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Synthesis of 1,4-benzothiazin-2-yl derivatives of 1,3-dicarbonyl compounds and benzothiazinone spiro derivatives by the reaction of 2-chloro-1,4-benzothiazin-3-ones with 'push–pull' enamines

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Abstract

The reaction of 2-chloro-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazines with 'push–pull' enamines was investigated. The reaction with the enamines occurs at the β-carbon atom in the presence of a small excess of triethylamine. As a result, a set of 3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl derivatives of 1,3-dicarbonyl compounds and benzothiazinone spiro derivatives was prepared. On acidic hydrolysis of ethyl 2-ethyl-3-(methylimino)-2-(3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)butanoate, a new rearrangement affording ethyl 11-ethyl-2,3-dimethyl-4-oxo-2,3,4,5-tetrahydro-1*H*-2,5-methano-6,1,3-benzothiadiazocine-11-carboxylate was discovered. A plausible mechanism and factors influencing the course of the reaction are discussed.

Keywords: Chloro derivatives; Enamines; Electrophilic substitution; Spiro heterocycles; Rearrangement

1. Introduction

2-Chloro-2*H*-1,4-benzothiazin-3-one derivatives **1** are known to be convenient intermediates in the synthesis of 2-functionalized 2*H*-1,4-benzothiazin-3-ones with biological activity.[1] The chlorine atom in the molecules of **1** is readily substitutable by various nucleophiles thus offering wide possibilities for modification of the 1,4-benzothiazin-3-one nucleus. Compounds **1** enter into a number of reactions with amines, alcohols, and some other nucleophilic reagents.[2] The Friedel–Crafts reaction with **1** has been extensively used to obtain 2-aryl-substituted 2*H*-1,4-benzothiazin-3-ones.[3]

We have previously demonstrated that chloro derivatives **1** can react as electrophiles with *C*-nucleophiles such as electron-rich heterocycles[4] and tertiary enamines derived from cyclic ketones.[5] This strategy provides a facile route to 3,4-dihydro-2*H*-1,4-benzothiazin-3-one derivatives bearing a heterocyclic or ketonic residue at position 2. To systematically study the reactivity of **1** towards *C*-nucleophiles, one needs to explore the reaction between **1a**,**b** and enamines containing conjugated electron-acceptor groups ('push–pull' enamines) **2** (Fig. 1).

The enamines **2** are known to be attacked by electrophiles at different nucleophilic centres depending on the nature of the electrophile. For instance, acylation, alkylation and reactions with isocyanates and isothiocyanates are directed to the

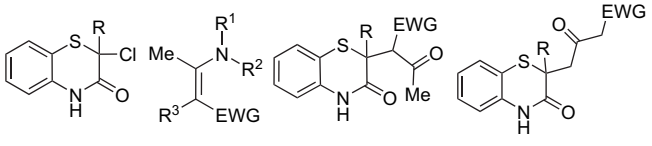

Figure 1.

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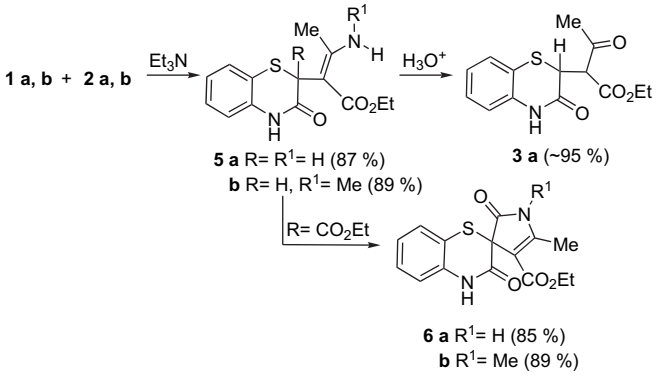
Table 1
The structures of starting 'push–pull' enamines **2a–f**

	R^1	R^2	R^3	EWG
2a	H	H	H	CO_2Et
2b	H	Me	H	CO_2Et
2c	$(CH_2)_2O(CH_2)_2$		H	CO_2Et
2d	$(CH_2)_2O(CH_2)_2$		H	COMe
2e	$(CH_2)_2O(CH_2)_2$		H	COPh
2f	H	Me	Et	CO_2Et

β-carbon atom,[6] whereas carbonyl compounds, iminium salts, and diazonium salts attack the methyl group of the enamine molecule.[7] Moreover, the primary amino group of **2** can also be involved. [8] Thus, one would expect that the reaction between **1** and **2** followed by hydrolysis of the initial products can finally yield both derivatives **3** (as a result of the electrophilic attack on the β-carbon atom) and **4** (arising from the involvement of the methyl group as a nucleophilic centre). The two possible products are both useful as intermediates in the synthesis of 2-hetaryl and 2-spiro-substituted 3,4-dihydro-2*H*-1,4-benzothiazin-3-ones. To establish the position of the electrophilic attack and to reveal the key features of the reaction in relation to the reagent and substrate constitution, we have studied the condensation of secondary and tertiary chloro derivatives **1a**,**b** with various types of 'push–pull' enamines **2a–f** (Table 1).

2. Results and discussion

Compounds **1** and **2** were reacted in boiling methylene chloride in the presence of a slight excess of triethylamine. The reaction mixture was washed with water (to remove triethylammonium hydrochloride) and dried, followed by evaporation of the solvent and analysis of the residue. As found, the reaction of **1a** with primary and secondary enamines (**2a**,**b**) under the conditions indicated furnishes the 3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl derivatives of 3-amino- and 3-methylaminocrotonic acids (**5a**,**b**) in high yields (87 and 89%, respectively) (Scheme 1). The signals of a single geometric isomer were detected in the ^{1}H NMR spectra of both unpurified products **5a** and **5b**. The amino group of **5a** gives rise to two proton resonances appearing as broadened singlets at 8.61 and 7.24 ppm. The strongly differing chemical



Scheme 1. Reactions of **1a**,**b** with primary and secondary enamines.

shifts suggest the configuration at which one of the protons forms an intramolecular hydrogen bond with the ethoxycarbonyl group so that its signal is significantly shifted downfield from that of the unchelated proton. In a similar manner, secondary enamine **5b** induces a rather downfield broadened singlet at 9.66 ppm corresponding to the chelated NH-proton of the methylamino group. Thus, enamines **5a**,**b** resulting from the reaction of **1a** with **2a**,**b** have the *E* configuration, as was also corroborated by the NOESY experiment.

