Regio- and Stereoselective Synthesis of Spiro[1-benzothiepine-4(5*H*), 3'(3*H*)-pyrazol]-5-ones

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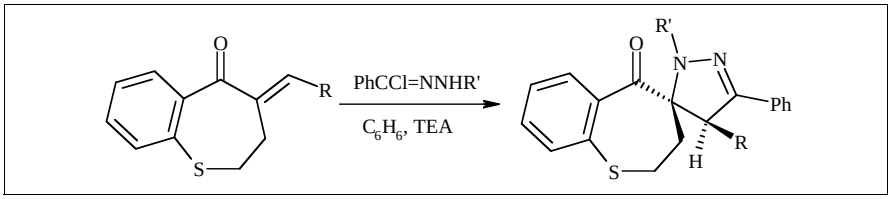

Reaction of (4*E*)-4-arylmethylene-3,4-dihydro-1-benzothiepin-5(2*H*)-ones **3a-e** with nitrilimines (generated *in situ via* triethylamine dehydrohalogenation of the corresponding hydrazonoyl chlorides **4a, b**) in refluxing benzene, afforded 2',4',5'-triaryl-2,2',3,4'-tetrahydro-spiro[1-benzothiepine-4(5*H*),3'(3*H*)-pyrazol]-5-ones **5a-i** and not the isomeric forms spiro[1-benzothiepine-4(5*H*),4'(4*H*)-pyrazol]-5-ones **6** in high regioselective manner. Single crystal X-ray diffraction studies of **5a, f, g** indicated that the isolated products are 3'*R*, 4'*S*.

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Introduction.

Hydrazonoyl halides have been proved to be versatile precursors for synthesis of nitrilimines which intensively used for construction of various heterocyclic systems [1]. 1,3-Dipolar cycloaddition reactions of nitrilimines with alkenes [2-5], alkynes [6,7], azomethines [8], allenes [9,10] as well as heterocyclic residues [11-13] were the basic points of interest for many researchers due to their unique properties, especially regio- and stereoselective behaviours.

In the present work, it is intended to investigate 1,3-dipolar cycloaddition reaction of nitrilimines with 1-benzothiepine bearing exocyclic olefinic linkage. This investigation could allow isolation of many spiro 1-benzothiepine containing pyrazoline heterocyclic derivatives. Regioselectivity of the reactions as well as stereochemical structure of the isolated products will be also taken into consideration.

The interest for synthesis of spiro-containing 1-benzothiepine heterocycle is originated from the well established biological and pharmacological properties associated with this ring system. For example, 1-benzothiepine derivatives were found as ileal bile acid transport and tourocholate uptake inhibitors, which reveal their useful applications for prophylaxis and treatment of hyperlipidemic conditions such as those associated with atherosclerosis or hypercholesterolemia [14-20]. Other derivatives were reported to be useful as anti-proliferative drugs (for treatment of diseases associated with hyper-proliferation of cells). Specific proliferative diseases against which psychotropic agents were found to be effective are cancer, including multi-drug resistant cancer and diseases associated with hyper-proliferation of skin cells, such as psoriasis and hyperkeratosis [21]. Recent investigations show their tumor selective cytotoxic action against human oral tumor cell lines (HSC-2, HSC-3, HSG) [22].

Many other studies reported that, 1-benzothiepines were CC chemokine receptor 5 (CCR5) antagonists. CCR5 was found to be a co-receptor for the entry of macrophage-tropic human immunodeficiency virus type 1 (HIV-1) into host cells, indicating the inhibitory properties of 1-benzothiepine derivatives against HIV-1 infections [23-25]. Other derivatives were found to be useful as neuroprotective agents to reduce neurotoxic injury associated with conditions of hypoxia, anoxia or ischemia which follow stroke, myocardial infarct, perinatal asphyxia or hypoglycemic events [26]. Moreover, many 1-benzothiepine analogues were found to be useful for treatment of pollakiuria and urinary incontinence [27]. Other investigations revealed their stimulation properties of β_3 adrenaline receptors reflecting their ability for treatment of obesity, diabetes, depression…etc. [28].

In addition, the biological and pharmacological properties of pyrazoline containing compounds also prompted the present work. For example, many substituted pyrazolines were reported to exhibit human acyl CoA cholesterol acyltransferase [29], low-density lipoprotein oxidation inhibition [30], antidepressant properties [31-34] as well as monoamine oxidase inhibitory activities [35,36].

Results and Discussion.

3,4-Dihydro-4-[(2-thienyl)methylene]-1-benzothiepin-5(2*H*)-one (**3e**) was prepared in a modified synthetic experimental method related to the previously described

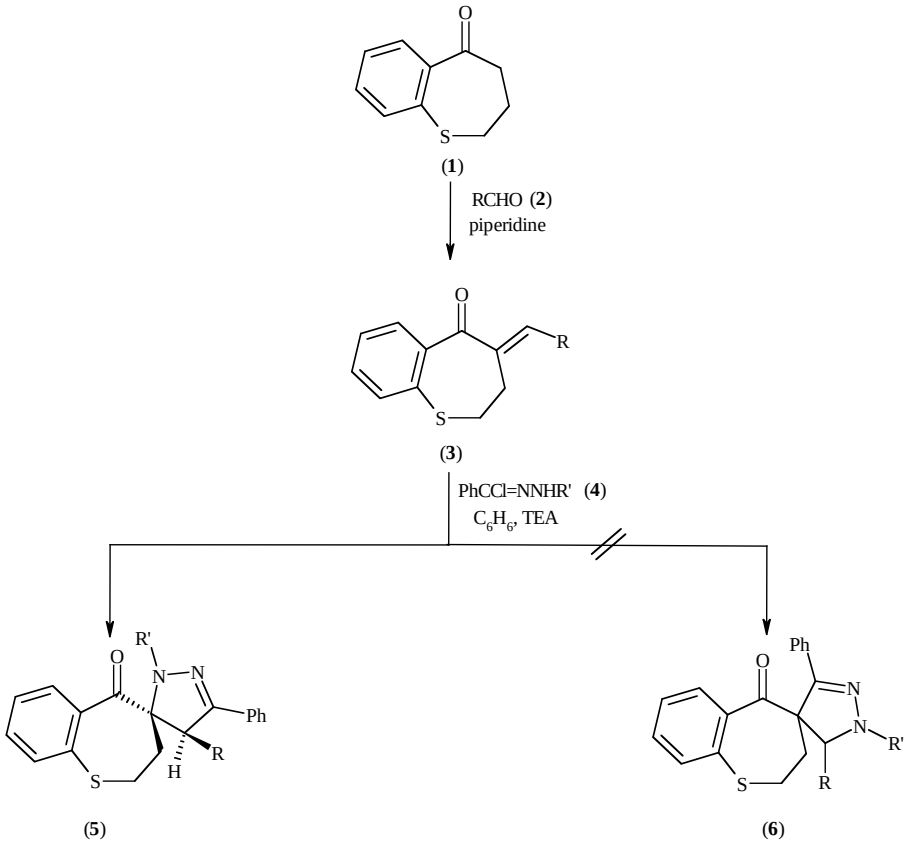
derivatives **3a-d** [37,38] *via* condensation of 3,4-dihydro-1-benzothiepin-5(2*H*)-one (**1**) [39] with thiophene-2-carbaldehyde (**2e**) in the presence of piperidine as a basic catalyst at 160-170 °C. The structure of **3e** was inferred from spectroscopic (IR, ^{1}H-NMR, MS) and elemental analyses data.

