

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

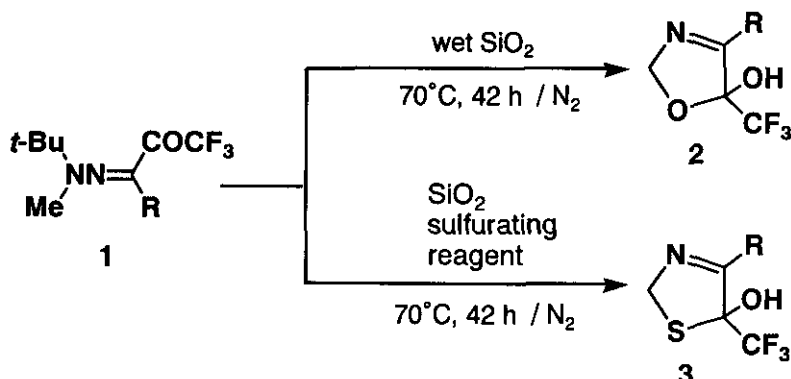
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**Abstract** - 5-Trifluoromethyl-3-thiazolines (**3**) and 5-trifluoromethyl-2,3,4,5-tetrahydro-1,2,4 triazine (**5**) were conveniently synthesized from 3-(*N-tert*-butyl-*N*-methylhydrazono)-1,1,1-trifluoroalkan-2-ones (**1**) with the use of silica 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.<sup>1</sup> 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,<sup>2,3</sup> affording 5-trifluoromethyl-3-oxazolines (**2**). In this reaction, "wet" silica gel acts as an effective catalyst to give good yields of **2**.<sup>4</sup> 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.<sup>2,3</sup> As



sulfuring reagents,  $\text{Na}_2\text{S}$ ,  $\text{NaHS}$ ,  $(\text{NH}_4)_2\text{S}$ , and  $\text{P}_2\text{S}_5$  were examined for a substrate (**1b**) with the use of  $\text{SiO}_2$  as a catalyst. As shown in Table 1, desired **3b** was obtained in any cases except for that of  $(\text{NH}_4)_2\text{S}$  and the best result was obtained when  $\text{NaHS}$  was used. However  $\text{Al}_2\text{O}_3$  did not catalyze the desired reaction. Quite similarly, by the use of  $\text{NaHS}$  and  $\text{SiO}_2$  several hydrazones (**1a**, **c-f**) were successfully converted to the corresponding thiazolines (**3a**, **c-f**) in moderate yields.<sup>5</sup> These are summarized in Table 2. In any cases, 5-trifluoromethylthiazole (**4**) formed through 1,4-elimination of  $\text{H}_2\text{O}$  was not detected. When **3b** was treated with  $\text{P}_2\text{S}_5$  in hot benzene, the corresponding **4** ( $\text{R} = p\text{-Tol}$ ) was obtained in 76% yield.<sup>6</sup> One-pot synthesis of **4** ( $\text{R} = p\text{-Tol}$ ) from **1b** was also possible. In this case,  $\text{P}_2\text{S}_5$  and benzene were immediately added to the reaction vessel in which conversion of **1b** to **3b** under the conditions in Table 2 completed, and the whole

Table 1. Synthesis of Thiazoline (**3b**).<sup>a</sup>

Reagent	Yield of <b>3b</b> , %
$\text{P}_2\text{S}_5$	25
$\text{Na}_2\text{S}$	35
$\text{NaHS}$	59
$\text{NaHS}^b$	0
$(\text{NH}_4)_2\text{S}$	0

a) Reactions were carried out for 20 h at  $70^\circ\text{C}$  under  $\text{N}_2$  with the use of  $\text{SiO}_2$  (3 g) and reagent (3 mmol) for **1b** (1 mmol). b)  $\text{Al}_2\text{O}_3$  (Woelm acid tlc) was used instead of  $\text{SiO}_2$ .

