Novel Regioselective Synthesis of 3'*H*,4*H*-Spiro[chromene-3,2'-[1,3,4]thiadiazol]-4-one Containing Compounds

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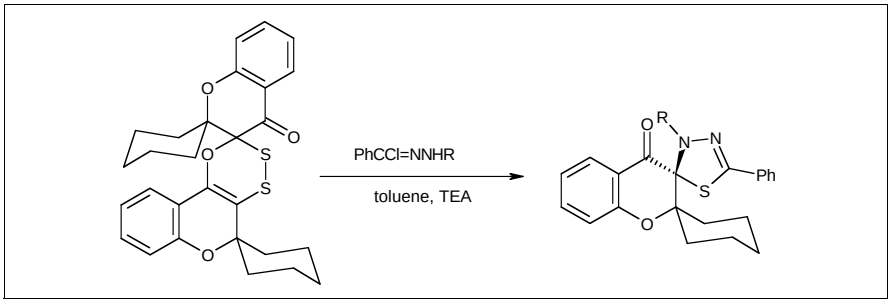

A variety of 3'',5''-diaryl-3''*H*,4'*H*-dispiro[cyclohexane-1,2'-chromene-3',2''-[1,3,4]thiadiazol]-4'-ones **3a-c** were synthesized regioselectively through the reaction of 4'*H*,5*H*-trispiro[cyclohexane-1,2'-chromene-3',2''-[1,3,4]oxadithiino[5,6-*c*]chromene-5'',1'''-cyclohexan]-4'-one (**1**) with nitrilimines (generated *in situ via* triethylamine dehydrohalogenation of the corresponding hydrazonoyl chlorides **2a-c**) in refluxing dry toluene. Single crystal X-ray diffraction studies of **3a,b** add support for the established structure. Similarly, 3',5'-diaryl-2,2-dimethyl-3'*H*,4*H*-spiro[chromene-3,2'-[1,3,4]thiadiazol]-4-ones **5a-c** were obtained in a regioselective manner through the reaction of 2,2,5',5'-tetramethyl-4*H*,5'*H*-spiro[chromene-3,2'-[1,3,4]oxadithiino[5,6-*c*]chromen]-4-one (**4a**) with nitrilimines under similar reaction conditions. On the other hand, reaction of 2,5'-diethyl-2,5'-dimethyl-4*H*,5'*H*-spiro[chromene-3,2'-[1,3,4]oxadithiino-[5,6-*c*]chromen]-4-one (**4b**) with nitrilimines in refluxing dry toluene afforded the corresponding 3',5'-diaryl-2-ethyl-2-methyl-3'*H*,4*H*-spiro[chromene-3,2'-[1,3,4]thiadiazol]-4-ones **5d-f** as two unisolable diastereoisomeric forms.

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Introduction.

The 1,3-dipolar cycloaddition reaction is one of the most versatile methods for the construction of five-membered heterocycles [1]. The interest in the field of 1,3-dipolar cycloaddition is due to its ability for providing a wide variety of heterocyclic systems in enantiopure forms [2-7]. Nitrilimines represent an important class of highly reactive 1,3-dipoles used intensively for cycloaddition reactions with numerous unsaturated functional groups (*e.g.* alkenes [6-9], alkynes [10,11], azomethines [12], allenes [13,14]) as well as heterocyclic residues [5,15].

In the present work, it is intended to investigate the reaction of nitrilimines as a highly reactive 1,3-dipole system with a variety of 1,3,4-oxadithiin containing compounds **1,4** in an attempt to isolate the corresponding 3'*H*,4*H*-spiro[chromene-3,2'-[1,3,4]thiadiazol]-4-one compounds **3,5**. As far as we are aware, 1,3-dipolar cycloaddition reactions at the mentioned ring systems have not been reported. Regioselectivity of the reactions as well as stereochemical structure of the isolated products will be also taken into considerations.

The interest for construction of 1,3,4-thiadiazole ring system containing compounds is due to biological properties associated with its structure. Where many publications reported that different 1,3,4-thiadiazole derivatives exhibit anticonvulsant [16,17], anti-tuberculosis [18,19] and leishmanicidal [20] activities. In addition to cytotoxic effects (on human non-small cell lung cancer A549) [21] as well as potent and selective PDE7 inhibitors [22,23]. Moreover, chromanones constitute an important class of naturally occuring substances [24-26] and draw the attention of many researchers due to their well known properties as anti-human immunodeficiency virus (HIV-1) that causes the acquired immuno deficiency syndrome (AIDS) [27-30] and anti-tuberculosis [31] activity. The present work is also prompted by the previously well-established results describing the regioselective behaviour of various 1,3-dipole systems with thione-containing compounds. Where, nitrones (azomethine oxides) were reported to react with many thioketones affording 1,4,2-oxathiazolidines [32]. Similarly, diazomethane interacted with thiobenzophenone at -78 °C in THF giving

thiadiazoline derivative [33]. Also, regiospecific dipolar cycloaddition reactions of nitrilimine derivatives with thiobenzophenone have been described [34].

Results and Discussion.

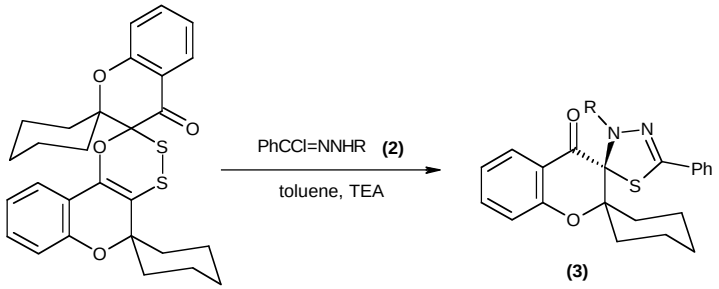
Reaction of 4'*H*,5*H*-trispiro[cyclohexane-1,2'-chromene-3',2''-[1,3,4]oxadithiino[5,6-*c*]chromene-5'',1'''-cyclohexan]-4'-one (**1**) with a variety of nitrilimines (generated *in situ via* triethylamine dehydrohalogenation of the corresponding hydrazonoyl chlorides **2**) in refluxing dry toluene afforded only one regioisomeric product as indicated by TLC. The structure of the isolated product was established to be 3'',5''-diaryl-3''*H*,4'*H*-dispiro[cyclohexane-1,2'-chromene-3',2''-[1,3,4]thiadiazol]-4'-ones **3a-c** based on spectroscopic (IR, ^{1}H, ^{13}C-NMR, MS) and elemental analyses data.

