Synthesis and properties of polyfluorinated oxazoles

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Defluorination of polyfluorinated acylimines by zinc on heating in dioxane gave polyfluorinated oxazoles. The behavior of polyfluorinated oxazoles in nucleophilic substitution was studied.

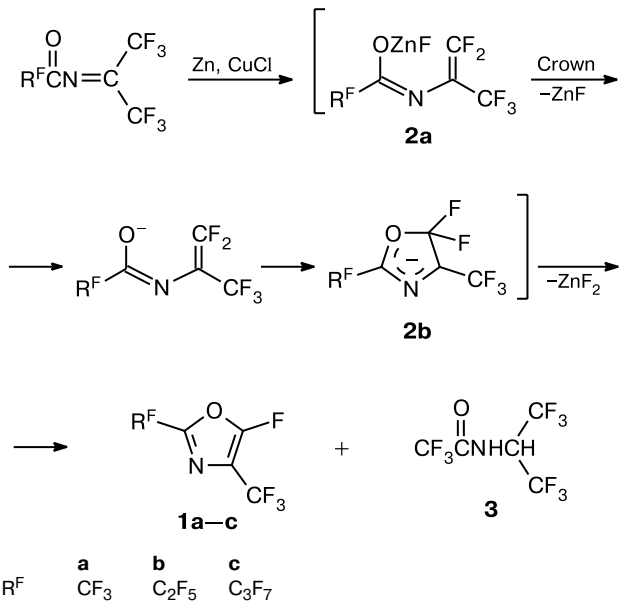
Key words: oxazole, acylimine, nucleophilic substitution

Fluorinated oxazoles are widely studied as sources of biologically active fluorinated amino acids and their derivatives.[1—3] The synthesis of fluorinated oxazoles from fluorinated acetyldiazoacetic esters and nitriles was first reported[4] in 1961. Fluorinated oxazoles have been prepared from oxazol-5-ones and by acylation of hexafluorovaline.[5] A number of methods for the preparation of 2-aryl- and 2-heteroaryl-substituted fluorinated oxazoles are based on transformations of acylimines of hexafluoroacetone.[6—8]

Fully fluorinated oxazoles have never been prepared by these methods; only *N*-methyl-*N*-perfluoroacyl-2-aminoperfluoropropenes are formed from perfluoroacylimines of hexafluoroacetone.[9] The present work continues the study of the routes to polyfluorinated oxazoles and gives an account of their properties.

A study of cyclodefluorination of perfluoroacylimines of hexafluoroacetone with metals (Sn, Mg, Al) and with a mild reducing agent, $SnCl_2$, has shown that on heating to 50—150 °C in ether or dioxane, perfluorooxazoles are formed in low yields (10%) if at all. The reaction of perfluoroacylimines with zinc is more successful when carried out in dioxane starting from 80 °C. The reactions are promoted by catalytic amounts of Cu^I salts and crown ethers. The yields of oxazoles **1a,b,c** reach 62, 51, and 30%, respectively. The key process is the reduction, which starts with a single-electron transfer. The creation of a zinc—copper pair and activation of the zinc surface promotes the formation of imidate salt **2a** in this step. A similar mechanism of the single-electron transfer is described below in relation to the reaction of other hexafluoroacetone imines with metals.[10] The role of crown ether is apparently reduced to the assistance to the dissociation of salt **2a**, which results in the intramolecular cyclization to oxazoles **1a—c** (Scheme 1).

Scheme 1



It is noteworthy that the syntheses of oxazoles **1a—c** in dioxane are complicated by side processes, one of these being the reduction of acylimines. Under drastic conditions, the reaction of trifluoroacetylimine of hexafluoroacetone with zinc gave trifluoroacetic acid *N*-α-hydrohexafluoroisopropylamide (**3**) apart from oxazole **1a**. Amide **3** was also obtained by an alternative route including acylation of hexafluoroisopropylamine with trifluoroacetic anhydride.

Cyclodehalogenation of the trifluoroacetylimine of chloropentafluoroacetone proceeds under similar conditions giving rise to oxazole **1a** in 56% yield.