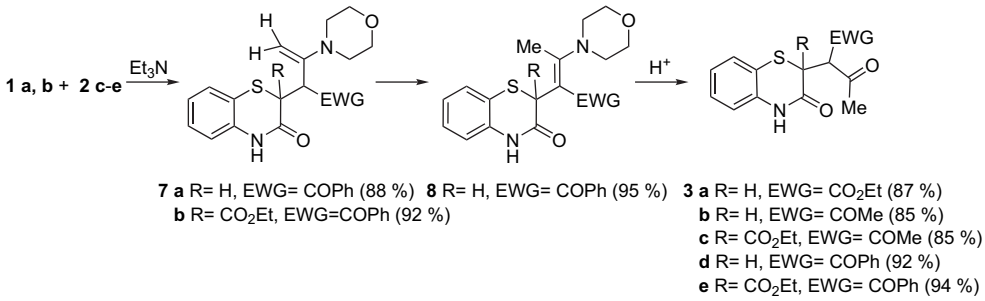
On boiling in 2 N HCl for a short time, compounds **5a**,**b** readily hydrolyzed to give the same product, ethyl 3-oxo-2-(3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)butyrate **3a**, which was isolated as a 3:2 mixture of two diastereomers.

Ethoxycarbonyl derivative **1b** reacts with **2a**,**b** similar to **1a**, with the difference that the reaction is accompanied by the intramolecular interaction between the ethoxycarbonyl group and the amino group thus leading to spiro compounds **6a**,**b**. It should be noted that the analogous spiro products were obtained by us formerly by the reaction of **1b** with 4-aminouracils.[4] Unlike compounds **5a**,**b**, their spiro counterparts **6a**,**b** proved to be hydrolytically stable even on boiling in 2 N HCl for a long time.

The reaction of **1a**,**b** with tertiary enamines also involves the β-carbon atom, with the constitution and stability of the reaction products governed by the starting compounds (Scheme 2). When **1a**,**b** were reacted with the derivatives of acetoacetic ester and acetylacetone (**2c**,**d**), the product mixtures were formed, which hydrolyzed to quantitatively yield the corresponding β-dicarbonyl compounds **3**. Judging by the ^{1}H NMR spectra of unpurified products of the reaction between **1a**,**b** and **2c**,**d** isomeric enamines **7** and **8** are formed and also diketones **3** resulting from their hydrolysis. Compound **7** exhibits two singlet peaks in the region of 4.1–4.2 ppm corresponding to the protons at the terminal double bond, whereas **8** is characterized by the signal at 5.15 ppm arising from the H-2 atom of the benzothiazine ring. The attempts of separating the reaction mixture by crystallization or chromatography on silica gel resulted merely in an increased amount of hydrolysis products **3**, so that we failed to isolate compounds **7** and **8** in the pure state. The reaction with **1b** was often accompanied by the elimination of the ethoxycarbonyl group from the C-2 atom of the benzothiazine ring. Thus, when reacted with **2c**, **1b** provided a complex mixture of inseparable products, which was hydrolyzed by 2 N HCl to give compound **3a**.

Benzoylacetone derivative **2e** reacts with **1a**,**b** to produce solely enamines **7a**,**b** containing a terminal double bond, with only one of two possible diastereomers formed in both cases; the products can be isolated in the pure state.

Enamine **7a** slowly isomerizes to **8** on standing in a DMSO solution. A half-reaction period at room temperature is about 72 h. Pure product **8** was obtained by recrystallizing compound **7a** twice from a mixture of DMF–isopropanol. The structures of **7a** and **8** were unambiguously confirmed by ^{1}H and ^{13}C NMR spectra and no reconversion **8**→**7a** was observed, which, taken together, suggests that **7a** and **8** are kinetically and thermodynamically controlled products, respectively. Unlike compound **7a**, its ethoxycarbonyl-substituted



Scheme 2. Reactions of **1a**,**b** with tertiary enamines.

analogue **7b** does not undergo isomerization to **8** even on long standing in a DMSO solution or after repeated recrystallization from DMF. Thus, it became possible to obtain a monocrystal of **7b** and to analyze it by X-ray diffraction, which provided good evidence for the terminal double bond in this molecule (Fig. 2).

Interestingly, compound **7b** isolated as a single diastereomer produces a 3:2 diastereomeric mixture of β-diketones **3d** on boiling in 10% HCl. Formation of the second diastereomer necessarily implies a configuration inversion at the C-2 atom of the enamine moiety, which would be impossible in the hydrolysis of **7b** containing a terminal double bond. One can thus assume that the isomerization **7b**→**8** in acidic medium precedes the hydrolysis of **8** finally affording two diastereomers **3d**.

There is scarce evidence in the literature on enamines derived from β-dicarbonyl compounds and lacking conjugation between the carbonyl group and the double bond.[9] As a rule, such compounds bear a *N*-acyl group stabilizing their molecules. In our case, the preferential formation of enamines **7** is likely to result from the destabilization of the competing enamine structure **8** by the bulky benzothiazinone residue. The molecular stability of 'push–pull' enamines **8** is more sensitive to the size of the substituent at the C-2 atom as compared to isomeric compounds **7**. Indeed, this substituent, if bulky enough, causes significant steric hindrance in the former structure because it is spatially close to the double bond, the most rigid molecular unit. In contrast, the latter isomer is less sterically strained even with a large-size group at the C-2 atom, as it is relatively distant from the double bond.

