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Chemoselective fluorination of 2-hydroxy-3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-ones using DAST

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ABSTRACT

In this study, diethylaminosulfur trifluoride (DAST) was successfully applied in monofluorination reactions of some trifluoromethyl substituted 2-hydroxy-2*H*-chromenones, employing a general, mild, and efficient methodology. The fluorinated compounds (2-fluoro-2*H*-chromenones) were synthesized as unique products by a chemoselective reaction in 63–81% yield despite the presence of different reactive sites subjected to reactions with DAST.

Multi-component reactions (MCRs), by virtue of their convergence, productivity, facile execution, and generally high yields of products, have attracted much attention from the vantage point of combinatorial chemistry.

Recently obtained also by MCR's, functionalized chromenes and benzopyranes are an important class of compounds, which have received considerable attention in recent years due to their wide range of biological activities. They display not only spasmolytic, diuretic, clotting, antiviral, anti-tumoral and anti-anaphylactic activities, but can also be used as pigments, photo active materials, and biodegradable agrochemicals.[1]

On the other hand, fluorine substitution can alter the chemical properties, disposition, and biological activity of drugs.[2] Many fluorinated compounds are currently widely used in the treatment of diseases. These include antidepressants, antiinflammatory agents, antimalarial drugs, antipsychotics, antiviral agents, steroids, and general anesthetics.[3] The chemistry and medicinal chemistry of fluoro-organic compounds and drugs have been reviewed.[2,4–6] The development of new fluorinating agents has vastly increased the potential for synthesis of novel fluorinated drugs. In addition, the development of sophisticated noninvasive analytical techniques based on fluorine nuclear magnetic resonance (NMR) and positron emission topography has transformed the study of fluorinated drugs in man and animals.[7]

The inclusion of a fluorine atom in a drug molecule can influence both the disposition of the drug and the interaction of the drug with its pharmacological target. For example, the effects of fluorine substitution on the inter- and intramolecular forces that affect the binding of ligands, and thus introduce the receptor subtype selectivity, at cholinergic and adrenergic receptors are now well understood.[8]

Fluorine substitution can also have a profound effect on drug disposition, in terms of distribution, drug clearance, route(s), and extent of drug metabolism.[9] Such changes can be used constructively by medicinal chemists to improve both the safety and the efficacy of a drug.

Thus, considering the importance described and based on the works previously published by us,[10,11] the aim of this work is to report a facile, efficient, and chemoselective fluorination of 2-hydroxy-2*H*-chromenones **1** using DAST.

Commercially available diethylaminosulfur trifluoride (DAST) reacts with aldehydes and ketones under mild conditions to give *geminal* difluorides,[11] while organic acids react with DAST to give acid fluorides.[12] Reaction of mono alcohols with DAST replaces the hydroxy group[13] with fluorine while reaction with diols allows isolation of difluorides, sulfite esters, or cyclic ethers.[14] In addition, reactions of propargylic ketones and acetophenone in the presence of 2 equiv of DAST furnished *gem*-difluoro derivatives.[15] α,β-Unsaturated ketones, such as 2(1*H*)-naphthalenones were converted also to *gem*-difluoro-naphathalenes by dehydroxy-fluorination using DAST.[16] Recently, a ring enlargement and contraction[17] as well as cyclization reactions of α-acylaminoketones[18] promoted by DAST were described.

Thus, considering the wide reactivity of DAST, we initially examined several possibilities of reaction in 2-hydroxy-2*H*-chromenones (**1a–e**), previously synthesized by us,[19] since there are different reactive sites present in these compounds (one hydroxyl and two carbonyl groups), offering the possibility to obtain different products, such as di- or monofluorinated, dehydrated products among others. Moreover, because of the two enolization possibilities (Fig. 1) of the ketone function at the C-5, and at the aroyl substituent attached to the C-3, the alternative dehydroxy-fluorinations cannot be ruled out.[15,16]

In an attempt to evaluate the behavior of 2-hydroxy-2*H*-chromenones (**1a–e**) in the presence of DAST, we initially carried

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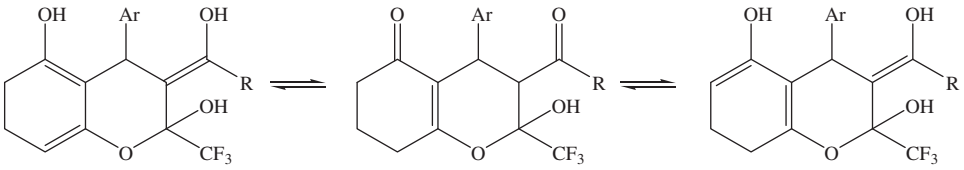
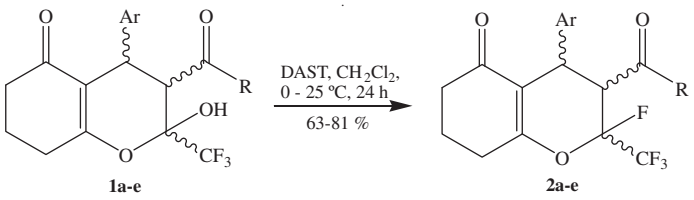


Figure 1. Tautomeric forms of chromenones **1**.



