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Three-Component Coupling Approach for the Synthesis of Diverse Heterocycles Utilizing Reactive Nitrilium Trapping

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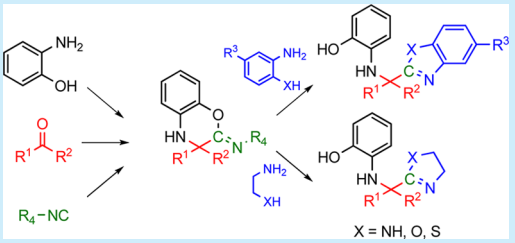
Supporting Information

ABSTRACT: The formation of an unexpected heterocyclic scaffold, a benzoxazole, in a three-component reaction between a ketone, isocyanide, and 2-aminophenol was encountered. This reaction involved a benzo[*b*][1,4]oxazine intermediate resulting from intramolecular attack of the aminophenol hydroxyl group on the nitrilium ion. Unlike previous literature examples, the trapped nitrilium benzo[*b*][1,4]oxazine could readily be subjected to ring opening with bis-nucleophiles. The reaction scope includes simple linear as well as complex cyclic ketones and substituted 2-aminophenols. A representative benzoxazole product could be further diversified to yield drug-like compounds.

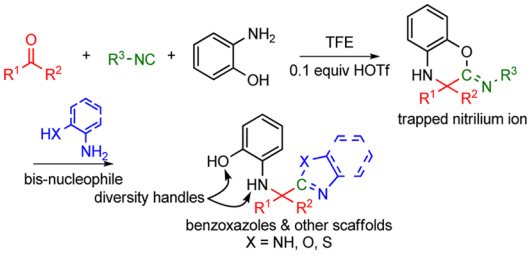


Multicomponent reactions (MCRs) involve the simultaneous reaction of more than two starting materials to form a single product.[1] The extreme variety of products that can be achieved through the reaction of readily available reagents as well as their one-pot nature and high atom efficiency make MCRs suitable for the synthesis of highly diverse drug-like libraries.[2] Isocyanide-based reactions form the backbone of today's MCR armada, among which the most widely applied examples commonly employ amines, aldehydes or ketones, isocyanides, carboxylic acids, and phenols.[3]

Heterocycles play a critical role in the design and synthesis of bioactive small molecules: the vast majority of marketed drugs contain at least one heterocyclic ring. Numerous nitrogen-containing heterocycles including dihydrothiazoles, benzoxazoles, benzothiazoles, and benzimidazoles possess biological activity.[4] The synthesis of heterocycles is traditionally accomplished through multistep routes and/or harsh reaction conditions, particularly of benzoxazoles,[5] and while MCR approaches can also be taken,[6] there is a need for a more resource-efficient, preferably one-pot method for their synthesis.[7] Metal catalyzed insertions of isocyanides leading to heterocycles are known and usually utilize harsh conditions and have somewhat limited scope in terms of diversity.[8]

Herein we report a novel MCR between a ketone, 2-aminophenol, and isocyanide that leads to the synthesis of benzoxazoles and other heterocycles (Scheme 1). The postulated reaction route proceeds via a benzo[*b*][1,4]oxazine (benzoxazine intermediate). The formation of benzoxazine occurs by intramolecular trapping of the reactive nitrilium ion by the adjacent phenolic hydroxyl of 2-aminophenol. While trapping of nitrilium species by heteroatoms is a known process,[9] the novelty of our approach is the reactive nature of the trapped intermediate. Owing to its reactivity, the oxazine ring of the trapped nitrilium intermediate can be opened up by a second molecule of aminophenol or other bis-nucleophiles leading to the elimination of an isocyanide-derived amine, finally yielding benzoxazoles or other heterocyclic scaffolds. The reaction generates two additional points of diversity that were utilized to synthesize various bis-heterocyclic scaffolds.

Scheme 1. Synthesis of Heterocyclic Scaffolds Using Our Three-Component Reaction



While performing a Ugi four-component reaction in 2,2,2-trifluoroethanol (TFE) with 1 equiv of 2-aminophenol, 1 equiv of *N*-methyl-4-piperidone, 1 equiv of 4-methoxyphenyl isocyanide, and 1 equiv of acetic acid at 55 °C, an unusual heterocyclic (benzo[*d*]oxazol-2-yl)-1-methylpiperidine (benzoxazole) product **1** in 50% yield with only trace amounts of

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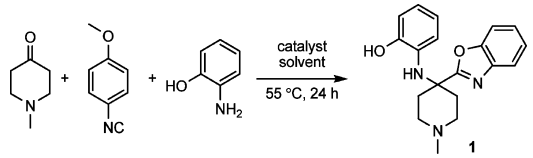
the expected Ugi four-component reaction product was observed.

