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Three-Component Reactions of Aromatic Amines, 1,3-Dicarbonyl Compounds and *α*-Bromoacetaldehyde Acetal to Access *N*-Aryl/HetAryl-4,5-Unsubstituted Pyrroles

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Abstract

N-Aryl/HetAryl-4,5-unsubstituted pyrroles were synthesized from Ar/HetAr-amines, 1,3-dicarbonyl compounds and *α*-bromoacetaldehyde acetal by using aluminum(III) chloride as a Lewis acid catalyst through [1 + 2 + 2] annulation. This new versatile methodology provides a wide scope for the synthesis of different functional *N*-Aryl/HetAryl-4,5-unsubstituted pyrrole scaffolds, which can be further derived to access multi-substituted pyrrole-3-carboxamides. In the presence of 1.2 equiv. of KI, polysubstituted pyrazolo[3,4-b]pyridine derivative was also successfully synthesized.

Keywords

Pyrroles; [1+ 2 + 2] Annulation; Acid catalyst; KI; Pyrazolo[3,4-b]pyridine

Introduction

Among nitrogen-containing heterocycles, pyrroles have garnered significant attention in the literature because of their presence in various natural products[1] and pharmaceutically concerning drugs.[2] Accordingly, numerous synthetic methods to construct pyrrole skeletons were reported, including classical Hantzsch pyrrole synthesis[3] and Paal-Knorr pyrrole synthesis[4] which have been developed to harvest the pyrrole frameworks. In the past few years, interest has rapidly grown in developing new methods to synthesize this heterocyclic motif, transition-metal-catalyzed cyclization[5] and multicomponent reactions[6] are some of the commonly used approaches for the construction of pyrrole scaffolds. Additionally, the biocatalytic synthesis of substituted pyrroles also was developed.[7] Though sustained efforts[8] have been achieved to develop efficient synthetic methods for the preparation of this structural motif, the development of cost-effective methods to access functionalized pyrrole skeletons has remained an ongoing challenge.

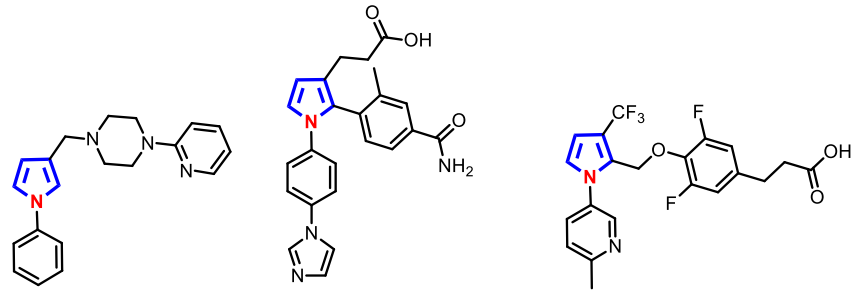
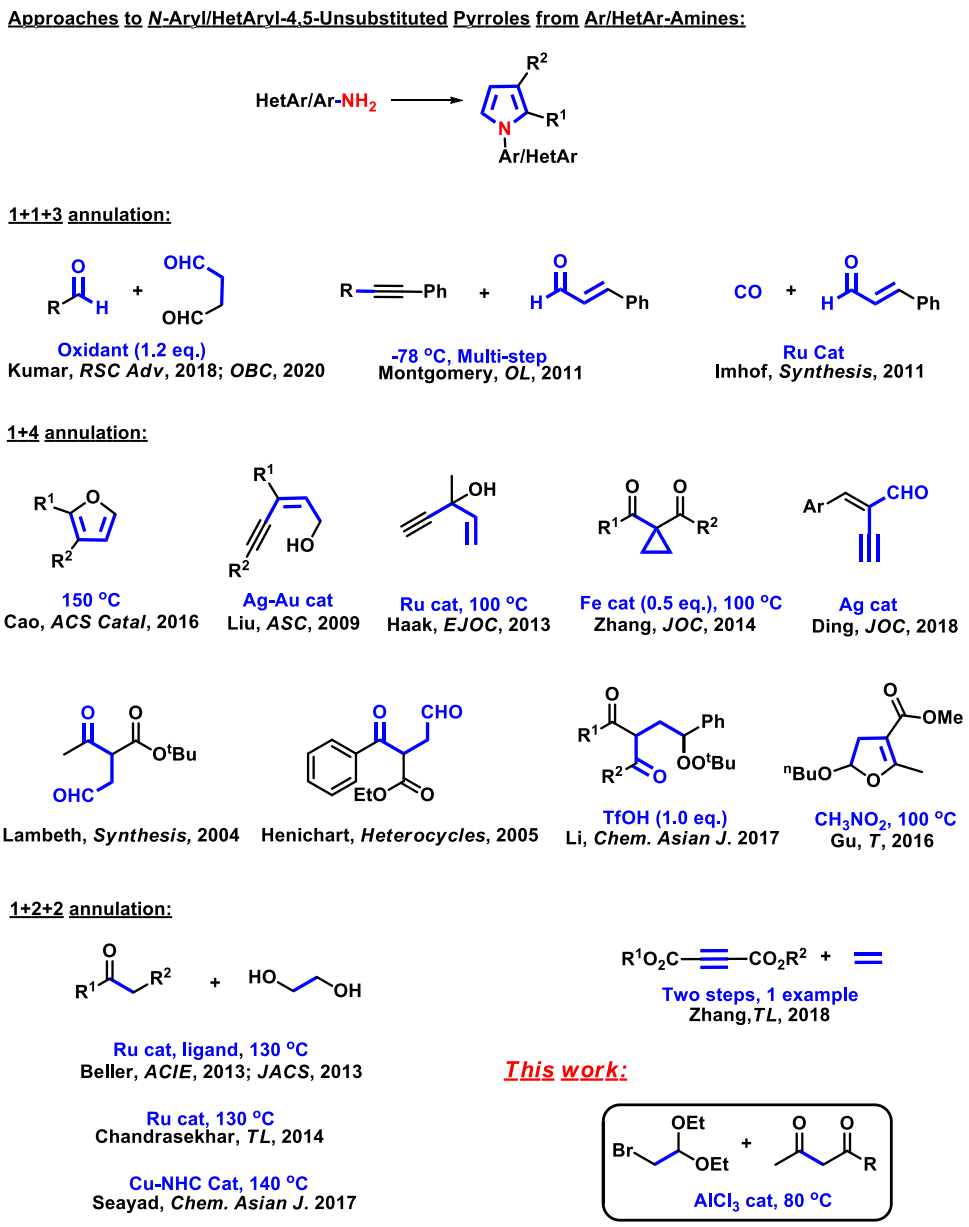


