A CONVENIENT SYNTHESIS OF 5-TRIFLUOROMETHYL-3-THIAZOLINES AND 5-TRIFLUOROMETHYL-2,3,4,5-TETRAHYDRO-1,2,4-TRIAZINES

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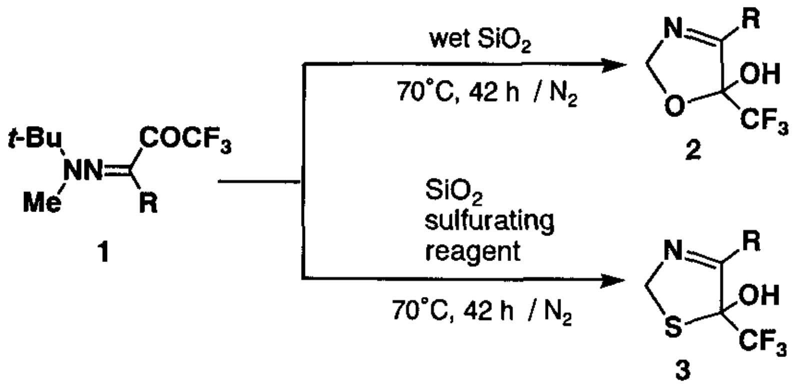
Abstract - 5-Trifluoromethyl-3-thiazolines (**3**) and 5-trifluoromethyl-2,3,4,5-tetrahydro-1,2,4 triazine (**5**) were conveniently synthesized from 3-(*N-tert*-butyl-*N*-methylhydrazono)-1,1,1-trifluoroalkan-2-ones (**1**) with the use of silica gel as an effective catalyst. 5-Trifluoromethylimidazole (**6**) was also obtained in good yield from **1**.

Fluorine-containing heterocycles are one of the most fascinating targets for synthetic organic chemists because of their potential biological activities.[1] Recently we reported an interesting cyclization reaction of 3-(*N-tert*-butyl-*N*-methylhydrazono)-1,1,1-trifluoroalkan-2-ones (**1**) which are readily preparable from aldehyde *N-tert*-butyl-*N*-methylhydrazones and trifluoroacetic anhydride,[2,3] affording 5-trifluoromethyl-3-oxazolines (**2**). In this reaction, "wet" silica gel acts as an effective catalyst to give good yields of **2**.[4] Apparently oxygen atom in **2** derived from water adsorbed on "wet" silica gel. Above result suggests us that some other heteroatoms might be incorporated in heterocyclic ring system, if cyclization reaction was carried out in the presence of suitable heteroatom source and silica gel. This prompted us to try a synthesis of 5-trifluoromethyl-3-thiazoline (**3**) from **1** and sulfurating reagents in the presence of silica gel as a catalyst. Now we wish to report our results.

Several hydrazones (**1**) were prepared from the corresponding aldehydes by usual manner.[2,3] As

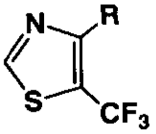


sulfurating reagents, Na_2S, NaHS, $(NH_4)_2S$, and P_2S_5 were examined for a substrate (**1 b**) with the use of SiO_2 as a catalyst. As shown in Table 1, desired **3 b** was obtained in any cases except for that of $(NH_4)_2S$ and the best result was obtained when NaHS was used. However Al_2O_3 did not catalyze the desired reaction. Quite similarly, by the use of NaHS and SiO_2 several hydrazones (**1 a, c~f**) were successfully converted to the corresponding thiazolines (**3 a, c~f**) in moderate yields.[5] These are summarized in Table 2. In any cases, 5-trifluoromethylthiazole (**4**) formed through 1,4-elimination of H_2O was not detected. When **3 b** was treated with P_2S_5 in hot benzene, the corresponding **4** (**R**= *p*-Tol) was obtained in 76% yield.[6] One-pot synthesis of **4** (**R**= *p*-Tol) from **1 b** was also possible. In this case, P_2S_5 and benzene were immediately added to the reaction vessel in which conversion of **1 b** to **3 b** under the conditions in Table 2 completed, and the whole

Table 1. Synthesis of Thiazoline (**3 b**).[a]

Reagent	Yield of **3 b**, %
P_2S_5	25
Na_2S	35
NaHS	59
NaHS[b]	0
$(NH_4)_2S$	0

a) Reactions were carried out for 20 h at 70°C under N_2 with the use of SiO_2 (3 g) and reagent (3 mmol) for **1 b** (1 mmol). b) Al_2O_3 (Woelm acid tlc) was used instead of SiO_2.



