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A simple and efficient one step synthesis of benzoxazoles and benzimidazoles from carboxylic acids

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Abstract—Benzoxazoles or benzimidazoles can be rapidly and efficiently synthesized from a variety of carboxylic acids with 2-aminophenols or 1,2-phenylenediamines in one simple step, respectively. The use of commercially available PS-PPh_3 resin combined with microwave heating delivered a variety of benzoxazoles and benzimidazoles in high yields and purities.

Lead optimization is one of the most critical phases within the drug discovery paradigm. Lead compounds must display favorable properties for further development, including desirable chemical features that can facilitate medicinal chemistry optimization efforts.[1] Frequently, a critical part of the lead molecular skeleton has been studied and shown to be crucial for a particular biological activity, while other parts of the molecular skeleton need chemical modifications so as to achieve the desired properties of a development candidate. Such processes include fine tuning the activity through SAR studies and improving the selectivity and pharmacokinetics of the lead compound.

Over the past decade, focused libraries have been successfully utilized throughout the lead optimization process in order to incorporate modifications to targeted regions of the lead molecular skeleton, which in turn, helps to establish initial SAR studies and determine future optimization strategies. Frequently, analogs bearing this common molecular skeleton differ only by discrete and different substituents. It is in this context then, that in order to increase the chance of finding an optimal drug candidate, our goal has been to maximize the structural complexity and skeletal diversity of a library whilst still maintaining critical pharmacophores, hence differing from the traditional focused library approach.

To this end, we have been actively involved in the preparation of diverse biologically relevant heterocycles from precursors containing common chemical functionalities. In recent letters, we have reported general and efficient reaction protocols for the preparation of 1,2,4-oxadiazoles **1**[2] and 1,3,4-oxadiazoles **2**.[3] Notably, both methods start from easily accessible carboxylic acids as the common precursor and utilize the same reagent combination PS-PPh_3/CCl_3CN[4] under microwave heating conditions. The key advantage of this approach is that from a common carboxylic acid scaffold, by simply using common reagents and a common operation, distinct structures can be easily accessed by utilizing a matrix of distinct monomer units (Fig. 1). In this letter, we report the further extension of our strategy to synthesize benzoxazoles **3** and benzimidazoles **4**, both of which

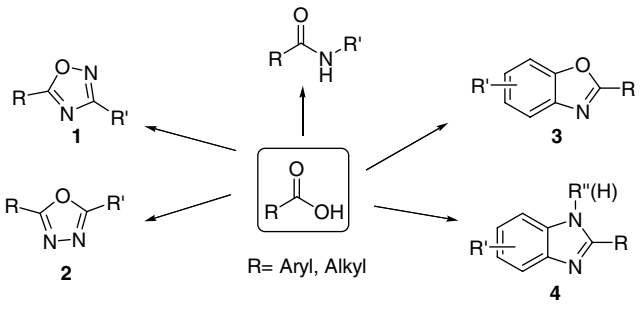

Figure 1. Syntheses of diverse structural motifs from carboxylic acid with PS-PPh_3/CCl_3CN.

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are important structural motifs in drug discovery programs, from carboxylic acids (Fig. 1).[5]

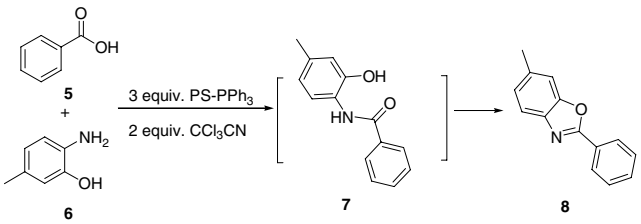
Common synthetic routes to benzoxazoles and benzimidazoles have typically involved coupling of carboxylic acids or their derivatives with 2-aminophenols or 1,2-phenylenediamines in the presence of strong acids at high temperatures.[6] As mentioned previously, we have shown that the reagent combination of PS-PPh_3 and CCl_3CN is particularly effective in enabling the transformation of carboxylic acids into their corresponding 1,2,4-oxadiazole and 1,3,4-oxadiazole derivatives in a facile manner. We were delighted to find that the same reagent combination also worked equally well for the expeditious generation of benzoxazoles and benzimidazoles from carboxylic acids.

