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Synthesis of β-heteroaryl propionates via trapping of carbocations with π-nucleophiles

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ABSTRACT

A variety of heterocyclic alcohols and acetates were coupled with silyl ketene acetals and other π-nucleophiles in the presence of trimethylsilyl trifluoromethanesulfonate to provide an array of substituted β-heteroaryl propionates, including those with contiguous quaternary centers, as well as vinylogs thereof. This reaction also proceeds with high diastereoselectivity when the π-nucleophile bears a chiral auxiliary.

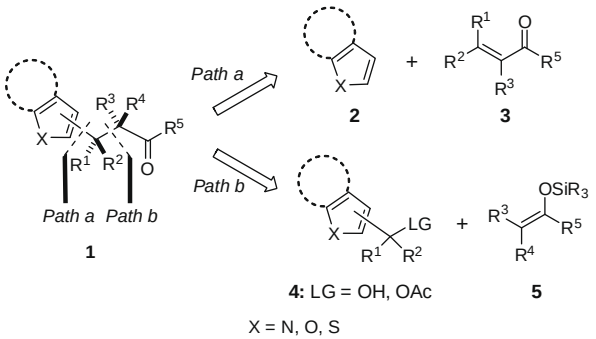
In the context of several ongoing projects in alkaloid synthesis, we were confronted with the task of preparing substituted derivatives of β-heteroaryl propionic acids of the general structure **1**. After examining the literature, it was apparent that there were two different approaches that might be applied to the synthesis of such compounds, and these are outlined in Scheme 1.

The first approach, which is depicted in Path a, involves the conjugate addition of electron-rich heteroaromatic rings to α,β-unsaturated carbonyl compounds via a process in which the heterocycle serves as the nucleophile (Scheme 1, Path a). This approach is well precedented in the literature, and methods for preparing both achiral and chiral products in high enantioselectivity are known.[1,2] The scope of these methods is, however, limited in several ways. For example, substitution occurs on the heteroaromatic ring *only* at those positions that are favored in classical electrophilic substitution reactions of electron-rich heterocycles with the vast majority of examples being pyrroles and indoles. The preparation of compounds of the general structure **1** (R^1, R^2 = alkyl) is also rather limited,[1b,3] whereas compounds such as **1** (R^3, R^4 = alkyl) appear to be inaccessible via this path.

The second option (Scheme 1, Path b) involves a S_N1-type reaction in which a compound bearing a benzylic-like leaving group undergoes ionization, typically in the presence of a suitable Lewis acid, and the resulting carbocation is trapped by a π-nucleophile. Although there are some examples of reactions of cations generated from a secondary thiophen-2-yl chloride,[4] furan-2-yl acetate,[5] and several heteroaryl carbinols,[6] the scope of this bond construction appears to be limited to relatively few combinations of heteroaromatic systems and π-nucleophiles. Moreover, there are no examples of the enantioselective synthesis of compounds of type **1** by this construction.

It was thus evident that there were limitations to existing methods for preparing compounds generally related to **1**, and there was no direct precedent for a number of possible bond-forming processes. After considering the available options, we concluded that the disconnection depicted in Path b offered the greatest opportunity to develop new chemistry and expand upon that which was known. We now report some results of our preliminary studies.

The first objective was to conduct two sets of exploratory experiments to examine the reactivity of indol-3-yl and indol-2-yl carbinol derivatives. Although precedent for the former construction was reported after we initiated these studies,[7] we are aware of no precedent for the latter. As a prelude to more general studies, we examined the Lewis acid-catalyzed reaction of the alcohol **6** with the silyl ketene acetal **7** under a variety of conditions to furnish **8**, eventually finding that the reaction proceeded in an optimized yield of 92% using THF as the solvent, 0.9 equiv of trimethylsilyl trifluoromethanesulfonate (TMSOTf) as the Lewis acid, and a reaction temperature of −40 °C (Scheme 2, method A).



