Tetrahedron Letters 50 (2009) 1392–1394

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

DAST promotes the synthesis of new 5-(trifluoromethyl)-3-(1,1-difluoroethan-2-yl)-1*H*-pyrazoles

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ARTICLE INFO

Article history:
Received 25 July 2008
Revised 30 December 2008
Accepted 6 January 2009
Available online 10 January 2009

ABSTRACT

This study describes, firstly, the synthesis of a new precursor, 4,6,6-trimethoxy-1,1,1-trifluorohex-3-en-2-one (**1**), from the trifluoroacetylation reaction of 1,1,3,3-tetramethoxybutane, in 65% yields. Afterwards, the reaction of **1** with two hydrazines (NH_2NHR, where R = 2-furanoyl, C_6F_5) led to a new series of 4,5-dihydro-1*H*-pyrazoles, containing an acetal-protected aldehyde function as substituent, in 90–97% yields. In a subsequent step, the dehydration reactions of these 4,5-dihydro-1*H*-pyrazoles gave the respective aromatic 1*H*-pyrazoles. Finally, we report the results of the deprotection reactions of the acetals to obtain the respective aldehyde function, as well as, the subsequent fluorination reaction using DAST, leading to new difluorinated derivatives in 55–60% yields.

Pyrazoles are important compounds that have many derivatives with a wide range of interesting properties, such as anti-hyperglycemic, analgesic, anti-inflammatory, anti-pyretic, anti-bacterial, and hypoglycemic and sedative-hypnotic activities.[1] Many compounds that present phenylpyrazoles in their structures are known to have significant pharmacological activities, such as Celecoxib (Celebra®), an anti-inflammatory that acts as a selective inhibitor of the enzyme prostaglandin endoperoxide synthase-2 (PGHS-2),[2] Fipronil, which belongs to a second generation of *N*-phenylpyrazoles[3] insecticides, and sildenafil citrate (Viagra®), used against erectile dysfunction.

Due to the importance of this class of compounds, since the 1980s we have developed synthetic routes to obtain strategically substituted heterocycles that provide possibilities for chemical derivatizations, leading to a substance, or its structural analogue, with proven applications.[4] The synthesis of pyrazoles that have a protected aldehyde function as an acetal moiety, obtained in a single-reaction step, deserves considerable attention, because this substituent shows great chemical potential and serves as an intermediary compound for a wide range of synthetic routes.

The presence of difluoro- and trifluoromethyl substituents in heterocycle rings is also of importance, because of the properties presented by fluorine atoms. For example, in contrast to the single replacement of a hydrogen by fluorine, the replacement of a methylene function with a difluoromethylene function (CH_2 for CF_2) can have a significant effect on both conformation and physical properties.[5] In fact, the difluoromethylene moiety has been used as an electronic mimic of labile oxygen atoms in phosphate esters (R–CF2–PO_3^{2-} ←vs R–OPO_3^{2-}). This functional group has been extensively used in the design of inhibitors of enzymes that hydrolyze or bind phosphate esters.[6] The CF_2 has been proposed as an adequate isosteric and isopolar replacement for the hydroxyl group, because of its size, electron distribution, and ability to act as a hydrogen bond acceptor.[7–9]

Various research groups are developing CF_3 containing substituted compounds, which have attracted considerable attention due to their biological and pharmacological characteristics. The influence of the trifluoromethyl substituent on physiological activity is due mainly to the increased lipophilicity of the molecules, causing greater cell permeability.[10]

Moreover, compounds that have more than one CF_3 group present in the molecule are of even greater prominence, and have been obtained fairly over the last few years. For example, 3,5-bis(trifluoromethyl) pyrazoles (BTP's)[11] are known as a new class of inhibitors of cytokine. Furthermore, these compounds have also proven useful in the treatment of autoimmune diseases and in the rejection of transplant organs.[12,13]

However, despite the importance of fluorine molecules, 1*H*-pyrazoles simultaneously containing trifluoromethyl and difluoroalkyl substituents have not yet been described. So far, our research group has conducted the introduction of fluorine atoms in heterocyclic molecules through the employment of 1,3-dielectrophile trifluoromethyl-substituted precursors from the reaction of trifluoroacetylation of enol ethers or acetals with trifluoroacetic anhydride.[14]

Due to the fact that the existing methods for direct fluorination or trifluoroacetylation of organic compounds do not always allow for the introduction of fluorine atoms at the desired position, approaches based on the use of synthetic precursors containing