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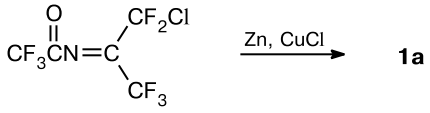
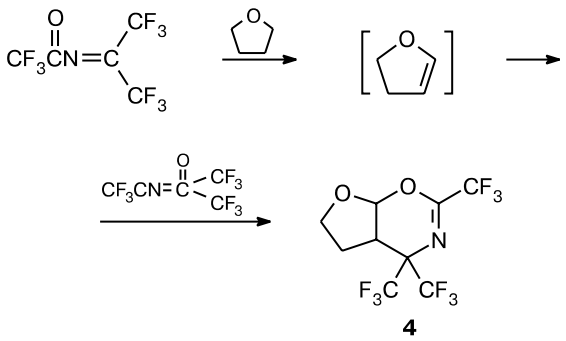


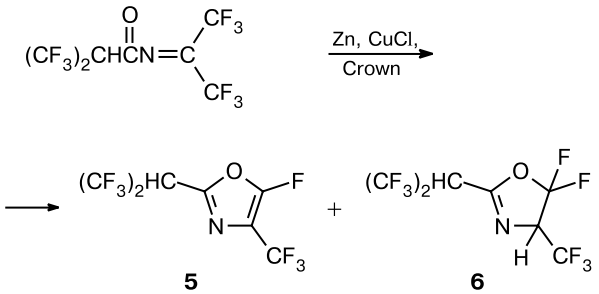
A change of the solvent does not increase the yield of oxazoles **1a—c**; the replacement of dioxane by diglyme substantially decreases the yield of oxazole **1a**, whereas tetrahydrofuran is dehydrogenated under the reaction conditions to give dihydrofuran, which undergoes *in situ* [2+4]-cycloaddition with acetylimine of hexafluoroacetone to afford bicyclodioxaazanonene **4** (Scheme 2).

Scheme 2



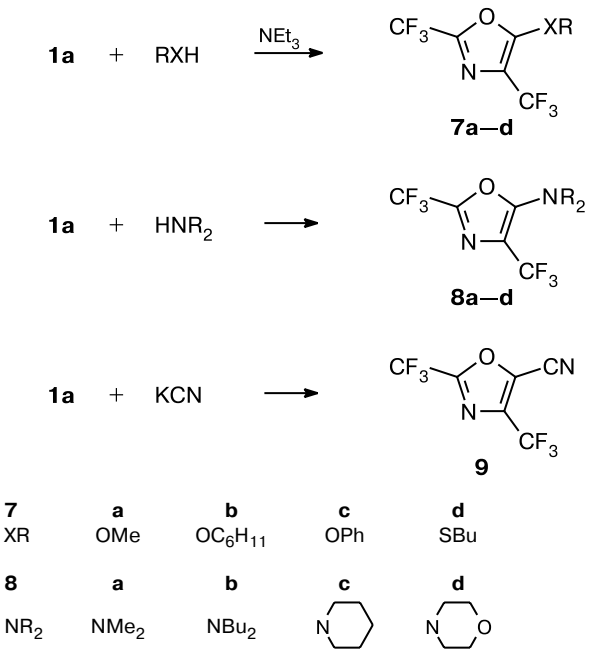
The reactions of partially fluorinated acylimines of hexafluoroacetone with Zn follow a more complicated pattern; we did not succeed in preparing oxazole from difluoroacetylimine of hexafluoroacetone. Hexafluoroisobutyroylimine of hexafluoroacetone reacts with Zn ambiguously giving a mixture of oxazole **5** and oxazoline **6** in 3 : 2 ratio in a moderate yield. Oxazoline **6** is probably formed upon protonation of intermediate **2b** at high temperatures (Scheme 3).