Because the carboxylic acid substrate was not incorporated into the product, the reaction was carried out without the addition of any carboxylic acid. Benzoxazole **1** was obtained again, suggesting that the product formation proceeded via a three-component MCR between 2-aminophenol, isocyanide, and ketone. The formation of benzoxazole **1** was then optimized (Table 1). By using 3 equiv of 2-aminophenol, the

Table 1. Yield of Benzoxazole 1 under Different Reaction Conditions



entry	catalyst (equiv)	solvent	yield [%]
1	none	MeOH	0
2	none	TFE	84
3	Sc(III)OTf (0.1)	TFE	58
4	Zn(II)OTf (0.1)	TFE	62
5	HOTf (0.1)	TFE	100
6	HOTf (0.1)	MeOH	82
7	HOTf (0.1)	toluene	24

yield of the isolated product increased to 84% (entry 2). Performing the reaction at room temperature afforded lower yields (42%). Similarly, heating the mixture to 80 °C gave no improvement in yield. The role of solvent in product formation was investigated next, and to our surprise the reaction failed in all solvents (including methanol, the solvent of choice for traditional MCRs) except TFE, suggesting the slight acidity of the solvent (pK_a = 12.37) played a crucial role in the reaction. Because MCRs have been shown to be catalyzed by acids,[10] the reaction was investigated using an array of Lewis and Brønsted acids. Transition metal triflates gave no advantage in yields. However, using 0.1 equiv of trifluoromethanesulphonic acid (HOTf) afforded quantitative yields of benzoxazole **1** (entry 5). The HOTf-catalyzed reaction also afforded a high yield (82%) in methanol (entry 6), a solvent in which benzoxazole formation had previously failed. The acid catalyzed reaction in toluene yielded 24% (entry 7) product suggesting that, besides acid catalysis, a polar solvent is preferred for this reaction to proceed to completion.

With the optimized conditions in hand the scope of this reaction was investigated by using different ketones and substituted 2-aminophenols (Scheme 2). The desired benzoxazole products (**2**−**8**, **9a**−**d**) were obtained in good yields in most cases. The reaction was effective for a variety of ketones including the complex, multifunctional semisynthetic natural product-like naloxone (**7**), a clinically used opioid antagonist, highlighting the good functional group tolerance of this reaction. The scope of this heterocycle-forming MCR was investigated using various isocyanides (Table 2).

While 4-methoxyphenyl isocyanide provided the best yield (entry 2), nearly all other isocyanides were also effective in the reaction, except 2,6-dimethylphenyl isocyanide (entry 7). It should be pointed out that the isocyanide contributes only one carbon atom toward benzoxazole **1**; therefore the reaction outcome is independent of the nature of isocyanide used. The

Scheme 2. Scope of Heterocycle-Forming MCR with Various Ketones and Substituted 2-Aminophenols

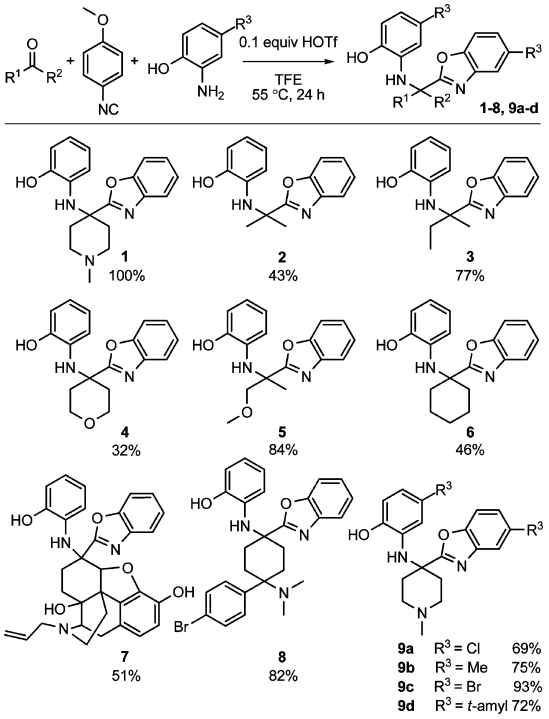
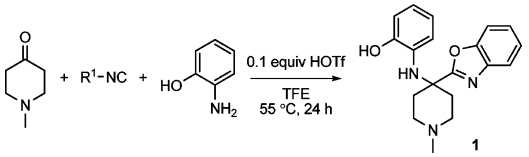


Table 2. Yield of Heterocycle-Forming MCR with Different Isocyanides



entry	R^1	yield [%]
1	cyclohexyl	70
2	4-OMe-Ph	100
3	4-F-Ph	28
4	naphth-2-yl	59
5	*t*Bu	90
6	1-adamantyl	61
7	2,6-diMe-Ph	0

aryl or alkyl amine moiety acts as the leaving group, leading to an insertion of only the isocyanide carbon into the benzoxazole moiety.