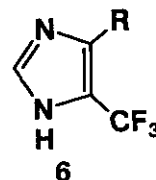
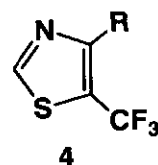
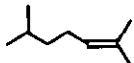


Table 2. Synthesis of 5-Trifluoromethyl-3-thiazolines (**3**).

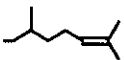
	R	Time, h	Yield, %	mp °C <sup>a</sup> (solvent)	<sup>1</sup> H Nmr (CDCl <sub>3</sub> /TMS) <sup>b</sup> δ
<b>3 a</b>	Ph	42	33	75.5 (C <sub>6</sub> H <sub>14</sub> )	4.73-5.53 (ABq, <i>J</i> = 16 Hz, 2H, CH <sub>2</sub> ), 4.20-4.57 (br, 1H, OH), 7.00-7.97 (m, 5H, ArH)
<b>3 b</b>	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	20	59	106.0 ( <i>c</i> -C <sub>6</sub> H <sub>12</sub> )	2.33 (s, 3H, Me), 4.97-5.53 (ABq, <i>J</i> = 16 Hz, 2H, CH <sub>2</sub> ), 4.27-4.68 (br, 1H, OH), 6.97 and 7.70 (d and d, 4H, <i>J</i> = 8 Hz, ArH)
<b>3 c</b>	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	72	29	116.0 ( <i>c</i> -C <sub>6</sub> H <sub>12</sub> )	3.78 (s, 3H, OMe), 4.17-4.63 (br, 1H, OH), 4.95-5.57 (ABq, <i>J</i> = 16 Hz, 2H, CH <sub>2</sub> ), 6.90 and 7.97 (d and d, <i>J</i> = 9 Hz, 4H, ArH)
<b>3 d</b>	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	48	43	110.0 ( <i>c</i> -C <sub>6</sub> H <sub>12</sub> )	3.90-4.10 (br, 1H, OH), 5.07-5.63 (ABq, <i>J</i> = 16 Hz, 2H, CH <sub>2</sub> ), 7.27 and 7.87 (d and d, <i>J</i> = 8 Hz, 4H, ArH)
<b>3 e</b>	Et	7	23	60.0 <sup>c</sup>	1.23 (t, <i>J</i> = 7 Hz, 3H, Me), 2.57 (q, <i>J</i> = 7 Hz, 2H, CH <sub>2</sub> ), 3.43-4.03 (br, 1H, OH), 4.97-5.47 (ABq, <i>J</i> = 16 Hz, 2H, CH <sub>2</sub> )
<b>3 f</b>		24	28	pale yellow oil <sup>d</sup>	0.67-2.83 (m, 16H, CH, CH <sub>2</sub> , Me), 3.50-4.33 (br, 1H, OH), 5.00 (t, <i>J</i> = 7 Hz, 1H, =CH), 5.07-5.37 (br, 2H, CH <sub>2</sub> )

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).

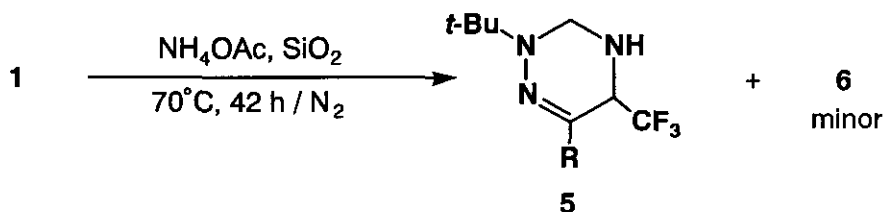
mixture was refluxed for 4 h to give **4** (R = *p*-Tol) in 23% yield. The structure of **3** was confirmed by <sup>1</sup>H and <sup>13</sup>C nmr, and ir spectra, and micro combustion analysis.<sup>7</sup> For example, <sup>13</sup>C nmr of **3 b** revealed thiazoline ring carbon at 61.6 (C2), 101.7 (C5, <sup>2</sup>*J*<sub>C-F</sub> = 32.5 Hz), 168.1 (C4).

