

Perfluoro-1,3,4-oxadiazoles

N.V. Vasiliev*, Yu. E. Lyashenko**, A.E. Patalakha and G.A. Sokolski

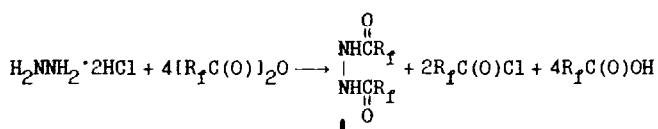
A.N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 117813 Moscow (Russian Federation)

Abstract

Some new polyfluorinated 1,3,4-oxadiazoles have been obtained via a two-step method. The cycloadditions of the 1,3,4-oxadiazoles have been studied and an analysis of the energies of the frontier orbitals calculated by the MNDO method indicates a LUMO-dependent pathway for cycloaddition.

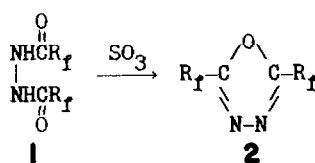
Introduction

The first polyfluorinated 3,4-oxadiazoles were obtained 30 years ago, but the chemical properties of these symmetrical endodienes have not been studied to any great extent. The synthesis of the polyfluorinated 1,3,4-oxadiazoles is based on the dehydration of 1,2-bis(polyfluoroacyl)hydrazines with phosphorus pentoxide [1, 2]. Knunyants and co-workers have used phosphorus oxychloride [3] and trifluoroacetic anhydride to prepare the bis-1,2,4-oxadiazoles [4]. Recently, a two-step method for the synthesis of 1,3,4-oxadiazoles was described [5] in which hydrazine dihydrochloride was converted to 1,2-bis(polyfluoroacyl)hydrazines, when treated with a large excess of the polyfluorocarbon acid anhydride.



Compound	1a	1b	1c	1d	1e
R _f	CF ₃	CHF ₂	C ₂ F ₅	C ₃ F ₇	CHF ₂ CF ₂

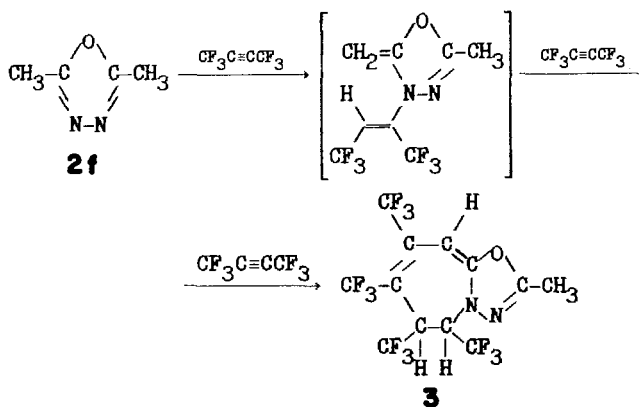
In a second step, the 1,2-bis(polyfluoroacyl)hydrazines were treated with oleum (60%) with heating.



Compound	2a	2b	2c	2d	2e
R _f	CF ₃	CHF ₂	C ₂ F ₅	C ₃ F ₇	CHF ₂ CF ₂

The dehydrating effect of highly concentrated oleum has also been used previously for obtaining perfluorinated 1,3,5-oxadiazines [6], perfluoroacylimines [6, 7] and hexafluoroacetone azine [8].

It is known that the donor 1,3,4-oxadiazoles do not undergo cycloaddition [9–11]. In particular, 2,5-dimethyl-1,3,4-oxadiazole (**2f**) does not form (4+2)-cycloaddition products with acceptor dienophiles, and its interaction with perfluoro-but-2-yne results in the formation of adduct **3** [12].

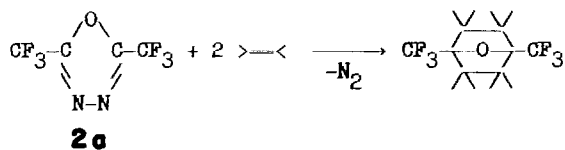


Recently, the cycloaddition reactions of 1,3,4-oxadiazole (**2a**), a representative of the polyfluorinated oxadiazoles, have been reported [13–17]. It turns out

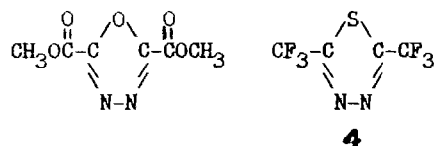
*To whom all correspondence should be addressed.

