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# Synthesis of novel biaryl 2-benzimidazoles and 2-benzothiazoles

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ABSTRACT

Herein, we describe the synthesis of the novel 4-(1*H*-benzo[*d*]imidazol-2-yl)isoxazol-5-amine (**7**) and 4-(1*H*-benzo[*d*]thiazol-2-yl)isoxazol-5-amine scaffolds (**8**). Initial attempts following literature procedures for the synthesis of similar compounds did not yield the desired product. Instead we obtained the ring-opened adduct 2-(1*H*-benzo[*d*]imidazol-2(3*H*)-ylidene)-2-cyanoacetamide (**5**). We were able to modify reaction conditions and successfully synthesize the desired product. We also describe a convenient one-pot microwave-assisted relay reaction for the synthesis of novel and reported 2-substituted benzimidazoles and benzothiazoles from inexpensive, commercially available reagents, 2-benzothiazole acetonitrile (**2**) and 2-benzimidazole acetonitrile (**1**). In all cases, good yields of products were obtained and reaction times were significantly reduced.



2-Heterocyclic benzimidazolyl derivatives have been previously reported as kinase inhibitors.[1,2] We envisioned the synthesis of 2-benzimidazole and 2-benzothiazole-substituted heterocycles from the commercially available 2-benzimidazole acetonitrile (**1**) and 2-benzothiazole acetonitrile (**2**). Following this strategy, we attempted the synthesis of the previously unreported 4-(1*H*-benzo[*d*]imidazol-2-yl)isoxazol-5-amine (**7**). In our initial effort, we utilized the procedure reported in the literature for the synthesis of 4-(1*H*-benzo[*d*]thiazol-2-yl)isoxazol-5-amine (**8**).[3]

As shown in Figure 1, 2-benzimidazol acetonitrile (**1**) was reacted with *N,N*-dimethylformamide dimethyl acetal (DMFDMA) which afforded the 2-(benzo[*d*]imidazol-2-yl)-3-(dimethylamino) acrylonitrile (**3**) intermediate in 91% yield. This intermediate was further reacted with hydroxylamine hydrochloride and potassium carbonate under reflux conditions. However, the product obtained was not the desired 4-(1*H*-benzo[*d*]imidazol-2-yl)isoxazol-5-amine (**7**) but rather 2-(1*H*-benzo[*d*]imidazol-2(3*H*)-ylidene)-2-cyanoacetamide (**5**). We also attempted to reproduce the literature synthesis of 4-(1*H*-benzo[*d*]thiazol-2-yl)isoxazol-5- amine (**8**).[3] Yet, in our hands this procedure did not yield the final product but instead gave 2-(1*H*-benzo[*d*]thiazol-2(3*H*)-ylidene)-2-cyanoacetamide (**6**). Since the desired (**7**) and attained (**5**) product have the same molecular weight, we relied on $^1$H NMR and FTIR data to distinguish between the two. The absence of the isoxazole proton signal in the $^1$H NMR at 8 ppm and existence of nitrile signature at 2100 wavenumbers in the FTIR data were consistent with the products being **5** and **6**, respectively. We propose a possible mechanism for the formation of **5** and **6** as shown in Figure 2. It is known in the literature that isoxazole rings are sensitive to thermal and basic conditions.[7–10] Specifically deprotonation of the acidic hydrogen on the isoxazole ring could facilitate ring opening to **5** or **6**.

Given these results, we hypothesized that isoxazole ring formation and retention might occur under neutral to slightly acidic conditions. Furthermore, we reasoned that replacing the acidic labile proton with a methyl group would result in a stable product, 4-

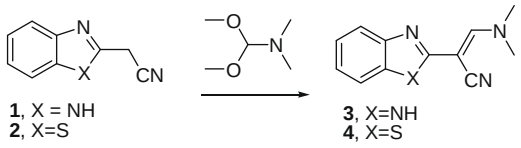


**Figure 1.** Synthesis of 2-(benzo[*d*]imidazol-2-yl)-3-(dimethylamino) acrylonitrile, **3**, and 2-(benzo[*d*]thiazol-2-yl)-3-(dimethylamino) acrylonitrile, **4**.

