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General method for dehydration, intramolecular cyclization, and fluorination of trifluoromethyl-1*H*-pyrazoles using DAST

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ABSTRACT

In this study, the versatile diethylaminosulfur trifluoride (DAST), a well-known fluorinating agent, was applied in the dehydration, intramolecular cyclization, and mono- and difluorination reactions of some 5-trifluoromethyl-1*H*-pyrazoles and 2-pyrazolines employing a general, mild, and efficient methodology. The azole precursors were synthesized from the reactions of acyclic and cyclic trifluoroacetylated enol ethers with hydrazines [NH_2NHR, where R = C_6H_5, C_6F_5, 2-Furanoyl] and showed a differentiated chemical behavior in the presence of DAST.

α,β-Unsaturated ketones with a trifluoromethyl substituent represent interesting building blocks for the synthesis of trifluoromethyl-containing compounds, especially heterocyclic systems, for example, pyrazoles, which often show high biological activities, such as anti-hyperglycemic, analgesic, anti-inflammatory, anti-pyretic, anti-bacterial, hypoglycemic, and sedative-hypnotic activities.[1]

Due to the importance of this class of compounds, since the 1980s we have been developing synthetic routes to obtain strategically substituted pyrazoles that provide possibilities for chemical derivatizations, leading to a substance, or its structural analogue, with proven applications.[2]

Fluorine occupies a unique place among all elements of the periodic classification due to its high electronegativity and its specific properties. Thus, organofluorine chemistry is of great importance, due to this singular nature of the fluorine atom, combined with the unique physical and chemical properties that fluorine imparts to compounds that contain it. The strong electronic contribution and negligible steric demands of fluorine present interesting and unusual properties. Indeed, the specific physicochemical properties of fluorinated organic compounds are of huge interest in a wide range of applications.[3,4] Consequently, organofluorine chemistry has been steadily growing and today possesses a distinctive role in highly diverse technological developments (fluoropolymers, pharmaceutical and agrochemical products, materials science, etc.).[5,6] Therefore the development of new methods to introduce fluorine into molecules is of great interest to organic and medicinal chemists.

One of the better methods to introduce a trifluoromethyl group into heterocycles is based on the trifluoromethylated building block approach. This approach relies on the trifluoroacetylation of enolethers or acetals to give, in one-step and good yields, 4-alkoxy-4-alkyl(aryl/heteroaryl)-1,1,1-trifluoroalk-3-en-2-ones which proved to be useful building blocks for the regiospecific synthesis of numerous heterocyclic compounds.[7]

Aminosulfur trifluoride reagents are an important class of fluorinating agents. Commercially available diethylaminosulfur trifluoride (DAST)[8] has been utilized more than the other aminosulfur trifluorides. DAST reacts with aldehydes and ketones under mild conditions to give geminal difluorides,[9] while organic acids react with DAST to give acid fluorides.[10] Reaction of mono alcohols with DAST replaces the hydroxy group[11] with fluorine while reaction with diols allows isolation of difluorides, sulfite esters, or cyclic ethers.[12]

In this study, a typical methodology for the fluorination of some 5-trifluoromethyl-1*H*-pyrazoles, derived from acyclic (**1a–c**) and cyclic vinyl ketones (**4**, **5**), was employed with the aim of evaluating the chemical behavior of these azoles in the presence of DAST, under mild reaction conditions.

Thus, in an effort to synthesize new fluorinated compounds with promising biological properties, in this paper we describe a synthetic strategy for dehydration, intramolecular cyclization, and fluorination of trifluoromethyl-1*H*-pyrazoles and 2-pyrazolines, using a standard methodology.

While the fluorination reactions using DAST are well known, few examples of the application of DAST as a dehydration reagent are found in the literature. Whitehead et al.[13] carried out extensive investigations into the application of aminosulfur trifluorides as reagents for the fluorodeoxygenation of organic substrates and described reactions with substrates possessing several unprotected hydroxy groups. However, this reaction needed special conditions, such as an inert atmosphere, and led to a mixture of dehydrated and fluorinated products.