IR spectrum of **3e** exhibits a strong absorption band at ν = 1679 cm^{-1} assignable for the α, β-unsaturated carbonyl stretching vibration. Moreover, ^{1}H-NMR spectrum of **3e** reveals each of the benzothiepine methylene protons as triplet signals at δ = 3.08, 3.21 (*J* = 6.3 Hz). The olefinic ylidene proton appears as a sharp singlet signal at δ = 8.04 which supports the isolation of *E*-form geometrically stereochemical isomer.

1,3-Dipolar cycloaddition reaction of 4-arylmethylene-3,4-dihydro-1-benzothiepin-5(2*H*)-ones **3a-e** with nitrilimines (generated *in situ via* triethylamine dehydrohalogenation of the corresponding hydrazonoyl chlorides **4a, b**) in refluxing dry benzene, afforded only one product as indicated by TLC. The structure of which was established to be 2',4',5'-triaryl-2,2',3,4'-tetrahydro-spiro[1-benzothiepine-4(5*H*),3'(3*H*)-pyrazol]-5-ones **5a-i** rather than 2',3',5'-triaryl-2,2',3,3'-tetrahydro-spiro[1-benzothiepine-4(5*H*),4'(4*H*)-pyrazol]-5-ones **6a-i** based on spectroscopic (IR, ^{1}H, ^{13}C-NMR, MS) and elemental analyses data (Scheme 1).

IR spectra of **5a-i** exhibit the presence of a strong carbonyl stretching vibration band at ν = 1690-1669 cm^{-1} excluding any cycloaddition reaction pathway taking place with this moiety. ^{1}H-NMR spectra of **5a-i** reveal the appearance of each of the two adjacent benzothiepine methylene protons as multiplet signals at δ = 2.27-3.10

Scheme (1)



2a, **3a**, R = 4-ClC_6H_4
2b, **3b**, R = 4-BrC_6H_4
2c, **3c**, R = 4-H_3CC_6H_4
2d, **3d**, R = 4-H_3COC_6H_4
2e, **3e**, R = 2-thienyl

4a, R' = Ph
4b, R' = 3-ClC_6H_4

5a, R= 4-ClC_6H_4, R' = Ph
5b, R= 4-ClC_6H_4, R' = 3-ClC_6H_4
5c, R= 4-BrC_6H_4, R' = Ph
5d, R= 4-BrC_6H_4, R' = 3-ClC_6H_4
5e, R= 4-H_3CC_6H_4, R' = Ph
5f, R= 4-H_3COC_6H_4, R' = Ph
5g, R= 4-H_3COC_6H_4, R' = 3-ClC_6H_4
5h, R= 2-thienyl, R' = Ph
5i, R= 2-thienyl, R' = 3-ClC_6H_4

region. The pyrazoline *H*-4' is recognized as a sharp singlet signal at δ = 5.04-5.44 region. The appearance of this signal at the mentioned chemical shift value supports the isolation of **5** [40,41], where the other presumed regio-isomeric form **6** used to reveal its characteristic *H*-3' signal at a chemical shift value downfield than δ>5.6 [42].

^{13}C-NMR (on-resonance & APT) spectra of **5g** "as a representative example" adds a good support for the established structure, where it reveals the two benzothiepine methylene carbons at δ = 28.89, 32.06, in addition to the methoxy and carbonyl carbons at δ = 55.08, 204.65, respectively. The pyrazoline *HC*-4' and spiro-carbon (quaternary *C*-3') were observed at δ = 59.52, 81.03, respectively. These values are in accord with many other similar reported heterocyclic system values [41,43,44].

