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THE REACTION OF β-DICARBONYL COMPOUNDS WITH TRIFLUOROMETHYLSULPHENYL CHLORIDE.*
PART II. THE SYNTHESIS OF 3-SCF_3 SUBSTITUTED 2- AND 4-QUINOLINONES.

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SUMMARY

3-SCF_3 substituted 4-methyl-2(1H)-, 4-phenyl-2(1H)-, 2-methyl-4(1H)-, and 2-phenyl-4(1H)-quinolinones were obtained by cyclization of the respective -SCF_3 submitted acetoacetanilides or benzoylacetanilides or their β-phenylimino analogues in concentrated sulphuric acid upon heating. The structures of the compounds obtained were elucidated by elemental analysis and their IR, ^1H and ^{19}F NMR, and mass spectra.

INTRODUCTION

Trifluoromethylthio- substituted heterocycles have been proved interesting both from biological [1] and chemical [2, 3, 4, 5] points of view. They are usually obtained by the reaction of trifluoromethylsulphenyl chloride with the parent heterocycles. Such electrophilic substitution goes relatively smoothly for five-membered rings but is very difficult in the case of six-membered heterocycles, e.g. pyridine.

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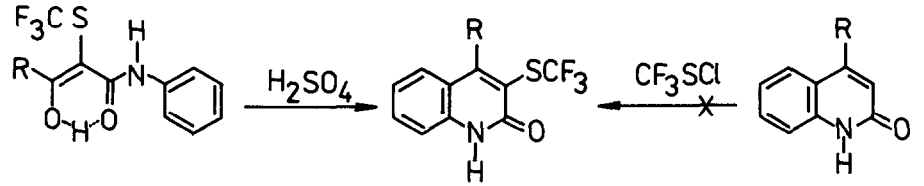
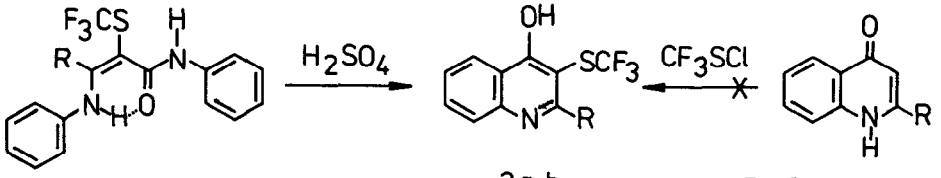
RESULTS AND DISCUSSION

In order to eliminate the synthetical problems, I have used $-SCF_3$ substituted derivatives of β-keto acids, described in the first part of this series [6] and cyclized them to the respective 3-SCF_3 substituted quinolinone derivatives:



1a,b



2a,b

a R= CH_3

b R = C_6H_5

Scheme 1

All the attempts to carry out the reaction of phenyl- and methyl- derivatives of 2(1H)- and 4(1H)-quinolinones with CF_3SCl were unsuccessful even when triethylamine or pyridine were used to trap hydrogen chloride.

The cyclization of acetoacetanilide to 4-methyl-2(1H)quinolinone [7], benzoylacetanilide to 4-phenyl-2(1H)quinolinone [8], ethyl β-(phenylamino)crotonate to 2-methyl-4(1H)quinolinone [9], and ethyl β-(phenylamino)cinnamate to 2-phenyl-4(1H)-quinolinone [10] are well known in the literature [11]. The influence of acidic catalysts on quinolinone cyclization was also discussed [12]. Better results were obtained when polyphosphoric acid was used instead of concentrated sulphuric acid. In the case of $-SCF_3$ substituted derivatives of β-keto acids

polyphosphoric acid cannot be used because they are completely insoluble in this cyclizing agent even upon heating. So I used hot concentrated sulphuric acid to cyclize α-(trifluoromethylthio)acetoacetanilide to 3-(trifluoromethylthio)-4-methyl-2(1H)-quinolinone 1a, α-(trifluoromethylthio)benzoylacetanilide to 3-(trifluoromethylthio)-4-phenyl-2(1H)quinolinone 1b, α-(trifluoromethylthio)-β-(phenylamino)crotonanilide to 2-methyl-3-(trifluoromethylthio)-4(1H)quinolinone 2a, and α-(trifluoromethylthio)-β-(phenylamino)cinnamanilide to 2-phenyl-3-(trifluoromethylthio)-4(1H)quinolinone 2b respectively. This resulted in some loss of the products mentioned that was caused by the slight decomposition of starting materials to α-(trifluoromethylthio)acetone and ω-(trifluoromethylthio)acetophenone respectively. Lower temperature of cyclization in order to avoid this decomposition leads also to lower yields of the products.