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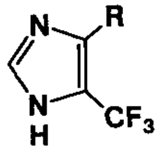

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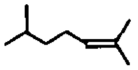
Table 2. Synthesis of 5-Trifluoromethyl-3-thiazolines (**3**).

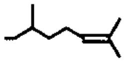
	R	Time, h	Yield, %	mp °C[a] (solvent)	^1H Nmr ($CDCl_3$/TMS)[b] δ
3a	Ph	42	33	75.5 (C_6H_{14})	4.73-5.53 (ABq, *J* = 16 Hz, 2H, CH_2), 4.20-4.57 (br, 1H, OH), 7.00-7.97 (m, 5H, ArH)
3b	*p*-MeC_6H_4	20	59	106.0 (*c*-C_6H_{12})	2.33 (s, 3H, Me), 4.97-5.53 (ABq, *J* = 16 Hz, 2H, CH_2), 4.27-4.68 (br, 1H, OH), 6.97 and 7.70 (d and d, 4H, *J* = 8 Hz, ArH)
3c	*p*-$MeOC_6H_4$	72	29	116.0 (*c*-C_6H_{12})	3.78 (s, 3H, OMe), 4.17-4.63 (br, 1H, OH), 4.95-5.57 (ABq, *J* = 16 Hz, 2H, CH_2), 6.90 and 7.97 (d and d, *J* = 9 Hz, 4H, ArH)
3d	*p*-ClC_6H_4	48	43	110.0 (*c*-C_6H_{12})	3.90-4.10 (br, 1H, OH), 5.07-5.63 (ABq, *J* = 16 Hz, 2H, CH_2), 7.27 and 7.87 (d and d, *J* = 8 Hz, 4H, ArH)
3e	Et	7	23	60.0[c]	1.23 (t, *J* = 7 Hz, 3H, Me), 2.57 (q, *J* = 7 Hz, 2H, CH_2), 3.43-4.03 (br, 1H, OH), 4.97-5.47 (ABq, *J* = 16 Hz, 2H, CH_2)
3f		24	28	pale yellow oil[d]	0.67-2.83 (m, 16H, CH, CH_2, Me), 3.50-4.33 (br, 1H, OH), 5.00 (t, *J* = 7 Hz, 1H, =CH), 5.07-5.37 (br, 2H, CH_2)

a) Uncorrected, measured with Mitamura Riken model 7-12 apparatus. b) Recorded at 60 MHz on a JEOL PMX60SI. c) Distilled by Kugelrohr (120°C/ 3 torr). d) Purified by silica gel column chromatography (benzene/AcOEt = 95/5).

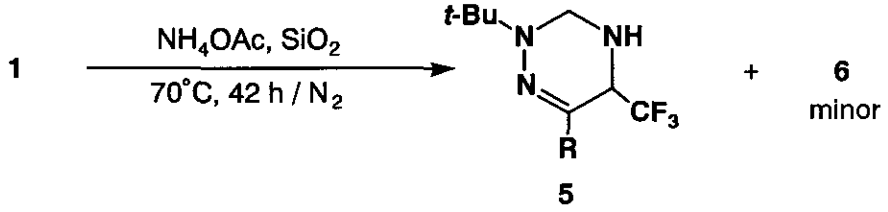
mixture was refluxed for 4 h to give **4** (**R**= *p*-Tol) in 23% yield. The structure of **3** was confirmed by ^1H and ^{13}C nmr, and ir spectra, and micro combustion analysis.[7] For example, ^{13}C nmr of **3b** revealed thiazoline ring carbon at 61.6 (C2), 101.7 (C5, $^2J_{C\text{-}F}$ = 32.5 Hz), 168.1 (C4).

