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N-difluoromethylation of phenylazoles

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Abstract

In the presence of one equivalent of NaH, 2- and 4-phenylimidazole and 3-phenyl-1,2,4-triazole can be N-difluoromethylated with $ClCF_2H$. The difluoromethylation of 5-phenyltetrazole requires two equivalents of NaH. A mechanism is proposed to account for these differences.

1. Introduction

The replacement of hydrogen by fluorine is a common strategy used in the design and optimization of biologically active compounds [1]. The success of this approach in the Agrochemical field has resulted in a number of new fluorinated products entering the market place over the past decade [2]. Recent examples include the new herbicides, sulfentrazone (**1**) [3] and carfentrazone–ethyl (**2**) [4], both possessing a difluoromethyl group. Partially fluorinated organic compounds often possess properties that are desirable for enhanced biological efficacy. The high electronegativity of the fluorine atom combined with its similar size to hydrogen often imparts an increased oxidative and hydrolytic stability of the fluorinated alkyl over the parent alkyl group [5]. For sulfentrazone, replacement of the N-methyl with an N-difluoromethyl group significantly improves the herbicidal potency. [6,7]

There are very few reports describing the reaction of difluorocarbene with nitrogen-containing heterocycles. Recent examples include the difluoromethylation of imidazole and benzimidazole with difluorocarbene generated from $ClCF_2H$ and alkali or CF_3CO_2Na under neutral conditions [8] and the difluoromethylation of benzotriazole, benzimidazole, indole, and imidazole with difluorocarbene generated from the thermal decomposition of fluorosulfonyldifluoroacetic acid. [9]

While working on the synthesis of sulfentrazone analogs, we difluoromethylated a variety of 2-aryl-1,2,4-triazolinones (**3**) using $ClCF_2H$ and NaH in THF. Although successful, we were rarely rewarded with more than moderate yields of N-difluoromethyl product unless the reaction was run at elevated temperature or with excess base. In contrast, we obtained near quantitative yields when imidazole **4** [10] was N-difluoromethylated under similar conditions [11]. In order to better understand this process, we investigated the N-difluoromethylation of other azole heterocycles.

2. Results

2.1. Difluoromethylation of phenylimidazoles

2-Phenylimidazole (**5**) does not react with $ClCF_2H$ in THF at ambient temperature. Deprotonation of **5** with NaH followed by treatment with excess $ClCF_2H$ produces 1-N-difluoromethyl-2-phenylimidazole (**6**) as the sole product in a 75% isolated yield (Scheme 1). Likewise, the anion of 4-phenylimidazole (**7**) reacts with $ClCF_2H$ to produce a 3 : 2 mixture of 1 and 3-difluoromethyl-4-phenylimidazole, **8** and **9** (Scheme 2).

2.2. Difluoromethylation of phenyltriazole

Deprotonation of 3-phenyl-1,2,4-triazole (**10**) with NaH followed by reaction with $ClCF_2H$ produces a mixture of 1, 2, and 4-difluoromethyl-3-phenylimidazoles (**11**, **12**, and **13,** respectively) with the 1-isomer predominating (Scheme 3). The identification of the isomers was made through a NOE experiment (Fig. 1). Irradiation of H_5 of **11** or **13** results in a NOE enhancement in the difluoromethyl hydrogen whereas **12** shows no difluoromethyl NOE effect. Irradiation of the phenyl ortho hydrogen of **12** or **13** also produced a positive difluoromethyl **NOE** effect which was lacking in **11**.

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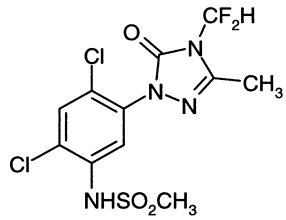
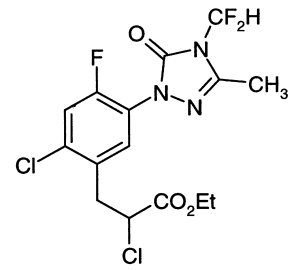
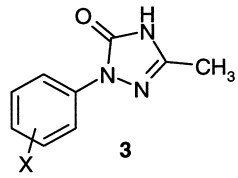


sulfentrazone (1)



carfentrazone-ethyl (2)



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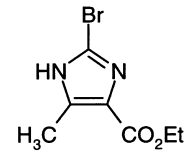