Compounds 1a - 2b are stable species that sublime easily and show intensive molecular ions in their mass spectra. Their structure was fully confirmed also by elemental analysis, IR, ^{1}H, and ^{19}F NMR spectra. Spectral data for compounds 2a and 2b, i. e. the lack of NH signals in ^{1}H NMR spectra and the lack of C=O stretching vibrations in IR spectra show the usual interesting feature of that type of compound. They are present mainly as quinolinones, whereas quinoline derivatives unsubstituted in position 3 but with oxygen at C-2 or C-4 exist practically entirely in the carbonyl form [13].

EXPERIMENTAL

Melting points are not corrected. ^{1}H NMR spectra were recorded in DMSO-d_6 with TMS as internal standard on Tesla 100 MHz spectrometer. ^{19}F NMR spectra were taken in pyridine with C_6F_6 as internal standard on Bruker HX 60/5 for compounds 1a and 1b and in $CDCl_3$ with C_6F_6 as internal standard on Bruker WP 80 for compounds 2a and 2b. Positive values of chemical shift are given upfield from $CFCl_3$. IR spectra were measured in KBr pellets on Zeiss UR 10 apparatus. Mass spectra were recorded at 70 eV on LKB 2091 spectrometer for compounds 1a, 1b, and 2b, and on Varian CH 5 MAT spectrometer for compound 2a; m/z, relative abundance in % and supposed assignment are given.

3-(Trifluoromethylthio)-4-methyl-2(1H)quinolinone 1a

α-(Trifluoromethylthio)acetoacetanilide (1.0 g, 3.6 mmole) was dissolved in 5 ccm of concentrated sulphuric acid and the mixture was heated at 80 - 90°C for 15 minutes. The dark solution was then poured into 50 ccm of stirred cold water and the product 1a was filtered off (0.7 g, 77% yield) and crystallized from methanol or acetone to give colourless needles, m.p.: 236 - 236.5°C.
Analysis calc. for $C_{11}H_8F_3NOS$ (259.240): 51.0% C, 3.1% H, 5.4% N, 12.4% S; found 51.1% C, 3.0% H, 5.5% N, 12.5% S.
^1H NMR δ [ppm]: 2.85, s, 3H, CH_3; 7.25 - 8.0, m, 4H, aromatic; 12.25, m, 1H, NH.
^{19}F NMR δ [ppm]: 41.4, m, SCF_3.
IR ν [cm^{-1}]: 3550 - 3350 vw, b, 3300 vw, 3200 - 2500 b, 1640 - 1660 s, b, 1170, 1130 - 1090 s.
MS: 259, 100.0, M^+; 240, 8.0; 190, 61.8; 162, 41.2; 161, 6.4; 160, 4.5; 146, 34.0; 130, 33.2; 128, 38.0; 118, 16.1; 117, 14.3; 116, 4.5; 103, 11.6; 102, 11.3; 101, 8.2; 93, 3.5; 89, 10.6; 77, 22.5; 69, 24.9, CF_3^+; 52, 5.8; 51, 11.5; 50, 6.8; 39, 10.7; 38, 4.1; 28, 4.1 .

3-(Trifluoromethylthio)-4-phenyl-2(1H)quinolinone 1b

α-(Trifluoromethylthio)benzoylacetanilide (10.9 g, 32.1 mmole) was dissolved in 25 ccm of concentrated sulphuric acid and the mixture was heated with stirring at 90°C for 5 minutes and then at 70 - 80°C for 25 minutes. After cooling the dark solution was poured into cold water and the precipitate of product 1b was filtered off, washed with 20% water solution of potassium hydroxide, then with water (4.4 g, 43% yield) and crystallized from methanol giving colourless needles, m.p.: 240 - 241°C. Analysis calc. for $C_{16}H_{10}F_3NOS$ (321.306): 59.8% C, 3.1% H, 4.4% N, 10.0% S; found: 59.7% C, 3.2% H, 4.5% N, 9.9% S.
^1H NMR δ [ppm]: 7.0 - 7.8, m, 9H, aromatic; 12.5 broad s, 1H, NH.
^{19}F NMR δ [ppm]: 40.9, m, SCF_3.
IR ν [cm^{-1}]: 3550 - 3350 vw, b, 3330 - 2600 b, 1640 - 60 vs, b, 1170, 1160, 1130, 1105 s.
MS: 321, 100.0, M^+; 254, 7.4; 252, 97.3; 234, 79.3; 223, 22.5; 222, 14.9; 219, 5.0; 218, 4.3; 197, 5.6; 196, 5.3; 195, 5.3;