The IR spectra of **3a-c** reveal a strong band at ν = 1683-1708 cm^{-1} region assignable for the carbonyl stretching vibration band. ^{1}H-NMR spectra of **3a-c** exhibit the cyclohexyl protons as multiplet signals at δ = 1.06-2.45 region beside the expected aromatic protons. ^{13}C-NMR spectrum of **3a** (on-resonance and APT) adds a good support for the established structure. Where, the five cyclohexyl methylene carbons "*C*-3, *C*-5, *C*-4, *C*-2, *C*-6" appear at δ = 20.90, 21.00, 25.07, 29.72, 30.28 respectively. The spiro-carbons "*C*-2', *C*-3'" are recognized at δ = 85.63, 95.37 respectively. In addition, the imino and carbonyl carbons are exhibited at δ = 157.60, 185.66. Mass spectra (EI) of **3a-c** reveal the parent molecular ion peaks as base peaks (Scheme 1).

Single crystal X-ray diffraction studies of **3a,b** (Figure 1,2) add support for the established structure [35]. It has been noticed that, the cyclohexyl moiety adopts the chair configuration. The reaction presumably, takes place *via* cycloreversion of the oxadithiin ring system **1**, under the applying refluxing toluene reaction conditions, giving two molecules of the chromanone-3-thiones. The latter due to dipolar cycloaddition across its C=S unit with nitrilimines furnished finally dispiro analogues **3a-c**.

Similarly, reaction of 2,2,5',5'-tetramethyl-4*H*,5'*H*-spiro[chromene-3,2'-[1,3,4]oxadithiino[5,6-*c*]chromen]-

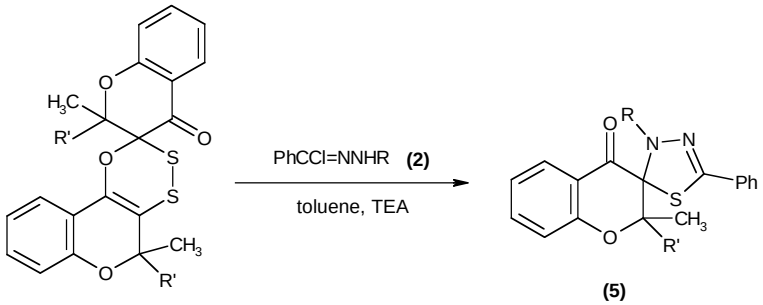
Scheme 1



(1) (3)

2a, 3a; R = Ph
2b, 3b; R = 3-ClC$_6$H$_4$
2c, 3c ; R = 4-H$_3$CC$_6$H$_4$

Scheme (2)



(4) (5)

2a, R = Ph
2b, R = 3-ClC$_6$H$_4$
2c, R = 4-H$_3$CC$_6$H$_4$
4a, R' = CH$_3$
4b, R' = C$_2$H$_5$

5a, R = Ph, R' = CH$_3$
5b, R = 3-ClC$_6$H$_4$, R' = CH$_3$
5c, R = 4-H$_3$CC$_6$H$_4$, R' = CH$_3$
5d, R = Ph, R' = C$_2$H$_5$
5e, R = 3-ClC$_6$H$_4$, R' = C$_2$H$_5$
5f, R = 4-H$_3$CC$_6$H$_4$, R' = C$_2$H$_5$

4-one (**4a**) with nitrilimines afforded the corresponding 3',5'-diaryl-2,2-dimethyl-3'*H*,4*H*-spiro[chromene-3,2'-[1,3,4]thiadiazol]-4-ones **5a-c**. The spectral (IR, ^{1}H, ^{13}C-NMR, MS) as well as elemental analyses data support the established structure. Where the IR spectra of **5a-c** exhibit the carbonyl stretching vibration band at ν = 1696 cm^{-1}. The ^{1}H-NMR spectra reveal the two methyl groups as two singlet signals at δ = 1.57-1.81 region. Moreover, the mass spectral data are consistent with the established structure exhibiting the parent molecular ion peaks either as a base peak (as in case of **5b**) or in high relative intensity values (as in case of **5a,c**). ^{13}C-NMR spectrum of **5b** adds sharp evidence for the regiochemical assumed structure, which reveals the two methyl carbons at δ = 23.36, 23.77. In addition to the *C*-2 and spiro-carbon "*C*-3" at δ = 84.73, 94.45 respectively (Scheme 2).