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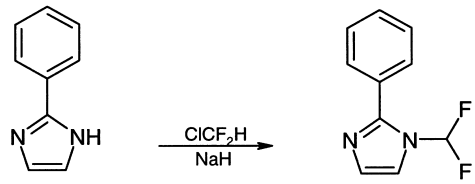
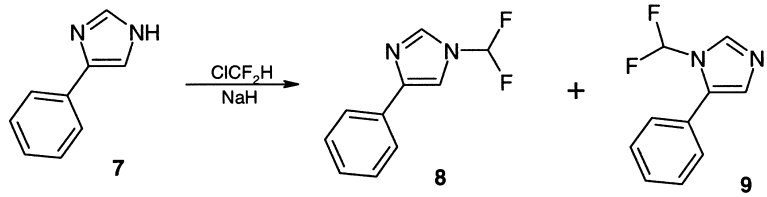


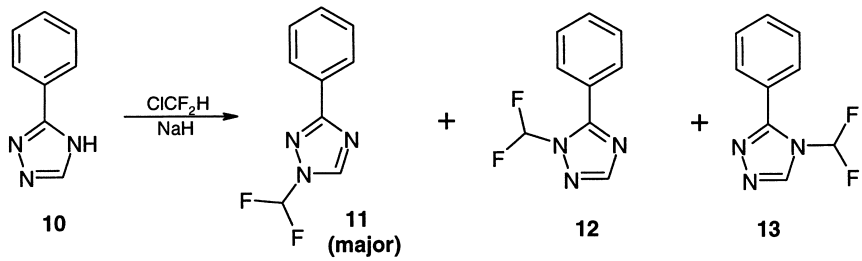
5 **6**

Scheme 1.



7 **8** **9**

Scheme 2.

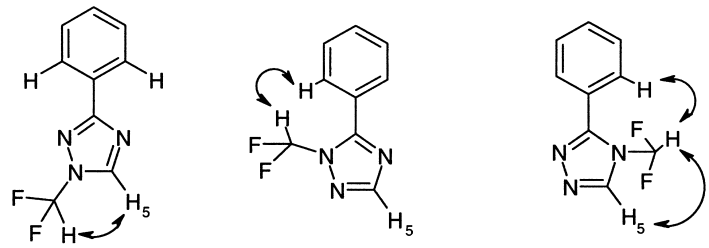


10 **11 (major)** **12** **13**

Scheme 3.

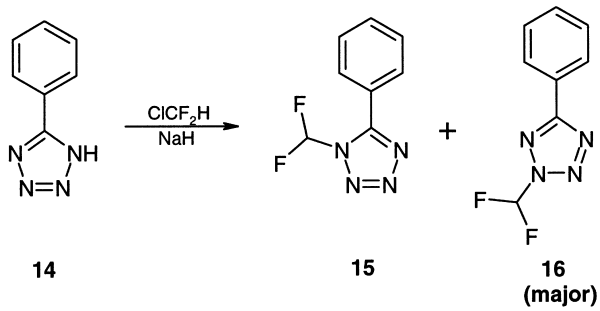
2.3. Difluoromethylation of phenyltetrazole

When 5-phenyltetrazole (**14**) was deprotonated with one equivalent of NaH and then reacted with excess $ClCF_2H$ only starting material was recovered. Repeating the reaction with two equivalents of NaH produced a 1 : 2 mixture of the difluoromethylated tetrazoles, **15** and **16** (Scheme 4). The electron ionization mass spectrum for **15** indicated a loss of N_3 (42 *m/e*) and for **16**, a loss of N_2 (28 *m/e*), consistent with the structural assignments (Fig. 2).



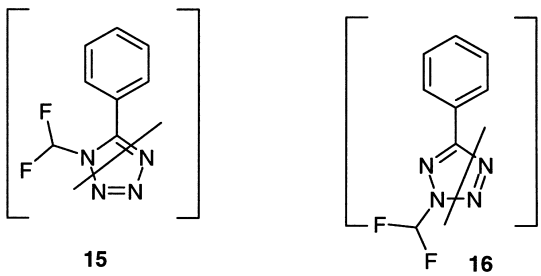
11 12 13

Fig. 1. NOE experiment (double arrows indicate a positive NOE effect).