Scheme 1.

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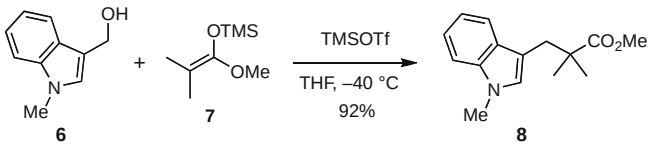
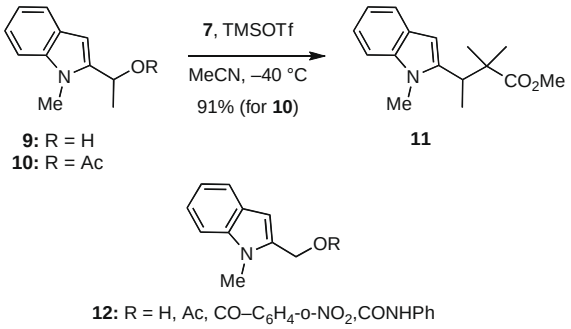


Scheme 2.

Encouraged by this result, the same conditions (method A)[7] were applied to the reactions of other indol-3-yl carbinols with several different π-nucleophiles in order to explore the scope of this route to indol-3-yl propionate derivatives (Table 1). As is evident from examination of the results in Table 1, the reaction works well with primary, secondary, and tertiary alcohols. The indole nitrogen atom may either be unsubstituted or may bear an alkyl residue such as a methyl group. Finally, π-nucleophiles having different substitution patterns at the reacting center may be employed. This feature enables the facile construction of not only quaternary centers, but also contiguous quaternary centers, arguably one of the most difficult challenges in synthesis.[8]

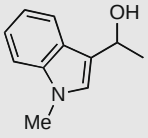
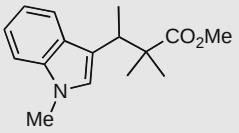
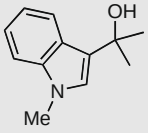
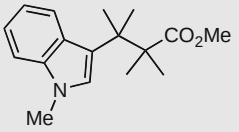
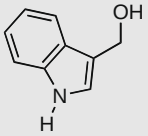
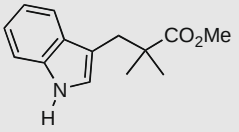
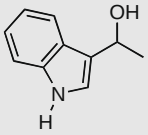
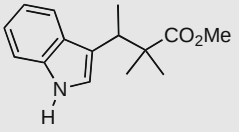
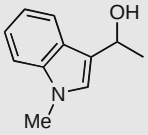
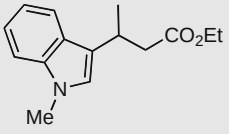
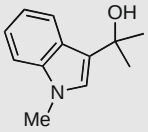
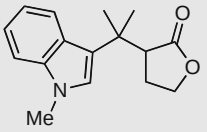
The optimized conditions for the reaction of **6** with **7** were then applied to the reaction of the indol-2-yl carbinol **9** with **7**, but **11** was obtained in low yield (Scheme 3). Reasoning that the low yield in this transformation might be a consequence of the decreased reactivity toward ionization of **9** relative to **6**, we thought that the corresponding acetate **10** might be more reactive. Accordingly, acetylation of **9** with acetic anhydride afforded **10**, which then underwent reaction with **7** under the previously defined conditions to give **11** in moderate yield. After a quick survey of different solvents and temperatures, it was found that the yield of **11** could be improved to 91% by changing the solvent to acetonitrile and by performing the reaction at –40 °C with one full equivalent of TMSOTf (method B).[9]



Scheme 3.