On the other hand, reaction of 2,5'-diethyl-2,5'-dimethyl-4*H*,5'*H*-spiro[chromene-3,2'-[1,3,4]oxadithiino-[5,6-*c*]chromen]-4-one (**4b**) with a variety of nitrilimines under the same previously described reaction conditions "as in the case of **4a**" afforded only one product which purified on silica gel column chromatography and identified as 3',5'-diaryl-2-ethyl-2-methyl-3'*H*,4*H*-spiro-[chromene-3,2'-[1,3,4]thiadiazol]-4-ones **5d-f**. The structure of the isolated products was established to be two unisolable diastereoisomeric forms based on the fact that, ^{1}H-NMR spectra of **5d-f** reveal two methyl signals at

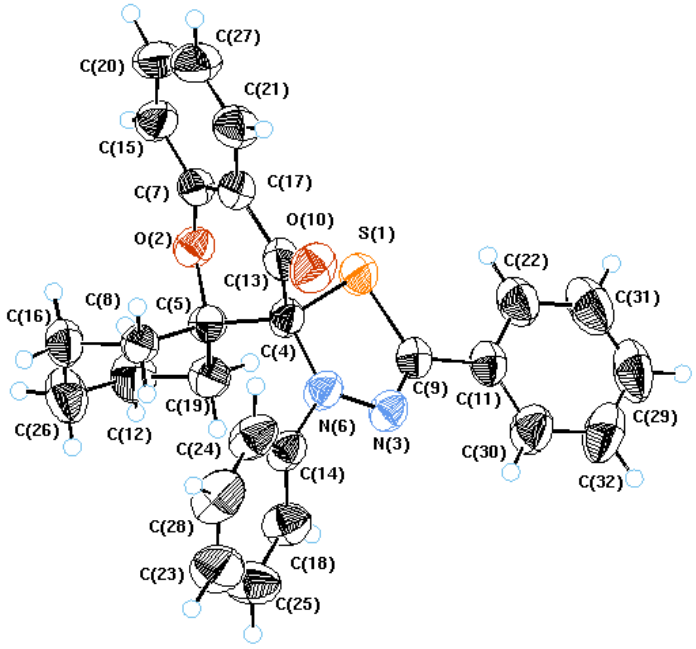


Figure 1. Single crystal X-ray diffraction of **3a**.

Selected intramolecular bond lengths (Å) and bond angles (°) of **3a**.
S(1)-C(4) = 1.8562(15), S(1)-C(9) = 1.758(2), O(2)-C(5) = 1.469(2), O(2)-C(7) = 1.367(2), N(3)-N(6) = 1.367(2), N(3)-C(9) = 1.285(2), C(4)-C(5) = 1.562(2), C(4)-N(6) = 1.471(2), C(4)-C(13) = 1.537(2), C(5)-C(8) = 1.540(2), C(5)-C(19) = 1.510(2), N(6)-C(14) = 1.436(2), C(7)-C(15) = 1.391(2), C(7)-C(17) = 1.396(2), C(8)-C(16) = 1.524(2), C(9)-C(11) = 1.465(2), O(10)-C(13) = 1.213(2), C(11)-C(22) = 1.381(2), C(11)-C(30) = 1.383(2), C(12)-C(19) = 1.527(2), C(12)-C(26) = 1.519(2), C(13)-C(17) = 1.474(2), C(14)-C(18) = 1.381(2), C(14)-C(24) = 1.373(2), C(15)-C(20) = 1.366(3), C(16)-C(26) = 1.515(2), C(17)-C(21) = 1.400(2), C(18)-C(25) = 1.378(2), C(20)-C(27) = 1.383(2), C(21)-C(27) = 1.359(2), C(22)-C(31) = 1.387(3), C(23)-C(25) = 1.365(3), C(23)-C(28) = 1.363(3), C(24)-C(28) = 1.385(3), C(29)-C(31) = 1.364(3), C(29)-C(32) = 1.374(3), C(30)-C(32) = 1.385(3), C(4)-S(1)-C(9) = 90.42(7), C(5)-O(2)-C(7) = 116.82(10), N(6)-N(3)-C(9) = 113.77(12), S(1)-C(4)-C(5) = 109.84(9), S(1)-C(4)-N(6) = 102.63(9), S(1)-C(4)-C(13) = 102.90(10), C(5)-C(4)-N(6) = 116.58(12), C(5)-C(4)-C(13) = 109.50(12), N(6)-C(4)-C(13) = 114.19(12), O(2)-C(5)-C(4) = 104.99(11), O(2)-C(5)-C(8) = 107.91(11), O(2)-C(5)-C(19) = 105.53(11), C(4)-C(5)-C(8) = 114.60(11), C(4)-C(5)-C(19) = 113.09(12), C(8)-C(5)-C(19) = 110.05(12), N(3)-N(6)-C(4) = 117.14(11), N(3)-N(6)-C(14) = 115.84(12), C(4)-N(6)-C(14) = 124.65(12), O(2)-C(7)-C(15) = 117.56(13), O(2)-C(7)-C(17) = 122.45(13), C(15)-C(7)-C(17) = 120.0(2), C(5)-C(8)-C(16) = 111.43(12), S(1)-C(9)-N(3) = 115.23(12), S(1)-C(9)-C(11) = 121.40(12), N(3)-C(9)-C(11) = 123.16(14), C(9)-C(11)-C(22) = 121.0(2), C(9)-C(11)-C(30) = 120.2(2), C(22)-C(11)-C(30) = 118.7(2), C(19)-C(12)-C(26) = 111.45(13), C(4)-C(13)-O(10) = 122.68(14), C(4)-C(13)-C(17) = 113.89(13), O(10)-C(13)-C(17) = 123.4(2), N(6)-C(14)-C(18) = 119.31(14), N(6)-C(14)-C(24) = 121.1(2), C(18)-C(14)-C(24) = 119.5(2), C(7)-C(15)-C(20) = 118.9(2), C(8)-C(16)-C(26) = 111.79(14), C(7)-C(17)-C(13) = 119.95(14), C(7)-C(17)-C(21) = 119.37(14), C(13)-C(17)-C(21) = 120.67(15), C(14), C(18)-C(25) = 120.1(2), C(5)-C(19)-C(12) = 112.29(13), C(15)-C(20)-C(27) = 121.8(2), C(17)-C(21)-C(27) = 120.1(2), C(11)-C(22)-C(31) = 120.4(2), C(25)-C(23)-C(28) = 119.6(2), C(14)-C(24)-C(28) = 119.4(2), C(18)-C(25)-C(23) = 120.3(2), C(12)-C(26)-C(16) = 111.46(14), C(20)-C(27)-C(21) = 119.8(2), C(23)-C(28)-C(24) = 121.0(2), C(31)-C(29)-C(32) = 119.8(2), C(11)-C(30)-C(32) = 120.5(2), C(22)-C(31)-C(29) = 120.5(2), C(29)-C(32)-C(30) = 120.1(2), C(5)-C(8)-H(8A) = 109.99(13), C(5)-C(8)-H(8B) = 109.14(14), C(19)-C(12)-H(12A) = 108.0(2), C(19)-C(12)-H(12B) = 109.9(2), C(8)-C(16)-H(16A) = 108.97(14), C(8)-C(16)-C(16B) = 109.36(15), C(5)-C(19)-H(19A) = 109.70(15), C(5)-C(19)-H(19B) = 109.08(13), C(12)-C(26)-H(26A) = 109.8(2), C(12)-C(26)-H(26B) = 107.7(2).

