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# Synthesis of (*E*)-2,5-disubstituted 1,3,4-thiadiazolyl-2,3-diphenylpropenones from alkenylidene-hydrazinecarbothioamides

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ABSTRACT

Conjugated alkenylidene-hydrazinecarbothioamides react in high yield with 2,3-diphenylcyclopropenone to give a series of (*E*)-2,5-disubstituted 1,3,4-thiadiazolyl-2,3-diphenylpropenones.

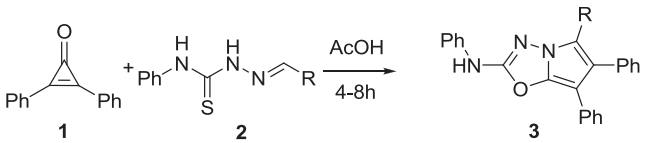


## 1. Introduction

Cyclopropenones undergo several interesting cycloaddition reactions that provide useful starting materials for a variety of compounds.[1–3] 2,3-Diphenylcycloprop-2-enone (**1**) is stable, has aromatic character and reacts with both electrophilic and nucleophilic reagents. Due to its strained ring, 2,3-diphenylcycloprop-2-enone (**1**) acts as an ambident electrophile with the potential for nucleophilic addition at the carbonyl group or conjugate addition.[4–7] These factors allow participation in a wide variety of synthetically useful reactions and the use of diphenylcyclopropenone in the preparation of a plethora of heterocyclic systems has been systematically studied over the past few decades.[8–16]

Cycloaddition chemistry plays a major role in the synthetic versatility of 2,3-diphenylcycloprop-2-enone (**1**). Compound **1** reacts with a wide range of imine and other compounds containing the C=N moiety to form azacyclopentenones (pyrrolinones) via a formal [2+3] cycloaddition reaction.[9–16] The formal [2+3] cycloaddition of a twofold excess of **1** to azomethine imines generated from aryl-1,5-diazabicyclo[3.1.0]hexanes afforded diazacyclopenta[*cd*]-inden-7-ones.[17]

*N*-Imidoylthioureas reacted with **1** to give pyrimidin-4(3*H*)-ones.[18] Substituted pyrrol-3-ones were formed during the reaction of $N^1$, $N^2$-diarylacetamidines, diimines and azines with **1**, through a formal [2+3] cycloaddition reaction.[19,20] Reaction of diphenylcyclopropenone with 2 equiv of substituted thiosemicarbazides results in the formation of 1,2,4-triazolo-[4,3-*b*]pyridazinethiones.[21] *N*-Substituted hydrazine derivatives of thiosemicarbazides react stoichiometrically to yield pyridazinethiones.[21] In each case, the reaction proceeds mechanistically via a formal [3+3] cycloaddition.[21] Recently, we reported that the reaction of various aldehyde 4-phenylthiosemicarbazones **2** with 2,3-diphenylcycloprop-2-enone (**1**) in acetic acid effected the formation of pyrrolo[2,1-*b*][1,3,4]oxadiazoles **3** (Scheme 1).[22]




**2,3**: R= 4-MeO-$C_6H_4$; 4-HO-$C_6H_4$; 4-Cl-$C_6H_4$; 2-Thienyl; Ph

**Scheme 1.** Pyrrolo[2,1-*b*][1,3,4]oxadiazoles from diphenylcyclopropenone and thiosemicarbazones.

On the other hand, the reaction of aldehyde and ketone thiosemicarbazones with acid anhydrides or acid chlorides gave 1,3,4-thiadiazoline derivatives.[23,24]

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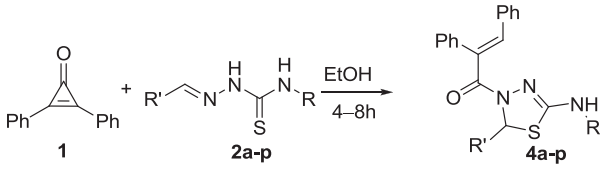
This fascinating versatility in the reaction of aldehyde 4-phenylthiosemicarbazones **2** with **1** justifies further investigation of the reactivity of diphenylcyclopropenone **1** towards alkenylidene-hydrazinecarbothioamides **2a**–**p** (Scheme 2).




| 2,4 | R | R' | Yield |
|---|---|---|---|
| A | Ph- | Ph-CH=CH (*E*) | 82 |
| B | Bn- | Ph-CH=CH (*E*) | 75 |
| C | $CH_2$=CH-$CH_2$- | Ph-CH=CH (*E*) | 70 |
| D | Ph- | 2-MeO-$C_6H_4$-CH=CH (*E*) | 72 |
| E | Bn- | 2-MeO-$C_6H_4$-CH=CH (*E*) | 76 |
| F | $CH_2$=CH-$CH_2$- | 2-MeO-$C_6H_4$- CH=CH(*E*) | 68 |
| G | Ph- | Ph-CH=C(Me) (*E*) | 84 |
| H | Ph- | Me-$(CH_2)_2$-CH=CH- (*E*) | 83 |
| I | Bn- | Me-$(CH_2)_2$-CH=CH- (*E*) | 65 |
| J | $CH_2$=CH-$CH_2$ | Me$(CH_2)_2$-CH=CH- (*E*) | 71 |
| K | Ph- | Me-CH=CH- (*E*) | 75 |
| L | Bn- | Me-CH=CH- (*E*) | 71 |
| M | $CH_2$=CH-$CH_2$- | Me-CH=CH- (*E*) | 67 |
| N | Ph- | $(Me)_2$-CH- | 76 |
| O | Bn- | $(Me)_2$-CH- | 74 |
| P | $CH_2$=CH-$CH_2$- | $(Me)_2$-CH- | 69 |

**Scheme 2.** Reaction of 2,3-diphenylcycloprop-2-enone (**1**) and alkenylidene-hydrazinecarbothioamides **2**.

## 2. Results and discussion

Compounds **2a**–**p** may react at least with their sulfur atom, $N^2$ and $N^4$ as well as azomethine-nitrogen as nucleophilic sites. Thus, several options for interactions between **1** and **2** may be envisaged, as will be outlined later.