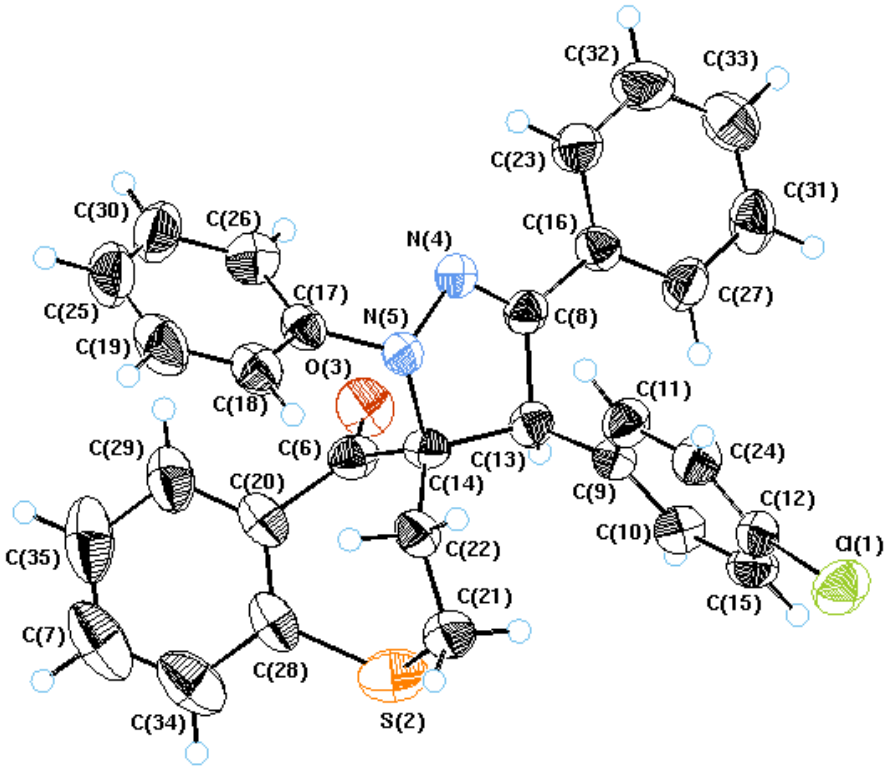


Fig. (1): Single crystal X-ray diffraction of **5a**

Selected intramolecular bond lengths (Å) and bond angles (°) of **5a**.

Cl(1)-C(12) = 1.738(3), S(2)-C(21) = 1.815(4), S(2)-C(28) = 1.773(4), O(3)-C(6) = 1.212(3), N(4)-N(5) = 1.414(3), N(4)-C(8) = 1.268(4), N(5)-C(14) = 1.507(4), N(5)-C(17) = 1.426(4), C(6)-C(14) = 1.555(4), C(6)-C(20) = 1.499(4), C(7)-C(34) = 1.362(6), C(7)-C(35) = 1.378(7), C(8)-C(13) = 1.523(4), C(8)-C(16) = 1.475(4), C(9)-C(10) = 1.379(4), C(9)-C(11) = 1.387(4), C(9)-C(13) = 1.503(4), C(10)-C(15) = 1.388(4), C(11)-C(24) = 1.380(4), C(12)-C(15) = 1.380(4), C(12)-C(24) = 1.374(4), C(13)-C(14) = 1.561(4), C(14)-C(22) = 1.517(4), C(16)-C(23) = 1.399(4), C(16)-C(27) = 1.385(4), C(17)-C(18) = 1.394(4), C(17)-C(26) = 1.384(4), C(18)-C(19) = 1.373(5), C(19)-C(25) = 1.379(5), C(20)-C(28) = 1.393(5), C(20)-C(29) = 1.377(5), C(21)-C(22) = 1.515(4), C(23)-C(32) = 1.374(4), C(25)-C(30) = 1.372(5), C(26)-C(30) = 1.389(5), C(27)-C(31) = 1.381(4), C(28)-C(34) = 1.398(5), C(29)-C(35) = 1.381(5), C(31)-C(33) = 1.387(5), C(32)-C(33) = 1.372(5), C(21)-S(2)-C(28) = 102.1(2), N(5)-N(4)-C(8) = 109.2(3), N(4)-N(5)-C(14) = 108.9(2), N(4)-N((5)-C(17) = 113.3(2), C(14)-N(5)-C(17) = 121.0(2), O(3)-C(6)-C(14) = 120.0(3), O(3)-C(6)-C(20) = 119.6(3), C(14)-C(6)-C(20) = 120.3(3), C(34)-C(7)-C(35) = 120.6(4), N(4)-C(8)-C(13) = 114.1(3), N(4)-C(8)-C(16) = 121.8(3), C(13)-C(8)-C(16) = 124.1(3), C(10)-C(9)-C(11) = 117.9(3), C(10)-C(9)-C(13) = 120.9(3), C(11)-C(9)-C(13) = 121.2(3), C(9)-C(10)-C(15) = 121.6(3), C(9)-C(11)-C(24) = 121.8(3), Cl(1)-C(12)-C(15) = 119.8(3), Cl(1)-C(12)-C(24) = 118.9(3), C(15)-C(12)-C(24) = 121.3(3), C(8)-C(13)-C(9) = 111.3(2), C(8)-C(13)-C(14) = 100.2(2), C(9)-C(13)-C(14) = 114.9(2), N(5)-C(14)-C(6) = 106.1(2), N(5)-C(14)-C(13) = 100.3(2), N(5)-C(14)-C(22) = 109.2(2), C(6)-C(14)-C(13) = 109.9(2), C(6)-C(14)-C(22) = 112.6(2), C(13)-C(14)-C(22) = 117.5(3), C(10)-C(15)-C(12) = 118.6(3), C(8)-C(16)-C(23) = 118.7(3), C(8)-C(16)-C(27) = 123.0(3), C(23)-C(16)-C(27) = 118.3(3), N(5)-C(17)-C(18) = 119.9(3), N(5)-C(17)-C(26) = 121.7(3), C(18)-C(17)-C(26) = 118.4(3), C(17)-C(18)-C(19) = 120.6(3), C(18)-C(19)-C(25) = 120.9(3), C(6)-C(20)-C(28) = 118.7(3), C(6)-C(20)-C(29) = 121.6(3), C(28)-C(20)-C(29) = 119.8(3), S(2)-C(21)-C(22) = 115.5(2), C(14)-C(22)-C(21) = 116.4(3), C(16)-C(23)-C(32) = 120.6(3), C(11)-C(24)-C(12) = 118.7(3), C(19)-C(25)-C(30) = 118.8(3), C(17)-C(26)-C(30) = 120.3(3), C(16)-C(27)-C(31) = 121.0(3), S(2)-C(28)-C(20) = 119.8(3), S(2)-C(28)-C(34) = 120.1(3), C(20)-C(28)-C(34) = 119.8(4), C(20)-C(29)-C(35) = 119.8(4), C(25)-C(30)-C(26) = 120.9(4), C(27)-C(31)-C(33) = 119.7(3), C(23)-C(32)-C(33) = 120.5(3), C(31)-C(33)-C(32) = 119.9(3), C(7)-C(34)-C(28) = 119.6(4), C(7)-C(35)-C(29) = 120.4(4).

