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Selective, C-3 Friedel-Crafts acylation to generate functionally diverse, acetylated Imidazo[1,2-*a*]pyridine derivatives

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ABSTRACT

Carbon-carbon bonds are integral for pharmaceutical discovery and development. Frequently, C–C bond reactions utilize expensive catalyst/ligand combinations and/or are low yielding, which can increase time and expenditures in pharmaceutical development. To enhance C–C bond formation protocols, we developed a highly efficient, selective, and combinatorially applicable Friedel-Crafts acylation to acetylate the C-3 position of imidazo[1,2-*a*]pyridines. The reaction, catalyzed by aluminum chloride, is both cost effective and more combinatorial friendly compared to acetylation reactions requiring multiple, stoichiometric equivalents of $AlCl_3$. The protocol has broad application in the construction of acetylated imidazo[1,2-*a*]pyridines with an extensive substrate scope. All starting materials are common and the reaction requires inexpensive, conventional heating methods for adaptation in any laboratory. Further, the synthesized compounds are predicted to possess GABA activity through a validated, GABA binding model. The developed method serves as a superior route to generate C-3 acetylated imidazo[1,2-*a*]pyridine building-blocks for combinatorial synthetic efforts.

1. Introduction

Several strategies have been utilized to expeditiously achieve the construction of chemical libraries for drug discovery. One of the most fundamental, sought after transformations is the creation of carbon-carbon bonds. As such, numerous strategies have been developed employing metal catalysis, which typically require electron-rich ligand counterparts, to construct novel drug-like libraries. Although operationally friendly, metal/ligand based carbon-carbon bond formation can be cost prohibitive and carries the burden of environmental impact. Therefore, combinatorial synthetic efforts can be unreasonably expensive generating large amounts of metal/ligand waste. Because of our interest in imidazo[1,2-*a*]pyridine chemistry [1–3] and the medicinal relevance of the imidazo[1,2-*a*]pyridine scaffold [4–14], we developed a high-yielding, Friedel-Crafts C-3 acetylation completed under neat conditions utilizing catalytic amounts of $AlCl_3$. The acetylation, which is operationally simplistic, requires only conventional heating, and is exceptionally well-suited for combinatorial chemistry efforts.

The imidazo[1,2-*a*]pyridine scaffold has proved very significant in therapeutic development serving as the backbone in many marketed therapeutics including alpidem [4] (**1**) (anxiolytic), necopidem [5] (**2**) (anxiolytic), saripidem [7] (**3**) (anxiolytic), zolpidem [8] (**4**) (insomnia), olprinone [9] (**5**) (cardiotonic), minodronic acid [10] (**6**) (bisphosphonate), and zolimidine [11] (**7**) (antiulcer) (Fig. 1). Imidazo[1,2-*a*]pyridines also exhibit a wide range of biological activities and have been investigated as kinase inhibitors for PI3K[12], CDK [13], IRAK [14], FLT3 [1], and RET [6]. Typically, the imidazo[1,2-*a*]pyridine occupies the same region as

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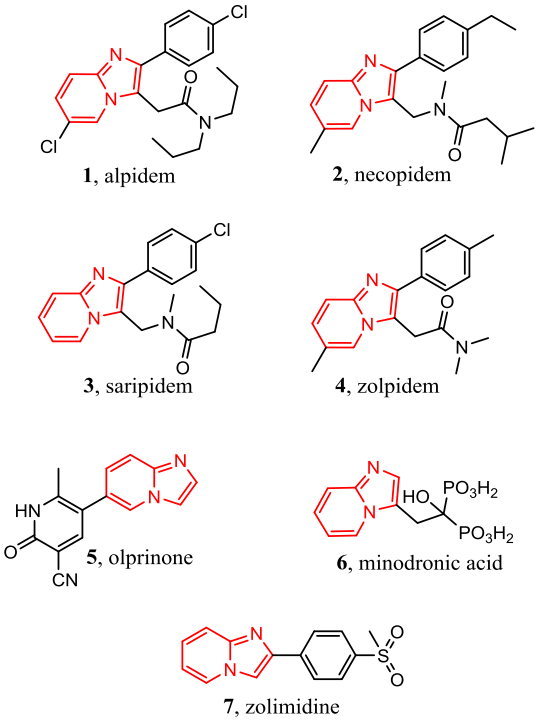
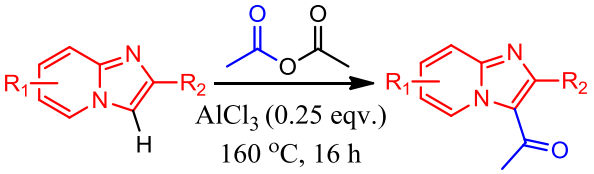


Fig. 1. Marketed drugs bearing an imidazo[1,2-*a*]pyridine core.

adenine from ATP at the kinase active site [1,6].

