Reactions of 2,2-Dialkyl-3-thioxochroman-4-one S-(1-Adamantylimides) with Some Nitrilimines

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(E)-3-Thioxospiro[chroman-2,1′-cyclohexane]-4-one S-(1-adamantylimide) (1) reacted with numerous nitrilimines (generated in situ via triethylamine dehydrohalogenation of the corresponding hydrazonoyl chlorides 2a – i) in refluxing dry toluene to afford 3‴,5‴-disubstituted-3‴H,4‴H-dispiro[cyclohexane-1,2′-chromene-3,2‴-[1,3,4]thiadiazole]-4‴-ones 3a – i. Similarly, reaction of 2,2-dimethyl-3-thioxochroman-4-one S-(1-adamantylimide) (4) with nitrilimines in refluxing dry toluene afforded the corresponding 3‴,5‴-disubstituted-3,3-dimethyl-3‴H,4‴H-spiro[chromene-3,2‴-[1,3,4]thiadiazole]-ones 5a – i.

Key words: Thioxo S-Imides, Nitrilimines, 1,3,4-Thiadiazole

Introduction

Thiocumulenes behave as 1,3-dipoles or dienophiles in cycloaddition reactions with a large variety of multiple bond-containing compounds. According to the proposal of Inagaki and Okazaki [1, 2], thioxo S-imides are 1,3-dipoles. However, the fluorenethioxo S-tosylimide reacts both as a 1,3-dipole and as a dienophile [3, 4]. 2,2-Dialkyl-3-thioxochroman-4-one S-(1-adamantylimides) react as 1,3-dipoles with Lawesson’s reagent (LR) [5]. Nitrilimines (generated in situ from hydrazonoyl chlorides) represent an important class of highly reactive 1,3-dipoles which have been used intensively for cycloaddition reactions with numerous dienophiles [6]. Many publications have reported that different 1,3,4-thiadiazole derivatives exhibit antimycobacterial [7], antibacterial [8], anticonvulsant [9, 10], and leishmanicidal [11] activities. Moreover, chromanones constitute an important class of naturally occurring substances [12 – 14] and have drawn the attention of many researchers due to their well known properties as agents against the antihuman immunodeficiency virus (HIV-1) that causes the acquired immune deficiency syndrome (AIDS) [15 – 17].

In the present work, we wished to explore the behavior of 2,2-dialkyl-3-thioxochroman-4-one S-(1-adamantylimides) toward cycloaddition reactions with some nitrilimines.

Results and Discussion

The reaction of (E)-3-thioxospiro[chroman-2,1′-cyclohexane]-4-one S-(1-adamantylimide) (1) with numerous nitrilimines (generated in situ via triethylamine dehydrohalogenation of the corresponding hydrazonoyl chlorides 2a – i) in refluxing dry toluene afforded all only one identified product. The structures of the isolated products were established to be that of 3‴,5‴-disubstituted-3‴H,4‴H-dispiro[cyclohexane-1,2′-chromene-3,2‴-[1,3,4]thiadiazole]-4‴-ones 3a – i based on spectroscopic (IR, 1H, 13C NMR, MS) and elemental analyses data (Scheme 1). The formation of 1,3,4-thiadiazole derivatives can be explained by the effect of hydrogen chloride (HCl) on the thioxo S-imide derivatives to generate the superdipolarophilic α-oxo-thioketone intermediates which un-
underwent a cycloaddition with nitrilimines \([18, 19]\) (Scheme 2).

Compounds 3a – c are identical in all respects (IR, \(^1\)H NMR, MS, and physical data) with those published previously \([6]\). The IR spectra of compounds 3d – i show a strong band at \(\nu = 1665 – 1701 \text{ cm}^{-1}\) assignable to a carbonyl stretching vibration band. The \(^1\)H NMR spectra of 3d, g – i revealed the presence of cyclohexyl protons through multiplet signals at \(\delta = 1.00 – 2.65 \text{ ppm}\), and \(\delta\) (CH\(_3\)CO) in the region of cyclohexyl protons, beside the expected aromatic signals. The mass spectra (EI) of 3d – i showed the molecular ions as base peaks.

