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Rhodium-Catalyzed Regioselective Synthesis of Isocoumarins through Benzothiadiazine-Fused Frameworks

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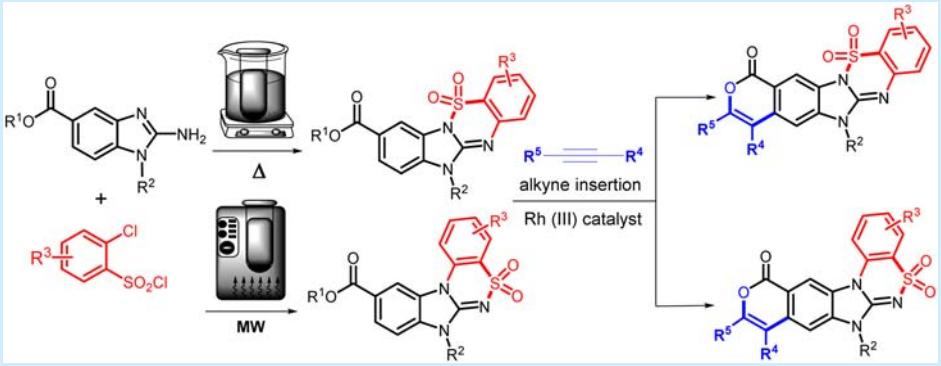
Supporting Information



ABSTRACT: An unprecedented two-step, one-pot synthesis of benzimidazothiadiazine 5,5-dioxides is presented. Reaction condition based regioselectivity has been achieved where fused benzimidazo[1,2-*b*][1,2,4]thiadiazines are exclusively formed under thermal conditions, whereas benzimidazo[2,1-*c*][1,2,4]thiadiazines were created only under microwave irradiation. The salient features of this protocol include a regioselective sulfonylation of 2-aminobenzimidazole with *o*-halo sulfonyl chlorides followed by N−C bond formation. The acid forms of these fused regioisomers have been used to introduce novel guanidine-containing isocoumarin frameworks.

Cyclic guanidine is a key structural element of marine alkaloids[1] and plant species.[2] Many of these compounds and their synthetic analogues have exhibited promising cytotoxic activities.[3] Similarly, sultam, a cyclic sulfonamide with a wide range of biological activities,[4] is a structural moiety present in the nonsteroidal anti-inflammatory agent ampiroxicam.[5] Derivatives of the 3-amino-1,2,4-benzothiadiazine 1,1-dioxide of fused guanidine and sultam are being investigated as potassium channel agonists (Figure 1).[6,7] Very few reports are available on the synthesis of isocoumarin-fused guanidine-like substructures.[8,9] Hybrid heterocycles of this type have demonstrated interesting potential activity. For example, 3-ethoxy-4-chloro-7-guanidinoisocoumarin is an inhibitor of thrombin and trypsin-like enzymes,[10] and amino pyrimidinyl isochromonone has shown significant analgesic activity in comparison with that of diclofenac sodium[11] (Figure 1).

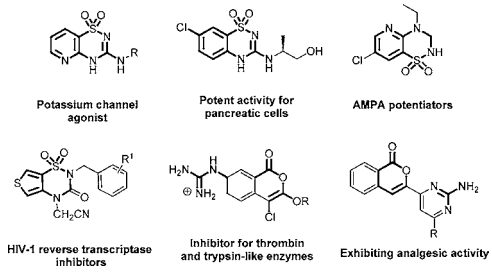


Figure 1. Biologically active compounds comprising cyclic guanidine-, sultam-, and guanidine-fused isocoumarin scaffolds.

A literature survey revealed only a few works describing the synthesis of ring systems involving N/S annulation with benzimidazoles, which further emphasizes the importance of new methodologies to creating new molecular skeletons.[12] For this reason, a built-in cyclic guanidine moiety synthesized from 2-aminobenzimidazole was designed as a building block for the construction of a benzothiadiazine dioxide skeleton via the condensation with *o*-chloro sulfonyl chlorides.

