

CONVENIENT SYNTHESIS OF 5-TRIFLUOROMETHYL-3-OXAZOLINES AND  
5-TRIFLUOROMETHYLOXAZOLES

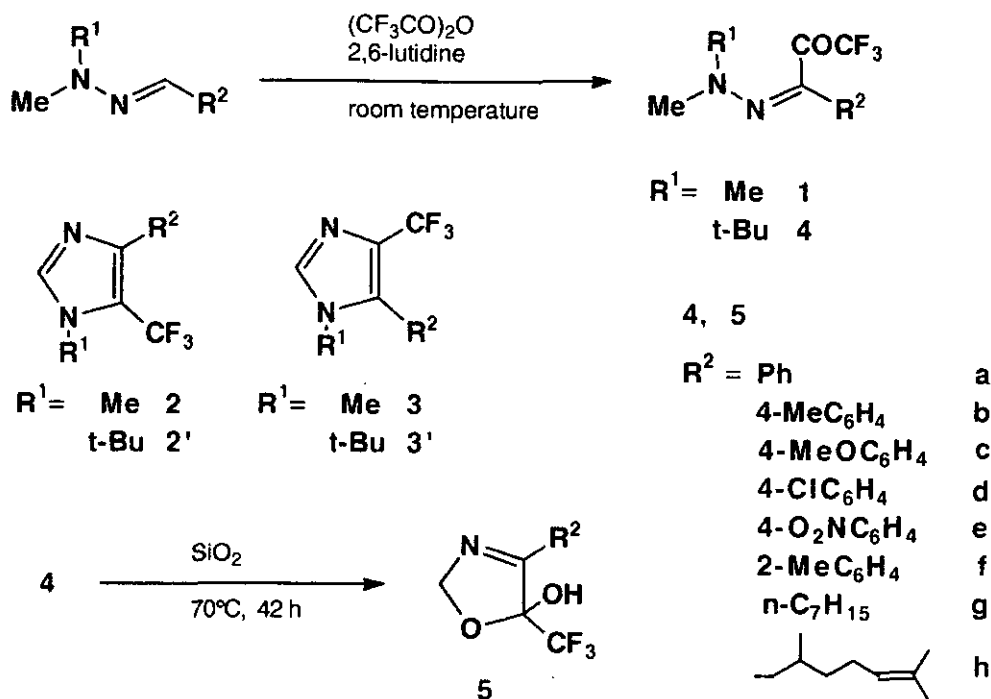
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**Abstract**— Aldehyde tert-butyl(methyl)hydrazones were acylated with tri-  
fluoroacetic anhydride to afford 3-tert-butyl(methyl)hydrazono-1,1,1-tri-  
fluoroalkan-2-ones (4) in good yields. Several 5-hydroxy-5-trifluoro-  
methyl-3-oxazolines (5) were successfully synthesized by thermally induced  
reaction of 4 adsorbed on silica gel. Treatment of 5 with POCl<sub>3</sub>/pyridine  
and subsequent dehydrochlorination with diisopropylethylamine gave 5-  
trifluoromethyloxazoles (6) in high yields.

Fluorine-containing heterocycles are very attractive target for many synthetic organic chemists because of their potential biological activities.<sup>1</sup> Recently we reported a novel cyclization reaction of 3-dimethylhydrazono-1,1,1-trifluoroalkan-2-ones (1) which are easily prepared from aldehyde dimethylhydrazones and trifluoroacetic anhydride,<sup>2,3</sup> affording trifluoromethylimidazoles (2) and (3).<sup>4</sup> A product obtained from 1 in refluxing toluene was mainly 5-trifluoromethylimidazole (2), whereas 4-trifluoromethylimidazole (3) was exclusively obtained when 1 was heated in the presence of silica gel. Similarly 3-tert-butyl(methyl)hydrazono-1,1,1-trifluoroalkan-2-ones (4) also afforded the corresponding 5-trifluoromethylimidazoles (2') as a sole product.<sup>4</sup> However behavior of 4 under the condition of the thermal reaction in the presence of silica gel was quite different. None of the expected 4-trifluoromethylimidazoles (3') was formed in this reaction, but 5-trifluoromethyl-3-oxazolines (5) was mainly obtained instead of 3'. These results prompted us to develop a new convenient synthetic method affording 5

## Scheme 1

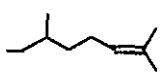


and 5-trifluoromethyloxazoles (**6**).