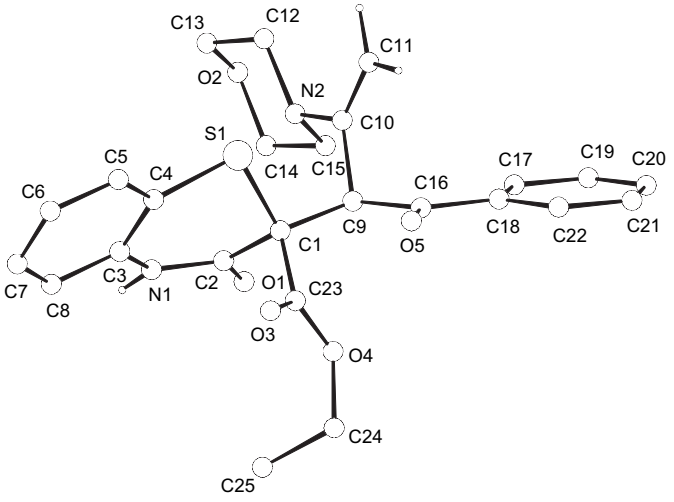
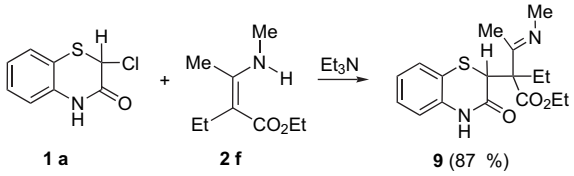


Figure 2. X-ray structure of **7b**.

We attempted to change the position of the electrophilic attack using, as a substrate, secondary enamine **2f**, which contains an ethyl group at the β-C atom. Taking into consideration the steric congestion of substituents at the C-2 atom of **1**,[4] one might expect that the reaction would involve either the nitrogen atom or the C-4 atom of compound **2f**, so as to avoid enhanced steric interactions. It has been found that **1a** and **2f** react to produce, in 87% yield, a 10:1 diastereomeric mixture of products; one of them was isolated in the pure state by recrystallization from isopropanol (Scheme 3).

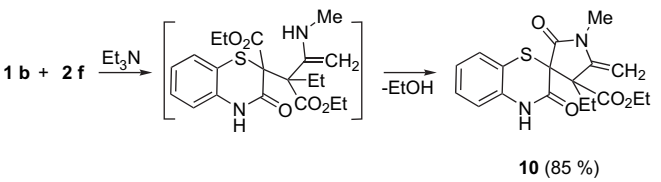


Scheme 3.

The ^{1}H and ^{13}C NMR as well as IR spectral data suggest that the compound obtained (**9**) is the α,α-disubstituted imine of acetoacetic ester resulting from the electrophilic attack on the β-C atom of enamine **2f**. The ^{1}H NMR spectrum displays a singlet at 1.67 ppm assigned to the methyl group of acetoacetic ester. At the same time, the ^{13}C NMR spectrum lacks the signal of the enaminic β-C atom in the region of 80–90 ppm, which was observed for all the compounds bearing the enamine moiety (**5**, **7** and **8**), irrespective of the double bond position.

The assumed direction of the reaction is also supported by the formation of spiro derivative **10** (Scheme 4), with its structure determined by X-ray diffraction analysis (Fig. 3).

Product **10** was formed as a result of the electrophilic attack on the β-C atom of enamine **2f** accompanied by the intramolecular cyclization, which leads to the only diastereomer of the spiro heterocycle with a terminal double bond.



Scheme 4.

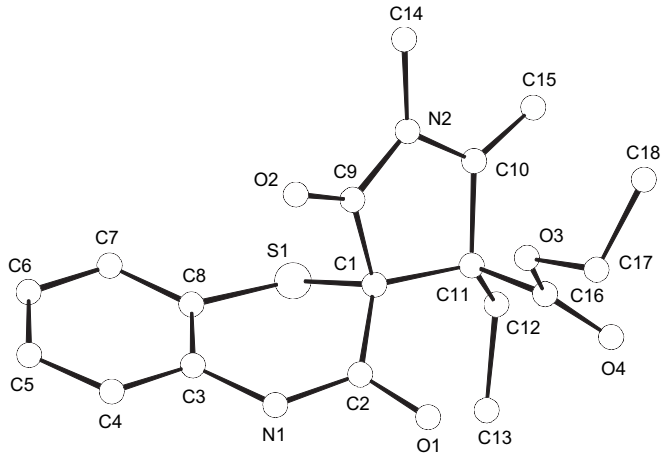
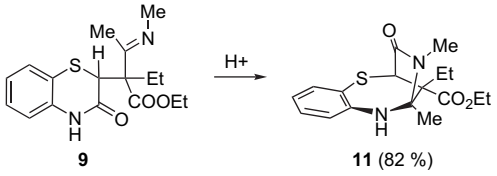


Figure 3. X-ray structure of **10**.

On attempted acid hydrolysis of **9**, we discovered a non-trivial ring-extension rearrangement affording ethyl 11-ethyl-2,3-dimethyl-4-oxo-2,3,4,5-tetrahydro-1*H*-2,5-methano-6,1,3-benzothiadiazocine-11-carboxylate **11** in 82% yield (Scheme 5); it was with the X-ray diffraction method that we succeeded in structural determination of the heterocycle obtained (Fig. 4).



Scheme 5.

Further research on the rearrangement has revealed that imine **9** is converted into **11** in the presence of catalytic acid (10% HCl or CH_3COOH) at room temperature, whereas the reaction does not proceed at all in alkaline or neutral medium even on heating for a long time. The conversion is completely diastereoselective: the diastereomeric mixture has much the same component ratio (10:1) for starting compound **9** and product **11**. Accordingly, a pure diastereomer of **9** gives rise to a single diastereomer of **11**.

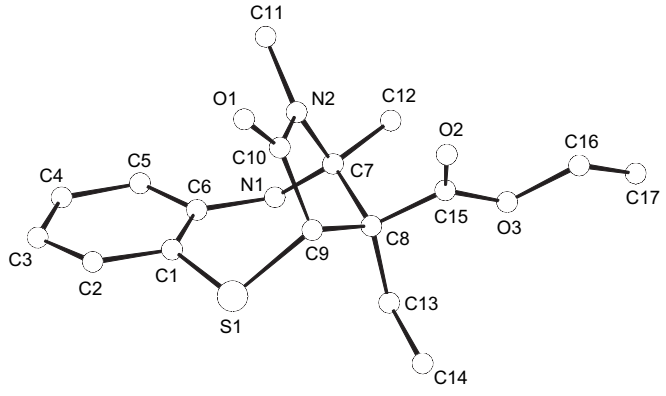
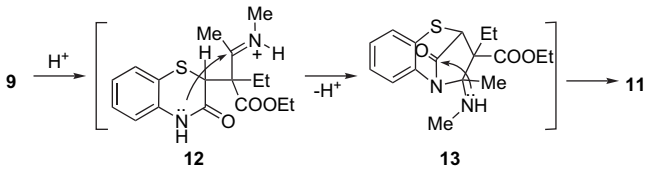


Figure 4. X-ray structure of **11**.

