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Solid-phase synthesis of tetrasubstituted 2-imino-1,3-thiazolines using a functionalizing cleavage strategy

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This paper is dedicated to the memory of Professor Charles Mioskowski, who passed away on June 2, 2007

Abstract

A novel solid-phase synthesis of tetrasubstituted 2-imino-1,3-thiazolines using a functionalizing cleavage strategy is described. The synthetic route utilized the ambident reactivity of a dithiocarbamate functionality to synthesize the key resin-bound electrophilic thiazolium intermediate. The desired products were efficiently obtained in high purity by the reaction of various amines with the thiazolium salt.

In its early days, combinatorial chemistry focused on the synthesis of very large libraries of biologically active oligomers, such as peptides and oligonucleotides. It quickly became apparent that because of their biophysical properties, such oligomers could be employed as drugs or lead compounds in only few cases.[1] To solve this problem, peptidomimetics, compounds that act as substitutes for peptides in their interaction with receptors, have been synthesized.[2] Therefore, combinatorial chemistry evolved to the preparation of small molecule libraries and more specifically, heterocyclic compounds known to be key therapeutic agents.[3]

In this respect, 2-imino-1,3-thiazolines have proven to be a structural feature providing a broad spectrum of activity, such as fungicides,[4] insecticides,[5] analgesics,[5] and antibacterials.[6] This moiety is also key in the development of drugs for hypertension,[7] inflammation,[8] and cancer therapies.[9] Therefore this small, highly functionalized structure is a target of prime interest for the development of solid-phase synthetic methods. One example of solid-phase synthesis of trisubstituted 2-imino-1,3-thiazolines has been described in the literature.[10] Surprisingly however, to the best of our knowledge no solid-phase synthesis of tetrasubstituted 2-imino-1,3-thiazolines has been reported in the literature (Table 1).

The solution-phase synthesis of 2-imino-1,3-thiazolines mainly focuses on the Hantsch reaction, namely, the condensation of unsymmetrical thioureas with α-chloroketones.[11] This method leads to a mixture of regioisomers depending upon the reaction conditions.[12] To overcome this problem, unsubstituted thiourea could be used followed by regioselective alkylation of the nitrogen atom.[13] A different approach is the reaction of α-haloimines with potassium thiocyanate.[12] However, only di- or trisubstituted 2-imino-1,3-thiazolines were prepared through these processes. An additional alkylation step of the nitrogen atom is required to obtain fully substituted heterocyclic compounds. Alternatively, the treatment of 4-thiazoline-2-ones with alkylating reagents followed by the addition of amines yields tetrasubstituted 2-imino-1,3-thiazolines.[14]

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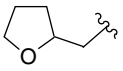
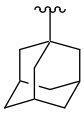
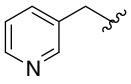
Table 1

No.	R^1	R^2	R^3	R^4	Yields[a] (%)
9	*i*-Bu	Br	H		45
10		NO_2	H	*n*-Bu	49
11	Cy	H	Me	Bn	59
12	Ph	NO_2	H	*i*-Bu	55
13	*n*-Bu	H	Ph		33
14	$-(CH_2)_2SEt$	H	Ph		35
15	*i*-Pr	Ph	H	$-(CH_2)_3SMe$	60
16		Br	H	Allyl	37
17	*i*-Bu	H	Me		62
18	*n*-Bu	Br	H	4-MeOBn	51
19	4-F-Ph	H	Ph	Cy	30

[a] Overall isolated yields.

All of these methods have a common drawback which makes them ineffective in their application on solid support. At least one of the substituents of the 2-imino-1,3-thiazoline moiety has to be directly connected to the solid phase. This significantly limits the number of diversity of the final products since an additional cleavage step is required in order to release the final product from the solid support (a step that does not add any diversity).