Scheme 3



Polyfluorine-containing oxazoles **1a—c** and **5** are thermally stable volatile liquids; they do not react with water, alcohols, or thiols for a long period of time at room temperature. Nucleophilic reactions have been studied in more detail in relation to oxazole **1a**. It was found that alcohols, phenol, and mercaptans react with oxazole **1a** only in the presence of tertiary amines to give oxazoles **7a—d** (Scheme 4). Secondary amines react with **1a** even in the cold yielding amine-substituted oxazoles **8a—d**, while KCN reacts only on heating in the presence of crown ethers as catalysts.

Scheme 4



The polyfluorinated oxazoles synthesized underlay the synthesis of other fluorinated heterocyclic compounds.[11]

Experimental

^{1}H NMR spectra were recorded on a Bruker AC-300 spectrometer operating at 300 MHz; ^{19}F NMR spectra were measured on a Bruker WP-200 SY spectrometer operating at 188.31 MHz. The chemical shifts (δ) are referred to external $SiMe_4$ (^{1}H) or CF_3COOH (^{19}F). The IR spectra were recorded on a UR-20 spectrometer for thin films. The data of the ^{1}H NMR, ^{19}F NMR, and IR spectra, the physicochemical characteristics, the elemental analysis data, and the yields of substances are summarized in Table 1. Commercial chemicals and solvents were treated prior to use according to known recommendations.[12] Hexafluoroacetone perfluoroacylimines were synthesized by a known procedure;[13] oxazoles **1a,b** were synthesized by a procedure we described previously.[14]

The reaction of polyfluoro-containing acylimines with zinc. Oxazoles (1a—c, 5), oxazoline (6) (general procedure). A mixture of acylimine (38 mmol), Zn (61 mmol, 4.0 g), CuCl (1 mmol, 0.1 g), and dicyclohexyl-18-crown-6 (0.2 mmol, 0.07 g) or 18-crown-6 (0.3 mmol, 0.08 g) in anhydrous dioxane (10 mL) was heated in a glass tube for 4 h at 90 °C with occasional stirring, then the temperature was raised to 110—130 °C and the mixture was heated for an additional 30 h. The volatile compo-

Table 1. Data of the IR, ^{1}H and ^{19}F NMR ($CDCl_3$), elemental analysis, physicochemical characteristics and yields of the synthesized compounds