The rearrangement **9**→**11** is likely to proceed via a three-step pathway (Scheme 6). At the first stage, the nitrogen atom of the imino group is protonated to form iminium salt **12**. Then the intramolecular attack on the amide nitrogen atom (a variation of the Mannich reaction[10]) follows, which results in intermediate **13**. Bicyclic system **13** appearing as a so-called twisted amide[11] has a rigid geometry, which rules out the conjugation between the lone electron pair of the nitrogen atom and the carbonyl group. Such amides normally act as acylating agents towards nucleophiles,[12] so that the further conversion **13**→**11** occurs easily as a result of intramolecular reacylation.



Scheme 6.

3. Conclusions

In summary, we have studied the reaction of 2-chloro-2*H*-1,4-benzothiazin-3-ones with ‘push–pull’ enamines, which offers a convenient synthetic access to a variety of β-dicarbonyl compounds containing the 3-oxo-3,4-dihydro-2*H*-benzothiazin-2-yl moiety as well as to benzothiazinone spiro derivatives. Further research in this line will be aimed at the application of the newly synthesized β-dicarbonyl compounds in the preparation of 2-hetaryl-substituted 2*H*-1,4-benzothiazin-3-ones.

4. Experimental

4.1. General

CH_2Cl_2 for the reactions was freshly distilled and dried by standard method. All solvents for the crystallization were used without additional purification. The ^1H and ^{13}C NMR (500 and 125 MHz, respectively) were recorded on a Bruker Avance DRX 500 with DMSO-d_6 as the solvent and TMS as an internal standard. EIMS were recorded on a mass spectrometer MX-1321 using direct sample insertion into the ion source with an ionizing electron accelerating voltage of 70 V and an ionization chamber temperature of 150 °C. LC/MS spectra were recorded using chromatography/mass spectrometric system that consists of high-performance liquid chromatograph ‘Agilent 1100 Series’ equipped with diode-matrix and mass-selective detector ‘Aligent LC/MSD SL’. The parameters of chromatography–mass analysis: Column: Zorbax SB-C18, 1.8 μm×4.6 mm×15 mm. Solvents: A acetonitrile–water (95:5), 0.1% TFA, B water (0.1% of TFA). Eluent flow: 3 mL/s. The volume of injected sample: 1 μL. UV-detectors operate at 215, 254 and 265 nm. Ionization method: chemical ionization under atmospheric pressure (APCI). Ionization mode: simultaneous scanning of positive and negative ions in the mass range of *m*/*z* 80–1000. Microanalyses were

performed in the Microanalytical Laboratory of the Institute of Organic Chemistry, National Academy of Sciences of Ukraine. IR spectra were recorded on a Nexus-470 spectrometer for samples in KBr disks. Melting points (mp) were determined with electrothermal capillary melting point apparatus.

4.2. General procedure for the synthesis of **5–10**

To a stirred solution of an appropriate enamine (5 mmol) and Et_3N (0.72 mL, 5.1 mmol) in anhydrous CH_2Cl_2 (30 mL), **1a** (5 mmol) or **1b** (5 mmol) was added. The reaction mixture was boiled with a reflux condenser for 4 h, cooled and washed with water (2×30 mL). Organic phase was dried over Na_2SO_4 and evaporated in vacuo. The crude product was crystallized from an appropriate solvent.

4.2.1. Ethyl 3-amino-2-(3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-yl)but-2-enoate (**5a**)

Colourless solid, mp 188–189 °C, yield (solvent): 1.27 g, 87% (2-PrOH); [Found: C, 57.50; H, 5.50; N, 9.53. $C_{14}H_{16}N_2O_3S$ requires C, 57.52; H, 5.52; N, 9.58%]; δ_H 10.28 (1H, s, CO*NH*), 8.61 (1H, br s, NH_2), 7.24 (1H, br s, NH_2), 7.12 (1H, d, *J* 7.5 Hz, C*H*), 7.05 (1H, t, *J* 7.5 Hz, 1H, C*H*), 6.85–6.92 (2H, m, Ar), 4.86 (1H, br s, SC*H*), 3.96 (2H, q, *J* 7.0 Hz, OCH_2CH$_3$,), 2.04 (3H, s, *Me*), 1.11 (3H, t, *J* 7.0 Hz, OCH$_2$CH_3); δ_C 168.9, 168.4, 163.1, 137.7, 126.7, 126.4, 122.9, 121.7, 117.0, 86.5, 58.7, 41.1, 20.6, 14.8; MS [*m/z* (%)] 292 (M^+) (25.46), 246 (100), 218 (47.223), 91 (27.31), 44 (74.91); IR (cm^{-1}): 3420, 3310, 2950, 1680 (br), 1620 (br), 1595.

4.2.2. Ethyl 3-(methylamino)-2-(3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-yl)but-2-enoate (**5b**)

Colourless solid, mp 176–177 °C, yield (solvent): 1.36 g, 89% (2-PrOH); [Found: C, 58.82; H, 5.93; N, 9.17. $C_{15}H_{18}N_2O_3S$ requires C, 58.80; H, 5.92; N, 9.14]; δ_H 10.41 (1H, s, CO*NH*), 9.66 (1H, br s, N*H*Me), 7.19 (1H, d, *J* 7.8 Hz, CH), 7.12 (1H, t, *J* 7.5 Hz, C*H*), 6.90–6.96 (2H, m, Ar), 5.08 (1H, br s, SC*H*), 3.94–3.99 (2H, q, *J* 7.2 Hz, OCH_2CH$_3$), 2.92 (3H, d, *J* 4.8 Hz, NH*Me*), 2.08 (3H, s, *Me*), 1.09 (3H, t, *J* 7.2 Hz, OCH$_2$CH_3); δ_C 168.8, 168.2, 165.3, 137.2, 126.3, 126.2, 122.6, 121.4, 116.6, 79.2, 58.5, 40.6, 29.7, 18.5, 14.4; MS [*m/z* (%)]: 306 (M^+) (29.05), 260 (49.76), 108 (62.04), 82 (56.57), 56 (100.00); IR (cm^{-1}): 3340 (w), 1680, 1640, 1595.