When $(NH_4)_2S$ was used as a sulfurating reagent, a very interesting result was obtained. Main product in this reaction was unexpected 5-trifluoromethyl-2,3,4,5-tetrahydro-1,2,4-triazine (**5b**). Apparently not sulfur atom but nitrogen atom was incorporated in the ring system, and, in addition, we could detected a small amount of imidazole (**6b**) in which nitrogen atom is incorporated in the same fashion for the case of sulfur atom in **3b**. We examined several ammonium salts for the conversion of **1b** to **5b** in the presence of silica gel. Consequently, NH_4OAc afforded the best yield of **5b**. Thus, to **1b** adsorbed on silica gel was added NH_4OAc, and the whole was well mixed and

Table 3. Synthesis of 5-Trifluoromethyl-2,3,4,5-tetrahydro-1,2,4-triazines (**5**).

	R	$(NH_4)OAc$ equiv.	Temp °C	Time d	Yield %	mp, °C[a] (solvent)	^1H Nmr ($CDCl_3$/TMS)[b] δ
5a	Ph	50	60	2	36	69 (C_6H_{14})	1.28 (s, 9H, *t*-Bu), 2.05-2.83 (br, 1H, NH), 3.68-4.30 (ABq, *J* = 12 Hz, 2H, CH_2), 4.30 (q, *J* = 8 Hz, 1H, CH), 7.10-7.60 (m, 5H, ArH)
5b	*p*-MeC_6H_4	20	50	4	52	78[c]	1.29 (s, 9H, *t*-Bu), 1.90-2.17 (br, 1H, NH), 2.30 (s, 3H, Me), 3.57-4.33 (ABq, *J* = 10 Hz, 2H, CH_2), 4.12 (q, *J* = 8 Hz, 1H, CH), 6.98 and 7.33 (d and d, *J* = 8 Hz, 4H, ArH)
5c	*o*-MeC_6H_4	20	70	1	37	$101/_{4\,Torr}$[d]	1.67 (s, 9H, *t*-Bu), 2.35 (s, 3H, Me), 3.53-4.30 and 4.06 (ABq and q, *J* = 12 Hz and 8 Hz, 3H, CH_2 and CH), 7.03-7.27 (m, 4H, ArH)
5d	*p*-$MeOC_6H_4$	30	50	5	36	63 (C_6H_{14})	1.23 (s, 9H, *t*-Bu), 3.50-4.24, 3.79 and 3.89 (ABq, s and q, *J* = 12 Hz and 8 Hz, 6H, CH_2, OMe and CH), 6.72 and 7.30 (d and d, *J* = 8 Hz, 4H, ArH)
5e	*p*-ClC_6H_4	50	60	2	38	59 (*c*-C_6H_{12})	1.26 (s, 9H, *t*-Bu), 3.60-4.36 and 4.12 (ABq and q, *J* = 12 Hz and 8 Hz, 3H, CH_2 and CH), 7.06-7.47 (q, *J* = 9Hz, 4H, ArH)
5f	Et	100	50	2	16	pale yellow oil[e]	1.07 and 1.17 (t and s, *J* = 6.4 Hz, 12H, $CH_2\underline{Me}$ and *t*-Bu), 2.31 (q, *J* = 6.4 Hz, 2H, $C\underline{H_2}Me$), 3.26-4.14 and 3.47 (ABq and q, *J* = 11.5 Hz and 8 Hz, 3H, CH_2 and CH)
5g		20	50	2	18	pale yellow oil[e]	0.80-2.30 and 1.15 (m and s, 25H, CH_3, CH_2, CH, and *t*-Bu), 3.20-4.03 and 3.34 (ABq and q, *J* = 11 Hz and 8 Hz, 3H, NCH_2 and NCH), 5.01 (t, br, *J* = 8 Hz, 1H, =CH)

a) Uncorrected, measured with Mitamura Riken model 7-12 apparatus. b) Recorded at 60 MHz on a JEOL PMX60SI. In the cases of **5 e** and **5 g** CCl_4 was used as a solvent. c) Distilled by Kugelrohr (165°C/$_{5\,torr}$). d) Oven temperature of Kugelrohr distillation. e) Purified by silica gel column chromatography (benzene / AcOEt = 95 / 5).