Figure 1. Representative biologically active *N*-Aryl/HetAryl-4,5-unsubstituted pyrrole scaffolds.

The *N*-Aryl/HetAryl-4,5-unsubstituted pyrroles are one of the most important types of pyrroles which are frequently used as the core scaffold in pharmaceuticals[9] (**Figure 1**). Therefore, many

efforts have been paid on the synthesis of these privileged *N*-Aryl/HetAryl-4,5-unsubstituted pyrroles. Ar/HetAr-amines are readily available chemicals. The direct conversion of Ar/HetAr-amines into *N*-Aryl/HetAryl-4,5-unsubstituted pyrroles has an intrinsically high synthetic potential. At present, the transformations can generally be realized through the following three approaches (**Scheme 1**): (i) [1 + 1 + 3] annulation, in which Ar/HetAr-amines are reacted with a 3C donor and a 1C donor to construct pyrrole scaffolds. Kumar et al.[10] developed a proline-catalyzed Mannich reaction-cyclization sequence of succinaldehyde and an *in situ* generated Ar-imine, in which the succinaldehyde contributes three carbons of the pyrrole ring. *α,β*-Unsaturated aldehyde has also been used as the 3C donor to construct pyrrole scaffolds;[11] (ii) [1 + 4] annulation, in which Ar/HetAr-amines are reacted with a 4C donor to form the pyrrole ring; Many functional molecules, such as bioderived furans,[12] (Z)-enynols,[13] 1-vinylpropargyl alcohols,[14] doubly activated cyclopropanes,[15] enynals,[16] can be used as 4C counter reagents. The carbon-based 1,4-biselectrophiles, such as the 1,4-dicarbonyl compounds,[17] *γ*-carbonyl tert-butylperoxides[18] and dihydrofurans[19] also have been reported to construct the pyrrole skeletons through this type of annulation; and (iii) [1 + 2 + 2] annulation, in which Ar/HetAr-amines are reacted with two different molecules, and each of them contribute two carbons to construct a pyrrole ring.[20] Among these three approaches, the third is considered the most attractive route for *N*-Aryl/HetAryl-4,5-unsubstituted pyrrole synthesis, the reasons are twofold: (i) it uses easily available substrates, and (ii) it is able to synthesize pyrroles with a high potential of molecular diversity and complexity. However, to date, the productivity for creating molecular diversity and complexity has yet to be fully displayed. In addition, some of the reported approaches were established on the basis of using expensive and non-recyclable homogeneous

