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Synthesis of 4-trifluoromethyl-1,2,4-trioxanes, simplified analogues of Artemisinin

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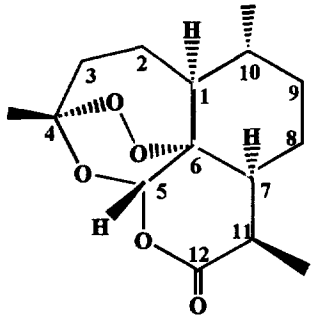
Abstract

A short synthesis of C_4 trifluoro-substituted 1,2,4-trioxanes with antimalarial potential is reported. This is the first example using a trifluorosilylated enol ether function as a protective group for a trifluoromethyl carbonyl.

Keywords: Fluorinated-1,2,4-trioxanes; Silyl enol ether; Wittig homologation

1. Introduction



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Artemisinin 1 is the active principle of the Chinese medicinal Quinghaosu (*Artemisia annua* L.) [1] and presents a significant antimalarial activity against chloroquino-resistant malaria [2].

Owing to its poor solubility in both oil and water [3], and because the introduction of fluorine into molecules modifies the physiological activity of the resulting compounds, the development of fluorinated analogues has received increasing attention in recent years. In this way, Pu et al. [4] prepared several Artemisinin derivatives by introduction of fluorine atoms on C_9, C_{10} and C_{12}. More recently, Abouabdellah et al. [5] synthesised fluorinated hemiketal analogues by the reaction of Ruppert et al.'s reagent [6] ($TMSCF_3$) on Artemisinin. In the great majority of cases, the fluorinated analogues presented higher activities than non-fluorinated derivatives.

In continuing our efforts [7,8] to find new antimalarial agents, we have synthesised two epimeric fluorinated 1,2,4-trioxanes **2** in six steps by reaction of singlet oxygen on enol ethers containing a trifluoromethylketone function (Scheme 1). We postulated that the presence of the electron withdrawing group could increase the stability of the 1,2,4-trioxane ring which is crucial for biological activity.

2. Results and discussion

The trifluoromethylketone **3** was prepared from the corresponding carboxylic acid sodium salt according to the methodology of Boivin et al. [9] in 68% yield. To protect the trifluoromethylketone which was reactive towards phosphorus ylides, we prepared the silylated enol ether **4** by the use of lithium diisopropylamide (LDA) and *tert*-butyldimethylsilylchloride (TBDMSCl) [10]. Oxidative deprotection of the cyclic carbonyl was achieved with $HgCl_2$ and was compatible with the presence of a silylated enol ether function (89% yield based on **4**). Wittig homologation followed by quantitative regeneration of the trifluoromethylketone led to *Z* and *E* enol ethers **7** precursors of 1,2,4-trioxanes **2**. Photooxygenation of a mixture of **7Z** and **7E** [1] followed by

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[1] Photooxygenation of *Z* and *E* enol ethers led to same 1,2,4-trioxanes in approximately the same yield.

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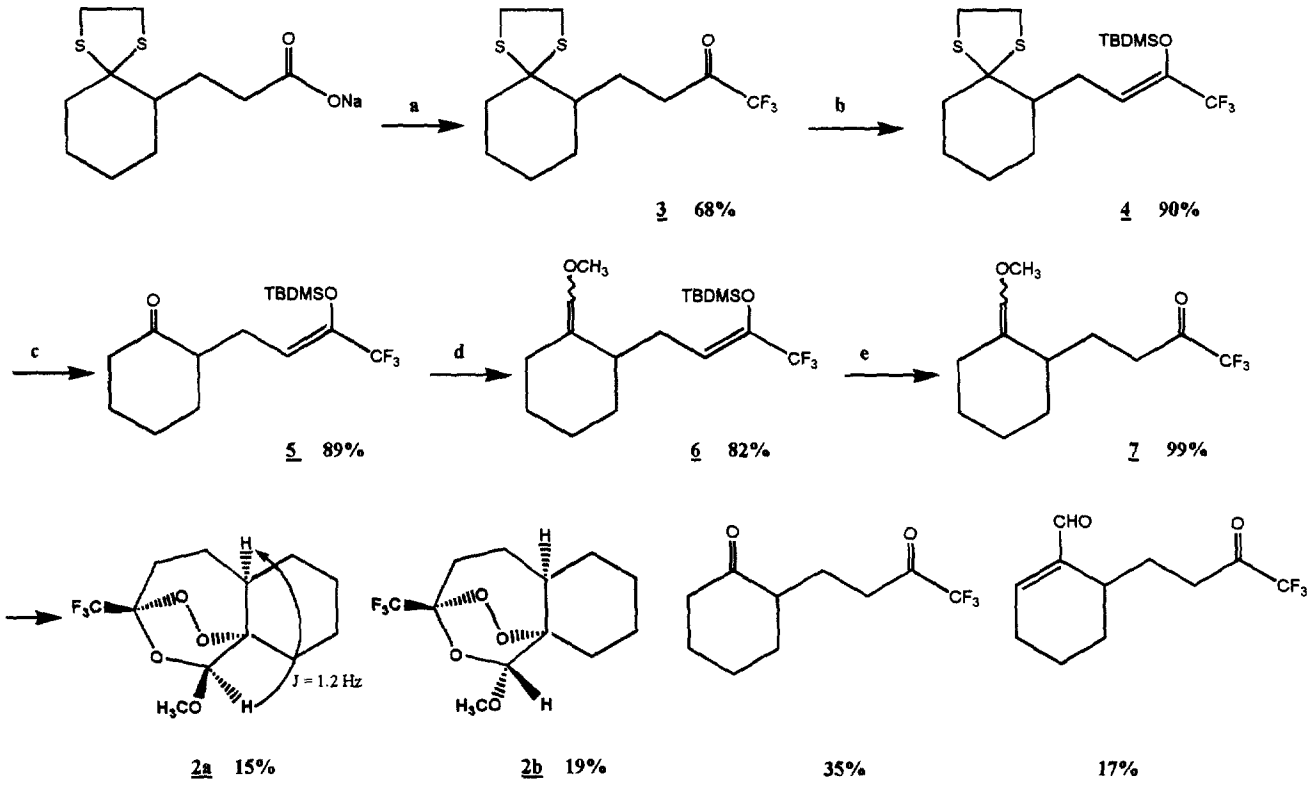