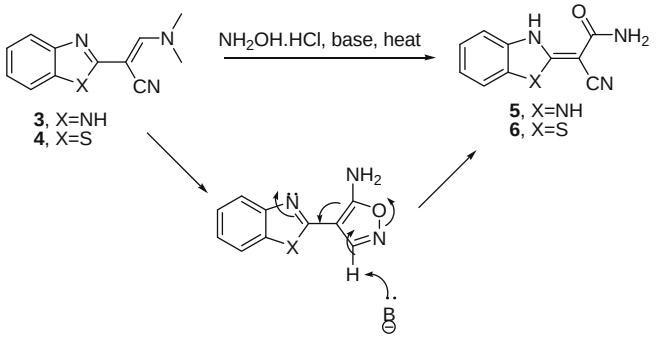


**Figure 2.** Proposed mechanism of 2-(1*H*-benzo[*d*]imidazol-2(3*H*)-ylidene)-2-cyanoacetamide, **5**, and/or 2-(1*H*-benzo[*d*]thiazol-2(3*H*)-ylidene)-2-cyanoacetamide, **6**. After formation of the isoxazole ring, the acidic hydrogen is deprotonated by base, and facilitates the ring-opening.

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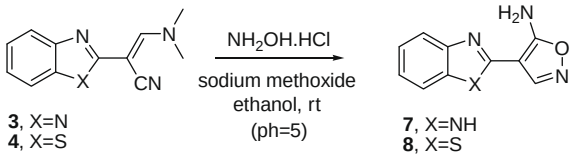



**Figure 3.** Synthesis of 4-(1*H*-benzo[*d*]imidazol-2-yl)isoxazol-5-amine **7**, and/or 4-(1*H*-benzo[*d*]thiazol-2-yl)isoxazol-5-amine, **8**.

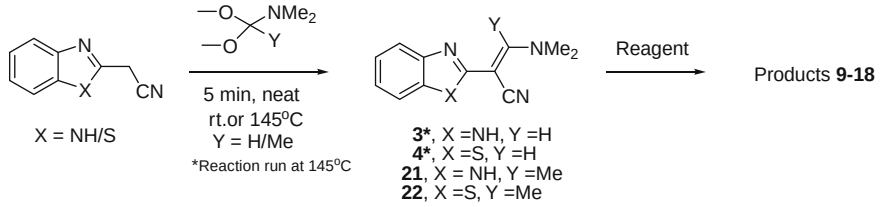
(1*H*-benzo[*d*]imidazol-2-yl)-3-methylisoxazol-5-amine **9** that would not ring-open. Attempts to prepare **7** under slight acidic conditions (pH 5) indeed gave the desired product in 82% yield, Figure 3. Similarly, these conditions were applied to the benzothiazole scaffold and furnished product **8** in 95% yield.

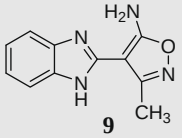
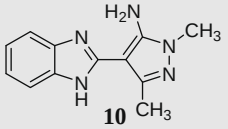
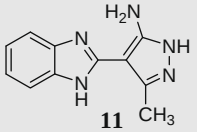
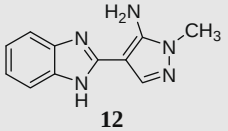
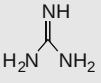
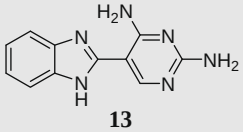
In order to better understand the sensitivity of the isoxazole ring, we exposed products **7** and **8** to heat and basic conditions, respectively. Both of these studies were initially monitored via HPLC and then confirmed with $^1$H NMR. Compound **7** when heated to 80 °C under neutral conditions in ethanol for 20 min underwent clean conversion to **5**. Exposure of **7**–0.1 M potassium carbonate for 10 min in water and at rt also gave complete conversion to **5**. Compound **8** when subjected to the same thermal or basic conditions similarly yielded the ring-opened product **6**.

