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# New 2-functionalized 2*H*-3,4-dihydro-1,4-benzothiazin-3-ones and their application in the synthesis of spiro heterocycles

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**Abstract**—The reaction of 2-chloro-3,4-dihydro-2*H*-1,4-benzothiazin-3-ones **1** with enamines is an efficient synthetic method to produce 2-substituted derivatives. The resulting bifunctional compounds such as **6a**,**b**, **7c**,**d** and **8b** react with hydrazines to furnish the spiro derivatives of *N*-aminopyrrole or 3-pyridazinone depending on the direction of the primary nucleophilic attack and the nature of the nucleophile. Under the reaction conditions, spiro pyridazinones **13** are converted into the 3-pyridazinone-4-carboxylic acid derivatives **9** via the 1,4-thiazine ring opening.


## 1. Introduction

Many 2*H*-1,4-benzothiazin-3-one derivatives exhibit a broad spectrum of biological activities, so that the purposeful modification of their structure attracts great interest in pharmacology and other related fields.[1] Generally methods for preparing these compounds rely on condensation of 2-aminothiophenols with α,β-unsaturated acids or α-haloacetic acids (or esters).[2] The limited availability of such acids is the major disadvantage of the method. As an alternative method, one can use 2-chloro-2*H*-1,4-benzothiazin-3-ones (**1**), easily accessible starting materials, in the synthesis of various 2-substituted 1,4-benzothiazin-3-ones. Like any α-halogeno sulfides, compounds **1** are distinguished by an extremely easy nucleophilic substitution of the chlorine atom. For instance, they react with alcohols, primary and secondary amines and triethyl phosphite.[3] An efficient synthetic route to 2-aryl-2*H*-1,4-benzothiazin-3-ones (useful as $Ca^{2+}$ antagonists, blood platelet aggregation inhibitors and vascular agents) is offered by the Friedel–Crafts reaction of compounds **1** with aromatics.[4] Recently we have prepared 2-heteroaryl-2*H*-1,4-benzothiazin-3-ones by the reaction of **1** with electron-rich heterocycles.[5] The research work presented here is a part of the program aimed at the development of methods for synthesis of 2-heteroaryl and 2-spiro derivatives of 1,4-benzothiazin-3-one.

The carbethoxy group at the c-2 position in compound **1b** greatly extends its synthetic potential, especially in the molecular design of the various spiro derivatives of 2*H*-1,4-benzothiazin-3-one. It is noteworthy that although spiro heterocycles have been a subject of a large number of publications,[6] only few syntheses of 2*H*-1,4-benzothiazin-3-one spiro derivatives have been reported hitherto.[5,7] For instance, one of the present authors has previously described the synthesis of 1,4-benzothiazin-2-spiro-(2′-aryliminothiazolidin-5′-3-ones) (**2**) by the amine-induced cyclization of isothiocyanates readily obtained from compound **1b**.[7b] As we found in our preceding study on the synthesis of 2-heteroaryl-2*H*-1,4-benzothiazin-3-ones, the reaction between **1b** and 6-aminouracils involves the C-5 atom of the pyrimidine ring and likewise results in the intramolecular spirocyclization to provide spiro[1,4-benzothiazine-2,7′-pyrrolo[3,2-*d*]pyrimidine] (**3**) derivatives (Fig. 1).[5]

A remarkably high reactivity of **1a** and **b** towards electron-rich heterocycles suggests that these compounds can be reacted in a similar manner with other C-nucleophiles to form a new C–C bond. The present work addresses the reaction of compounds **1a** and **b** with enamines **4a**,**b** and **5** as

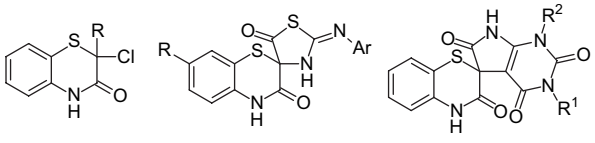


**Figure 1**.

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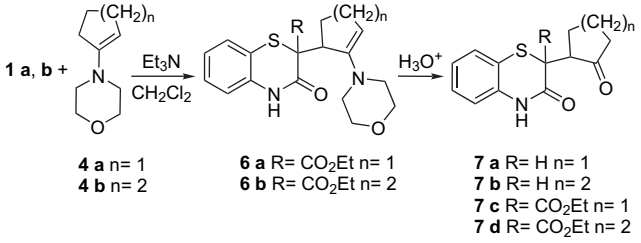
a synthetic entry into 2-functionalized 2*H*-1,4-benzothiazin-3-ones and also describes their further use as starting compounds in the synthesis of 1,4-benzothiazin-3-one spiro derivatives.