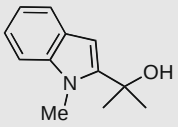
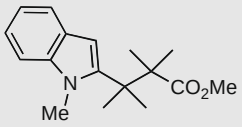
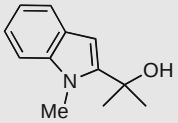
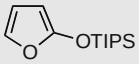
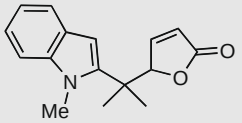
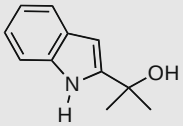
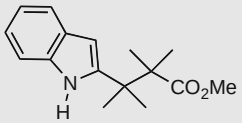
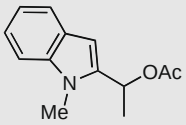
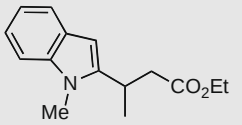
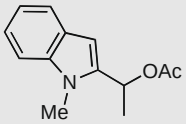
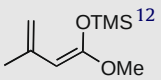
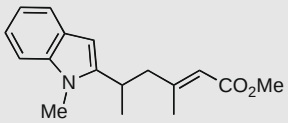
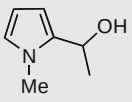
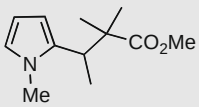
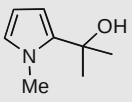
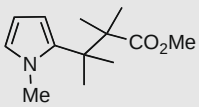
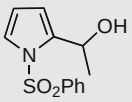
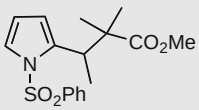
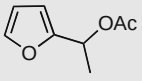
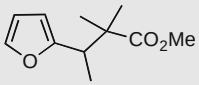
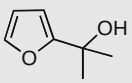
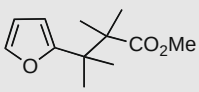
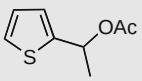
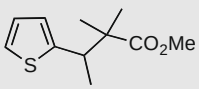
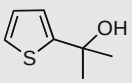
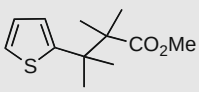
Having optimized the conditions for the reaction of **10** with **7**, the scope of this reaction was further explored (Table 2). The reaction works well with indol-2-yl, pyrrol-2-yl, furan-2-yl, and thiophen-2-yl carbinol derivatives. Although the presence of an *N*-sulfonyl group on a pyrrole is deactivating, carbon–carbon bond formation proceeds in modest yield (entry 8).[10] In general, the

Table 1
Lewis acid-catalyzed reactions of indol-3-yl carbinols with π-nucleophiles[7]

Entry	Alcohol	π-Nucleophile	Product	Yield (%)
1		**7**		93
2		**7**		95
3		**7**		76
4		**7**		78
5				87
6				77

reactions involving tertiary alcohols were most efficient (entries 1, 7, and 12), presumably owing to their relative ease of ionization. The reactions of secondary acetates were generally superior to those of their corresponding alcohols. Because the secondary acetates derived from pyrrol-2-yl carbinols are known to be unstable,[11] these were not examined as substrates. The reactions of primary alcohols appear to be more challenging. For example, in preliminary experiments, we found that Lewis acid-catalyzed reactions of **7** with the indol-2-yl carbinol derivatives **12** did not afford isolable quantities of the desired coupling product. It should be noted, however, that primary furan-2-yl acetates are known to participate in such reactions,[5] so our findings relative to **12** are clearly

