

# An Unexpected Reaction of Trimethylsilyl Fluorosulfonyldifluoroacetate (TFDA) with Imidazoles. Formation of *N*-Difluoromethylthioureas

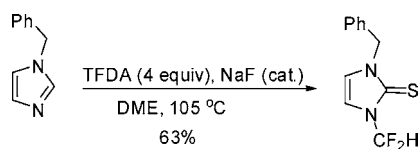
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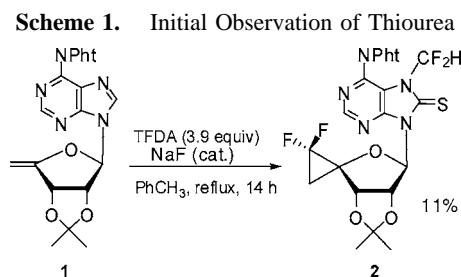
## ABSTRACT



A new reaction of the efficient difluorocarbene-generating reagent trimethylsilyl fluorosulfonyldifluoroacetate (TFDA) is reported in which molecules containing an *N*-alkylimidazole or benzimidazole structure undergo an unexpected one-pot conversion to *N*-difluoromethylthioureas.

In a search for novel inhibitors of ribonucleoside reductases,<sup>1</sup> the synthesis of spirodifluorocyclopropyl nucleoside analogues was attempted.<sup>2</sup> Our approach was to react difluorocarbene,<sup>3</sup> as generated in the usual manner from trimethylsilyl fluorosulfonyldifluoroacetate (TFDA),<sup>4</sup> with carbohydrate and nucleoside precursors having an exomethylene double bond. Unexpectedly, it was found that treatment of the protected 4',5'-unsaturated adenosine analogue **1**<sup>5</sup> with TFDA

not only led to addition of the electrophilic difluorocarbene to the electron-rich vinyl ether in the sugar moiety but also modified the adenine ring as well (Scheme 1). Column



chromatography of the complex reaction mixture led to isolation of a product (**2**), among others, that showed two sets of signals in the <sup>19</sup>F NMR spectrum: one from the expected difluorocyclopropane ring<sup>6</sup> and the second from a

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(1) For reviews on structure, function, mechanism, and inhibition of ribonucleotide reductases, critical enzymes that catalyze all new production of deoxynucleotides for DNA synthesis by reducing the corresponding ribonucleotides, see: (a) Stubbe, J.; van der Donk, W. A. *Chem. Biol.* **1995**, *2*, 793–801. (b) Eukland, H.; Uhlin, U.; Färnegårdh, M.; Logan, D. T.; Nordlund, P. *Prog. Biophys. Mol. Biol.* **2001**, *77*, 177–268. (c) Kolberg, M.; Strand, K. R.; Graff, P.; Andersson, K. K. *Biochim. Biophys. Acta* **2004**, *1699*, 1–34.

(2) For examples on the synthesis of nucleoside spirocyclopropane (unfluorinated) analogues, see: (a) Samano, V.; Robins, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 4007–4008. (b) Czernecki, S.; Mulard, L.; Valery, J.-M.; Commercon, A. *Can. J. Chem.* **1993**, *71*, 413–416. (c) Samano, V.; Robins, M. J. *Tetrahedron Lett.* **1994**, *30*, 3445–3448.

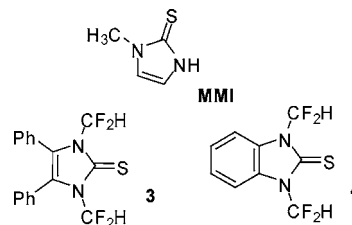
difluoromethyl group. The corresponding  $^1\text{H}$  NMR spectrum indicated that only one hydrogen remained on the adenine base, and the characteristic triplet ( $J = 58$  Hz) deriving from a  $\text{CF}_2\text{H}$  group was also present as an AB system centered at  $-100.2$  ppm.

These results suggested a “formal insertion” of difluorocarbene either at the C8 position or at the N7 nitrogen atom in the purine ring with additional modifications at C8. The mass spectrum indicated the presence of an additional sulfur atom, and on the basis of the overall spectroscopic evidence and studies of the reaction of TFDA with model imidazole systems (vide infra), including an X-ray structure determination, a thiourea entity bearing a difluoromethyl group attached at N7 was proposed as the structure of **2**. The presence of an 8-thione function was supported by a strong bathochromic shift in the UV spectrum of **2** (**1**,  $\lambda_{\text{max}}$  276 nm; **2**,  $\lambda_{\text{max}}$  319 nm), which was in agreement with literature values for 8-mercaptoadenosine derivatives that exist as the thione tautomer.<sup>7,8</sup>