In an attempt to evaluate the behavior of 4,5-dihydro-1*H*-pyrazoles (**2a–c**) in the presence of DAST, we carried out reactions

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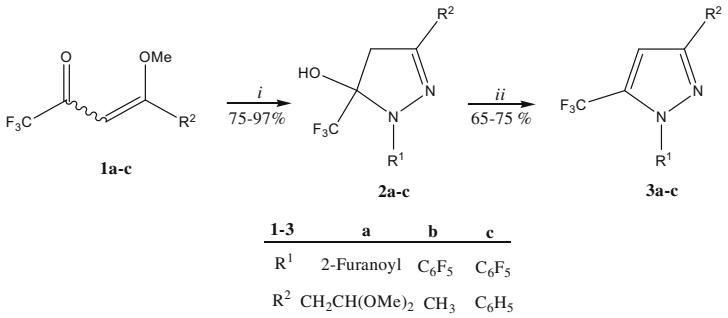


Scheme 1. Reagents and conditions: (i) NH_2NHR_1, EtOH, reflux, 20 h; (ii) DAST, CH_2Cl_2, 0–25 °C, 24 h.

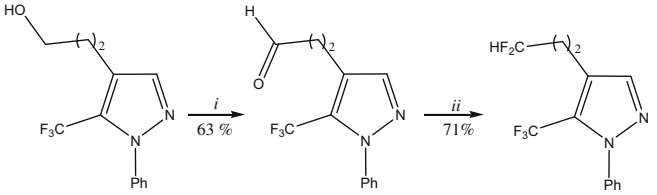
employing DAST in a 1:2 molar ratio, in dichloromethane as solvent, for 24 h at room temperature. These reactions demonstrated that only a dehydration reaction occurred (**3a–c**) and the presence of the monofluorinated compounds was not observed (Scheme 1).[14,15]

Thus, due to the relative difficulty of this type of dehydration, the present methodology was simple, mild, and efficient for the dehydration of these azoles, preventing the elimination of the N-1 substituent [C(O)–N bond cleavage] as well as, undesirable reactions on the acetal moiety of the 2-pyrazoline ring **2a**, furnishing compounds **3** in good yields (65–75%). Compounds **2a–c** were previously synthesized from the reaction of 4-methoxy-1,1,1-trifluoroalk-3-en-2-ones (**1**) with the respective hydrazines according to the procedure from the literature.[9]

Shellhamer et al.[12] demonstrated that DAST reacts with dialcohols to give difluorides, sulfite esters, or cyclic ethers depending on the number of carbons separating the alcohol functions, where semiempirical calculations indicate a preference for cyclic intermediates when four or less carbons separate the two hydroxy groups. Thus, we decided to perform reactions with previously described 4,5-dihydro-1*H*-pyrazoles (R = C_6F_5) (**6**,**7**) containing four and five carbon atoms between the two hydroxy substituents, respectively, being one primary and one tertiary alcohol (Scheme 2).

Surprisingly, when these reactions were carried out, also at a molar ratio of 1:2 (DAST excess), using dichloromethane as solvent, for 24 h, the new geminated oxacyclopyrazoles (**8**, **9**) were isolated in good yields.[14,16] The products were isolated as solids by filtration and purified by a simple washing with cold ethanol.

However, when the dehydrated azoles **10** and **11** were submitted to the same reaction condition as described above for **6** and **7**,

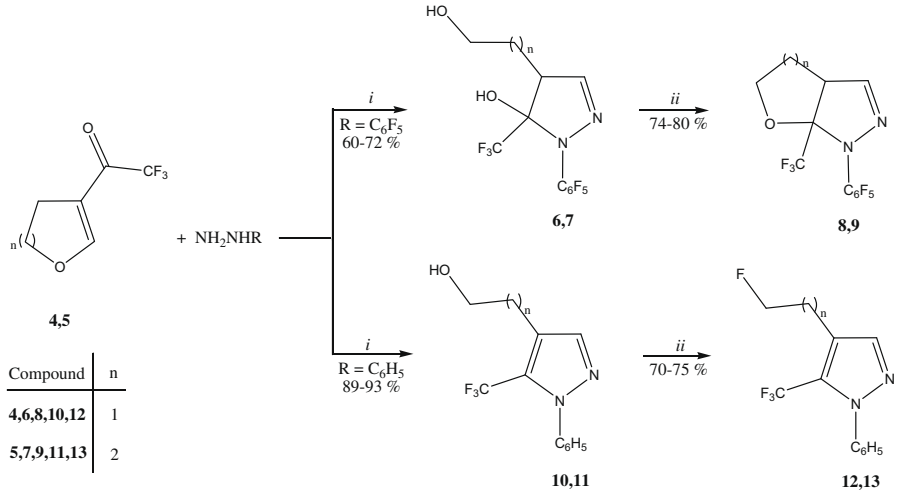


Scheme 3. Reagents and conditions: (i) PCC, CH_2Cl_2, reflux, 3 h; (ii) DAST, CH_2Cl_2, 0–25 °C, 24 h.