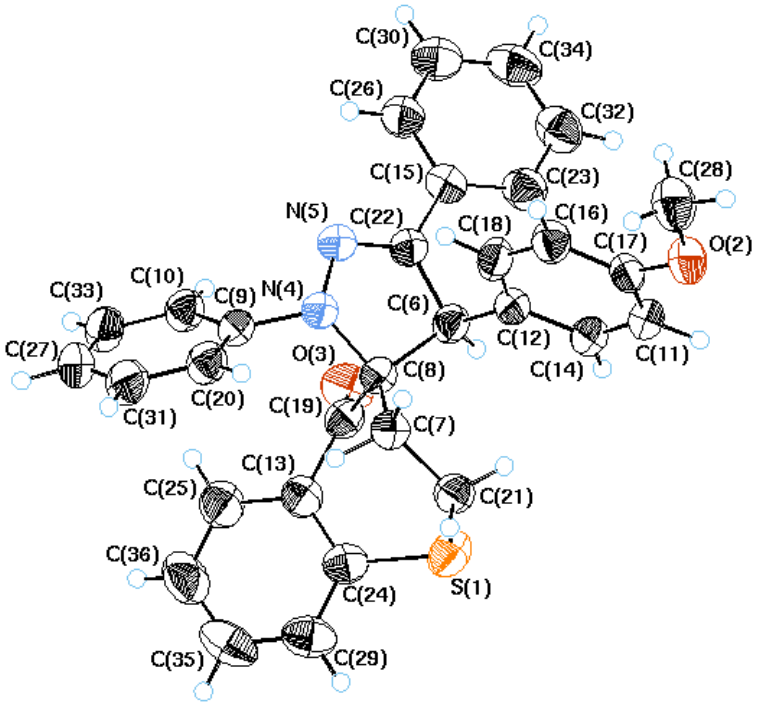


Fig. (2): Single crystal X-ray diffraction of **5f**.

Selected intramolecular bond lengths (Å) and bond angles (°) of **5f**.
S(1)-C(21) = 1.8189(12), S(1)-C(24) = 1.7761(12), O(2)-C(17) = 1.3732(13), O(2)-C(28) = 1.420(2), O(3)-C(19) = 1.2101(13), N(4)-N(5) = 1.3976(12), N(4)-C(8) = 1.5136(13), N(4)-C(9) = 1.4371(14), N(5)-C(22) = 1.2836(13), C(6)-C(8) = 1.556(2), C(6)-C(12) = 1.515(2), C(6)-C(22) = 1.5250(15), C(7)-C(8) = 1.522(2), C(7)-C(21) = 1.5229(15), C(8)-C(19) = 1.5507(14), C(9)-C(10) = 1.377(2), C(9)-C(20) = 1.387(2), C(10)-C(33) = 1.389(2), C(11)-C(14) = 1.382(2), C(11)-C(17) = 1.377(2), C(12)-C(14) = 1.3923(15), C(12)-C(18) = 1.381(2), C(13)-C(19) = 1.499(2), C(13)-C(24) = 1.401(2), C(13)-C(25) = 1.388(2), C(15)-C(22) = 1.463(2), C(15)-C(23) = 1.386(2), C(15)-C(26) = 1.392(2), C(16)-C(17) = 1.383(2), C(16)-C(18) = 1.384(2), C(20)-C(31) = 1.379(2), C(23)-C(32) = 1.391(2), C(24)-C(29) = 1.375(2), C(25)-C(36) = 1.383(2), C(26)-C(30) = 1.369(2), C(27)-C(31) = 1.372(2), C(27)-C(33) = 1.369(2), C(29)-C(35) = 1.379(2), C(30)-C(34) = 1.379(2), C(32)-C(34) = 1.371(2), C(35)-C(36) = 1.363(2), C(21)-S(1)-C(24) = 101.94(5), C(17)-O(2)-C(28) = 117.39(10), N(5)-N(4)-C(8) = 109.05(8), N(5)-N(4)-C(9) = 113.51(8), C(8)-N(4)-C(9) = 120.18(8), N(4)-N(5)-C(22) = 109.32(8), C(8)-C(6)-C(12) = 116.59(9), C(8)-C(6)-C(22) = 100.44(8), C(12)-C(6)-C(22) = 110.60(8), C(8)-C(7)-C(21) = 116.44(9), N(4)-C(8)-C(6) = 99.84(8), N(4)-C(8)-C(7) = 110.03(9), N(4)-C(8)-C(19) = 106.31(7), C(6)-C(8)-C(7) = 116.73(8), C(6)-C(8)-C(19) = 109.52(9), C(7)-C(8)-C(19) = 113.15(9), N(4)-C(9)-C(10) = 122.06(11), N(4)-C(9)-C(20) = 118.49(9), C(10)-C(9)-C(20) = 119.45(10), C(9)-C(10)-C(33) = 119.83(13), C(14)-C(11)-C(17) = 120.19(10), C(6)-C(12)-C(14) = 120.86(10), C(6)-C(12)-C(18) = 121.61(9), C(14)-C(12)-C(18) = 117.49(10), C(19)-C(13)-C(24) = 118.95(10), C(19)-C(13)-C(25) = 121.54(10), C(24)-C(13)-C(25) = 119.40(11), C(11)-C(14)-C(12) = 121.29(11), C(22)-C(15)-C(23) = 120.83(10), C(22)-C(15)-C(26) = 120.67(11), C(23)-C(15)-C(26) = 118.47(12), C(17)-C(16)-C(18) = 119.75(11), O(2)-C(17)-C(11) = 115.86(9), O(2)-C(17)-C(16) = 124.64(10), C(11)-C(17)-C(16) = 119.49(10), C(12)-C(18)-C(16) = 121.75(10), O(3)-C(19)-C(8) = 120.16(10), O(3)-C(19)-C(13) = 119.68(10), C(8)-C(19)-C(13) = 120.01(10), C(9)-C(20)-C(31) = 119.85(11), S(1)-C(21)-C(7) = 115.84(7), N(5)-C(22)-C(6) = 113.21(10), N(5)-C(22)-C(15) = 122.39(9), C(6)-C(22)-C(15) = 124.34(9), C(15)-C(23)-C(32) = 120.61(13), S(1)-C(24)-C(13) = 118.54(9), S(1)-C(24)-C(29) = 121.21(9), C(13)-C(24)-C(29) = 119.99(11), C(13)-C(25)-C(36) = 119.52(13), C(15)-C(26)-C(30) = 120.66(13), C(31)-C(27)-C(33) = 119.46(13), C(24)-C(29)-C(35) = 119.82(13), C(26)-C(30)-C(34) = 120.44(13), C(20)-C(31)-C(27) = 120.75(13), C(23)-C(32)-C(34) = 119.79(14), C(10)-C(33)-C(27) = 120.63(13), C(30)-C(34)-C(32) = 119.97(14), C(29)-C(35)-C(36) = 120.63(14), C(25)-C(36)-C(35) = 120.59(14).

