CONVENIENT SYNTHETIC METHODS FOR 5-TRIFLUOROMETHYL-OXAZOLES AND 5-TRIFLUOROMETHYLTHIAZOLES

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Abstract - 5-(Trifluoromethyl)oxazoles (**3**) and 5-(trifluoromethyl)thiazoles (**4**) were conveniently as well as effectively synthesized from 3-(N-*tert*-butyl-N-methylhydrazono)-1,1,1-trifluoroalkan-2-ones (**1**) *via* 5-(trifluoromethyl)-3-oxazoline (**2**). One-pot conversion of **1** to **4** also proceeded successfully.

Fluorine-containing heterocycles are very attractive compounds because of their potentially high biological activities.[1] In previous paper,[2] we reported the synthesis of 5-(trifluoromethyl)-3-oxazolines (**2**) and 5-(trifluoromethyl)oxazoles (**3**), in which **2** was synthesized from 3-N-*tert*-butyl-N-methylhydrazono)-1,1,1-trifluoroalkan-2-ones (**1**) by a thermal treatment in the presence of silica gel and **3** was obtainable by two steps conversion including chlorination of **2** and subsequent dehydrochlorination. As for the conversion of **2** to **3**, we found recently more efficient and facile method. In addition, we also found very convenient method for conversion of **2** to 5-(trifluoromethyl)thiazoles (**4**). Now, we wish to communicate about these two effective methods accessing **3** and **4**.

According to usual method[3] **1** was obtained from aldehyde N-*tert*-butyl-N-methylhydrazones and trifluoroacetic anhydride (TFAA). By heating **1** adsorbed on wet silica gel gave the corresponding 5-(trifluoromethyl)-3-oxazolines (**2**) in moderate to good yields.[2] Thus obtained **2b** was reacted with 2.4 molar equiv. of $POCl_3$ in the presence of 8.8 molar equiv. of pyridine for 2 h at 90°C affording the corresponding 5-(trifluoromethyl)oxazole (**3b**) in 96% yield. Quite similarly **2a-g**

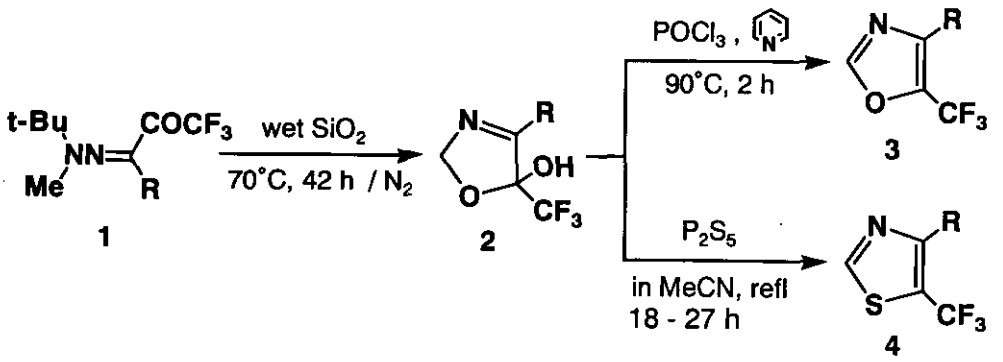


Table 1. Synthesis of 5-Trifluoromethyloxazoles (**3**).

Product	R	Yield, %[a] This work	Lit[2]
3a	Ph	94	72
3b	4-MeC_6H_4	96	80
3c	2-MeC_6H_4	98	56
3f	4-$O_2NC_6H_4$	92	79
3g	n-C_7H_{15}	100[b]	76

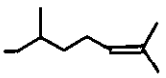
a) Pure isolated yield. b) In this case, longer reaction time, 4 h was needed.

could be dehydrated to the corresponding **3 a-g**, in excellent to quantitative yields. In each cases the yields of **3** were superior to those in the case of the previously reported two steps method.[2] These are summarized in Table 1.

Conversion of **2** to 5-(trifluoromethyl)thiazoles (**4**) was examined with the use of several sulfurating reagents under a variety of conditions. Among them, use of P_2S_5 as a sulfurating reagent in acetonitrile under reflux conditions led to the best result. For instance **2 b** (1 mmol) and P_2S_5(1 mmol) was dissolved in acetonitrile (10 ml) under N_2, and the mixture was refluxed for 16 h. The reaction mixture was diluted with CH_2Cl_2 (100 ml), then washed thoroughly with aq. Na_2CO_3, and dried over Na_2SO_4. The solvent was removed and the residue was chromatographed on silica gel, eluting with benzene, to give 4-(*p*-tolyl)-5-(trifluoromethyl)thiazole (**4 b**) in 55% yield.

Also one-pot conversion of hydrazone (**1**) to thiazole (**4**) was examined. To silica gel[4] (3 g) was added water (0.12 ml) and the whole was mixed well. Thus obtained wet silica gel and a solution o

Table 2. Synthesis of 5-(Trifluoromethyl)thiazoles by One-pot Method.

