Tetrahedron 69 (2013) 5008–5015

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Azodicarboxylates: valuable reagents for the multicomponent synthesis of novel 1,3,4-thiadiazoles and imidazo[2,1-*b*][1,3,4]thiadiazoles

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ARTICLE INFO

Article history:
Received 22 January 2013
Received in revised form 6 March 2013
Accepted 26 March 2013
Available online 2 April 2013

Keywords:
Azodicarboxylates
Isocyanides
Thiones
Imidazo[2,1-*b*][1,3,4]thiadiazoles
Multicomponent reactions
Thiadiazoles

ABSTRACT

Upon reaction of 4,5-disubstituted-*N*-arylaminoimidazole-2-thiones with isocyanides in the presence of azodicarboxylates (1.2 equiv) at rt, the imidazo[2,1-*b*][1,3,4]thiadiazoles were formed as the only reaction products in very good yields, whereas by using higher reaction temperatures, along with the imidazo[2,1-*b*][1,3,4]thiadiazoles, the three component reaction products, namely thiadiazoles, were also isolated, their formation being dependent on the 5-thione substituent. The thiadiazoles became the only reaction products, formed in very good yield by using 2 equiv of azodicarboxylates. The sodium cyanoborohydride and sodium borohydride reductions to thiadiazoles **11**, and **12** were also studied. Plausible mechanistic schemes for the formation of the thiadiazoles are proposed.

1. Introduction

The practically planar and rigid heteroaromatic imidazo[2,1-*b*][1,3,4]thiadiazole ring system is expected to have interesting physicochemical and biological properties, because of the presence of four heteroatoms and two condensed heterocycles with different π-conjugation. Indeed, imidazo[2,1-*b*][1,3,4]thiadiazole, but also thiadiazole derivatives, are known to possess interesting pharmacological properties, such as anticancer,[1,2] antitubercular,[3,4] antibacterial,[5,6] antifungal,[7] anti-inflammatory,[8] antimicrobial,[9,10] anticonvulsant and analgesic,[11] and antisecretory[12] activities.

The classical method for the synthesis of imidazo[2,1-*b*][1,3,4]thiadiazole derivatives involves reaction of 2-amino[1,3,4]thiadiazoles with appropriate α-haloketones,[13] whereas very recently a synthesis involving Suzuki–Miyaura cross-coupling reactions has been reported.[14]

As a continuation of our work on imidazole derivatives[15] and also on isocyanide multicomponent chemistry[16] we wish in the present work to describe our study concerning a one-pot method for the construction of the imidazo[2,1-*b*][1,3,4]thiadiazole scaffold by using imidazole-2-thiones, isocyanides, and azodicarboxylates as a basic catalyst. The subsequent transformation of the isolated imidazo[2,1-*b*][1,3,4]thiadiazole derivatives to new interesting multi-substituted [1,3,4]thiadiazoles by using excess of azodicarboxylates, acting as an electrophile in the presence of the five-membered heterocycle, is also described. Finally, the synthesis of the same multi-substituted [1,3,4]thiadiazoles through a one-pot multicomponent reaction between imidazole-2-thiones, isocyanides and excess of DEAD is reported.

2. Results and discussion

Initially, the reactivity of the imidazole-2-thione **1a** toward isocyanides was examined by reacting imidazolethione **1a** with cyclohexylisocyanide in the presence of a Lewis acid ($BF_3 \cdot Et_2O$) whereupon after stirring at ambient temperature for 4 h the imidazoformamidine **3a** was isolated in good yield (70%, Scheme 1).

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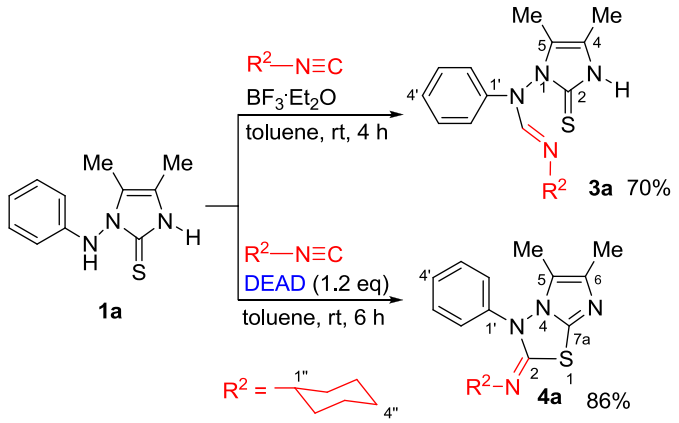
http://dx.doi.org/10.1016/j.tet.2013.03.096

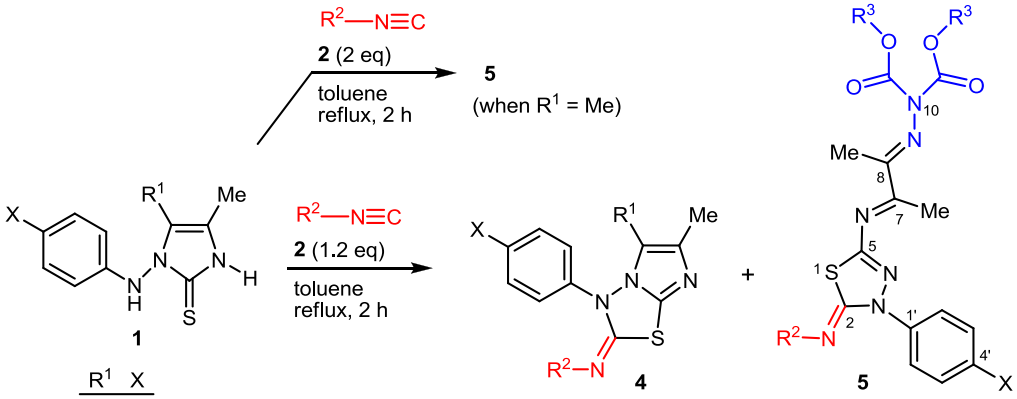


Scheme 1. Reaction of thione **1a** with cyclohexylisocyanide at ambient temperature in the presence or absence of azodicarboxylates.

An analogous reaction of benzothiazoles with isocyanides leading to different formamidine derivatives has very recently been reported in the literature.[17] In contrast, by using DEAD (1.2 equiv), 4,5-dimethyl-thione **1a**, and cyclohexylisocyanide, after stirring at room temperature for 6 h the imidazo[2,1-*b*][1,3,4]thiadiazole **4a** was isolated as the only reaction product in 86% yield (Scheme 1). However, when the same reaction was repeated in boiling toluene for 2 h, two products were formed, **4a** isolated in 55% yield and a three component product the tri-substituted thiadiazole **5a** isolated in 25% yield (Scheme 2). By using longer reaction times the yield of the three component product **5a** was slightly increased at the expense of **4a**, whereas by using 2 equiv of DEAD **5a** was isolated as the only reaction product in 87% yield. The reaction proceeded analogously by using other 4,5-dimethyl substituted thiones **1a**–**c** or other isocyanides, such as *tert*-butyl-, benzyl-, or phenylisocyanide and the results are shown in Scheme 2 and Table 1. However, when the 4-phenyl-5-methyl thione **1d** was used (entries 16 and 17, Table 1), even with 2 equiv of DEAD, regardless of the reflux time, the imidazothiadiazoles **4** were isolated as the only reaction products in high yields, and no trace of compounds **5** was detected. Analogous results were obtained by using DIAD instead of DEAD (entries 19–21, Table 1).

Finally, the imidazothiadiazole **4a** could be transformed into thiadiazole **5a** by refluxing with 1.2 equiv of DEAD in toluene for 2 h, and to imidazolethiones **6** after 5 h reflux in CH_2Cl_2 in the presence of acetic acid (Scheme 3).

