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

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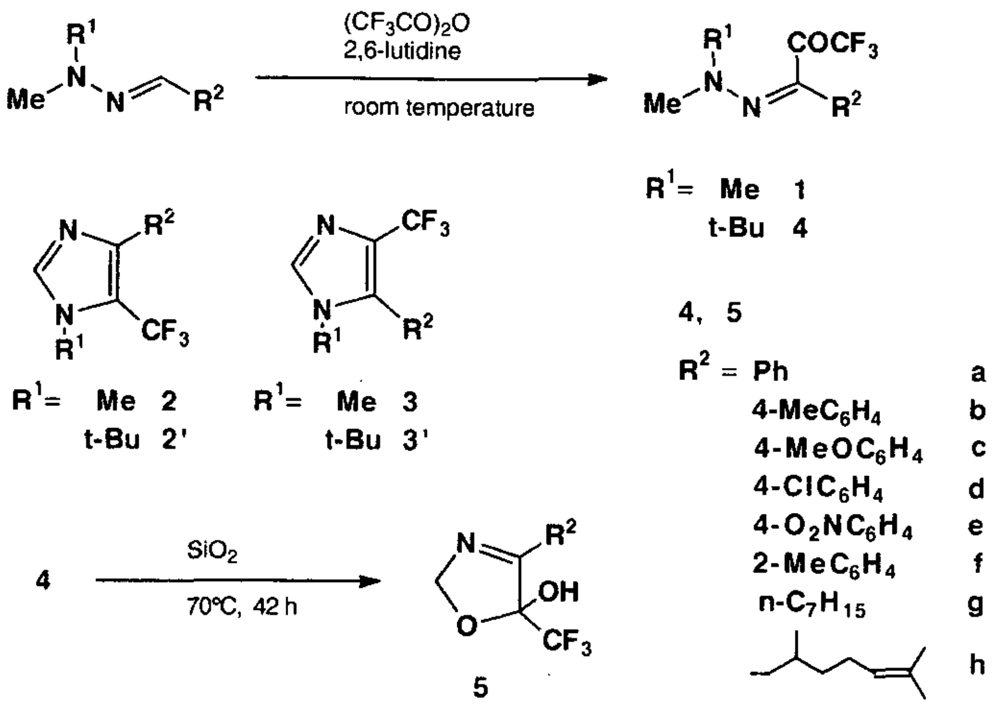
Abstract- Aldehyde tert-butyl(methyl)hydrazones were acylated with trifluoroacetic anhydride to afford 3-tert-butyl(methyl)hydrazono-1,1,1-trifluoroalkan-2-ones (4) in good yields. Several 5-hydroxy-5-trifluoromethyl-3-oxazolines (5) were successfully synthesized by thermally induced reaction of 4 adsorbed on silica gel. Treatment of 5 with $POCl_3$/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.[1] 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,[2,3] affording trifluoromethylimidazoles (2) and (3).[4] 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.[4] 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

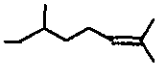


and 5-trifluoromethyloxazoles (6).

Several 4 were prepared from the corresponding aldehydes by an usual manner.[2,3] 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$_6$H$_4$) 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[5] and molecular sieves[6], 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		Yield[a]	mp, °C	^{1}H nmr ($CDCl_3$/TMS)[c]
	R^2	%	(solvent)	δ
5a	Ph	67	90.5 (cyclohexane)	2.65-3.13 (br, 1H, OH), 5.46-6.00 (ABq, J= 15 Hz, 2H, CH_2), 7.35-7.65, 7.98-8.19 (m, $5H_{arom}$)
5b	4-MeC_6H_4	50	120.5 (cyclohexane)	2.35 (s, 3H, CH_3), 3.15-4.10 (br, 1H, OH), 5.50-5.87 (ABq, J= 14 Hz, 2H, CH_2), 7.15, 7.90 (d, J= 8 Hz, $4H_{arom}$)
5c	4-$MeOC_6H_4$	43	118.5 (cyclohexane)	2.51-2.91 (br, 1H, OH), 3.81 (s, 3H, OCH_3), 5.50-6.00 (ABq, J= 15 Hz, 2H, CH_2), 6.92, 8.05 (d, J= 8 Hz, $4H_{arom}$)
5d	4-ClC_6H_4	48	128.0 (cyclohexane /benzene)	3.20-3.45 (br, 1H, OH), 5.70-5.93 (ABq, J= 15 Hz, 2H, CH_2), 7.42, 8.02 (d, J= 8 Hz, $4H_{arom}$)
5e	4-$O_2NC_6H_4$	43	143.5 ($EtOH/H_2O$)	3.70-4.25 (br, OH, 1H), 5.51-6.05 (ABq, J= 15 Hz, 2H, CH_2), 8.20 (s, $4H_{arom}$)
5f	2-MeC_6H_4	44	119.0 (cyclohexane)	2.33 (s, 3H, CH_3), 3.40-3.69 (br, 1H, OH), 5.69 (s, 2H, CH_2), 7.05-7.23, 7.50-7.72 (m, $4H_{arom}$)
5g	n-C_7H_{15}	32	160/4 torr[d]	0.79-2.70 (m, 15H, n-C_7H_{15}), 3.70-4.13 (br, 1H, OH), 5.50 (s, 2H, CH_2)
5h		47	140/4 torr[d]	0.83-2.80, 1.57, 1.65 (m, s and s, 16H, CH_3, CH_2, CH), 2.53-3.74 (br, 1H, OH), 5.00 (t, J= 7 Hz, 1H, =CH-), 5.30-5.67 (s, 2H, NCH_2O)