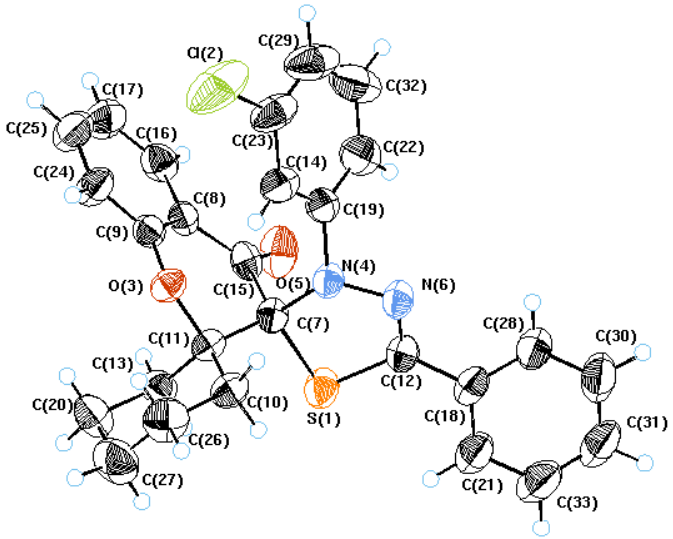


Figure 2. Single crystal X-ray diffraction of **3b**.

Selected intramolecular bond lengths (Å) and bond angles (°) of **3b**.

S(1)-C(7) = 1.826(2), S(1)-C(12) = 1.755(2), Cl(2)-C(23) = 1.740(3), O(3)-C(9) = 1.366(2), O(3)-C(11) = 1.460(2), N(4)-N(6) = 1.389(2), N(4)-C(7) = 1.517(2), N(4)-C(19) = 1.441(2), O(5)-C(15) = 1.214(2), N(6)-C(12) = 1.273(2), C(7)-C(11) = 1.546(2), C(7)-C(15) = 1.555(2), C(8)-C(9) = 1.393(2), C(8)-C(15) = 1.465(2), C(8)-C(16) = 1.395(3), C(9)-C(24) = 1.380(3), C(10)-C(11) = 1.525(2), C(10)-C(26) = 1.505(3), C(11)-C(13) = 1.523(2), C(12)-C(18) = 1.474(3), C(13)-C(20) = 1.531(3), C(14)-C(19) = 1.393(3), C(14)-C(23) = 1.381(3), C(16)-C(17) = 1.364(3), C(17)-C(25) = 1.385(3), C(18)-C(21) = 1.388(3), C(18)-C(28) = 1.381(3), C(19)-C(22) = 1.367(3), C(20)-C(27) = 1.515(3), C(21)-C(33) = 1.384(3), C(22)-C(32) = 1.395(3), C(23)-C(29) = 1.367(4), C(24)-C(25) = 1.376(3), C(26)-C(27) = 1.524(3), C(28)-C(30) = 1.385(3), C(29)-C(32) = 1.366(4), C(30)-C(31) = 1.380(3), C(31)-C(33) = 1.357(4), C(7)-S(1)-C(12) = 90.81(8), C(9)-O(3)-C(11) = 118.12(13), N(6)-N(4)-C(7) = 114.20(12), N(6)-N(4)-C(19) = 111.69(14), C(7)-N(4)-C(19) = 119.35(13), N(4)-N(6)-C(12) = 113.72(14), S(1)-C(7)-N(4) = 103.06(10), S(1)-C(7)-C(11) = 110.57(12), S(1)-C(7)-C(15) = 110.58(11), N(4)-C(7)-C(11) = 113.06(13), N(4)-C(7)-C(15) = 109.29(14), C(11)-C(7)-C(15) = 110.09(14), C(9)-C(8)-C(15) = 120.5(2), C(9)-C(8)-C(16) = 118.5(2), C(15)-C(8)-C(16) = 120.9(2), 0(3)-C(9)-C(8) = 122.2(2), O(3)-C(9)-C(24) = 117.1(2), C(8)-C(9)-C(24) = 120.6(2), C(11)-C(10)-C(26) = 112.4(2), O(3)-C(11)-C(7) = 108.87(13), O(3)-C(11)-C(10) = 104.56(13), O(3)-C(11)-C(13) = 108.28(13), C(7)-C(11)-C(10) = 113.96(14), C(7)-C(11)-C(13) = 110.40(14), C(10)-C(11)-C(13) = 110.46(15), S(1)-C(12)-N(6) = 116.11(14), S(1)-C(12)-C(18) = 121.15(14), N(6)-C(12)-C(18) = 122.7(2), C(11)-C(13)-C(20) = 112.18(15), C(19)-C(14)-C(23) = 118.5(2), O(5)-C(15)-C(7) = 121.0(2), O(5)-C(15)-C(8) = 123.3(2), C(7)-C(15)-C(8) = 115.6(2), C(8)-C(16)-C(17) = 120.9(2), C(16)-C(17)-C(25) = 119.6(2), C(12)-C(18)-C(21) = 120.8(2), C(12)-C(18)-C(28) = 120.1(2), C(21)-C(18)-C(28) = 119.1(2), N(4)-C(19)-C(14) = 118.2(2), N(4)-C(19)-C(22) = 121.5(2), C(14)-C(19)-C(22) = 120.3(2), C(13)-C(20)-C(27) = 110.7(2), C(18)-C(21)-C(33) = 120.2(2), C(19)-C(22)-C(32) = 119.6(2), Cl(2)-C(23)-C(14) = 118.5(2), Cl(2)-C(23)-C(29) = 119.6(2), C(14)-C(23)-C(29) = 121.9(2), C(9)-C(24)-C(25) = 119.4(2), C(17)-C(25)-C(24) = 120.8(2), C(10)-C(26)-C(27) = 112.4(2), C(20)-C(27)-C(26) = 111.2(2), C(18)-C(28)-C(30) = 120.2(2), C(23)-C(29)-C(32) = 118.9(2), C(28)-C(30)-C(31) = 119.9(2), C(30)-C(31)-C(33) = 120.3(2), C(22)-C(32)-C(29) = 120.8(2), C(21)-C(33)-C(31) = 120.3(2).