In this paper we describe the synthesis of (*E*)-2,5-disubstituted-1,3,4-thiadiazolyl-2,3-diphenylpropenones **4a**–**p** from the reaction of 2,3-diphenylcycloprop-2-enone (**1**) and alkenylidene-hydrazinecarbothioamides **2a**–**p** by refluxing equimolar amounts of the reactants in ethanol as solvent. Compounds **4a**–**p** were obtained as crystalline solids in 69–84% yield (Scheme 2).

Elemental analyses and mass spectra of these molecules clearly revealed that the products were formed by the addition of one molecule of **1** to one molecule of **2a**–**p** without any elimination. The IR spectra of the isolated compounds from the reaction of **1** with **2a**–**p** showed absorptions of the NH group at 3315–3280 $cm^{-1}$ and two strong bands at 1690–1670, 1630–1615 $cm^{-1}$ due to the carbonyl group and C=N vibration, respectively. The IR spectra did not reveal absorption due to C=S or OH groups. The $^1$H NMR spectra of compounds **4a**–**p** show the absence of any signals due to H–$N^2$ or azomethine (CH=N–) groups but show the NH proton signals at $\delta_H$=7.30–7.67 (NH–Ph), 6.65–6.90 (NH–$CH_2$Ph) and 6.15–6.65 (NH-allyl), the signal of thiadiazole–CH proton at 6.15–6.58, as well as the substituents (R′), in addition to the aromatic protons.

In the $^{13}$C NMR spectra of **4a**–**p** signals at $\delta_C$=66.1–68.5 ppm were assigned to (thiadiazole–CH), 147.0–156.3 due to (thiadiazole–C=N) and 164.7–168.2 ppm (CO). The following additional remarks are necessary: the $^1$H NMR spectrum of **4k** shows the presence of one doublet at $\delta_H$=(1.70 ppm, *J*=6.7 Hz), due to methyl group and two multiplets at 5.64 and 5.83–5.85 ppm due to (Ar–CH=CH), a broad band at 7.44 ppm due to NH, in addition to the aromatic protons. The $^{13}$C NMR spectrum of **4k** showing two downfield lines at 166.5 and 152.5 ppm due to (CO) and thiadiazole–C=N, respectively. The $^{13}$C NMR spectrum supported the $^1$H NMR spectroscopic data by distinctive appearance of carbon signals representing Ar–*C*H=*C*H at 118.2 and 122.6 ppm, whereas the thiadiazole–*C*H group resonated at 67.52 ppm.

The molecular formulae of **4a**–**p** are supported by the mass spectra, which gave the predicted molecular ion peaks. It should also be noted that the mass spectra of compounds **4a**–**p** are characterized by four fragments common to all products [$M^+$–RN=C=S], 207 (Ph–CH=CPh)$CO^+$, 178 (Ph–C≡C–Ph) and RN=C=S.

Moreover, the structure of **4k** has been unambiguously confirmed by a single crystal X-ray structure analysis (Fig. 1, and Tables 1–5 in the Supplementary data), which confirms a *cisoid* geometry with respect to the central C42–C43 double bond (note that the crystallographic numbering does not correspond to the systematic IUPAC numbering rules), showing a bond length of 1.338 (3) Å and thus being slightly longer than an unperturbed C=C double bond, with a dihedral angle C(421)–C(42)–C(43)–C(431) of −7.7(3)°. The sum of C(41)–N(4)–N(3), C(41)–N(4)–C(5) and N(3)–N(4)–C(5) angles is close to 360° as are the sums of the angles around C(41), C(42) and C(43) demonstrating planarity around N(4), C(41), C(42) and C(43), whereas the sum of angles N(4)–C(5)–C(51), N(4)–C(5)–S1 and C(51)–C(5)–S1 is 327.11°, revealing a pyramidalization at C5. On the other hand, each angle of N(4)–C(5)–H(5), C(51)–C(5)–H(5) and S1–C(5)–H(5) is equal to 109.8°. Also, from the data of the X-ray crystal structure the C(2)–N(3)–N(4) angle is 109.37° and therefore close to those of $sp^3$ nitrogen. One may conclude that the lone pair on this nitrogen is not contributing much to the actual state of the molecule; although, the thiadiazole ring is almost planar.

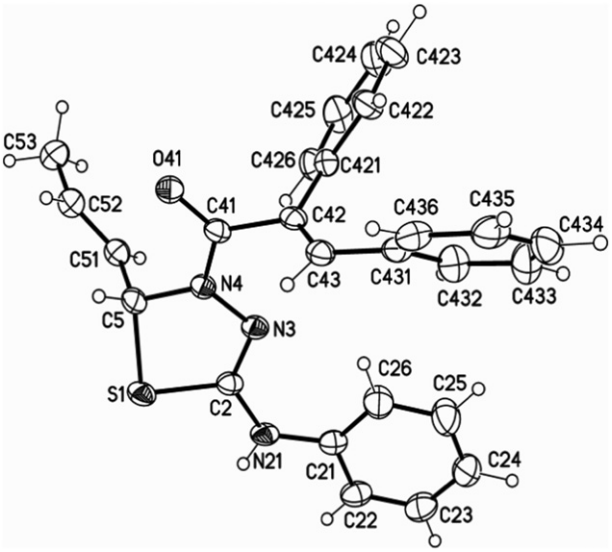
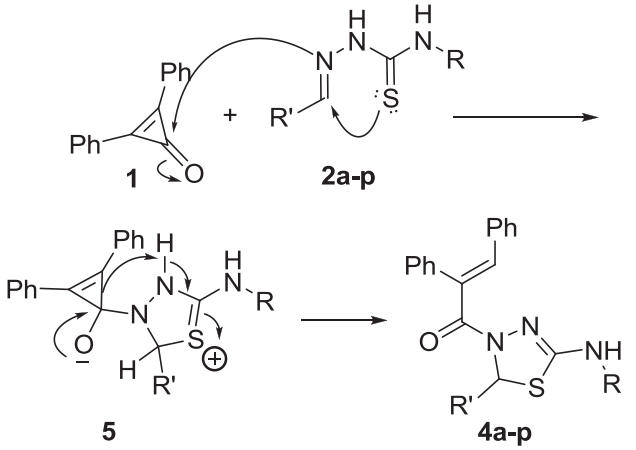



**Fig. 1.** Molecular structure of **4k** in the crystal (displacement parameters are drawn at 50% probability level). The crystallographic numbering does not reflect the systematic IUPAC numbering.