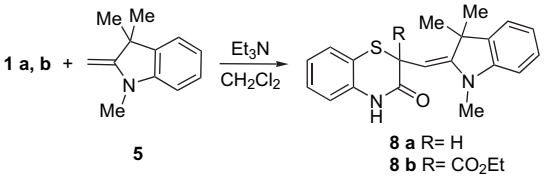
## 2. Results and discussion

Compounds **1a**,**b** and **4a**,**b** were reacted in methylene chloride at room temperature in the presence of a slight excess of triethylamine (see Scheme 1). Under these conditions, no notable distinctions are observed in the reactivity of the secondary and tertiary chloro derivatives **1a** and **b**, in contrast to the case when they are reacted with electron-rich heterocycles. If morpholinocycloalkenes **4a** and **b** are replaced with their more reactive 1-pyrrolidinyl-substituted counterparts, pronounced resinification of the reaction mixture occurs and the yields of the target products drop. If the reaction is conducted with **1a**, treatment of the resulting reaction mixture with water immediately affords the hydrolysis products, ketones **7a** and **b**, in high yields, since the initially formed enamines are too labile to be isolated. Intermediate enamines **6a** and **b** containing a carbethoxy group proved to be more stable towards hydrolysis and were both isolated as a mixture of two diastereomers. On heating in 10% hydrochloric acid, these compounds are readily hydrolyzed to furnish γ-ketoesters **7c** and **d** in nearly quantitative yields.




**Scheme 1**.

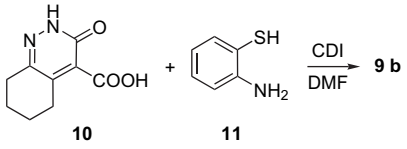
Heterocyclic enamine **5** likewise smoothly reacts with compounds **1a** and **b** under the same conditions to produce monosubstituted indolines **8a** and **b** (see Scheme 2). The readiness and equally good yields of the reaction with **4a** and **b** (70–90%) and **5** (70–75%) are attributable, on the one hand, to the high electrophilic reactivity of reagents **1a** and **b** and, on the other hand, to their sterically hindered reaction centre precluding polysubstitution of the enamines.[8]



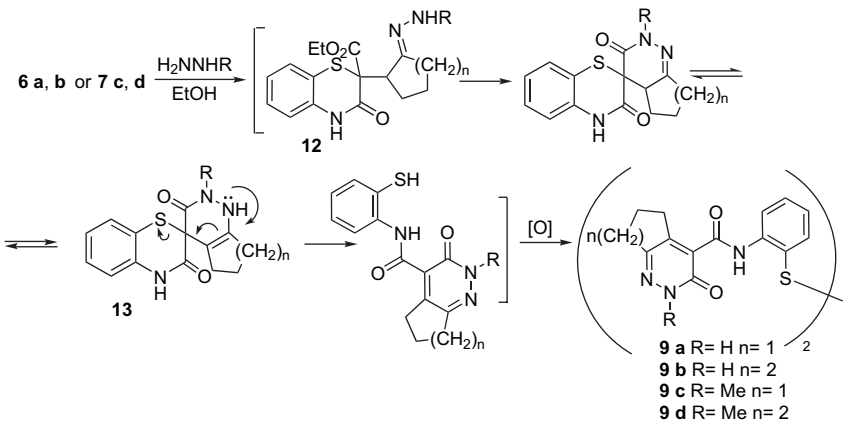

**Scheme 2**.

The prepared γ-ketoesters **7c** and **d** as well as enamines **6a**,**b** and **8b** are 1,4-biselectrophiles and show promise in the synthesis of 2*H*-1,4-benzothiazin-3-one spiro derivatives. Here we study the reaction of these compounds with the simplest 1,2-bisnucleophiles, hydrazine and methylhydrazine, in an effort to synthesize the 1,4-benzothiazin-3-one-2-spiro-4[1]-3[1]-oxopyridazine derivatives **13**. On boiling **6a** and **b** or **7c** and **d** in ethanol with a slight excess of hydrazine hydrate or methylhydrazine, we isolated, in moderate yields, high-melting yellow solids that was recrystallized from DMF or DMSO (see Scheme 3). The $^{1}H$, $^{13}C$ NMR, IR and mass spectroscopic data led us to infer that the compounds formed were disulfides **9a–d**, 3-pyridazinone-4-carboxylic acid derivatives, rather than the desired spiro systems **13**.

For unequivocal structural determination of compounds **9a–d**, one of them was obtained by alternate synthesis. Following the known procedure,[9] we started from diethyl mesoxalate and cyclohexanone, and thus came, in three stages, to 3-oxo-2,3,5,6,7,8-hexahydro-4-cinnoline carboxylic acid **10** (see Scheme 4). Acylation of *ortho*-aminophenol **11** with acid **10** (CDI, DMF) resulted in a product identical with compound **9b** as judged from the melting point and spectral characteristics.




**Scheme 4**.




**Scheme 3**.