δ = 1.67-1.68 and 1.53-1.54 corresponding to the major and minor isomers, respectively.

Single Crystal X-ray Crystallographic Data of **3a,b**.

The crystallographic data were collected at T = 298 K on a Kappa CCD Enraf Nonius FR 590 diffractometer using a graphite monochromator with *Mo-*K_α radiation (λ = 0.71073 Å).

Compound **3a**.

The crystal structure was determined by SIR97 [36] and refined by maXus [37] (Bruker Nonius, Delft and MacScience, Japan). Chemical formula $C_{27}H_{24}N_2O_2S$, M_r = 440.565, orthorhombic, crystallizes in space group Pbca, Cell lengths "a = 13.3842(4), b = 12.5325(3), c = 27.1484(7) Å", Cell angles "α = 90.00, β = 90.00, γ = 90.00°", V = 4553.8(2) Å^3, Z = 8, D_c = 1.285 g/cm^3, θ values 2.910-27.485°, absorption coefficient μ (*Mo-*K_α) = 0.17 mm^{-1}, F(000) = 1855. The unique reflections measured 6038 of which 2184 reflections with threshold expression $I>3\sigma(I)$ were used in the structural analysis. Convergence for 289 variable parameters by least-squares refinement on F^2 with $w = 1/[\sigma^2(F_o^2)+0.10000\ F_o^2]$. The final agreement factors were R = 0.041 and wR = 0.065 with a goodness-of-fit of 1.715.

Compound **3b**.

The crystal structure was determined by SIR92 [38] and refined by maXus [37] (Bruker Nonius, Delft and MacScience, Japan). Chemical formula $C_{27}H_{23}ClN_2O_2S$, M_r = 475.010, monoclinic, crystallizes in space group $P2_1/c$, Cell lengths "a = 12.7242(6), b = 12.4407(6), c = 18.2181(10) Å",

Cell angles "α = 90.00, β = 13.0(18), γ = 90.00°", V = 2324.0(2) Å^3, Z = 4, D_c = 1.358 g/cm^3, θ values 2.910-21.491°, absorption coefficient μ (*Mo-K*$_\alpha$) = 0.28 mm^{-1}, F(000) = 992. The unique reflections measured 2846 of which 1910 reflections with threshold expression $I>3\sigma(I)$ were used in the structural analysis. Convergence for 298 variable parameters by least-squares refinement on F^2 with $w = 1/[\sigma^2(F_o^2)+0.10000\ F_o^2]$. The final agreement factors were $R = 0.036$ and $wR = 0.067$ with a goodness-of-fit of 1.526.

EXPERIMENTAL

Melting points are uncorrected and recorded on a digital Electrothermal 9100 melting point apparatus. IR spectra (KBr) were recorded on a Bruker Vector 22 spectrophotometer. NMR spectra were recorded on a Varian MERCURY 300 (^{1}H: 300 MHz; ^{13}C: 75 MHz) spectrometer. Mass spectra were recorded on Schimadzu GCMS-QP 1000EX (EI, 70 eV) and Hewlett-Packard (EI, 70 eV) spectrometers. The starting compounds **1** [39], **2a-c** [40,41] and **4a,b** [42] were prepared according to previously reported procedures.

Synthesis of 3'',5''-Diaryl-3''*H*,4'*H*-dispiro[cyclohexane-1,2'-chromene-3',2''-[1,3,4]thiadiazol]-4'-ones **3a-c** (General Procedure).

A mixture of **1** (1.5 mmol) and the appropriate hydrazonoyl chloride **2a-c** (3 mmol) in dry toluene (20 ml) containing triethylamine (3 mmol) was boiled under reflux for 6 h. The formed triethylamine hydrochloride was separated by filtration and the clear reaction mixture was evaporated till dryness under reduced pressure. The formed solid upon triturating the residue with methanol (5 ml), was collected and crystallized from ethanol affording the corresponding **3a-c** as yellow crystals.

3'',5''-Diphenyl-3''*H*,4'*H*-dispiro[cyclohexane-1,2'-chromene-3',2''-[1,3,4]thiadiazol]-4'-one (**3a**).