metal catalysts. To alleviate all these problems, herein, we used easily available α-bromoacetaldehyde acetal and a simple 1,3-dicarbonyl compound as a reagent couple to react with Ar/HetAr-amines. The established [1 + 2 + 2] annulation reaction provided a straightforward approach for accessing various *N*-Aryl/HetAryl-4,5-unsubstituted pyrroles, and some of the pyrrole products are not accessible with the hitherto reported methods.

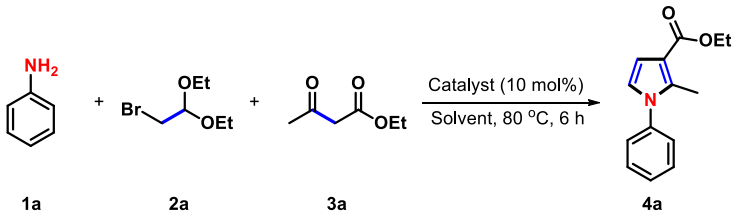


Scheme 1. Typical routes for *N*-Aryl/HetAryl-4,5-unsubstituted pyrrole synthesis.

Results and discussion

Initially, a mixture of aniline **1a**, *α*-bromoacetaldehyde acetal **2a**, and ethyl acetoacetate **3a** was treated under the conditions, the obtained results are listed in **Table 1**. The mixture was heated in 1,4-dioxane at 80 °C. No reaction occurred in the absence of the catalyst (entry 1), however, in the presence of a strong Lewis acid, $Bi(OTf)_3$, the expected product **4a** was obtained in 36% of yield after 6 h of reaction (entry 2). To our surprise, a *N*-Aryl-4,5-unsubstituted pyrrole derivative, **4a**, was isolated in 80% yield when 10 mol% of $AlCl_3$ was used as the catalyst (entry 3). $FeCl_3$ and $NiCl_2$ were proven also able to catalyze this reaction, but the yields of **4a** were inferior as compared with those obtained by $AlCl_3$ (entries 4 and 5). *p*-Toluenesulfonic acid (PTSA), a strong Brønsted acid, also exhibited a promising catalytic ability, and the yield of **4a** reached 73% (entry 6). When HAc was used, only unreacted starting materials were recovered (entry 7). The effect of solvents on the model reaction was also examined. Screening of some solvents including anhydrous ethanol, acetonitrile, toluene and DMSO did not bring any improvement with respect to the yield of **4a** (entries 8-11). The decrease of the catalyst loading from 10 mol% to 5 mol% resulted in a slight decrease of the reaction yield (entry 12). Further investigations revealed that the reaction was also affected by the temperature and time, only 51% yield was obtained at 50 °C (entries 13 and 14). Therefore, the optimized reaction conditions were confirmed as the followings: 10 mol % of $AlCl_3$ as a catalyst, 1,4-dioxane as a solvent, 6 h and 80 °C. It is worth noting that the reaction can be effectively scaled up with similar efficiency. In a gram-scale synthesis of **4a**, the corresponding pyrrole product can be obtained in 72% of yield (entry 15).

Table 1. Condition optimization of the reaction between **1a**, **2a**, and **3a**.[a]