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0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.01.005

fluorine are necessary. An alternate route is to use reagents that in the first step transform the substituent into a good leaving group, which will be replaced by fluorine in the second step. Within this alternative proposal, one important and widely used reagent in the fluorination of nucleosides, carbohydrates, and other organic compounds is DAST (diethylaminosulfur trifluoride).[15–17]

With the intention of carrying out future biological evaluations, it seemed desirable to develop a general method for the synthesis of trifluoromethyl- and 1,1-difluoroethan-2-yl-1*H*-pyrazoles. Thus, as an extension of our research program, we wish to report the first regiospecific preparation of the precursor 4,6,6-trimethoxy-1,1,1-trifluorohex-3-en-2-one **(1)** (Scheme 1), as well as, an alternative and efficient route to obtain new trifluoromethyl-4,5-dihydro-1*H*-pyrazoles, which contain an acetal-protected aldehyde function, as substituent. In a subsequent step, the dehydration reactions of 4,5-dihydro-1*H*-pyrazoles are reported, leading also to protected 1*H*-pyrazoles. Finally, this study reports the deprotection of the acetal function to obtain the respective carbonyl compounds and the subsequent fluorination reactions, using diethylaminosulfur trifluoride (DAST), leading to the difluorinated analogues (Scheme 2).

4,6,6-Trimethoxy-1,1,1-trifluorohex-3-en-2-one **(1)** is a readily available *CCC* synthetic block, and was prepared from the trifluoroacetylation reaction of 1,1,3,3-tetramethoxybutane, derived from 4,4-dimethoxybutan-2-one, with trifluoroacetic anhydride (Scheme 1).[21,22]

In this study, we found that 4,6,6-trimethoxy-1,1,1-trifluorohex-3-en-2-one **(1)**, when treated with hydrazines in a molar ratio of 1:1, respectively, in ethanol as solvent for 4–20 h, at reflux, produced regiospecifically 3-(1,1-dimethoxyetan-2-yl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazoles **(2a–b)** in a one-step reaction and in 90–97% yields (Scheme 2).[23,24]

The dehydration reaction of compounds **2a–b** was carried out by the methodology described by Padwa,[18] which has the advantage of obtaining heterocycles **3a–b**[25,26] while maintaining the aldehyde group in the form of an acetal and also, in our case, preventing the loss of the N1 substituent of the pyrazoline ring.

After the dehydration reaction of the 5-hydroxy-4,5-dihydro-1*H*-pyrazoles (**2a–b**), we sought to carry out the difluorination of the aromatic compounds **3a–b**. However, the desired products were not isolated. Instead, we isolated the starting material (5-trifluoromethyl-1*H*-pyrazoles) demonstrating that DAST does not react with the acetal function, even when it is connected to an aromatic heterocycle, as in the case of compounds **3a–b**. As the 5-trifluoromethyl-1*H*-pyrazoles **(3a–b)** did not react with DAST, we sought alternative routes to achieve the difluorination of these compounds. The method proposed herein is the deprotection of the acetal function of the pyrazoline ring, leading to the corresponding carbonyl compounds, and the subsequent introduction of fluorine atoms into the molecules.

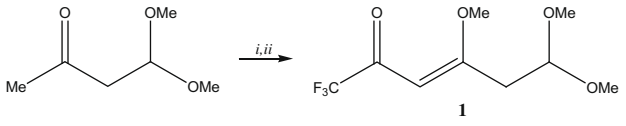
In order to isolate the carbonyl derivatives, an acetal deprotection reaction was carried out. Several methods were tested,[19] and the procedure described by Elisson et al.,[20] using trifluoroacetic acid in chloroform, showed the best results. This procedure, after optimization, allowed attainment of 3-(formylmethyl)-5-trifluoromethyl-1*H*-pyrazoles **(4a–b)** in 55–65% yields.[27,28] After obtaining carbonyl compounds **4a–b**, a difluorination step using DAST was carried out in dichloromethane, at room temperature for 24 h, leading to the isolation of difluorinated compounds 3-(1,1-difluoroethan-2-yl)-5-(trifluoromethyl)-1*H*-pyrazoles **(5a–b)** in 55–60% yields (Scheme 2).[29,30]

An important feature in the ^{1}H NMR spectra of compounds **5a–b** is the presence of a triplet in the region of 6.1–6.2 ppm, resulting from the coupling of the H-7 with two fluorine atoms, with a constant coupling of J = 55 Hz and with two hydrogen methylene atoms, with a constant coupling of J = 5 Hz. Another feature is the presence of a triplet of doublet in the region of 3.2–3.3 ppm from the coupling of the H-6 (CH_2) with two fluorine atoms (triplet with J = 17 Hz) and with the atom of hydrogen H-7 (CHF_2) (doublet with J = 5 Hz).