M.p. 148-151°C, yield 45%. IR: ν 1708, 1602, 1490 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.15-1.22 (m, 1H, cyclohexyl H), 1.55-1.74 (m, 7H, 7 cyclohexyl H), 2.22 (br. s, 1H, cyclohexyl H), 2.41-2.45 (br. d, 1H, cyclohexyl H), 6.89-7.72 (m, 14H, arom. H). ^{13}C-NMR "on-resonance & APT" ($CDCl_3$): δ 20.90, 21.00 (cyclohexyl *C*-3, *C*-5), 25.07 (cyclohexyl *C*-4), 29.72, 30.28 (cyclohexyl *C*-2, *C*-6), 85.63 (cyclohexyl *C*-1 "spiro *C*-2'"), 95.37 (spiro *C*-3'), 118.22, 121.53, 125.75, 126.63, 127.57, 128.07, 128.47, 129.50, 136.58 (arom. CH), 121.06 (*C*-4'a), 130.60 (quaternary Ph-*C*), 143.57 (*C*-8'a), 157.60 (*C*-5'' "C=N"), 185.66 (*C*-4' "C=O"). MS *m/z* (%): 441 [(M+1), 37], 440 (M, 100), 320 (46), 239 (20).

Anal. Calcd. for $C_{27}H_{24}N_2O_2S$: C, 73.61; H, 5.49; N, 6.36. Found: C, 73.72; H, 5.58; N, 6.50.

3''-(3-Chlorophenyl)-5''-phenyl-3''*H*,4'*H*-dispiro[cyclohexane-1,2'-chromene-3',2''-[1,3,4]thiadiazol]-4'-one (**3b**).

M.p. 169-171°C, yield 64%. IR: ν 1683, 1591, 1464 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.06-1.18 (m, 1H, cyclohexyl H), 1.46-1.68 (m, 7H, 7 cyclohexyl H), 2.17-2.20 (br. d, 1H, cyclohexyl H), 2.29-2.32 (br. d, 1H, cyclohexyl H), 6.86-7.70 (m, 13H, arom. H). MS *m/z* (%): 475 [(M+1), 31], 474 (M, 100), 354 (48), 273 (22).

Anal. Calcd. for $C_{27}H_{23}ClN_2O_2S$: C, 68.27; H, 4.88; N, 5.90. Found: C, 68.13; H, 4.74; N, 5.98.

3''-(4-Methylphenyl)-5''-phenyl-3''*H*,4'*H*-dispiro[cyclohexane-1,2'-chromene-3',2''-[1,3,4]thiadiazol]-4'-one (**3c**).

M.p. 79-81°C, yield 38%. IR: ν 1694, 1604, 1507 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.15-1.25 (m, 1H, cyclohexyl H), 1.53-1.73 (m, 7H, 7 cyclohexyl H), 2.18 (s, 3H, CH_3), 2.25-2.27 (m, 1H, cyclohexyl H), 2.39-2.43 (br. d, 1H, cyclohexyl H), 6.85-7.69 (m, 13H, arom. H). MS *m/z* (%): 455 [(M+1), 39], 454 (M, 100), 334 (67), 253 (30).

Anal. Calcd. for $C_{28}H_{26}N_2O_2S$: C, 73.98; H, 5.77; N, 6.16. Found: C, 73.78; H, 5.60; N, 6.11.

Synthesis of 2,2-Dialkyl-3',5'-diaryl-3'*H*,4*H*-spiro[chromene-3,2'-[1,3,4]thiadiazol]-4-ones **5a-f** (General Procedure).

A mixture of **4a,b** (2.5 mmol) and the appropriate hydrazonoyl chloride **2a-c** (5 mmol) in dry toluene (20 ml) containing triethylamine (5 mmol) was boiled under reflux for 6 h. The formed triethylamine hydrochloride was separated by filtration and the clear reaction mixture was evaporated till dryness under reduced pressure. Then, purified over column chromatography (silica gel 60, particle size 0.06-0.20 mm) using diethyl ether – light petroleum (40-60°C) as 1:10 v/v for elution, affording **5a-f** as pale yellow oils.

2,2-Dimethyl-3',5'-diphenyl-3'*H*,4*H*-spiro[chromene-3,2'-[1,3,4]-thiadiazol]-4-one (**5a**).

Yield 56%. IR: ν 1696, 1600, 1487 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.79 (s, 3H, CH_3), 1.81 (s, 3H, CH_3), 7.06-7.96 (m, 14H, arom. H). MS *m/z* (%): 401 [(M+1), 22], 400 (M, 83), 313 (19), 280 (77).

Anal. Calcd. for $C_{24}H_{20}N_2O_2S$: C, 71.97; H, 5.03; N, 7.00. Found: C, 72.06; H, 5.11; N, 6.89.

3'-(3-Chlorophenyl)-2,2-dimethyl-5'-phenyl-3'*H*,4*H*-spiro-[chromene-3,2'-[1,3,4]thiadiazol]-4-one (**5b**).

Yield 92%. IR: ν 1696, 1602, 1462 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.58 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 6.89-7.79 (m, 13H, arom. H). ^{13}C-NMR "APT" ($CDCl_3$): δ 23.36, 23.77 (2 CH_3), 84.73 (*C*-2); 94.45 (spiro *C*-3); 118.36, 121.85, 122.86, 124.94, 125.42, 126.67, 127.79, 128.57, 129.06, 129.86, 137.03 (arom. *CH*), 120.37 (*C*-4a), 130.22, 133.85 (quaternary Ph-*C*), 144.67 (*C*-8a), 158.21 (*C*-5' "C=N"), 185.36 (C=O). MS *m/z* (%): 435 [(M+1), 33], 434 (M, 100), 347 (11), 314 (78).

Anal. Calcd. for $C_{24}H_{19}ClN_2O_2S$: C, 66.27; H, 4.40; N, 6.44. Found: C, 66.32; H, 4.46; N, 6.57.

2,2-Dimethyl-3'-(4-methylphenyl)-5'-phenyl-3'*H*,4*H*-spiro-[chromene-3,2'-[1,3,4]thiadiazol]-4-one (**5c**).

