One-pot synthesis of tetracyclic fused imidazo[1,2-a]pyridines via a three-component reaction

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Abstract
A novel three-component reaction has been developed to assemble biologically and pharmaceutically important tetracyclic fused imidazo[1,2-a]pyridines in a one-pot fashion utilizing readily available 2-aminopyridines, isatins and isocyanides. The three-component coupling proceeds through the Groebke–Blackburn–Bienaymé reaction followed by a retro-aza-ene reaction and subsequent nucleophilic reaction of the in-situ generated imidazo[1,2-a]pyridines bearing an isocyanate functional group.

Introduction
Multicomponent reactions (MCRs) have attracted considerable attention in organic and medicinal chemistry due to their high efficiency, simple operability, atom economy and unmatched versatility [1-6]. Especially, these reactions serve as an ideal synthetic tool for the assembly of structurally diverse and biologically relevant heterocycles, and thus have been extensively investigated by organic and medicinal chemists to explore lead compounds in drug discovery efforts [7-10].

The imidazo[1,2-a]pyridine scaffold is a pharmaceutically important drug template, and its derivatives display a broad range of biological activities such as antibacterial [11-13], antiviral [14,15], anti-inflammatory [16,17], antitumor [18-20], and anti-HIV [21]. It is found as the core structure in several drugs such as Zolpidem, Alpidem and Zolimidine (approved for treatments of insomnia, anxiety and peptic ulcers, respectively) [22]. As such, the imidazo[1,2-a]pyridine structure represents an intriguing synthetic target, and its further functionalization is leading to polycyclic fused heterocycles that may have interesting biological profiles [23].

Impressively, the imidazo[1,2-a]pyridine scaffolds can be constructed in great diversity by a multicomponent reaction of amidines, aldehydes and isocyanides. This MCR, a variant of the Ugi reaction [24,25], was discovered independently by three groups and is known as the Groebke–Blackburn–Bienaymé reaction. However, the fact that the Groebke–Blackburn–Bienaymé reaction has some limitations such as the requirement of pre-functionalization of reagents, low yields and multiple steps, which is not in line with the principle of one-pot reactions. Therefore, the development of a new and efficient method for the one-pot synthesis of imidazo[1,2-a]pyridines is of significant significance. In this contribution, we describe a novel and efficient method for the one-pot synthesis of imidazo[1,2-a]pyridines via a three-component reaction.
(GBB) reaction [26-29]. The reaction involves a formal \([4 + 1]\) cycloaddition of isocyanides [30] and imines, generated from the amidines and aldehydes, allowing straightforward access to diverse imidazo[1,2-\(a\)]azines [31-33].

In view of the significance of the GBB reaction and the imidazo[1,2-\(a\)]pyridine core structure, the further development of new GBB-based methods for the efficient synthesis of novel polycyclic fused imidazo[1,2-\(a\)]pyridines is highly desirable. In an earlier study, we have developed a GBB/lactamization MCR strategy, which provided the rapid access to isoquino林one-fused imidazo[1,2-\(a\)]pyridines with potent and selective CDK2 inhibition properties [34,35]. As a continuing effort, we report herein our recent efforts in the development of a GBB-based MCR method for the one-pot synthesis of diverse quinazolin-2-one fused imidazo[1,2-\(a\)]pyridines (Scheme 1). Parts of the work have been disclosed in a previous patent [36].

Results and Discussion

It is noteworthy that there was no report on a ketone-involving GBB reaction, and several attempts to explore the GBB reaction utilizing ketones as carbonyl reactant failed [27,37]. These difficulties could be partially explained in terms of the electronic and steric effect of the ketone involved. More importantly, when a ketone is used in the reaction the formed unstable \([4 + 1]\) cycloaddition adduct could not undergo a \([1,3]\)-alkyl shift. On the other hand the reaction with an aldehyde allows further conversion through a \([1,3]\)-hydride shift to form a stable and aromatic imidazole. Therefore, we envisioned that a ketone-involved reaction could proceed, if the \([4 + 1]\) cycloaddition adduct can further rearrange to form an aromatic imidazole. With this idea in mind, we started to study an isatin-involved reaction utilizing ketones as carbonyl reactant failed [27,37]. These difficulties could be partially explained in terms of the electronic properties of the amidines and aldehydes, allowing straightforward access to diverse imidazo[1,2-\(a\)]azines [31-33].

