Reactions of fluoroalkyl-containing bis-β-diketones with hydrazine and hydroxylamine

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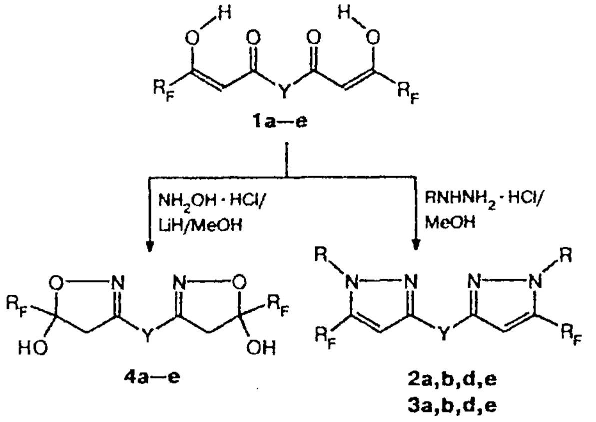
Polyfluoroalkyl-containing bispyrazoles, bis(5-hydroxy-Δ^2-isoxazolines), and bisisoxazoles were synthesized for the first time by reactions of polyfluoroalkyl-containing bis-β-diketones with hydrazine, phenylhydrazine, and hydroxylamine, respectively.

Key words: bis-β-diketones, bispyrazoles, bis(5-hydroxy-Δ^2-isoxazolines), bisisoxazoles.

1,3-Dicarbonyl compounds find wide application in the synthesis of various heterocyclic compounds. One approach which is most widely used for the synthesis of pyrazoles and isoxazoles involves the reactions of β-diketones with the corresponding hydrazines and hydroxylamines.[1,2] In this case, fluorine-containing β-diketones give pyrazoles, hydroxy-Δ^2-pyrazolines, and hydroxy-Δ^2-isoxazolines, respectively.[3,4] Bisheterocyclic compounds can be obtained by analogous reactions from bis-β-diketones.[5—8]

In this work, we investigated the reactions of fluoroalkyl-containing bis-β-diketones (**1a—e**)[9] with hydrazine, phenylhydrazine, and hydroxylamine (Scheme 1).

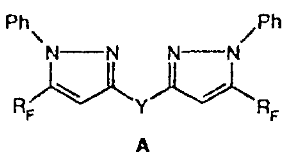
Scheme 1



Y = p-C_6H_4 (**a**), CH_2CH_2 (**b—e**)
R_F = CF_3 (**a,b**), C_3F_7 (**c**), C_4F_9 (**d**), C_6F_{13} (**e**)
R = H (**2**), Ph (**3**)

The heterocyclization products, *viz.*, bispyrazoles (**2** and **3**) and bis(5-hydroxy-Δ^2-isoxazolines) (**4**), were characterized by IR and ^{1}H NMR spectroscopy (Tables 1 and 2).

According to the published data,[3,4] the sp^3-hybridized N atom in nonsubstituted polyfluoroalkyl-containing bispyrazoles **2** is bound to the C atom at the polyfluoroalkyl substituent. However, three regioisomers, **A**, **B**, and **C**, can be formed in the case of *N,N'*-diphenyl-substituted bispyrazoles **3**.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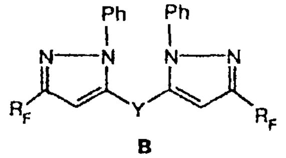
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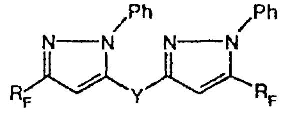
C

The ^{1}H NMR spectra of compounds **3** have one singlet signal for the protons of the methine group and a singlet signal for the protons of the Y group (see Table 1), which indicates that the bispyrazoles obtained are symmetrical compounds. A comparison of the chemical shifts of the methine protons in compounds **2** and **3** suggested that regioisomer **A** was formed. This conclusion was indirectly confirmed by comparing the yields. Thus the yield of products **3d,e** sharply decreases (compared to the yield of compound **3b**) as the length of the polyfluoroalkyl substituent increases, while the decrease in the yield is less significant when the Y group is replaced by a bulkier group (**3a**).