From these data it can be concluded that the S=C–NH–N=CHR′ group was changed, thus both the thioxo sulfur and azomethine groups had taken part in the heterocyclization. Since the electrophilic cyclopropenone could be attacked by the following nucleophilic sites, sulfur atom, $N^2$ and $N^1$ or the azomethine carbon

of **2a**–**p**, which had to act as a nucleophile in the sense of an 'umpolung'.[25] This behaviour is not unexpected since aldehyde hydrazones are known to react as azaenamines[26–28] towards suitable electrophiles. This behaviour should consequently also be open to aldehyde thiosemicarbazones, since the substituted thiocarbamoyl group is not a strong acceptor and may even be sterically hindered. The formation of **4a**–**p** may be rationalized as an initial attack of azomethine (CH=N) nitrogen atom of the alkenylidene-hydrazinecarbothioamides **2a**–**p** to the carbonyl group of cyclopropenone **1**. A spontaneous intramolecular nucleophilic addition from the lone pair of the sulfur atom on the CH=N group followed by cyclization to yield the intermediate **5**, which rearranges to the final structures, the 2,5-disubstituted 1,3,4-thiadiazolyl-2,3-diphenylpropenones **4a**–**p**. The structure of the obtained products excluded formal [2+3] cycloaddition pathways, such as proposed by Eicher.[9–12] (Scheme 3).




**Scheme 3.** Mechanism rationale for the formation of (*E*)-2,5-disubstituted-1,3,4-thiadiazolyl-2,3-diphenylpropenones **4**.

## 3. Conclusion

The present investigation clearly indicates that the products obtained from the conjugate addition of alkenylidene-hydrazinecarbothioamides **2a**–**p** to 2,3-diphenylcycloprop-2-enone (**1**), followed by heterocyclization, are neither the result of [2+3] or [3+3] cycloadditions as reported earlier. Novel (*E*)-2,5-disubstituted 1,3,4-thiadiazolyl-2,3-diphenylpropenones are observed due to the azaenamine reactivity shown by the starting materials **2a**–**p**. This reactivity requires the availability of the azomethine carbon, $N^2$, $N^4$ and sulfur atom as nucleophilic sites.

## 4. Experimental

### 4.1. Chemistry

All melting points were determined using open capillaries on a Gallenkamp melting point apparatus. The IR spectra were recorded with a Shimadzu 408 instrument using potassium bromide. The 400 MHz $^1$H NMR and 100 MHz $^{13}$C NMR spectra were observed on a Bruker AM 400 spectrometer with tetramethylsilane as the internal standard, br=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. The $^{13}$C NMR signals were assigned on the basis of DEPT 135/90 spectra. The mass spectra (70 eV, electron impact mode) were recorded on Finnigan MAT instrument.

Elemental analyses carried out at the Microanalytical Center, Cairo University, Egypt. Preparative layer chromatography (plc) used air-dried 1.0 mm thick layers of slurry applied silica gel (Merck Pf254) on 48 cm wide and 20 cm high glass plates using the solvents listed. Zones were detected by quenching of indicator fluorescence upon exposure to 254 nm light and eluted with acetone. The solvents used were purified and dried according to standard procedures.[29]

### 4.2. Starting materials

Substituted alkenylidene-hydrazinecarbothioamides **2a**–**p** were prepared by the reaction of 4-substituted thiosemicarbazide with the proper aldehyde according to published procedures in literature: (**2a**),[30] (**2b**),[31] (**2c**),[32] (**2d**),[33] (**2e**),[31] (**2f**),[31] (**2g**),[34] (**2h**),[33] (**2i**),[31] (**2j**),[31] (**2k**),[35] (**2l**),[31] (**2m**),[31] (**2n**),[33] (**2o**),[36] (**2p**).[31]

### 4.3. Products

A mixture of substituted (ylidene)hydrazinecarbothioamide **2a**–**p** (1.00 mmol) in absolute ethanol (25 mL) and a solution of **1** (0.206 g, 1.00 mmol) in absolute ethanol (20 mL) were mixed dropwise with stirring. The mixture was refluxed with stirring for 4–6 h (the reaction was monitored by TLC analyses). The solvent was concentrated and the residue was subjected to preparative layer chromatography (plc) using toluene/ethyl acetate (2:1) as the developing solvent to give one main zone. The zones were extracted and recrystallized from the appropriate solvent and identified as follows:

*4.3.1. (2E)-2,3-Diphenyl-1-[5-(phenylamino)-2-styryl-1,3,4-thiadiazol-3(2H)-yl]prop-2-en-1-one (**4a**).* Colourless crystals (0.398 g, 82%), mp 158–160 °C (acetonitrile). IR (KBr) $\nu$=3290 (NH), 3060 (Ar–CH), 1680 (CO), 1625 (C=N), 1600 (Ar–C=C) cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta_H$=7.67 (br, 1H, NH), 6.90–7.41 (m, 12H, Ar–H), 6.79–6.81 (m, 6H, Ar–H), 6.71–6.73 (m, 4H, Ar–H), 6.39 (m, 1H, Ar–H), 6.31–6.34 (m, 1H, thiadiazole–CH); $^{13}$C NMR ($CDCl_3$): $\delta_C$=166.7 (CO), 147.0 (thiadiazole C-5), 138.3, 136.1, 135.0, 134.9, 134.5 (Ar C), 132.6, 131.1, 128.7, 128.3, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 126.8, 126.0, 125.7, 125.1 (Ar CH), 66.8 (thiadiazole–CH); MS: *m*/*z* 487 ($M^+$, 11), 352 (17), 207 (19), 179 (36), 135 (100), 77 (56), 65 (46). Anal. Calcd for $C_{31}H_{25}N_3OS$ (487.61): C, 76.36; H, 5.17; N, 8.62; S, 6.58. Found: C, 76.45; H, 5.23; N, 8.49; S, 6.77.