1,2	a	b	c	d	e
Ar	Ph	Ph	Ph	Ph	4-ClPh
R	Ph	4-FPh	2-furyl	2-thienyl	2-thienyl

Scheme 1.

out reactions employing DAST in a 1:2 molar ratio (excess of the DAST), in dichloromethane as a solvent, for 24 h at room temperature (Scheme 1).[20] These reactions demonstrated that only a monofluorination reaction in the 2 position occurred (**2a–e**) with 100% chemoselectivity and no other product was obtained. The products 2a–**e** were easily isolated as solids by filtration and purified by simple washing with cold ethanol, in good yields.[21]

With the goal of also promoting the difluorination reaction on the carbonyl functions present, we carried out reactions employing DAST in different molar ratios (1:3, 1:4 and 1:5), in dichloromethane as solvent, for 24, 36, and 48 h, at room temperature. However, under any condition, again only the fluorination reaction in the 2 position was observed (**2a–e**) and the presence of the difluorinated or dehydrated compounds was not observed.

Compounds **2** are constituted by a 3,4,7,8-tetrahydro- 2*H*-chromen-5(6*H*)-one ring which is the core of the structure and it has four main substituents attached: a fluorine and a trifluoromethyl group at the C2-position and an acyl and an aryl substituent at the C3- and C4-positions, respectively. The structures of compounds **2** were fully confirmed by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, MS with chemical ionization, in the positive mode (CI+), and elemental analysis.[21]

Thus, for example, compound **2b**, obtained as a yellow solid, showed a [M+1] ion peak at *m/z* 437 in the mass spectrum, according to the molecular formula $C_{23}H_{17}F_5O_3$. ^{1}H NMR spectra showed the H-3 at δ 4.5 ppm as a doublet (J = 6 Hz), characterizing the coupling with fluorine atom. The H-4 of the chromenone appeared at δ 4.0 ppm as one singlet peak. Due to the presence of the fluorine and a

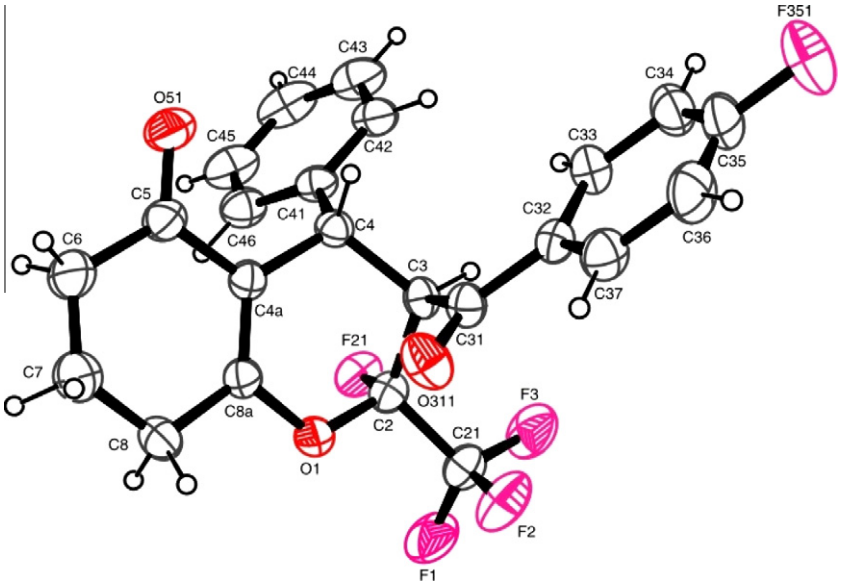


Figure 2. A perspective view of 2-fluoro-3-(4-fluorobenzoyl)-4-phenyl-2-(trifluoromethyl)- 3,4,7,8-tetra-hydro-2*H*-chromen-5(6*H*)-one (**2b**) with atoms labeled (CCDC 794627).[22] Displacement ellipsoids are drawn at 50% probability level.