This condensation resulted in the formation of regioisomers of fused benzimidazothiadiazine under different reaction conditions. These benzimidazothiadiazine 5,5-dioxides were utilized as the building blocks to synthesize the guanidine-fused isocoumarin framework through metal-catalyzed reactions.[13,14] Following this strategy, an acid group of imidazothiadiazine was used as a directing group to build a new class of pentacyclic heterocycles via oxidative annulation with internal alkynes. To

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the best of our knowledge, this is the first application of such annulation on a complex system that can access highly diversified pentacyclic isocoumarin derivatives.

The N-1-substituted 2-aminobenzimidazoles **5** were obtained from 4-fluoro-3-nitrobenzoic acid (see Scheme S1). The reaction of 2-aminobenzimidazoles **5a** with 2-chlorobenzenesulfonyl chlorides **6b** (R^3 = 6-Cl) in dichloromethane at ambient temperature afforded two products, **7j** (72%) and **9j** (3%). The formation of the two sulfonamides was due to the nucleophilic attack of the ring nitrogen and the amino group of benzimidazole on the sulfonyl chloride.[15] The difference between the two isomeric sulfonamides lies in the linkage of the sulfone moiety with the nitrogen. The sulfone moiety of **9j** is linked to azomethine nitrogen, which was confirmed by its X-ray structure[16] (Figure 2). The second step of sulfonamide

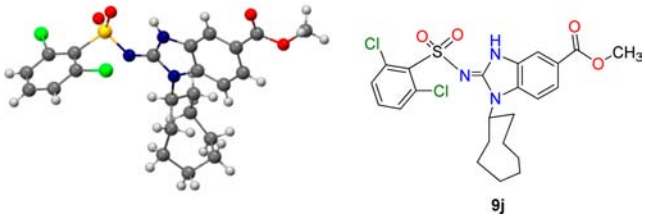
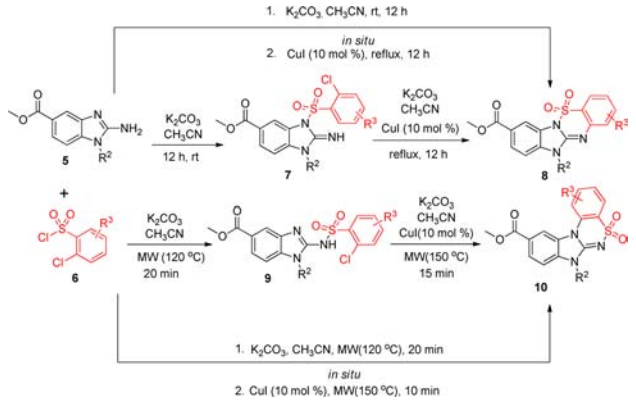


Figure 2. ORTEP diagram of sulfonamide **9j**.

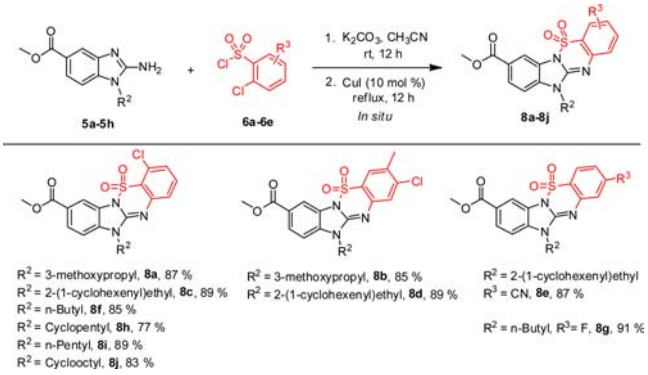
cyclization relies on an intramolecular aromatic nucleophilic substitution (S_NAr) reaction by an *ipso* chloro displacement to C−N bond formation. Therefore, benzothiadiazine 5,5-dioxide **8** was synthesized in refluxing acetonitrile for 12 h with CuI (10 mol %) and K_2CO_3. However, under microwave conditions (150 °C, CH_3CN) for 15 min, the isomeric sulfonamide **9** yielded S_NAr product **10** (Scheme 1). This type of regioselectivity is quite unusual and is revealed for the first time in the literature.