When (NH<sub>4</sub>)<sub>2</sub>S 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 (**5 b**). Apparently not sulfur atom but nitrogen atom was incorporated in the ring system, and, in addition, we could detected a small amount of imidazole (**6 b**) in which nitrogen atom is incorporated in the same fashion for the case of sulfur atom in **3 b**. We examined several ammonium salts for the conversion of **1 b** to **5 b** in the presence of silica gel. Consequently, NH<sub>4</sub>OAc afforded the best yield of **5 b**. Thus, to **1 b** adsorbed on silica gel was added NH<sub>4</sub>OAc, 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 <sub>4</sub> )OAc equiv.	Temp °C	Time d	Yield %	mp, °C <sup>a</sup> (solvent)	<sup>1</sup> H Nmr (CDCl <sub>3</sub> /TMS) <sup>b</sup> δ
5a	Ph	50	60	2	36	69 (C <sub>6</sub> H <sub>14</sub> )	1.28 (s, 9H, <i>t</i> -Bu), 2.05-2.83 (br, 1H, NH), 3.68-4.30 (ABq, <i>J</i> = 12 Hz, 2H, CH <sub>2</sub> ), 4.30 (q, <i>J</i> = 8 Hz, 1H, CH), 7.10-7.60 (m, 5H, ArH)
5b	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	20	50	4	52	78 <sup>c</sup>	1.29 (s, 9H, <i>t</i> -Bu), 1.90-2.17 (br, 1H, NH), 2.30 (s, 3H, Me), 3.57-4.33 (ABq, <i>J</i> = 10 Hz, 2H, CH <sub>2</sub> ), 4.12 (q, <i>J</i> = 8 Hz, 1H, CH), 6.98 and 7.33 (d and d, <i>J</i> = 8 Hz, 4H, ArH)
5c	<i>o</i> -MeC <sub>6</sub> H <sub>4</sub>	20	70	1	37	101 <sub>4</sub> Torr <sup>d</sup>	1.67 (s, 9H, <i>t</i> -Bu), 2.35 (s, 3H, Me), 3.53-4.30 and 4.06 (ABq and q, <i>J</i> = 12 Hz and 8 Hz, 3H, CH <sub>2</sub> and CH), 7.03-7.27 (m, 4H, ArH)
5d	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	30	50	5	36	63 (C <sub>6</sub> H <sub>14</sub> )	1.23 (s, 9H, <i>t</i> -Bu), 3.50-4.24, 3.79 and 3.89 (ABq, s and q, <i>J</i> = 12 Hz and 8 Hz, 6H, CH <sub>2</sub> , OMe and CH), 6.72 and 7.30 (d and d, <i>J</i> = 8 Hz, 4H, ArH)
5e	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	50	60	2	38	59 ( <i>c</i> -C <sub>6</sub> H <sub>12</sub> )	1.26 (s, 9H, <i>t</i> -Bu), 3.60-4.36 and 4.12 (ABq and q, <i>J</i> = 12 Hz and 8 Hz, 3H, CH <sub>2</sub> and CH), 7.06-7.47 (q, <i>J</i> = 9 Hz, 4H, ArH)
5f	Et	100	50	2	16	pale yellow oil <sup>e</sup>	1.07 and 1.17 (t and s, <i>J</i> = 6.4 Hz, 12H, CH <sub>2</sub> Me and <i>t</i> -Bu), 2.31 (q, <i>J</i> = 6.4 Hz, 2H, CH <sub>2</sub> Me), 3.26-4.14 and 3.47 (ABq and q, <i>J</i> = 11.5 Hz and 8 Hz, 3H, CH <sub>2</sub> and CH)
5g		20	50	2	18	pale yellow oil <sup>e</sup>	0.80-2.30 and 1.15 (m and s, 25H, CH <sub>3</sub> , CH <sub>2</sub> , CH, and <i>t</i> -Bu), 3.20-4.03 and 3.34 (ABq and q, <i>J</i> = 11 Hz and 8 Hz, 3H, NCH <sub>2</sub> and NCH), 5.01 (t, br, <i>J</i> = 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 5e and 5g CCl<sub>4</sub> 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**)<sup>8</sup> obtained from several substrates (**1**) by similar manner.<sup>5</sup> In all cases in Table 3, 5-trifluoromethylimidazoles (**6**)<sup>9</sup> 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<sub>4</sub>OAc 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<sub>2</sub>Cl<sub>2</sub> was added silica gel<sup>10</sup> (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<sub>2</sub> 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 **3 c-f**) were also synthesized.