CF_3 group in the C-2 position, compounds **2** presented characteristic ^{13}C chemical shifts. The C-2 exhibited signals at δ 103.7 ppm, as a characteristic doublet of quartet, with $^1J_{CF}$ = 236 Hz, $^2J_{C-CF}$ = 36 Hz, due to the attachment to a fluorine and a CF_3 group. The CF_3 group showed a signal at δ 118.6 ppm, as a quartet of doublet, with $^1J_{CF}$ = 286 Hz; $^2J_{C-CF}$ = 36 Hz. Unexpectedly and with the exception for **2a** (Ar = R), the ^{19}F NMR spectra for **2b–e** (Ar ≠ R) showed two singlets for the fluorine atom attached to the C-2 and one singlet for the CF_3 group bonded to the same carbon (C-2). Complementarily, the X-ray diffraction measurement was carried out for compound **2b** (Fig. 2)[22] proving that the fluorine atom replaced the hydroxyl group in the 2 position. In addition, this paper confirmed what had been suggested by Arbilla et al.[23] The author proposed that the mechanism by which the reaction occurred with DAST should be an SN_2 type. This fact was confirmed by us as we watched the inversion of configuration at C-2 in comparison to the spectroscopy and X-ray diffraction data for the precursors **1**.[19]

In the present Letter, we have demonstrated that using a mild and an efficient protocol for the chemoselective fluorination reaction of the 2-hydroxy-tetrahydro-2*H*-chromenones by DAST in CH_2Cl_2 at 0–25 °C for 24 h, 2-fluoro-2*H*-chromenones can be easily obtained in good yields (63–81%) and as a unique product, because no side reaction products were observed or isolated.

Unless otherwise indicated all common reagents and solvents were used as obtained from commercial suppliers without further purification. All melting points were determined on a Reichert Thermovar apparatus. ^1H, ^{13}C and ^{19}F NMR spectra were acquired on a Bruker DPX 200 spectrometer (^1H at 200.13 MHz) and Bruker DPX 400 (^{13}C at 100.32 MHz and ^{19}F at 376.3 MHz) spectrometer, 5 mm sample tubes, 298 K, digital resolution ±0.01 ppm, in $CDCl_3$, using TMS as internal reference (^1H and ^{13}C) or fluorobenzene as external reference (^{19}F). The CHN elemental analyses were performed on a Perkin Elmer 2400 CHN elemental analyzer (São Paulo University–USP/Brazil). Mass spectra were registered in a HP 5973 MSD connected to a HP 6890 GC and interfaced by a Pentium PC. The GC was equipped with a split-splitless injector, autosampler, cross-linked HP-5 capillary column (30 m, 0.32 mm of internal diameter), and He was used as the carrier gas.

Acknowledgments

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20. *Synthesis of 2-fluoro-2H-chromenones* (**2a–e**). General Procedure: To a stirred solution of **1a–e** (1 mmol) in dichloromethane (10 mL) was added dropwise DAST (2 mmol) in dichloromethane (5 mL) at 0 °C. After addition, the reaction mixture was stirred at 25 °C for 24 h, and then the reaction was quenched by the slow addition of aqueous $NaHCO_3$ solution until effervescence was completed. The dichloromethane layer was separated, dried over anhydrous Na_2CO_3, and filtered. The solvent was evaporated under reduced pressure, obtaining the corresponding compounds **2a–e**, which were isolated as solids by filtration and purified by simple washing with cold ethanol.
21. Compounds **2** were obtained as solids and were characterized by ^1H, ^{13}C and ^{19}F NMR and GC–MS. Data of 2-fluoro-3-(4-fluorobenzoyl)-4-phenyl-2-(trifluoromethyl)- 3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-one (**2b**): Yield 74%, mp 70–72 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.0–8.04 (m, 2H, Ph), 7.1–7.3 (m, 7H, Ph), 4.5 (d, 1H, *J* = 6, H-3), 4.0 (d, 1H, H-4), 2.7–2.8 (m, 2H, H-6), 2.4–2.5 (m, 2H, H-8), 2.1–2.2 (m, 2H, H-7). ^{13}C NMR ($CDCl_3$): δ = 196.2 (C=O), 191.0 (C-5), 165.6 (d, J_{C-F} = 253), 165.1 (C-8a), 140.4, 131.2, 128.6, 127.2, 121.2, 120.8, 111.8 (Ph), 118.6 (qd, CF_3, $^1J_{CF}$ = 286, $^2J_{CF}$ = 36), 106.4 (C-4a), 103.7 (dq, C-2, $^1J_{CF}$ = 236, $^2J_{CF}$ = 36), 46.2 (d, C-3, *J* = 21), 36.8 (C-6), 31.6 (C-4), 27.6 (C-8), 20.3 (C-7). ^{19}F NMR = δ (376 MHz, $CDCl_3$) −67.2 and −108.7 (CF); −81.8 (CF_3). GC–MS (CI+): *m*/*z* (%) 437 (M+1, 100), 313 (17), 217 (14), 123 (10). Anal. Calcd: C, 63.31; H, 3.93. Found: C, 63.57; H, 4.22%. Melting points and yields of new compounds **2**: Compd. [mp (°C), yield (%)]: **2a** [60–62, 63]; **2c** [88–90, 65]; **2d** [54–56, 78]; **2e** [74–76, 81];
22. Crystallographic data for the structure of **2b**, reported in this paper have been deposited with the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 794627. Copies of the data can be obtained free of charge, on application to CCDC 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.com.ac.uk).
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