**Institute of Physiological Active Substances, Russian Academy of Sciences, Chernogolovka, Russian Federation.

that this compound undergoes interaction with aliphatic, cyclic and functional alkenes via a two-step mechanism to form derivatives of 1,4-bis(trifluoromethyl)-7-oxabicyclo[2.2.1]heptanes.



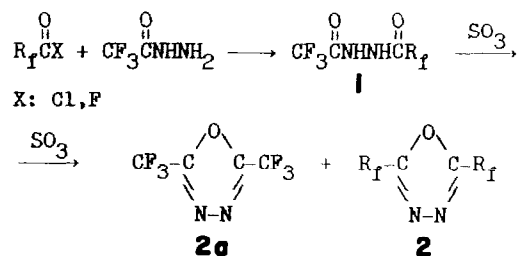
Such reactions have also been carried out with 2,5-bis(methoxycarbonyl)-1,3,4-oxadiazole [16] and 2,5-bis(trifluoromethyl)-1,3,4-thiadiazole (4) [15, 16].



Conversions of this type open up extensive possibilities for the synthesis of various heterocyclic compounds and could stimulate further studies of the behaviour of polyfluorinated 1,3,4-oxadiazoles and polyfluorinated azoles in cycloaddition reactions.

Results and discussion

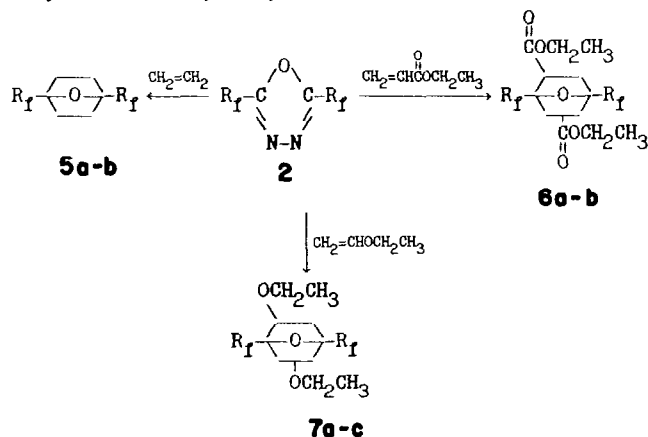
Synthesis of the polyfluorinated 1,3,4-oxadiazoles was carried out using a previously described method [5]. All the bis(polyfluoroacyl)hydrazines **1a-e** and **1f** ($R_f = (\text{CF}_3)_2\text{CH}$) may be readily obtained in quite high yield, and, as a rule, compounds **1a-f** do not need further purification after removal of volatile components. Dehydration of 1,2-bis(polyfluoroacyl)hydrazines gives oxadiazoles **2a-e** and **2g** ($R_f = (\text{CF}_3)_2\text{CH}$). This method is especially useful for obtaining the perfluorinated oxadiazoles **2a**, **2c** and **2d**. It should be noted that unsymmetrical 1,3,4-oxadiazoles cannot be prepared via this method, since the unsymmetrical polyfluoroacylhydrazines **1g,h** mainly form a mixture of symmetrical oxadiazoles **2h-j** and **2a** when treated with oleum.



Compound	1g	1h	2h	2j
R_f	C_4F_9	$t\text{-C}_4\text{F}_9$	C_4F_9	$t\text{-C}_4\text{F}_9$

In continuing investigations of the properties of oxadiazole **2a** [17], the cycloaddition reactions of the

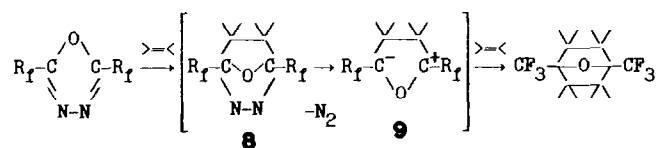
polyfluorinated oxadiazoles **2b-d** with ethylene, ethyl acrylate and ethyl vinyl ether have been studied.