4.2.3. Ethyl 5′-methyl-2′,3-dioxo-1′,2′,3,4-tetrahydrospiro-[1,4-benzothiazine-2,3′-pyrrole]-4′-carboxylate (**6a**)

Colourless solid, mp 242–243 °C, yield (solvent): 1.35 g, 85% (EtOH); [Found: C, 56.57; H, 4.41; N, 8.77. $C_{15}H_{14}N_2O_4S$ requires C, 56.59; H, 4.43; N, 8.80%]; δ_H 10.81 (1H, s, CO*NH*), 10.68 (1H, br s, N*H*), 7.09–7.15 (2H, m, Ar), 6.92–6.96 (2H, m, Ar), 4.06 (2H, q, *J* 7.0 Hz, OCH_2CH$_3$), 2.35 (3H, s, *Me*), 1.16 (3H, t, *J* 7.0 Hz, OCH$_2$CH_3); δ_C 174.9, 162.9, 162.4, 157.7, 137.4, 127.3, 127.2, 123.6, 116.9, 116.3, 105.1, 59.8, 53.4, 14.6, 14.1; MS [*m/z* (%)]: 318 (M^+) (100.00), 272 (83.78), 244 (52.62), 155 (50.49), 42 (60.50); IR (cm^{-1}): 3300, 3070, 3000, 1720, 1690 (br), 1625, 1595.

4.2.4. Ethyl 1′,5′-dimethyl-2′,3-dioxo-1′,2′,3,4-tetrahydrospiro[1,4-benzothiazine-2,3′-pyrrole]-4′-carboxylate (**6b**)

Colourless solid, mp 191–192 °C, yield (solvent): 1.48 g, 89% (EtOH); [Found: C, 57.83; H, 4.87; N, 8.45. $C_{16}H_{16}N_2O_4S$ requires C, 57.82; H, 4.85; N, 8.43%]; δ_H 10.88 (1H, s, CO*NH*), 7.10–7.15 (2H, m, Ar), 6.92–6.98 (2H,m, Ar), 4.08 (2H, q, *J* 7.0 Hz, OCH_2CH$_3$), 3.02 (3H, s, N*Me*), 2.52 (3H, s, *Me*), 1.16 (3H, t, *J* 7.0 Hz, OCH$_2$CH_3); δ_C 173.3, 162.4, 161.9, 159.0, 136.9, 126.9, 126.8, 123.2, 116.5, 115.7, 104.2, 59.5, 52.0, 26.5, 14.1, 12.6; MS [*m/z* (%)]: 332 (M^+) (41.64), 286 (64.76), 244 (22.21), 169 (16.00), 81 (20.25), 56 (100.00); IR (cm^{-1}): 3000, 1720, 1690 (br), 1625, 1595.

4.2.5. 2-(1-Benzoyl-2-morpholin-4-ylprop-2-en-1-yl)-2H-1,4-benzothiazin-3(4H)-one (**7a**)

Yellow solid, mp 220–221 °C, yield (solvent): 1.73 g, 88% (2-PrOH); [Found: C, 67.00; H, 5.64; N, 7.13. $C_{22}H_{22}N_2O_3S$ requires C, 66.98; H, 5.62; N, 7.10%]; δ_H 10.66 (1H, s, CO*NH*), 8.04 (2H, d, *J* 7.5 Hz, Ar), 7.64 (1H, t, *J* 7.4 Hz, C*H*), 7.53 (2H, t, *J* 7.2 Hz, Ar), 7.37 (1H, d, *J* 7.8 Hz, C*H*), 7.22 (1H, t, *J* 7.5 Hz, C*H*), 6.94–7.04 (2H, m, Ar), 4.76 (1H, d, *J* 10.2 Hz, C*H*), 4.28 (1H, d, *J* 10.2 Hz, SC*H*), 4.17 (1H, s, C=CH_2), 4.19 (1H, s, C=CH_2), 3.50–3.60 (4H, m, O(CH_2)$_2$), 2.80–2.90 (4H, m, N(CH_2)$_2$); δ_C 196.5, 166.5, 150.3, 137.8, 137.4, 133.5, 129.1, 129.0, 128.4, 128.0, 127.7, 123.4, 121.1, 117.7, 94.6, 66.6, 49.2, 44.0, 40.1; MS [*m/z* (%)]: 394 (M^+) (3), 307 (86.78), 289 (100), 105 (57.04), 77 (46.02); IR (cm^{-1}): 3065, 2950 (br), 1720, 1680 (br), 1595.

4.2.6. Ethyl 2-(1-benzoyl-2-morpholin-4-ylprop-2-en-1-yl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazine-2-carboxylate (**7b**)

Colourless solid, mp 167–168 °C, yield (solvent): 2.14 g, 92% (MeOH); [Found: C, 64.38; H, 5.60; N, 5.97. $C_{25}H_{26}N_2O_5S$ requires C, 64.36; H, 5.62; N, 6.00%]; δ_H 10.82 (1H, s, CO*NH*), 7.87 (2H, d, *J* 7.5 Hz, Ar), 7.59 (1H, t, *J* 7.1 Hz, C*H*), 7.49 (2H, t, *J* 7.2 Hz, Ar), 7.16 (1H, d, *J* 7.5 Hz, C*H*), 7.06 (1H, t, *J* 7.4 Hz, C*H*), 6.88–6.96 (2H, m, Ar), 5.44 (1H, s, C*H*), 4.17 (1H, s, C=CH_2), 4.08 (1H, s, C=CH_2), 3.93–4.05 (2H, m, OCH_2CH$_3$), 3.60 (4H, br s, O(CH_2)$_2$), 2.97–3.08 (2H, m, N(CH_2)$_2$), 2.34–2.42 (2H, m, N(CH_2)$_2$), 0.97 (3H, t, *J* 7.1 Hz, OCH$_2$CH_3); δ_C 168.1, 163.8, 148.2, 136.3, 135.2, 133.0, 128.7, 128.2, 126.2, 126.1, 123.1, 117.9, 116.2, 99.9, 65.7, 61.8, 57.9, 51.4, 49.7, 13.4; MS [*m/z* (%)]: 466 (M^+) (4.05), 379 (28.11), 315 (51.67), 105 (100), 77 (47.80); IR (cm^{-1}): 3070, 2950, 1740, 1680, 1620, 1595.