Single crystal X-ray diffraction studies of **5a, f, g** add good support for the established structure. It has been noticed that, the thiepine ring system takes a modified boat form configuration. It was expected that, the isolated products are mixture of different stereoisomeric forms. However, the obtained data indicated that, the isolated crystalline form products are 3'*R*, 4'*S* (Fig. 1-3).

From all the above it could be concluded that, 1,3-dipolar cycloaddition reaction of nitrilimines to enone system **3** takes place in high regioselective manner under the described reaction conditions. Where, the dipole compound approaches the olefinic linkage of dipolarofile suprafacially, or in other words from the less hindered face affording eventually **5**.

EXPERIMENTAL

Melting points are uncorrected and were recorded on an Electrothermal 9100 digital melting point apparatus. IR spectra (KBr) were recorded on a Nexus 670 FT-IR spectrophotometer. NMR spectra were recorded on a Varian MERCURY spectrometer (^{1}H: 300, ^{13}C: 75 MHz) in $CDCl_3$. Mass spectra

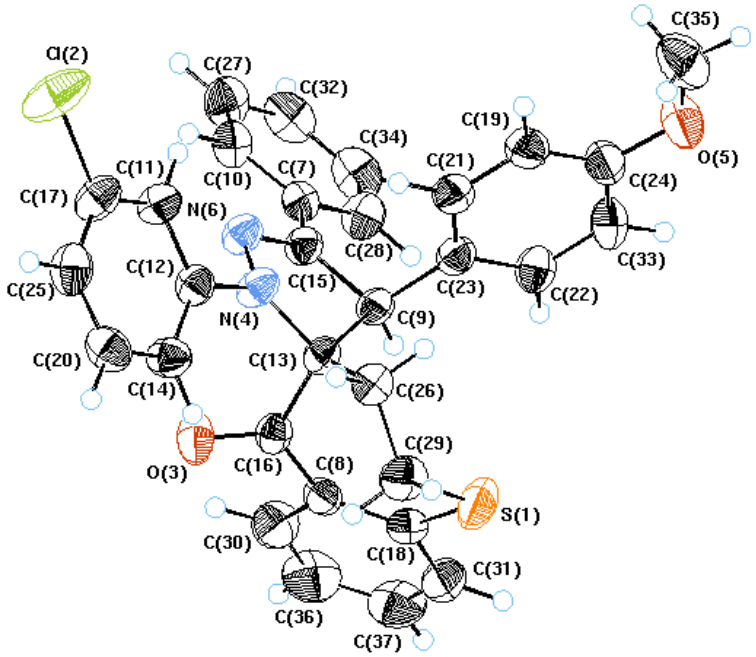


Fig. (3): Single crystal X-ray diffraction of **5g**.

