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Report

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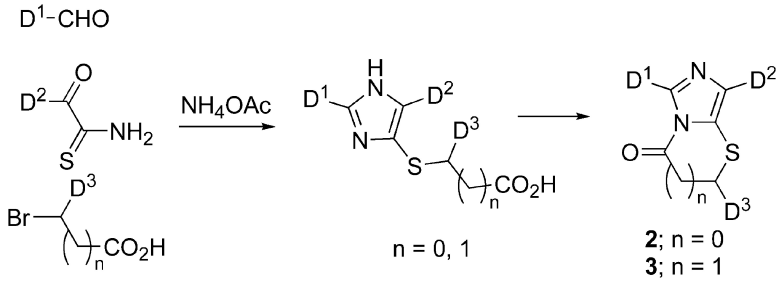

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Reports

Imidazo[5,1-*b*]thiazol-3-ones/thiazin-4-ones: Synthesis and Reactivity Investigation for Library Generation

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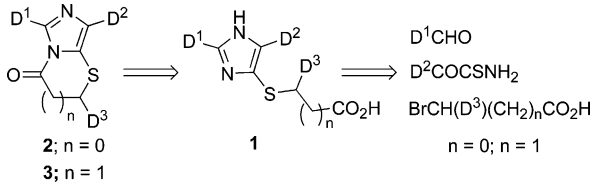
Heterocyclic compounds have been a traditional focal point for the development of new anticancer agents, with the development of combinatorial approaches to new ring systems being of current interest. The relatively efficient solution phase combinatorial synthesis of many fused-ring heterocycles coupled with their potential for postsynthesis structural elaboration has led to an increased number of such compounds being developed as new therapeutic classes.[1] In our work to develop new routes to diversely substituted druglike heterocyclic scaffolds, we have targeted the [5-5] and [5-6] fused-ring systems imidazo[5,1-*b*]thiazol-3-ones **2** and imidazo[5,1-*b*]thiazin-4-ones **3**, respectively (Scheme 1). Derivatives of the imidazo[2,1-*b*]thiazole ring system have previously shown some initial promise as anticancer agents, but the isomeric [5,1-*b*] system has not been previously investigated.[2]

Previously reported literature methods to the [5-5] fused ring system **2** are few, and all require harsh dehydrating conditions to construct the bicyclic architecture, whereas a route to the [5-6] ring system **3** has yet to be reported.[3] Similarly, the chemical reactivity of **2** is relatively unexplored, with the only reactions described to date being the oxidation to sulfone of substituted imidazo[5,1-*b*]thiazoles, nucleophilic substitution on the imidazole ring, and their reactivity in 1,4-cycloadditions.[3f,4] To the best of our knowledge, the chemistry of the thiazolone ring of **2** or the thiazinone ring of **3** has not been previously examined. This we anticipated would be of particular interest due to the five- and six-membered lactams contained within these structures. Our goal was to devise a robust synthetic route to both ring systems that would have the potential to be applied to a solution-phase parallel library format and to carry out preliminary reactivity investigations to determine possible methods for further structural elaboration.

Scheme 1. Two-Step Route to Imidazo[5,1-*b*]thiazolones **2** and Imidazo[5,1-*b*]thiazinones **3**



Our approach to both compound classes **2** and **3** was to affect an intramolecular coupling of a carboxylic acid with the imidazole nitrogen from the substituted sulfanyl imidazoles **1** (Scheme 1). The synthesis of **1** is an extended utility of our reported three-component 4(5)-sulfanyl-1*H*-imidazole library synthesis, from the reaction of an aldehyde (D^1), 2-oxothioacetamide (D^2), and an alkylbromide (D^3) (Scheme 1).[5] If both steps could be achieved in a combinatorially friendly manner, this would facilitate the generation of a library from a library.

The 3-component sulfanylimidazole synthesis was applied to three different aldehydes (R^1), 2-oxo-2-phenylthioacetamide, and four different bromo acids (R^2) as a representative test sample (Table 1). The bromo acids used in the reaction sequence were bromoacetic acid, 2- and 3-bromopropionic acid, and 2-bromobutyric acid.