Compound	B.p. (*p*/Torr)	M.p. /°C	n_D^{20}	Yield (%)	Found / Calculated (%) C	H	N	Molecular formula	^{1}H and ^{19}F NMR δ (*J*/Hz)	IR, ν/cm^{-1}
1a	61—62	—	1.2985	62	26.95 26.91	—	6.56 6.28	C_5F_7NO	^{19}F: −10.8 (s, 3 F, CF_3); −14.1 (d, 3 F, CF_3, *J* = 10.0); 36.9 (br.q, 1 F, CF)	1770 (C=N); 1740 (C=C)
1b	72—74	—	1.3125	51	26.86 26.37	—	5.42 5.13	C_6F_9NO	^{19}F: −12.3 (d, 3 F, CF_3, *J* = 10.5); 7.4 (br.s, 3 F, CF_3); 38.6 (br.q, 1 F, CF); 39.7 (br.s, 2 F, CF_2)	1760 (C=N); 1730 (C=C)
1c	87	—	1.3100	30	25.65 25.74	—	3.90 3.75	$C_7F_{11}NO$	^{19}F: −13.1 (d, 3 F, CF_3, *J* = 11.0); 4.8 (t, 3 F, CF_3, *J* = 6.0); 10.0 (q, 2 F, CF_2); 37.0 (br.q, 1 F, CF); 47.0 (s, 2 F, CF_2)	1770 (C=N); 1720 (C=C)
3	93 (15)	65	—	36	22.95 22.81	0.81 0.76	5.46 5.32	$C_5H_2F_9NO$	^{1}H: 5.2 (sept, H, $CH(CF_3)_2$, *J* = 7.5); 9.4 (br.s, H, HN); ^{19}F: −6.8 (d, 6 F, $(CF_3)_2CH$); −2.8 (s, 3 F, CF_3)	1650 (C=O); 3150—3500 (N—H)
4	90 (45)	—	1.3690	31	32.48 32.62	2.01 1.80	4.24 4.22	$C_9H_6F_9NO_2$	^{1}H: 2.0, 2.25 (both m, 1 H each, CH_2); 2.9 (m, 1 H, CH); 4.1, 4.3 (both m, 1 H each, CH_2O); 5.9 (s, 1 H, CHO); ^{19}F: −3.9 (q, 3 F, CF_3); −2.9 (q, 3 F, CF_3, *J* = 12.0); −1.6 (s, 3 F, CF_3);	1700 (C=N); 2950—3000 (C—H)
5*	103—106	—	1.3152	56	—	—	—	—	^{1}H: 4.3 (sept, 1 H, $CH(CF_3)_2$, *J* = 6.5); ^{19}F: −11.6 (d, 6 F, $(CF_3)_2CH$); −13.0 (d, 3 F, CF_3, *J* = 9.5); 39.0 (q, F, CF)	1770 (C=N); 1710 (C=C)
6*					—	—	—	—	^{1}H: 4.6 (sept, 1 H, $CH(CF_3)_2$, *J* = 7.0); 4.8 (m, 1 H, CH); ^{19}F: −12.1 (d, 6 F, $(CF_3)_2CH$); −11.0 (ddq, 1 F, CF, *J* = 3.2, 149.1, 13.0); −4.8 (ddd, 3 F, CF_3, *J* = 9.0, 11.8, 3.2); 7.0 (ddq, 1 F, CF, *J* = 11.8, 149.1, 12.0)	1770 (C=N)
7a	125	—	1.3469	60.1	30.65 30.63	1.07 1.28	5.80 5.95	$C_6H_3F_6NO_2$	^{1}H: 3.5 (s, 3 H, Me); ^{19}F: −16.4, −11.8 (both s, 3 F each, CF_3)	1760 (C=N); 1730 (C=C); 2950 (C—H)
7b	90 (13)	—	1.4285	40.5	43.16 43.54	3.30 3.63	5.21 4.62	$C_{11}H_{11}F_6NO_2$	^{1}H: 1.3 (m, 6 H, CH_2); 1.7 (m, 4 H, CH_2); 3.6 (m, 1 H, CH); ^{19}F: −15.1, −12.1 (both s, 3 F each, CF_3)	1770 (C=N); 1710 (C=C); 2980 (C—H)
7c	105 (35)	—	1.4250	46.2	44.28 44.41	1.67 1.68	4.53 4.71	$C_{11}H_5F_6NO_2$	^{1}H: 7.1 (m, 2 H, CH); 7.3 (m, 1 H, CH); 7.45 (m, 2 H, CH); ^{19}F: −14.5, −10.5 (both s, 3 F each, CF_3)	1760 (C=N); 1730 (C=C)

(*to be continued*)

Table 1 (*continued*)

Compound	B.p. (*p*/Torr)	M.p. /°C	n_D^{20}	Yield (%)	Found / Calculated (%) C	H	N	Molecular formula	^{1}H and ^{19}F NMR δ (*J*/Hz)	IR, ν/cm^{-1}
7d	85 (18)	—	1.4021	53.5	36.49 36.83	2.65 3.07	4.51 4.77	$C_9H_9F_6NOS$	^{1}H: 1.0 (br.t, 3 H, Me, *J* = 7.0); 1.8 (m, 4 H, CH_2); 2.7 (br.t, 2 H, CH_2, *J* = 6.5); ^{19}F: −15.8, −11.8 (both s, 3 F each, CF_3)	1700 (C=N); 1680 (C=C); 2950 (C—H)
8a	50 (6)	—	1.3911	66.1	33.95 33.86	2.81 2.42	11.46 11.29	$C_7H_6F_6N_2O$	^{1}H: 3.1 (m, 6 H, Me); ^{19}F: −22.6, −10.6 (both s, 3 F each, CF_3)	1680 (C=N); 1640 (C=C); 2975 (C—H)
8b	110 (10)	—	1.4130	47.5	46.86 46.95	5.18 5.42	9.92 8.43	$C_{13}H_{18}F_6N_2O$	^{1}H: 0.95 (t, 6 H, Me, *J* = 7.0); 1.35, 1.60 (both m, 4 H each, CH_2); 3.03 (t, 4 H, CH_2, *J* = 7.0) ^{19}F: −19.1, −11.0 (both s, 3 F each, CF_3)	1690 (C=N); 1650 (C=C)
8c	87 (10)	—	1.4255	73	41.75 41.64	3.07 3.47	9.80 9.72	$C_{10}H_{10}F_6N_2O$	^{1}H: 1.3 (m, 6 H, CH_2); 3.4 (m, 4 H, CH_2N); ^{19}F: −20.5, −10.5 (both s, 3 F each, CF_3)	1700 (C=N); 1660 (C=C)
8d	69 (13)	40	—	64	37.10 37.22	2.30 2.76	9.24 9.65	$C_9H_8F_6N_2O_2$	^{1}H: 3.5, 3.9 (both m, 4 H each, CH_2); ^{19}F: −14.8, −10.1 (both s, 3 F each, CF_3)	1700 (C=N); 1660 (C=C)
9	107—108	—	1.3570	42.7	31.65 31.30	—	12.43 12.17	$C_6F_6N_2O$	^{19}F: −10.1, −11.7 (both s, 3 F each, CF_3)	2250 (C≡N); 1720 (C=N); 1620 (C=C)