4.2.7. 2-(1-Benzoyl-2-morpholin-4-ylprop-1-en-1-yl)-2H-1,4-benzothiazin-3(4H)-one (**8**)

Yellow solid, mp 217–218 °C, yield (solvent): 1.64 g, 95% (2-PrOH–DMF 2:1); [Found: C, 66.97; H, 5.61; N, 7.09.

$C_{22}H_{22}N_2O_3S$ requires C, 66.98; H, 5.62; N, 7.10%]; δ_H 10.46 (1H, s, CO*NH*), 7.40–7.58 (5H, m, Ar), 7.21 (1H, d, *J* 7.8 Hz, C*H*), 7.14 (1H, t, *J* 6.9 Hz, Ar), 6.90–6.99 (2H, m, Ar), 5.17 (1H, s, SC*H*), 3.23 (4H, br s, $O(CH_2)_2$), 2.81 (4H, br s, $N(CH_2)_2$), 2.22 (3H, s, *Me*); δ_C 193.2, 166.9, 146.8, 141.0, 137.4, 130.4, 128.5, 128.0, 126.7, 126.7, 126.6, 122.7, 121.3, 116.9, 105.3, 65.7, 51.2, 42.9, 18.7; MS [*m/z* (%)]: 394 (M^+) (100), 307 (86.78), 289 (56.46), 105 (54.56), 77 (46.02); IR (cm^{-1}): 3000, 1710, 1650, 1595.

*4.2.8. Ethyl 2-ethyl-3-(methylimino)-2-(3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-yl)butanoate (**9**)*

Colourless solid, mp 149–150 °C, yield (solvent): 1.45 g, 87% (2-PrOH); [Found: C, 61.03; H, 6.65; N, 8.35. $C_{17}H_{22}N_2O_3S$ requires C, 61.05; H, 6.63; N, 8.38%]; δ_H 10.45 (1H, s, CO*NH*), 7.22 (1H, d, *J* 6.9 Hz, C*H*), 7.08 (1H t, *J* 7.7 Hz, C*H*), 6.86–6.93 (2H, m, Ar), 4.14 (1H, s, SC*H*), 4.05–4.14 (2H, m, OCH_2CH_3), 2.71 (3H, s, N*Me*), 2.06–2.12 (1H, m, CH_2CH_3), 1.82–1.88 (1H, m, CH_2CH_3), 1.63 (3H, s, *Me*), 1.20 (3H, t, *J* 7.4 Hz, OCH_2CH_3), 0.82 (3H, t, *J* 7.4 Hz, CH_2CH_3); δ_C 171.4, 167.3, 163.8, 136.9, 126.6, 122.6, 118.7, 116.4, 61.1, 60.5, 44.6, 38.0, 28.0, 17.6, 13.8, 9.2; MS [*m/z* (%)]: 334 (M^+) (14.92), 261 (61.33), 136 (12.58), 126 (12.65), 56 (100.00); IR (cm^{-1}): 3010, 1725, 1670 (br), 1585.

*4.2.9. Ethyl 4′-ethyl-1′-methyl-5′-methylene-2′,3-dioxo-3,4-dihydrospiro[1,4-benzothiazine-2,3′-pyrrolidine]-4′-carboxylate (**10**)*

Colourless solid, mp 199–200 °C, yield (solvent): 1.53 g, 85% (EtOH); [Found: C, 60.00; H, 5.60; N, 7.80. $C_{18}H_{20}N_2O_4S$ requires C, 59.98; H, 5.59; N, 7.77%]; δ_H 10.95 (1H, s, CO*NH*), 7.24 (1H, d, *J* 7.8 Hz, C*H*), 7.16 (1H, t, *J* 8.0 Hz, C*H*), 6.93–6.98 (2H, m, Ar), 4.53 (1H, d, *J* 2.6 Hz, C=CH_2,), 4.42 (1H, d, *J* 2.6 Hz, C=CH_2,), 3.88–3.96 (2H, m, OCH_2CH_3), 2.09–2.20 (1H, m, CH_2CH_3), 1.67–1.79 (1H, m, CH_2CH_3), 0.96–1.09 (6H, m, OCH_2CH_3 and CH_2CH_3); δ_C 169.6, 168.2, 162.5, 147.3, 137.3, 127.9, 127.6, 123.6, 116.8, 116.3, 88.8, 61.4, 57.5, 56.6, 27.6, 26.2, 13.9, 9.7; MS [*m/z* (%)]: 360 (M^+) (82.58), 287 (46.63), 286 (100.00), 164 (82.82), 56 (54.11); IR: (cm^{-1}): 3060, 2950 (br), 1720, 1660 (br), 1595.

*4.3. General procedure for the synthesis of **3a–c***

To a stirred solution of an appropriate enamine (5 mmol) and Et_3N (0.72 mL, 5.1 mmol) in anhydrous CH_2Cl_2 (30 mL), **1a** (5 mmol) or **1b** (5 mmol) was added. The reaction mixture was boiled with a reflux condenser for 4 h. CH_2Cl_2 was evaporated in vacuo to dryness. The residue was triturated with acidified water (50 mL) and filtered. The crude product was crystallized from an appropriate solvent.