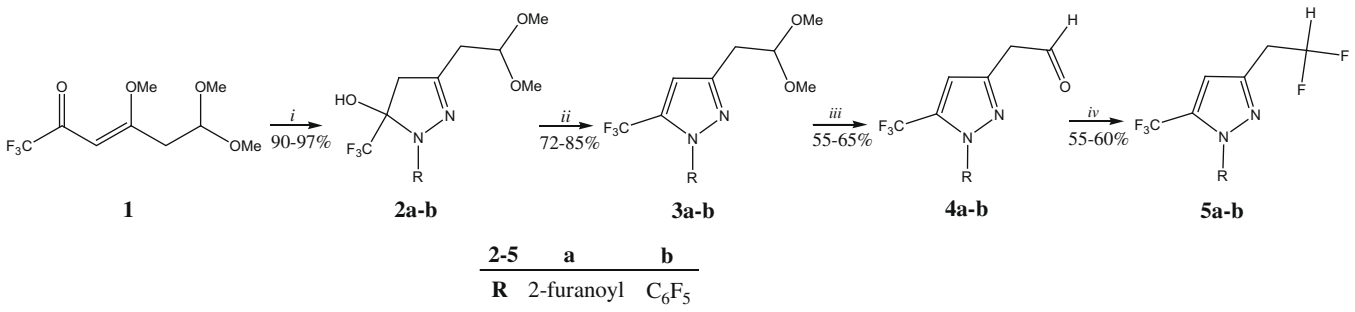
As for the ^{13}C{1H}NMR spectra for compounds **5a–b**, the presence of a triplet in the region of 114 ppm for the CHF_2 group with a constant coupling of J = 241 Hz and another triplet in the region of 33 ppm for the carbon C6, with J = 24 Hz, both resulting from the C–F coupling at the difluoroethyl substituent.

In summary, we developed the first efficient and regiospecific preparation of 4,6,6-trimethoxy-1,1,1-trifluorohex-3-en-2-one **(1)**, a new precursor for the synthesis of a novel series of 1*H*-pyrazoles (**2** and **3**), which contain an acetal-protected aldehyde function as substituent. Moreover, a synthetic procedure that allowed the regiospecific introduction of fluorine atoms was developed, leading to the simultaneous obtainment of trifluoromethyl- and difluoromethyl-substituted pyrazoles (**5**), in good yields.

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, and are uncorrected. ^{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 $CDCl_3$ for **2b**, **3a–b**, **4a–b**, **5a–b**, using TMS as internal reference. The CHN ele-



Scheme 1. Reagents and conditions: (i) =HC(OMe)$_3$, TsOH, MeOH, 24 h, rt (90%). (ii) =(CF$_3$CO)$_2$, Py, CHCl$_3$, 24 h, rt (65%).



Scheme 2. Reagents and conditions: (i) =NH$_2$NHR, EtOH, 4–20 h, reflux. (ii) =SOCl$_2$, Py, benzene, 1 h, 0–25 °C. (iii) =CF$_3$COOH, H$_2$O, CHCl$_3$, 4 h, 30 °C; (iv) =DAST, CHCl$_2$, 24 h, rt.

mental 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

The authors are thankful for the financial support from Conselho Nacional de Desenvolvimento Científico e Tecnológico—CNPq. Fellowships from Coordenação De Aperfeiçoamento de Pessoal de Nível Superior—CAPES are also acknowledged.