Compound	5a	5b	6a	6b	7a	7b	7c
R_f	C_2F_5	C_3F_7	CF_2H	C_2F_5	CF_2H	C_2F_5	C_3F_7

In a similar manner to oxadiazole **2a**, oxadiazoles **2b-d** only react under drastic conditions ($> 150^\circ\text{C}$) with loss of nitrogen and the formation of the 1,7-bis(polyfluoroalkyl)-7-oxabicyclo[2.2.1]heptanes (Table 1). In these reactions, a considerable excess of ethylene was necessary to achieve high conversion of the oxadiazoles. With ethyl vinyl ether and ethyl acrylate, the oxadiazole/dienophile ratio was 1:2.2. Oxabicycloheptanes **6** and **7** are formed as a mixture of two isomers.

The reactions of the oxadiazoles **2b-d**, like those of oxadiazole **2a**, should be considered as a two-step process including (2+4)-cycloaddition as the first step. The intermediate oxadiazabicycloheptanes **8** were not noted in any case. This fact is consistent with the thermal instability of the 1,3,4-oxadiazolines, which are inclined to eliminate nitrogen and form carbonyl ylides even under mild conditions [18]. It is probable that the oxadiazabicycloheptanes **8** undergo a similar elimination of nitrogen, and hence formation of the intermediate carbonyl ylides **9** cannot be ruled out. Thus, the second step may be regarded as a (2+3)-cycloaddition of carbonyl ylides.



Even under drastic conditions, oxadiazoles **2b-d** (like oxadiazole **2a**) do not react with acceptor dienophiles, viz. maleic anhydride, esters of maleic and fumaric acids, as well as polyfluoroalkenes. Interaction of oxadiazoles with acetylenes (acetylene, the ester of acetylenedicarboxylic acid) were also not noted although the authors [16] managed to react oxadiazole **2a** with dialkylamino-substituted acetylene.

TABLE 1. Yields of the corresponding 7-oxabicycloheptanes in the reaction of oxadiazoles with dienophiles

Oxadiazole	Reaction with ethylene			Reaction with ethyl acrylate			Reaction with ethyl vinyl ether		
	Yield (%)	Temp. (°C)	Time (h)	Yield (%)	Temp. (°C)	Time (h)	Yield (%)	Temp. (°C)	Time (h)
CF ₃ (C ₂ N ₂ O)CF ₃ ^a	79	220	20	60	170	10	84	160	10
CHF ₂ (C ₂ N ₂ O)CHF ₂	—	—	—	65	180	3	25	175	5
C ₂ F ₅ (C ₂ N ₂ O)C ₂ F ₅	78	210	68	11	180	6	12	175	4
C ₃ F ₇ (C ₂ N ₂ O)C ₃ F ₇	56	200	60	—	—	—	33	160	6

^aSee ref. 7.

TABLE 2. Frontier orbital energies and ionization potentials

No.	Compound	HOMO (eV)	LUMO (eV)	ΔE (eV)	Ionization potential (eV)
2f	CH ₃ (C ₂ N ₂ O)CH ₃	-10.46	0.02	10.48	10.32
2b	CHF ₂ (C ₂ N ₂ O)CHF ₂	-11.86	-1.21	10.65	11.74
2a	CF ₃ (C ₂ N ₂ O)CF ₃	-12.58	-1.89	10.69	12.08
2e	HCF ₂ CF ₂ (C ₂ N ₂ O)CF ₂ CF ₂ H	-12.36	-1.73	10.63	11.84
2c	C ₂ F ₅ (C ₂ N ₂ O)C ₂ F ₅	-12.66	-2.05	10.61	12.06
4	CF ₃ (C ₂ N ₂ S)CF ₃	-12.48	-2.59	9.88	11.60
10	CF ₃ (C ₃ H ₃ N ₃)CF ₃	-11.76	-1.27	10.48	10.88

The experimental data obtained suggest that the cycloaddition of polyfluorooxadiazoles is a LUMO-dependent process. Quantum-chemical calculations of oxadiazoles **2a–c**, **2e,f**, 2,5-bis(trifluoromethyl)-1,3,4-thiadiazole (**4**) and 4-methyl-3,5-bis(trifluoromethyl)-1,2,4-triazole (**10**) (Fig. 1 and Table 2) yield low energies for the LUMO and HOMO, confirming the conclusion regarding the cycloaddition pathway.