*4.3.2. (2E)-1-[5-(Benzylamino)-2-styryl-1,3,4-thiadiazol-3(2H)-yl]-3,3-diphenylprop-2-en-1-one (**4b**).* Colourless crystals (0.374 g, 75%), mp 166–168 °C (ethanol). IR (KBr) $\nu$=3295 (NH), 1680 (CO), 1630 (C=N), 1600 (Ar–C=C) cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta_H$=7.38–7.00 (m, 11H, Ar–H), 6.94–6.92 (m, 6H, Ar–H), 6.70 (br, 1H, NH), 6.58–6.55 (m, 4H, Ar–H), 6.36–6.34 (m, 2H, Ar–H), 6.20–6.18 (m, 1H, thiadiazole–CH), 4.2 (s, 2H, $CH_2$). $^{13}$C NMR ($CDCl_3$): $\delta_C$=165.7 (CO), 152.5 (thiadiazole–C-5), 138.1, 136.9, 136.6, 136.2, 135.2 (Ar–C), 132.1, 131.2, 128.8, 128.4, 127.6, 127.5, 127.4, 127.3, 127.0, 126.8, 126.7, 126.3, 126.0, 125.1, 124.5 (Ar–CH), 66.9 (thiadiazole–CH), 48.9 ($CH_2$); MS: *m*/*z* 501 ($M^+$, 16), 352 (21), 313 (32), 207 (22), 179 (39), 177 (58), 149 (36), 91 (100), 65 (18). Anal. Calcd for $C_{32}H_{27}N_3OS$ (501.64): C, 76.62; H, 5.43; N, 8.38; S, 6.39. Found: C, 76.78; H, 5.33; N, 8.30; S, 6.56.

*4.3.3. (2E)-1-[5-(Allylamino)-2-styryl-1,3,4-thiadiazol-3(2H)-yl]-2,3-diphenylprop-2-en-1-one (**4c**).* Colourless crystals (0.314 g, 70%), mp 142–143 °C (ethanol). IR (KBr) $\nu$=3280 (NH), 1675 (CO), 1625 (C=N), 1585 (Ar–C=C) cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta_H$=7.40–6.93 (m, 8H, Ar–H), 6.88–6.85 (m, 4H, Ar–H), 6.67–6.65 (m, 5H, Ar–H), 6.30 (br, 1H, NH), 6.23–6.20 (m, 1H, Ar–H), 6.17–6.15 (m, 1H, thiadiazole–CH), 5.76–5.73 (m, 1H, allyl–CH=), 5.05–5.03 (m, 2H, allyl–$CH_2$=), 4.07–4.05 (m, 2H, allyl–$CH_2$N). $^{13}$C NMR ($CDCl_3$): $\delta_C$=166.8 (CO), 152.3 (thiadiazole C-5), 134.6 (allyl–CH=), 136.6, 132.7, 132.6, 132.4 (Ar–C), 131.2, 130.6, 129.7, 128.8, 128.7, 127.6,

127.3, 127.2, 126.8, 126.3, 126.0, 125.1 (Ar–CH), 116.1 (allyl–$CH_2$=), 66.7 (thiadiazole–CH), 46.4 (allyl–$CH_2$N). MS (EI): *m*/*z*=451 ($M^+$, 11), 352 (8), 244 (42), 207 (26), 179 (59), 177 (100), 99 (24), 77 (26), 41 (47). Anal. Calcd for $C_{28}H_{25}N_3OS$ (451.58): C, 74.47; H, 5.58; N, 9.31; S, 7.10. Found: C, 74.58; H, 5.49; N, 9.18; S, 6.96.

*4.3.4. (2E)-1-[2-(2-Methoxystyryl)-5-(phenylamino)-1,3,4-thiadiazol-3(2H)-yl]-2,3-diphenyl-prop-2-en-1-one (**4d**).* Colourless crystals (0.371 g, 72%), mp 172–174 °C (acetonitrile). IR (KBr) *ν*=3310 (NH), 3050 (Ar–CH), 1680 (CO), 1620 (C=N), 1600 (Ar–C=C) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta_H$=7.58 (br, 1H, NH), 7.40–7.07 (m, 10H, Ar–H), 6.94–6.89 (m, 3H, Ar–H), 6.87–6.85 (m, 3H, Ar–H), 6.83–6.82 (m, 5H, Ar–H), 6.40–6.38 (m, 1H, Ar–H), 6.34–6.32 (m, 1H, thiadiazole–CH), 3.79 (s, 3H, $OCH_3$), $^{13}C$ NMR ($CDCl_3$): $\delta_C$=166.6 (CO), 156.3 (Ar–C–O), 156.2 (thiadiazole C-5), 136.6, 136.4, 136.2, 135.0, 134.7 (Ar–C), 132.7, 129.7, 128.7, 128.3, 127.9, 127.8, 127.6, 127.4, 127.2, 127.0, 126.9, 126.7, 126.6, 126.3, 125.1 (Ar–CH), 67.0 (thiadiazole–CH), 54.4 ($OCH_3$); MS (EI): *m*/*z*=517 ($M^+$, 8), 382 (26), 207 (21), 179 (177), 177 (100), 135 (24), 91 (17), 77 (26). Anal. Calcd for $C_{32}H_{27}N_3O_2S$ (517.64): C, 74.25; H, 5.26; N, 8.12; S, 6.19. Found: C, 74.36; H, 5.37; N, 7.97; S, 6.35.

