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Facile synthesis of *N*-acyl 2-aminobenzothiazoles by NHC-catalyzed direct oxidative amidation of aldehydes

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A mild, general, and high yielding synthesis of *N*-acyl 2-aminobenzothiazoles has been demonstrated by the N-heterocyclic carbene (NHC)-organocatalyzed direct amidation of aldehydes with 2-aminobenzothiazoles proceeding via the acyl azolium intermediates. The carbene generated from the triazolium salt under oxidative conditions was the key for the success of this reaction. The method was subsequently applied to the synthesis of various biologically important *N*-acyl 2-aminobenzothiazoles.

Functionalized 2-aminobenzothiazoles are an important class of heterocyclic scaffolds due to the presence of these motifs in numerous biologically active natural products and several pharmaceuticals.[1] For example, Riluzole (**A**) is an important drug belonging to this group, employed for the treatment of amyotrophic lateral sclerosis (ALS), a lethal neurodegenerative disease (Figure 1).[2] Specifically, 2-aminobenzothiazoles substituted on the endocyclic nitrogen are known to exhibit potential biological properties.[3] Among the functionalized *N*-acyl 2-aminobenzothiazoles, the 4-methoxy benzamide derivative of type **B** acts as 17β-hydroxysteroid dehydrogenase type 1 inhibitors.[4] Moreover, the 4-fluoro benzamide of type **C** exhibits non-xanthine based A_{2B} adenosine receptor antagonist activity,[5] 4-nitro benzamide derivative of the type **D** acts as raf-1 inhibitor,[6] and 4-chloro benzamide of type **E** is known to be potent and selective inhibitors of Candida albicans *N*-myristoyltransferase.[7] Since this class of compounds exhibit wide range of biological properties, developing simple and facile synthetic strategies towards functionalized 2-aminobenzothiazoles has attracted much attention from organic chemists.

Traditionally, the *N*-acyl 2-aminobenzothiazoles have been synthesized by the reaction of 2-aminobenzothiazoles with the corresponding carboxylic acids/derivatives.[8] However, in most cases, the reaction needs a coupling reagent and a stoichiometric byproduct will be formed at the end of the reaction. In this context, we envisioned the N-heterocyclic carbene (NHC)[9,10] organocatalyzed direct oxidative amidation of aldehydes with 2-aminobenzothiazoles as a straightforward route to access *N*-acyl 2-aminobenzothiazoles. Notably, NHC-catalyzed redox-amidation of α-functionalized aldehydes with amines has been independently reported by the Rovis[11] and Bode[12] groups.[13] In 2010, the Studer group uncovered the oxidative amidation of aldehydes using hexafluoroisopropanol (HFIP) as the acyl transfer agent.[14] Very recently, the Brown group disclosed the flow process for the NHC-*mediated* anodic oxidative amidation of aldehydes with amines.[15] Herein, we report the NHC-catalyzed direct oxidative amidation of aldehydes with 2-aminobenzothiazoles.[16,17] The reaction works under mild conditions without the aid of coupling agent or acyl transfer agent and the present method is extended to the synthesis of several drug analogs.

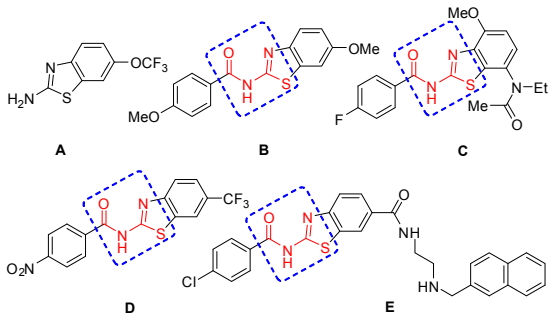

Figure 1. Biologically important 2-aminobenzothiazole derivatives

The present study commenced with the treatment of 4-chlorobenzaldehyhe **1a** and 2-aminobenzothiazole **2a** with the triazolium salt **4** in presence of oxidant **5** and Cs_2CO_3 as the base. Delightfully, under these conditions, a facile reaction occurred leading to the formation of the expected *N*-acyl 2-aminobenzothiazole **3a** in 83% yield (Table 1, entry 1). As anticipated, the reaction did not work at all in the absence of the triazolium salt **4** (entry 2). The performed reactions using