14 15 16 (major)

Scheme 4.



15 16

Fig. 2. Fragmentation of ionized phenyltetrazoles, **15** and **16**.

3. Discussion

Contrasting mechanisms for difluoromethylation of N-heterocyclic compounds have been proposed. Poludnenko et al. [8] suggest that the reaction takes place between difluoromethylcarbene and the non-dissociated heterocycle whereas Chen et al. [9] indicate that the formation of the heterocycle anion is required for addition to difluorocarbene. Our mechanism for the difluoromethylation of phenylimidazole or phenyltriazole with $ClCF_2H$ is depicted in Fig. 3. Abstraction of a proton from $ClCF_2H$ by the azole anion followed by loss of Cl^- produces difluorocarbene which then inserts into the N–H bond. Support for this mechanism comes from the observation that **6** can also be formed by the treatment of **5** with difluorocarbene generated in situ from $ClF_2CO_2CH_3$, KF, 18-C-6 in diglyme [12].

Since the difluoromethylation of phenyltetrazole with $ClCF_2H$ requires the addition of two equivalents of NaH we rationalized that either the tetrazole anion is not basic enough to deprotonate $ClCF_2H$ to generate difluorocarbene (Fig. 3, step b), or that the tetrazole anion is required to react with diflurorcarbene (Fig. 3, step e). Due to the higher acidity of the phenyltetrazole N–H compared with phenylimidazole or phenyltriazole ($pK_a = 13.3$ for **5**, 9.2 for **10**, and 4.8 for **14**) [13] we favored the former hypothesis. When **14** was reacted with difluorocarbene generated in situ from $ClF_2CO_2CH_3$, KF, and 18-C-6 in diglyme, the difluoromethylated tetrazoles **15** and **16** were obtained.

The above results strongly support the difluoromethylation mechanism proposed by Poludnenko et al. [8] and explain the reactivity observed with the triazolinone **3** and imidazole **4**. The anion of imidazole **4** is sufficiently basic to generate difluorocarbene from $ClCF_2H$ and results in high yields. The phenyltriazolinone **3**, similar in acidity to the phenyltetrazole, requires the second equivalent of NaH to generate the carbene.

4. Experimental details

Melting points were determined on a Thomas–Hoover capillary melting point apparatus and are uncorrected. The

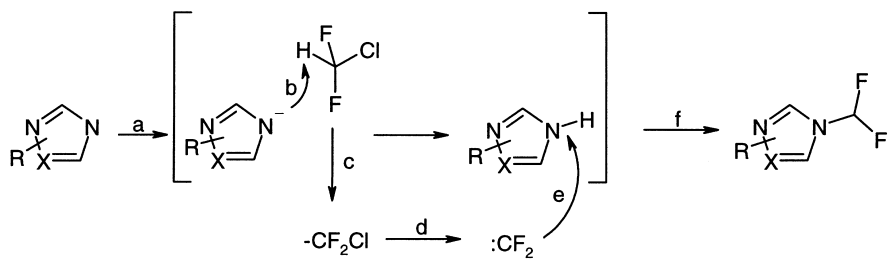


Fig. 3. Proposed reaction pathway for the difluoromethylation of phenylimidazole and phenyltriazole.

NMR spectra were recorded on a General Electric QE300 spectrometer (300 MHz ^{1}H) and a Brucker AMX2-500 (470 MHz ^{19}F). Deuteriochloroform was used as the NMR solvent unless otherwise specified. Chemical shifts are expressed in ppm downfield from internal tetramethysilane (^{1}H) and upfield from internal $CFCl_3$ (^{19}F). Mass spectra were recorded on a Kratos analytical profile instrument. Elemental analyses were determined at FMC Corporation, Analytical Services Department or at Quantitative Technologies, Whitehouse, NJ. Chromatography was performed using EM Silica Gel 60 (0.040–0.063 mm). Solvents and reagents were used as purchased.