The imidazole nucleus appears in a large number of naturally occurring and synthetic biologically active molecules,<sup>9</sup> and among imidazole derivatives, 1-methyl-2-mercaptoimidazole (methimazole, MMI) is commonly used as an anti-thyroid drug<sup>10,11</sup> and in the treatment of psoriasis.<sup>12</sup> MMI exists almost exclusively as the thiourea tautomer.<sup>11</sup>

There are examples in the literature of *N*-(difluoromethyl)-imidazoles and benzimidazoles,<sup>13,14</sup> but the only reports of

similar thioureas were Petko's syntheses of the 1,3-bis-(difluoromethyl)thioureas **3**<sup>15</sup> and **4** (Figure 1).<sup>16</sup>

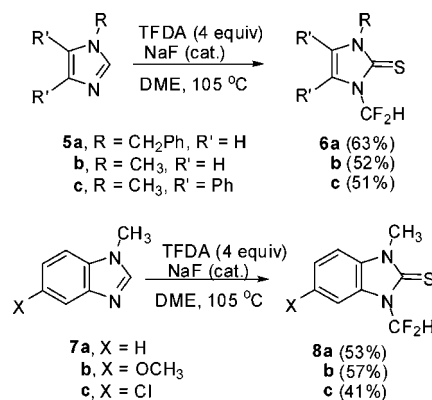


**Figure 1.** Examples of related thioureas.

Therefore we believe that there should be interest in the results that we present in this communication, where we report a general, one-pot procedure for converting *N*-alkylimidazoles and benzimidazoles to their respective *N*-alkyl-*N*-(difluoromethyl)thiourea compounds.

When 1-benzyl-1*H*-imidazole (**5a**) was allowed to react overnight with 4 equiv of TFDA in 1,2-dimethoxyethane (DME) at 105 °C, a 63% yield of 1-benzyl-3-(difluoromethyl)-1*H*-imidazole-2(3*H*)-thione (**6a**) was obtained.<sup>17</sup> The product had only two protons remaining that derived from the former imidazole ring, those appearing at  $\delta$  6.61 and 6.94 (doublets with  $J = 2.7$  Hz), whereas there was one signal in its  $^{19}\text{F}$  NMR spectrum, a doublet characteristic of a  $\text{CF}_2\text{H}$  group ( $J = 60$  Hz) appearing at  $\delta -100.4$ . X-ray crystal analysis confirmed the structure of this product to be that of **6a**. The results presented in Scheme 2 indicate

**Scheme 2.** Reactions of TFDA with Imidazoles and Benzimidazoles



that *N*-alkylimidazoles in general are good substrates for this reaction, as are *N*-alkyl benzimidazoles.

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(16) Petko, I. K.; Yagupol'skii, L. M. *J. Fluorine Chem.* **2001**, *108*, 211–214.

(17) All substrates are consumed and no other products were observed in significant yield by either  $^{19}\text{F}$  NMR of the product mixtures or as a result of column chromatography.

(3) For early reports on the synthesis of difluorocyclopropane analogues, see: (a) Nowak, I.; Robins, M. J. Bis(trifluoromethyl)mercury: New faces for an old reagent. *Abstract of Papers, Organic Divisions*, 229th National Meeting of the American Chemical Society, San Diego, CA, 13–17 March, 2005; ORGN-497. (b) Wnuk, S. F.; Rapp, M.; Mancinelli, A.; Cai, X.; Dolbier, W. R., Jr.; Robins, M. J. Spirodifluorocyclopropyl carbohydrate analogs. *Abstract of Papers, Carbohydrate Divisions*, 231th National Meeting of the American Chemical Society, Atlanta, GA, 26–30 March, 2006; CARB-74.

(4) Dolbier, W. R., Jr.; Tian, F.; Duan, J.-X.; Li, A.-R.; Ait-Mohand, S.; Bautista, O.; Buathong, S.; Baker, J. M.; Crawford, J.; Anselme, P.; Cai, X.-H.; Modzelewska, A.; Koroniak, H.; Battiste, M. A.; Chen, Q.-Y. *J. Fluorine Chem.* **2004**, *125*, 459–469.

(5) (a) Substrate **1** was prepared (76%) by reaction of 9-(2,3-*O*-isopropylidene-5-deoxy- $\beta$ -*D*-erythro-pent-4-enofuranosyl)adenine<sup>5b</sup> with phthaloyl dichloride<sup>5c</sup> in pyridine (see Supporting Information). (b) McCarthy, J. R., Jr.; Robins, R. K.; Robins, M. J. *J. Am. Chem. Soc.* **1968**, *90*, 4993–4999. (c) Phthaloyl, protection strategy has previously been used for the reaction of unsaturated amines with difluorocarbene generated from TFDA<sup>2</sup> and for the protection of 6-amino group in adenosine analogues: Beier, M.; Pfeleiderer, W. *Helv. Chim. Acta* **1999**, *82*, 633–644.