Scheme 1. Reaction of 2-Aminobenzimidazoles with 2-Chlorobenzene Sulfonyl Chlorides



After successful exploration of a stepwise N-sulfonylation and an intramolecular S_NAr reaction, all of our attempts failed to achieve regioselectivity in a single step because the mixtures of the regioisomers were isolated along with the formation of amidine **11** as a minor product[16] (Figure S2). Hence, the tunable reaction conditions were then studied to produce either intermediate regioisomers **7** or **9** selectively by using various solvents and bases. An intermediate sulfonamide **7** was found to form exclusively at room temperature with anhydrous potassium carbonate in acetonitrile. In the next step, the same reaction mixtures were refluxed for another 12 h with in situ addition of CuI (10 mol %) to produce desired product **8** in good yield. Therefore, this two-step, one-pot reaction provided direct access to the construction of the novel benzimidazo[1,2-*b*][1,2,4]thiadiazine 5,5-dioxide **8**. After that, the substrate scope was studied using differently substituted benzimidazoles **5** with sulfonyl chlorides to produce a diversified library in good yields (Scheme 2). The ORTEP diagram[16] for compound **8a** is depicted in Figure 3, and the proposed mechanism for the formation of these products is included in Scheme S3.

Scheme 2. Synthesis of Benzimidazo[1,2-*b*][1,2,4]thiadiazine 5,5-Dioxide 8



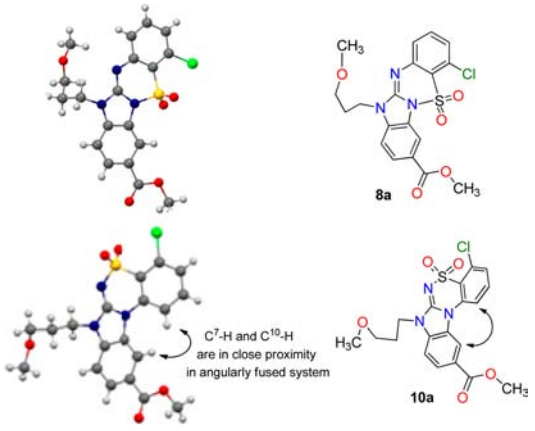


Figure 3. ORTEP diagrams of compounds **8a** and **10a**.

Subsequently, efforts were made to find the reaction conditions to address the selectivity for regioisomer **9**. The best outcome was obtained when benzimidazole and aryl sulfonyl chloride reacted in acetonitrile with anhydrous K_2CO_3 under MW irradiation at 120 °C for 20 min to form only intermediate **9** in good yields. Further treatment of sulfonamide **9** in the same pot with in situ addition of CuI (10 mol %) afforded angularly fused benzothiadiazine **10** in MW heating (150 °C) for an additional 15 min (Scheme 3). The X-ray structure for compound **10a** was confirmed, and the ORTEP diagram is presented in Figure 3.[16] An important difference between the two isomers is the spatial proximity, reflected in the ORTEP diagrams. The two aromatic protons C^7-H and C^{10}-H in the angular isomer **10a** are in close proximity, whereas this is not possible in the linear isomer **8a** (Figure 3).

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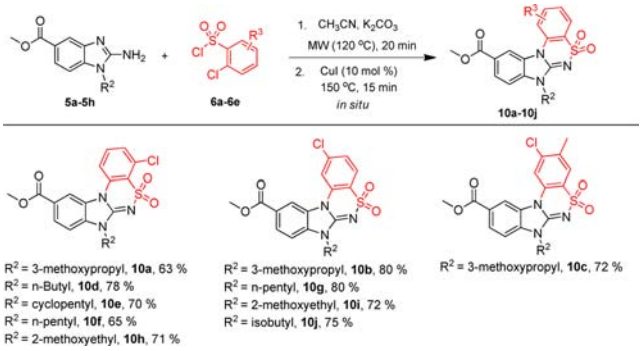
Scheme 3. Microwave-Assisted Synthesis of Benzimidazo[2,1-*c*][1,2,4]thiadiazine 5,5-Dioxide 10



This investigation discovered a unique N/S bond formation followed by a S_NAr reaction that demonstrates a structural sensitivity toward thermal and microwave conditions, leading ultimately to linear and angularly fused tertracyclic framework systems, respectively. This paper is the first report of the construction of this type of differently fused tetracyclic molecules under two reaction condition variations.