190, 26.1; 178, 4.1; 165, 23.8; 164, 8.3; 163, 9.9; 157, 8.7; 152, 5.4; 139, 4.8; 126, 5.7; 117, 5.1; 112, 6.5; 104, 5.9; 102, 4.8; 93, 4.0; 89, 6.4; 77, 8.5; 69, 36.3, CF_3^+; 51, 11.0; 39, 10.3; 28, 3.9 .

2-Methyl-3-(trifluoromethylthio)-4(1H)quinolinone 2a

α-(Trifluoromethylthio)-β-(phenylamino)crotonanilide (5.0 g, 2.84 mmole) was dissolved in 25 ccm of concentrated sulphuric acid and heated at 50 - 60°C for 30 minutes. After cooling the solution was poured into 250 ccm of cold water and the precipitate of product 2a was filtered off (2.0 g, 54% yield). Extraction of the acidic filtrate with ether gave 0.15 g of trifluoromethylthioacetone [6] and repeated extraction after basification yielded 0.95 g of aniline. Both compounds were identified by their IR spectra. After purification of the precipitate by sublimation under reduced pressure colourless plates of 2a were obtained, m.p.: 337-9°C. Analysis calc. for $C_{11}H_8F_3NOS$ (259.240): 51.0% C, 3.1% H, 5.4% N, 12.4% S; found 51.0% C, 3.2% H, 5.5% N, 12.5% S.
IR ν [cm^{-1}]: 3600 - 3350 b, 3260 m, 3220 m, 3200 - 2580 s, b, 1620 s, 1560 s, b, 1160 - 1110 vs, b.
MS: 257, 17.6, M^+ - 2H; 237, 4.4; 173, 4.4; 161, 13.2; 146, 47.1; 130, 5.9; 129, 5.9; 128, 5.9; 120, 11.7; 118, 20.5; 117, 14.7; 102, 8.8; 89, 8.8; 77, 55.9; 76, 38.2; 75, 16.2; 74, 10.2; 69, 100.0, CF_3^+; 65, 11.7; 64, 20.5; 63, 30.9; 51, 30.9;50, 75.0.

2-Phenyl-3-(trifluoromethylthio)-4(1H)quinolinone 2b

α-(Trifluoromethylthio)-β-(phenylamino)cinnamanilide (9.0 g, 21.7 mmole) was dissolved in 30 ccm of concentrated sulphuric acid and heated at 60 - 75°C for 20 minutes. After cooling the solution was poured into ice. The yellow oil was separated from water layer and boiled with benzene under Dean-Stark separator to remove traces of water. After evaporation of benzene the yellow oil was obtained. It was dissolved in benzene and resolved by column chromatography on Al_2O_3 in benzene and methanol. The first colourless fraction gave 0.1 g of

ω-trifluoromethylthioacetophenone [6] identified by its IR spectrum and the second yellow fraction gave product 2b (3.8 g, 54% yield) that was purified by sublimation under reduced pressure to give colourless needles, m.p.: 283 - 4°C. Analysis calc. for $C_{16}H_{10}F_3NOS$ (321.306): 59.8% C, 3.1% H, 4.4% N, 10.0% S; found: 59.3% C, 3.3% H, 4.4% N, 10.2% S.

^1H NMR δ [ppm]: 7.5 - 8.4, m, aromatic .

^{19}F NMR δ [ppm]: 42.6, m, SCF_3 .

IR ν [cm^{-1}]: 3600 - 3350 b, 3250 w, 3200 m, 3180 - 2500 vs, b, 1620 s, 1560 vs, b, 1170 - 1100 vs, b.

MS: 321, 36.3, M^+; 252, 100.0; 223, 16.6; 222, 5.4; 191, 4.2; 152, 3.2; 120, 4.4; 77, 7.1; 76, 6.8; 69, 5.3, CF_3^+; 50, 4.8 .

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