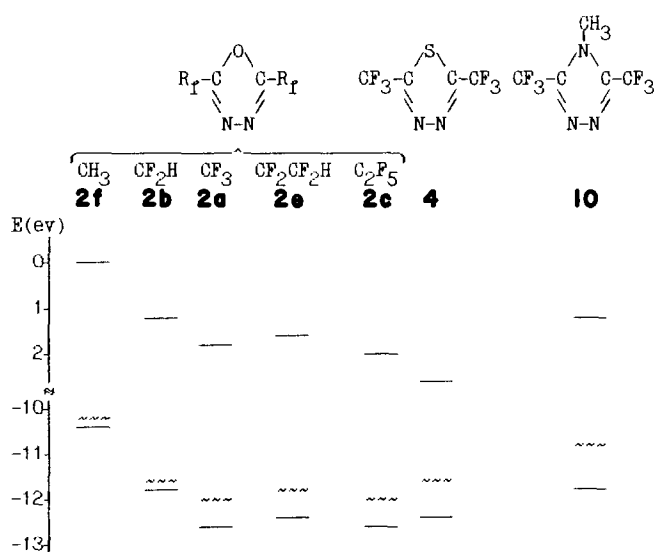


Fig. 1. HOMO and LUMO energies (—)^a and ionization potentials (---)^b. ^aCalculated by the MNDO method with preliminary optimization of the geometry by MM-2. ^bThe ionization potential of oxadiazole **2f** was taken from ref. 5, where an error was found: H should have been written instead of CH₃.

TABLE 3. Physical properties of compounds synthesized

No.	Compound	B.p. (°C/mmHg)	n _D ²⁰	M.p. (°C)
1b	C ₄ H ₄ F ₄ N ₂ O ₂	—	—	115
1e	C ₆ H ₄ F ₈ N ₂ O ₂	—	—	78
1f	C ₈ H ₄ F ₁₂ N ₂ O ₂	—	—	237 (dec.)
2g	C ₈ H ₂ F ₁₂ N ₂ O	—	—	98
1g	C ₇ H ₂ F ₁₂ N ₂ O ₂	—	—	148
1h	C ₇ H ₂ F ₁₂ N ₂ O ₂	—	—	146
2j	C ₁₀ F ₁₈ N ₂ O	135	1.3090	—
5a	C ₁₀ H ₈ F ₁₀ O	—	—	34
5b	C ₁₂ H ₈ F ₁₄ O	—	—	58
6a	C ₁₄ H ₁₈ F ₄ O ₅	118/5	1.4328	—
6b	C ₁₆ H ₁₆ F ₁₀ O ₅	95/5	1.3910	—
7a	C ₁₂ H ₁₈ F ₄ O ₃	75/5	1.4130	—
7b	C ₁₄ H ₁₆ F ₁₀ O ₃	65/5	1.3710	—
7c	C ₁₆ H ₁₆ F ₁₄ O ₃	80/5	1.3615	—
11	C ₅ H ₃ F ₆ N ₃	47/18	1.3505	—

The calculated energies of the HOMO and the ionization potentials taken from ref. 5 are in satisfactory agreement.

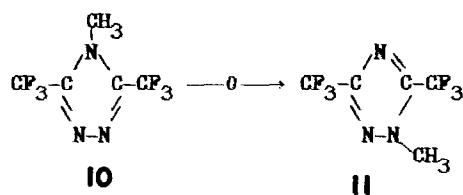
However, the frontier orbital method cannot explain all the reactivity patterns of oxadiazoles. Oxadiazole **2a** is the most reactive compound among the polyfluorinated oxadiazoles, but the energy of the LUMO of oxadiazole **2c** is lower. From the frontier orbital topology, 1,3,4-thiadiazole **4** should be a highly reactive 1,3-diene, but in reality it has a low reactivity as reported in ref. 15. The topology of the frontier orbitals for triazole **10** is comparable with that of oxadiazole **2b**,