Concerning the reaction mechanism, for the formation of the imidazothiadiazoles **4** it can be proposed that the zwitterion **7**, initially formed from the reaction between isocyanide and DEAD, abstracts the thione 2-NH proton forming finally intermediate **8**, which cyclizes to the end product **4** by loss of a diethyl (or diisopropyl) hydrazinedicarboxylate molecule (Scheme 4). However, by using excess of DEAD (2 equiv) and higher reaction temperatures (110 °C) a multicomponent reaction takes place, imidazothiadiazole **4** constituting in this case the reaction intermediate, formed during the first step of the reaction sequence. In the next step, an electrophilic attack of an azodicarboxylate molecule to the C5=C6 double bond of **4** leads initially to the formation of the dipolar intermediate **9** (Scheme 4), from which by formation of the diaziridine intermediate **10**, subsequent fission of the N4–C5 bond, and 'migration' of an ethoxycarbonyl group the end product **5** can be obtained. In favor of the proposed mechanism is the fact that the reaction proceeds only with the 5-methyl substituted thiones **1a**–**c**, whereas no reaction is observed using the 5-phenyl substituted thione **1d**. Most probably, steric hindrance but also extensive delocalization offered by the phenyl substituent renders the electrophilic attack of an azodicarboxylate molecule to C5=C6 double bond of **4f**–**g** unfavorable. An analogous electrophilic attack of a heterocyclic double bond to azodicarboxylate has also recently been



	R^1	X
a	Me	H
b	Me	Cl
c	Me	Me
d	Ph	H

	R^1	R^2	X
a	Me	*c*-Hex	H
b	Me	*t*-Bu	H
c	Me	Bn	H
d	Me	*c*-Hex	Cl
e	Me	*t*-Bu	Cl
f	Ph	*c*-Hex	H
g	Ph	*t*-Bu	H

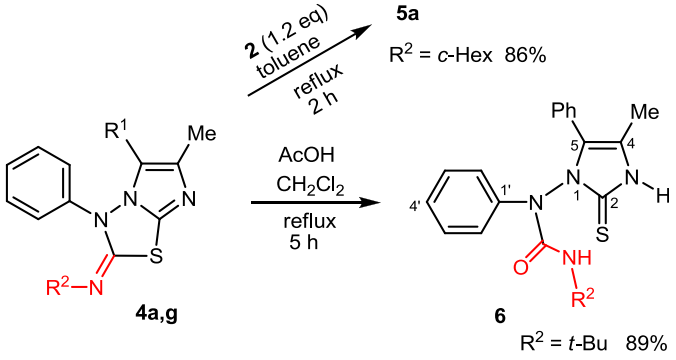
	R^2	R^3	X
a	*c*-Hex	Et	H
b	*t*-Bu	Et	H
c	Bn	Et	H
d	*c*-Hex	Et	Cl
e	*t*-Bu	Et	Cl
f	*t*-Bu	Et	Me
g	Ph	Et	H
h	*c*-Hex	*i*-Pr	H
i	*t*-Bu	*i*-Pr	H
j	*c*-Hex	*i*-Pr	Cl

Scheme 2. Reaction of thiones with isocyanides and azodicarboxylates.

Table 1
Summary of the reactions between imidazole-2-thiones **1a**–**d**, isocyanides, and azodicarboxylates

Entry	Thione	Isocyanide	Azodicarboxylate (equiv)	Reaction conditions	Product **4** (%)	Product **5** (%)
1	**1a**	Cyclohexyl	DEAD (1.2)	rt, 6 h	**4a** (86)	
2	**1a**	Cyclohexyl	DEAD (1.2)	rt, 5 d	**4a** (53)	**5a** (28)
3	**1a**	Cyclohexyl	DEAD (1.2)	Reflux, 2 h	**4a** (55)	**5a** (25)
4	**1a**	Cyclohexyl	DEAD (2.0)	Reflux, 2 h		**5a** (87)
5	**1a**	*tert*-Butyl	DEAD (1.2)	rt, 6 h	**4b** (81)	
6	**1a**	*tert*-Butyl	DEAD (1.2)	Reflux, 2 h	**4b** (51)	**5b** (29)
7	**1a**	*tert*-Butyl	DEAD (2.0)	Reflux, 2 h		**5b** (85)
8	**1a**	Benzyl	DEAD (1.2)	rt, 6 h	**4c** (77)	
9	**1a**	Benzyl	DEAD (1.2)	Reflux, 2 h	**4c** (56)	**5c** (26)
10	**1a**	Benzyl	DEAD (2.0)	Reflux, 2 h		**5c** (78)
11	**1b**	Cyclohexyl	DEAD (1.2)	rt, 6 h	**4d** (84)	
12	**1b**	Cyclohexyl	DEAD (2.0)	Reflux, 2 h		**5d** (73)
13	**1b**	*tert*-Butyl	DEAD (1.2)	rt, 6 h	**4e** (77)	
14	**1b**	*tert*-Butyl	DEAD (2.0)	Reflux, 2 h		**5e** (71)
15	**1c**	*tert*-Butyl	DEAD (2.0)	Reflux, 2 h		**5f** (72)
16	**1d**	Cyclohexyl	DEAD (1.2)	Reflux, 2 h	**4f** (87)[a]	
17	**1d**	*tert*-Butyl	DEAD (1.2)	Reflux, 2 h	**4g** (86)[a]	
18	**1a**	Phenyl	DEAD (2.0)	Reflux, 2 h		**5g** (78)
19	**1a**	Cyclohexyl	DIAD (2.0)	Reflux, 2 h		**5h** (74)
20	**1a**	*tert*-Butyl	DIAD (2.0)	Reflux, 2 h		**5i** (69)
21	**1b**	Cyclohexyl	DIAD (2.0)	Reflux, 2 h		**5j** (72)

[a] Using 2 equiv of **2** afforded the same results.



Scheme 3. Transformation reaction of imidazothiadiazoles **4** to thiadiazoles **5** and **6**.

observed,[18] and migration of a DEAD ethoxycarbonyl group has also been previously reported.[19]

Since compounds **5** are oils, thus unsuitable for crystallographic analysis, and their structure consists of many heteroatoms and only a few protons, rendering their identification by 2D NMR ambiguous, reduction was attempted in order to introduce some more protons into the molecule but also hoping to obtain solid reduction products.

Initially, sodium cyanoborohydride reduction was attempted on compounds **5b** and **5d** leading to the isolation of the thiadiazolylhydrazine carboxylates **11b** and **11d**, respectively, in high yields (80 and 77%), where only an ethoxycarbonyl group was expelled (Scheme 5). Fortunately, **11b** was a solid product, whose structure was confirmed by the use of crystal X-ray diffraction analysis[20] (Fig. 1). Reduction was also studied with sodium borohydride on compound **5e**, whereupon **12e** was isolated in 41% yield, as an oil with additional reduction of N6=C7 double bond (Scheme 5).

2.1. Structure assignments of the new compounds

The assigned molecular structures of the new compounds **4**, **5**, **11**, and **12** were based on rigorous spectroscopic analysis including IR, NMR (^{1}H, ^{13}C, H–H COSY, H–H NOESY, HMQC and HMBC), MS and elemental analysis data. The HMBC correlations of protons with carbons via ^2J, ^3J, and ^4J coupling are depicted in Fig. 2 for compounds **4a** and **5a**, and in Fig. 3 for compounds **11b** and **12e**.

Concerning the identification of compound **4a**, the ^{1}H NMR spectrum showed the presence of the thione and isocyanide moieties. The most characteristic HMBC correlation was the one between the 1″-H cyclohexyl proton with the C-5 thiadiazole carbon. Concerning compounds **5**, the presence in **5a** of a N=C(Me)–C(Me)=N moiety could be hinted by the absorption of the two carbons at 170.6 and 174.9 ppm correlating with both methyl group protons. In both **5a** and the cyanoborohydride reduction product **11b**, the C-5 thiadiazole side chain could be characterized from successive HMBC correlations as shown in Figs. 2 and 3. In compound **11b** the N=C(Me)–C(Me)=N moiety remained unchanged, one of the two carbons correlating with the newly formed NH proton, which was also correlating with the remaining carbonyl carbon of the ethoxycarbonyl group. The sodium borohydride product **12e** differs from compounds **11** only in the structure of the side chain. The position of the reduced double bond was confirmed by the HMBC correlations of the new-formed C–H group. The 7-H is correlated with the C-5 thiadiazole ring atom, indicating their neighborhood (Fig. 3).