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21. Synthesis of 4,6,6-trimethoxy-1,1,1-trifluorohex-3-en-2-one **(1)**. General procedure: To an ice-cold stirred mixture of 1,1,3,3-tetramethoxybutane (30 mmol), pyridine (60 mmol), and anhydrous chloroform (30 mL) was added dropwise pure trifluoroacetic anhydride (60 mmol), and after completion of the slow addition, the mixture was stirred for 24 more hours at room temperature. Then, the mixture was washed with aqueous solution of hydrochloric acid 0.1 M (3 × 15 mL) and water (2 × 15 mL), and was dried with magnesium sulfate. The solvent was evaporated to give the practically pure products **3**. The pure compound was obtained by distillation under reduced pressure (65% yield).
22. Compound **1** was characterized by ^{1}H and ^{13}C NMR. Spectral NMR data of compound **1**: ^{1}H NMR ($CDCl_3$) δ = 5.7 (s, 1H, H-3), 4.7 (t, 1H, J = 6.0, H-6), 3.8 (s, 3H, H-4a), 3.3 (s, 6H, H-6a-b), 3.1 (d, 2H, J = 6.0, H-5) ^{13}C NMR ($CDCl_3$) δ = 179.6 (C-4), 178.6 (q, ^{2}J = 33, C-2), 118.2 (q, CF_3, J = 292), 101.5 (C-6), 92.2 (C-3), 56.6 (C-6a-b), 53.1 (C-4a), 37.6 (C-5).MS: m/z (%) = 211 (66), 179 (71), 141 (36), 75 (100).Anal. Calcd: C, 44.63; H, 5.41. Found: C, 44.85; H, 5.13.
23. Synthesis of 3-(1,1-dimethoxyethan-2-yl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazole **(2a–b)**. General procedure: A stirred solution of 4,6,6-trimethoxy-1,1,1-trifluorohex-3-en-2-one **(1)** (2 mmol) with hydrazine (2 mmol) in 15 mL of dry ethanol was stirred at 80 °C for 4 h **(2b)** and 20 h **(2a)**. After the reaction time, the solvent was removed under reduced pressure, and the products were dried under vacuum, and isolated as a solid **(2a)** and an oil **(2b)** (yields 90–97%).
24. Compounds **2a–b** were characterized by ^{1}H and ^{13}C NMR. Spectral NMR data of compound **2a**: ^{1}H NMR (DMSO) δ = 7.9 (s, 1H, OH), 7.9 (s, 1H, H-5′), 7.5 (d, 1H, J = 3.0, H-3′), 6.7 (m, 1H, H-4'), 4.7 (t, 1H, J = 6.0, H-7), 3.4 (d, 1H, J = 19, H-4a), 3.3 (s, 6H, H-7a-b), 3.1 (d, 1H, J = 19, H-4b), 2.7 (d, 2H, J = 6.0, H-6). ^{13}C NMR (DMSO) δ = 155.2 (C=O), 154,1 (C-3), 146.6 (C-2′), 145.4 (C-5′), 123.3 (q, CF_3, J = 286), 120.1 (C-3′), 111.8 (C-4′), 101.1 (C-7), 91.3 (q, ^{2}J = 33, C-5), 52.9 (C-7a-b), 46.3 (C-4), 32.2 (C-6).MS: m/z (%) = 305 (20), 95 (97), 75 (100), 47 (47).Anal. Calcd: C, 46.43; H, 4.50; N, 8.33. Found: C, 46.95; H, 4.46; N, 8.49.Melting points and yields of new compounds **2**: Compd. [Mp (°C), Yield (%)]: Compound **2a** [120–122, 97]; Compound **2b** [oil, 90].Melting points and yields of new compounds **2**: **Compd.** [Mp (°C), Yield (%)]: Compound **2a** [(120–122), 97]; **2b** [(oil), 90].
25. Synthesis of 3-(1,1-dimethoxyethan-2-yl)-5-trifluoromethyl-1*H*-pyrazole **(3a–b)**. General procedure: A solution of 3-(1,1-dimethoxyethan-2-yl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazole **(2a–b)** (2.6 mmol) and pyridine (33.8 mmol) in 50 mL of benzene was cooled to 0 °C, and thionyl chloride (16.8 mmol) diluted in 25 mL of benzene was added dropwise over 10 min. The solution was stirred for an additional 30 min, during which time the temperature was allowed to rise to 20 °C. The mixture was then heated under reflux (bath temperature 80 °C) for 1 h, and was then filtered to remove the pyridine hydrochloride at room temperature. The solution was washed twice with water and dried over sodium sulfate. The solvent was evaporated, obtaining dark oils as pure compounds **(3a–b)**. (yields 75–85%).