Reactions were carried out in ethanol in the presence of sodium carbonate under reflux for 16 h. The reaction was successful in tolerating the diversity of functional groups with

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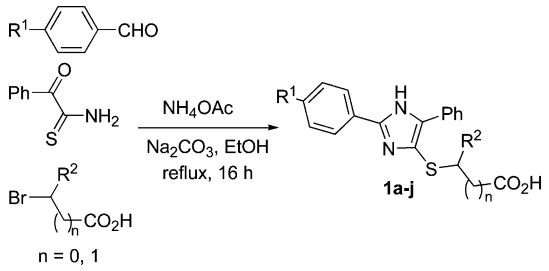
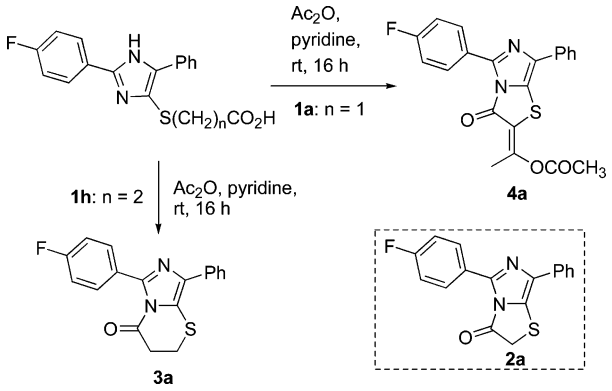
Table 1. Three-Component Route to Sulfanylimidazoles **1a**−**j**



entry	R^1	R^2	n	product	% purity[a]	% yield[b]
1	F	H	0	**1a**	92	76
2	F	Me	0	**1b**	81	75
3	MeO	H	0	**1c**	97	69
4	MeO	Me	0	**1d**	96	66
5	MeO	Et	0	**1e**	95	61
6	CF_3	H	0	**1f**	96	78
7	CF_3	Me	0	**1g**	85	80
8	F	H	1	**1h**	81	78
9	MeO	H	1	**1i**	98	58
10	CF_3	H	1	**1j**	98	66

[a] Purity of the precipitate by HPLC. [b] Isolated purified yield.

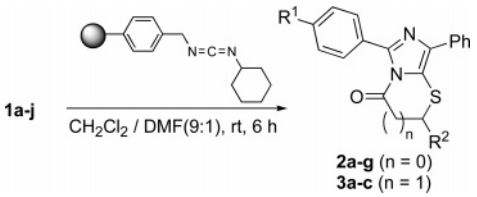
Scheme 2. Cyclization of **1a**,**h** with Acetic Anhydride



the desired product isolated in each case. The products were isolated by acid precipitation from the reaction mixture and, encouragingly, from a library generation point of view gave good purities, ranging from 81 to 98%, as judged by HPLC. If necessary, further purification was carried out by recrystallization or silica gel chromatography. The facile isolation of **1** in high purity is key because it indicates that it would be possible to take these compounds directly to the next step in a library format.

Our next goal was to determine the optimal approach for converting the substrates **1a**−**j** into our target ring systems **2** and **3** by intramolecular coupling of the carboxylic acid with the imidazole nitrogen. Substrates **1a** and **1h** were chosen as model compounds, with acetic anhydride/pyridine used to affect the desired transformation (Scheme 2). Under these reaction conditions, only **1h** yielded the expected bicyclic product **3a** in a 86% yield. Surprisingly, from the identical reaction of **1a**, only trace amounts of **2a** could be detected (Scheme 2, inset). The predominate product isolated was **4a**, obtained in a 82% yield. This reaction gave an early indication of the interesting reactivity of this ring system and could be explained by the further reaction of **2a** with acetic anhydride.

Table 2. Conversion of **1a**−**j** to **2a**−**g** and **3a**−**c**



entry	substrate	R^1	R^2	*n*	product	% yield[a]
1	**1a**	F	H	0	**2a**	75
2	**1b**	F	Me	0	**2b**	71
3	**1c**	MeO	H	0	**2c**	61
4	**1d**	MeO	Me	0	**2d**	67
5	**1e**	MeO	Et	0	**2e**	90
6	**1f**	CF_3	H	0	**2f**	71
7	**1g**	CF_3	Me	0	**2g**	65
8	**1h**	F	H	1	**3a**	72
9	**1i**	MeO	H	1	**3b**	71
10	**1j**	CF_3	H	1	**3c**	68

[a] Isolated purified yield.

