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PRELIMINARY NOTE

Functionalized Perfluorophenyl Azides: New Reagents for Photoaffinity Labeling

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SUMMARY

Several substituted perfluorophenyl azides capable of attachment to other molecules by an acylation reaction were synthesized for use as photoaffinity labeling reagents.

Photoaffinity labeling [1] is widely used to study the proximity of components within biological systems. Photolysis of the photolabel generates a nitrene or carbene intermediate which then reacts rapidly with nearby molecules to form a covalent bond. C-H bond insertion is a desirable reaction pathway. Therefore, it is important to have available photolabels which lead to efficient C-H insertion. Aryl azides are widely used as photolabels. Remarkably, the parent compound phenyl azide gives almost no C-H insertion products in hydrocarbon solvents [2] but instead mostly undergoes ring expansion to dehydroazepine [3].

Perfluoroaryl azides may constitute an improved series of photolabels [4] on the basis that a) thermal decomposition of 4-azido-2,3,5,6-tetrafluoropyridine in cyclohexane gave the C-H insertion product in 45% yield [5], and b) photolysis [6] of pentafluorophenyl azide in toluene gave C-H insertion products in 52% yield. Herein, we describe the synthesis of several perfluorophenyl azides that also contain a reactive group for convenient attachment of the new photolabels to other molecules.

Pentafluorophenyl compounds containing an electron withdrawing group such as $-CF_3$ [7] or -CN [8] are known to undergo nucleophilic aromatic substitution nearly exclusively at the 4-position [9]. Azide ion was the nucleophile in a few cases [10].

A solution of methyl pentafluorobenzoate (1.19 g, 5.26 mM) and sodium azide (344 mg, 5.29 mM) in 3:1 acetone-water (13 mL) was refluxed for 7 h. The solution

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was then cooled, diluted with water (5 mL), and extracted with ether. The extract was dried (Na_2SO_4) and evaporated, giving 1.14 g (87%) of azide **1**, mp 54-55 °C. Similarly prepared in >80% yield were azido benzamide **2**, mp 164-165 °C, azido benzaldehyde **3**, mp 44-45 °C, and azido acetophenone **4**, bp 50 °C/ 0.1 mm. Selective hydrolysis ($NaOH/MeOH/H_2O$, 25 °C, 8 h, 95%) of ester **1** gave azido acid **5**, mp 140-141 °C. Acid **5** was converted into acid chloride **6** (refluxing $SOCl_2/CH_2Cl_2$, 48 h, 70%; bp 47-49 °C/0.01 mm) and acylimidazole **7** (1,1-carbonyldiimidazole/THF, 1 h, 25 °C, 60%; mp 63-64 °C). Treatment of **2** with NH_3-saturated dry DMSO at 75 °C for 5 days gave amine **8** (50%), mp 160-161 °C. Oxidation of **8** by CF_3CO_3H [11] gave nitro azide **9**, mp 135-136 °C.

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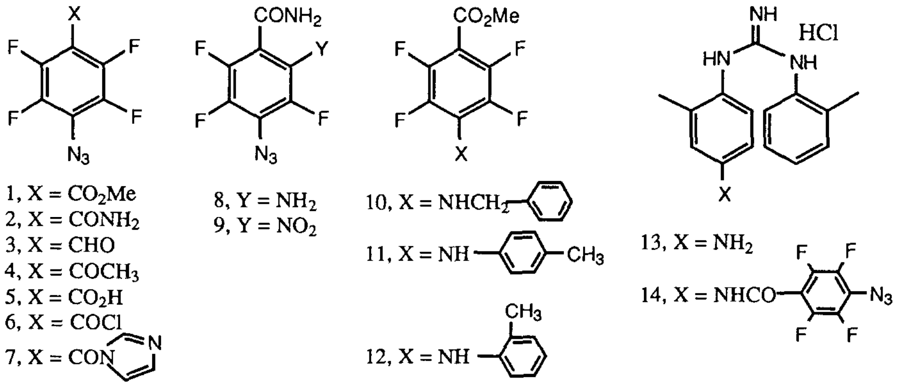

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[1] For compounds **1-7**, the ^{19}F NMR spectrum showed the expected AA'XX' pattern.

[2] For new compounds **1-9** and **14**, satisfactory IR, 300 MHz ^1H and 338.7 MHz ^{19}F NMR spectra together with either a C,H,N microanalysis or else a high resolution mass spectrum were obtained. UV max nm (log ε) (EtOH): **1**, 263 (4.17); **2**, 255 (4.30); **3**, 250 (4.11); **4**, 267 (4.23); **5**, 259 (4.07); **8**, 265 (3.89), 334 (3.23); **9**, 250 (4.53), sh 300 (3.84).

[3] For amine **8**, the position of the amino group was indicated by the presence of intramolecular H-bonding between the carbonyl group and the amino group in the IR spectrum. Also, the ^{19}F NMR spectrum showed that there was only one F atom (F-6) coupled to the carboxamide protons.

Photolysis (350 nm) of ester **1** (4.2×10^{-3} M) in toluene at 25 °C gave a mixture of formal C-H insertion products (**10**, 16%; **11**, 9%; **12**, 13%) in 38% yield. The products were separated by preparative TLC, identified by ^{1}H and ^{19}F NMR and mass spectrometry, and the structures were confirmed by independent synthesis. This result confirms that certain functionalized perfluoroaryl azides also show significant C-H insertion upon photolysis. Attachment of one of these new photolabels to another molecule is illustrated by the selective acylation of amino derivative **13** [12] of the mammalian brain sigma receptor ligand N,N'-di-*o*-tolylguanidine (DTG) [13] with acid chloride **6** to give amide **14**. This ligand shows an IC_{50} = 25 nanomolar against [^{3}H]-DTG [14]. This value is comparable to that of DTG itself and suggests that **14** may be a useful companion to photolabels already developed for the sigma receptor [12]. Other applications of these new photolabels is underway in our laboratory.

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14 This experiment was carried out by Dr. Eckard Weber, Oregon Health Sciences University, Portland, OR.