Next, we planned to expand the scope of the library by utilizing the acidic forms of benzothiadiazine derivatives. Several attempts failed to generate these acids under base-catalyzed hydrolysis because the N−SO_2 bond presented in ester **8a** was cleaved readily prior to the ester group in under basic conditions. Thus, the benzyl ester moieties of **16a−e** and **17a−e** were prepared (Scheme S2) as debenzylation was successfully carried out on palladium on charcoal through hydrogenolysis to produce acid forms **18a−e** and **19a−e** in 60−80% yields (Scheme S2). This study, aiming to synthesize pentacyclic compounds with a rare combination of guanidine, sultam, and isocoumarin templates, began with the condensation of an internal alkynes **20a−e** with acids **18** and **19**. The best result was obtained using catalyst $[Cp^*RhCl_2]_2$ (5 mol %), an oxidant $Cu(OAc)_2.H_2O$ (20 mol %) and an additive $AgSbF_6$ (10 mol %) in DMF at 65 °C for 6 h, resulting in 76% yield of the desired product (Table S1, entry 13). This catalytic system was developed earlier by Satoh and Miura.[13c] The detailed optimization study is summarized in the Supporting Information (Table S1). The outcome of our studies was confirmed by proton NMR analysis because two easily predictable singlets were observed in the aromatic region of the protons next to the isocoumarin linkage.

This result was also supported by X-ray crystal analysis[16] (Figure 4). The plausible reaction mechanism for the formation of these annulated products is described (Scheme S5). The "−SO_2" group next to the ring "N" atom of imidazole in acid **18** did not act as a directing group to assist in C^{21}−H bond activation, *ortho* to the acid group instead of activating C^7−H bond, yielding an annulated product **21** selectively.

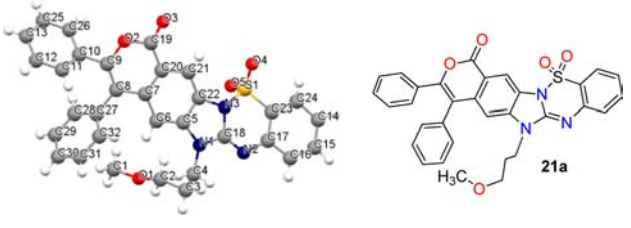
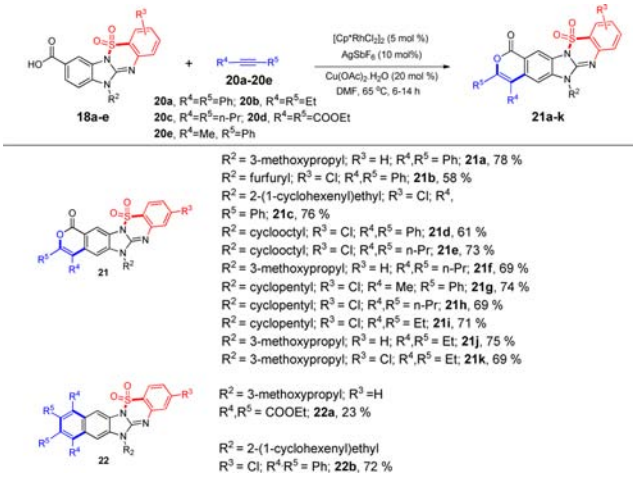


Figure 4. ORTEP diagram of compound **21a**.

A library of linearly fused benzimidazoisochromenothiadiazinone 12,12 dioxides **21a−d** were synthesized using our established reaction conditions (Scheme 4). The R^2 substituent

Scheme 4. Synthesis of Guanidine-Fused Derivatives of Isocoumarin 21 and Naphthalene 22



of acids **18** had little effect on the yield of the cyclized products because the heteroaromatic substituent produced 58% yield of **21b**, and a bulkier cyclooctyl substituent afforded 61% yield of **21d**. Furthermore, the use of symmetrical aliphatic internal alkynes 3-hexyne **20b** and 4-octyne **20c** yielded a variety of isocoumarins **21e−k** using the present method. In some of the cases, dechlorinated product was observed. Upon employing an alkyne with electron-withdrawing group **20d**, surprisingly, the benzonaphthoimidazothiadiazine derivative **22a** was isolated with a 23% yield with the recovery of starting material. The naphthalene derivative **22b** was obtained during the optimization of reaction conditions (Table S1, entry 9). Treatment of asymmetric alkynes, such as 1-phenyl-1-propyne **20e** with acid, was observed to produce only one isomer **21g** (Supporting Information).