Several **4** were prepared from the corresponding aldehydes by an usual manner.<sup>2,3</sup> Thus obtained **4b** adsorbed on silica gel was heated at 80°C for 42 h under nitrogen to afford 4-(p-tolyl)-5-trifluoromethyl-3-oxazoline (**5b**) and **2'** (R = 4-MeC<sub>6</sub>H<sub>4</sub>) in a ratio of 71/29. At lower temperatures, the proportion of **5b** in crude products was slightly increased but the reaction became very sluggish. We found that small amounts of water suppressed the formation of **2'** effectively, leading to higher yields of **5b**. The reaction of **4b** (1 mmol) at 70°C with the use of wet silica gel (3 g of silica gel and 0.12 ml of water) gave the best result. Under this reaction condition, no **2'** was obtained and isolated yield of **5b** after column chromatography became 50%.

We also tried the reaction with the use of alumina<sup>5</sup> and molecular sieves<sup>6</sup>, but **5** was not obtained in both cases. We could detect the formation of **5** when **4** was heated in acetic

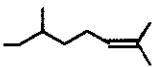
Table 1. 3-Hydroxy-5-trifluoromethyl-3-oxazolines (5).

Product	R <sup>2</sup>	Yield <sup>a</sup> %	mp, °C (solvent)	<sup>1</sup> H nmr (CDCl <sub>3</sub> /TMS) <sup>c</sup> δ
<u>5a</u>	Ph	67	90.5 (cyclohexane)	2.65–3.13 (br, 1H, OH), 5.46–6.00 (ABq, J= 15 Hz, 2H, CH <sub>2</sub> ), 7.35–7.65, 7.98–8.19 (m, 5H <sub>arom</sub> )
<u>5b</u>	4-MeC <sub>6</sub> H <sub>4</sub>	50	120.5 (cyclohexane)	2.35 (s, 3H, CH <sub>3</sub> ), 3.15–4.10 (br, 1H, OH), 5.50–5.87 (ABq, J= 14 Hz, 2H, CH <sub>2</sub> ), 7.15, 7.90 (d, J= 8 Hz, 4H <sub>arom</sub> )
<u>5c</u>	4-MeOC <sub>6</sub> H <sub>4</sub>	43	118.5 (cyclohexane)	2.51–2.91 (br, 1H, OH), 3.81 (s, 3H, OCH <sub>3</sub> ), 5.50–6.00 (ABq, J= 15 Hz, 2H, CH <sub>2</sub> ), 6.92, 8.05 (d, J= 8 Hz, 4H <sub>arom</sub> )
<u>5d</u>	4-ClC <sub>6</sub> H <sub>4</sub>	48	128.0 (cyclohexane /benzene)	3.20–3.45 (br, 1H, OH), 5.70–5.93 (ABq, J= 15 Hz, 2H, CH <sub>2</sub> ), 7.42, 8.02 (d, J= 8 Hz, 4H <sub>arom</sub> )
<u>5e</u>	4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	43	143.5 (EtOH/H <sub>2</sub> O)	3.70–4.25 (br, OH, 1H), 5.51–6.05 (ABq, J= 15 Hz, 2H, CH <sub>2</sub> ), 8.20 (s, 4H <sub>arom</sub> )
<u>5f</u>	2-MeC <sub>6</sub> H <sub>4</sub>	44	119.0 (cyclohexane)	2.33 (s, 3H, CH <sub>3</sub> ), 3.40–3.69 (br, 1H, OH), 5.69 (s, 2H, CH <sub>2</sub> ), 7.05–7.23, 7.50–7.72 (m, 4H <sub>arom</sub> )
<u>5g</u>	n-C <sub>7</sub> H <sub>15</sub>	32	160/4 torr <sup>d</sup>	0.79–2.70 (m, 15H, n-C <sub>7</sub> H <sub>15</sub> ), 3.70–4.13 (br, 1H, OH), 5.50 (s, 2H, CH <sub>2</sub> )
<u>5h</u>		47	140/4 torr <sup>d</sup>	0.83–2.80, 1.57, 1.65 (m, s and s, 16H, CH <sub>3</sub> , CH <sub>2</sub> , CH), 2.53–3.74 (br, 1H, OH), 5.00 (t, J= 7 Hz, 1H, =CH-), 5.30–5.67 (s, 2H, NCH <sub>2</sub> O)