Yield 88%. IR: ν 1696, 1602, 1461 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.57 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 2.20 (s, 3H, Ar*CH*$_3$), 6.84-7.73 (m, 13H, arom. H). MS *m/z* (%): 415 [(M+1), 31], 414 (M, 94), 327 (6), 294 (100).

Anal. Calcd. for $C_{25}H_{22}N_2O_2S$: C, 72.43; H, 5.35; N, 6.76. Found: C, 72.24; H, 5.21; N, 6.88.

3',5'-Diphenyl-2-ethyl-2-methyl-3'*H*,4*H*-spiro[chromene-3,2'-[1,3,4]thiadiazol]-4-one (**5d**).

Yield 77%. IR: ν 1699, 1604, 1462 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ (The ratio of the isolated isomers are 7:3 based on integrations of the observed methyl group signals) "The major

diastereoisomer" 0.93 (t, 3H, CH_3CH_2, J = 7.5 Hz), 1.68 (s, 3H, CH_3), 2.02 (q, 2H, CH_2, J = 7.5 Hz), 6.82-7.69 (m, 14H, arom. H), "The minor diastereoisomer" 0.88 (t, 3H, CH_3CH_2, J = 7.5 Hz), 1.53 (s, 3H, CH_3), 2.25 (q, 2H, CH_2, J = 7.5 Hz), 6.82-7.69 (m, 14H, arom. H). MS *m/z* (%): 414 (M, 0.6), 279 (1.6), 263 (1.2). *Anal*. Calcd. for $C_{25}H_{22}N_2O_2S$: C, 72.43; H, 5.35; N, 6.76. Found: C, 72.50; H, 5.46; N, 6.90.

3'-(3-Chlorophenyl)-2-ethyl-2-methyl-5'-phenyl-3'*H*,4*H*-spiro-[chromene-3,2'-[1,3,4]thiadiazol]-4-one (**5e**).

Yield 66%. IR: ν 1697, 1587, 1465 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ (The ratio of the isolated isomers are 7:3 based on integrations of the observed methyl group signals) "The major diastereo-isomer" 0.94 (t, 3H, CH_3CH_2, J = 7.2 Hz), 1.67 (s, 3H, CH_3), 2.05 (q, 2H, CH_2, J = 7.2 Hz), 6.88-7.70 (m, 13H, arom. H), "The minor diastereoisomer" 0.94 (t, 3H, CH_3CH_2, J = 7.2 Hz), 1.54 (s, 3H, CH_3), 2.20 (q, 2H, CH_2, J = 7.2 Hz), 6.88-7.70 (m, 13H, arom. H). MS *m/z* (%): 448 (M, 1.1), 313 (4.2), 297 (1.5).

Anal. Calcd. for $C_{25}H_{21}ClN_2O_2S$: C, 66.88; H, 4.72; N, 6.24. Found: C, 67.03; H, 4.80; N, 6.12.

2-Ethyl-2-methyl-3'-(4-methylphenyl)-5'-phenyl-3'*H*,4*H*-spiro-[chromene-3,2'-[1,3,4]thiadiazol]-4-one (**5f**).

Yield 52%. IR: ν 1699, 1605, 1464 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ (The ratio of the isolated isomers are 2:1 based on integrations of the observed methyl group signals) "The major diastereo-isomer" 0.93 (t, 3H, CH_3CH_2, J = 7.2 Hz), 1.67 (s, 3H, CH_3), 1.71 (q, 2H, CH_2, J = 7.2 Hz), 2.15 (s, 3H, ArCH_3), 6.81-7.68 (m, 13H, arom. H), "The minor diastereoisomer" 0.93 (t, 3H, CH_3CH_2, J = 7.2 Hz), 1.53 (s, 3H, CH_3), 2.00 (q, 2H, CH_2, J = 7.2 Hz), 2.21 (s, 3H, ArCH_3), 6.81-7.68 (m, 13H, arom. H). MS *m/z* (%): 428 (M, 3), 293 (14), 277 (5).

Anal. Calcd. for $C_{26}H_{24}N_2O_2S$: C, 72.87; H, 5.64; N, 6.54. Found: C, 72.69; H, 5.51; N, 6.35.

REFERENCES

[1] A. Padwa, Intramolecular 1,3-Dipolar Cycloaddition, Eds., B. M. Trost and I. Flemin, "Comprehensive Organic Chemistry" Pergamon, Oxford, Vol. **4**, p. 1069 (1991).

[2] A. Padwa and W. H. Pearson, "Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Towards Heterocycles and Natural Products", Wiley, New York (2002).

[3] S. Kanemasa, *Synlett*, 1371 (2002).

[4] S. Karlsson and E. H. Hőgberg, *Org. Prep. Proc. Int*., **33**, 1032 (2001).

[5] G. Molteni, G. Broggini and T. Pilati, *Tetrahedron: Asymmetry*, **13**, 2491 (2002).

[6] L. De Benassuti, L. Garanti and G. Molteni, *Tetrahedron: Asymmetry*, **15**, 1127 (2004).

[7] K. M. Dawood, *Tetrahedron,* **61**, 5229 (2005).

[8] A. F. Jalbout, Z. Jiang, H. Abou-Rachid and N. N. Benkaddour, *Spectrochimica Acta Part A*, **60**, 603 (2004).

[9] A. S. Girgis, Y. A. Ibrahim, N. Mishriky, J. N. Lisgarten, B. S. Potter and R. A. Palmer, *Tetrahedron*, **57**, 2015 (2001).

[10] G. Meazza and G. Zanardi, *J. Fluor. Chem*., **67**, 183 (1994).

[11] P. Dalla Croce, C. La Rosa and G. Zecchi, *J. Chem. Soc. Perkin Trans. I*, 2621 (1985).

[12] B. Alcaide, G. Escobar, R. Perez-Ossorio and J. Plumet, *An. Quim., Ser. C*, **81**, 85 (1985); *Chem. Abstr*., **106**, 196329 (1987).