We were surprised to find that 2,6-dimethylphenyl isocyanide, instead of benzoxazole **1**, yielded a spiro[benzo[*b*]-[1,4]oxazine]imine (benzoxazine) scaffold **10** in good yield (Table 3). The synthesis, isolation, and structure elucidation of this derivative provided us the first clues about the mechanism of this reaction (Figure 1).

When another, albeit sterically somewhat less hindered isocyanide, 2-chloro-6-methyl isocyanide, was used, **11** was isolated, which possessed the same benzoxazine scaffold as **10**. The reaction, however, also afforded benzoxazole **1**. Furthermore, the yield for **11** was significantly lower than that of **10**, highlighting the importance of steric hindrance in stabilizing the benzoxazine structure. Benzoxazines (**12** and **13**) were isolated even when sterically nonhindered isocyanides were

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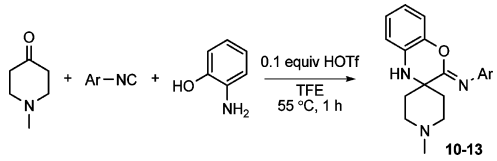
Table 3. Isolation of Trapped Nitrilium Intermediates, Benzoxazines 10−13



Ar	product	yield (%)
2,6-diMe-Ph	**10**	79
2-Me-6-Cl-Ph	**11** + **1**	37 (4)[a]
4-OMe-Ph	**12** + **1**	39 (24)[a]
naphth-2-yl	**13** + **1**	33 (12)[a]

[a]Yield of **1**.

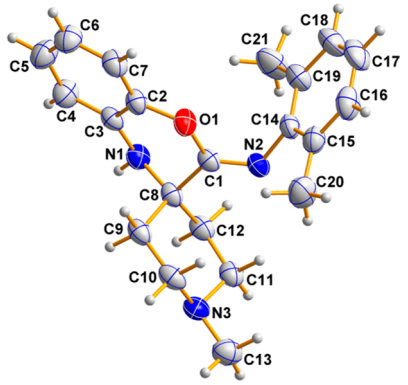
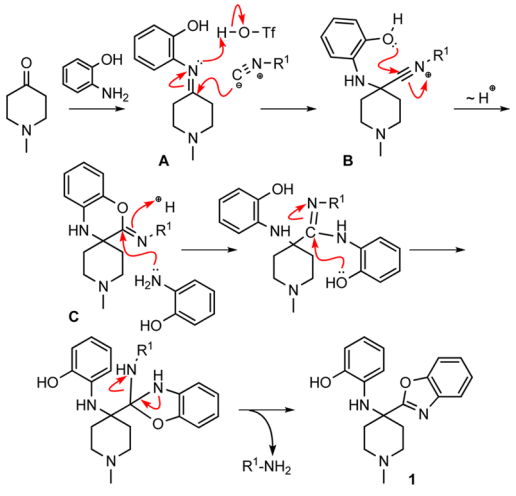


Figure 1. Molecular structure of benzoxazine intermediate **10**. Another conformer with a slightly different conformation was identified in the crystal structure (shown in the Supporting Information).

involved, in lower yields. A mixture of benzoxazole **1** and the appropriate benzoxazine was observed in these cases.

We hypothesized that benzoxazine **12** was an intermediate in the reaction route leading to benzoxazole **1**. The following reaction mechanism for the formation of benzoxazoles was envisioned (Scheme 3): the ketone first forms a Schiff base (imine, **A**) with 2-aminophenol, which in turn is activated by the acidity of the system (the acid catalyst HOTf and/or the solvent TFE) thereby facilitating an attack by the isocyanide yielding the highly reactive nitrilium **B**. The phenolic OH of 2-aminophenol then participates in an intramolecular nucleophilic attack on the reactive nitrilium carbon, thus trapping the nitrilium to give the benzoxazine intermediate **C**.

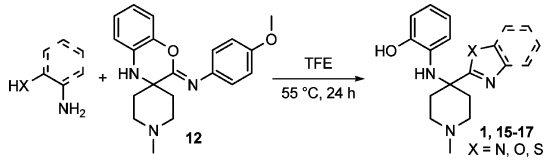
Scheme 3. Proposed Mechanism for the Formation of Benzoxazole 1



While **C** could be isolated (**10−13**), we found that it is very susceptible to nucleophilic attack by a second molecule of the bis-nucleophile 2-aminophenol. There is literature precedence for the intramolecular trapping of the nitrilium ion.[9] It must be noted that products formed in most cases are stable and easily isolable, while benzoxazines (**11−13**) in the present case are extremely reactive to nucleophiles. The unique, reactive nature of this intramolecular nitrilium trapping allowed us to utilize benzoxazine intermediates to synthesize substituted benzoxazoles and other heterocyclic systems as shown later.