*4.3.1. Ethyl 3-oxo-2-(3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-yl)butanoate (**3a**)*

Compound **3a** was obtained as a mixture of two diastereomers (3:2). Colourless solid, mp 159–160 °C, yield (solvent): 1.27 g, 87% (2-PrOH); [Found: C, 57.34; H, 5.16; N, 4.80. $C_{14}H_{15}NO_4S$ requires C, 57.32; H, 5.15; N, 4.77%]. The signals of major diastereomer: δ_H 10.73 (1H, s, CO*NH*), 7.27 (1H, t, *J* 6.5 Hz, Ar), 7.19 (1H, t, *J* 7.8 Hz, Ar), 7.03–6.98 (2H, m, Ar), 4.18–4.04 (3H, m, OCH_2CH_3 and SC*H*), 3.92 (1H, d, *J* 10 Hz, C*H*), 2.29 (3H, s, *Me*), 1.24 (3H, t, *J* 7.0 Hz, OCH_2CH_3); δ_C 200.0, 166.8, 165.1, 137.2, 128.2, 128.0, 123.8, 118.9, 117.9, 62.1, 58.3, 41.1, 29.7, 14.3; the signals of minor diastereomer: δ_H 10.71 (1H, s, CO*NH*), 7.27 (1H, t, *J* 6.5 Hz, Ar), 7.19 (1H, t, *J* 7.8 Hz, Ar), 7.00–6.95 (2H, m, Ar), 4.18–4.04 (3H, m, OCH_2CH_3 and SC*H*), 3.92 (1H, d, *J* 10 Hz, C*H*), 2.29 (3H, s, *Me*), 1.24 (3H, t, *J* 7.0 Hz, OCH_2CH_3); δ_C 200.6, 167.0, 165.0, 137.2, 128.2, 128.1, 123.7, 118.6, 117.8, 62.0, 58.3, 41.1, 30.0, 14.2; MS [*m/z* (%)]: 293 (M^+) (10.16), 250 (18.02), 204 (100.00), 99 (8.71), 43 (27.34); IR (cm^{-1}): 2950, 1730, 1710, 1670, 1595, 1670.

*4.3.2. 3-(3-Oxo-3,4-dihydro-2H-1,4-benzothiazin-2-yl)-pentane-2,4-dione (**3b**)*

Colourless solid, mp 123–124 °C, yield (solvent): 1.12 g, 85% (2-PrOH); [Found: C, 59.28; H, 4.97; N, 5.35. $C_{13}H_{13}NO_3S$ requires C, 59.30; H, 4.98; N, 5.32%]; δ_H 10.75 (1H, s, CO*NH*), 7.28 (1H, d, *J* 7.8 Hz, C*H*), 7.20 (1H, t, *J* 8.0 Hz, C*H*), 6.96–7.04 (2H, m, Ar), 4.21 (1H, d, *J* 10.5 Hz, C*H*), 4.18 (1H, d, *J* 10.5 Hz, SC*H*), 2.26 (3H, s, CO*Me*), 2.23 (3H, s, CO*Me*); δ_C 204.9, 201.5, 166.5, 137.4, 128.1, 127.7, 123.5, 119.1, 117.6, 65.8, 42.1, 36.7, 30.4; MS [*m/z* (%)]: 263 (M^+) (11.36), 221 (18.69), 220 (100.00), 178 (39.61), 43 (86.86); IR (cm^{-1}): 2950, 1710, 1670 (br), 1595.

*4.3.3. Ethyl 2-(1-acetyl-2-oxopropyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazine-2-carboxylate (**3c**)*

Colourless solid, mp 154–5 °C, yield (solvent): 1.20 g, 85% (2-PrOH); [Found: C, 57.28; H, 5.10; N, 4.15. $C_{16}H_{17}NO_5S$ requires C, 57.30; H, 5.11; N, 4.18%]; δ_H 10.98 (1H, br s, CO*NH*), 7.32 (1H, d, *J* 7.5 Hz, C*H*), 7.23 (1H, t, *J* 7.5 Hz, C*H*), 7.03–6.97 (2H, m, Ar), 4.56 (1H, s, C*H*), 3.90–4.05 (2H, m, OCH_2CH_3), 2.32 (3H, s, CO*Me*), 2.20 (3H, s, CO*Me*), 0.91 (3H, t, *J* 7.2 Hz, OCH_2CH_3); δ_C 203.3, 192.0, 171.3, 164.8, 136.9, 128.0, 127.3, 123.5, 117.5, 116.8, 58.8, 54.4, 49.6, 31.5, 23.6, 14.9; MS [*m/z* (%)]: 335 (M^+) (14.45), 262 (100.00), 163 (17.00), 105 (80), 77 (38.60); IR (cm^{-1}): 2950, 1710, 1690, 1640, 1595.

*4.4. General procedure for the synthesis of **3d**, **e**, **11***

To a stirred solution of HCl (2 N, 30 mL) **7a**,**b** (0.5 g) or **8** (0.5 g), or **9** (0.5 g) was added and heated at 60 °C for 30 min. The precipitate was filtered and recrystallized from EtOH.

*4.4.1. 2-(3-Oxo-3,4-dihydro-2H-1,4-benzothiazin-2-yl)-1-phenylbutane-1,3-dione (**3d**)*

Compound **3d** was obtained as a mixture of two diastereomers (3:2). Colourless solid, mp 207–208 °C, yield (solvent): 0.38 g, 92% (EtOH); [Found: C, 66.46; H, 4.67; N, 4.33. $C_{18}H_{15}NO_3S$ requires C, 66.44; H, 4.65; N, 4.30%]. The