In light of these results, we prepared the more stable and previously unreported 4-(1*H*-benzo[*d*]imidazol-2-yl)-3-methylisoxazol-5-amine, **9**. This compound was prepared under basic conditions (pH 8) and reflux. The acidic hydrogen on the isoxazole ring was replaced with an inert methyl group. The total reaction time was 24 h and gave **9** in 91% yield. These conditions also allowed us to prepare the benzothiazole compound, **14**. In contrast to **7** and **8**, these compounds did not undergo ring opening when subjected to heat and base, which is consistent with our hypothesis.

Having established the synthesis of **9**, we turned our attention to the synthesis of other 2-benzimidazole and 2-benzothiazole heterocycles from an acetonitrile intermediate.[1,4,5] Literature

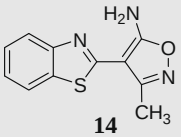
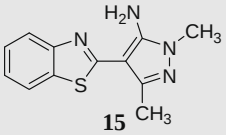
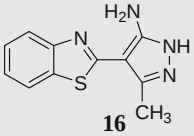
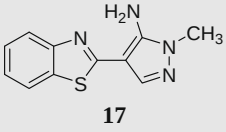
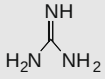
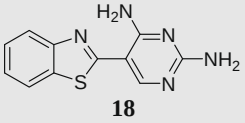
**Table 1**
Microwave reaction conditions for the preparation of benzimidazole based-scaffolds




| Microwave conditions | | | | | Product | Reflux conditions (80 °C (for comparison) | |
|---|---|---|---|---|---|---|---|
| Intermediate (not isolated) | Reagent | Time (min) | Temperature (°C) | Yield (%) | | Time (h) | Yield (%) |
| **21** | $NH_2OHHCl$ | 3 | 130 | 72 |  **9** | 24 | 91 |
| **21** | $NH_2NHCH_3$ | 3 | 120 | 66 |  **10** | 8 | 77 |
| **21** | $NH_2NH_2$ | 3 | 120 | 64 |  **11** | 1 | 71 |
| **3** | $NH_2NHCH_3$ | 3 | 120 | 75 |  **12** | 6 | 99 |
| **3** |  | 60 | 145 | 74 |  **13** | 28 | 93 |

In comparison to reflux reaction conditions, one-pot microwave-assisted reactions decrease total reaction time.

**Table 2**
Microwave reaction conditions for the preparation of benzothiazole based scaffolds

| Microwave conditions | | | | | Product | Reflux Conditions (80 °C) (for comparison) | |
|---|---|---|---|---|---|---|---|
| Intermediate (not isolated) | Reagent | Time (min) | Temperature (°C) | Yield (%) | | Time (h) | Yield (%) |
| **22** | $NH_2OHHCl$ | 6 | 130 | 85 |  **14** | 24 | 75 |
| **22** | $NH_2NH_2CH_3$ | 3 | 120 | 78 |  **15** | 8 | 83 |
| **22** | $NH_2NH_2$ | 5 | 130 | 99 |  **16** | 1 | 96[a] |
| **4** | $NH_2NHCH_3$ | 3 | 120 | 75 |  **17** | 6 | 99 |
| **4** |  | 30 | 145 | 91 |  **18** | 28 | 91 |

In comparison to reflux reaction conditions, one-pot microwave assisted reactions decrease total reaction time.
[a] Reflux conditions yielded several products and this reaction was conducted at rt.

reports of such compounds use a two step procedure.[1,4–6] The second step generally takes a long period of time (24 h) as observed with **9**. We envisioned a one-pot microwave-assisted relay reaction for the preparation of these compounds. In the first step, 2-benzimidazolyl-acetonitrile is reacted with *N,N*-dimethylacetamide dimethyl acetal (DMADMA) at rt to yield the 2-(1*H*-benzoimidazol-2-yl)-3-dimethylamino-but-2-enenitrile intermediate, **21**. To this reaction mixture, hydroxylamine hydrochloride and *N,N*-diisopropylethylamine were added and further reacted under microwave conditions giving the desired product, **9**, in 72% yield. The total time of preparation of the compound was reduced to below 10 min.