heated for 2 - 5 d to afford crude **5 b**. Preparative layer chromatography gave **5 b** (52 %) and **6** (R= *p*-Tol, 5 %). In Table 3 are listed the yields of 2,3,4,5-tetrahydro-1,2,4-triazines (**5**)[8] obtained from several substrates (**1**) by similar manner.[5] In all cases in Table 3, 5-trifluoromethylimidazoles (**6**)[9] were obtained only as minor by-products. In contrast we found that **6** (R= *p*-Tol) was exclusively obtained, when the mixture of **1 b**, NH_4OAc and AcOH was reacted for 42 h at 70 °C in the presence of silica gel. In this case, even trace amounts of **5** was not detected. Obviously silica gel in the absence of AcOH plays an important roll in a triazine formation from **1** to **5**.

We could present very convenient methods accessing fluorine-containing 3-thiazolines (**3**), 2,3,4,5-tetrahydro-1,2,4-triazines (**5**), and imidazoles (**6**).

EXPERIMENTAL

Synthesis of 5-trifluoromethyl-3-thiazoline (**3 b**) with the use of several sulfurating reagent.

Typical Procedure: To **1 b** (300 mg, 1 mmol) dissolved in 5 ml of CH_2Cl_2 was added silica gel[10] (3 g), and the mixture was stirred. The solvent was removed under vacuum to afford pale yellow powder. To this was added NaHS (168 mg, 3 mmol) and the mixture was well stirred. Under N_2 the whole mixture was heated to 70°C. After 20 h, to the reaction mixture was added AcOEt (100 ml) and insoluble material was filtered off. The filtrate was evaporated to dryness and the residue was submitted to column chromatography (benzene/AcOEt = 9/1) to afford pure 3-thiazoline (**3 b**) in 59 % (154 mg). In a similar manner for the preparation of **3 b**, thiazolines (**3 a**, and **3c-f**) were also synthesized.

5-Trifluoromethylthiazole (**4**, R= *p*-Tol).

A mixture of **3 b** (261 mg, 1 mmol) and P_2S_5 (666 mg, 3 mmol) in benzene (10 ml) was refluxed for 5 h under N_2. After being cooled to room temperature, the mixture was washed with water, dried over Na_2SO_4, and the solvent was removed to afford **4** (R= *p*-Tol) in 76% (185 mg). If necessary, further purification was carried out by silica gel column chromatography (benzene/AcOEt = 90/10) giving **4** (R= *p*-Tol) in 44% (107 mg).

One-pot Synthesis of 4 (R = *p*-Tol) from 1 b.

First step reaction from **1 b** to **3 b** was carried out by similar manner described previously. After 20 h, P_2S_5 and benzene (10 ml) was added to the reaction mixture and the whole was refluxed for 4 h under N_2 atmosphere. To the cooled reaction mixture was added AcOEt (100 ml) and the whole was stirred for 30 min. Silica gel was filtered off and washed thoroughly with additional AcOEt (50 ml). The combined filtrates were washed with water and dried over Na_2SO_4. The solvent was removed to afford **4** (R= *p*-Tol) in overall yield 23% (56 mg) from **1 b**.

5-Trifluoromethyl-2,3,4,5-tetrahydro-1,2,4-triazine (5). Typical Procedure:

Hydrazone **1 b** (300 mg, 1 mmol) was adsorbed on silica gel[10] (5 g) by similar procedure which is described for synthesis of **3 b** from **1 b**. To this was added NH_4OAc (1.54 g, 20 mmol) and well mixed, and the whole was heated at 50°C for 4 d under N_2. By similar workup procedure which is described for synthesis of **3 b** from **1 b**, crude **5 b** was obtained. This was fractionated by preparative layer chromatography (silica gel,[11] benzene/AcOEt = 95/5) to give **5 b** (52 %, 155 mg, Rf = 0.44) and **6** (R=*p*-Tol, 5 %, 11 mg, Rf = 0.33).