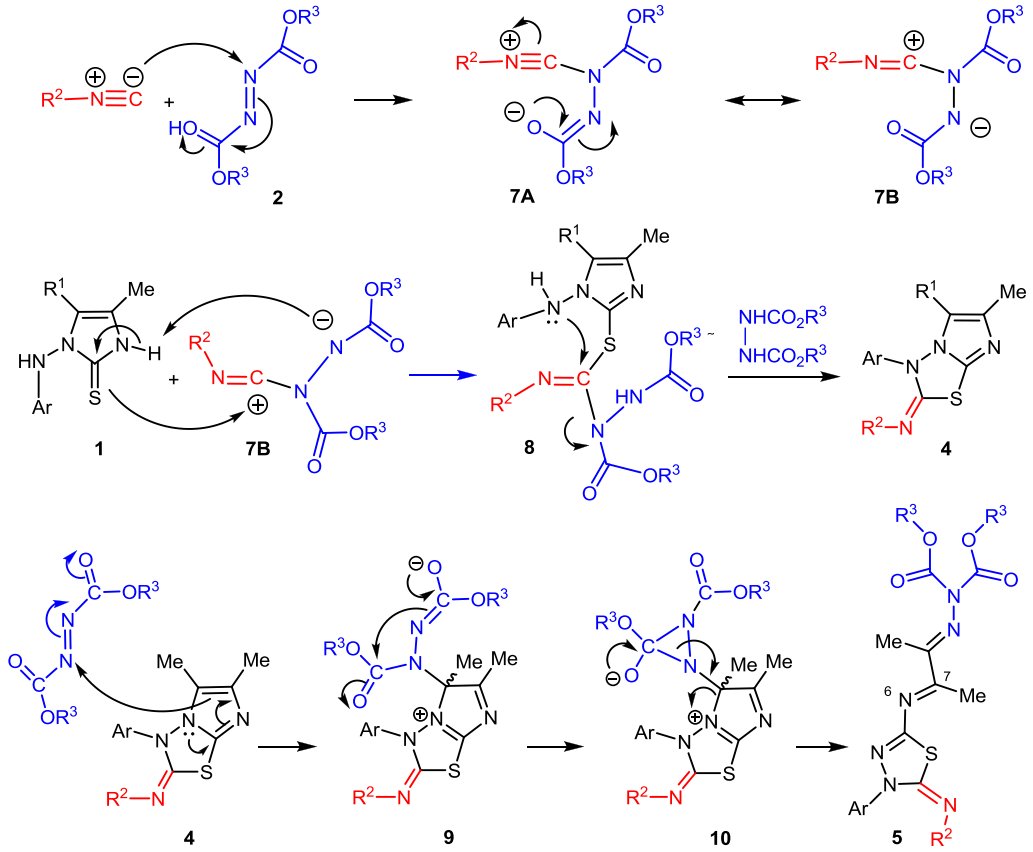
3. Conclusions

In conclusion, in the present work a new one-step method for the construction of the imidazo[2,1-*b*][1,3,4]thiadiazole scaffold, in very good yields, by using an unusual azodicarboxylate promoted reaction between imidazole-2-thiones and isocyanides is described. Moreover, the isolated imidazo[2,1-*b*][1,3,4]thiadiazoles could be transformed into new multi-substituted [1,3,4]thiadiazoles by refluxing with DEAD. The same multi-substituted [1,3,4] thiadiazoles were also formed through a one-pot multicomponent reaction between imidazole-2-thiones, isocyanides, and excess of DEAD. In addition, the ability of the azodicarboxylate moiety to act as an electrophile in the presence of five-membered heterocycles was established.

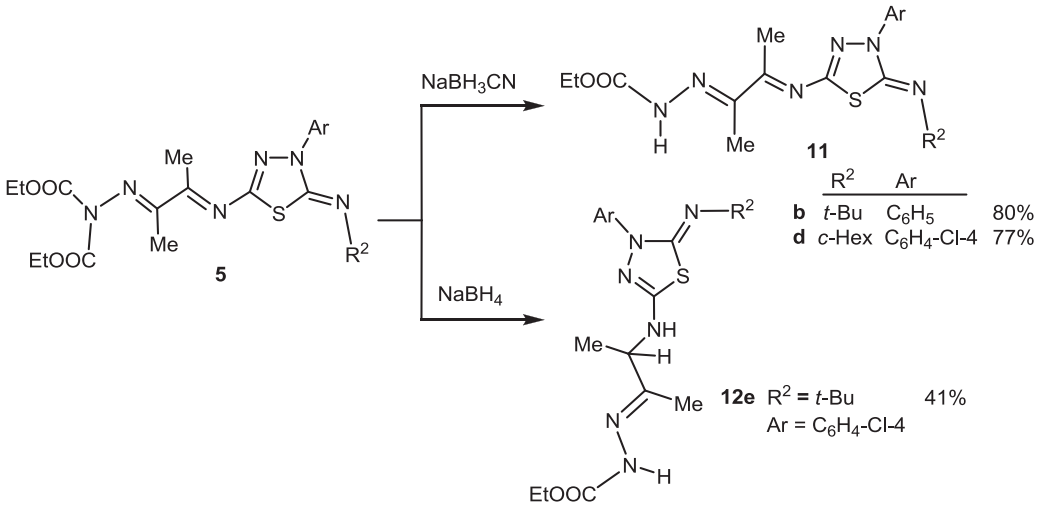
4. Experimental section

4.1. General

Thiones **1** were synthesized, as previously described, from substituted hydrazines, bromoketones, and potassium thiocyanate.[15a] Column chromatography was carried out using silica gel (70–230 mesh) and TLC was performed using precoated silica gel glass plates 0.25 mm containing fluorescent indicator UV_{254} using a 3:1 mixture of petroleum ether–ethyl acetate. Petroleum ether refers to the fraction boiling between 60 and 80 °C. NMR spectra were recorded at room temperature (25 °C) at 300 MHz for ^{1}H and 75 MHz for ^{13}C, respectively, using $CDCl_3$ as solvent. Chemical shifts are expressed in δ values (parts per million) relative to TMS as internal standard for ^{1}H and relative to TMS (0.00 ppm) or to $CDCl_3$ (77.05 ppm) for ^{13}C NMR spectra. Coupling constants ^nJ are reported in Hertz. Moreover, the complete assignment of ^{1}H and ^{13}C NMR signals was possible using 1D and 2D experiments using the standard commercial pulse programs. IR spectra were recorded on a FTIR spectrometer and are reported in wave numbers (cm^{-1}). Low-resolution mass spectra were obtained with the LC-ESI method at 1.65 eV ionization potential and are reported as *m*/*z* (relative intensity to the base peak), and elemental analyses performed with a CHN analyzer. For the XRD study we were able to identify the structure of this compound by measuring at synchrotron at 150 K.



Scheme 4. Rational mechanism for the formation of compounds **4** and **5**.



Scheme 5. Sodium borohydride and sodium cyanoborohydride reduction of thiadiazoles **5**.

4.2. Reaction of thione 1a with cyclohexylisocyanide in the presence of $BF_3 \cdot Et_2O$

To a mixture of thione **1a** (0.219 g, 1.0 mmol) and $BF_3 \cdot Et_2O$ (1.2 mmol) in toluene (25 mL), cyclohexylisocyanide (0.109 g, 1.0 mmol) was added. The reaction mixture was stirred at room temperature until thione was consumed completely (followed by TLC, approximately 4 h). The solvent was distilled off in vacuo and the resulting residue was dissolved in CH_2Cl_2, washed with water, dried, the solvent was evaporated, and the residue was subjected to column chromatography on silica gel using petroleum ether–AcOEt (1:1) as eluent to give 1-[[(*cyclohexylimino*)*methyl*]*phenylamino*]-2,3-*dihydro*-4,5-*dimethyl*-2-*thioxo*-1H-*imidazole* (**3a**). White solid; 0.230 g (70%); mp 177–179 °C (CH_2Cl_2–pet. ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10–1.50 (m, 5H, H_{ax}), 1.55–1.66 (m, 1H, 4″-H_{eq}), 1.67–1.84 (m, 4H, 2″,3″,5″,6″-H_{eq}), 1.89 (s, 3H, 5-CH_3), 2.06 (s, 3H, 4-CH_3), 3.12–3.25 (m, 1H, 1″-H), 7.04–7.14 (d, J=7.8 Hz, 2H, 2′,6′-H), 7.28–7.49 (m, 3H, 3′,4′,5′-H), 8.14 (s, 1H, N–CH=N), 10.2

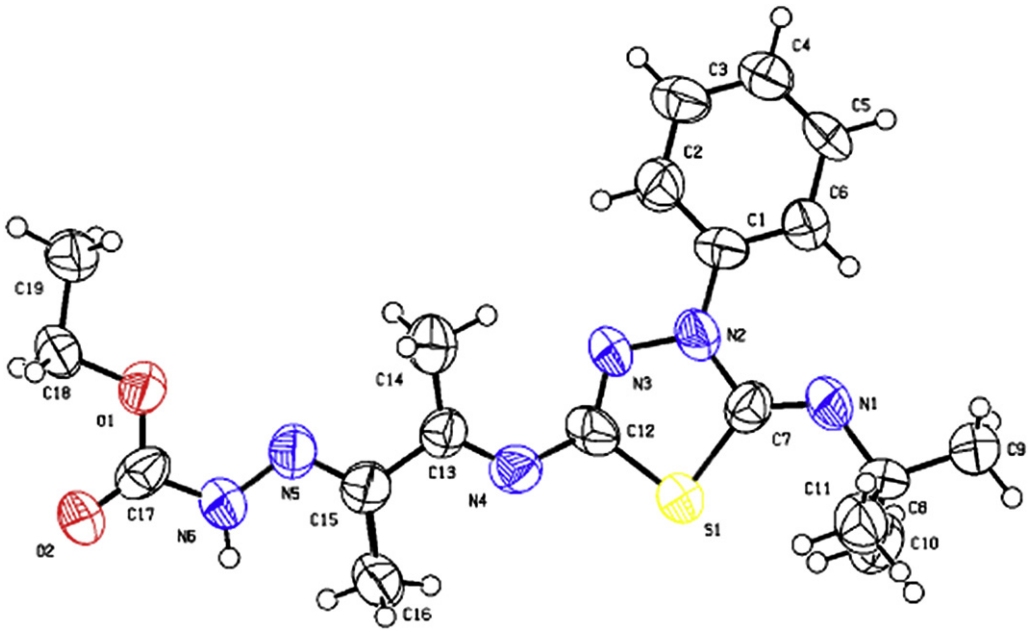


Fig. 1. ORTEP diagram of the molecular structure of compound **11b** as determined by crystal XRD (atoms ellipsoid probability 30%).