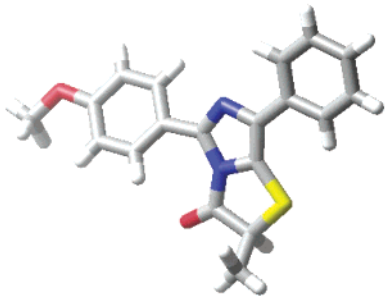


Figure 1. X-ray structure of **2d**.

Because our overall aim was to develop optimized synthetic routes to generate libraries, acetic anhydride was not a viable reagent, so as an alternative, we chose to exploit a solid-supported coupling reagent. We tested the polystyrene-supported *N*-benzyl-*N*′-cyclohexylcarbodiimide, the principal advantage of which is the routine separation of the urea byproduct from the reaction product by filtration.[6] The coupling reactions were carried out in dichloromethane/DMF at room temperature for 6 h. In each case, the reaction was successful, with purified products isolated in 61−90% yields, confirming the viability of this approach for the second synthetic operation in generating libraries of **2** and **3** (Table 2).

Infrared and ^{1}H NMR studies indicated that the lactam of **2** and **3** exist predominately in the keto form in both the solid and solution states. This was confirmed for the solid state by single-crystal X-ray structural determination of **2d** (Figure 1). An investigation of the potential for further structural elaboration of **2** and **3** based upon the reactivity of the cyclic amide bond of the thiazolone and thiazinone rings was carried out. Our aim was to test their reactivity toward enolization and nucleophilic ring opening, which would give a reactivity profile from which further libraries based upon the structures **2** and **3** could be achieved.

The enolization process was examined by monitoring deuterium incorporation by ^{1}H NMR over time (Figure 2). The imidazothiazolones **2a**, **2b**, and **2d** and the imidazothiazinone **3a** were dissolved in DMSO-d_6 containing 20%

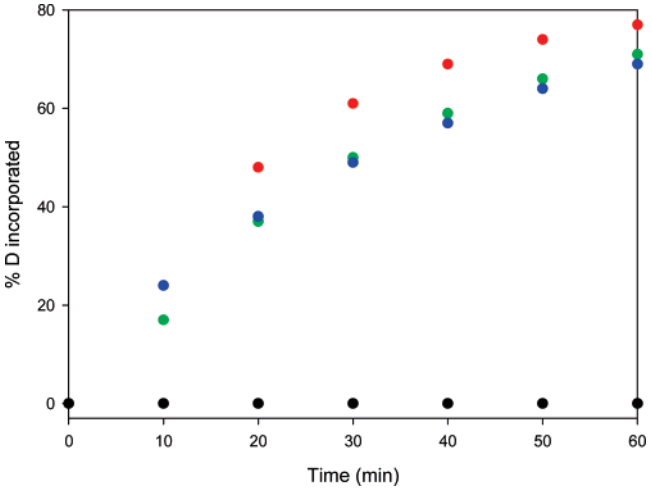
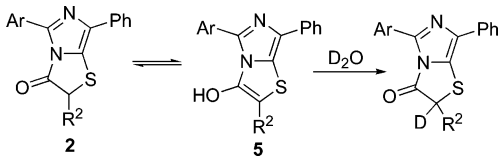


Figure 2. Deuterium exchange for **2a** (blue), **2b** (green), **2d** (red), and **3a** (black).

Scheme 3. Deuterium Incorporation by Enolization of **2**



D_2O, and the H/D exchange was monitored at 50 °C. The compounds **2a**, **2b**, and **2d** demonstrated an efficient incorporation of deuterium, with over 70% replacement within 1 h in each case (Figure 2). In the case of **2a**, both protons were exchanged. In contrast, for **3a**, no deuterium incorporation was observed in the ^{1}H NMR spectrum after 1 h.

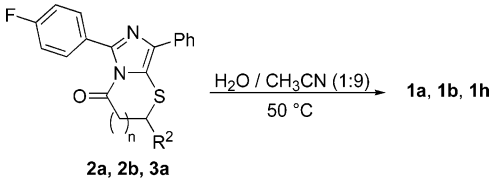
A possible reasoning would be that the thiazolone ring of **2** is in equilibrium with the 10-π aromatic enol intermediate **5**, thereby facilitating an exchange mechanism, which would not be possible for **3a** (Scheme 3). In addition, the potentially more acidic nature of the protons in **2** due to the α sulfur substituent could be a further contributor to the process.