only fluorinated products **12** and **13** were obtained (Scheme 2), also in good yields.[14,17] The difference between the electron-withdrawing effects of phenylhydrazine and pentafluorophenylhydrazine allowed the isolation of 4,5-dihydropyrazoles **6**, **7** which reacted with DAST as alkanodiols, leading to the 5,5- and 5,6-geminated heterocycles and not to fluorinated compounds. Previously, compounds **6**, **7**, **10**, and **11** were obtained from the reactions of trifluoroacetylated pyran and furan with phenyl- and pentafluorophenylhydrazine according to the described procedure.[1]

Finally, due to the importance of the insertion of a CF_2 group into organic molecules, we carried out an alcohol oxidation reaction of compound **11** using PCC in dichloromethane,[18] which allowed the isolation of aldehyde **14** in 63% yield.[19,20] According to our previous publication,[9] after obtaining the carbonyl pyrazole **14**, a difluorination step using DAST could be carried out.

Thus, **14** reacted with DAST also in dichloromethane for 24 h at room temperature[14] leading to the desired difluorinated compound **15** in 71% yield (Scheme 3).[21]



Scheme 2. Reagents and conditions: (i) EtOH, reflux, 20 h; (ii) DAST, CH_2Cl_2, 0–25 °C, 24 h.

In conclusion, this work demonstrated that the employment of DAST in CH_2Cl_2 at 0–25 °C for 24 h is a general, mild, and efficient procedure which can promote dehydration, intramolecular cyclization, or mono- and difluorination reactions, depending on whether a hydroxy-alkyl side chain is attached to the C4 of the trifluoromethylated 5-hydroxy-2-pyrazolines and 1*H*-pyrazoles.

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. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker DPX 200 spectrometer (^{1}H at 200.13 MHz and ^{13}C at 50.32 MHz), 5 mm sample tubes, 298 K, digital resolution ±0.01 ppm, in DMSO-d_6 for **2a** and **2c**, and $CDCl_3$ for others, using TMS as internal reference. 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.