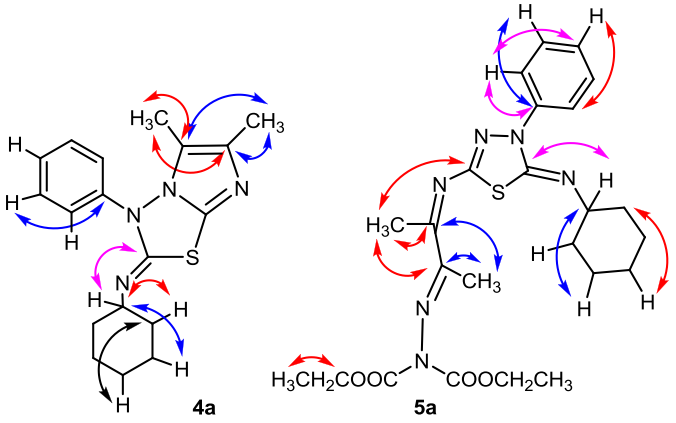


Fig. 2. Diagnostic HMBC correlations between protons and carbons (via $^{2}J_{C-H}$, $^{3}J_{C-H}$, and $^{4}J_{C-H}$) observed in compounds **4a** and **5a**.

(very broad, 1H, 3-NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.4 (5-CH_3), 9.5 (4-CH_3), 24.9 (C-3″,C-5″), 25.6 (C-4″), 35.09 and 35.13 (C-2″,C-6″), 64.6 (C-1″), 116.8 (C-2′,C-6′), 118.9 (C-5), 122.7 (C-4), 123.8 (C-4′), 129.5 (C-3′,C-5′), 141.8 (C-1′), 144.7 (N–CH=N), 160.3 (C-2); IR (KBr) 3436, 3090, 2924, 1649 cm^{-1}; LC–MS (ESI, 1.65 eV) *m*/*z* 329 [100, $(M+H)^+$]. Anal. Calcd for $C_{18}H_{24}N_4S$ (328.48): C, 65.82; H, 7.36; N, 17.06. Found: C, 65.99; H, 7.31; N 16.95.

4.3. General procedure for the reaction of thiones (1a–d) with isocyanides in the presence of azodicarboxylates

A reaction mixture of thione **1** (1.0 mmol), isocyanide (1.0 mmol) and DEAD or DIAD (1.2 mmol) in toluene (25 mL), was stirred at room temperature until thione **1** was consumed completely (followed by TLC, approximately 6 h). The solvent was distilled off in vacuo and the resulting residue was subjected to column chromatography on silica gel using petroleum ether–AcOEt (3:1) as eluent to give the isolated product **4** (Scheme 1). When the same reaction was repeated in refluxing toluene for 2 h a mixture of **5** and **4** was obtained in the above elution order. In addition, when the same

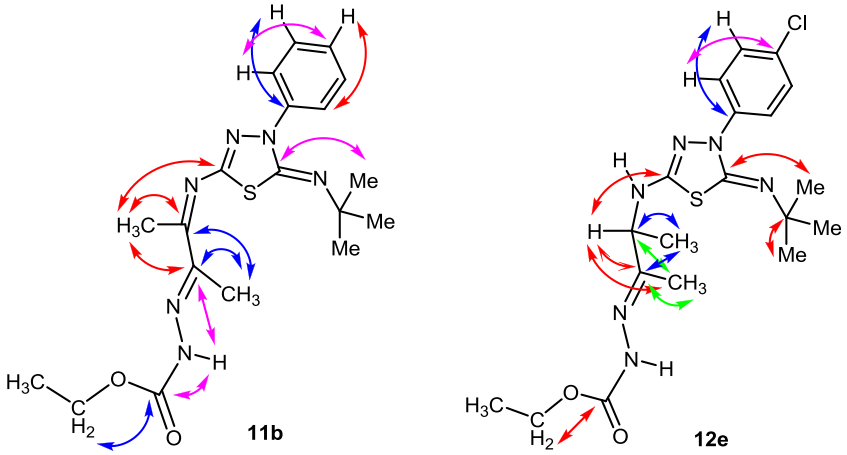


Fig. 3. Diagnostic HMBC correlations between protons and carbons (via $^{2}J_{C-H}$, $^{3}J_{C-H}$, and $^{4}J_{C-H}$) observed in compounds **11b** and **12e**.

reaction was repeated by using 2.0 equiv of azodicarboxylate in refluxing toluene for 2 h only compound **5** was isolated (Table 1, Scheme 2).

*4.3.1. 2-Cyclohexylimino-2,3-dihydro-5,6-dimethyl-3-phenyl-imidazo[2,1-b][1,3,4]thiadiazole (**4a**).* Yellow solid; 0.281 g (86%); mp 70–72 °C (CH_2Cl_2–pet. ether); ^1H NMR (300 MHz, $CDCl_3$) δ 1.20–1.45 (m, 5H, 2″,3″,4″,5″,6″-H_{ax}), 1.50–1.63 (m, 1H, 4″-H_{eq}), 1.63–1.77 (m, 4H, 2″,3″,5″,6″-H_{eq}), 1.79 (s, 3H, 5-CH_3), 2.17 (s, 3H, 6-CH_3), 2.88–2.92 (m, 1H, 1″-H), 7.26–7.42 (m, 5H, 2′,3′,4′,5′,6′-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.2 (5-CH_3), 13.2 (6-CH_3), 24.2 (C-3″,C-5″), 25.5 (4″-CH_3), 32.7 (C-2″,C-6″), 64.7 (C-1″), 120.2 (C-5), 123.5 (C-2′,C-6′), 127.5 (C-4′), 129.1 (C-3′,C-5′), 133.9 (C-7a), 135.4 (C-6), 144.6 (C-1′), 155.0 (C-2); IR (KBr) 1671, 1593 cm^{-1}; LC–MS (ESI, 1.65 eV) *m/z* 381 [100, $(M+MeOH+Na)^+$], 349 [30, $(M+Na)^+$], 327 [100, $(M+H)^+$]. Anal. Calcd for $C_{18}H_{22}N_4S$ (326.46): C, 66.22; H, 6.79; N, 17.16. Found: C, 66.07; H, 6.85; N, 17.18.

*4.3.2. 2,3-Dihydro-2-(tert-butylimino)-5,6-dimethyl-3-phenyl-imidazo[2,1-b][1,3,4]thiadiazole (**4b**).* Yellow solid; 0.243 g (81%); mp 55–57 °C (CH_2Cl_2–pet. ether); ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (s, 9H, $C(CH_3)_3$), 1.78 (s, 3H, 5-CH_3), 2.17 (s, 3H, 6-CH_3), 7.25–7.33 (m, 3H, 2′,4′,6′-H), 7.34–7.42 (m, 2H, 3′,5′-H); ^{13}C (75 MHz, $CDCl_3$) δ 9.0 (5-CH_3), 13.0 (6-CH_3), 28.2 ($C(CH_3)_3$), 55.0 ($C(CH_3)_3$), 120.0 (C-5), 123.2 (C-2′,C-6′), 127.1 (C-4′), 128.7 (C-3′,C-5′), 134.4 (C-7a), 135.1 (C-6), 144.8 (C-1′), 149.3 (C-2); IR (KBr) 1656 cm^{-1}; LC–MS (ESI, 1.65 eV) *m/z* 301 [100, $(M+H)^+$]. Anal. Calcd for $C_{16}H_{20}N_4S$ (300.42): C, 63.97; H, 6.71; N, 18.65. Found: C, 64.08; H, 6.65; N, 18.78.

*4.3.3. 2-(Benzyl)imino-2,3-dihydro-5,6-dimethyl-3-phenyl-imidazo [2,1-b][1,3,4]thiadiazole (**4c**).* Yellow solid; 0.257 g (77%); mp 145–147 °C (CH_2Cl_2–pet. ether); ^1H NMR (300 MHz, $CDCl_3$) δ 1.77 (s, 3H, 5-CH_3), 2.17 (s, 3H, 6-CH_3), 4.42 (s, 2H, CH_2), 7.14–7.30 (m, 5H, Ar–H), 7.32–7.48 (m, 5H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.3 (5-CH_3), 13.2 (6-CH_3), 58.2 (CH_2), 120.2 (C-5), 124.6 (C-2′,C-6′), 127.0 (C-4′), 127.2 (C-2″,C-6″), 128.1 (C-4″), 128.4 (C-3′,C-5′), 129.3 (C-3″,C-5″), 133.3 (C-7a), 136.2 (C-6), 138.4 (C-1″), 143.7 (C-1′), 158.4 (C-2); IR (KBr) 1676 cm^{-1}; LC–MS (ESI, 1.65 eV) *m/z* 389 [30, $(M+MeOH+Na)^+$], 358 [45, $(M+Na+H)^+$], 335 [100, $(M+H)^+$]; Anal. Calcd for $C_{19}H_{18}N_4S$ (334.44): C, 68.23; H, 5.42; N, 16.75. Found: C, 68.47; H, 5.35; N, 16.88.