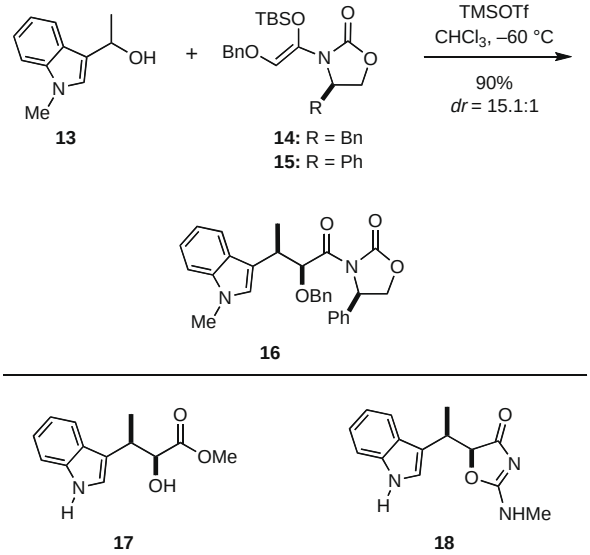
Table 2
Lewis acid-catalyzed reactions of heteroaryl carbinols with π-nucleophiles[9]

Entry	Alcohol	π-Nucleophile	Product	Yield (%)
1		**7**		93
2				88
3		**7**		77
4				68
5				47
6		**7**		49
7		**7**		88
8		**7**		42
9		**7**		62
10		**7**		45
11		**7**		79
12		**7**		84

not generally applicable to all primary heterocyclic carbinols. Suitable π-nucleophiles include not only simple enol derivatives such as **7,** but also cyclic and acyclic dienes (entries 2 and 5).

Having established that heteroaryl carbinol derivatives underwent facile reactions with several π-nucleophiles, we were inspired to explore such reactions with chiral π-nucleophiles in order to develop a diastereoselective variant of this process. That such a process might be feasible was supported by the findings of Fuentes and coworkers, who had shown that the presence of a chiral oxazolidinone on a π-nucleophile induced good diastereoselectivity in a reaction involving an *N*-acyl iminium ion and a π-nucleophile.[13] We first examined the reaction of the secondary alcohol **13** with the chiral π-nucleophile **14** in the presence of TMSOTf. Although this reaction proceeded in 76% yield, a mixture (4.4:1.6:1.6:1) of four stereoisomers was obtained. Toward achieving a higher level of diastereoselectivity, the enol derivative **15** was examined as a nucleophile. We were thus gratified that when **15** was allowed to react with **13**, a mixture (15.1:1) of stereoisomers was obtained in 90% yield from which **16** was isolated as the major product (Scheme 4). A crystal structure of **16** was obtained, thereby unequivocally establishing its stereochemistry.[14]

The efficient synthesis of **16** is noteworthy, because it illustrates the versatility of Path b in Scheme 1 and its potential for the enantioselective preparation of β-heteroaryl-α-hydroxy propionates, which are structural subunits of biologically interesting compounds. For example, **17**, which is the N-demethylated analog of **16**, may be envisioned as a precursor of the natural product (−)-indolmycin (**18**), which is an antibiotic that exhibits activity against *Staphylococci aureus*.[15,16] Hydroxy acids related to compounds like **16** are also useful precursors of depsi peptides, which may be used to probe hydrogen-bonding effects in bimolecular interactions involving proteins.[17] Furthermore, the reactions of **15** and other chiral π-nucleophiles with other heterocyclic carbinols or acetates could lead to a diverse array of β-heteroaryl-α-substituted propionate derivatives, including *inter alia*, unnatural amino acids.[18]



13 **14:** R = Bn **15:** R = Ph **16** **17** **18**

Scheme 4.

In summary, we have successfully coupled heterocyclic carbinols and their acetate derivatives with various π-nucleophiles in the presence of TMSOTf to deliver a number of β-heteroaryl propionate derivatives and vinylogs thereof, generally in yields exceeding 75%. The reaction can also be performed with high diastereoselectivity using chiral π-nucleophiles. Compounds with contiguous quaternary centers may also be easily prepared. This method will be useful for the synthesis of a wide variety of α,β-substituted heterocyclic propionates with defined stereocenters and alkyl and heteroatom substitution on the carbon backbone. The expansion and application of this methodology to the synthesis of compounds of biological interest are in progress, and will be reported in due course.

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Supplementary data

Characterization data for all β-heteroaryl propionates. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.018.

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