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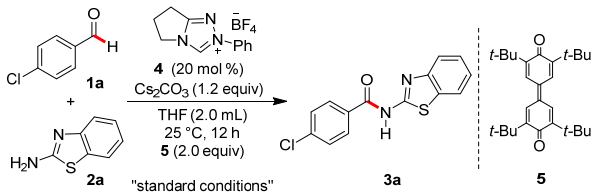
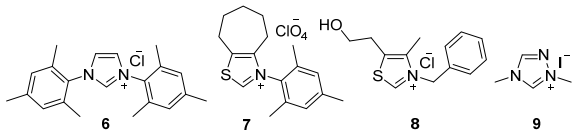
common NHCs derived from precursors **6**-**8** returned reduced yield of **3a** (entries 3-5), whereas, NHC derived from **9** furnished **3a** in comparable yield (entry 6). The reaction resulted in similar outcome when performed in DBU instead of Cs_2CO_3 (entry 7), whereas the other bases, such as DMAP, KO*t*-Bu and, K_2CO_3 furnished inferior results (entries 8-10). A quick solvent screening revealed that, solvents such as DME, 1,4-dioxane and toluene gave reduced yields (entries 11-13). Interestingly, the use of CH_2Cl_2 improved the yield of **3a** to 93% (entry 14). Moreover, decreasing the amount of the carbene precursor **4** resulted in reduced yield of the product (entry 15). Thus, the use of triazolium salt **4** (20 mol %) and Cs_2CO_3 as base (1.2 equiv) in CH_2Cl_2 at 25 °C with **5** as the oxidant was found to be the optimal conditions for this reaction (entry 14).

Table 1. Optimization of the reaction conditions[a]

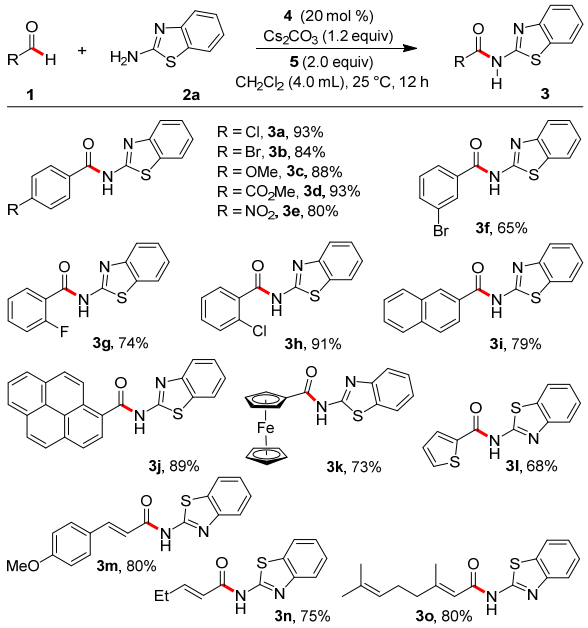


entry	variation of the standard conditions	yield of **3a** (%)[b]
1	none	83
2	without **4**	<5
3	**6** instead of **4**	60
4	**7** instead of **4**	35
5	**8** instead of **4**	54
6	**9** instead of **4**	80
7	DBU instead of Cs_2CO_3	78
8	DMAP instead of Cs_2CO_3	20
9	K_2CO_3 instead of Cs_2CO_3	58
10	KO*t*-Bu instead of Cs_2CO_3	35
11	DME instead of THF	66
12	1,4-dioxane instead of THF	78
13	toluene instead of THF	44
14	*CH_2Cl_2 instead of THF*	*93*
15	10 mol % **4** instead of 20 mol %	71

[a] Standard conditions: **1a** (0.50 mmol), **2a** (0.25 mmol), **4** (20 mol %), Cs_2CO_3 (1.2 equiv), **5** (2.0 equiv), THF (2.0 mL), 25 °C and 12 h. [b] Isolated yield after column chromatography.