Selected intramolecular bond lengths (Å) and bond angles (°) of **5g**.
S(1)-C(18) = 1.758(2), S(1)-C(29) = 1.798(2), Cl(2)-C(17) = 1.753(2), O(3)-C(16) = 1.206(2), N(4)-N(6) = 1.381(2), N(4)-C(12) = 1.407(2), N(4)-C(13) = 1.469(2), O(5)-C(24) = 1.377(2), O(5)-C(35) = 1.435(3), N(6)-C(15) = 1.290(2), C(7)-C(10) = 1.391(3), C(7)-C(15) = 1.469(3), C(7)-C(28) = 1.388(3), C(8)-C(16) = 1.507(3), C(8)-C(18) = 1.386(3), C(8)-C(30) = 1.396(3), C(9)-C(13) = 1.577(3), C(9)-C(15) = 1.523(3), C(9)-C(23) = 1.523(3), C(10)-C(27) = 1.381(3), C(11)-C(12) = 1.396(3), C(11)-C(17) = 1.380(3), C(12)-C(14) = 1.381(3), C(13)-C(16) = 1.567(3), C(13)-C(26) = 1.540(2), C(14)-C(20) = 1.377(3), C(17)-C(25) = 1.373(3), C(18)-C(31) = 1.397(3), C(19)-C(21) = 1.387(3), C(19)-C(24) = 1.378(3), C(20)-C(25) = 1.377(3), C(21)-C(23) = 1.391(3), C(22)-C(23) = 1.387(3), C(22)-C(33) = 1.380(3), C(24)-C(33) = 1.377(3), C(26)-C(29) = 1.510(3), C(27)-C(32) = 1.382(3), C(28)-C(34) = 1.391(3), C(30)-C(36) = 1.366(3), C(31)-C(37) = 1.366(3), C(32)-C(34) = 1.369(3), C(36)-C(37) = 1.377(4), C(18)-S(1)-C(29) = 103.02(10), N(6)-N(4)-C(12) = 116.51(15), N(6)-N(4)-C(13) = 110.88(13), C(12)-N(4)-C(13) = 129.7(2), C(24)-O(5)-C(35) = 118.3(2), N(4)-N(6)-C(15) = 108.87(15), C(10)-C(7)-C(15) = 119.7(2), C(10)-C(7)-C(28) = 118.6(2), C(15)-C(7)-C(28) = 121.7(2), C(16)-C(8)-C(18) = 127.8(2), C(16)-C(8)-C(30) = 114.3(2), C(18)-C(8)-C(30) = 117.9(2), C(13)-C(9)-C(15) = 98.77(14), C(13)-C(9)-C(23) = 117.35(14), C(15)-C(9)-C(23) = 111.46(15), C(7)-C(10)-C(27) = 121.0(2), C(12)-C(11)-C(17) = 118.9(2), N(4)-C(12)-C(11) = 116.9(2), N(4)-C(12)-C(14) = 124.1(2), C(11)-C(12)-C(14) = 119.0(2), N(4)-C(13)-C(9) = 99.84(14), N(4)-C(13)-C(16) = 108.73(15), N(4)-C(13)-C(26) = 111.06(14), C(9)-C(13)-C(16) = 106.57(14), C(9)-C(13)-C(26) = 117.1(2), C(16)-C(13)-C(26) = 112.60(15), C(12)-C(14)-C(20) = 120.4(2), N(6)-C(15)-C(7) = 120.3(2), N(6)-C(15)-C(9) = 112.8(2), C(7)-C(15)-C(9) = 127.0(2), O(3)-C(16)-C(8) = 119.2(2), O(3)-C(16)-C(13) = 119.2(2), C(8)-C(16)-C(13) = 121.2(2), Cl(2)-C(17)-C(11) = 118.4(2), Cl(2)-C(17)-C(25) = 118.9(2), C(11)-C(17)-C(25) = 122.6(2), S(1)-C(18)-C(8) = 126.1(2), S(1)-C(18)-C(31) = 114.4(2), C(8)-C(18)-C(31) = 119.5(2), C(21)-C(19)-C(24) = 119.4(2), C(14)-C(20)-C(25) = 121.6(2), C(19)-C(21)-C(23) = 121.8(2), C(23)-C(22)-C(33) = 121.2(2), C(9)-C(23)-C(21) = 122.1(2), C(9)-C(23)-C(22) = 120.5(2), C(21)-C(23)-C(22) = 117.4(2), O(5)-C(24)-C(19) = 124.3(2), O(5)-C(24)-C(33) = 115.9(2), C(19)-C(24)-C(33) = 119.7(2), C(17)-C(25)-C(20) = 117.5(2), C(13)-C(26)-C(29) = 114.89(15), C(10)-C(27)-C(32) = 119.9(2), C(7)-C(28)-C(34) = 119.9(2), S(1)-C(29)-C(26) = 114.25(15), C(8)-C(30)-C(36) = 122.1(2), C(18)-C(31)-C(37) = 121.2(2), C(27)-C(32)-C(34) = 119.7(2), C(22)-C(33)-C(24) = 120.5(2), C(28)-C(34)-C(32) = 120.9(2), C(30)-C(36)-C(37) = 119.6(2), C(31)-C(37)-C(36) = 119.7(2).

were recorded on Schimadzu GCMS-QP 1000 EX and Finnigan SSQ 7000 spectrometers (EI, 70 eV). The starting compounds **4a,b** [45,46] were prepared according to the previously reported procedures.

Synthesis of 3,4-dihydro-4-[(2-thienyl)methylene]-1-benzothiepin-5(2*H*)-one (**3e**).

A mixture of 3,4-dihydro-1-benzothiepin-5(2*H*)-one **1** (10 mmol), thiophene-2-carbaldehyde **2e** (11 mmol) and piperidine (10-12 drops) was heated in an oil bath at 160-170 °C for 4h. The separated solid upon triturating the reaction mixture with methanol (5 ml), was collected and crystallized from n-butanol affording **3e** as very pale yellow crystals, m.p. 141-143 °C, yield 70%. IR: $\nu_{max.}$ 1679, 1654, 1588 cm^{-1}. ^{1}H-NMR: δ 3.08 (t, 2H, SCH_2CH_2, *J* = 6.3 Hz), 3.21 (t, 2H, SCH_2, *J* = 6.3 Hz), 7.12-7.72 (m, 7H, arom. H), 8.04 (s, 1H, olefinic *CH*). MS *m/z* (%): 272 (M, 52), 244(100). *Anal.* for $C_{15}H_{12}OS_2$ (272.37): Calcd. C, 66.14; H, 4.44; Found C, 66.40; H, 4.63%.

Synthesis of 2,2',3,4'-tetrahydro-2',4',5'-triaryl-spiro[1-benzothiepine-4(5*H*),3'(3*H*)-pyrazol]-5-ones **5a-i**.

General procedure.

A mixture of equimolar amounts of **3a-e** (5 mmol) and the corresponding **4a,b** in dry benzene (25 ml) was boiled under reflux for the appropriate time. The reaction mixture was filtered off to remove the formed triethylamine hydrochloride

and the remaining reaction mixture was evaporated till dryness under reduced pressure. The separated solid upon triturating the residual oily material with methanol (5 ml) (except in case of **5i**, diethyl ether "5 ml" was used), was collected and crystallized from n-butanol affording the corresponding **5a-i**.

4'-(4-Chlorophenyl)-2',5'-diphenyl-2,2',3,4'-tetrahydro-spiro[1-benzothiepine-4(5*H*),3'(3*H*)-pyrazol]-5-one (**5a**).

Reaction time 40 h, yellow crystals, m.p. 208-210 °C, yield 81%. IR: $\nu_{max.}$ 1687, 1588, 1486 cm^{-1}. ^{1}H-NMR: δ 2.49-2.65 (m, 2H, SCH$_2$*CH$_2$*), 2.87-3.07 (m, 2H, S*CH$_2$*), 5.33 (s, 1H, *H*-4'), 6.79-7.83 (m, 18H, arom. H). MS *m/z* (%): 495 [(M+1), 8], 494 (M, 11), 358 (27), 357 (100), 344 (7), 343 (10). *Anal.* for $C_{30}H_{23}ClN_2OS$ (495.017): Calcd. C, 72.79; H, 4.68; N, 5.66; Found C, 72.96; H, 4.82; N, 5.95%.