Similarly, the reactions of 2,2-dimethyl-3-thioxochroman-4-one S-(1-adamantylimide) (4) with nitrilimines in refluxing dry toluene afforded the corresponding 3′,5′-disubstituted-3,3-dimethyl-3′H,4H-spiro[chromene-3,2′-1,3,4-thiadiazole]-ones 5a – i (Scheme 3). Compounds 5a – c are identical in all respects (IR, \(^1\)H NMR, MS, and physical data) with those published previously \([6]\). The IR spectra of compounds 5d – i show a strong band at \(\nu = 1665 – 1700 \text{ cm}^{-1}\) assignable to a carbonyl stretching vibration band. The \(^1\)H NMR spectra of compounds 5d, g – i exhibit CH\(_3\) resonances as singlet signals at \(\delta = 1.77 – 1.80 \text{ ppm}\), and CH\(_3\)CO signals at \(\delta = 2.61 \text{ ppm}\) beside the expected aromatic protons. The \(^1\)H NMR spectra of 3e, f revealed CH\(_3\)CH\(_2\) protons as quartet signals at \(\delta = 4.30 \text{ ppm}\) (\(J = 7.0 \text{ Hz}\)) beside CH\(_3\)CH\(_2\) protons as triplet signals at \(\delta = 1.35 \text{ ppm}\) (\(J = 7.0 \text{ Hz}\)), and aromatic protons. The mass spectra (EI) of 5d – i showed the molecular ions as base peaks.

**Experimental Section**

Melting points were determined on samples in open glass capillaries using an Electrothermal IA 9000 series digital melting point apparatus (Electrothermal, Essex, UK) and are uncorrected. Microanalyses were performed on an Elementar-Vario EL instrument, Microanalytical Unit, Central Services Laboratory, National Research Centre, Cairo, Egypt. IR spectra were obtained with a Bruker-Vector 22 spectrometer on KBr wafers (Micro-analytical Center of Cairo University). The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer. \(^1\)H NMR spectra were run at 300 MHz in CDCl\(_3\) as solvent, \(^13\)C NMR spectra were run at 75 MHz in CDCl\(_3\) as solvent (Cairo University, Faculty of Science). Splitting patterns were designed as follow: s singlet; d doublet; t triplet; m multiplet. Mass spectra were recorded on a Schimadzu GCMS-QP 1000EX spectrometer (EI, 70 eV) by the Micro-analytical Center of Cairo University. Compounds 1 \([20]\), 2a – i \([21–25]\) and 4 \([26]\) were prepared according to the literature.
Scheme 2. Formation of 1,3,4-thiadiazole derivatives.

Scheme 3. Synthesis of compounds 5a–i.

Reaction of thione S-imides (1) with hydrazonoyl chlorides (2)

The appropriate hydrazonoyl chloride 2 (2 mmol) was added to a solution of thione S-imide 1 (2 mmol) in dry toluene (20 mL) containing 1 mL of TEA. The reaction mixture was heated under reflux for 10 h. The formed solid was removed by filtration, and the filtrate was evaporated under reduced pressure to dryness. The residue was chromatographed (silica gel Merk 60, particle size 0.06 – 0.2 mm, as the stationary phase and petroleum ether 40–60-ethyl acetate 10 : 1 as the eluent) to give the corresponding 1,3,4-thiadiazole products 3a–i, respectively.

3''',5'''-Diphenyl-3'H,4'H-dispiro[cyclohexane-1,2'-chromene-3,2''-[1,3,4]thiadiazole]-4'-one (3a) [6]: M. p. 148 – 150 °C (ref. [6]: 148–151 °C); yield 65%.

3''-(3-Chlorophenyl)-5''-phenyl-3'H,4'H-dispiro[cyclohexane-1,2'-chromene-3,2''-[1,3,4]thiadiazole]-4'-one (3b) [6]: M. p. 169 – 170 °C (ref. [6]: 169–171 °C); yield 67%.
From 1 and 2d. Yield 45%; m. p. 220 – 223°C. – IR: νCO = 1697, 1701 cm⁻¹. – 1H NMR: δ = 1.16 – 2.50 (13H, m, 10 cyclohexyl H + CH₂CH₂), 2.18 (3H, s, CH₃), 4.30 (2H, q, J = 7.0 Hz, CH₂CH₂), 6.85 – 7.46 (8H, m, ArH) ppm. – MS: m/z (%) = 440 (100) [M]⁺, 349 (20), 320 (35), 120 (95). – C₂H₂ClN₂O₂S (440.93): calcd. C 67.95, H 5.45, N 9.31, S 8.09; found C 67.70, H 5.47, N 9.19, S 7.88.

