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Synthesis of fluorinated azulenes

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Abstract

Fluorinated azulenes were prepared in moderate yields under mild conditions and short reaction times using Selectfluor™, **I**, in methanol/acetonitrile solution.

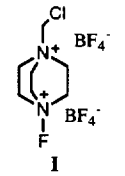
Keywords: Fluorination; Selectfluor™; Azulene

1. Introduction

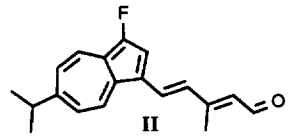
As part of our continued interest in retinoids of varied absorption properties [1,2], we were in need of azulenic retinoids labeled with a fluorine atom on the azulene ring rather than on the polyene side chain. Such label(s) may serve the additional role as NMR probes for gathering structural information related to the micro-environment of a retinoid binding protein [3,4]. A recent report described the synthesis of 1-fluoroazulene and 1,3-difluoro-azulene using *N*-fluoropyridinium salts [5]. However, long hours of reflux and low yields (~12%) are major drawbacks of the method. Recently, Selectfluor™, **I**, a powerful fluorinating agent[1] has been used to fluorinate a variety of aromatic compounds [7–9]. We wish to report herein the reaction of azulene and substituted azulenes with Selectfluor™.

2. Results and discussion

Initial experiments using acetonitrile as the solvent showed that reaction of azulene with **I** gave 1-fluoro and 1,3-difluoroazulene along with unreacted azulene and large amounts of polymeric material. The combined yield of the fluoroazulenes (only ~8%) was no better than that obtained earlier with *N*-fluoropyridinium salts [5]. The experimental conditions however were much milder since the reaction proceeded readily at room temperature. Since the reaction appeared to show some promise we decided to focus our attention on increasing the yield.



I



II

All the exploratory work was carried out with the relatively inexpensive sesquiterpene guaiazulene (entry 4 in Table 1). In acetonitrile, guaiazulene furnished only 5% of the monofluoro product. About 2% unreacted guaiazulene was recovered and the rest was an unidentified polymeric product. However, upon using methanol–acetonitrile as the solvent, the yield of the monofluoro product increased to 20%. Further increase in the yield to 31% was effected by adding the azulene to an acetonitrile/methanol solution of **I**. The yield could not be increased any further despite conducting the reaction in different solvent mixtures, e.g., CH_2Cl_2/CH_3CN and DMF/CH_3CN (the insolubility of **I** precluded the use of other common solvent mixtures). Therefore, we decided to subject azulene and substituted azulenes to the same reaction conditions as guaiazulene (see Section 3). The yields for various fluorinated azulenes are given in Table 1.

Examination of the data in Table 1 reveals that the yields of fluorinated azulenes are moderate in all cases but higher than the method reported earlier for the unsubstituted azulene [5]. We believe that the present method offers definite advantages over the previously reported synthesis [5] because of

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[1] For a general review of N–F fluorinating agents, see Ref. [6].

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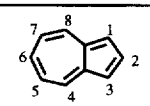
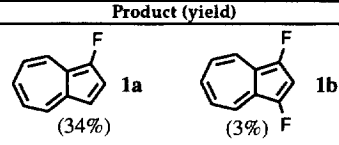
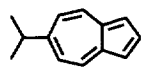
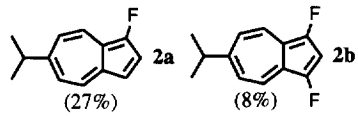
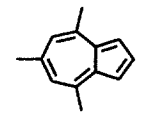
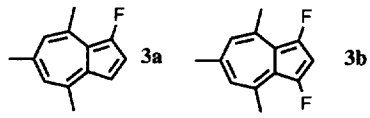
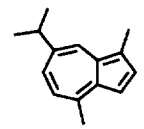
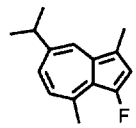
Table 1
Fluorination of azulene and substituted azulenes with **I**

	Substrate	Product (yield)
1		 **1a** (34%) **1b** (3%)
2		 **2a** (27%) **2b** (8%)
3		 **3a** (12%) **3b** (2%)
4		 **4a** 31%

All reactions were conducted at room temperature for 5 min.

the mild conditions, short reaction times and the cost effectiveness of the reagent.[2]

On a closing note, we would like to mention that the fluorinated azulenes could be functionalized uneventfully. For example, 6-isopropyl 1-fluoro azulene, **2a**, was readily converted to the 3-formyl derivative and subsequent chain extension furnished the diene aldehyde **II**. Incorporation of this retinoid analog in bacterioopsin resulted in a bacteriorhodopsin pigment analog with an absorption maximum of 674 nm [10]. Further studies aimed at understanding the interactions of this chromophore with the protein are currently in progress.