a) TFAA, Pyridine then H_2O b) LDA, TBDMSCl c) $HgCl_2$ d) PPh_3CHOMe e) TBAF f) $^1O_2$, Amberlyst 15

Scheme 1.

Amberlyst-catalyzed rearrangement led to the desired 1,2,4-trioxanes **2a** and **2b** in 15 and 19% yield respectively, 17% of the unsaturated aldehyde derived from *ene* reaction and 35% of the diketone which came from scission of the intermediate 1,2-dioxetane.

To our knowledge, this short synthesis is the first example using a trifluoro-silylated enol ether function to temporarily block a α-trifluoromethyl substituted carbonyl. This methodology permitted the synthesis in fair to good yields of two epimeric 1,2,4-trioxanes substituted on C_4 with antimalarial potential. Biological studies are in progress.

3. Experimental details

3.1. General

^1H NMR and ^{19}F spectra were recorded on a Brüker AC 200 (200.13 MHz) spectrometer and are reported in δ units (ppm) with TMS and CF_3Cl as external standards and $CDCl_3$ or benzene as solvents. Elemental analyses were performed on a Perkin-Elmer 2400 analyzer. Column chromatographies were carried out on silica gel (Merck, 230–400 mesh) using light petroleum ether (b.p. 45–65°C) and ethyl acetate as eluents.

3.2. 4-(1,4-Dithiaspiro[4,5]decan-6-yl)-1,1,1-trifluorobutan-2-one 3

3 was prepared according to literature [9] in 68% yield. ^1H NMR ($CDCl_3$) δ: 0.95–1.90 (m, 7H); 2.05–2.40 (m, 4H); 2.60–2.80 (m, 2H); 3.00–3.20 (m, 4H). ^{19}F NMR ($CDCl_3$) δ: −79.30. Anal. Calcd for $C_{12}F_3H_{17}OS_2$: C, 48.32; H, 5.70. Found: C, 48.50; H, 5.80%.

3.3. 2-(Tert-butyldimethylsilyloxy)-4-(1,4-dithiaspiro-[4,5]decan-6-yl)-1,1,1-trifluoro-but-2-ene 4

To a (THF/HMPA: 1/2) solution (30 ml) of 10 mmol of LDA prepared from $(i\text{-Pr})_2NH$ (1.01 g) and 1.6M BuLi/hexane (6.25 ml) was added at −78°C, 10 mmol (2.98 g) of **3** in THF/HMPA. After 5 min, 10 mmol (1.51 g) of TBDMSCl in solution in THF/HMPA were added on the resulting solution. The mixture was allowed to warm to 20°C and washed with a saturated $NaHCO_3$ solution. Extraction was achieved with pentane and organic layers concentrated in vacuo. Flash chromatography on silica gel yielded **4** (3.71 g, 90%). ^1H NMR (C_6D_6) δ: 0.30 (s, 6H); 1.10 (s, 9H); 0.90–1.30 (m, 3H); 1.50–2.00 (m, 6H); 2.20–2.50 (m, 2H), 2.85–2.90 (m, 4H); 5.50 (dd, J=8.5 Hz, J=5.6 Hz, 1H). ^{19}F NMR (C_6D_6) δ: −70.60. Anal. Calcd. for $C_{18}F_3H_{31}OS_2Si$: C, 52.43; H, 7.52. Found: C, 52.31; H, 7.49%.