*4.3.5. (2E)-1-[5-(Benzylamino)-2-(2-methoxy-styryl)-1,3,4-thiadiazol-3(2H)-yl]-2,3-diphenyl-prop-2-en-1-one (**4e**).* Colourless crystals (0.402 g, 76%), mp 177–179 °C (acetonitrile). IR (KBr) *ν*=3280 (NH), 1675 (CO), 1615 (C=N), 1585 (Ar–C=C) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta_H$=7.50–6.94 (m, 10H, Ar–H), 6.91–6.89 (m, 3H, Ar–H), 6.85–6.83 (m, 4H, Ar–H), 6.77–6.76 (m, 4H, Ar–H), 6.68 (br, 1H, NH), 6.42–6.40 (m, 1H, Ar–H), 6.37–6.36 (m, 1H, thiadiazole–CH), 3.95 (s, 2H, $CH_2$), 3.80 (s, 3H, $OCH_3$). $^{13}C$ NMR ($CDCl_3$): $\delta_C$=165.7 (CO), 156.3 (Ar–*C*–O), 152.7 (thiadiazole C-5), 136.8, 136.7, 136.6, 136.2, 135.2 (Ar–C), 132.6, 128.8, 128.3, 127.8, 127.6, 127.5, 127.4, 127.2, 127.0, 126.9, 126.7, 126.6, 126.5, 126.4, 125.8 (Ar–CH), 67.6 (thiadiazole–CH), 54.4 ($OCH_3$), 47.8 ($CH_2$). MS (EI): *m*/*z*=531 ($M^+$, 9), 382 (11), 207 (16), 179 (46), 177 (36), 149 (38), 91 (100), 77 (22). Anal. Calcd for $C_{33}H_{29}N_3O_2S$ (531.67): C, 74.55; H, 5.50; N, 7.90; S, 6.03. Found: C, 74.73; H, 5.39; N, 8.12; S, 5.89.

*4.3.6. (2E)-1-[5-(Allylamino)-2-(2-methoxy-styryl)-1,3,4-thiadiazol-3(2H)-yl]-2,3-diphenyl-prop-2-en-1-one (**4f**).* Colourless crystals (0.326 g, 68%), mp 150–151 °C (ethanol). IR (KBr) *ν*=3305 (NH), 3080 (Ar–CH), 1675 (CO), 1615 (C=N), 1580 (Ar–C=C) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta_H$=7.39–7.35 (m, 4H, Ar–H), 7.33–7.27 (m, 7H, Ar–H), 7.22–7.05 (m, 3H, Ar–H), 6.90–6.88 (m, 2H, Ar–H), 6.28 (br, 1H, NH), 6.26–6.25 (m, 1H, thiadiazole–CH), 6.22–6.20 (m, 1H, Ar–H), 5.69–5.68 (m, 1H, allyl–CH=), 5.02–5.00 (m, 2H, allyl–$CH_2$=), 4.13–4.10 (m, 2H, allyl–$CH_2$N), 3.80 (s, 3H, $OCH_3$). $^{13}C$ NMR ($CDCl_3$): $\delta_C$=166.7 (CO), 157.3 (Ar–*C*–O), 153.9 (thiadiazole C-5), 135.7 (allyl-CH=), 137.6, 137.2, 136.6, 136.3, 133.6 (Ar–C), 133.5, 130.7, 129.8, 129.5, 129.4, 128.6, 128.3, 127.9, 127.4, 126.8, 126.2, 125.4 (Ar–CH), 117.1 (allyl–$CH_2$=), 68.5 (thiadiazole–CH), 55.5 ($OCH_3$), 47.4 (allyl–$CH_2$N). MS (EI): *m*/*z*=481 ($M^+$, 8), 382 (11), 263 (38), 207 (24), 179 (100), 177 (71), 133 (21), 99 (48), 41 (42). Anal. Calcd for $C_{29}H_{27}N_3O_2S$ (481.61): C, 72.32; H, 5.65; N, 8.72; S, 6.66. Found: C, 72.46; H, 5.53; N, 8.59; S, 6.81.

*4.3.7. (2E)-2,3-Diphenyl-1-[5-(phenylamino)-2-(1-phenylprop-1-en-2-yl)-1,3,4-thiadiazol-3(2H)-yl]prop-2-ene-1-one (**4g**).* Colourless crystals (0.419 g, 84%), mp 166–168 °C (ethanol). IR (KBr) *ν*=3310 (NH), 3050 (Ar–CH), 1675 (CO), 1620 (C=N), 1590 (Ar–C=C) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta_H$=7.30–7.20 (m, 6H, Ar–H and NH), 7.18–7.05 (m, 10H, Ar–H), 7.00–6.85 (m, 6H, Ar–H), 6.67–6.65 (m, 1H, Ar–H), 6.43–6.42 (m, 1H, thiadiazole–CH), 1.85 (s, 3H, $CH_3$); $^{13}C$ NMR ($CDCl_3$): $\delta_C$=168.2 (CO), 148.0 (thiadiazole C-5), 137.5, 137.1, 136.5, 136.1, 135.6, 133.5 (Ar–C), 133.1, 129.7, 129.4, 129.3, 129.1, 128.9, 128.8, 128.6, 128.4, 128.1, 127.8, 127.5, 126.6, 126.4 (Ar–CH), 67.6 (thiadiazole–CH), 13.0 ($CH_3$); MS (EI): *m*/*z*=501 ($M^+$, 11), 366 (16), 222 (31), 207 (36), 179 (100), 177 (21), 135 (52), 91 (18), 77 (28). Anal. Calcd for $C_{32}H_{27}N_3OS$ (501.64): C, 76.62; H, 5.43; N, 8.38; S, 6.39. Found: C, 76.53; H, 5.51; N, 8.28; S, 6.57.