*4.3.4. 3-(4-Chlorophenyl)-2-cyclohexylimino-2,3-dihydro-5,6-dimethyl-imidazo[2,1-b][1,3,4]thiadiazole (**4d**).* Yellow solid; 0.303 g (84%); mp 98–100 °C (CH_2Cl_2–pet. ether); ^1H NMR (300 MHz, $CDCl_3$) δ 1.20–1.45 (m, 5H, H_{ax}), 1.52–1.62 (m, 1H, 4″-H_{eq}), 1.62–1.75 (m, 4H, 2″,3″,5″,6″-H_{eq}), 1.82 (s, 3H, 5-CH_3), 2.17 (s, 3H, 6-CH_3), 2.85–2.97 (m, 1H, 1″-H), 7.30 (d, *J*=9.0 Hz, 2H, 2′,6′-H), 7.37 (d, *J*=9.0 Hz, 2H, 3′,5′-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.1 (5-CH_3), 13.0 (6-CH_3), 24.0 (C-3″,C-5″), 25.3 (4″-CH_3), 32.6 (C-2″,C-6″), 64.5 (C-1″), 120.0 (C-5), 124.5 (C-2′,C-6′), 129.0 (C-3′,C-5′), 132.9 (C-4′), 133.7 (C-7a), 135.6 (C-6), 142.8 (C-1′), 154.4 (C-2); IR (KBr) 1671 cm^{-1}; LC–MS (ESI, 1.65 eV) *m/z* 415/417 [40, $(M+MeOH+Na)^+$], 383/385 [20, $(M+Na)^+$], 361/363 [100, $(M+H)^+$]. Anal. Calcd for $C_{18}H_{21}ClN_4S$ (360.90): C, 59.90; H, 5.86; N, 15.52. Found: C, 59.97; H, 5.75; N, 15.39.

*4.3.5. 3-(4-Chlorophenyl)-2,3-dihydro-2-(tert-butylimino)-5,6-dimethyl-imidazo[2,1-b][1,3,4]thiadiazole (**4e**).* Yellow solid (0.258 g, 77% yield), mp 67–68 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 9H, $C(CH_3)_3$), 1.81 (s, 3H, 5-CH_3), 2.17 (s, 3H, 6-CH_3), 7.26 (d, *J*=9.0 Hz, 2H, 2′,6′-H), 7.36 (d, *J*=9.0 Hz, 2H, 3′,5′-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.2 (5-CH_3), 13.2 (6-CH_3), 28.4 ($C(CH_3)_3$), 55.3 ($C(CH_3)_3$), 120.2 (C-5), 124.5 (C-3′,C-5′), 129.0 (C-2′,C-6′), 132.7 (C-4′), 134.7 (C-7a), 135.6 (C-6), 143.4 (C-1′), 149.1 (C-2); IR (KBr) 1664 cm^{-1}; LC–MS (ESI, 1.65 eV) *m/z* 389/387 [45, $(M+MeOH+Na)^+$], 357/359 [25, $(M+Na)^+$], 335/337 [100, $(M+H)^+$]; Anal. Calcd for $C_{16}H_{19}ClN_4S$ (334.87): C, 57.39; H, 5.72; N, 16.73. Found: C, 57.27; H, 5.65; N, 16.59.

*4.3.6. 2-Cyclohexylimino-2,3-dihydro-3,5-diphenyl-6-methyl-imidazo[2,1-b][1,3,4]thiadiazole (**4f**).* Yellowish solid (0.338 g, 87% yield), mp 105–106 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.15–1.46 (m, 5H, H_{ax}), 1.52–1.62 (m, 1H, 4″-H_{eq}), 1.63–1.75 (m, 4H, 2″,3″,5″,6″-H_{eq}), 2.35 (s, 3H, 6-CH_3), 2.88–3.00 (m, 1H, 1″-H), 6.98–7.18 (m, 8H, 3′,4′,5′-H and 5-Ph), 7.24–7.29 (m, 2H, 2′,6′-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4 (6-CH_3), 24.1 (C-3″,C-5″), 25.4 (C-4″), 32.7 (C-2″,C-6″), 64.8 (C-1″), 122.8 (C-2′,C-6′), 124.4 (C-5), 126.9 (C-4‴), 127.3 (C-4′), 127.86 and 127.91 (C-2‴,C-6‴ and C-3‴,C-5‴), 128.1 (C-1‴), 128.4 (C-3′,C-5′), 135.8 (C-7a), 137.0 (C-6), 144.4 (C-1′), 154.8 (C-2); IR (KBr) 1662, 1644 cm^{-1}; LC–MS (ESI, 1.65 eV) *m/z* 443 [25, $(M+MeOH+Na)^+$], 389 [100, $(M+H)^+$]. Anal. Calcd for $C_{23}H_{24}N_4S$ (388.53): C, 71.10; H, 6.23; N, 14.42. Found: C, 71.07; H, 6.35; N, 14.28.

*4.3.7. 2,3-Dihydro-2-(tert-butylimino)-3,5-diphenyl-6-methyl-imidazo[2,1-b][1,3,4]thiadiazole (**4g**).* Yellow solid; 0.312 g (86%); mp 110–111 °C (CH_2Cl_2–pet. ether); ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 9H, $C(CH_3)_3$), 2.34 (s, 3H, 6-CH_3), 6.95–7.17 (m, 8H, 3′,4′,5′-H and 5-Ph), 7.23–7.29 (m, 2H, 2′, 6′-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4 (6-CH_3), 28.3 ($C(CH_3)_3$), 55.2 ($C(CH_3)_3$), 122.8 (C-2′,C-6′), 124.3 (C-5), 126.7 (C-4‴), 127.2 (C-4′), 127.80 and 127.82 (C-2‴,C-3‴,C-5‴,C-6‴), 128.1 (C-1‴), 128.2 (C-3′,C-5′), 136.4 (C-7a), 136.8 (C-6), 144.8 (C-1′), 149.2 (2-C); IR (KBr) 1669 cm^{-1}; LC–MS (ESI, 1.65 eV) *m/z* 417 [45, $(M+Na)^+$], 385 [30, $(M+Na)^+$], 363 [100, $(M+H)^+$]. Anal. Calcd for $C_{21}H_{22}N_4S$ (362.49): C, 69.58; H, 6.12; N, 15.46. Found: C, 69.47; H, 6.05; N, 15.30.

*4.3.8. (2Z)-5-[[(1E,2E)-2-[2,2-Bis(ethoxycarbonyl)hydrazono]-1-methylpropylidene]amino]-2-(cyclohexylimino)-3-phenyl-2,3-dihydro-1,3,4-thiadiazole (**5a**).* Yellowish oil; 0.436 g (87%); ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (t, *J*=7.1 Hz, 6H, 2×$COOCH_2CH_3$), 1.25–1.45 (m, 5H, H_{ax}), 1.60–1.68 (1H, m, 4″-H_{eq}), 1.72–1.91 (m, 4H, 2″,3″,5″,6″-H_{eq}), 2.12 (s, 3H, 8-CH_3), 2.60 (s, 3H, 7-CH_3), 2.68–2.79 (m, 1H, 1″-H), 4.34 (q, *J*=7.1 Hz, 4H, 2×$COOCH_2CH_3$), 7.13–7.20 (m, 1H, 4′-H), 7.33–7.42 (m, 2H, 3′,5′-H), 8.00–8.05 (m, 2H, 2′,6′-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2 (2×$COOCH_2CH_3$), 14.3 (8-CH_3), 17.8 (7-CH_3), 24.6 (C-3″,C-5″), 25.8 (C-4″), 33.1 (C-2″,C-6″), 63.7 (2×$COOCH_2CH_3$), 68.2 (C-1″), 121.3 (C-2′,C-6′), 124.9 (C-4′), 128.5 (C-3′,C-5′), 140.2 (C-1′), 148.6 (C-5), 150.7 (2×CO), 151.0 (C-2), 170.6 (C-7), 174.9 (C-8); IR (neat) 1794, 1758, 1630 cm^{-1}; LC–MS (ESI, 1.65 eV) *m/z* 523 [100, $(M+Na)^+$], 501 [44, $(M+H)^+$]. Anal. Calcd for $C_{24}H_{32}N_6O_4S$ (500.62): C, 57.58; H, 6.44; N, 16.79. Found: C, 57.67; H, 6.35; N, 16.61.