5'-Acetyl-3'-4-(chlorophenyl)-3'H,4'H-dispiro[cyclohexane-1,2'-chromene-3,2''-[1,3,4]thiadiazol]-4'-one (3d)

From 1 and 2e. Yield 70%; m. p. 140 – 142°C. – IR: νCO = 1675, 1701 cm⁻¹. – 1H NMR: δ = 1.16 – 2.53 (13H, m, 10 cyclohexyl H) ppm. – MS: m/z (%) = 436 (100) [M]⁺, 316 (40) (M–CH₂), 287 (15), 184 (20), 121 (35), 92 (40). – C₂H₂N₂O₂S (436.51): calcd. C 66.48, H 5.67, N 6.15, S 7.06; found C 66.18, H 4.69, N 9.31, S 7.10; found C 60.97, H 4.49, N 9.09, S 6.89.

2,2-Dialkyl-3-thioxochroman-4-one (15), 121 (25). – C₂H₂N₂O₂S (420.52): calcd. C 68.54, H 5.75, N 6.66, S 7.62; found C 68.37, H 5.59, N 6.39, S 7.38.

5'-Acetyl-3'-4-(nitrophenyl)-3'H,4'H-dispiro[cyclohexane-1,2'-chromene-3,2''-[1,3,4]thiadiazol]-4'-one (3i)

From 1 and 2f. Yield 59%; m. p. 159 – 161°C. – IR: νCO = 1661, 1700 cm⁻¹. – 1H NMR: δ = 1.00 – 2.29 (10H, m, 10 cyclohexyl H), 2.52 (3H, s, CH₃CO), 6.98 – 8.09 (8H, m, ArH) ppm. – ¹³C NMR: δ = 20.54, 21.14, 24.95, 25.73, 30.08 (cyclohexyl-C), 30.98 (CH₃), 85.45 (cyclohexyl C-1), 96.24 (spiro C-3), 118.89, 120.4, 121.98, 122.75, 124.38, 128.37, 137.91, 143.88, 144.87, 148.17, 157.49 (arom. C), 184.11 (CH₂C=O), 190.18 (C=O) ppm. – MS: m/z (%) = 451 (100) [M]⁺, 331 (30), 229 (10), 120 (57), 92 (57). – C₂H₂N₂O₂S (451.48): calcd. C 61.18, H 4.69, N 9.31, S 7.10; found C 60.97, H 4.49, N 9.09, S 6.89.

5'-Acetyl-3'-4-(cholorophenyl)-3'H,4'H-dispiro[cyclohexane-1,2'-chromene-3,2''-[1,3,4]thiadiazol]-4'-one (3j)

From 1 and 2g. Yield 52%; m. p. 254 – 255°C. – IR: νCO = 1693, 1700 cm⁻¹. – 1H NMR: δ = 1.16 – 2.53 (16H, m, 10 cyclohexyl H + CH₂CO + CH₃), 6.79 – 7.24 (8H, m, ArH) ppm. – MS: m/z (%) = 420 (100) [M]⁺, 300 (35), 198 (15), 121 (25). – C₂H₂N₂O₂S (420.52): calcd. C 68.54, H 5.75, N 6.66, S 7.62; found C 68.37, H 5.59, N 6.39, S 7.38.