TABLE 4. Spectroscopic data for compounds synthesized

Compound	^{19}F NMR (ext. CF_3COOH) δ (ppm)	^1H NMR δ (ppm)	J (Hz)
1b	49.6 (d, 4F, CF_2H)		FH, 56.0
1e	62.3 (dt, 4F, CF_2H); 48.7 (dt, 4F, CF_2)		FH _{gem} , 57.0 FH _{vic} , 7.0 FF, 7.0 FH, 9.0 FH, 8.0
1f	-12.7 (d, 12F, CF_3)		
2g	-11.9 (d, 12F, CF_3)	5.8 (m, 2H, CH)	
1g	-2.3 (s, 3F, CF_3); 6.7 (t, 3F, CF_3); 33.2 (t, 2F, CF_2); 43.4 (q, 2F, CF_2); 48.5 (m, 2F, CF_2)		
1h	-14.7 (s, 3F, CF_3); -2.2 (s, 9F, CF_3)		
2j	-13.1 (s, 9F, CF_3)		
5a	2.9 (s, 6F, CF_3); 45.6 (s, 4F, CF_2)	2.1 (s, 8H, CH_2)	
5b	2.3 (t, 6F, CF_2); 46.1 (m, 4F, CF_2); 42.6 (m, 4F, CF_2)	2.2 (s, 8H, CH_2)	
6a^a	49.7 (d, CF_2H); 50.2 (d, CF_2H); 50.5 (d, CF_2H); 51.1 (d, CF_2H)	6.1 (t, CF_2H); 1.1 (t, CH_3); 4.1 (q, CH_2); 2.1 (m, CH_2); 3.2 (m, CH)	FH _{gem} , 56.0 HH, 6.0
6b^a	0.8 (s, CF_3); 1.6 (s, CF_3); 2.8 (s, CF_3); 4.8 (s, CF_3); 37.5 (s, CF_2); 40.5 (s, CF_2); 40.8 (s, CF_2); 45.6 (s, CF_2)	1.2 (t, CH_3); 4.0 (m, CH_2); 2.1-2.4 (m, CH_2); 3.2-3.4 (m, CH)	HH, 6.0
7a^a	50.1 (d, CF_2H); 50.5 (d, CF_2H); 54.8 (d, CF_2H)	1.2 (t, CH_3); 3.4 (q, CH_2); 6.6 (m, CF_2H); 1.5-2.3 (m, CH_2); 3.7-4.2 (m, CH)	FH _{gem} , 57.0 HH, 6.5
7b^a	3.5 (m, CF_3); 39.3 (m, CF_2); 41.0 (m, CF_2); 44.5 (m, CF_2); 47.4 (m, CF_2)	1.1 (t, CH_3); 3.3 (m, CH_2); 1.3-2.2 (m, CH_2); 3.6-4.5 (m, CH)	HH, 6.5
7c^a	3.7 (m, CF_3); 36.0 (m, CF_2); 41.5 (m, CF_2); 44.6 (m, CF_2); 46.5 (m, CF_2); 47.0 (m, CF_2); 47.7 (m, CF_2)	1.2 (t, CH_3); 3.4 (q, CH_2); 1.4-2.0 (m, CH_2); 3.6-4.1 (m, CH)	HH, 6.3
11	-10.8 (s, 3F, CF_3); -13.2 (s, 3F, CF_3)	3.5 (s, 3H, CH_3)	

^aNMR spectrum exhibited a double signal attributed to the existence of two isomers.

but triazole **10** does not react with various dienophiles even under drastic conditions. However, this fact can be explained by the rearrangement of triazole **10** into the unsymmetrical triazole **11**. The formation of the latter has been noted in the reaction medium employed even at temperatures above 150 °C.



Thus, although a common pathway for cycloaddition has been confirmed by the work reported in this paper, some aspects are still not quite clear.

Experimental

The physical properties of the new synthesized compounds are listed in Table 3 while their spectroscopic data are shown in Table 4. Elementary analysis data corresponded to calculations: C \pm 0.5; H \pm 0.5; N \pm 0.5.

Preparation of 1,2-bis(polyfluoroacyl)hydrazines **1a-f**: general procedure

A mixture of hydrazine dihydrochloride (50 mmol) and polyfluorocarboxylic acid anhydride (220 mmol) was boiled for 2–3 h until evolution of polyfluoroacyl chloride had ceased. Removal of the volatile products under vacuum led to the corresponding pure 1,2-bis(polyfluoroacyl)hydrazine in 97% (**1a**), 99% (**1b**), 99% (**1c**), 92% (**1d**), 95% (**1e**) and 98% (**1f**) yield. The products may be recrystallized or sublimed under vacuum.

Preparation of oxadiazoles **2a-e**, **2g-j**: general procedure

To 1,2-bis(polyfluoroacyl)hydrazine (50 mmol) was added oleum (65 mmol when calculated by SO_3 content) at room temperature. The volatile components were removed under vacuum while the mixture was heated slowly. The distillate was placed on ice and the organic layer washed with an equal quantity of water. Distillation gave the corresponding oxadiazoles in 75% (**2a**), 56% (**2b**), 78% (**2c**), 74% (**2d**), 48% (**2e**), 17% (**2h**) and 12% (**2i**) yield. Oxadiazole **2g** was obtained in 57% yield by sublimation of the mixture with magnesium sulfate.