a) Yields refer to pure isolated compounds. b) Uncorrected, measured with a Mitamura Riken model 7-12 apparatus. c) Recorded at 60 MHz on a JEOL PMX 60SI. d) Oven temperature of Kugelrohr distillation.



Table 2. 5-Trifluoromethyloxazoles (6).

Product	R <sup>2</sup>	Yield <sup>a</sup> %	bp <sup>b</sup> °C/torr	<sup>1</sup> H nmr (CDCl <sub>3</sub> /TMS) <sup>c</sup> δ
<u>6a</u>	Ph	72 (16)	68/6	7.10-7.68 (m, 5H <sub>arom</sub> ), 7.73 (s, 1H, CH)
<u>6b</u>	4-MeC <sub>6</sub> H <sub>4</sub>	80 (49)	57/5	2.37 (s, 3H, CH <sub>3</sub> ), 7.13, 7.67 (d, J= 8 Hz, 4H <sub>arom</sub> ), 7.78 (s, 1H, CH)
<u>6c</u>	4-MeOC <sub>6</sub> H <sub>4</sub>	89 (31)	100/6	3.77 (s, 3H, CH <sub>3</sub> ), 6.86, 7.58 (d, J= 9 Hz, 4H <sub>arom</sub> ), 7.83 (s, 1H, CH)
<u>6d</u>	4-ClC <sub>6</sub> H <sub>4</sub>	73 (43)	70/5	7.27-7.80 (q, J= 8 Hz, 4H <sub>arom</sub> ), 7.89 (s, 1H, CH)
<u>6e</u>	4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	(79)	71.5 <sup>d</sup> (cyclohexane)	7.85, 8.28 (d, J= 9 Hz, 4H <sub>arom</sub> ), 8.03 (s, 1H, CH)
<u>6f</u>	2-MeC <sub>6</sub> H <sub>4</sub>	56	65/6	2.24 (s, 3H, CH <sub>3</sub> ), 7.12 (s, 4H <sub>arom</sub> ), 7.79 (s, 1H, CH)
<u>6g</u>	n-C <sub>7</sub> H <sub>15</sub>	76 (27)	80/5	0.67-2.00 (m, 13H, n-C <sub>6</sub> H <sub>13</sub> ), 2.63 (t, J= 7 Hz, 2H, n-C <sub>6</sub> H <sub>13</sub> CH <sub>2</sub> ), 7.72 (s, 1H, CH)
<u>6h</u>		49	90/4	0.88, 1.58, 1.66, 1.00-2.67 (d, s, s and m, 16H, CH <sub>3</sub> , CH <sub>2</sub> , CH), 4.97 (t, J= 7 Hz, 1H, =CH-), 7.67 (s, 1H, OCH)

a) Yields refer to pure isolated compounds. Diisopropylethylamine was used for dehydrochlorination. Yields in parentheses are those when DBU was used. b) Oven temperature of Kugelrohr distillation. c) Recorded at 60 MHz on a JEOL PMX 60SI. d) Uncorrected mp measured with a Mitamura Riken model 7-12 apparatus.

5b to 6b with the use of POCl<sub>3</sub> and a variety of tertiary amines instead of pyridine under several reaction conditions was carried out. However the yield of 6b could not be improved so much. Complete conversion of 5b' to 6b was achieved when the crude initial product(5b) was treated with DBU or some other tertiary amines. This dehydrochlorination

step proceeded at room temperature and overall yield of 6b from 5b was 49% when DBU was used as a base. Quite similarly several oxazolines (5) in Table 1 could be successfully converted to the corresponding oxazoles (6). These are summarized in Table 2, where in most of the cases yields of 6 much increased when diisopropylethylamine instead of DBU was used for this process.