The ^{1}H NMR spectral data (see Table 2) (the presence of an AB system for the CH_2 group of the heterocycle and a singlet signal for the protons of the Y group, which indicate that the chiral C(5) center is located closer to the methylene group of the heterocycle than to

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Table 1. Physicochemical parameters and spectral data for bispyrazoles **2** and **3**

Compound	R_F	Y	R	M.p./°C	Yield (%)	IR, ν/cm^{-1}	^{1}H NMR, δ
2a	CF_3	*p*-C_6H_4	H	290—291	88	3155 (NH); 1580 (C=N)	7.84 (s, 4 H, C_6H_4); 7.01 (s, 2 H, 2 =CH)
2b	CF_3	CH_2CH_2	H	220—221	87	3150 (NH); 1575 (C=N)	6.39 (s, 2 H, 2 =CH); 3.08 (s, 4 H, C_2H_4)
2d	C_4F_9	CH_2CH_2	H	228—229	79	3140 (NH); 1580 (C=N)	6.31 (s, 2 H, 2 =CH); 3.04 (s, 4 H, C_2H_4)
2e	C_6F_{13}	CH_2CH_2	H	187—188	90	3150 (NH); 1560 (C=N)	6.29 (s, 2 H, 2 =CH); 3.04 (s, 4 H, C_2H_4)
3a	CF_3	*p*-C_6H_4	Ph	215—216 (CCl_4)	62	1590 (C=N)	7.36—7.24 (m, 10 H, 2 Ph); 7.84 (s, 4 H, C_6H_4); 7.01 (s, 2 H, 2 =CH)
3b	CF_3	CH_2CH_2	Ph	207—208 (CCl_4)	86	1585 (C=N)	7.51—7.15 (m, 10 H, 2 Ph); 6.34 (s, 2 H, 2 =CH); 2.92 (s, 4 H, C_2H_4)
3d	C_4F_9	CH_2CH_2	Ph	125—126 (pentane)	36	1580 (C=N)	7.49—7.11 (m, 10 H, 2 Ph); 6.32 (s, 2 H, 2 =CH); 2.92 (s, 4 H, C_2H_4)
3e	C_6F_{13}	CH_2CH_2	Ph	133—134 (pentane)	34	1580 (C=N)	7.50—7.11 (m, 10 H, 2 Ph); 6.32 (s, 2 H, 2 =CH); 2.93 (s, 4 H, C_2H_4)

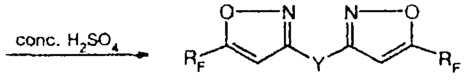
Table 2. Physicochemical parameters and spectral data for bis(5-hydroxy-Δ^2-isoxazolines) **4** and bisisoxazoles **5**

Compound	R_F	Y	M.p./°C	Yield (%)	IR, ν/cm^{-1}	^{1}H NMR, δ (*J*/Hz)
4a	CF_3	*p*-C_6H_4	>250	77	3200 (OH); 1590 (C=N)	7.78 (s, 4 H, C_6H_4); 6.03 (br.s, 2 H, 2 OH); 3.38 and 4.03 (2 H_AH_B, J_{AB} = 18.51)
4b	CF_3	CH_2CH_2	203—204	89	3220 (OH); 1620 (C=N)	5.68 (br.s, 2 H, 2 OH); 3.07 and 3.41 (2 H_AH_B, J_{AB} = 18.7); 2.68 (s, 4 H, C_2H_4)
4c	C_3F_7	CH_2CH_2	221—222	80	3210 (OH); 1620 (C=N)	5.78 (br.s, 2 H, 2 OH); 3.09 and 3.49 (2 H_AH_B, J_{AB} = 18.9); 2.69 (s, 4 H, C_2H_4)
4d	C_4F_9	CH_2CH_2	222—223	71	3180 (OH); 1615 (C=N)	5.82 (br.s, 2 H, 2 OH); 3.13 and 3.51 (2 H_AH_B, J_{AB} = 19.0); 2.72 (s, 4 H, C_2H_4)
4e	C_6F_{13}	CH_2CH_2	231—232	67	3150 (OH); 1610 (C=N)	5.66 (br.s, 2 H, 2 OH); 3.15 and 3.52 (2 H_AH_B, J_{AB} = 18.1); 2.71 (s, 4 H, C_2H_4)
5a	CF_3	*p*-C_6H_4	218—219	78	3110 (=CH); 1590 (C=N)	7.84 (s, 4 H, C_6H_4); 6.23 (s, 2 H, 2 =CH)
5b	CF_3	CH_2CH_2	72—73	80	3125 (=CH); 1610 (C=N)	6.23 (s, 2 H, 2 =CH); 3.22 (s, 4 H, C_2H_4)
5c	C_3F_7	CH_2CH_2	96—97	83	3145 (=CH); 1600 (C=N)	6.63 (s, 2 H, 2 =CH); 3.24 (s, 4 H, C_2H_4)
5d	C_4F_9	CH_2CH_2	108—109	83	3140 (=CH); 1600 (C=N)	6.61 (s, 2 H, 2 =CH); 3.23 (s, 4 H, C_2H_4)
5e	C_6F_{13}	CH_2CH_2	134—135	70	3140 (=CH); 1600 (C=N)	6.61 (s, 2 H, 2 =CH); 3.24 (s, 4 H, C_2H_4)

Y) confirm the structures of the bis(5-hydroxy-Δ^2-pyrazolines) obtained, which agree with the published data.[4] Dehydration to the corresponding bisisoxazoles was not observed either in the course of the reaction or in their isolation. The corresponding bisisoxazoles **5a—e** were prepared by dehydration of bis(5-hydroxy-Δ^2-pyrazolines) under the action of concentrated H_2SO_4 (Scheme 2).