[13] G. Molteni and A. Ponti, *Tetrahedron*, **59**, 5225 (2003).

[14] A. Padwa, S. P. Craig, U. Chiacchio and D. N. Kline, *J. Org. Chem*., **53**, 2232 (1988).

[15] N. M. Elwan, H. A. Abdelhadi, T. A. Abdallah and H. M. Hassaneen, *Tetrahedron*, **52**, 3451 (1996).

[16] H. N. Dogan, A. Duran, S. Rollas, G. Sener, M. K. Uysal and D. Gűlen, *Bioorg. Med. Chem*., **10**, 2893 (2002).

[17] E. E. Chufán, J. C. Pedregosa, O. N. Baldini and L. Bruno-Blanch, *Farmaco*, **54**, 838 (1999).

[18] A. Foroumadi, Z. Kiani and F. Soltani, *Farmaco*, **58**, 1073 (2003).

[19] A. Foroumadi, A. Asadipour, M. Mirzaei, J. Karimi and S. Emami, *Farmaco*, **57**, 765 (2002).

[20] A. Foroumadi, S. Pournourmohammadi, F. Soltani, M. Asgharian-Rezaee, S. Dabiri, A. Kharazmi and A. Shafiee, *Bioorg. Med. Chem. Lett*., **15**, 1983 (2005).

[21] J. Chou, S. Lai, S. Pan, G. Jow, J. Chern and J. Guh, *Biochem. Pharm*., **66**, 115 (2003).

[22] F. Vergne, P. Bernardelli, E. Lorthiois, N. Pham, E. Proust, C. Oliveira, A. Mafroud, F. Royer, R. Wrigglesworth, J. K. Schellhaas, M. R. Barvian, F. Moreau, M. Idrissi, A. Tertre, B. Bertin, M. Coupe, P. Berna and P. Soulard, *Bioorg. Med. Chem. Lett*., **14**, 4607 (2004).

[23] F. Vergne, P. Bernardelli, E. Lorthiois, N. Pham, E. Proust, C. Oliveira, A. Mafroud, P. Ducrot, R. Wrigglesworth, F. Berlioz-Seux, F. Coleon, E. Chevalier, F. Moreau, M. Idrissi, A. Tertre, A. Descours, P. Berna and M. Li, *Bioorg. Med. Chem. Lett*., **14**, 4614 (2004).

[24] M. A. Ponce, J. M. Scervino, R. Erra-Balsells, J. A. Ocampo and A. M. Godeas, *Phytochemistry*, **65**, 3131 (2004).

[25] F. Cottiglia, B. Dhanapal, O. Sticher and J. Heilmann, *J. Nat. Prod*., **67**, 537 (2004).

[26] J. Mutanyatta, B. Matapa, D. D. Shushu and B. M. Abegaz, *Phytochemistry*, **62**, 797 (2003).

[27] J. Wu, X. Wang, Y. Yi and K. Lee, *Bioorg. Med. Chem. Lett*., **13**, 1813 (2003).

[28] T. Ishikawa, Y. Oku, T. Tanak and T. Kumamoto, *Tetrahedron Lett*., **40**, 3777 (1999).

[29] Z. Q. Xu, R. W. Bucheit, T. L. Stup, M. T. Flavin, A. Khilevich, J. D. Rezzo, L. Lin and D. E. Zembower, *Bioorg. Med. Chem. Lett*., **8**, 2179 (1998).

[30] M. T. Flavin, J. D. Rezzo, A. Khilevich, A. Kucherenko, A. K. Sheinkman, V. Vilaychack, L. Lin, W. Chen and E. M. Greenwood, *J. Med. Chem*., **39**, 1303 (1996).

[31] Y. Lin, Y. Zhou, M. T. Flavin, L. Zhou, W. Nie and F. Chen, *Bioorg. Med. Chem*., **10**, 2795 (2002).

[32] R. Huisgen, L. Fisera, H. Giera and R. Sustmann, *J. Am. Chem. Soc*., **117**, 9671 (1995).

[33] I. Kalwinsch, X. Li, J. Gottstein and R. Huisgen, *J. Am. Chem. Soc*., **103**, 7032 (1981).

[34] J. B. F. Dunstan, G. M. Elsey, R. A. Russell, G. P. Savage, G. W. Simpson and E. R. T. Tiekink, *Aust. J. Chem*. **51**, 499 (1998).

[35] Full crystallographic details, excluding structure factors, have been deposited at Cambridge Crystallographic Data Centre (CCDC) as supplementary publication numbers CCDC 603407, CCDC 603408 for compounds **3a** and **3b**, respectively.

[36] A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni and R. Spagna, *J. Appl. Cryst*., **32**, 115 (1999).

[37] S. Mackay, C. J. Gilmore, C. Edwards, N. Stewart and K. Shankland, *maXus Computer Program for the Solution and Refinement of Crystal Structures. Bruker Nonius, The Netherlands, MacScience, Japan & The University of Glasgow* (1999).

[38] A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori and M. Camalli, *J. Appl. Cryst*., **27**, 435 (1994).

[39] M. I. Hegab, F. M. E. Abdel-Megeid, F. A. Gad, S. A. Shiba, J. Møller, and A. Senning, *Sulf. Lett*., **22**, 9 (1998).

[40] R. Huisgen, M. Seidel, G. Wallbillich and H. Kunpfer, *Tetrahedron*, **17**, 3 (1962).

[41] A. F. Hegarty, J. A. Kearney and F. L. Scott, *J. Chem. Soc. Perkin Trans. 2*, 1422 (1973).

[42] F. A. G. El-Essawy, S. M. Yassin, I. A. El-Sakka, A. F. Khattab, I. Støfter, J. Møller and A. Senning, *Sulf. Lett*., **22**, 19 (1998).