We first explored the reaction of 2-aminopyridine (2a), isatin (3a) and tert-butyl isocyanide (4a). Under the classical reaction conditions (entry 1, Table 1), the product 1a was isolated only in 4\% yield. Performing the reaction under reflux conditions slightly improved the yield to 11\%. We next examined solvent effects in this MCR reaction and various solvents were screened, as summarized in Table 1.

We observed that protic solvents with medium polarity can facilitate the reaction by product precipitation from the reaction mixture and \(n\)-BuOH proved to be the most suitable solvent in the reaction. Performing the reaction in refluxing \(n\)-BuOH in the presence of one equivalent of \(\text{HClO}_4\) for 8 h, compound 1a was obtained in 30\% isolated yield. Other acids including \(p\)-toluenesulfonic acid (PTSA), HCl, and HOAc were also screened, and the results indicated that the use of PTSA led to a slightly decreased yield, and weaker acids failed to promote this process. It is worth noting that the reaction proceeded incompletely and significant amounts of isatin (3a) were recovered. When increased amounts (1.35 equiv) of 2-aminopyridine (2a) and tert-butyl isocyanide (4a) were used, the yield of 1a could be further improved to 42\%.

Under the optimized reaction conditions, we started to investigate the reaction scope. The MCR of various 2-aminopyridines, isatins and isocyanides proceeded well under the optimized conditions and the combinational synthesis delivered structurally diverse quinazolin-2-one fused imidazo[1,2-\(a\)]pyridines (Figure 1). It was found that the electronic properties of the

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**Table 1:** Synthesis of imidazo[1,2-\(a\)]pyridine derivatives in indicated conditions [38].

| Entry | Solvent | Acid      | Temperature | Yield (%) |
|-------|---------|-----------|-------------|-----------|
| 1     | MeOH    | \(\text{HClO}_4\) | rt          | 4         |
| 2     | MeOH    | \(\text{HClO}_4\) | reflux      | 11        |
| 3     | MeCN    | \(\text{HClO}_4\) | reflux      | -b        |
| 4     | DMF     | \(\text{HClO}_4\) | 100 °C      | 10        |
| 5     | EtOH    | \(\text{HClO}_4\) | reflux      | 17        |
| 6     | iPrOH   | \(\text{HClO}_4\) | reflux      | 22        |
| 7     | \(n\)-BuOH | \(\text{HClO}_4\) | reflux      | 30        |
| 8     | \(t\)-BuOH | \(\text{HClO}_4\) | reflux      | 21        |
| 9     | \(t\)-BuOH | \(\text{HClO}_4\) | reflux      | 19        |
| 10    | isopentyl alcohol | \(\text{HClO}_4\) | reflux      | 17        |
| 11    | CF\(_2\)CH\(_2\)OH | \(\text{HClO}_4\) | reflux      | 13        |
| 12    | \(n\)-BuOH | PTSA       | reflux      | 20        |
| 13    | \(n\)-BuOH | HCl        | reflux      | -         |
| 14    | \(n\)-BuOH | AcOH       | reflux      | -         |
| 15    | \(n\)-BuOH | \(\text{HClO}_4\) | reflux      | 42\%      |

*Conditions: 2a (1 mmol), 3a (1 mmol), 4a (1 mmol), and acid \(\text{HX}\) (1 mmol) in 4 mL of solvent; \(\text{HX}^\text{a}\) indicates that the product was not obtained; ^b^conditions: 2a (1.35 mmol), 3a (1 mmol), 4a (1.35 mmol), and acid \(\text{HX}\) (1 mmol) in 4 mL of solvent.*
Figure 1: Syntheses of imidazo[1,2-a]pyridine derivatives. Reaction conditions: 2 (1.35 mmol), 3 (1 mmol), 4 (1.35 mmol), HClO₄ (1 mmol), n-BuOH (4 mL), reflux. Yields refer to isolated yields. 2b R¹ = 4-Cl; 3b R² = 5-OMe; 3c R² = 5-Cl; 3d R² = 5-Br; 3e R² = 5,7-Me₂; 3f R² = 7-F; 3g R² = 5-i; 4b R³ = cyclohexyl.
Figure 2: Mechanistic rationale for the MCR [36].
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