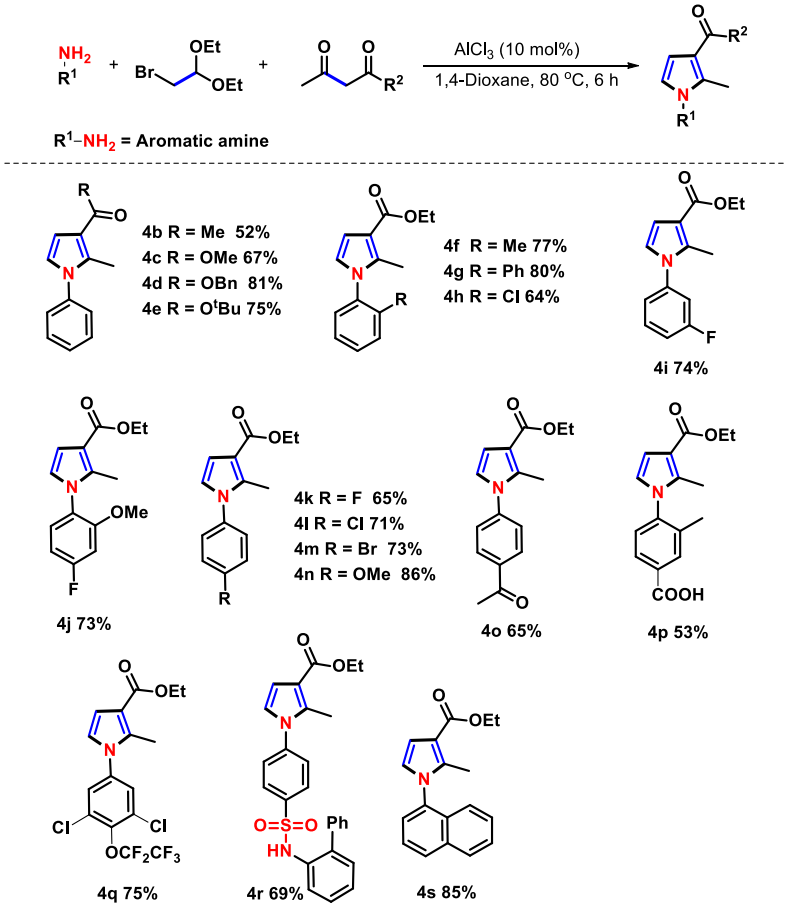
1a 2a 3a 4a

Entry	Catalyst	Solvent	Yield (%)[b]
1	—	1,4-Dioxane	0
2	$Bi(OTf)_3$	1,4-Dioxane	36
3	$AlCl_3$	1,4-Dioxane	80
4	$FeCl_3$	1,4-Dioxane	44
5	$NiCl_2$	1,4-Dioxane	21
6	*p*-TsOH	1,4-Dioxane	73
7	HAc	1,4-Dioxane	trace
8	$AlCl_3$	EtOH	31
9	$AlCl_3$	MeCN	50
10	$AlCl_3$	PhMe	27
11	$AlCl_3$	DMSO	62
12[c]	$AlCl_3$	1,4-Dioxane	55
13[d]	$AlCl_3$	1,4-Dioxane	51
14[e]	$AlCl_3$	1,4-Dioxane	40
15[f]	$AlCl_3$	1,4-Dioxane	72

[a] **1a**: 0.5 mmol, **2a**: 0.6 mmol, **3a**: 0.6 mmol; catalyst: 0.05 mmol; solvent: 1 mL; 80 °C; 6 h. [b] Isolated yield, calculated with respected to **1a**. [c] $AlCl_3$, 0.025 mmol. [d] 50 °C. [e] 2 h. [f] 10 mmol scale reaction.

The scope of this pyrrole synthesis protocol was then investigated under the optimized reaction conditions. The substrate scope of the 1,3-dicarbonyl component was first examined (**Scheme 2**). Acetylacetone reacted smoothly with **1a** and **2a** to form **4b** in 52% yield. 1,3-dicarbonyl compounds bearing ester groups participated in this reaction readily, affording the desired pyrroles in moderate to good yields (**4c**-**4e**). Notably, methyl 2-methyl-1-phenyl-1*H*-pyrrole-3-carboxylate **4c** is a key intermediate in the synthesis of a TRPM8 antagonist.[21] The substrate scope of the aromatic amines component was then examined, the remarkable efficiency of our pyrrole synthesis was reflected by the tolerance of a broad range of functional groups attached to the aromatic amines. For example, aniline bearing methyl (**4f**), phenyl (**4g**) and halo (**4h**-**4m**)

functionalities were readily compatible with the $AlCl_3$/1,4-dioxane system. In these cases, the pyrrole products were isolated in moderate to good yields. The presence of an electron-donating group in the phenyl ring facilitated, to some extent, the progress of the reaction (**4n**). Anilines with electron-withdrawing groups, such as acetyl and carboxyl, can also be used in the reaction, but the yields obtained are slightly inferior (**4o** and **4p**). Gratifyingly, a 3,5-dichloro-4-(1,1,2,2-tetrafluoroethoxy)aniline also participated smoothly in this reaction, and the expected product **4q** can be obtained in 75% yield. This fluorinated substituted on the aniline

