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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

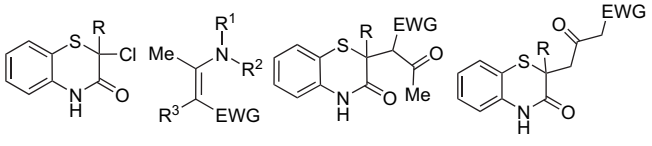


Figure 1.

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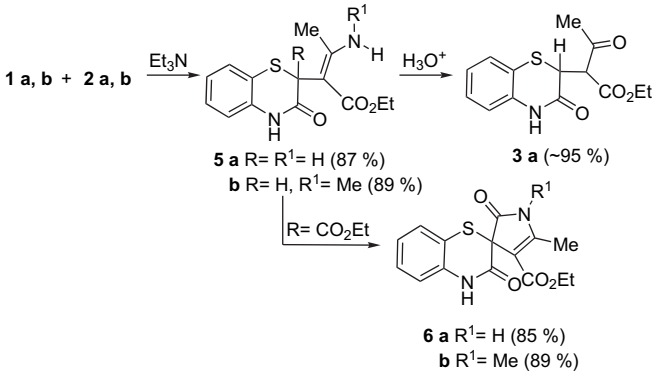
Table 1
The structures of starting 'push–pull' enamines **2a–f**

| | $R^1$ | $R^2$ | $R^3$ | 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