4.1. Difluoromethylation of 2-phenylimidazole and 1-N-difluoromethyl-2-phenylimidazole (**6**)

Method A: Sodium hydride (60% dispersion in mineral oil, 0.49 g, 12.2 mmol) was washed with petroleum ether and then suspended in anhydrous THF (10 ml). The mixture was stirred at ambient temperature as 2-phenylimidazole (**5**) (1.75 g, 12.2 mmol) dissolved in THF (10 ml) was added dropwise. After the addition, the mixture was stirred at ambient temperature for 30 min and $CHClF_2$ was bubbled into the reaction mixture until saturated (excess $CHClF_2$ was contained using a dry ice condenser). The mixture was stirred for 1 h and then poured into 100 ml of water. After extraction with CH_2Cl_2 (2 × 100 ml) and drying ($MgSO_4$) the solvent was evaporated in vacuo and the crude product distilled to yield 1.8 g (75%) of an oil, with b.p. 102° at 1.4 mm Hg.

^{1}H-NMR δ: 7.03 (*t*, 1H, $J_{H-F} = 60$ Hz), 7.20 (d, 1H, $J_{H-F} = 1.5$ Hz), 7.37 (d, 1H, $J_{H-F} = 1.5$ Hz), 7.48 (m, 3H), 7.57 (m, 2H) ppm. ^{19}F-NMR δ: −90.9 ($J_{F-H} =$ 60 Hz). *Anal*. Calc. for $C_{10}H_8F_2N_2$: C, 61.85; H, 4.15; N, 14.43. Found: C, 62.10; H, 3.99; N, 14.62.

Method B: A mixture of 18-crown-6 (1 g), KF (0.42 g, 7.6 mmol), 2-phenylimidazole (1.1 g, 7.6 mmol), methyl chlorodifluoroacetate (0.8 ml, 7.6 mmol), and 2-methoxyethyl ether (10 ml) was heated at 85° for 16 h. Work-up as in method A afforded 0.75 g (50%) of a clear oil identical to **6**.

4.2. Difluromethylation of 4-phenylimidazole, 1-N-difluoromethyl-4-phenylimidazole (**8**) and 3-N-difluoromethyl-4-phenylimidazole (**9**)

Prepared using method A from 4-phenylimidazole (1 g, 6.9 mmol), THF (30 ml), NaH (60% dispersion in mineral oil, 6.9 mmol), and $CHClF_2$ to yield after chromatography; 0.58 g (43%) of **8**, white solid, m.p. 90–92° and 0.41 g (30%), clear oil.

8, ^{1}H-NMR δ: 7.08 (*t*, 1H, $J_{H-F} = 61$ Hz), 7.29–7.42 (m, 3H), 7.47 (s, 1H), 7.79 (d, 2H), 7.86 (s, 1H); ^{19}F-NMR δ: −91.8 ($J_{F-H} = 61$ Hz) *Anal*. Calc. for $C_{10}H_8F_2N_2$: C, 61.85; H, 4.15; N, 14.43. Found: C, 61.70; H, 4.05; N, 14.30.

9, ^{1}H-NMR δ: 6.96 (*t*, 1H, $J_{H-F} = 61$ Hz), 7.11 (s, 1H) 7.37–7.47 (m, 5H), 8.00 (s, 1H); ^{19}F-NMR δ: −91.3 ($J_{F-H} =$ 61 Hz) *Anal*. Calc. for $C_{10}H_8F_2N_2$: C, 61.85; H, 4.15; N, 14.43. Found: C, 61.39; H, 4.09; N, 14.11.

4.3. Difluoromethylation of 3-phenyl-1,2,4-triazole. Difluoromethylation of 3-phenyl-1,2,4-triazole 1-difluoromethyl-3-phenyl-1,2,4-triazole (**11**), 2-difluoromethyl-3-phenyl-1,2,4-triazole (**12**), and 4-difluoromethyl-3-phenyl-1,2,4-triazole (**13**)

Prepared using method A from 3-phenyl-1,2,4-triazole [14], 3.0 g, (21 mmol), DMF (25 ml), NaH (1.0 g, 25 mmol), and $CHClF_2$ to yield 3.9 g of a mixture of three compounds which were chromatographed using CH_2Cl_2 followed by CH_2Cl_2–CH_3OH (95 : 5) to afford **11**, clear oil, 2.0 g (66%), Rf = 0.1 (CH_2Cl_2), **12**. Clear oil, 0.42 g (14%), Rf = 0.3 (CH_2Cl_2), and **13**. White solid, m.p. 57–58°, 0.61 g (20%), Rf = 0.6 (CH_2Cl_2).