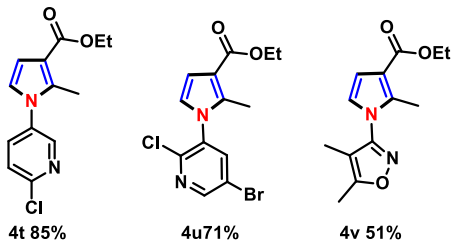


Scheme 2. Substrate scope of the pyrrole synthesis.

ring has been identified as the key precursor to access the insect growth regulators.[22] It is noteworthy that the sulfonamide group survived during this transformation, and the desired pyrrole product, **4r**, can be obtained in 69% yield. A high yield was also obtained when the phenyl

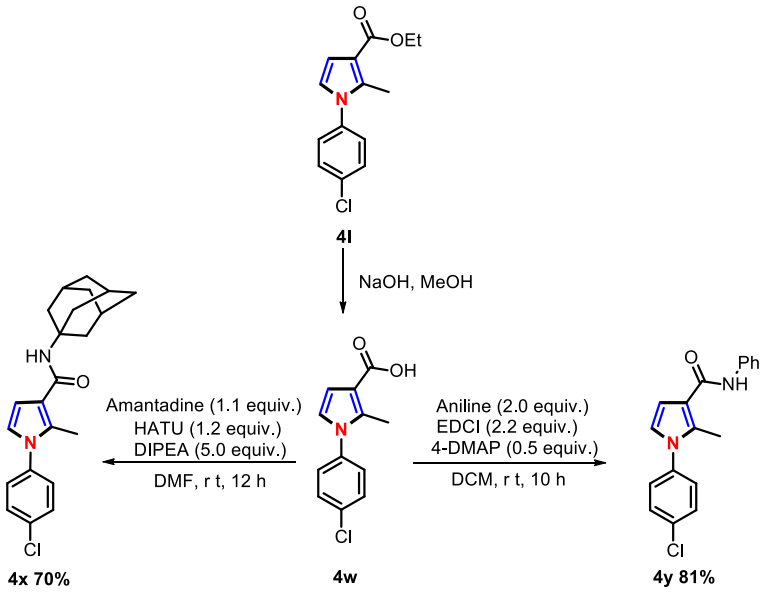
group was replaced with a naphthyl group (**4s**). Subsequently, aliphatic primary amines and ammonia, such as benzyl amine and *N*-butyl amine, also be examined as N donors, however, no desired product was detected.

Then, we attempted to synthesize pharmaceutically active *N*-heterocyclic pyrrole derivatives with the aid of this three-component reaction. To our great delight, some *N*-heterocyclic pyrrole skeletons were successfully synthesized in 51% to 85% yields by using our protocol (**Scheme 3**, **4t**-**4v**). It should be mentioned that, the obtained *N*-pyridyl pyrroles **4t** and **4u** are a class of very important intermediates for synthesizing the soluble guanylyl cyclase (SGC) activator. A reported method for accessing these similar scaffolds suffers from low product yields and harsh conditions (32% yield, 130 °C).[23]



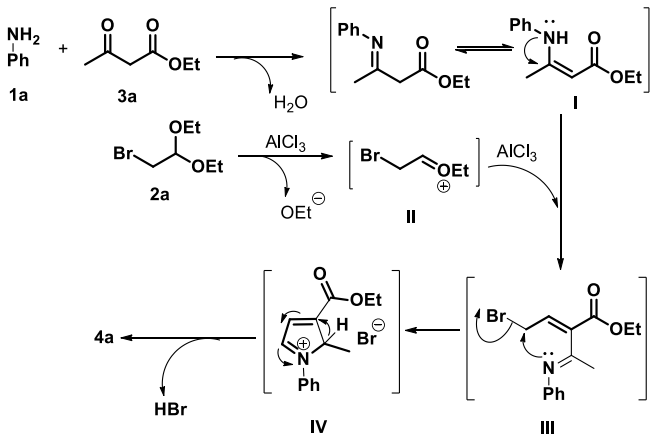
Scheme 3. Synthesis of *N*-heterocyclic pyrroles.