Using this one-pot procedure, we have been able to prepare 1,3-dimethyl-pyrazol-5-amine (**10**, **15**), 3-methyl-1*H*-pyrazol-5-amine (**11**, **16**), 1-methyl-pyrazol-5-amine (**12**, **17**) and pyrimidine-2,4-diamine (**13**, **18)** heterocycles. These reactions are summarized in Tables 1 and 2 for the benzimidazole and benzothiazole scaffolds, respectively. In all cases, reaction times were significantly reduced and products were obtained in good yield.

In conclusion, we have reported the synthesis of novel compounds 4-(1*H*-benzo[*d*]imidazol-2-yl)isoxazol-5-amine, **7**, and 4-(1*H*-benzo[*d*]thiazol-2-yl)isoxazol-5-amine, **8**. Due to the sensitivity of the isoxazole rings in basic and thermal conditions, we prepared the more stable and previously unreported 4-(1*H*-benzo[*d*]imidazol-2-yl)-3-methylisoxazol-5-amine, **9** and 4-(1*H*-benzo[*d*]thiazol-2-yl)-3-methylisoxazol-5-amine, **14**. A convenient one-pot microwave-assisted synthesis was developed which enabled us to prepare amino heterocycles that are 2-substituted on benzothiazole and benzimidazole scaffolds from commercially available and inexpensive starting materials.

## General procedure for preparation of 3-methylisoxazol-5-amine via microwave-assisted chemistry

### Preparation of 4-(1*H*-benzo[*d*]imidazol-2-yl)-3-methylisoxazol-5-amine, 9

2-Benzimidazolyl-acetonitrile (0.100 g), 0.102 g of DMADMA (1.2 equiv) and 0.500 ml of ethanol were placed into a microwave reaction vessel equipped with a magnetic stir bar. The reaction mixture was simply stirred at rt for 5 min. Upon completion, 0.177 g of hydroxylamine hydrochloride (4 equiv) and 0.443 ml of Hunig's base (2 equiv) were added into the reaction mixture. The entire reaction vessel was placed in the microwave and heated for 3 min at 130 °C. The reaction mixture was evaporated and precipitated in water giving the desired product in 72% yield.

## General procedure for preparation of 1-methyl-1*H*-pyrazol-5-amine under reflux conditions

### Preparation of 4-(benzo[*d*]thiazol-2-yl)-1-methyl-1*H*-pyrazol-5-amine, 12

2-(Benzo[*d*]thiazol-2-yl)acetonitrile (0.100 g), 0.075 g of DMFDMA (1.1 equiv) and 0.500 ml of ethanol were placed in a

round-bottomed flask equipped with a magnetic stir bar. The reaction mixture was stirred at rt for 1 h. Upon completion, the precipitated solid was filtered off, washed with ether and dried. The solid was dissolved in 0.500 ml of ethanol, and 0.053 g of 1-methylhydrazine was added to it. The reaction was stirred at 80 °C for 6 h. The solid was filtered off and washed with ether to give the desired product in 99% yield.

### Preparation of 4-(1*H*-benzo[*d*]imidazol-2-yl)isoxazol-5-amine, 7

To a 50 ml round-bottomed flask equipped with a magnetic stir bar, 0.102 g of sodium methoxide (2.0 equiv), 0.262 g of hydroxylamine hydrochloride (4.0 equiv) and 4 ml of ethanol were added and stirred under nitrogen flow for 10 min. 2-(1*H*-Benzo[*d*]imidazol-2-yl)-3-(dimethylamino)acrylonitrile (0.100 g) was added to this mixture and allowed to stir at rt for 16 h. Upon completion, the product precipitated from the reaction mixture. The precipitate was isolated and washed with water and dried under vacuum giving the final product in 82% yield.

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