5'-Acetyl-3'-4-(nitrophenyl)-3'H,4'H-dispiro[cyclohexane-1,2'-chromene-3,2''-[1,3,4]thiadiazol]-4'-one (3k)

From 1 and 2h. Yield 65%; m. p. 101 – 103°C. – IR: νCO = 1671, 1696 cm⁻¹. – 1H NMR: δ = 1.35 (3H, t, J = 7.0 Hz, CH₃CH₂), 1.78 (3H, s, CH₃), 1.80 (3H, s, CH₃), 4.30 (2H, q, J = 7.0 Hz, CH₂CH₂), 7.06 – 7.94 (9H, m, ArH) ppm. – MS: m/z (%) = 396 (100) [M⁺], 367 (45) [M–C₂H₅]⁺, 320 (56). – C₂H₂N₂O₂S (396.44): calcd. C 63.62, H 5.09, N 7.07, S 8.09; found C 63.51, H 4.98, N 6.79, S 7.81.
$S$'-Ethoxycarbonyl-$S'$-(4-methylphenyl)-2,2-dimethyl-$S'$H,4H-spiro[chromene-3,2'-1,3,4-thiadiazol]-4-one (5f)

From 4 and 2f. Yield 40%; m. p. 154–155°C. – IR: $v_{CO} = 1670, 1697 \text{ cm}^{-1}$. – $^1H$ NMR: $\delta = 1.36$ (3H, t, $J = 7.0 \text{ Hz}, CH_2CH_3$), $1.80$ (6H, s, $2 CH_3$), $2.20$ (3H, s, CH$_3$), $4.30$ (2H, q, $J = 7.0 \text{ Hz}, CH_2CH_3$), $7.06 – 7.94$ (8H, m, ArH) ppm. – MS: $m/z(\%) = 410 (100) [M]^+$, $380 (45) [M–C2H5]^+$, $336 (56), 303 (35), – C22H22N2O2S (410:53):$ calc'd. C 64.36, H 5.41, N 7.62, S 7.80; found C 64.18, H 4.28, N 6.69, S 7.61.

$S$'-Acetyl-$S'$-phenyl-2,2-dimethyl-$S'$H,4H-spiro[chromene-3,2'-1,3,4-thiadiazol]-4-one (5g)

From 4 and 2g. Yield 43%; m. p. 184–186°C. – IR: $v_{CO} = 1681, 1701 \text{ cm}^{-1}$. – $^1H$ NMR: $\delta = 1.77$ (3H, s, CH$_3$), $1.79$ (3H, s, CH$_3$), $2.51$ (3H, s, CH$_3$), $7.06 – 7.94$ (9H, m, ArH) ppm. – MS: $m/z(\%) = 366 (100) [M]^+$, $351 (45) [M–CH3]^+$, $336 (56), 293 (30), 269 (20), - C20H14N2O2S (366.41):$ calc'd. C 65.55, H 4.95, N 7.64, S 8.75; found C 65.38, H 4.84, N 7.46, S 8.57.

$S$'-Acetyl-$S'$-(4-methylphenyl)-2,2-dimethyl-$S'$H,4H-spiro[chromene-3,2'-1,3,4-thiadiazol]-4-one (5h)

From 4 and 2h. Yield 80%; m. p. 190–191°C. – IR: $v_{CO} = 1665, 1692 \text{ cm}^{-1}$. – $^1H$ NMR: $\delta = 1.78$ (3H, s, CH$_3$), $1.79$ (3H, s, CH$_3$), $2.22$ (3H, s, CH$_3$), $2.51$ (3H, s, CH$_3$), $6.96 – 7.84$ (8H, m, ArH) ppm. – MS: $m/z(\%) = 380 (100) [M]^+$, $337 (43), 117 (10). – C21H14N2O2S (380.48):$ calc'd. C 66.28, H 5.31, N 7.56, S 8.43; found C 66.01, H 5.16, N 7.19, S 8.26.

$S$'-Acetyl-$S'$-(4-nitrophenyl)-2,2-dimethyl-$S'$H,4H-spiro[chromene-3,2'-1,3,4-thiadiazol]-4-one (5i)

From 4 and 2i. Yield 50%; m. p. 195–197°C. – IR: $v_{CO} = 1667, 1699 \text{ cm}^{-1}$. – $^1H$ NMR: $\delta = 1.80$ (3H, s, CH$_3$), $1.81$ (3H, s, CH$_3$), $2.49$ (3H, s, CH$_3$), $6.86 – 7.72$ (8H, m, ArH) ppm. – MS: $m/z(\%) = 411 (100) [M]^+$, $382 (43), 122 (25), – C20H17N1O2S (411.46):$ calc'd. C 58.32, H 4.17, N 10.21, S 7.79; found C 58.09, H 3.97, N 9.99, S 7.61.

References