Benzoic acid **5** and 2-aminophenol **6** were chosen for the model study. When the reaction was carried out in CH_2Cl_2 or CH_3CN at room temperature for an extended 20 h period, only the acylation product **7** was observed by LC/MS analysis along with other unidentified peaks. At higher temperature (75 °C) in CH_3CN, we were able to obtain the desired product although the reaction was not clean as observed from crude LC/MS analysis. Optimal result was obtained when the reaction mixture was heated in the microwave at 150 °C for 15 min in acetonitrile. Inferior results were obtained when either the reaction temperature was lowered to 140 °C or the reaction time was cut to 10 min. With 1.5 equiv of CCl_3CN, both the acylated product **7** and the cyclized product **8** were observed by LC/MS analysis of the crude mixture. Exploitation of microwave technology allowed us to quickly identify the optimized reaction conditions within a short time frame (Table 1).

With this protocol at hand, we quickly found that this one step procedure worked well for a variety of alkyl and aryl carboxylic acids as well as a diverse selection of 2-aminophenols (Table 2). Of particular note is the fact that the reaction was very easy to workup by simple filtration of the resin and evaporation of the solvents. In many cases, simple flash chromatography afforded the desired benzoxazole in high purity.[7]

Naturally, having now developed a general and efficient protocol for benzoxazole synthesis starting from 2-aminophenol and carboxylic acid, we wondered if substitution of the 2-aminophenol scaffold with 2-aminothiophenol and 1,2-phenylenediamines, would allow access

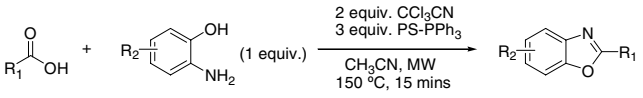
Table 1. Optimization of reaction conditions for the synthesis of representative benzoxazole **8**

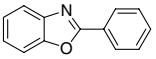
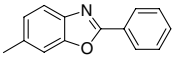
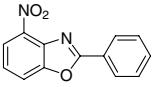
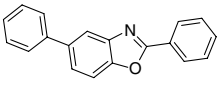
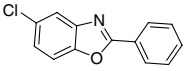
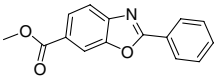
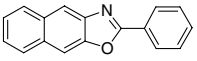
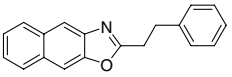
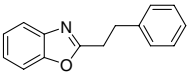
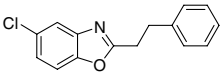
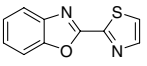
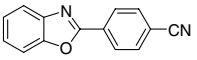
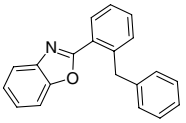
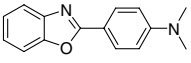


Entry	Reaction condition	**7** (%)[a]	**8** (%)[a]
1	CH_2Cl_2, rt, >20 h	90	—[c]
2	CH_3CN, rt, >20 h	55	—[c]
3	CH_3CN, 75 °C, >14 h	15	80
4	MW, CH_3CN, 140 °C, 15 min	—[b]	70
5	MW, CH_3CN, 150 °C, 10 min	—[b]	80
6	MW, CH_3CN, 150 °C, 15 min	—[b]	97

[a] Conversion based on crude LC/MS analysis.
[b] The % conversion was not determined.
[c] Trace amount of 8 was observed.

Table 2. Synthesis of benzoxazoles from carboxylic acids and 1,2-aminophenol with PS-PPh_3/CCl_3CN