3. Experimental details

Selectfluor™, azulene and guaiazulene were obtained from Aldrich and used without further purification. 6-Isopropyl and 4,6,8-trimethyl azulene were prepared according to the Hafner procedure [11]. ^{1}H-NMR and ^{19}F-NMR were recorded at 400 MHz and 376 MHz, respectively, on a Varian Unity Inova 400 MHz instrument. Chemical shifts are given in parts per million with TMS as an internal standard for ^{1}H-NMR and CF_3COOH as the external standard for F-NMR. NOE and HMQC data were obtained for unambiguous assignment of all signals in the ^{1}H-NMR. Mass spectra were recorded at 70 eV on a VG analytical 70-SE mass spectrometer. All compounds had the characteristic azulene-like blue color. Only **1a** and **1b** could be obtained as crystalline solids [5], the rest were viscous liquids.

A typical experimental procedure for fluorination of azulene is as follows: a solution of azulene, 0.128 g, (1 mmol) in methanol was added to a solution of **I**, 0.356 g, (1 mmol) in acetonitrile:methanol (1:5, total volume: 25 ml) via cannula under an atmosphere of argon. The reaction mixture was then allowed to stir for 5 min at room temperature and poured into a saturated solution of bicarbonate. After extracting with hexane, the residue was chromatographed on silica gel with hexane:pentane (50:50) to yield the pure fluorinated azulenes **1a** and **1b** in 34% and 3% yields, respectively. The yields for the other fluorinated azulenes are given in Table 1.

Selected spectral data for compounds **2a–4a** are given below. Compounds **1a** and **1b** are known [5]. (**2a**) ^{1}H NMR δ 8.20 (C8–H, d, 10.4 Hz, 1H), 8.10 (C4–H, dd, 10.0 Hz, 3.2 Hz, 1H), 7.41 (C2–H, d, 4.8 Hz, 1H), 7.06 (C3–H, t, 4.8 Hz, 1H), 6.96 (C5 and C7–H, d, 10.0 Hz, 2H), 3.01 (CH_3–CH–CH_3, m, 1H), 1.34 (CH_3–CH–CH_3, d, 7.1 Hz, 6H) ppm. ^{19}F NMR δ: −148.3 ppm, m. Exact mass calculated for $C_{13}H_{13}F$: 188.1001. Found (M^+): 188.0982. (**2b**) ^{1}H NMR δ 8.10 (C4 and C8–H, d, 10.5 Hz, 2H), 7.04 (C2–H, s, 1H), 6.77 (C5 and C7–H, d, 10.5 Hz, 2H), 2.95 (CH_3–CH–CH_3, m, 1H), 1.31 (CH_3–CH–CH_3, d, 6.6 Hz, 6H) ppm. ^{19}F NMR δ: −149.7 ppm, br. s. Exact mass calculated for $C_{13}H_{12}F_2$: 206.0907. Found (M^+): 206.0927. (**3a**) ^{1}H NMR δ 7.25 (C2–H, d, 4.8 Hz. 1H), 7.11 (C3–H, t, 4.8 Hz, 1H), 6.86 (C7–H, s, 1H), 6.79 (C5–H, s, 1H), 2.73 (C8–CH_3, d, 4.8 Hz, 3H), 2.78 (C4–CH_3, s, 3H), 2.56 (C6–CH_3, s, 3H) ppm. ^{19}F NMR δ: −137.01 ppm, m. Exact mass calculated for $C_{13}H_{13}F$ 188.1001. Found (M^+): 188.1011. (**3b**) ^{1}H NMR δ 6.87 (C2–H, s, 1H), 6.52 (C5 and C7H, s, 2H), 2.83 (C4 and C8 CH_3, br. s, 6H), 2.45 (C6–CH_3, s, 3H) ppm. ^{19}F NMR δ: −137.44 ppm, br. s. Exact mass calculated for $C_{13}H_{12}F_2$: 206.0907. Found (M^+): 206.0925. (**4a**) ^{1}H NMR δ 8.03 (C8–H, dd, 1.2 Hz, 3.2 Hz, 1H), 7.22 (C6–H, dd, 1.6 Hz, 10.4 Hz, 1H), 7.24 (C2–H, s, 1H), 6.66 (C5–H, d, 10.4 Hz, 1H), 2.97 (CH_3–CH–CH_3, m, 1H), 2.87 (C4–CH_3, d, 4 Hz, 3H), 2.61 (C1–CH_3, s, 3H), 1.33 (CH_3–CH–CH_3, d, 6.8 Hz, 6H) ppm. ^{19}F NMR δ: −140.8 ppm, m. Exact mass calculated for $C_{15}H_{17}F$: 216.1314. Found (M^+): 216.1319.

Acknowledgements

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[2] The current prices (Aldrich) for 5 g of Selectfluor™ and 1-fluoro-2,4,6-trimethyl pyridinium triflate are US$9 and US$111.75, respectively. For commercial scale synthesis, Selectfluor™ is available from Air Products at US$0.50 per gram (1 kg minimum).

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