*4.3.8. (2E)-1-[[2-(Pent-1-enyl)-5-(phenylamino)-1,3,4-thiadiazol-3(2H)-yl]-2,3-diphenyl-prop-2-en-1-one (**4h**).* Colourless crystals (0.374 g, 83%), mp 143–144 °C (ethanol). IR (KBr) *ν*=3310 (NH), 3070 (Ar–CH), 2980 (Ali–CH), 1675 (CO), 1620 (C=N), 1590 (Ar–C=C) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta_H$=7.38–7.35 (m, 4H, Ar–H and NH), 7.32–7.25 (m, 5H, Ar–H), 7.22–7.09 (m, 6H, Ar–H), 6.87–6.85 (m, 2H, Ar–H), 6.56–6.55 (m, 1H, thiadiazole–CH), 5.67–5.65, 5.42–5.40 (m, 2H, CH=CH), 1.97–1.95 (m, 2H, $CH_2$), 1.32–1.30 (m, 2H, $CH_2$), 0.85 (t, *J*=7.6 Hz, 3H, $CH_3$); $^{13}C$ NMR ($CDCl_3$): $\delta_C$=166.5 (CO), 149.0 (thiadiazole C-5), 136.3, 135.0, 134.7, 133.2 (Ar–C), 132.2, 128.7, 128.3, 127.9, 127.6, 127.4, 127.0, 126.7, 126.6, 125.0 (Ar–CH), 121.6, 117.4 (CH=CH), 67.6 (thiadiazole–CH), 33.7 ($CH_2$), 21.8 ($CH_2$), 13.6 ($CH_3$); MS (EI): *m*/*z*=453 ($M^+$, 15), 384 (38), 356 (53), 318 (54), 22 (19), 207 (36), 179 (100), 177 (62), 135 (22), 91 (16), 77 (18). Anal. Calcd for $C_{28}H_{27}N_3OS$ (453.60): C, 74.14; H, 6.00; N, 9.26; S, 7.07. Found: C, 74.22; H, 6.07; N, 9.45; S, 6.93.

*4.3.9. (2E)-1-[5-(Benzylamino)-2-(pent-1-enyl)-1,3,4-thiadiazol-3(2H)-yl]-2,3-diphenyl-prop-2-en-1-one (**4i**).* Colourless crystals (0.302 g, 65%), mp 147–148 °C (ethanol). IR (KBr) *ν*=3285 (NH), 3040 (Ar–CH), 2970 (Ali–CH), 1675 (CO), 1625 (C=N), 1600 (Ar–C=C) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta_H$=7.39–7.35 (m, 5H, Ar–H), 7.33–7.27 (m, 5H, Ar–H), 7.25–7.05 (m, 4H, Ar–H), 6.90–6.88 (m, 2H, Ar–H), 6.85 (br, 1H, NH), 6.33–6.32 (m, 1H, thiadiazole–CH), 5.85–5.83, 5.64–5.62 (m, 2H, CH=CH), 4.10 (s, 2H, $CH_2$), 2.05–2.07 (m, 2H, $CH_2$), 1.38–1.39 (m, 2H, $CH_2$), 0.84 (t, *J*=7.7 Hz, 3H, $CH_3$); $^{13}C$ NMR ($CDCl_3$): $\delta_C$=164.7 (CO), 149.1 (thiadiazole C-5), 136.3, 135.8, 135.1, 135.0 (Ar–C), 133.8, 129.6, 128.9, 127.9, 127.6, 127.0, 126.9, 126.4, 126.0, 125.8 (Ar–CH), 123.1, 118.3 (CH=CH), 67.8 (thiadiazole–CH), 46.8 ($CH_2$–Ph), 33.8 ($CH_2$), 20.8 ($CH_2$), 12.6 ($CH_3$); MS: *m*/*z* 467 ($M^+$, 12), 318 (41), 222 (28), 207 (38), 179 (100), 177 (46), 91 (12). Anal. Calcd for $C_{29}H_{29}N_3OS$ (467.63): C, 74.48; H, 6.25; N, 8.99; S, 6.86. Found: C, 74.66; H, 6.31; N, 8.87; S, 7.05.

*4.3.10. (2E)-1-[5-(Allylamino)-2-(pent-1-enyl)-1,3,4-thiadiazol-3(2H)-yl]-2,3-diphenylprop-2-en-1-one (**4j**).* Colourless crystals (0.295 g, 71%), mp 126–127 °C (ethanol). IR (KBr) *ν*=3305 (NH), 3060 (Ar–CH), 2980 (Ali–CH), 1690 (CO), 1630 (C=N), 1595 (Ar–C=C) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta_H$=7.37–7.30 (m, 4H, Ar–H), 7.25–7.18 (m, 5H, Ar–H), 7.15–7.00 (m, 2H, Ar–H), 6.36–6.35 (m, 1H, thiadiazole–CH), 6.25 (br, 1H, NH), 6.03–6.00, 5.96–5.95, 6.00–6.03 (m, 2H, CH=CH), 5.86–5.85 (m, 1H, allyl–CH=), 5.13–5.10 (m, 2H, allyl–$CH_2$=), 3.96–3.95 (m, 2H, allyl–$CH_2$N), 2.07–2.05 (m, 2H, $CH_2$), 1.44–1.42 (m, 2H, $CH_2$), 0.87 (t, *J*=7.6 Hz, 3H, $CH_3$); $^{13}C$ NMR ($CDCl_3$): $\delta_C$=164.7 (CO), 149.1 (thiadiazole C-5), 135.9 (allyl–CH=), 135.1, 134.9 (Ar–C), 122.1, 118.4 (CH=CH), 129.6, 128.9, 128.3, 127.9, 127.4, 127.0, 126.1, 125.8 (Ar–CH), 115.9 (allyl–$CH_2$=), 66.7 (thiadiazole–CH), 45.5 (allyl–$CH_2$N), 33.8 ($CH_2$), 20.8 ($CH_2$), 12.6 ($CH_3$); MS (EI): *m*/*z*=417 ($M^+$, 8), 222 (22), 207 (28), 179 (100), 177 (42), 77 (23). Anal. Calcd for $C_{25}H_{27}N_3OS$ (417.57): C, 71.91; H, 6.52; N, 10.06; S, 7.68. Found: C, 72.08; H, 6.44; N, 9.93; S, 7.87.