To test our proposed mechanism that the benzoxazine **C** is an intermediate in the synthesis of benzoxazoles, intermediate **12** was reacted with 2 equiv of 2-aminophenol in the presence of 0.1 equiv of HOTf in TFE, mimicking our one-pot reaction; benzoxazole **1** could be isolated in good yields (Table 4).

Table 4. Conversion of Benzoxazine Intermediate 12 to Diverse Heterocycles with Bis-Nucleophiles



bis-nucleophile	product	yield (%)
2-aminophenol	**1**	87
2-amino-4-chlorophenol	**14**	63
1,2-diaminobenzene	**15**	98
2-aminothiophenol	**16**	93
cysteamine	**17**	44

4-Chloro-2-aminophenol was also reacted with **12**. Thus, a benzoxazole with a chloro substituent (**14**) was isolated increasing the diversity of this reaction. The scope was further enhanced by reacting the isolated benzoxazine intermediate with a series of bis-nucleophiles including 1,2-diaminobenzene, 2-aminothiophenol, and cysteamine to synthesize benzimidazole, benzothiazole, and dihydrothiazole derivatives (**15−17**), respectively. Owing to the hindered sterics of the system, benzoxazine **10** derived from sterically hindered 2,6-dimethylphenyl isocyanide was significantly more resistant to nucleophilic attack by bis-nucleophiles. Reactions at 55 °C failed in most cases, and only low conversion to the corresponding heterocycles was seen even at 85 °C.

To enhance the diversity and thus the possible biological relevance of the benzoxazole scaffold we decided to exploit the free phenolic OH and secondary aromatic amine of **1** to make second generation derivatives (Figure 2). The NH and the OH were cyclized using carbonyldiimadazole to make the bis-heterocyclic **18** carrying a benzoxazolone ring.[11] The phenolic OH was also alkylated (**22**), carbamoylated (**24**), acylated (**25**), and converted to triflate. The triflate was in turn taken into Suzuki coupling[12] with 2-bromophenylboronic acid, followed by Buchwald−Hartwig amination[13] to generate a carbazole scaffold **21**.[14] The versatile leaving group triflate could be converted to a nitrile[15] (**23**) which opens up routes to

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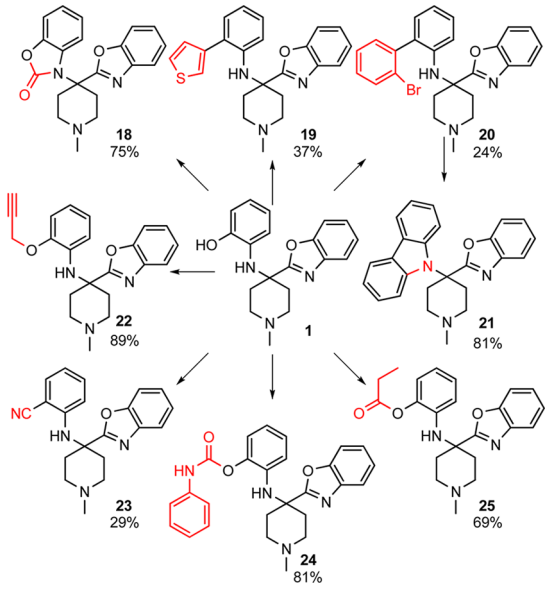

Figure 2. Diversification of the novel benzoxazole scaffold **1**.

countless other derivatives well beyond the scope of the present publication (amines, amides, tetrazoles, halogens).

In summary, we discovered a convenient, triflic acid catalyzed, isocyanide-based heterocycle-forming three-component reaction between 2-aminophenols, isocyanides, and ketones that leads to benzoxazoles and other heterocycles. The reaction progresses via a benzoxazine intermediate formed by intramolecular nucleophilic trapping of the reactive nitrilium intermediate by an adjacent phenolic group. Previous literature examples of nitrilium trapping yielded stable products, whereas in our case the trapped intermediates could be opened up by bis-nucleophiles. The reactivity of benzoxazine to bis-nucleophiles was leveraged to synthesize an array of heterocyclic scaffolds including benzimidazoles, dihydrothiazoles, and benzothiazoles. The reaction showed good functional group tolerance and is compatible with different ketones and aminophenols, ideal for the generation of molecule libraries under mild reaction conditions. The reactivity of the phenolic hydroxyl and the aromatic secondary amine was further exploited to diversify the scaffolds. Our future studies will focus on investigating and controlling the stereoselectivity of this reaction pathway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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