Preparation of 1-trifluoroacetyl-2-polyfluoroacetylhydrazines 1g, 1h: general procedure

A mixture consisting of 1-trifluoroacetylhydrazine (50 mmol) and the corresponding polyfluorocarboxylic acid chloride or fluoride (80 mmol) was boiled for 8 h. Volatile products were removed under vacuum and sublimation of the residue gave the corresponding 1-trifluoroacetyl-2-polyfluoroacetylhydrazine in 77% (**1g**) 70% (**1h**) yield.

Preparation of 1,4-bis(polyfluoroalkyl)-7-oxabicyclo[2.2.1]heptanes: general procedure

A mixture consisting of an oxadiazole (25 mmol) and a corresponding dienophile (56 mmol; in the case of ethylene, 150 mmol) was heated in a closed vessel (temperatures and times of reaction are listed in Table 1). The corresponding 1,4-bis(polyfluoroalkyl)-7-oxabicyclo[2.2.1]heptane was obtained on distillation.

Preparation of 1-methyl-3,5-bis(trifluoromethyl)-1,2,4-triazole (11)

4-Methyl-3,5-bis(trifluoromethyl)-1,2,4-triazole (**10**) (3.1 g, 14 mmol) was heated in a closed vessel for 2 h at 200 °C. Distillation of the residue gave 1-methyl-3,5-bis(trifluoromethyl)-1,2,4-triazole (**11**) (1.8 g, 58%).

References

- H.C. Brown, M.T. Cheng, L.J. Parcell and D. Pilipovich, *J. Org. Chem.*, **26** (1961) 4407.
- W.J. Chambers and D.D. Coffman, *J. Org. Chem.*, **26** (1961) 4410.
- M.P. Krasuskaya, D.P. Deltsova and I.L. Knunyants, *Izv. Akad. Nauk USSR, Ser. Khim.*, (1965) 2039.
- I.L. Knunyants, M.P. Krasuskaya and D.P. Deltsova, *Izv. Akad. Nauk USSR, Ser. Khim.*, (1966) 577.
- A.V. Golyavin, N.V. Vasiliev, A.A. Rodin, A.F. Kolomietz and L.M. Reingand, *Zh. Obshch. Khim.*, **59** (1989) 2698.
- Yu. V. Sinyakov, N.V. Vasiliev, A.F. Kolomietz and G.A. Sokolski, *Zh. Org. Khim.*, **24** (1989) 642.
- V.L. Vershinin, N.V. Vasiliev, A.F. Kolomietz and G.A. Sokolski, *Zh. Org. Khim.*, **20** (1984) 1333.
- V.L. Vershinin, N.V. Vasiliev, A.F. Kolomietz and G.A. Sokolski, *Zh. Org. Khim.*, **20** (1984) 1806.
- D.L. Boger, *Chem. Rev.*, **86** (1986) 782.
- D.L. Boger, *Tetrahedron*, **39** (1983) 2900.
- D.L. Boger, *Hetero-Diels-Alder Methodology in Organic Synthesis. Organic Chemistry*, Academic Press, London, 1987, Vol. 47.
- V.M. Koshelev, A.N. Chechlov, N.V. Vasiliev, A.F. Gontar and I.V. Martynov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, (1988) 744.
- N.V. Vasiliev, Y.E. Lyashenko, A.F. Kolomietz and G.A. Sokolski, *Khim. Geterotsikl. Soedin. SSSR*, (1987) 562.
- Yu. E. Lyashenko, A.L. Paramonov, N.V. Vasiliev, P.F. Potashnikov, A.F. Kolomietz and G.A. Sokolski, *Abs. 5th Symp. Fluorine Chem.*, Moscow, (1986) p. 52.
- C. Seitz and H. Wassmuth, *Chem.-Ztg.*, **112** (1988) 80.
- F. Thalhammer, V. Wallfahrer and J. Sauer, *Tetrahedron Lett.*, **29** (1988) 3231.
- N.V. Vasiliev, Yu. E. Lyashenko, M.V. Galahov, A.F. Kolomietz, A.F. Gontar and G.A. Sokolski, *Khim. Geterotsikl. Soedin. SSSR*, (1990) 95.
- H. Van der Plas, *Ring Transformation of Heterocycles*, Academic Press, London/New York, 1973, Vol. 1, pp. 14 and 364.