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

A mixture of **3 b** (261 mg, 1 mmol) and P<sub>2</sub>S<sub>5</sub> (666 mg, 3 mmol) in benzene (10 ml) was refluxed for 5 h under N<sub>2</sub>. After being cooled to room temperature, the mixture was washed with water, dried over Na<sub>2</sub>SO<sub>4</sub>, 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<sub>2</sub>S<sub>5</sub> and benzene (10 ml) was added to the reaction mixture and the whole was refluxed for 4 h under N<sub>2</sub> 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<sub>2</sub>SO<sub>4</sub>. 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<sup>10</sup> (5 g) by similar procedure which is described for synthesis of **3 b** from **1 b**. To this was added NH<sub>4</sub>OAc (1.54 g, 20 mmol) and well mixed, and the whole was heated at 50°C for 4 d under N<sub>2</sub>. 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,<sup>11</sup> benzene/AcOEt = 95/5) to give **5 b** (52 %, 155 mg, R<sub>f</sub> = 0.44) and **6** (R=*p*-Tol, 5 %, 11 mg, R<sub>f</sub> = 0.33).

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

Hydrazone (**1 b**, 300 mg, 1 mmol) adsorbed on silica gel<sup>10</sup> (3 g) by similar procedure which is described for synthesis of **3 b** from **1 b**. To this was added NH<sub>4</sub>OAc (385 mg, 5 mmol) and AcOH (2 ml), and the whole was maintained at 70°C for 42 h under N<sub>2</sub>. 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<sub>2</sub>CO<sub>3</sub>. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent was removed to afford **6** (R= *p*-Tol) in 93% (210 mg).

## REFERENCES AND NOTES

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3. Y. Kamitori, M. Hojo, R. Masuda, T. Yoshida, S. Ohara, K. Yamada, and T. Yokoyama, *J. Org. Chem.*, 1988, **53**, 519.
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 **1 b** via 5-trifluoromethyloxazoline (ref. 4) was superior to that via 5-trifluoromethylthiazoline (**3 b**).
7. For instance **3 b**: 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<sup>-1</sup>. Anal. Calcd for C<sub>11</sub>H<sub>10</sub>NOF<sub>3</sub>S: 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 <sup>1</sup>H nmr and ir spectra, and micro combustion analysis. For instance **5 b**: <sup>13</sup>C Nmr (CDCl<sub>3</sub>, 62.5 MHz) 21.2 (Me), 27.0, 57.7 (*t*Bu), 49.6 (<sup>2</sup>J<sub>C-F</sub> = 29 Hz, CH), 52.4 (CH<sub>2</sub>), 124.3 (<sup>1</sup>J<sub>C-F</sub> = 284 Hz, CF<sub>3</sub>), 133.5 (N=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<sup>-1</sup>. Anal. Calcd for C<sub>15</sub>H<sub>20</sub>N<sub>3</sub>F<sub>3</sub>: 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); <sup>1</sup>H nmr (CDCl<sub>3</sub> / CD<sub>3</sub>OD, 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<sup>-1</sup>.
10. Wako gel C300 (Wako Pure Chemical Co.) dried for 2 h at 180°C under reduced pressure was used.
11. Silica gel 60PF<sub>254</sub> (Nakarai Chemical Co.) was used.

Received, 8th November, 1993