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.

acid containing small amounts of water. However the yield of 5 in this reaction was very low presumably because hydrolysis of 4 or initially formed 5 were occurred to produce 1,1,1-trifluoroalkan-2,3-diones as the main products .

Under the optimum conditions for 4b with the use of wet silica gel, 4a-f were also successfully converted to the corresponding 5a-f. In the cases of 4g and 4h where R is aliphatic groups, the reaction leading to the corresponding 5g and 5h, respectively, proceeded more rapidly and completed within 4 h. In contrast, 1 did not afford 5 even with the use of wet silica gel, and 3-isopropyl(methyl)hydrazono-1,1,1-trifluoroalkan-2-ones, under the same reaction conditions, gave minor amounts of 5 together with 1-isopropyl-4-trifluoromethylimidazoles as major products. Bulkiness of a tert-butyl group in 4 definitely plays an important role in the reaction to 5.

As for conversion of 5 to the corresponding oxazoles (6), several dehydration methods were examined. However 5 resisted toward conventional dehydration reagents and catalysts, and, therefore, all attempts to access 6 directly from 5 resulted in failure. Two steps conversion including chlorination of 5 and subsequent dehydrochlorination was successfully performed for this conversion. Thus 5b was treated with 2.4 molar equiv. of $POCl_3$ in the presence of pyridine. Main product of this reaction was chloride (5'), but a small amount of the expected oxazole (6b) was also detected in the reaction mixture. This suggests that dehydrochlorination of 5b' undergoes after initial conversion of 5b to 5b' under this reaction condition. Therefore one-pot conversion of

Scheme 2

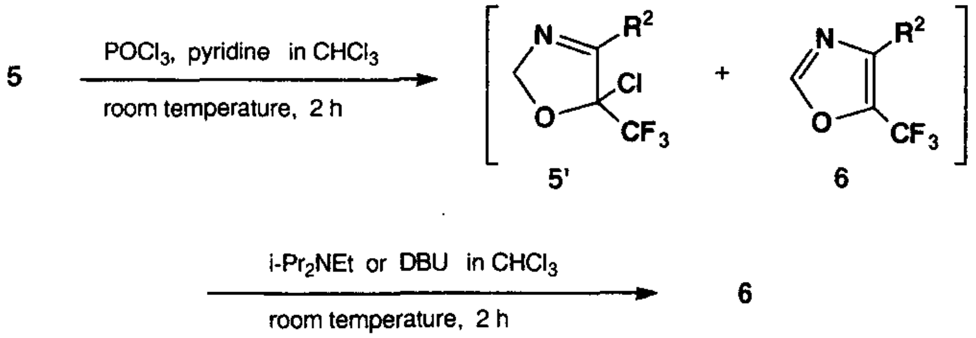
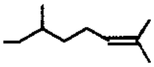


Table 2. 5-Trifluoromethyloxazoles (6).