26. Compounds **3a–b** were characterized by ^{1}H and ^{13}C NMR. Spectral NMR data of compound **3a**: ^{1}H NMR ($CDCl_3$) δ = 7.9 (d, 1H, J = 4.0, H-5′), 7.7 (s, 1H, H-3′), 6.8 (s, 1H, H-4), 6.6 (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, ^{2}J = 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).MS: 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.Yields of new compounds **3**: Compd. [Mp (°C), Yield (%)]: Compound **3a** [oil, 75]; Compound **3b** [oil, 85].
27. Synthesis of 3-(formylmethyl)-5-trifluoromethyl-1*H*-pyrazole **(4a–b)**. General procedure: A stirred solution of 3-(1,1-dimethoxyethan-2-yl)-5-trifluoromethyl-1*H*-pyrazole **(3a–b)** (2 mmol) in 8 mL of chloroform is added to an 4 mL aqueous solution of trifluoroacetic acid (1:1). The solution was stirred for 4 h at 30 °C, and was then washed twice with water and dried over sodium sulfate. The solvent was evaporated, obtaining a yellow solid **(4a)** or a dark oil **(4b),** as pure compounds.
28. Compounds **4a–b** were characterized by ^{1}H and ^{13}C NMR. Spectral NMR data of compound **4a**: ^{1}H NMR ($CDCl_3$) δ = 9.9 (t, 1H, J = 2.0, H-7), 7.9 (d, 1H, J = 4.0, H-5′), 7.7 (s, 1H, H-3′), 6.9 (s, 1H, H-4), 6.6 (m, 1H, H-4′), 3.9 (d, 2H, J = 2.0, H-6).). ^{13}C NMR ($CDCl_3$) δ = 196.2 (CH=O, C-7), 153.6 (C=O), 148.9 (C-3), 147.1 (C-2′), 144.2 (C-5′), 135.7 (q, ^{2}J = 41, C-5), 125.2 (C-3′), 120.8 (q, CF_3, J = 269), 113.8 (C-4′), 112.7 (C-4), 42.5 (C-6).MS: m/z (%) = 244 (10), 216 (4), 95 (100).Anal. Calcd: C, 48.54; H, 2.59; N, 10.29. Found: C, 48.63; H, 2.78; N, 10.04.Melting points and yields of new compounds **4**: Compd. [Mp (°C), Yield (%)]: Compound **4a** [123–124, 55]; Compound **4b** [oil, 65].
29. Synthesis of substituted 3-(1,1-difluoroethan-2-yl)-5-(trifluoromethyl)-1*H*-pyrazoles **(5a–b)**. General procedure: To a stirred solution of 3-(formylmethyl)-5-trifluoromethyl-1*H*-pyrazole **(4a–b)** (2 mmol) in dichloromethane (10 mL) was added dropwise DAST (4 mmol) in dichloromethane (5 mL) at −5 °C. 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 complete. The dichloromethane layer was separated, dried over anhydrous $NaCO_3$, and filtered. The solvent was evaporated, obtaining a yellow solid **(5a)** and dark oil **(5b)**. Compound **5a** was recrystallized from diethylether and compound **5b** was purified by chromatography on silica, using an ethyl acetate and hexane mixture.
30. Compounds **5a–b** were characterized by ^{1}H and ^{13}C NMR. Spectral NMR data of compound **5a**: ^{1}H NMR ($CDCl_3$) δ = 7.8 (d, 1H, J = 4.0, H-5′), 7.8 (s, 1H, H-3′), 6.9 (s, 1H, H-4), 6.6 (m, 1H, H-4′), 6.2 (1H, tt, J_{HF} = 55, J_{HH} = 5.0, CHF), 3.3 (2H, td, J_{HF} = 17, J_{HH} = 5.0, H-6). ^{13}C NMR ($CDCl_3$) δ = 153.6 (C=O), 148.9 (C-3), 147.3 (C-2′), 144.2 (C-5′), 135.8 (q, ^{2}J = 41, C-5), 125.2 (C-3′), 119.8 (q, CF_3, J = 269), 114.6 (t, CF_2, J = 241), 113.6 (C-4), 112.7 (C-4′), 33.7 (C-6).MS: m/z (%) = 294 (M^+, 5), 266 (70), 188 (5), 95 (100).Anal. Calcd: C, 44.91; H, 2.40; N, 9.52. Found: C, 44.63; H, 2.51; N, 9.47.Melting points and yields of new compounds **5**: Compd. [Mp (°C), Yield (%)]: Compound **5a** [128–130, 55]; Compound **5b** [oil, 60].