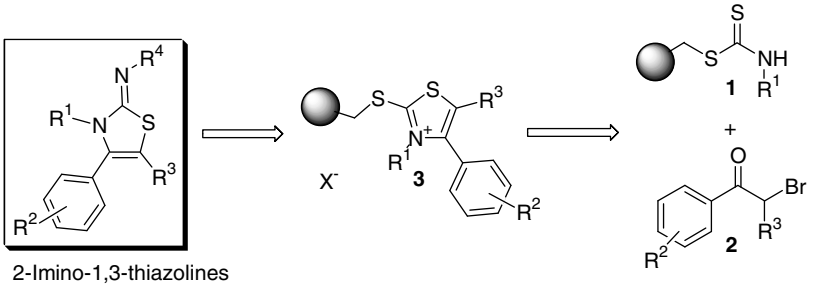
The sulfur-linker developed in our group offers a unique possibility to immobilize and modify a dithiocarbamate functionality on solid support. The solid-phase synthesis of thioureas[15] and guanidines[16] has already been demonstrated. In our continuous efforts to develop solid-phase strategies that allow both efficient generation of diversity and cleavage through structural inter-conversion reactions, we report herein the first and unique solid-phase synthesis of tetrasubstituted 2-imino-1,3-thiazolines. The three-step synthetic scheme relies on a key resin-bound electrophilic thiazolinium intermediate **3** that allows the release of the target skeleton and concomitant introduction of diversity (Scheme 1).

The reactive thiazolium intermediate **3** is obtained by the reaction of a resin-bound dithiocarbamate **1** with α-bromoketones **2**. The dithiocarbamate is prepared as previously described[14] by the reaction of a primary amine with Merrifield resin in the presence of CS_2. This versatile, three-step sequence allows a combination of readily available building blocks, namely primary amines and α-bromoketones, and leads to the target structure in a traceless fashion.

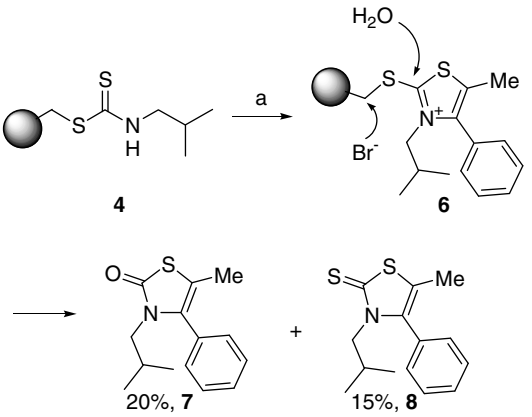
In our previous work, we had shown that the synthesis of the resin-bound dithiocarbamate could be achieved in high yield by the reaction of the Merrifield resin with carbon disulfide in the presence of a primary amine under basic conditions.[14] This reaction proved to be compatible with a wide variety of primary amines.

The first attempt for the formation of the thiazolium intermediate through cyclo-condensation was performed by heating the resin-bound dithiocarbamate **4** with α-bromoacetophenone **5** in acetonitrile at 80 °C for 12 h. After thorough washing, IR analysis of the resin showed signals at 1718, 1669, 1266, and 1069 cm^{-1}, characteristic of the resin-bound thiazolium salt **6**. However, analysis of the washing solvents revealed the presence of two products, imidazolinone **7** and imidazolinethione **8**, arising from untimely cleavage reactions. The first one (20% determined after chromatographic purification and based on the initial loading of the starting Merrifield resin) results from the hydrolysis of the resin-bound thiazolinium and the second one from nucleophilic attack of the bromide at the resin-thiazolinium benzylic position (15%) (Scheme 2).

We then investigated the use of additives capable of scavenging both water and nucleophilic anion (bromide) generated in the reaction media in order to inhibit these side reactions. Toxic reagents (such as mercury(II) oxide)



Scheme 1. Retrosynthetic scheme for the solid-phase synthesis of 2-imino-1,3-thiazolines.