Similarly, angularly fused benzimidazoisochromenothiadiazinone 5,5-dioxides **23** were synthesized with the acid forms of **19** under the same reaction conditions (Scheme 5). Under these circumstances, the use of diphenyl acetylene **20a** delivered a good yield of products; however, the use of a heteroaromatic R^2 substituent on an acid resulted in an inferior yield (58%, **23f**). The cyclooctyl group (R^2) of acid did not result in any product because of steric hindrance at the reaction site.

On the other hand, a similar bulky group (R^2) resulted in only 13% of product **23j** when 3-hexyne was subjected to annulation. Next, aliphatic internal alkynes 3-hexyne and 4-octyne were found to provide good yields. The dechlorinated product **23d** was isolated in 15% yield along with the desired product **23c**. The benzonaphthoimidazothiadiazine derivative **24a** was synthesized under optimized conditions (Table S1, entry 9) with 61% yield. For the regioisomer **19**, the "−SO_2" group renders away and should not take part in such C^{21}−H bond activation in our opinion. We obtained the planar, linear products in both cases with C^7−H activation only over a presumed C^{21}−H activation.

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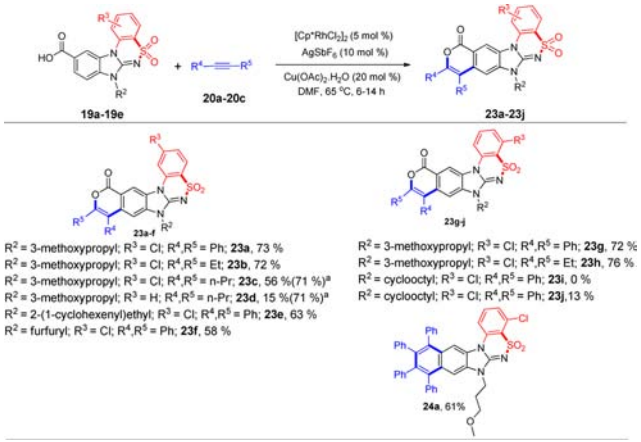
Scheme 5. Synthesis of Benzothiadiazine-Fused Isocoumarins 23 and Naphthalene 24



In conclusion, we have discovered a novel one-pot, two-step domino reaction for the scaffold-fused synthesis of benzimidazothiadiazine dioxides. This is the first report of the synthesis of unique regioisomers through the [3 + 3] approach where the influence of reaction conditions on the regioselective formation of a product is addressed. This challenge has been achieved with unusual tethering of nitrogen on 2-aminobenzimidazole with chloro sulfonyl chloride selectively in conventional heating and MW irradiation. The acid forms of both regioisomers were utilized efficiently to build a novel pentacyclic isocoumarin framework. The guanidine-fused isocoumarin was constructed via rhodium(III)-catalyzed dehydrogenative oxidative annulation with various aromatic and aliphatic internal alkynes. Three points of diversity have been introduced to increase the chemical space of target molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01408.

Spectroscopic data (^{1}H and ^{13}C NMR, HRMS) of essential representative intermediates **12**−**19** and final compounds **8a**−**j**, **10a**−**j**, **21a**−**n**, **22a**,**b**, **23a**−**j**, and **24a** (PDF)

X-ray data for **9j** (CIF)

X-ray data for **11** (CIF)

X-ray data for **8a** (CIF)

X-ray data for **10a** (CIF)

X-ray data for **21a** (CIF)

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Notes

The authors declare no competing financial interest.

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(16) The crystal data have been deposited at the Cambridge Crystallographic Data Centre (CCDC nos. CCDC 845109, 845110, 1458960, 1480161, and 1480163). Copies of the data can be obtained free of charge via www.ccdc.ac.uk/conts/retrieving.html or CCDC, 12 Union Rd, Cambridge CB2 1EZ, U.K.

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