signals of major diastereomer: δ_H 10.68 (1H, s, CO*NH*), 8.03 (2H, t, *J* 7.5 Hz, Ar), 7.70–7.66 (1H, m, Ar), 7.56 (2H, t, *J* 7.5 Hz, Ar), 7.36 (1H, d, *J* 7.5 Hz, Ar), 7.21 (1H, t, *J* 7.5 Hz, Ar), 7.03–6.95 (2H, m, Ar), 5.24 (1H, d, *J* 10.0 Hz, SC*H*), 4.40 (1H, d, *J* 10.0 Hz, C*H*), 2.21 (3H, s, *Me*); δ_C 201.2, 193.7, 165.1, 137.4, 136.4, 134.3, 129.4, 129.1, 128.2, 128.1, 123.7, 119.3, 117.9, 60.6, 42.0, 29.8; the signals of minor diastereomer: δ_H 10.79 (1H, s, CO*NH*), 8.03 (2H, t, *J* 7.5 Hz, Ar), 7.70–7.66 (1H, m, Ar), 7.56 (2H, t, *J* 7.5 Hz, Ar), 7.23–7.18 (2H, m, Ar), 7.00–6.92 (2H, m, Ar), 5.31 (1H, d, *J* 10 Hz, SC*H*), 4.37 (1H, d, *J* 10 Hz, C*H*), 2.23 (3H, s, *Me*); δ_C 200.3, 193.1, 165.6, 137.3, 136.6, 134.8, 129.6, 129.3, 128.0, 128.0, 123.7, 119.1, 117.9, 59.9, 42.2, 29.8; MS [*m*/*z* (%)]: 325 (M^+) (10.79), 282 (74.69), 220 (100.00), 105 (85.41), 77 (42.59); IR (cm^{-1}): 2950, 1720, 1670 (br), 1595.

4.4.2. Ethyl 2-(1-benzoyl-2-oxopropyl)-3-oxo-3,4-dihydro-2H-1,4-benzothiazine-2-carboxylate (*3e*)

Compound **3e** was obtained as a mixture of two diastereomers (3:2). Colourless solid, mp 157–158 °C, yield (solvent): 0.40 g, 94% (EtOH); [Found: C, 63.47; H, 4.83; N, 3.55. $C_{21}H_{19}NO_5S$ requires C, 63.46; H, 4.82; N, 3.52%]. The signals of major diastereomer: δ_H 10.99 (1H, s, CO*NH*), 8.05 (2H, d, *J* 7.5 Hz, Ar), 7.70 (1H, t, *J* 7.0 Hz, Ar), 7.58 (2H, t, *J* 7.8 Hz, Ar), 7.33 (1H, d, *J* 8.0 Hz, Ar), 7.22 (1H, t, *J* 7.8 Hz, Ar), 7.06–6.98 (2H, m, Ar), 5.55 (1H, s, C*H*), 3.95–3.75 (2H, m, OCH_2CH$_3$), 2.19 (3H, s, *Me*), 0.75 (3H, t, *J* 7.0 Hz, OCH$_2$CH_3); δ_C 194.2, 167.3, 163.0, 136.3, 136.1, 133.6, 128.8, 128.4, 127.5, 127.2, 123.1, 116.5, 116.4, 61.8, 59.9, 54.9, 30.6, 13.0; the signals of minor diastereomer: δ_H 11.08 (1H, s, CO*NH*), 7.81 (2H, d, *J* 7.5 Hz, Ar), 7.65 (1H, t, *J* 7.0 Hz, Ar), 7.49 (2H, t, *J* 7.8 Hz, Ar), 7.22 (1H, t, *J* 7.8 Hz, Ar), 7.13 (1H, d, *J* 8.0 Hz, Ar), 7.02–6.93 (2H, m, Ar), 5.44 (1H, s, C*H*), 4.12–3.95 (2H, m, OCH_2CH$_3$), 2.23 (3H, s, *Me*), 1.00 (3H, t, *J* 7.0 Hz, OCH$_2$CH_3); δ_C 193.6, 166.5, 162.7, 136.7, 136.1, 133.6, 128.6, 128.2, 127.5 127.3, 123.1, 117.2, 116.8, 62.1, 59.3, 55.6, 30.6, 13.2; MS [*m*/*z* (%)]: 397 (M^+) (14.95), 351 (8.43), 282 (17.01), 105 (100.00), 77 (38.63); IR (cm^{-1}): 2950, 1710, 1690, 1640, 1595.

4.4.3. Ethyl 11-ethyl-2,3-dimethyl-4-oxo-2,3,4,5-tetrahydro-1H-2,5-methano-6,1,3-benzothiadiazocine-11-carboxylate (*11*)

Colourless solid, mp 158–159 °C, yield (solvent): 1.19 g, 82% (MeOH); [Found: C, 61.03; H, 6.61; N, 6.37. $C_{17}H_{22}N_2O_3S$ requires C, 61.05; H, 6.63; N 6.38%]; δ_H 7.03–7.11 (3H, m, Ar), 6.70–6.75 (1H, m, C*H*), 6.02 (1H, s, N*H*), 4.08–4.22 (2H, m, OCH_2CH$_3$), 3.73 (1H, s, SC*H*), 2.42–2.55 (1H, m, CH_2CH$_3$), 2.27 (3H, s, N*Me*), 1.85–1.98 (1H, m, CH_2CH$_3$), 1.47 (3H, s, *Me*), 1.21 (3H, t, *J* 7.2 Hz, OCH$_2$CH_3), 0.82 (3H, t, *J* 7.2 Hz, CH$_2$CH_3); δ_C 170.5, 169.6, 145.6, 130.5, 127.8, 121.4, 121.4, 120.7, 78.2, 62.1, 59.7, 46.6, 28.6, 23.6, 21.0, 14.1, 9.6; MS [*m*/*z* (%)]: 334 (M^+) (54.48), 261 (100.00), 138 (35.26), 126 (21.45), 56 (82.76); IR (cm^{-1}): 3320, 2950, 1720, 1690, 1595.

4.5. X-ray crystal structure determination of compounds *7b*, *10* and *11*

The crystallographic measurements for compounds **7b** and **10** were performed at 18 °C, for compound **11** at −70 °C. All data were corrected for Lorentz and polarization effects; empirical absorption correction based on azimuthal scan data[13] was applied for **7b** and **10**, absorption correction using the SADABS procedure[14] was applied for **11**. All structures were solved by direct methods. All atoms were refined on F_{obs} by full-matrix least-squares technique in the anisotropic approximation. Chebushev weighting scheme[15] was used. All structural calculations were carried out using CRYSTALS program package.[16] The hydrogen atoms for the all structures were located in the difference Fourier maps and refined isotropically.

The full crystallographic data sets (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 646354 for **7b** and CCDC 603949 for **10** and CCDC 646353 for **11**. Copies of data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.02.049.

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