2'-(3-Chlorophenyl)-4'-(4-chlorophenyl)-5'-phenyl-2,2',3,4'-tetrahydro-spiro[1-benzothiepine-4(5*H*),3'(3*H*)-pyrazol]-5-one (**5b**).

Reaction time 42 h, colourless crystals, m.p. 155-158 °C, yield 83%. IR: $\nu_{max.}$ 1686, 1590, 1482 cm^{-1}. ^{1}H-NMR: δ 2.34-2.50 (m, 2H, SCH$_2$*CH$_2$*), 2.74-2.94 (m, 2H, S*CH$_2$*), 5.05 (s, 1H, *H*-4'), 6.95-7.60 (m, 17H, arom. H). MS *m/z* (%): 529 [(M+1), 5], 528 (M, 11), 392 (42), 391 (100), 378 (3), 377 (8). *Anal.* for $C_{30}H_{22}Cl_2N_2OS$ (529.47): Calcd. C, 68.05; H, 4.19; N, 5.29; Found C, 68.36; H, 4.33; N, 5.20%.

4'-(4-Bromophenyl)-2',5'-diphenyl-2,2',3,4'-tetrahydro-spiro[1-benzothiepine-4(5*H*),3'(3*H*)-pyrazol]-5-one (**5c**).

Reaction time 45 h, yellow crystals, m.p. 209-211 °C, yield 89%. IR: $\nu_{max.}$ 1688, 1592, 1486 cm^{-1}. ^{1}H-NMR: δ 2.30-2.47 (m, 2H, SCH$_2$*CH$_2$*), 2.68-2.88 (m, 2H, S*CH$_2$*), 5.13 (s, 1H, *H*-4'), 6.59-7.64 (m, 18H, arom. H). MS *m/z* (%): 539 [(M+1), 6], 538 (M, 14), 402 (47), 401 (100), 388 (3), 387 (3). *Anal.* for $C_{30}H_{23}BrN_2OS$ (539.473): Calcd. C, 66.79; H, 4.30; N, 5.19; Found C, 66.98; H, 4.33; N, 5.45%.

4'-(4-Bromophenyl)-2'-(3-Chlorophenyl)-5'-phenyl-2,2',3,4'-tetrahydro-spiro[1-benzothiepine-4(5*H*),3'(3*H*)-pyrazol]-5-one (**5d**).

Reaction time 45 h, pale yellow crystals, m.p. 169-171 °C, yield 87%. IR: $\nu_{max.}$ 1683, 1589, 1479 cm^{-1}. ^{1}H-NMR: δ 2.34-2.50 (m, 2H, SCH$_2$*CH$_2$*), 2.75-2.95 (m, 2H, S*CH$_2$*), 5.05 (s, 1H, *H*-4'), 6.96-7.60 (m, 17H, arom. H). MS *m/z* (%): 573 [(M+1), 6], 572 (M, 8), 437 (100), 436 (39), 435 (86), 422 (2), 421 (3). *Anal.* for $C_{30}H_{22}BrClN_2OS$ (573.926): Calcd. C, 62.78; H, 3.86; N, 4.88; Found C, 62.54; H, 3.73; N, 5.21%.

2',5'-Diphenyl-4'-(4-methylphenyl)-2,2',3,4'-tetrahydro-spiro[1-benzothiepine-4(5*H*),3'(3*H*)-pyrazol]-5-one (**5e**).

Reaction time 50 h, yellow crystals, m.p. 196-198 °C, yield 76%. IR: $\nu_{max.}$ 1690, 1593, 1487 cm^{-1}. ^{1}H-NMR: δ 2.51 (s, 3H, CH$_3$), 2.53-2.70 (m, 2H, SCH$_2$*CH$_2$*), 2.84-3.02 (m, 2H, S*CH$_2$*), 5.33 (s, 1H, *H*-4'), 6.78-7.87 (m, 18H, arom. H). MS *m/z* (%): 474 (M, 20), 338 (27), 337 (100), 324 (6), 323 (16). *Anal.* for $C_{31}H_{26}N_2OS$ (474.604): Calcd. C, 78.45; H, 5.52; N, 5.90; Found C, 78.09; H, 5.33; N, 5.69%.

2',5'-Diphenyl-4'-(4-methoxyphenyl)-2,2',3,4'-tetrahydro-spiro-[1-benzothiepine-4(5*H*),3'(3*H*)-pyrazol]-5-one (**5f**).

Reaction time 50 h, yellow crystals, m.p. 170-172 °C, yield 82%. IR: $\nu_{max.}$ 1686, 1594, 1488 cm^{-1}. ^{1}H-NMR: δ 2.27-2.39 (m, 2H, SCH$_2$*CH$_2$*), 2.61-2.75 (m, 2H, S*CH$_2$*), 3.69 (s, 3H, OCH$_3$), 5.04 (s, 1H, *H*-4'), 6.51-7.57 (m, 18H, arom. H). MS *m/z* (%): 490 (M, 100), 354 (16), 353 (80), 340 (4), 339 (21). *Anal.* for $C_{31}H_{26}N_2O_2S$ (490.604): Calcd. C, 75.89; H, 5.34; N, 5.71; Found C, 75.64; H, 5.15; N, 5.34%.

2'-(3-Chlorophenyl)-4'-(4-methoxyphenyl)-5'-phenyl-2,2',3,4'-tetrahydro-spiro[1-benzothiepine-4(5*H*),3'(3*H*)-pyrazol]-5-one (**5g**).