With the optimized reaction conditions, we evaluated the substrate scope of this NHC-catalyzed amidation reaction. First, tolerance of this reaction with various aldehydes has been tested (Scheme 1). Aldehydes bearing electron-donating and -withdrawing groups at the *para*-position of the aryl ring were well tolerated, resulting in the synthesis of *N*-acyl 2-aminobenzothiazoles in high yields of >80% in all cases (**3a**-**3e**). Additionally, substitution at the *meta*-position as well as *ortho*-position of aryl ring of **1** resulted in the smooth conversion to the desired product in good yield (**3f**-**3h**). Furthermore, polycyclic aromatic aldehydes such as naphthyl and pyrene carboxaldehydes afforded the desired product (**3i**, **3j**) in good yields. Moreover, interesting aldehydes such as ferrocene carboxaldehyde and thiophene 2-carboxaldehyde also furnished the corresponding products in good yields, further expanding the scope of this direct amidation reaction (**3k**, **3l**). Notably, α,β-unsaturated aldehydes with aromatic as well as aliphatic groups at the β-position underwent smooth amidation reaction to form the products in moderate to good yields (**3m, 3n**). Interestingly, citral can also be used as a coupling partner and the corresponding amide (**3o**) was isolated in 80% yield, demonstrating the versatility of this reaction.



Scheme 1. Substrate Scope for the Direct Amidation of Aldehydes: Variation of Aldehydes. Reaction conditions: **1** (1.0 mmol), **2a** (0.5 mmol), **4** (20 mol %), **5** (2.0 equiv), Cs_2CO_3 (1.2 equiv), CH_2Cl_2 (4.0 mL), 25 °C and 12 h. Given are yields of isolated products after silica gel flash column chromatography.

Next, we focused our attention on the variation of 2-aminobenzothiazoles (Scheme 2). 2-aminobenzothiazoles with electron-donating and -withdrawing groups at 6-position of aryl ring underwent efficient amidation reaction with 4-chlorobenzaldehyde to afford the desired benzamide products (**3p**-**3t**) in good yields. Moreover, difluoro substitution in aryl ring of benzothiazole furnished the amide **3u** in 75% yield. Interestingly, 2-amino thiazole can also be used as coupling partner, and the target product **3v** was formed in 42% yield.

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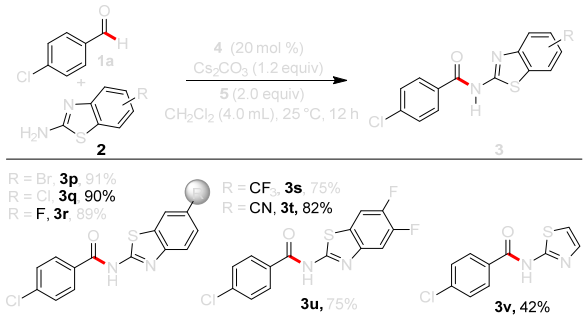
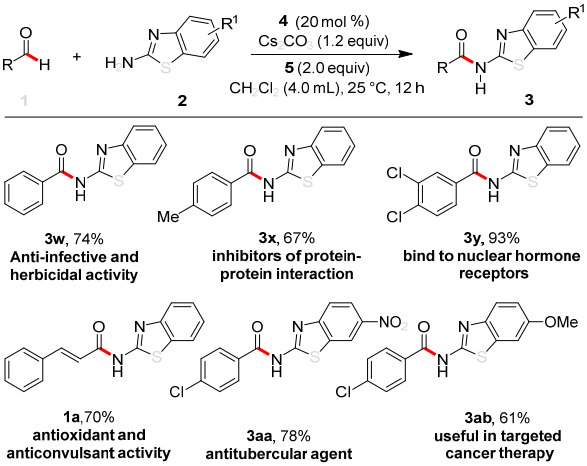


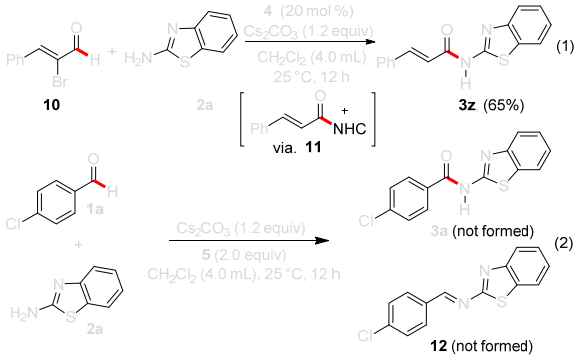
Scheme 2. Variation of 2-Aminobenzothiazoles. Reaction conditions: **1a** (1.0 mmol), **2** (0.5 mmol), **4** (20 mol %), **5** (2.0 equiv), Cs_2CO_3 (1.2 equiv), CH_2Cl_2 (4.0 mL), 25 °C and 12 h. Given are yields of isoalted products after silica gel flash column chromatography.