*4.3.11. (2E)-2,3-Diphenyl-1-[5-(phenylamino)-2-(prop-1-enyl)-1,3,4-thiadiazol-3(2H)-yl]prop-2-en-1-one (**4k**).* Colourless crystals (0.317 g, 75%), mp 132–133 °C (ethanol). IR (KBr) *ν*=3290 (NH), 3050 (Ar–CH), 1675 (CO), 1630 (C=N), 1595 (Ar–C=C) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta_H$=7.44 (br, 1H, NH), 7.40–7.38 (m, 3H, Ar–H), 7.36–7.25 (m, 8H, Ar–H), 7.23–7.08 (m, 3H, Ar–H), 6.97–6.91 (m, 2H, Ar–H), 6.65–6.63 (m, 1H, thiadiazole–CH), 5.85–5.83, 5.64 (m, 2H, CH=CH), 1.70 (d, *J*=6.6 Hz, 3H, $CH_3$); $^{13}C$ NMR ($CDCl_3$): $\delta_C$=166.5 (CO),

152.5 (thiadiazole C-5), 138.4, 136.2, 144.0, 134.7 (Ar C), 132.7, 128.7, 128.3, 128.1, 127.9, 127.8, 127.6, 127.4, 127.0, 126.2 (Ar CH), 122.6, 118.2 (CH=CH), 67.5 (thiadiazole CH), 17.3 ($CH_3$); MS (EI): $m/z$=425 ($M^+$, 12), 290 (26), 222 (14), 207 (36), 179 (100), 177 (61), 150 (13), 135 (18), 77 (21). Anal. Calcd for $C_{26}H_{23}N_3OS$ (425.55): C, 73.38; H, 5.45; N, 9.87; S, 7.54. Found: C, 73.56; H, 5.57; N, 9.73; S, 7.71.

*4.3.12. (2E)-1-[5-(Benzylamino)-2-(prop-1-enyl)-1,3,4-thiadiazol-3(2H)-yl]-2,3-diphenyl-prop-2-en-1-one (**4l**).* Colourless crystals (0.310 g, 71%), mp 139–140 °C (acetonitrile). IR (KBr) $\nu$=3310 (NH), 3070 (Ar–CH), 1680 (CO), 1630 (C=N), 1600 (Ar–C=C) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta_H$=7.30–7.25 (m, 5H, Ar–H), 7.22–7.15 (m, 6H, Ar–H), 7.12–7.00 (m, 5H, Ar–H), 6.90 (br, 1H, NH), 6.51–6.50 (m, 1H, thiadiazole–CH), 5.84–5.82, 5.56–5.55 (m, 2H, CH=CH), 4.10 (s, 2H, $CH_2$Ph), 1.65 (d, $J$=6.6 Hz, 3H, $CH_3$); $^{13}C$ NMR ($CDCl_3$): $\delta_C$=165.9 (CO), 151.5 (thiadiazole C-5), 136.7, 136.6, 135.8, 134.7 (Ar–C), 132.6, 129.7, 128.8, 128.3, 126.6, 127.6, 127.4, 127.2, 126.9, 126.2 (Ar–CH), 121.8, 118.2 (CH=CH), 67.8 (thiadiazole–CH), 47.8 ($CH_2$), 16.4 ($CH_3$); MS (EI): $m/z$=439 ($M^+$, 19), 370 (10), 290 (29), 207 (35), 179 (100), 177 (58), 149 (14), 91 (64). Anal. Calcd for $C_{27}H_{25}N_3OS$ (439.57): C, 73.77; H, 5.73; N, 9.56; S, 7.29. Found: C, 73.96; H, 5.61; N, 9.72; S, 7.22.

*4.3.13. (2E)-1-[5-(Allylamino)-2-(prop-1-enyl)-1,3,4-thiadiaz-ol-3(2H)-yl]-2,3-diphenyl-prop-2-en-1-one (**4m**).* Colourless crystals (0.259 g, 67%), mp 110–111 °C (ethanol). IR (KBr) $\nu$=3280 (NH), 3060 (Ar–CH), 1680 (CO), 1620 (C=N), 1600 (Ar–C=C) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta_H$=7.42–7.26 (m, 5H, Ar–H), 7.22–7.15 (m, 4H, Ar–H), 7.12–6.90 (m, 2H, Ar–H), 6.30 (br, 1H, NH), 6.27–6.25 (m, 1H, thiadiazole–CH), 5.92–5.90 (m, 1H, allyl–CH=), 5.81–5.80, 5.52–5.50 (m, 2H, CH=CH), 5.06–5.05 (m, 2H, allyl–$CH_2$=), 4.13–4.10 (m, 2H, allyl–$CH_2$N), 1.70 (d, $J$=6.7 Hz, 3H, $CH_3$); $^{13}C$ NMR ($CDCl_3$): $\delta_C$=164.7 (CO), 149.0 (thiadiazole C-5), 135.9 (allyl–CH=), 136.1, 135.2, 134.9 (Ar–C), 132.8, 129.6, 128.9, 127.8, 127.4, 126.9, 125.4 (Ar CH), 122.1, 118.8 (CH=CH), 116.1 (allyl–$CH_2$=), 67.9 (thiadiazole CH), 45.2 (allyl–$CH_2$N), 17.6 ($CH_3$); MS (EI): $m/z$=389 ($M^+$, 9), 290 (26), 222 (19), 207 (33), 179 (100), 177 (56), 77 (12), 41 (18). Anal. Calcd for $C_{23}H_{23}N_3OS$ (389.51): C, 70.92; H, 5.95; N, 10.79; S, 8.23. Found: C, 71.11; H, 5.87; N, 10.94; S, 8.35.

*4.3.14. (E)-1-[2-Isopropyl-5(phenylamino)-1,3,4-thiadiazol-3(2H)-yl]-2,3-diphenylprop-2-en-1-one (**4n**).* Colourless crystals (0.323 g, 76%), mp 134–135 °C (ethanol). IR (KBr) $\nu$=3310 (NH), 3070 (Ar–CH), 2980 (Ali–CH), 1670 (CO), 1620 (C=N), 1600 (Ar–C=C) $cm^{-1}$; 1H NMR (CDCl3): $\delta_H$=7.45 (br, 1H, NH), 7.40–7.29 (m, 6H, Ar–H), 7.28–7.00 (m, 6H, Ar–H), 6.93–6.90 (m, 4H, Ar–CH), 6.53–6.52 (m, 1H, thiadiazole–CH), 2.42–2.44 (m, 1H, CH), 0.90 (d, $J$=6.7 Hz, 6H, $2CH_3$); $^{13}C$ NMR ($CDCl_3$): $\delta_C$=167.4 (CO), 153.8 (thiadiazole C-5), 136.6, 135.2, 135.1, 134.7 (Ar–C), 131.7, 129.7, 128.7, 128.6, 128.2, 127.9, 127.6, 127.3, 127.0, 126.6 (Ar CH), 67.2 (thiadiazole CH), 31.9 (CH), 17.3 ($CH_3$); MS (EI): $m/z$=427 ($M^+$, 20), 384 (11), 292 (14), 219 (62), 207 (58), 179 (91), 177 (100), 150 (61), 118 (42), 77 (54). Anal. Calcd for $C_{26}H_{25}N_3OS$ (427.56): C, 73.04; H, 5.89; N, 9.83; S, 7.50. Found: C, 73.22; H, 5.98; N, 10.02; S, 7.35.