Product	R^2	Yield[a] %	bp[b] °C/torr	^1H nmr ($CDCl_3$/TMS)[c] δ
6a	Ph	72 (16)	68/6	7.10-7.68 (m, 5H_{arom}), 7.73 (s, 1H, CH)
6b	4-MeC_6H_4	80 (49)	57/5	2.37 (s, 3H, CH_3), 7.13, 7.67 (d, J= 8 Hz, 4H_{arom}), 7.78 (s, 1H, CH)
6c	4-$MeOC_6H_4$	89 (31)	100/6	3.77 (s, 3H, CH_3), 6.86, 7.58 (d, J= 9 Hz, 4H_{arom}), 7.83 (s, 1H, CH)
6d	4-ClC_6H_4	73 (43)	70/5	7.27-7.80 (q, J= 8 Hz, 4H_{arom}), 7.89 (s, 1H, CH)
6e	4-$O_2NC_6H_4$	(79)	71.5[d] (cyclohexane)	7.85, 8.28 (d, J= 9 Hz, 4H_{arom}), 8.03 (s, 1H, CH)
6f	2-MeC_6H_4	56	65/6	2.24 (s, 3H, CH_3), 7.12 (s, 4H_{arom}), 7.79 (s, 1H, CH)
6g	n-C_7H_{15}	76 (27)	80/5	0.67-2.00 (m, 13H, n-C_6H_{13}), 2.63 (t, J= 7 Hz, 2H, n-$C_6H_{13}\underline{CH_2}$), 7.72 (s, 1H, CH)
6h		49	90/4	0.88, 1.58, 1.66, 1.00-2.67 (d, s, s and m, 16H, CH_3, CH_2, 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 $POCl_3$ 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).

		Calcd, %				Found, %			
Compound	Formula	C	H	N	F	C	H	N	F
5a	$C_{10}H_8NO_2F_3$	51.96	3.49	6.06	24.66	52.32	3.83	6.03	24.35
5b	$C_{11}H_{10}NO_2F_3$	53.88	4.11	5.71	23.24	53.70	4.13	5.74	23.24
5c	$C_{11}H_{10}NO_3F_3$	50.58	3.86	5.36		50.73	3.97	5.52	
5d	$C_{10}H_7NO_2ClF_3$	45.22	2.66	5.27	21.46	45.12	2.55	5.34	21.47
5e	$C_{10}H_7N_2O_4F_3$	43.49	2.56	10.14	20.64	43.54	2.49	10.11	20.51
5f	$C_{11}H_{10}NO_2F_3$	53.88	4.11	5.71		53.80	4.04	5.78	
5g	$C_{11}H_{18}NO_2F_3$	52.17	7.16	5.53		52.06	7.21	5.41	
5h	$C_{13}H_{20}NO_2F_3$	55.91	7.22	5.02		55.72	7.51	4.77	
6a	$C_{10}H_6NOF_3$	56.35	2.84	6.57	26.74	56.45	2.88	6.58	26.49
6b	$C_{11}H_8NOF_3$	58.16	3.55	6.17		57.84	3.80	5.86	
6c	$C_{11}H_8NOF_3$	54.33	3.32	5.76		54.60	3.44	5.73	
6d	$C_{10}H_5NOClF_3$	48.51	2.04	5.66		48.53	1.98	5.69	
6e	$C_{10}H_5N_2O_3F_3$	46.53	1.95	10.85		46.81	2.24	10.81	
6f	$C_{11}H_8NOF_3$	58.16	3.55	6.17		58.36	3.55	6.25	
6g	$C_{11}H_{16}NOF_3$	56.16	6.86	5.95		55.98	6.99	6.11	
6h	$C_{13}H_{18}NOF_3$	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.[2,3,7,8] The physical and spectral data of **4a** and **4c**-**g** are given below.[9]

4a; Yield: 91%; mp 84.0°C (hexane); ^{1}H nmr ($CDCl_3$/TMS) δ 1.30 (s, 9H), 2.50 (s, 3H), 6.80-7.50 (m, 5H).

4c; Yield: 80%; mp 83.5°C (cyclohexane); ^{1}H nmr ($CDCl_3$/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_4); ^{1}H nmr ($CDCl_3$/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_2O); ^{1}H nmr ($CDCl_3$/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); ^{1}H nmr (CCl_4/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); ^{1}H nmr (CCl_4/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_2Cl_2 (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_2Cl_2 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 $CHCl_3$ (1 ml) was added dropwise $POCl_3$ (368 mg, 2.4 mmol) with continuous stirring. After stirring for 2 h, the reaction mixture was diluted with CH_2Cl_2 (50 ml), washed with 1N HCl (100 ml), then with water (100 ml), and finally with 10% aq. Na_2CO_3 (100 ml). The organic layer was dried (Na_2SO_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 $CHCl_3$ (3 ml) was added diisopropylethylamine (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 CH_2Cl_2 (50 ml). The extract was washed with water (100 ml) and subsequently with 10% aq. Na_2CO_3 (50 ml). The organic layer was dried (Na_2SO_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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