5-Trifluoromethylimidazole (6, R= *p*-Tol).

Hydrazone (**1 b**, 300 mg, 1 mmol) adsorbed on silica gel[10] (3 g) by similar procedure which is described for synthesis of **3 b** from **1 b**. To this was added NH_4OAc (385 mg, 5 mmol) and AcOH (2 ml), and the whole was maintained at 70°C for 42 h under N_2. To the cooled reaction mixture was added AcOEt (100 ml) and the whole was stirred for 30 min. Silica gel was filtered off and washed thoroughly with AcOEt (50 ml). Filtrate and washings were combined, and washed with 10 % aq. Na_2CO_3. The organic layer was dried over Na_2SO_4 and the solvent was removed to afford **6** (R= *p*-Tol) in 93% (210 mg).

REFERENCES AND NOTES

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2. Y. Kamitori, M. Hojo, R. Masuda, T. Fujitani, S. Ohara, and T. Yokoyama, *J. Org. Chem.*, 1988, **53**, 129.

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4. Y. Kamitori, M. Hojo, R. Masuda, T. Takahashi, and M. Wada, *Heterocycles,* 1992, **34**, 1047.
5. Alumina (Woelm acid tlc dried for 2h at 180°C before use) instead of silica gel did not catalyze these cyclization reactions of **1** to **3** and **5** at all.
6. Total yield of **4** (R= *p*-Tol) from **1b** *via* 5-trifluoromethyloxazoline (ref. 4) was superior to that *via* 5-trifluoromethylthiazoline (**3b**).
7. For instance **3b**: Ir (KBr) 3600-2400 (br), 1634 (m), 1616 (m), 1516 (m), 1290 (s), 1249 (s), 1184 (s), 1120 (s), 1045 (s), 1026 (s), 827 (s) cm^{-1}. Anal. Calcd for $C_{11}H_{10}NOF_3S$: C, 50.57; H, 3.86; N, 5.36. Found: C, 50.59; H,3.83; N, 5.31.
8. Structures of triazines (**5**) were confirmed by ^1H nmr and ir spectra, and micro combustion analysis. For instance **5b**: ^{13}C Nmr ($CDCl_3$, 62.5 MHz) 21.2 (Me), 27.0, 57.7 (*t*-Bu), 49.6 ($^2J_{C\text{-}F}$ = 29 Hz, CH), 52.4 (CH_2), 124.3 ($^1J_{C\text{-}F}$ = 284 Hz, CF_3), 133.5 ($N{=}\underline{C}$-), 125,7 128.7, 135.3, 137.5 (Ar); ir (KBr) 3030 (m), 1530 (w), 1381 (m), 1256 (s), 1176 (s), 1123 (s), 922 (m), 821 (m) cm^{-1}. Anal. Calcd for $C_{15}H_{20}N_3F_3$: C, 60.19; H, 6.73; N, 14.04; F, 19.04. Found: C, 60.07; H, 6.47; N, 14.14; F, 19.32.
9. **6** *(R= p-Tol): mp 195.0-197°C (MeOH);* ^1H *nmr (*$CDCl_3$ */* CD_3OD*, 60 MHz)* 2.34 (s, 3H, Me), 3.27-3.50 (br, 1H, NH), 7.23 and 7.40 (d and d, *J* = 7 Hz, 4H, ArH), 7.60 (s, 1H, CH); ir (KBr) 3600-3320 (br), 1514 (m), 1326 (m), 1308 (m), 1179 (m), 1161 (s), 1102 (s), 978 (m), 959 (m), 822 (m) cm^{-1}.
10. Wako gel C300 (Wako Pure Chemical Co.) dried for 2 h at 180°C under reduced pressure was used.
11. Silica gel $60PF_{254}$ (Nakarai Chemical Co.) was used.

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