **2** with Lawesson reagent in refluxing benzene under standard conditions. The sulfurization reaction occurred with subsequent cyclization to thiadiazine derivatives **5**. None of the expected intermediate thiocarbonyl compound **4** remained in the crude products. Compound **4** was not observed at any stage of the reaction on monitoring the reaction by ^{1}H-NMR spectroscopy, it was concluded that rapid conversion of **4** to **5** occurred in refluxing benzene.

Representative results are summarized in the Table, where several *C*-trifluoroacetylated dialkylhydrazones of aromatic and aliphatic aldehydes **2a–g** were successfully converted to the corresponding thiadiazine derivatives **5a–g** in 34–76% yield. The cyclization of **2d**, **2g**, and especially, the sterically hindered **2e** to the corresponding thiadiazines, **5d**, **5g** and **5e** occurred as easily as that of **2a** to **5a**. This is in contrast to the analogous cyclization of **2d**, **2e** and **2g** to the corresponding oxadiazines **3**, which



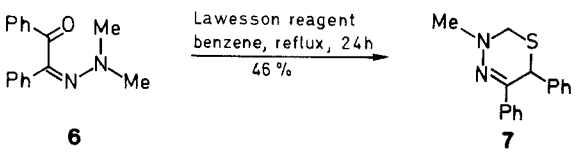
2 **4** **5**

2, 4, 5	R^1	R^2	R^3
a	4-MeC_6H_4	Me	H
b	4-$O_2NC_6H_4$	Me	H
c	4-MeC_6H_4	Et	H
c'	4-MeC_6H_4	Me	Me
d	4-MeC_6H_4	Et	Me
e	4-MeC_6H_4	*i*-Pr	Me_2
f	Et	*t*-Bu	H
g	H	Me	H

occurred in very low yield by our efficient method[4] with the use of silica gel. We also attempted thermal cyclization[5] in addition to silica gel catalyzed reaction. However, in this case, too, **2d** afforded only complex mixtures, and **2e** and **2g** remained intact. In the case of **2c**, two possible isomers **5c** and **5c'** were obtained in the ratio of 56:44. This result is not compatible with the selective conversion of **2c** to oxadiazine derivatives, where the ring closure occurred at the *N*-methyl and not at the methylene of the *N*-ethyl group.[4] Thus it is apparent that the formation of thiadiazine is much less influenced by steric hindrance than the formation of oxadiazine.

Oxadiazine derivative **3** (R^1 = 4-MeC_6H_4, R^2 = CH_3) on treatment with Lawesson reagent under similar conditions also gave the corresponding thiadiazine **5a** in 86% yield. As it is already known that thermolysis of **2** gives **3**,[5] the reaction path **2** → **3** → **5** may be an alternative pathway to **1** → **4** → **5**. However, the former seems to be unlikely taking into account the difference between the cyclization reaction of **2c**, **2d**, **2e**, and **2g** to **5** and as well as to **3**.

We also attempted the reaction of benzil monodimethylhydrazone (**6**) with Lawesson reagent under the same conditions in the Table. In this case too, the corresponding thiadiazine **7** was obtained in 46% yield. Thus the