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14. *Synthesis of 5-trifluoromethyl substituted pyrazoles* (**3a–c, 8, 9, 12, 13, 15**). *General procedure*: To a stirred solution of **2a–c**, **6**, **7**, **10**, **11**, or **14** (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 **3a–c, 8, 9, 12, 13**, or **15**, which were purified following the next procedures.
15. Compounds **3** were obtained as oils (**3a–b**) or solid (**3c**). The solid was recrystallized from diethyl ether. Compounds **3a–b** were characterized by ^{1}H and ^{13}C NMR and GC–MS. Data of 3-(1,1-dimethoxyethyl)-5-trifluoromethyl-1*H*-1-(furan-2-oyl) pyrazole (**3a**): Yield 71%, oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.9 (d, 1H, J = 4.0, H-5′), 7.7 (s, 1H, H-3′), 6.8 (s, 1H, H-4), 6.60–6.68 (m, 1H, H-4′), 4.7 (t, 1H, J = 6.0, H-7), 3.4 (s, 6H, H-7a-b), 3.0 (d, 2H, J = 6.0, H-6). ^{13}C NMR ($CDCl_3$): δ 153.7 (C=O), 151.3 (C-3), 148.5 (C-2′), 144.4 (C-5′), 135.2 (q, ^2J = 41 Hz, C-5), 124.9 (C-3′), 120.5 (q, CF_3, J = 269 Hz), 113.9 (C-4′), 112.5 (C-4), 102.8 (C-7), 53.4 (C-7a-b), 32.1 (C-6). GC–MS (EI, 70 eV): *m/z* (%) 287 (20), 149 (12), 95 (93), 75 (100). Anal. Calcd: C, 49.06; H, 4.12; N, 8.80. Found: C, 48.91; H, 4.22; N, 9.19. Melting points and yields of new compounds **3**: Compd. [Mp (°C), Yield (%)]: **3b** [oil, 75]; **3c** [76–77, 65].
16. Compounds **8** and **9** were obtained as solids, and after the solvent was evaporated, the solids were washed with cold ethanol and dried under vacuum. Compounds **8** and **9** were characterized by ^{1}H and ^{13}C NMR and GC–MS. Data of 1-(pentafluorophenyl)-6a-(trifluoromethyl)-3a,4,5,6a-tetrahydro-1*H*-furo[2,3-*c*]pyrazole (**8**): Yield 80%, mp 80–81 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.8 (s, 1H, H-3), 4.2–4.3 (m, 1H, H-4, J = 8), 3.9–4.1 (m, 2H, H-7), 2.3–2.4 (m, 2H, H-6). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.8, 144.0, 140.0, 134.9 (C_6F_5), 143.2 (C-3), 125.0 (q, CF_3, J = 281), 100.7 (q, ^2J = 32, C-5), 70.7 (C-7), 56.0 (C-6), 29.7 (C-4). GC–MS (EI, 70 eV): *m/z* (%) 346 (M^+, 95), 277 (19), 181 (100), 167 (20). Anal. Calcd: C, 41.63; H, 1.75; N, 8.09. Found: C, 41.61; H, 1.72; N, 8.01. Compd. **9**: Yield 74%, mp 75–77 °C.
17. Compound **12** was obtained as oil and was characterized by ^{1}H and ^{13}C NMR and GC–MS. Data of 4-(2-fluoroethyl)-5-trifluoromethyl-1*H*-1-phenylpyrazole (**12**): Yield 70%, oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.6 (s, 1H, H-3), 7.4 (s, 5H, Ph), 4.6 (td, 2H, H-7, J_{HF} = 47, J_{HH} = 6), 2.9–3.1 (m, 2H, H-6). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7 (C-3), 139.4, 129.2, 125.8 (Ph), 127.0 (q, ^2J = 38, C-5), 121.0 (q, CF_3, J = 269), 119.5 (C-4), 82.0 (d, C-7, CF, J = 165), 25.0 (d, C-6, J = 19). GC–MS (EI, 70 eV): *m/z* (%) 258 (M^+, 52), 225 (100), 178 (5), 77 (23). Anal. Calcd: C, 55.82; H, 3.90; N, 10.85. Found: C, 55.64; H, 4.19; N, 10.83. Compd. **13:** Yield 75%, oil.
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19. *Synthesis of 4-(formylethyl)-5-trifluoromethyl-1H-1-phenylpyrazole* (**14**). *General procedure*: To a solution of 4-(3-hydroxypropyl)-5-trifluoromethyl-1*H*-1-phenylpyrazole (**11**) (2 mmol) in dichloromethane (10 mL) was added PCC (3.5 mmol) at room temperature. The reaction mixture was stirred at reflux for 3 h, and then the solvent was evaporated. Then, an aqueous NaOH solution (15 mL) was added and the mixture was extracted with diethyl ether (2 × 15 mL). The organic layer was separated, dried over anhydrous Na_2CO_3, and filtered. The solvent was evaporated, and compound **14** was obtained as an oil.
20. Compound **14** was characterized by ^{1}H and ^{13}C NMR and GC–MS. Data of 4-(formylethyl)-5-trifluoromethyl-1*H*-1-phenylpyrazole (**14**): Yield 63%, oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.8 (s, 1H, H-8), 7.5 (s, 1H, H-3), 7.4 (s, 5H, Ph), 3.0 (t, 2H, H-6, J = 7), 2.82 (t, 2H, H-7, J = 7). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.3 (C=O), 140.3 (C-3), 139.4, 129.1, 128.8, 125.1 (Ph), 128.5 (q, ^2J = 41, C5), 122.6 (C-4), 120.5 (q, CF_3, J = 270), 44.2 (C-7), 16.3 (C-6). GC–MS (EI, 70 eV): *m/z* (%) 268 (M^+, 70), 225 (50), 212 (100), 77 (48). Anal. Calcd: C, 58.21; H, 4.13; N, 10.44. Found: C, 58.47; H, 4.30; N, 10.44.
21. Compound **15** was obtained as oil and was characterized by ^{1}H and ^{13}C NMR and GC–MS. Data of 4-(1,1-difluoro-3-propyl)-5-trifluoromethyl-1*H*-1-phenylpyrazole (**15**): Yield 71%, oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.5 (s, 1H, H-3), 7.4 (s, 5H, Ph), 5.8 (tt, 1H, H-8, J_{HF} = 56, J_{HH} = 4), 2.84 (t, 2H, H-6, J = 7), 2.1–2.2 (m, 2H, H-7). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.1 (C-3), 139.0, 129.2, 128.1 (Ph), 122.0 (C-4), 127.0 (q, ^2J = 39, C-5), 122.0 (q, CF_3, J = 270), 116.0 (t, CF_2, C-8, J = 240), 35.0 (t, C-7, J = 20), 16.6 (C-6). GC–MS (EI, 70 eV): *m/z* (%) 290 (M^+, 48), 225 (100), 128 (9), 77 (20). Anal. Calcd: C, 53.80; H, 3.82; N, 9.65. Found: C, 53.67; H, 3.71; N, 9.58.