Scheme 2

4a—e



5a—e

Table 3. Data of elemental analysis of the synthesized compounds

Compound	Found/Calculated (%)				Molecular formula
	C	H	F	N	
2a	48.85	2.41	33.08	16.47	$C_{14}H_8F_6N_4$
	48.57	2.33	32.92	16.18	
2b	40.42	2.91	38.08	18.65	$C_{10}H_8F_6N_4$
	40.28	2.70	38.23	18.79	
2d	32.01	1.27	57.69	9.12	$C_{16}H_8F_{18}N_4$
	31.81	1.33	57.59	9.27	
2e	30.25	1.02	62.04	6.99	$C_{20}H_8F_{26}N_4$
	30.09	1.01	61.88	7.02	
3a	62.56	3.00	23.13	11.12	$C_{26}H_{16}F_6N_4$
	62.78	3.04	22.92	11.26	
3b	58.84	3.38	25.12	12.30	$C_{22}H_{16}F_6N_4$
	58.80	3.36	25.37	12.47	
3d	42.86	2.12	47.31	7.52	$C_{26}H_{16}F_{18}N_4$
	42.99	2.22	47.08	7.71	
3e	38.61	1.54	53.55	6.15	$C_{30}H_{16}F_{26}N_4$
	38.89	1.74	53.32	6.05	
4a	43.97	2.72	29.81	7.26	$C_{14}H_{10}F_6N_2O_4$
	43.76	2.62	29.67	7.29	
4b	35.93	3.02	33.98	8.33	$C_{10}H_{10}F_6N_2O_4$
	35.73	3.00	33.90	8.33	
4c	31.17	1.87	49.86	5.15	$C_{14}H_{10}F_{14}N_2O_4$
	31.36	1.88	49.60	5.22	
4d	30.32	1.64	54.01	4.43	$C_{16}H_{10}F_{18}N_2O_4$
	30.21	1.58	53.75	4.40	
4e	28.63	1.34	58.98	3.37	$C_{20}H_{10}F_{26}N_2O_4$
	28.73	1.21	59.06	3.35	
5a	48.48	1.85	32.51	8.27	$C_{14}H_6F_6N_2O_2$
	48.29	1.74	32.74	8.04	
5b	40.28	1.92	37.76	9.33	$C_{10}H_6F_6N_2O_2$
	40.02	2.01	37.98	9.33	
5c	33.71	1.06	53.30	5.53	$C_{14}H_6F_{14}N_2O_2$
	33.62	1.21	53.17	6.40	
5d	32.02	1.12	56.73	4.70	$C_{16}H_6F_{18}N_2O_2$
	32.02	1.00	56.98	4.67	
5e	30.32	0.79	62.01	3.49	$C_{20}H_6F_{26}N_2O_2$
	30.02	0.75	61.73	3.50	

Experimental

The ^1H NMR spectra were recorded on a Tesla BS-587A spectrometer (Me_4Si as the internal standard). The IR spectra were obtained on a Specord IR-75 instrument as Nujol mulls.

Bis-β-diketones were synthesized according to a known procedure.[9]

The data of elemental analysis of the compounds synthesized are given in Table 3.

Synthesis of bispyrazoles 2 and 3. A mixture of bis-β-diketone (1 mmol) and $NH_2NH_2 \cdot 2HCl$ or $PhNHNH_2 \cdot HCl$ (3 mmol) in MeOH (50 mL) was boiled for 2 h, poured into cold water (200 mL), and neutralized with a saturated $NaHCO_3$ solution. The precipitate that formed was filtered off, washed with water (100 mL), dried, and reprecipitated from MeOH with CCl_4 or recrystallized (see Table 1).

Synthesis of bis(5-hydroxy-Δ²-isoxazolines) 4. A mixture of bis-β-diketone (1 mmol), LiH (3 mmol), and $NH_2OH \cdot HCl$ (3 mmol) in MeOH (50 mL) was boiled for 2 h and poured into cold water (200 mL). The precipitate that formed was filtered off, washed with water (100 mL), dried, and recrystallized from xylene (see Table 2).

Dehydration of bis(5-hydroxy-Δ²-isoxazolines) 4. Bis(5-hydroxy-Δ²-isoxazoline) 4 (1.5 mmol) was dissolved in concentrated H_2SO_4 (5 mL) on heating (80—90 °C). Then the reaction mixture was slowly cooled to 20 °C, poured into cold water (100 mL), and neutralized with a 20% Na_2CO_3 solution. The precipitate that formed was filtered off, dried *in vacuo*, and recrystallized from pentane.

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