*4.3.9. (2Z)-5-[[(1E,2E)-2-[2,2-Bis(ethoxycarbonyl)hydrazono]-1-methylpropylidene]amino]-2-(tert-butylimino)-3-phenyl-2,3-dihydro-1,3,4-thiadiazole (**5b**).* Yellowish oil; 0.403 g (85%); ^1H NMR (300 MHz, $CDCl_3$) δ 1.335 (t, *J*=7.1 Hz, 6H, 2×$COOCH_2CH_3$), 1.36 (s, 9H, $(C(CH_3)_3)$), 2.12 (s, 3H, 8-CH_3), 2.62 (3H, s, 7-CH_3), 4.32 (q, *J*=7.1 Hz, 4H, 2×$COOCH_2CH_3$), 7.12–7.19 (1H, m, 4′-H), 7.32–7.40 (2H, m, 3′,5′-H), 7.96–8.01 (m, 2H, 2′,6′-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0 (2×$COOCH_2CH_3$), 14.1 (8-CH_3), 17.7 (7-CH_3), 27.7 ($C(CH_3)_3$), 54.0 ($C(CH_3)_3$), 63.4 (2×$COOCH_2CH_3$), 122.0 (C-2′,C-6′), 124.8 (C-4′), 128.0 (C-3′,C-5′), 140.3 (C-1′), 145.4 (C-2), 148.2 (C-5), 150.5 (2×CO), 170.1 (C-7), 174.6 (C-8); IR (neat) 1765, 1759, 1754, 1632 cm^{-1}; LC–MS (ESI, 1.65 eV) *m/z* 529 [20, $(M+MeOH+Na)^+$], 497 [80, $(M+Na)^+$], 475 [100, $(M+H)^+$]. Anal. Calcd for $C_{22}H_{30}N_6O_4S$ (474.58): C, 55.68; H, 6.37; N, 17.71. Found: C, 55.56; H, 6.30; N, 17.62.

*4.3.10. (2Z)-2-(Benzylimino)-5-[[(1E,2E)-2-[2,2-bis(ethoxycarbonyl) hydrazono]-1-methylpropylidene]amino]-3-phenyl-2,3-dihydro-1,3,4-thiadiazole (**5c**).* Yellowish oil; 0.397 g (78%); ^1H NMR

(300 MHz, $CDCl_3$) δ 1.34 (t, J=7.1 Hz, 6H, 2×$COOCH_2CH_3$), 2.12 (s, 3H, 8-CH_3), 2.61 (s, 3H, 7-CH_3), 4.33 (q, J=7.1 Hz, 4H, 2×$COOCH_2CH_3$), 4.44 (s, 2H, CH_2), 7.17–7.22 (m, 1H, 4′-H), 7.22–7.28 (m, 1H, 4″-H), 7.31–7.36 (m, 2H, 3′,5′-H), 7.35–7.45 (m, 4H, 2″,3″,5″,6″-H), 7.99–8.05 (m, 2H, 2′,6′-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.25 (2×$COOCH_2CH_3$), 14.36 (8-CH_3), 17.9 (7-CH_3), 61.5 (CH_2), 63.8 (2×$COOCH_2CH_3$), 122.0 (C-2′,C-6′), 125.6 (C-4′), 126.9 (C-4″), 127.5 (C-2″,C-6″), 128.4 (C-3′,C-5′), 128.7 (C-3″,C-5″), 139.5 (C-1″), 140.0 (C-1′), 148.8 (C-5), 150.8 (2×CO), 155.1 (C-2), 171.3 (C-7), 174.7 (C-8); IR (neat) 1762, 1750, 1629 cm^{-1}; LC–MS (ESI, 1.65 eV) m/z 563 [25, $(M+MeOH+Na)^+$], 531 [92, $(M+Na)^+$], 509 [100, $(M+H)^+$]. Anal. Calcd for $C_{25}H_{28}N_6O_4S$ (508.59): C, 59.04; H, 5.55; N, 16.52. Found: C, 58.87; H, 5.41; N, 16.67.

*4.3.11. (2Z)-5-[[(1E,2E)-2-[2,2-Bis(ethoxycarbonyl)hydrazono]-1-methylpropylidene]amino]-3-(4-chlorophenyl)-2-(cyclohexylimino)-1,3,4-thiadiazole (**5d**).* Yellowish oil; 0.391 g (73%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (t, J=7.1 Hz, 6H, 2×$COOCH_2CH_3$), 1.30–1.67 (m, 5H, 2″,3″,4″,5″,6″-H_{ax}), 1.73–1.90 (m, 5H, 2″,3″,4″,5″,6″-H_{eq}), 2.12 (s, 3H, 8-CH_3), 2.53 (s, 3H, 7-CH_3), 2.66–2.78 (m, 1H, 1″-H), 4.34 (q, J=7.1 Hz, 4H, 2×$COOCH_2CH_3$), 7.33 (d, J=7.3 Hz, 2H, 3′,5′-H), 8.02 (d, J=7.3 Hz, 2H, 2′,6′-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2 (2×$COOCH_2CH_3$), 14.4 (8-CH_3), 17.8 (7-CH_3), 24.6 (C-3″,C-5″), 25.7 (C-4″), 33.1 (C-2″,C-6″), 63.8 (2×$COOCH_2CH_3$), 68.2 (C-1″), 122.2 (C-2′,C-6′), 128.5 (C-3′,C-5′), 129.8 (C-4′), 138.8 (C-1′), 148.9 (C-5), 150.68 (2×CO), 150.73 (C-2), 171.2 (C-7), 174.7 (C-8); IR (neat) 1761, 1633 cm^{-1}; LC–MS (ESI, 1.65 eV) m/z 589/591 [5, $(M+MeOH+Na)^+$], 557/559 [20, $(M+Na)^+$], 535/537 [100, $(M+H)^+$]. Anal. Calcd for $C_{24}H_{31}ClN_6O_4S$ (535.06): C, 53.87; H, 5.84; N, 15.71. Found: C, 53.69; H, 5.74; N, 15.60.

*4.3.12. (2Z)-5-[[(1E,2E)-2-[2,2-Bis(ethoxycarbonyl)hydrazono]-2,3-dihydro-1-methylpropylidene]amino]-3-(4-chlorophenyl)-2-(tert-butylimino)-1,3,4-thiadiazole (**5e**).* Yellowish oil; 0.361 g (71%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (9H, s, $(C(CH_3)_3)$), 1.35 (6H, t, J=7.1 Hz, 2×$COOCH_2CH_3$), 2.12 (3H, s, 8-CH_3), 2.60 (3H, s, 7-CH_3), 4.33 (4H, q, J=7.1 Hz, 2×$COOCH_2CH_3$), 7.32 (d, J=8.9 Hz, 2H, 3′,5′-H), 7.98 (d, J=8.9 Hz, 2H, 2′,6′-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2 (2×$COOCH_2CH_3$), 14.4 (8-CH_3), 17.9 (7-CH_3), 27.8 ($C(CH_3)_3$), 54.3 ($C(CH_3)_3$), 63.8 (2×$COOCH_2CH_3$), 123.1 (C-2′,C-6′), 128.3 (C-3′,C-5′), 129.9 (C-4′), 138.9 (C-1′), 145.4 (C-2), 148.8 (C-5), 150.7 (2×CO), 170.8 (C-7), 174.9 (C-8); IR (neat) 1758, 1632 cm^{-1}; LC–MS (ESI, 1.65 eV) m/z 563/565 [5, $(M+MeOH+Na)^+$], 531/533 [40, $(M+Na)^+$], 509/511 [100, $(M+H)^+$]. Anal. Calcd for $C_{22}H_{29}ClN_6O_4S$ (509.02): C, 51.91; H, 5.74; N, 16.51. Found: C, 51.77; H, 5.89; N, 16.68.

*4.3.13. (2Z)-5-[[(1E,2E)-2-[2,2-Bis(ethoxycarbonyl)hydrazono]-2,3-dihydro-1-methylpropylidene]amino]-2-(tert-butylimino)-3-(4-methylphenyl)-1,3,4-thiadiazole (**5f**).* Yellowish oil; 0.352 g (72%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 9H, $(C(CH_3)_3)$), 1.35 (t, J=7.1 Hz, 6H, 2×$COOCH_2CH_3$), 2.12 (s, 3H, 8-CH_3), 2.37 (s, 3H, 4′-CH_3), 2.61 (s, 3H, 8-CH_3), 4.33 (q, J=7.1 Hz, 4H, 2×$COOCH_2CH_3$), 7.17 (d, J=8.6 Hz, 2H, 3′,5′-H), 7.82 (d, J=8.6 Hz, 2H, 2′,6′-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3 (2×$COOCH_2CH_3$), 14.4 (8-CH_3), 17.9 (7-CH_3), 21.0 (4′-CH_3), 27.9 ($C(CH_3)_3$), 54.2 ($C(CH_3)_3$), 63.8 (2×$COOCH_2CH_3$), 122.3 (C-2′,C-6′), 128.9 (C-3′,C-5′), 134.8 (C-4′), 137.8 (C-1′), 145.7 (C-2), 148.0 (C-5), 150.7 (2×CO), 169.7 (C-7), 175.3 (C-8); IR (neat) 1770, 1762, 1633, 1626 cm^{-1}; LC–MS (ESI, 1.65 eV) m/z 511 [40, $(M+Na)^+$], 489 [100, $(M+H)^+$]. Anal. Calcd for $C_{23}H_{32}N_6O_4S$ (488.60): C, 56.54; H, 6.60; N, 17.20. Found: C, 56.77; H, 6.73; N, 17.41.