Reaction time 55 h, pale yellow crystals, m.p. 181-183 °C, yield 76%. IR: $\nu_{max.}$ 1684, 1591, 1480 cm^{-1}. ^{1}H-NMR: δ 2.58-2.69 (m, 2H, SCH$_2$*CH$_2$*), 2.91-3.10 (m, 2H, S*CH$_2$*), 3.97 (s, 3H, OCH$_3$), 5.23 (s, 1H, *H*-4'), 7.06-7.82 (m, 17H, arom. H). ^{13}C-NMR "on-resonance & APT": δ 28.89, 32.06 (2*CH$_2$*), 55.08 (O*CH$_3$*), 59.52 (*HC*-4'), 81.03 (spiro *C*-3'), 114.34, 117.94, 120.33, 122.30, 126.46, 127.84, 128.20, 128.59, 129.43, 129.50, 131.38, 131.46 (arom. *CH*), 127.32, 131.30, 132.22, 134.33, 141.47, 145.43, 152.81 (arom. quaternary *C*), 159.35 (*C*=N), 204.65 (*C*=O). MS *m/z* (%): 525 [(M + 1), 14], 524 (M, 48), 388 (29), 387 (100), 374 (8), 373 (19). *Anal.* for $C_{31}H_{25}ClN_2O_2S$ (525.047): Calcd. C, 70.91; H, 4.80; N, 5.34; Found C, 71.02; H, 4.97; N, 5.28%.

2',5'-Diphenyl-2,2',3,4'-tetrahydro-4'-(2-thienyl)-spiro[1-benzothiepine-4(5*H*),3'(3*H*)-pyrazol]-5-one (**5h**).

Reaction time 50 h, pale yellow crystals, m.p. 201-203 °C, yield 73%. IR: $\nu_{max.}$ 1689, 1592, 1485 cm^{-1}. ^{1}H-NMR: δ 2.54-2.71 (m, 2H, SCH$_2$*CH$_2$*), 2.76-2.97 (m, 2H, S*CH$_2$*), 5.44 (s, 1H, *H*-4'), 6.82-7.68 (m, 17H, arom. H). MS *m/z* (%): 467 [(M + 1), 16], 466 (M, 48), 330 (24), 329 (100), 316 (10), 315 (36). Anal. for $C_{28}H_{22}N_2OS_2$ (466.60): Calcd. C, 72.07; H, 4.75; N, 6.01; Found C, 72.36; H, 4.97; N, 6.18%.

2'-(3-Chlorophenyl)-5'-phenyl-2,2',3,4'-tetrahydro-4'-(2-thienyl)-spiro[1-benzothiepine-4(5*H*),3'(3*H*)-pyrazol]-5-one (**5i**).

Reaction time 55 h, pale yellow crystals, m.p. 180-182 °C, yield 70%. IR: $\nu_{max.}$ 1669, 1589, 1478 cm^{-1}. ^{1}H-NMR: δ 2.48-2.78 (m, 2H, SCH$_2$*CH$_2$*), 2.81-3.01 (m, 2H, S*CH$_2$*), 5.35 (s, 1H, *H*-4'), 6.95-7.63 (m, 16H, arom. H). MS *m/z* (%): 501 [(M + 1), 19], 500 (M, 54), 364 (42), 363 (100), 350 (10), 349 (20). *Anal.* for $C_{28}H_{21}ClN_2OS_2$ (501.043): Calcd. C, 67.12; H, 4.23; N, 5.59; Found C, 67.08; H, 4.10; N, 5.38%.

Single crystal X-ray crystallographic data of **5a, f, g** [47].

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

Compound 5a: For X-ray crystallographic studies, compound **5a** was recrystallized as yellow prismatic crystals from n-butanol. The crystal structure was determined by SIR92[48] and refined by maXus[49] (Bruker Nonius, Delft and MacScience, Japan). Chemical formula $C_{30}H_{23}ClN_2OS$, M_r = 495.044, triclinic, crystallizes in space group *P*-1, Cell lengths "a = 10.7287(7), b = 11.1582(9), c = 12.1761(12) Å", Cell angles "α = 68.334(4), β = 78.557(5), γ = 64.544(5)°", V = 1221.8(2) Å^3, Z = 2, D_c = 1.346 mg/m^3, θ values 2.910-22.986°, absorption coefficient μ (*Mo-Kα*) = 0.27 mm^{-1}, F(000) = 516. The unique reflections measured 4802 of which 1622 reflections with threshold expression $I>3\sigma(I)$ were used in the structural analysis. Convergence for 316 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 = 0.051 and wR = 0.105 with a goodness-of-fit of 1.747.

Compound 5f: For X-ray crystallographic studies, compound **5f** was recrystallized as yellow prismatic crystals from n-butanol. The crystal structure was determined by SIR92 [48] and refined by maXus [49] (Bruker Nonius, Delft and MacScience, Japan). Chemical formula $C_{31}H_{26}N_2O_2S$, M_r = 490.625, monoclinic, crystallizes in space group *C-2lc*, Cell lengths "*a* = 17.5813(3), *b* = 15.9834(4), *c* = 18.1402(5) Å", Cell angles "α = 90.00, β = 93.4409(8), γ = 90.00°", *V* = 5088.4(2) Å^3, Z = 8, D_c = 1.281 mg/m^3, θ values 2.910-27.485°, absorption coefficient μ (*Mo-K*α) = 0.16 mm^{-1}, *F*(000) = 2063. The unique reflections measured 10142 of which 3130 reflections with threshold expression $I>3\sigma(I)$ were used in the structural analysis. Convergence for 373 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* = 0.043 and *wR* = 0.072 with a goodness-of-fit of 2.060.

Compound 5g: For X-ray crystallographic studies, compound **5g** was recrystallized as pale yellow platlet crystals from n-butanol. The crystal structure was determined by SIR92 [48] and refined by maXus [49] (Bruker Nonius, Delft and MacScience, Japan). Chemical formula $C_{31}H_{25}ClN_2O_2S$, M_r = 525.070, monoclinic, crystallizes in space group *P-2$_1$lc*, Cell lengths "*a* = 9.7548(2), *b* = 14.1909(3), *c* = 18.9092(6) Å", Cell angles "α = 90.00, β = 90.4986(8), γ = 90.00°", *V* = 2617.49(11) Å^3, Z = 4, D_c = 1.332 mg/m^3, θ values 2.910-26.022°, absorption coefficient μ (*Mo-K*α) = 0.26 mm^{-1}, *F*(000) = 1096. The unique reflections measured 8919 of which 3266 reflections with threshold expression $I>3\sigma(I)$ were used in the structural analysis. Convergence for 334 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* = 0.045 and *wR* = 0.073 with a goodness-of-fit of 1.568.

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