3.4. 2-[3-(Tert-butyldimethylsilyloxy)-4,4,4-trifluorobut-2-en-1-yl]cyclohexan-1-one 5

The following were stirred at room temperature for 12 h in 20 ml of (CH_3CN/H_2O: 85/15): 4.85 mmol (2 g) of **4**, 14.55 mmol of $HgCl_2$ (3.95 g) and a catalytic amount of BF_3–Et_2O. The solution was then extracted with pentane and concentrated in vacuo. Flash chromatography on silica gel yielded **5** (1.44 g, 89%). ^1H NMR (C_6D_6) δ: 0.15 (s, 6H); 0.90 (s, 9H); 0.85–2.20 (m, 10H); 2.50–2.60 (m, 1H); 5.40 (t, $J=7.6$ Hz, 1H). ^{19}F NMR (C_6D_6) δ: −70.70. Anal. Calcd for $C_{16}F_3H_{27}O_2Si$: C, 57.14; H, 8.04. Found: C, 56.97; H, 8.01%.

3.5. 4-[2-(Methoxymethylidene)cyclohexyl]2-(tert-butyldimethylsilyloxy)-1,1,1-tri-fluoro-but-2-ene 6

Under argon, a solution of methoxymethyltriphenyl phosphonium chloride (1.5 g 4.37 mmol) in THF (30 ml) was stirred at 0°C for 20 min with potassium hexamethyldisilylamide (KHMDS) (8.74 ml 0.5 M). Then, 1.32 g (3.93 mmol) of **5** in THF (20 ml) was added to the resulting mixture. After 2 h, hexane (30 ml) was added and removal of the precipitate by filtration over Celite gave a solution, which was concentrated in vacuo. Flash chromatography on silica gel yielded **6Z** and **6E** (1.27 g 82%) which could not be separated and clearly identified but integration of the mixture by ^1H NMR indicated a 4:1 ratio. ^1H NMR (C_6D_6) δ: 0.15 (s, 6H); 1.10 (s, 9H); 1.05–2.60 (m, 11H); 3.18 (s, 0.6H); 3.24 (s, 2.4H); 5.70–5.80 (t, $J=7.6$ Hz, 1H); 5.82 (s, 0.2H); 5.86 (s, 0.8H). ^{19}F NMR (C_6D_6) δ: −70.51 (minor isomer); −70.53 (major isomer). Anal. Calcd. for $C_{18}F_3H_{31}O_2Si$: C, 59.34; H, 8.52. Found: C, 59.29; H, 8.40%.

3.6. 4-[2-(Methoxymethylidene)cyclohexyl]-1,1,1-trifluorobutan-2-one 7

One gram (2.74 mmol) of **6** and 0.86 g (2.74 mmol) of tetrabutylammonium fluoride trihydrate were stirred for 1 min in THF (5 ml) at room temperature. Then 5 ml of H_2O was added and the resulting solution was extracted with ether and organic layers were concentrated in vacuo. Flash chromatography on silica gel yielded **7** (0.68 g 99%). ^1H NMR (C_6D_6) δ: 1.20–2.20 (m, 11H); 2.30–2.70 (m, 2H); 3.20 (s, 3H); 5.50 (s, 0.8H); 5.65 (s, 0.2H). ^{19}F NMR (C_6D_6) δ: −79.05 (minor isomer); −79.20 (major isomer). Anal. Calcd. for $C_{12}F_3H_{17}O_2$: C, 57.60; H, 6.80. Found: C, 57.44; H, 6.80%.

3.7. 12-Methoxy-9-trifluoromethyl-10,11,13-trioxatricyclo[7.2.2.$0^{1,6}$]tridecane 2a and 2b

Three hundred milligrams (1.2 mmol) of **7** and Methylene Blue (2 mg) in CH_2Cl_2 (15 ml) were photooxygenated at −78°C for 1 h. Amberlyst-15 (50 mg) was added to the resulting mixture which was then stirred for 24 h at −55°C. Removal of the catalyst by filtration and purification by flash chromatography afforded **2a** (48 mg 15%) and **2b** (61 mg 19%). **2a** ^1H NMR ($CDCl_3$) δ: 1.00–1.95 (m, 10H); 2.20–2.40 (m, 2H); 3.56 (s, 3H); 5.06 (d, $J=1.2$ Hz, 1H). ^{19}F NMR ($CDCl_3$) δ: −83.65. Anal. Calcd. for $C_{12}F_3H_{17}O_4$: C, 51.06; H, 6.03. Found: C, 51.00; H, 5.96%.

2b ^1H NMR ($CDCl_3$) δ: 1.00–2.05 (m, 2H); 2.10–2.45 (m, 3H); 3.58 (s, 3H); 5.12 (s, 1H). ^{19}F NMR ($CDCl_3$) δ: −83.67. Anal. Calcd for $C_{12}F_3H_{17}O_4$: C, 51.06; H, 6.03. Found: C, 50.85; H, 5.86%.

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