*4.3.15. (E)-1-[5-(Benzylamino)-2-isopropyl-1,3,4-thiadiazol-3(2H)-yl]-2,3-diphenylprop-2-en-1-one (**4o**).* Colourless crystals (0.325 g, 74%), mp 141–142 °C (benzene). IR (KBr) $\nu$=3305 (NH), 3080 (Ar–CH), 2970 (Ali–CH), 1675 (CO), 1630 (C=N), 1590 (Ar–C=C) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta_H$=7.31–7.22 (m, 5H, Ar–H), 7.20–7.00 (m, 6H, Ar–H), 6.96–6.90 (m, 5H, Ar–H), 6.65 (br, 1H, NH), 6.59–6.58 (m, 1H, thiadiazole–CH), 4.10 (s, 2H, $CH_2$), 2.41–2.40 (m, 1H, CH), 0.80 (d, $J$=6.6 Hz, 6H, 2 $CH_3$); $^{13}C$ NMR ($CDCl_3$): $\delta_C$=167.9 (CO), 153.0 (thiadiazole C-5), 137.9, 136.9, 135.8, 132.8 (Ar–C) 130.5, 129.8, 127.7, 129.3, 128.8, 128.4, 127.9, 127.3, 126.9, 125.7 (Ar–CH), 66.4 (thiadiazole CH), 18.4 ($CH_3$), 48.7 ($CH_2$), 33.0 (CH); MS (EI): $m/z$=441 ($M^+$, 24), 387 (26), 292 (18), 207 (78), 179 (100), 177 (68), 91 (97), 77 (14). Anal. Calcd for $C_{27}H_{27}N_3OS$ (441.59): C, 73.44; H, 6.16; N, 9.52; S, 7.26. Found: C, 73.61; H, 6.27; N, 9.42; S, 7.45.

*4.3.16. (E)-1-[5-(Allylamino)-2-isopropyl-1,3,4-thiadiazol-3(2H)-yl]-2,3-diphenyl-2-en-1-one (**4p**).* Colourless crystals (0.268 g, 69%), mp 112–113 °C (benzene). IR (KBr) $\nu$=3315 (NH), 3090 (Ar–CH), 2975 (Ali–CH), 1680 (CO), 1630 (C=N), 1605 (Ar–C=C) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta_H$=7.38–7.22 (m, 5H, Ar–H), 7.20–6.95 (m, 6H, Ar–CH), 6.29–6.28 (m, 1H, thiadiazole–CH), 6.15 (br, 1H, NH), 5.67–5.65 (m, 1H, allyl–CH=), 5.0 (m, 2H, allyl-$CH_2$=), 4.12–4.10 (m, 2H, allyl–$CH_2$N), 2.39–2.38 (m, 1H, CH), 0.85 (d, $J$=6.6 Hz, 6H, $2CH_3$); $^{13}C$ NMR ($CDCl_3$): $\delta_C$=167.9 (CO), 153.0 (thiadiazole C-5), 138.3, 136.9, 133.8 (Ar C), 135.8 (allyl–CH=), 132.8, 129.8, 129.3, 128.7, 128.2, 128.1, 127.9, 127.6 (Ar–CH), 116.9 (allyl-$CH_2$=), 47.1 (allyl–$CH_2$N), 66.1 (thiadiazole–CH), 33.0 (CH), 18.4 ($CH_3$); MS (EI): $m/z$=391 ($M^+$, 57), 349 (18), 292 (14), 207 (64), 179 (100), 177 (84), 99 (17), 41 (15). Anal. Calcd for $C_{23}H_{25}N_3OS$ (391.53): C, 70.56; H, 6.44; N, 10.73; S, 8.19. Found: C, 70.39; H, 6.38; N, 10.62; S, 8.36.

### 4.4. Single crystal X-ray structure determination of 4k

Suitable crystals were obtained by recrystallization from absolute ethanol. The single crystal X-ray diffraction study were carried out on a Bruker-Nonius ApexII diffractometer at 123(2) K using MoK$\alpha$ radiation ($\lambda$=0.71073 Å). Direct Methods (SHELXS-97[35]) were used for structure solution and refinement was carried out using SHELXL-97[37] (full-matrix least-squares on $F^2$). Hydrogen atoms were localized by difference electron density determination and refined using a riding model.

Compound **4k**: $C_{26}H_{23}N_3OS$, $M_r$=425.53 g $mol^{-1}$, colourless crystals, crystal size 0.35×0.25×0.10 mm, monoclinic, space group $P2(1)/c$ (No. 14), $a$=8.5272(2) Å, $b$=16.6230(6) Å, $c$=15.4999(6) Å, $\beta$=91.254(2)°, V=2196.55(13) $Å^3$, $Z$=4, $D_{calcd}$=1.287 $Mgm^{-3}$, $\mu$=0.171 $mm^{-1}$, $T$=123(2) K, 17,105 reflections, 4983 unique [$R_{int}$=0.031], $2\theta_{max}$=55°, $R_1$ [for $I>2\sigma(I)$]=0.050, $wR2$ (all data)=0.117, largest diff. peak and hole=0.696/−0.378 e $Å^{-3}$.

Crystallographic data (excluding structure factors) for the structures reported in this work have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 876005 (**4k**) Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge DB2 1EZ, UK (Fax: int. code+(1223)336-033; e-mail: deposit@ccdc.cam.ac.uk).

## Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2012.07.063.

## References and notes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