(6) The *S* stereochemistry at C4' has been tentatively assigned based on the NOESY experiments and is also in harmony with exclusive hydrogenation of the 9-(2,3-*O*-isopropylidene-5-deoxy- $\beta$ -*D*-erythro-pent-4-enofuranosyl)adenine from  $\beta$ -face.<sup>5b</sup>

(7) (a) Holmes, R. E.; Robins, R. K. *J. Am. Chem. Soc.* **1964**, *86*, 1242–1245. (b) Uesugi, S.; Ikehara, M. *J. Am. Chem. Soc.* **1977**, *99*, 3250–3253.

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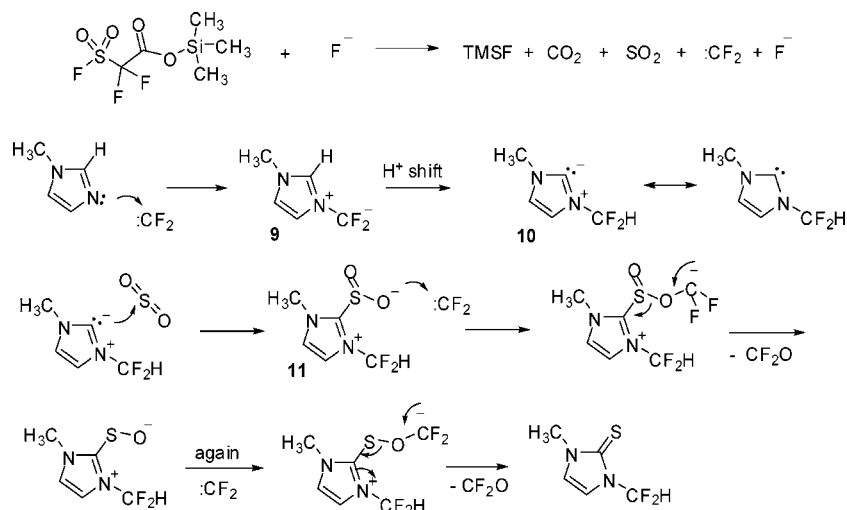
(11) Roy, G.; Muges, G. *J. Am. Chem. Soc.* **2005**, *127*, 15207–15217.

(12) Elias, A. N. *Med. Hypotheses* **2004**, *62*, 431–437.

(13) Bissky, G.; Rosenthaler, G. V.; Lork, E.; Barten, J.; Medebielle, M.; Staninets, V.; Kolomeitsev, A. A. *J. Fluorine Chem.* **2001**, *109*, 173–181.

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**Scheme 3.** Proposed Mechanism



Thus, the serendipitous discovery of this unusual reaction during our preliminary studies with an adenine system (**1**) has led to the discovery of a new and apparently general reaction of TFDA with *N*-alkylimidazoles and benzimidazoles.

Since the only source of the thione sulfur in products **6** and **8** is the  $\text{SO}_2$  that is evolved during the difluorocarbene-forming decomposition of TFDA, it is quite remarkable that products such as **6** and **8** that are totally bereft of oxygen can be obtained in decent yields, as is observed. Lacking any direct evidence for the mechanism, we nevertheless feel compelled to suggest a possible mechanism for this unprecedented reaction (Scheme 3).

TFDA releases difluorocarbene in a fluoride-catalyzed chain process in which both  $\text{CO}_2$  and  $\text{SO}_2$  are also generated.<sup>18</sup> Ylide **9** could then be formed by reaction of the difluorocarbene with the imidazole species.<sup>16,19</sup> This could be followed by a proton shift (uni- or bimolecular) to form the nucleophilic carbene **10**,<sup>20–22</sup> which could react with  $\text{SO}_2$  to form sulfinate anion **11**.<sup>23</sup> We then propose that excess

$:\text{CF}_2$  could strip the sulfinate of its oxygens in the manner shown to give the thione product plus 2 equiv of the very stable carbonyl fluoride.

The mechanism is currently under active investigation, as is the evaluation of the scope of this reaction as it might pertain to other heterocyclic systems.

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**Supporting Information Available:** Complete experimental details, including full characterization of all new compounds; ORTEP drawing of **6a**; CIF file containing X-ray structural data for compound **6a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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