Product	R	Time[a] h	Yield[b] %	Oven. temp.[c] °C / torr	^{1}H Nmr (CCl_4/TMS)[d]
4a	Ph	21	30	90 / 6	7.17-7.73 (m, 5H$_{arom}$), 8.68 (s, 1H, CH)
4b	4-MeC_6H_4	18	36	75 / 5	2.40 (s, 3H, CH_3), 7.18, 7.60 (d, J= 8 Hz, 4H$_{arom}$), 8.77 (s, 1H, CH)
4d	4-MeOC_6H_4	27	18	100 / 4	3.78 (s, 3H, OCH_3), 6.80, 7.54 (d, J= 9 Hz, 4H$_{arom}$), 8.67(s, 1H, CH)
4e	4-ClC_6H_4	27	25	100 / 6	7.27, 7.54 (d, J= 9 Hz, 4H$_{arom}$), 8.71 (s, 1H, CH)
4f	4-$O_2N C_6H_4$	21	30	119.5-120.5[e] (cyclohexane)	7.74, 8.19 (d, J= 9Hz, 4H$_{arom}$), 8.82 (s, 1H, CH)[f]
4h		18	18	95 / 6	0.87-2.85 (d, J= 6Hz, s, s and m, 16H, CH_3, CH_2, CH), 4.95 (t, J= 6 Hz, 1H, =CH-), 8.53 (s, 1H, CH)

a) Reaction time of second step from **2** to **4**. b) Yield refer to pure isolated compounds. c) Oven temperature of Kugelrohr distillation. d) Recorded at 60 MHz on a JEOL PMX60SI. e) mp uncollected, measured with a Mitamura Riken model 7-12 apparatus. f) As a solvent $CDCl_3$ was used.

1 (1 mmol) in CH_2Cl_2 (1 ml) were combined and the whole was stirred thoroughly, and was evaporated to dryness. The powder was introduced into a flask flashed with nitrogen and heated for 42 h[5] at 70°C. The reaction mixture was allowed to cool to room temperature, then P_2S_5 (3 mmol) and acetonitrile (10 ml) was added, and the mixture was stirred for 18 - 27 h under reflux conditions. Silica gel was filtered off and washed thoroughly with CH_2Cl_2. Washings and filtrate were combined, and the mixture was washed with aq. Na_2CO_3 and water. The organic layer was dried over Na_2SO_4 and the solvent was removed. The residual material was fractionated by silica gel column, eluting with benzene, to afford pure **4**. In all cases in Table 2, one-pot conversion of **1** to **4** proceeded successfully. The yield (36%) of **4b**, for example is apparently higher than that

(27.5%) as the result of two-pot method *via* isolation of **2 b**.

The structure of **4** was confirmed mainly by ^{1}H nmr and ir spectra, and microanalysis.[6] In ^{13}C nmr spectra (in $CDCl_3$),[7] thiazole ring carbons of **4 b** appear at δ 153.3 (C2, $^1J_{CH}$ = 212.4 Hz), 157.2 (C4, $^3J_{CF}$ = 2.4 Hz), and 120.5 (C5, $^2J_{CF}$ = 37.8 Hz).

In conclusion we can present very convenient synthetic methods accessing 5-(trifluoromethyl)-oxazoles (**3**) and 5-(trifluoromethyl)thiazoles (**4**) starting from aldehyde *tert*-butyl(methyl)-hydrazones.

REFERENCES AND NOTES

1. Review: R. Filler, " Organofluorine Chemicals and their Industrial Applications", ed. R. E. Banks, Ellis Horwood: London, 1979, p.123.
2. Y. Kamitori, M. Hojo, R. Masuda, T. Takahashi, and M. Wada, *Heterocycles*, 1992, **3 4**, 1047.
3. Y. Kamitori, M. Hojo, R. Masuda, T. Fujitani, S. Ohara, and T. Yokoyama, *J. Org. Chem.*, 1988, **5 3** 129.
4. Wakogel C300 for column chromatography dries at 180°C for 2 h under reduced pressure before use.
5. In the case of **1 h**, 2 h was sufficient for the complete conversion.
6. **4 a**: Ir (KBr) 1422 (m), 1342 (s), 1168 (s), 1127 (s), 1096 (m), 1014 (s), 908 (m) cm^{-1}. Anal. Calcd for $C_{10}H_6NF_3S$: C, 52.40; H, 2.64; N, 6.11. Found C, 52.35; H, 2.56; N, 6.12. **4 b**: Ir (KBr) 1501 (s) 1350 (s), 1168 (s), 1130 (s), 1096 (s), 1013 (s), 912 (m), 815 (m) cm^{-1}. Anal. Calcd for $C_{11}H_{18}NF_3S$: C, 54.32; H, 3.31; N, 5.76. Found C, 54.20; H, 3.32; N, 5.76. **4 d**: Ir (KBr) 1600 (m), 1490 (s), 1342 (s), 1260 (s), 1165 (s), 1122 (s), 1009 (s), 907 (m), 828 (s) cm^{-1}. Anal. Calcd for $C_{11}H_8NOF_3S$: C, 50.96; H, 3.11; N, 5.40. Found C, 51.37; H, 3.39; N, 5.61. **4 e**: Ir (KBr) 1525 (m), 1481 (s), 1345 (s), 1277 (m), 1219 (m), 1170 (s), 1130 (2), 1088 (s), 1014 (s), 909 (s) cm^{-1}. Anal. Calcd for $C_{10}H_5NClF_3S$: C, 45.55; H, 1.91; N, 5.31. Found C, 45.28; H, 2.19; N, 5.15. **4 f**: Ir (KBr) 1601 (m), 1528 (s), 1345 (s), 1300 (s), 1164(s), 1131 (s), 1092 (s), 1014 (s), 910 (m), 857 (s) cm^{-1}. Anal. Calcd for $C_{10}H_5N_2O_2F_3S$: C, 43.80; H, 1.84; N, 10.22. Found C, 44.00; H, 1.86; N, 10.51. 4h: Ir (KBr) 2960 (m), 2920 (m), 1530 (m), 1340 (s), 1293 (m), 1161 (s), 1130 (s), 1018 (s), cm-1. Anal. Calcd for $C_{12}H_{18}NF_3S$: C, 56.30; H, 6.54; N, 5.05. Found C, 55.85; H, 6.42; N, 4.77.
7. Recorded at 59.5 MHz on a Bruker AC250.

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