One of the obtained *N*-aryl-4,5-unsubstituted pyrroles, **4l**, can underwent a hydrolysis reaction to form a (pyrrol-3-yl)carboxylic acid **4w**. The latter can react readily with aniline or vanillylamine in the presence of HATU or EDCI to form multi-substituted pyrrole-3-carboxamide derivatives, **4x** and **4y**. These skeletons have been proven to be promising inhibitors for the production of cytokinesm.[24]



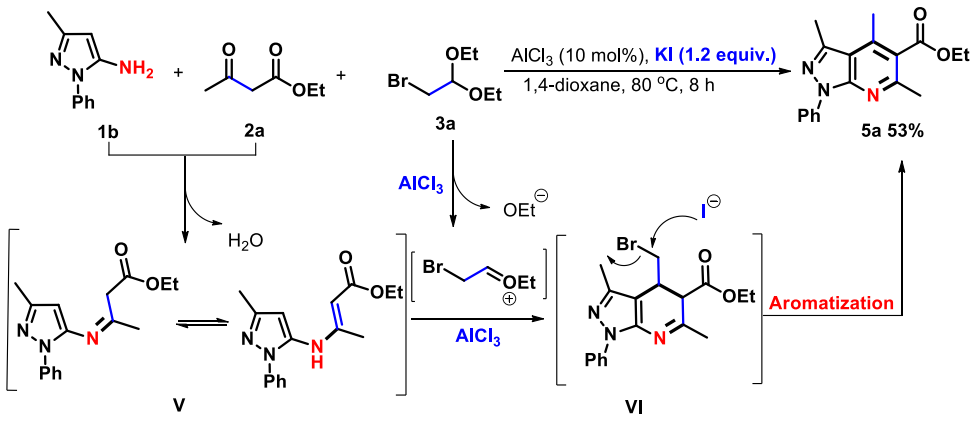
Scheme 4. Direct synthesis of pyrrole-3-carboxamide derivatives.

A plausible mechanism for the model reaction was proposed, and depicted in **Scheme 5**. Initially, a reaction of **1a** and **3a** occurred, providing an imine intermediate **I**, which tautomerized to the corresponding enamine form. Meanwhile, activation of **2a** with $AlCl_3$ allowed the formation of a carbocation intermediate **II**, which was then trapped by the enamine intermediate **I** to generate another intermediate **III**. Subsequently, **III** underwent an intramolecular electrophilic substitution to form intermediate **IV**. Finally, **IV** underwent an elimination of HBr and spontaneous aromatization to afford the pyrrole product **4a**.[25]



Scheme 5. Plausible mechanism of the three-component reaction.

Apart from pyrrole synthesis, we also observed an unexpected reaction, in which pyrazolo[3,4-b]pyridine scaffold was constructed under an analogous conditions. As shown in **Scheme 6**, In the presence of a catalytic amount of $AlCl_3$ and 1.2 equiv. of KI, 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **1b** reacted smoothly with **2a** and **3a**, affording a polysubstituted pyrazolo[3,4-b]pyridine **5a** in 53% of yield. The formation of an imine intermediate **V** may be involved in the reaction mechanism, and the enamine form of **V** contained two nucleophilic sites to react with a molecule of the simultaneous existence of an electrophilic aldehyde-carbonyl to generate an intermediate **VI**. Finally, **VI** underwent an aromatization to produce **5a**. **KI** may play a key role in the last step, and we suspected that it can promote the remove of Br^-. Although **5a** can be theoretically synthesized through a three-component reaction of **1b**, **2a** and an appropriate aldehyde, for example, acetoaldehyde,[26] owing to the insufficient reaction of aliphatic aldehyde, the reaction in **Scheme 6** should be a wise choice for implementing the synthesis of **5a**-type product. This point deserves further investigation.



Scheme 6. Synthesis of polysubstituted pyrazolo[3,4-b]pyridine derivative.

Conclusion

In summary, an efficient and practical one-pot multicomponent reaction of Ar/HetAr-amines with *α*-bromoacetaldehyde acetal and 1,3-dicarbonyl compounds was developed by using $AlCl_3$ as a catalyst. The developed chemistry is also successful for the synthesis of functionalized pyrazolo[3,4-b]pyridine derivative. This study offered a complementary method to construct pyrrole scaffolds through [1 + 2 + 2] annulation, thus enriching the product diversity of the pyrrole derivatives.

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Supporting Information

The experimental procedures and copies of NMR spectra can be found in the Supporting Information

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