Mechanistic studies for a transformation process of 4 to 5 are now undergoing. At present, however, it seems plausible that mechanisms for conversion of 4 to 6 and that of 4 to 2' (or 1 to 2) resemble to each other, because C2 atoms of both 5 and 2' are thought to be come from the N-methyl carbon atom of 4. Probably these two mechanisms include common key steps.

In conclusion, the above results present a very convenient method for construction of new fluorine-containing heterocycles, 5-trifluoromethyl-3-oxazolines (5) and 5-trifluoromethyloxazoles (6).

Table 3. Analytical data of Oxazolines (5) and Oxazoles (6).

Compound	Formula	Calcd, %				Found, %			
		C	H	N	F	C	H	N	F
<u>5a</u>	C <sub>10</sub> H <sub>8</sub> NO <sub>2</sub> F <sub>3</sub>	51.96	3.49	6.06	24.66	52.32	3.83	6.03	24.35
<u>5b</u>	C <sub>11</sub> H <sub>10</sub> NO <sub>2</sub> F <sub>3</sub>	53.88	4.11	5.71	23.24	53.70	4.13	5.74	23.24
<u>5c</u>	C <sub>11</sub> H <sub>10</sub> NO <sub>3</sub> F <sub>3</sub>	50.58	3.86	5.36		50.73	3.97	5.52	
<u>5d</u>	C <sub>10</sub> H <sub>7</sub> NO <sub>2</sub> C1F <sub>3</sub>	45.22	2.66	5.27	21.46	45.12	2.55	5.34	21.47
<u>5e</u>	C <sub>10</sub> H <sub>7</sub> N <sub>2</sub> O <sub>4</sub> F <sub>3</sub>	43.49	2.56	10.14	20.64	43.54	2.49	10.11	20.51
<u>5f</u>	C <sub>11</sub> H <sub>10</sub> NO <sub>2</sub> F <sub>3</sub>	53.88	4.11	5.71		53.80	4.04	5.78	
<u>5g</u>	C <sub>11</sub> H <sub>18</sub> NO <sub>2</sub> F <sub>3</sub>	52.17	7.16	5.53		52.06	7.21	5.41	
<u>5h</u>	C <sub>13</sub> H <sub>20</sub> NO <sub>2</sub> F <sub>3</sub>	55.91	7.22	5.02		55.72	7.51	4.77	
<u>6a</u>	C <sub>10</sub> H <sub>6</sub> NOF <sub>3</sub>	56.35	2.84	6.57	26.74	56.45	2.88	6.58	26.49
<u>6b</u>	C <sub>11</sub> H <sub>8</sub> NOF <sub>3</sub>	58.16	3.55	6.17		57.84	3.80	5.86	
<u>6c</u>	C <sub>11</sub> H <sub>8</sub> NOF <sub>3</sub>	54.33	3.32	5.76		54.60	3.44	5.73	
<u>6d</u>	C <sub>10</sub> H <sub>5</sub> NOClF <sub>3</sub>	48.51	2.04	5.66		48.53	1.98	5.69	
<u>6e</u>	C <sub>10</sub> H <sub>5</sub> N <sub>2</sub> O <sub>3</sub> F <sub>3</sub>	46.53	1.95	10.85		46.81	2.24	10.81	
<u>6f</u>	C <sub>11</sub> H <sub>8</sub> NOF <sub>3</sub>	58.16	3.55	6.17		58.36	3.55	6.25	
<u>6g</u>	C <sub>11</sub> H <sub>16</sub> NOF <sub>3</sub>	56.16	6.86	5.95		55.98	6.99	6.11	
<u>6h</u>	C <sub>13</sub> H <sub>18</sub> NOF <sub>3</sub>	59.76	6.94	5.36		59.97	7.15	5.37	

## EXPERIMENTAL

3-tert-Butyl(methyl)hydrazono-1,1,1-trifluoroalkan-2-ones (4a-h) were prepared according to the literature.<sup>2,3,7,8</sup> The physical and spectral data of 4a and 4c-g are given below.<sup>9</sup>

4a; Yield: 91%; mp 84.0°C (hexane); <sup>1</sup>H nmr (CDCl<sub>3</sub>/TMS) δ 1.30 (s, 9H), 2.50 (s, 3H), 6.80-7.50 (m, 5H).