The existence of this enolization demonstrates that the reaction of **2** with suitable electrophiles could be a viable route to introduce further functionality onto the scaffold.[7] In this context, the isolation of **4a** as product in the attempted conversion of **1a** into **2a** utilizing acetic anhydride could be explained by a double acylation of **2a** by excess acetic anhydride (Scheme 2). This was confirmed by the efficient conversion of **2a** with acetic anhydride into **4a** under identical reaction conditions. The formation of a comparable enol species for **3** would not be favored, because it would be nonaromatic, which could explain the successful generation of **3a** from **1h** under the acetic anhydride conditions (Scheme 2).

The reactivity of the compounds **2a**, **2b**, and **3a** to nucleophilic attack at the amide carbonyl was determined by the monitoring of their hydrolysis in water/acetonitrile solutions at 50 °C (Scheme 4).

Comparison of the three substrates tested showed that the [5-5] membered rings of **2a** and **2b** were more reactive, with ring opening 70 and 20% complete in 8 h, respectively. In

Scheme 4. Lactam Hydrolysis of **2** and **3**



comparison, the [5-6] ring system **3a** remained virtually unreacted under identical conditions (Figure 3), although **3a** could be induced to undergo rapid ring hydrolysis to **1h** using a pH 10 buffered water/acetonitrile (1:9) solution with conversion complete within 2 h. A similar rate increase was observed for **2a**,**b** at this higher pH.

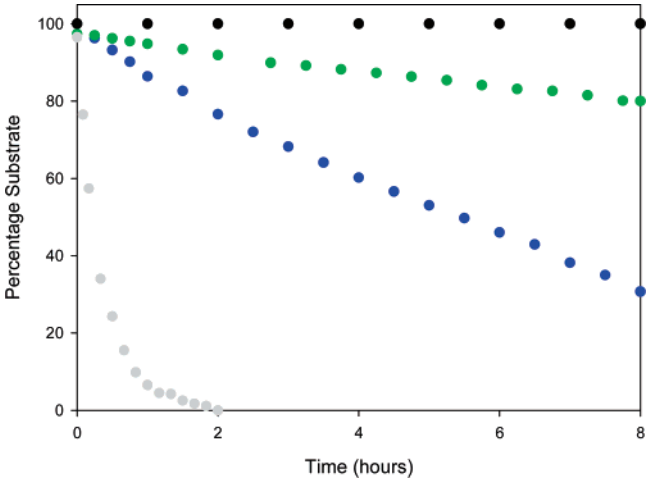


Figure 3. Comparative hydrolysis of **2a** (blue), **2b** (green), and **3a** (black) in pH 7.3 buffered water/acetonitrile and **3a** (grey) in pH 10 buffered water/acetonitrile.

This amide bond hydrolysis could be explained by comparison to the hydrolysis and acyl transfer reactions of acetylimidazole, which is due to the nitrogen lone pair being part of the aromatic sextet, resulting in ineffective amide stabilization.[8] Currently, this reactivity is being explored for a range of amine and alcohol nucleophiles as another means to generate further structural classes.

In summary, imidazo[5,1-*b*]thiazol-3-ones or thiazin-4-ones can be readily generated in two efficient steps. An effective three-component reaction in combination with the use of a solid-supported coupling agent could facilitate the generation of a library from a library[9] of these compounds. The ease of generation and the potential for further structural elaboration by a variety of chemical transformations make these compounds attractive building blocks for a diversity-orientated synthesis approach to further library generation.[10] The utility of the described methods is currently being explored for parallel library generation in tandem with the controlled exploitation of peripheral heterocycle reactivity as an excellent way to structurally elaborate preexisting libraries.

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Supporting Information Available. Detailed experimental procedures and characterization data for **1a**−**j**, **2a**−**g**, **3a**−**c**, and **4a**. X-ray crystallographic data of **2d** as a CIF file. This material is free of charge via the Internet at http://pubs.acs.org.

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