Then, we turned our attention on application of the present method for the synthesis of various biologically active *N*-acyl 2-aminobenzothiazoles (Scheme 3). The direct amidation of benzaldehyde with 2-aminobenzothiazole under optimized reaction conditions afforded benzamide **3w** in 74% yield. The compound **3w** is known to exhibit anti-infective and herbicidal activity.[3] The reaction of 4-toluadehyde with **2a** furnished the benzamide **3x** in 67% yield, and **3x** is known to act as inhibitors of protein-protein interaction between KRS and a laminin receptor.[18] The benzamide **3y,** derived from 3,4-dichlobenzaldehyde and **2a** in 93% yield is known to bind to the nuclear hormone receptors.[19] The α,β-unsaturated amide **3z** was synthesized from cinnamaldehyde and **2a** in 70% yield and **3z** possesses antioxidant and anticonvulsant activity.[20] Moreover, the reaction of 4-chloro benzaldehyde and 6-nitro 2-aminobenzothiazole afforded the antitubercular agent **3aa** in 78% yield.[21] Finally, the benzamide **3ab** was synthesized from 4-chlorobenzaldehyde and 6-methoxy 2-amino benzothiazole in 61% yield, and is useful in targeted cancer therapy.[22]



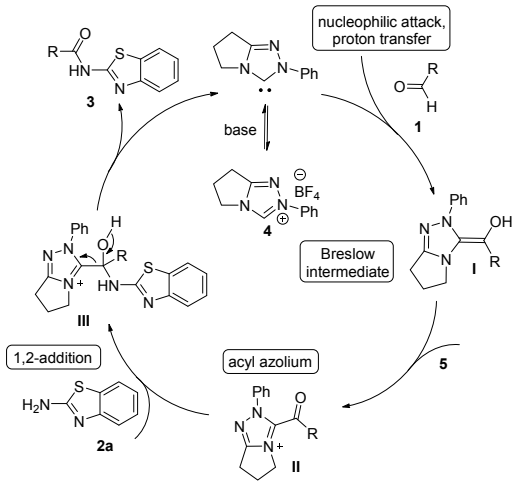
Scheme 3. Synthesis of biologically active *N*-Acyl 2-Aminobenzothiazoles. Reaction conditions: **1** (1.0 mmol), **2** (0.5 mmol), **4** (20 mol %), **5** (2.0 equiv), Cs_2CO_3 (1.2 equiv), CH_2Cl_2 (4.0 mL), 25 °C and 12 h. [b] Isolated yields are given.

To get insight into the mechanism of this reaction, we have carried out mechanistic experiments. When the reaction was performed under optimized conditions in the absence of **5** using 2-bromoenal **10**, the unsaturated benzamide **3z** was formed in 65% yield (Scheme 4, eq 1). This indicates the intermediacy of NHC-bound acyl azolium **11** in the present reaction. Moreover, mixing **1a** with **2a** in the absence of NHC precatalyst **4** did not afford the amide product **3a** as well as the imine **12**, and the unreacted **1a** and **2a** were quantitatively recovered (eq 2). It may be mentioned that the absence of imine formation rules out the amide formation directly from imines under oxidative conditions.[23,24]



Scheme 4. Mechanistic Experiments

The tentative mechanism of this NHC-catalyzed amidation reaction is shown in Scheme 5. The NHC generated from **4** under basic conditions undergoes nucleophilic attack on the aldehyde **1** followed by a proton transfer generating the nucleophilic Breslow intermediate **I**.[25] In the presence of **5**, **I** undergoes oxidation to generate **II**, which is the key acyl-azolium intermediate. Nucleophilic 1,2 addition of the amine **2a** on to intermediate **II** will form the aminal intermediate **III**. The intermediate **III,** upon regeneration of carbene affords the desired amide **3**.



Scheme 5. Proposed Mechanism of the Reaction

In conclusion, we have demonstrated the NHC-catalyzed oxidative amidation route for the synthesis of *N*-acyl 2-

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aminobenzothiazoles. The reaction proceeds via the generation of the NHC-bound acyl azolium intermediates. Mild reaction conditions without the aid of a coupling/acyl transfer agent, good functional group compatibility, high yields of products, convenient synthesis of drug analogs are the notable features of the present reaction.

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