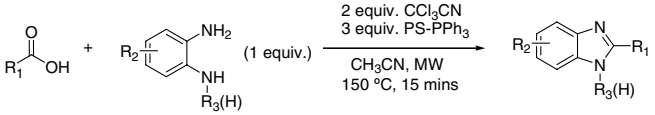


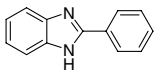
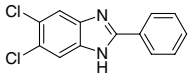
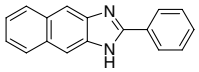
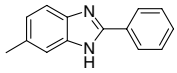
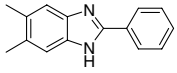
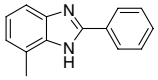
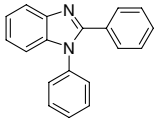
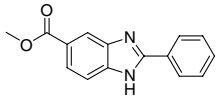
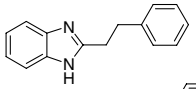
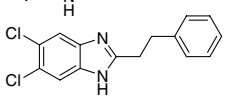
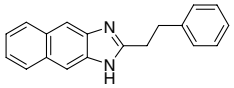
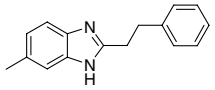
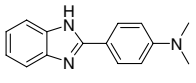
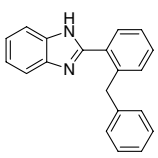
Entry	Product	Yield[a] (%)
1		97
2		93
3		79
4		85
5		94
6		83
7		89
8		77
9		85
10		93
11		94
12		86
13		80
14		91

[a] Isolated yield after purification.

to the corresponding benzthiazole and benzimidazole derivatives. In practice, with 2-aminothiophenol under the same reaction conditions, the desired benzthiazole was obtained along with several side products as shown from the crude LC/MS analysis and the isolated yield was low. No further attempts were made to optimize the protocol with this reagent system and attention was focused on the benzimidazoles. Gratifyingly, with 1,2-phenylenediamines, again under the same reaction conditions, benzimidazoles were obtained with high yields and purities. As with the benzoxazoles, this protocol worked for a variety of carboxylic acids and 1,2-phenylenediamines to afford the corresponding benzimidazole in good yields in a single step (Table 3).[7] Significantly, fair to good yields of the corresponding benzimidazoles were also obtained with electron deficient 4,5-dichlorobenzene-1,2-diamine (Table 3, entries 2 and 10), which is generally a recalcitrant substrate for acylation paradigms.

Table 3. Synthesis of benzoxazoles from carboxylic acids and 1,2-phenylenediamine with PS-PPh_3/CCl_3CN



Entry	Product	Yield[a] (%)
1		79
2		76
3		94
4		87
5		89
6		85
7		93
8		80
9		90
10		90
11		83
12		89
13		80
14		69

[a] Isolated yields after purification.

In summary, we have developed an efficient and general reaction protocol for the synthesis of benzoxazoles and benzimidazoles starting from carboxylic acids. The generality of these reactions, as demonstrated in Tables 2 and 3, is important for library analog production as diverse substituent patterns are often used with one set of reaction conditions in a single library. More importantly, the methods we have developed fit into our overall strategy where starting from a common precursor, in our case a carboxylic acid, using a combination of the same reagents and a common operation, multiple heterocyclic scaffolds with distinct structure complexity and diversity can be easily accessed. We believe that this approach combines the advantages of both focused library synthesis and diversity-oriented synthesis. Because of the generality of the reaction protocols that we have been developed, thorough SAR studies are possible within the structure skeletons that are constructed. More importantly, diverse structure skeletons can also be obtained within one library to greatly facilitate either a hit to lead or the lead optimization process.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.05.052.

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3. Wang, Y.; Sauer, D. R.; Djuric, S. W. *Tetrahedron Lett.* **2006**, *47*, 105–108.
4. For the use of CCl_3CN/PS-PPh_3 in acylation, see: (a) Jang, D. O.; Park, D. J.; Kim, J. *Tetrahedron Lett.* **1999**, *43*, 5323–5326; (b) Buchstaller, H.; Ebert, H. M.; Anlauf, U. *Synth. Commun.* **2001**, *31*, 1001–1005.
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7. General procedure: A Smith process vial (0.5–2 mL) was charged with a stir bar. To the vessel were added 0.2 mmol of the carboxylic acid and 0.2 mmol of the 2-aminophenol or 1,2-phenylenediamine in 1.5 mL dry CH_3CN. 0.6 mmol PS-PPh_3 (3 mmol/g) was added to the reaction mixture followed by 0.4 mmol CCl_3CN. The reaction vessel was sealed and heated in microwave to 150 °C for 15 min. After cooling, the reaction vessel was uncapped and the resin was filtered and washed by additional CH_3CN and MeOH. The desired benzoxazole or benzimidazole was isolated by flash chromatography. All products thus obtained were greater than 98% pure as determined by LC/MS and ^1H NMR analysis.