11, ^{1}H-NMR δ: 7.10 (*t*, 1H, $J_{H-F} = 59$ Hz), 7.52–7.65 (m, 5H), 8.59 (s, 1H). ^{19}F-NMR δ: −91.9 ($J_{F-H} = 59$ Hz). *m/z* 195, 194, 104, 89, 77, 63, and 51; *Anal*. Calc: for $C_9H_7F_2N_3$: C, 55.39; H, 3.62; N, 21.53. Found: C, 55.66; H, 3.81; N, 21.40.

12, ^{1}H-NMR δ: 7.30 (*t*, 1H, $J_{H-F} = 59$ Hz), 7.46 (m, 3H), 8.13 (m, 2H), 8.53 (s, 1H). ^{19}F-NMR δ: −96.3 ($J_{F-H} =$ 59 Hz). *m/z* 195, 168, 149, 89, 77, 63, and 51; *Anal*. Calc. for $C_9H_7F_2N_3$: C, 55.39; H, 3.62; N, 21.53. Found: C, 55.74; H, 3.92; N, 21.83. **13**, ^{1}H-NMR δ: 7.29 (*t*, 1H, $J_{H-F} = 59$ Hz), 7.48–7.75 (m, 5H), 8.08 (s, 1H). ^{19}F-NMR δ: −94.6 ($J_{F-H} =$ 59 Hz). *m/z* 195, 167, 149, 104, 89, 77, 63, and 51; *Anal*. Calc. for $C_9H_7F_2N_3$: C, 55.39; H, 3.62; N, 21.53. Found: C, 55.74; H, 3.92; N, 21.83.

4.4. Difluoromethylation of 5-phenyltetrazole using one equivalent of NaH

The reaction was run using method A from 5-phenyltetrazole (2.92 g, 20 mmol), DMF (40 ml), NaH (60% dispersion in mineral oil, 0.8 g, 20 mmol) and excess $CHClF_2$ to yield a quantitative recovery of the starting material.

4.5. Difluoromethylation of 5-phenyltetrazole using two equivalents of NaH, 1-N-difluoromethyl-5-phenyltetrazole (**15**), and 2-N-difluoromethyl-5-phenyltetrazole (**16**)

The reaction was run using method A from 5-phenyltetrazole (2.92 g, 20 mmol), DMF (40 ml), NaH (60% dispersion in mineral oil, 1.6 g, 40 mmol) and excess $CHClF_2$ to yield 3.8 g of a crude mixture which was chromatographed using ethyl acetate and heptane (1 : 4) to afford **15**, oil, 1.0 g, (26%), lower Rf and **16**; higher Rf, 1.9 g (48%) of a solid, m.p. 29–30°.

15, ^{1}H-NMR δ: 7.48 (*t*, 1H, $J_{H-F} = 56$ Hz), 7.60 (m, 3H), 7.84 (m, 2H); ^{19}F-NMR δ: −95.3 ($J_{F-H} = 56$ Hz), *m/z* 196,

154, 118, 104, 89, 77, and 63; *Anal*. Calc. for $C_8H_6F_2N_4$: C, 48.95; H, 3.08; N, 28.56. Found: C, 49.60; H, 3.38; N, 28.85. 16, ^{1}H-NMR δ: 7.69 (*t*, 1H, $J_{H-F} = 56$ Hz), 7.52 (m, 3H), 8.22 (m, 2H); ^{19}F-NMR δ: −98.4 ($J_{F-H} = 56$ Hz); *m/z* 196, 168, 149, 118, 103, 89, 77, and 63. *Anal*. Calc. for $C_8H_6F_2N_4$: C, 48.95; H, 3.08; N, 28.56. Found: C, 50.96; H, 3.54; N, 27.76.

4.6. Difluoromethylation of 5-phenyltetrazole using difluorocarbene generated in situ from methyl chlorodifluoroacetate (method b)

A mixture of 18-crown-6 (1 g), KF (0.42 g, 7.6 mmol), 5-phenyltetrazole (1.1 g, 7.6 mmol), methyl chlorodifluoroacetate (0.8 ml, 7.6 mmol), and 2-methoxyethyl ether (10 ml) was heated at 85° for 8 h. Work-up as described by Section 4.1 afforded 0.31 g (21%) of **15** and 70 mg (5%) of **16**.

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