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Communication

Synthesis of 3-perfluoroalkyl-, including 3-trifluoromethyl-, substituted pyrazoles from perfluoroalkylacetylenes

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Abstract

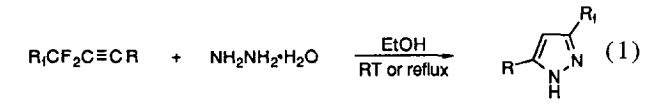
3-Perfluoroalkylpyrazoles **2** have been prepared in excellent yield by the reactions of perfluoroalkylacetylenes **1** with hydrazine monohydrate under mild conditions.

Keywords: Perfluoroalkylpyrazoles; Synthesis; Perfluoroalkylacetylenes; Hydrazene; Nucleophilic addition

It is now recognized that the regioselective replacement of hydrogen in an aromatic or heterocyclic system by a perfluoroalkyl group may have a profound influence on the physical and biological properties of such molecules [1]. As a result, considerable effort has been devoted to the development of synthetic methodologies for the preparation of perfluoroalkyl-substituted heterocycles [2]. One such method is based on the use of a building block with a fluorine-containing substituent.

Perfluoroalkylacetylenes have been found to be good electrophiles since the perfluoroalkyl group R_f significantly enhances the electrophilic character of the triple bond [3]. Use of perfluoroalkylacetylenes for the incorporation of fluorine into molecules and numerous reactions involving their use as either nucleophilic and electrophilic synthons have been described [4]. In particular, nucleophilic additions to perfluoroalkylacetylenes by *N*-nucleophiles [5], *O*-nucleophiles [6], *S*-nucleophiles [7], as well as *C*-nucleophiles [8] and others have been reported. In connection with the preparation of a series of perfluoroalkyl-substituted heterocycles with potential high biological activities, we were interested in examining the interaction of perfluoroalkylacetylenes 1 with dinucleophiles. Here we describe preliminary results on the reaction of perfluoroalkylacetylenes **1** with hydrazine monohydrate leading to the synthesis of 3-perfluoroalkylpyrazoles **2** in excellent yield.

Perfluoroalkylacetylenes 1 reacted smoothly with hydrazine monohydrate under reflux in ethanol to give 3-perfluoroalkylpyrazoles **2** as the sole product [Eq. (1)]. The spectral data for **2** indicate that the perfluoroalkyl group of the product is one carbon atom less than that of the starting material.

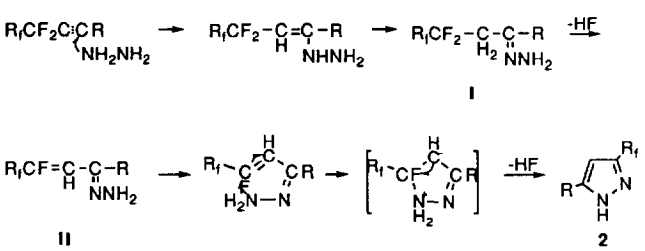


1 2

Examination of the reaction conditions showed unequivocally that at least 3 equiv. of hydrazine monohydrate were essential for the complete conversion of the perfluoroalkylacetylenes.

On the basis of this fact [3,9], this reaction is assumed to proceed via nucleophilic attack of hydrazine monohydrate on perfluoroalkylacetylenes to give a hydrazone intermediate **I**, which eliminates hydrogen fluoride to form the intermediate **II**. Such intramolecular nucleophilic addition, followed by elimination of another molecular hydrogen fluoride to give the 3-perfluoroalkylpyrazoles, occurs as shown in Scheme 1.

In a typical procedure, hydrazine monohydrate (35 mmol) was added to a solution consisting of 10 mmol of 3,3,4,4,5,5,6,6,6-nonafluoro-1-phenyl-1-hexyne, $CF_3(CF_2)_3C\equiv$



Scheme 1.

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Table 1
Preparation of 3-perfluoroalkylpyrazoles (2)

Entry No.	Acetylenes		Conditions [a]		Products [b]	M.p. (°C)	Yield (%) [c]
	R_f	R	Temp. (°C)	Time (h)			
1	$F(CF_2)_3$	Ph (1a)	reflux	4	**2a**	93–94	96
2	$Cl(CF_2)_3$	Ph (1b)	reflux	6	**2b**	90–92	95
3	$F(CF_2)_5$	Ph (1c)	reflux	6	**2c**	72–73	98
4	CF_3	Ph (1d)	reflux	4	**2d** [11]	120–121	94
5	CF_3	CH_2OH (1e)	25	3	**2e** [12]	115–116	95
6	CF_3	CH(OH)Me (1f)	25	4	**2f** [12]	93–94	92
7	CF_3	$C(OH)Me_2$ (1g)	reflux	4	**2g** [12]	150–151	94
8	$Cl(CF_2)_3$	CH_2OH (1h)	25	3	**2h** [13]	118–119	95
9	$Cl(CF_2)_3$	CH_2OH (1h)	reflux	0.5	**2h** [13]		90
10	$Cl(CF_2)_5$	CH_2OH (1i)	25	4	**1i** [13]	170–172	96
11	$Cl(CF_2)_3$	H (1j)	25	6	**1j** [14]	66–68	89
12	$Cl(CF_2)_5$	H (ik)	25	6	**1k** [14]	52–54	90

[a] All reactions were carried out in ethanol with 3–4 equiv. of hydrazine monohydrate being employed.
[b] All new compounds were characterized by mass spectrometry, IR, ^1H NMR, ^{19}F NMR spectroscopy and microanalysis.
[c] Isolated yield.

CPh, (**1a**) in 20 ml of 95% ethanol. The reaction mixture thus obtained was heated to reflux for 2 h, then cooled and diluted with water (40 ml). The resulting precipitate was collected by filtration and purified by recrystallization from petroleum ether to give 3-heptafluoropropyl-5-phenylpyrazole (**2a**) [1].

Representative examples are summarized in Table 1. The reaction can be applied to a wide variety of perfluoroalkylacetylenes and the yields are invariably high. The substitution pattern at skeletal atoms 3 and 5 of the pyrazole ring can be altered by choosing the appropriate perfluoroalkylacetylenes. Therefore, this reaction can serve as a convenient route to 3-perfluoro-alkyl substituted pyrazole derivatives emerging as a new kind of fluorine-containing compound possessing high biological activities such as herbicides, fungicides, insecticides, etc [10]. Based on the supposed reaction mechanism, we envisage that this method may have great potential for further application to other dinucleophiles for preparing perfluoroalkylated heterocycles. This study is in progress.

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[1] Compound **2a**: M.p. 92.5–94.0 °C. ^{19}F NMR (CD_3COCD_3/TFA) δ: 4.0 (s, 3F); 33.9 (s, 2F); 50.9 (s, 2F) ppm. ^1H NMR (CD_3COCD_3/Me_4Si) δ: 7.03 (s, 1H); 7.43 (m, 3H); 7.77 (m, 2H) ppm. IR (KCl) ν (cm^{-1}): 3100, 1580; 1480; 1360; 1120; 710. MS m/z (%): 312 (M^+, 58.50); 313 ($M^+ + 1$, 8.30); 293 (8.45); 193 ($M^+ - C_2F_5$, 100.00); 164 (21.25); 115 (16.50); 77 (10.00). Satisfactory elemental analyses were obtained for **2a**.

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