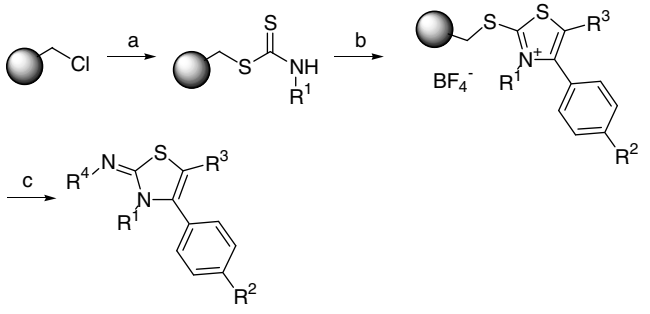


Scheme 2. Preparation of the resin-bound thiazolium intermediate. Reagents and conditions: α-bromoacetophenone **5**, CH_3CN, 80 °C, 12 h. Yields are given for isolated products.

were not considered in order to avoid any contamination of the final product. The combination of chlorotrimethylsilane and tetrabutylammonium tetrafluoroborate proved to be efficient since no noticeable premature cleavage products were detected after 12 h at 80 °C. Under these conditions, IR analysis of the resin showed characteristic signals of the thiazolium moiety. The byproducts disiloxane and tetrabutylammonium halide formed in the reaction were easily removed by washing the resin-bound thiazolium with dry CH_2Cl_2. The stability of this quaternary salt in solution has already been demonstrated with UV absorption at 290 nm which shows a fully conjugated π system.[17] The resin-bound thiazolium was found to be relatively stable and can be stored under nitrogen at low temperature (−5 °C) for several days.

The presence of the quaternary thiazolium salt in the polymeric matrix was not a complication. The resin was swelled with dry toluene and was treated with a primary amine at 80 °C. The reaction was monitored by IR analysis of the resin and was found to be complete after 10–12 h and resulted in the formation of the 2-imino-1,3-thiazoline structure (Scheme 3).

The reactivity of the thiazolium was not affected by the solid support and, after concentration under vacuum of the



Scheme 3. Functionalizing cleavage strategy for solid-phase synthesis of 2-imino-1,3-thiazolines. Reagents and conditions: (a) CS_2, DIEA, R_1NH_2, THF, 12 h, rt; (b) α-bromoketone, n-Bu_4NBF_4, TMSCl, CH_3CN, 80 °C, 12 h; (c) R^4NH_2, toluene, 80 °C, 12 h.

crude cleavage materials, the ^1H NMR analysis showed the desired heterocycle together with the excess primary amines. Purification was carried out by filtration over a cartridge of silica gel. The purity of the 2-imino-1,3-thiazoline was found to be greater than 95% according to ^1H NMR analysis. The isolated yields are reflective of the overall efficiency of the reaction scheme.

This protocol was successfully applied to a variety of primary amines including aliphatic, benzylic, allylic, and less nucleophilic amines like anilines. Also, primary amines bearing heterosubstituted functionalities like tetrahydrofuran, pyridine, ethers, and sulfide could be used in the sequence. The cyclocondensation reaction could be accomplished with a wide variety of α-bromo ketones bearing an aromatic group substituted with bromide, phenyl, or electron-withdrawing functionalities (nitro), and electron-donating (methoxy). Moreover hindered α-bromopropiophenone or desyl bromide proved to be compatible with the reaction sequence.

In conclusion, we have developed the first example of solid-phase synthesis of tetrasubstituted 2-imino-1,3-thiazolines, starting from readily available primary amines and α-bromoketones. The products were obtained in good yields and high degrees of purity. The method allows for the formation of the precursor dithiocarbamate and the use of its ambident reactivity toward electrophiles. The stability of the intermediate thiazolium on solid support and its reactivity has been demonstrated. Each step of the synthesis is used to add diversity to the final product with no unnecessary steps that would ultimately increase the cost of a library synthesis. The mildness of the reaction and functionalizing cleavage conditions using the sulfur-linker make this process well suited to automated synthesis for the construction of large libraries.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.02.160.

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