6 **7**

Table. Compounds **5a–g** and **7** Prepared

Product	Reaction Time (h)	Yield[a] (%)	mp (°C) or bp (°C)/mbar	Molecular Formula[c]	^{1}H-NMR ($CDCl_3$/TMS)[d] δ, J(Hz)
5a	18	76	125/1.5	$C_{12}H_{13}F_3N_2S$ (274.3)	2.31 (s, 3H, CH_3), 3.20 (s, 3H, NCH_3), 3.80–4.43, 4.33 (ABq and q, J = 13, 8.2, 3H, CH_2 and CH), 7.05, 7.96 (d, J = 8.0, $4H_{arom}$)
5b	12	36	143	$C_{11}H_{10}F_3N_3O_2S$ (305.3)	3.35 (s, 3H, CH_3), 3.94–4.63, 4.33 (ABq and q, J = 13, 8.2, 3H, CH_2 and CH), 7.56, 8.01 (d, J = 8.8, $4H_{arom}$)
5c	24	37	154/1	$C_{13}H_{15}F_3N_2S$ (288.3)	1.25 (t, 3H, J = 7.2, $CH_2C\underline{H}_3$), 2.32 (s, 3H, CH_3), 3.50 (q, 2H, J = 7.2, $C\underline{H}_2CH_3$), 3.90–4.56, 4.36 (ABq and q, 3H, J = 13, 8.2, CH_2 and CH), 7.06, 7.36 (d, J = 8.2, $4H_{arom}$)
5c'		36	145/5	$C_{13}H_{15}F_3N_2S$ (288.3)	1.61 (d, 3H, J = 6.2, $CHC\underline{H}_3$), 2.30 (s, 3H, CH_3), 3.14 (s, 3H, NCH_3), 4.26 (q, 1H, J = 6.2, $C\underline{H}CH_3$), 4.41 (q, 1H, J = 8.0, $CHCF_3$), 7.03, 7.33 (d, J = 8, $4H_{arom}$)
5d	24	53	125/1	$C_{14}H_{17}F_3N_2S$ (302.4)	1.16 (t, 3H, J = 7.1, $CH_2C\underline{H}_3$), 1.62 (d, 3H, J = 8.0, $CHC\underline{H}_3$), 2.30 (s, 3H, CH_3), 3.53 (q, 2H, J = 6.4, CH_2), 4.34, 4.39 (q and q, 2H, J = 6.4, 8.0, $C\underline{H}CH_3$ and $CHCF_3$), 7.00, 7.33 (d, $4H_{arom}$)
5e	14	68	175/0.5	$C_{16}H_{21}F_3N_2S$ (330.4)	1.23, 1.25 (d, 6H, J = 6.2, $CHC\underline{H}_3$), 1.63 [s, 6H, $C(C\underline{H}_3)_2$], 2.30 (s, 3H, CH_3), 3.18 (hept, 1H, J = 6.2, $C\underline{H}CH_3$), 4.50 (q, 1H, J = 8.8, CH), 7.02, 7.35 (d, J = 8.2 $4H_{arom}$)
5f	24	34	90/5	$C_{10}H_{17}F_3N_2S$ (254.3)	1.12 (t, 3H, J = 7.2, CH_3), 1.25 (s, 9H, t-C_4H_9), 2.13–2.70 (m, 2H, $C\underline{H}_2CH_3$), 3.48 (q, 1H, J = 8.6, CH), 3.63–4.36 (ABq, 2H, J = 13, CH_2)
5g	1.5	49	60/10	$C_5H_7F_3N_2S$ (184.2)	3.00 (s, 3H, CH_3), 3.54 (dq, 1H, J = 8.2, $C\underline{H}CF_3$), 3.87 (s, 2H, CH_2), 6.71 (d, 1H, J = 4.6, CH)
7	24	46	170/4	$C_{16}H_{16}N_2S$ (268.4)	3.22 (s, 3H, CH_3), 3.98 (s, 2H, CH_2), 4.94 (s, 1H, CH), 7.00–7.63, 7.13 (m and s, $10H_{arom}$)

[a] Yield refer to pure isolated compounds.
[b] Oven temperature of Kugelrohr distillation.
[c] The microanalyses are satisfactory agreement with the calculated values: C ±0.40%, H ±0.24%, N ±0.41%, F ±0.34%.
[d] Recorded at 60 MHz on a JEOL PMX 60SI.
[e] Recrystallized from $EtOH/H_2O$.

present thiadiazine formation is also applicable to hydrazones bearing acyl group, which are not as strongly electron-withdrawing as trifluoroacetyl group.
Detailed mechanistic study of this reaction and assay for pharmaceutical activity are now in progress.

3-Dialkylhydrazono-1,1,1-trifluoro-2-alkanones, **2a–g** were prepared according to literature and the physical and spectral data of **2a–c** and **2g** have been already reported.[4–6] Those of new compounds are as follows.

2d: Yield 66%; mp 75°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 = 1.05 (t, 6H, J = 6.8 Hz, $CH_2C\underline{H}_3$), 2.32 (s, 3H, $ArC\underline{H}_3$), 3.30 (q, 4H, J = 6.8 Hz, $C\underline{H}_2CH_3$), 7.03 (s, $4H_{arom}$).

2e: Yield 90%; mp 146°C (cyclohexane).

$C_{16}H_{21}F_3N_2O$ (328.4) calc. C 61.13 H 6.73 F 18.13 N 8.91
found 61.05 6.70 18.14 8.78

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.12 (d, 12H, J = 6.6 Hz, $CHC\underline{H}_3$), 2.35 (s, 3H, $ArC\underline{H}_3$), 3.85 (hept, 2H, J = 6.6 Hz, $C\underline{H}CH_3$), 6.81 ~ 7.10 (q, J = 8.0 Hz, $4H_{arom}$).

2f: Yield 76%; oven temperature 80°C/2 mbar (Kugelrohr distillation).

$C_{10}H_{17}F_3N_2O$ (238.3) calc. C 50.41 H 7.19 F 23.92 N 11.76
found 50.53 7.19 23.23 11.70

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.07, 1.30 (t and s, 12H, J = 7.0 Hz, $CH_2C\underline{H}_3$ and t-C_4H_9), 2.62 (q, 2H, J = 7.0 Hz, $C\underline{H}_2CH_3$), 3.12 (s, 3H, NCH_3).

3-Alkyl-6-trifluoromethyl-3,6-dihydro-2*H*-1,3,4-thiadiazines 5 and 3-Methyl-5,6-diphenyl-3,6-dihydro-2*H*-1,3,4-thiadiazine (7); General Procedure:

To a solution of **2** (1 mmol) in benzene (5 mL) is added Lawesson reagent (0.5 mmol) and the whole mixture is refluxed for 5 ~ 24 h. After evaporation of the solvent , products **5** and **7** are isolated, respectively by preparative TLC (silica gel/Merck 60PF) using benzene as an eluent. If necessary additional purification is done by Kugelrohr distillation or recrystallization (Table). In the case of **5g** the crude product is purified directly by Kugelrohr distillation.

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