4c; Yield: 80%; mp 83.5°C (cyclohexane); <sup>1</sup>H nmr (CDCl<sub>3</sub>/TMS) δ 1.33(s, 9H), 2.60 (s, 3H), 3.72 (s, 3H), 6.68, 7.00 (d, J= 8 Hz, 4H).

4d; Yield: 78%; mp 65.5°C (hexane/CCl<sub>4</sub>); <sup>1</sup>H nmr (CDCl<sub>3</sub>/TMS) δ 1.35 (s, 9H), 2.62 (s, 3H), 7.08, 7.32 (d, J= 8 Hz, 4H).

4e; Yield: 67%; mp 103.0°C (EtOH/H<sub>2</sub>O); <sup>1</sup>H nmr (CDCl<sub>3</sub>/TMS) δ 1.38 (s, 9H), 2.65 (s, 3H), 7.34, 8.17 (d, J= 8 Hz, 4H).

4f; Yield: 83%; mp 75.5°C (hexane); <sup>1</sup>H nmr (CCl<sub>4</sub>/TMS) δ 1.33 (s, 9H), 2.13 (s, 3H), 2.55 (s, 3H), 7.03 (s, 4H).

4g; Yield: 95%; 120°C/2 torr (oven temperature of Kugelrohr distillation); <sup>1</sup>H nmr (CCl<sub>4</sub>/TMS) δ 0.50-2.85, 1.31 (m and s, 24H), 3.13 (s, 3H).

5-Hydroxy-5-trifluoromethyl-3-oxazolines (5). General Procedure:

To silica gel (3 g, Wakogel C300 for column chromatography dried at 180°C for 2 h under reduced pressure just before use) was added water (0.12 mL) and the whole was mixed well. Thus obtained wet silica gel and a solution of 4 (1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 ml) were combined and the whole was stirred thoroughly, and was evaporated to dryness under vacuum. The powder was introduced into a flask flashed with nitrogen and heated for 42 h (2 h in the cases of 4g and 4h) at 70°C. To the mixture was added ethyl acetate (50 ml) and the whole was stirred for 30 min. Silica gel was filtered off and washed with ethyl acetate (2 X 25 ml). The filtrate and washings were combined, and the solvent was removed. Thus obtained crude 5 was purified by recrystallization or Kugelrohr distillation. If necessary, crude 5 was submitted to preparative tlc (silica gel Merk 60PF) using CH<sub>2</sub>Cl<sub>2</sub> as eluent before recrystallization or Kugelrohr distillation.

5-Trifluoromethyloxazoles (6). General Procedure:

To a mixture of 5 (1 mmol) and pyridine (695 mg, 8.8 mmol) in CHCl<sub>3</sub> (1 ml) was added

dropwise  $\text{POCl}_3$  (368 mg, 2.4 mmol) with continuous stirring. After stirring for 2 h, the reaction mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (50 ml), washed with 1N HCl (100 ml), then with water (100 ml), and finally with 10% aq.  $\text{Na}_2\text{CO}_3$  (100 ml). The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent was removed to afford a mixture of 5-chloro-5-trifluoromethyl-3-oxazoline (5') and (6). To the mixture dissolved in  $\text{CHCl}_3$  (3 ml) was added diisopropyl-ethylamine (646 mg) or DBU (761 mg, 5 mmol). After stirring for 2 h (3 h in the cases of 5g and 5h), the mixture was poured into 1N HCl (50 ml) and extracted thoroughly with  $\text{CH}_2\text{Cl}_2$  (50 ml). The extract was washed with water (100 ml) and subsequently with 10% aq.  $\text{Na}_2\text{CO}_3$  (50 ml). The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent was removed. The residue was submitted to Kugelrohr distillation or recrystallization to afford pure 6 (Table 2).

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