*4.3.14. (2Z)-5-[[(1E,2E)-2-[2,2-Bis(ethoxycarbonyl)hydrazono]-2,3-dihydro-1-methylpropylidene]amino]-3-phenyl-2-(phenylimino)-1,3,4-thiadiazole (**5g**).* Yellowish oil; 0.386 g (78%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (t, J=7.1 Hz, 6H, 2×$COOCH_2CH_3$), 2.09 (s, 3H, 8-CH_3), 2.58 (s, 3H, 7-CH_3), 4.33 (q, J=7.1 Hz, 4H, 2×$COOCH_2CH_3$), 7.07 (d, J=8.1 Hz, 2H, 2″,6″-H), 7.12 (t, J=7.5 Hz, 1H, 4′-H), 7.27 (t, J=7.1 Hz, 1H, 4″-H), 7.37 (dd, J=8.4, 7.5 Hz, 2H, 3′,5′-H), 7.45 (dd, J=8.2, 7.1 Hz, 2H, 3″,5″-H), 8.01 (d, J=8.4 Hz, 2H, 2′,6′-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3 (2×$COOCH_2CH_3$), 14.4 (8-CH_3), 17.9 (7-CH_3), 63.9 (2×$COOCH_2CH_3$), 120.8 (C-2″,C-6″), 122.3 (C-2′,C-6′), 124.2 (C-4′), 126.1 (C-4″), 128.8 (C-3′,C-5′), 129.7 (C-3″,C-5″), 139.5 (C-1′), 149.2 (C-5), 150.7 (2×CO), 151.8 (C-2), 155.2 (C-1″), 171.9 (C-7), 174.6 (C-8); IR (neat) 1760, 1752, 1619 cm^{-1}; LC–MS (ESI, 1.65 eV) m/z 549 [5, $(M+MeOH+Na)^+$], 517 [100, $(M+Na)^+$], 495 [75, $(M+H)^+$]. Anal. Calcd for $C_{24}H_{26}N_6O_4S$ (494.57): C, 58.28; H, 5.30; N, 16.99. Found: C, 58.37; H, 5.42; N, 17.18.

*4.3.15. (2Z)-5-[[(1E,2E)-2-[2,2-Bis[(1-methylethoxy)carbonyl]hydrazono]-1-methylpropylidene]amino]-2-(cyclohexylimino)-3-phenyl-1,3,4-thiadiazole (**5h**).* Yellowish oil; 0.391 g (74%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (d, J=7.5 Hz, 12H, 2×$COOCH(CH_3)_2$), 1.25–1.55 (m, 5H, H_{ax}), 1.56–1.66 (m, 1H, 4″-H_{eq}), 1.75–1.92 (m, 4H, 2″,3″,5″,6″-H_{eq}), 2.10 (s, 3H, 8-CH_3), 2.59 (s, 3H, 7-CH_3), 2.70–2.80 (m, 1H, 1″-H), 5.05–5.15 (m, 2H, 2×$COOCH(CH_3)_2$), 7.15 (t, J=7.3 Hz, 1H, 4′-H), 7.37 (dd, J=8.4, 7.3 Hz, 2H, 3′,5′-H), 8.04 (d, J=8.4 Hz, 2H, 2′,6′-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4 (8-CH_3), 17.7 (7-CH_3), 21.8 (2×$COOCH(CH_3)_2$), 24.6 (C-3″,C-5″), 25.9 (4″-CH_3), 33.2 (C-2″,C-6″), 68.2 (C-1″), 71.9 (2×$COOCH(CH_3)_2$), 121.3 (C-2′,C-6′), 124.9 (C-4′), 128.5 (C-3′,C-5′), 140.4 (C-1′), 148.7 (C-5), 150.6 (2×CO), 151.0 (C-2), 171.0 (C-7), 173.8 (C-8); IR (neat) 1762, 1754, 1631 cm^{-1}; LC–MS (ESI, 1.65 eV) m/z 583 [5, $(M+MeOH+Na)^+$], 551 [45, $(M+Na)^+$], 529 [100, $(M+H)^+$]. Anal. Calcd for $C_{26}H_{36}N_6O_4S$ (528.67): C, 59.07; H, 6.86; N, 15.90. Found: C, 58.92; H, 6.95; N, 17.08.

*4.3.16. (2Z)-5-[[(E)-2-[(E)-2,2-Bis[(1-methylethoxy)carbonyl]hydrazono]-1-methylpropylidene]amino]-2-(tert-butylimino)-3-phenyl-1,3,4-thiadiazole (**5i**).* Yellowish oil; 0.347 g (69%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.330 (d, J=6.3 Hz, 12H, 2×$COOCH(CH_3)_2$), 1.335 (9H, s, $C(CH_3)_3$), 2.11 (s, 3H, 8-CH_3), 2.61 (s, 3H, 7-CH_3), 5.08 (sept, J=6.3 Hz, 2H, 2×$COOCH(CH_3)_2$), 7.14 (t, J=7.5 Hz, 1H, 4′-H), 7.35 (dd, J=7.9, 7.5 Hz, 2H, 3′,5′-H), 8.00 (d, J=7.9 Hz, 2H, 2′,6′-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3 (CH_3), 17.8 (CH_3), 21.7 (2×$COOCH(CH_3)_2$), 27.9 ($C(CH_3)_3$), 54.2 ($C(CH_3)_3$), 71.8 (2×$COOCH(CH_3)_2$), 122.1 (C-2′,C-6′), 124.9 (C-4′), 128.2 (C-3′,C-5′), 140.5 (C-1′), 145.5 (C-5), 148.4 (C-2), 150.5 (2×CO), 170.5 (C-7), 173.8 (C-8); IR (neat) 1753, 1635 cm^{-1}; LC–MS (ESI, 1.65 eV) m/z 557 [10, $(M+MeOH+Na)^+$], 525 [45, $(M+Na)^+$], 503 [100, $(M+H)^+$]. Anal. Calcd for $C_{24}H_{34}N_6O_4S$ (502.63): C, 57.35; H, 6.82; N, 16.72. Found: C, 57.49; H, 6.90; N, 16.92.

*4.3.17. (2Z)-5-[[(E)-2-[(E)-2,2-Bis[(1-methylethoxy)carbonyl]hydrazono]-1-methylpropylidene]amino]-2-(cyclohexylimino)-3-(4-chlorophenyl)-1,3,4-thiadiazole (**5j**).* Yellowish oil; 0.405 g (72%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (d, J=6.3 Hz, 12H, 2×$COOCH(CH_3)_2$), 1.20–1.55 (m, 5H, H_{ax}), 1.55–1.67 (m, 1H, 4″-H_{eq}), 1.75–1.90 (m, 4H, 2″,3″,5″,6″-H_{eq}), 2.10 (s, 3H, CH_3), 2.59 (s, 3H, CH_3), 2.67–2.78 (m, 1H, 1″-H), 5.10 (sept, J=6.3 Hz, 2H, 2×$COOCH(CH_3)_2$), 7.33 (d, J=8.8 Hz, 2H, 3′,5′-H), 8.02 (d, J=8.8 Hz, 2H, 2′,6′-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5 (8-CH_3), 17.8 (7-CH_3), 21.8 (2×$COOCH(CH_3)_2$), 24.6 (C-3″,C-5″), 25.7 (4″-CH_3), 33.2 (C-2″,C-6″), 68.3 (C-1″), 72.1 (2×$COOCH(CH_3)_2$), 122.3 (C-2′,C-6′), 128.5 (C-3′,5′), 129.8 (C-4′), 138.8 (C-1′), 149.1 (C-2), 150.6 (2×CO), 150.9 (C-2), 171.4 (C-7), 173.5 (C-8); IR (neat) 1757, 1635 cm^{-1}; LC–MS (ESI, 1.65 eV) m/z 595/597 [30, $(M+MeOH+H)^+$], 563/565 [20, $(M+H)^+$], 437/439 (100). Anal. Calcd for $C_{26}H_{35}ClN_6O_4S$ (563.11): C, 55.46; H, 6.26; N, 14.92. Found: C, 55.62; H, 6.15; N, 15.09.