Owing to the attractive biological properties of imidazo[1,2-*a*]pyridines, a variety of strategies to modify the core structure at the C-3 position have been developed [15–18]. Carbon-hydrogen activating, pseudo-Heck reactions that couple an aryl halide have been investigated with palladium metal and a ligand [19] and also in ligand free conditions [20–23]. Very recently, palladium and copper catalyzed direct C–H arylations of imidazo[1,2-*a*]pyridines at C-3 have been extensively studied [19–24]. Beyond carbon-carbon bond formation, synthetic advancement has been completed with diethyl azodicarboxylate (DEAD) as an amination agent [3] and *n*-bromosuccinimide (NBS) as a halogenating agent [14]. Further, Vilsmeier-Haack reactions can selectively alkylate the C-3 position of imidazo[1,2-*a*]pyridine with DMF as the alkylation source, yet presenting with very low yields [25]. C-3 acetylations have also successfully been completed [26–36]. This has been accomplished in multiple steps, employing halogenated imidazo[1,2-*a*]pyridine C-3 derivatives with a strong base such as *n*-BuLi [37]. In another method, three molar equivalents of $AlCl_3$, as well as one molar equivalent of carbon disulfide, are necessary to acetylate the C-3 position [38]. In general, known C-3 acetylation reactions of imidazo[1,2-*a*]pyridines are low yielding, must occur in multiple steps, and/or employ multiple molar equivalents of $AlCl_3$ for reaction conversion.

Although arylations of imidazo[1,2-*a*]pyridines have been extensively investigated and optimized [1,2,12,17,18], the more simplistic C-3 acetylation is still low yielding, typically completed in step-wise fashion, and requires non-catalytic amounts of a Lewis acid [26,27,29–36], which is not optimal for combinatorial chemistry efforts. Therefore, it is important to develop an operationally-simplistic, inexpensive, high-yielding C-3 acetylation procedure, which employs a Lewis acid in catalytic amounts. The synthetic approach can be applied to the development of drug-like libraries, with more ecofriendly production that can further define the biological roles of imidazo[1,2-*a*]pyridine derivatives.



Scheme 1. C-3 Friedel-Crafts Acetylation of Imidazo[1,2-*a*]pyridine.

Combination of the C-3 directed imidazo[1,2-*a*]pyridine research, with further optimization for operational simplicity, we developed a one pot, single addition approach to acetylate imidazo [1,2-*a*]pyridine at the C-3 position requiring a catalytic amount of $AlCl_3$ (Scheme 1). Herein, we report the successful employment of this methodology to the synthesis of 38 imidazo[1,2-*a*]pyridine derivatives. Investigation into the mechanism and a computational reaction coordinate diagram was completed to justify reaction conditions. Select derivatives were screened in a validated GABA receptor computational model and ligand/receptor binding was predicted. The acetylated derivatives can serve as drug-like building blocks or novel molecular probes to further define imidazo[1,2-*a*]pyridine biological properties.

2. Results and discussion

The identified method is able to effectively acetylate imidazo [1,2-*a*]pyridine and imidazo[1,2-*a*]pyridine analogues. The optimization of the procedure was focused on a simple set up, applicability to a wide range of imidazo[1,2-*a*]pyridine substrates, provision of high yield and purity, and catalytic requirement of a Lewis acid. We avoided reaction conditions that produced heterogeneous mixtures and incomplete conversion because, under parallel synthetic library production, complicated product mixtures can confound synthetic efficiency.

Initial evidence for the acetylation of imidazo[1,2-*a*]pyridine stemmed from the amination of imidazo[1,2-*a*]pyridine using DEAD [3]. Under the amination conditions, imidazo[1,2-*a*]pyridines can be successfully aminated at the C-3 position in aprotic solvents with gentle heating [3]. We utilized similar conditions in which DEAD was replaced with acetic anhydride under gentle heating to acetylate starting material **8** (Table 1). However, only trace amounts of conversion were observed (Table 1, Entry 1). To help progress the reaction, a variety of metal catalysts with carbonyl-activating properties were investigated (Table 1, Entry 2–8). Best conversion was observed with $La(OTf)_3$ and $AlCl_3$, yet conversion was very modest only producing the desired acetylation product in 32–40% yields. Because of laboratory availability and extremely minor cost, reaction optimization continued with $AlCl_3$ as the Lewis acid catalyst.

Increasing catalytic load from 0.10 to 1.00 equivalent had a positive impact on yield, but the yield plateaued due to formation of undesired side products (Table 1, Entry 8–12). The $AlCl_3$ load was decreased to 0.25 equivalence while the reaction duration was doubled, which furnished a desirable increase in yield (Table 1, Entry 9, 13). Various reaction solvents were investigated and acetonitrile provided the desired acetylation product in highest yields (Table 1, Entry 14–23). We concluded that reaction kinetics maybe important for conversion, and reactions were completed with acetic anhydride as solvent to increase reactant concentration (Table 1, Entry 24–27). An increase in yield was identified, especially when reaction temperature and duration were increased to 160 °C for 16 h (Table 1, Entry 17). With these conditions, the desired acetylated imidazo[1,2-*a*]pyridine product underwent 100% conversion and was isolated in 99% yield only requiring