* A mixture of compounds **5** and **6** is formed.

nents were evaporated *in vacuo*, and the mixture was washed with H_2O (3×10 mL), dried with $MgSO_4$, and fractionated.

N*-α-Hydrohexafluoroisopropylamide of trifluoroacetic acid (3).** ***A. Amide **3** can be isolated upon the synthesis of oxazole **1a** by four successive fractionations of the high-boiling fraction, yield 8%.

B. Trifluoroacetic anhydride (30 mmol, 6.3 g) was slowly added at 0 °C to hexafluoroisopropylamine (30 mmol, 5.0 g). The reaction mixture was heated to boiling, kept at reflux for 30 min, and distilled.

2,4,4-Tris(trifluoromethyl)-4a,5,6,7a-tetrahydro-4*H*-furo[3,2-*e*]-[1,3]oxazine (4). A mixture of trifluoroacetylimine of hexafluoroacetone (9.3 g, 38 mmol), anhydrous tetrahydrofuran (15 mL), and Zn (4.0 g, 61 mmol) was heated at 90 °C for 4 h and then at 120 °C for 10 h. The volatile components were evaporated *in vacuo* (1 Torr), washed with H_2O (3×10 mL), dried with $MgSO_4$, and fractionated *in vacuo*.

Reaction of oxazole 1a with alcohols, phenol, and thiols. Preparation of oxazoles (7a—d) (general procedure). Triethylamine NEt_3 (13 mmol, 1.3 g) was added with stirring and cooling (~10 °C) to a mixture of oxazole **1a** (13.5 mmol, 3.0 g) and alcohol, phenol, or thiol (13.5 mmol) in anhydrous ether (10 mL). The mixture was kept for 4 h at room temperature, CH_2Cl_2 (4 mL) was added, the mixture was washed with H_2O (3×10 mL), and the organic layer was fractionated *in vacuo*.

The reaction of oxazole 1a with secondary amines and ammonia. Preparation of oxazoles (8a—d) (general procedure). Amine (27.3 mmol) was added with stirring and cooling (−20 °C) to a solution of oxazole **1a** (13.5 mmol, 3.0 g) in anhydrous ether (7 mL). The mixture was warmed-up to room temperature, kept for 4 h, filtered, and fractionated *in vacuo*.

2,4-Bis(trifluoromethyl)-5-cyanooxazole (9). A mixture of oxazole **1a** (22.4 mmol, 5.0 g), KCN (30.8 mmol, 2.0 g), and dicyclohexyl-18-crown-6 (0.5 mmol, 0.17 g) in anhydrous dioxane (10 mL) was heated with stirring for 30 h at 50—60 °C. The volatile components were evaporated *in vacuo*, washed with H_2O (3×10 mL), dried with $MgSO_4$, and fractionated.

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