*4.3.18. Reduction of compounds **5** with $NaBH_4$ and $NaBH_3CN$.* A mixture of compound **5** (1.0 mmol) and $NaBH_3CN$ (or $NaBH_4$, 1.1 mmol) was dissolved in MeOH (5 mL) and was stirred at ambient temperature for 2 h and then concentrated in vacuum. The residue was in partition with ethyl acetate (10 mL) and water

(10 mL). The organic layer was separated, and the aqueous layer was extracted again with ethyl acetate (10 mL). The organic layers were combined, washed with brine, dried with anhydrous Na_2SO_4, concentrated in vacuum, and purified with silica gel column chromatography using petroleum ether–AcOEt (1:1) as eluent to give the isolated product **11** or **12** depending on the use of $NaBH_3CN$ or $NaBH_4$, respectively.

*4.3.19. (2Z)-2-(tert-Butylimino)-5-[[(1E,2E)-2-[2-(ethoxycarbonyl) hydrazono]-1-methylpropylidene]amino]-3-phenyl-1,3,4-thiadiazole (**11b**).* Yellow solid; 0.322 g (80%); mp 160–162 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 9H, (CH_3)$_3$)), 1.36 (t, J=7.1 Hz, 3H, $COOCH_2CH_3$), 2.11 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 4.33 (q, J=7.1 Hz, 2H, $COOCH_2CH_3$), 7.13 (t, J=7.5 Hz, 1H, 4′-H), 7.34 (dd, J=8.1, 7.5 Hz, 2H, 3′,5′-H), 7.99 (d, J=8.1 Hz, 2H, 2′,6′-H), 8.03 (br s, 1H, N–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.6 (8-CH_3), 14.5 ($COOCH_2CH_3$), 17.0 (7-CH_3), 28.0 (CH_3)$_3$), 54.2 (C(CH_3)$_3$), 62.5 ($COOCH_2CH_3$), 122.0 (C-2′,C-6′), 124.7 (C-4′), 128.2 (C-3′,C-5′), 140.8 (C-1′), 145.9 (C-2), 149.2 (C-8),* 149.3 (C-5),* 153.1 (CO), 171.0 (C-7); IR (KBr) 3442, 3237, 1702, 1633 cm^{-1}; LC–MS (ESI, 1.65 eV) m/z 425 [30, (M+Na)$^+$], 403 [100, (M+H)$^+$]. Anal. Calcd for $C_{19}H_{26}N_6O_2S$ (402.52): C, 56.69; H, 6.51; N, 20.88. Found: C, 56.22; H, 6.65; N, 20.61. (*The assignment may be interchanged).

*4.3.20. (2Z)-3-(4-Chlorophenyl)-2-(cyclohexylimino)-5-[[(1E,2E)-2-[2-(ethoxycarbonyl)hydrazono]-1-methylpropylidene]amino]-1,3,4-thiadiazole (**11d**).* Yellowish oil; 0.356 g (77%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, J=7.1 Hz, 3H, $COOCH_2CH_3$), 1.30–1.64 (m, 6H, 2″,3″,4″,5″,6″-H_{ax},4″-H_{eq}), 1.73–1.90 (m, 4H, 2″,3″,5″,6″-H_{eq}), 2.10 (s, 3H, 8-CH_3), 2.52 (s, 3H, 7-CH_3), 2.70–2.80 (m, 1H, 1″-H), 4.33 (q, J=7.1 Hz, 2H, $COOCH_2CH_3$), 7.30 (d, J=9.1 Hz, 2H, 3′,5′-H), 7.95 (br s, 1H, N–H), 8.02 (d, J=9.1 Hz, 2H, 2′,6′-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.6 (8-CH_3), 14.5 ($COOCH_2CH_3$), 16.9 (7-CH_3), 24.6 (C-3″,C-5″), 25.8 (C-4″), 33.3 (C-2″,C-6″), 62.6 ($COOCH_2CH_3$), 68.2 (C-1″), 122.2 (C-2′,C-6′), 128.5 (C-3′,C-5′), 129.6 (C-4′), 139.1 (C-1′), 149.1 (C-5),* 149.8 (C-8),*,§ 151.0 (C-2),§ 153.0 (CO), 171.9 (C-7); IR (neat) 3442, 3237, 1705, 1630 cm^{-1}; LC–MS (ESI, 1.65 eV) m/z 567/569 [15, (M+Na)$^+$], 535/537 [100, (M+H)$^+$]. Anal. Calcd for $C_{21}H_{27}ClN_6O_2S$ (463.00): C, 54.48; H, 5.88; N, 18.15. Found: C, 54.56; H, 5.97; N, 18.48. (*,§The assignment may be interchanged).

*4.3.21. (2Z)-3-(4-Chlorophenyl)-2-(tert-butylimino)-5-[[2-[2-(ethoxycarbonyl)hydrazino]-1-methylpropylidene]amino]-1,3,4-thiadiazole (**12e**).* Yellowish oil; 0.180 g (41%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (s, 9H, C(CH_3)$_3$), 1.32 (t, J=7.1 Hz, 3H, $COOCH_2CH_3$), 1.45 (d, J=6.7 Hz, 3H, 7-CH_3), 1.88 (s, 3H, 8-CH_3), 4.28 (q, J=7.1 Hz, 2H, $COOCH_2CH_3$), 4.44 (qui, J=6.7 Hz, 1H, 7-H), 5.37 (br d, J=6.7 Hz, 1H, N6–H), 7.24 (d, J=9.3 Hz, 2H, 3′,5′-H), 7.95 (br s, 1H, N10–H), 8.02 (d, J=9.1 Hz, 2H, 2′,6′-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.0 (8-CH_3), 14.5 ($COOCH_2CH_3$), 19.0 (7-CH_3), 28.3 (C(CH_3)$_3$), 54.2 (C(CH_3)$_3$), 54.6 (C-7), 62.0 ($COOCH_2CH_3$), 121.4 (C-2′,C-6′), 127.5 (C-4′), 128.0 (C-3′,C-5′), 140.3 (C-1′), 144.1 (C-2), 147.6 (C-5), 151.9 (C-8), 154.0 (CO); IR (neat) 3291, 1719, 1638, 1601 cm^{-1}; LC–MS (ESI, 1.65 eV) m/z 461/463 [100, (M+Na)$^+$], 439/441 [90, (M+H)$^+$]. Anal. Calcd for $C_{19}H_{27}ClN_6O_2S$ (438.97): C, 51.99; H, 6.20; N, 19.14. Found: C, 52.15; H, 5.99; N, 19.03.

*4.3.22. Reaction of compound **4g** with AcOH.* The compound **4g** (1.0 mmol) dissolved in dichloromethane (5 mL) and AcOH (1.1 mmol) were refluxed for 5 h. The reaction mixture was washed with water, dried with Na_2SO_4, concentrated in vacuum and purified with silica gel column chromatography using petroleum ether–AcOEt (3:1) as eluent to give the isolated product **6**.

*4.3.23. 1-[[(1-(tert-Butylimino)carbonyl)](phenyl)amino]-4-methyl-5-phenyl-2-thioxo-2,3-dihydro-1H-imidazole (**6**).* White solid; 0.339 g (89%), mp 86–88 °C (CH_2Cl_2–pet. ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (s, 9H, C(CH_3)$_3$), 2.16 (s, 3H, 4-CH_3), 4.80 (s, 1H, CONH), 7.09–7.22 (m, 5H), 7.26–7.31 (m, 2H), 7.32–7.40 (m, 3H), 12.12 (br s, 1H, 3-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.9 (4-CH_3), 29.2 (C(CH_3)$_3$), 51.7 (C(CH_3)$_3$), 121.0 (C-4), 125.1 (C-2′,C-6′), 126.6 (C-4′), 126.9 (C-5), 127.3 (C-1″), 128.4 (C-2″,C-6″), 128.90 (C-3″,C-5″), 128.92 (C-4″), 129.6 (C-3′,C-5′), 140.5 (C-1′), 153.2 (N–CO), 162.5 (C-2); IR (KBr) 3431, 3061, 1705 cm^{-1}; LC–MS (ESI, 1.65 eV) m/z 403 [45, (M+Na)$^+$], 381 [100, (M+H)$^+$]. Anal. Calcd for $C_{21}H_{24}N_4OS$ (380.51): C, 66.29; H, 6.36; N, 14.72. Found: C, 66.58; H, 6.45; N 14.99.

Supplementary data

^{1}H and ^{13}C NMR spectra of all compounds. Crystallographic data, bond lengths, bond angles and structure refinement for compound **11b** are included. This material is available free of charge via the Internet at http://pubs.acs.org. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.03.096. These data include MOL files and InChiKeys of the most important compounds described in this article.

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20. Complete crystallographic data for compound **11b** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication No. CCDC 887831. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336 033, e-mail: deposit@ccdc.cam.ac.uk.