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DMAP-promoted in situ activation of bromoacetic acid as a 2-carbon synthon for facile synthesis of pyridines and fused pyridin-2-ones

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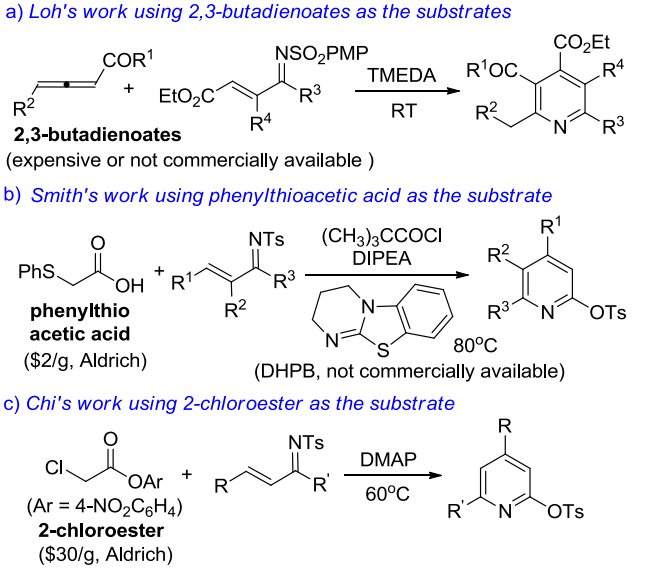
ABSTRACT

A general and simple synthesis of 2,4,6-trisubstituted pyridines and fused pyridine-2-ones from bromoacetic acid is developed via a DMAP-promoted in situ activation strategy. In this protocol, readily accessible bromoacetic acid has been effectively employed as a 2C synthon to undergo formal [2+4] cycloadditions with diverse acyclic and cyclic 1-azadienes. Low costs of the reagents and materials, mild reaction conditions and broad functional-group tolerance make this protocol applicable for practical and scalable synthesis.

1. Introduction

Functionalized pyridines are recognized as attractive privileged structures and important building blocks due to their prevalence in numerous natural products, pharmaceuticals and functional materials.[1] Thus, they have become common synthetic targets among organic community.[2] However, among exisiting synthetic methods,[3] relatively high reaction temperature is usually required or toxic transition-metals are used as the catalysts. Besides, the substrates applied for pyridine synthesis are sometimes not readily accessible. Therefore, the development of more general and environmentally benign (metal-free) methods that allow rapid access to the pyridine motif from readily accessible starting materials is highly desirable.

Recently, organocatalysis has been established as a powerful tool for the synthesis of substituted pyridines owing to the non-toxic nature and unique reactivity of organocatalysts. Loh and co-workers[4] reported a synthetic approach to functionalized pyridines via an amine-catalyzed aza-Rauhut–Currier/cyclization/desulfonation cascade reaction of 2,3-butadienoates with *N*-sulfonyl-1-azadienes (Scheme 1, eq a). Smith and co-workers[5] developed an isothiourea-catalyzed one-pot synthesis of polysubstituted pyridines bearing a readily derivatived 2-sulfonate functionality by the reaction of (phenylthio)acetic acid with *N*-sulfonyl-1-azadienes (Scheme 1, eq b). Chi and co-workers[6] reported DMAP-catalyzed facile synthesis of similar 2-sulfonate functionalized trisubstituted pyridines from α-chloro acetic ester



Scheme 1. Previous organocatalytic synthesis of pyridines from 1-azadienes.

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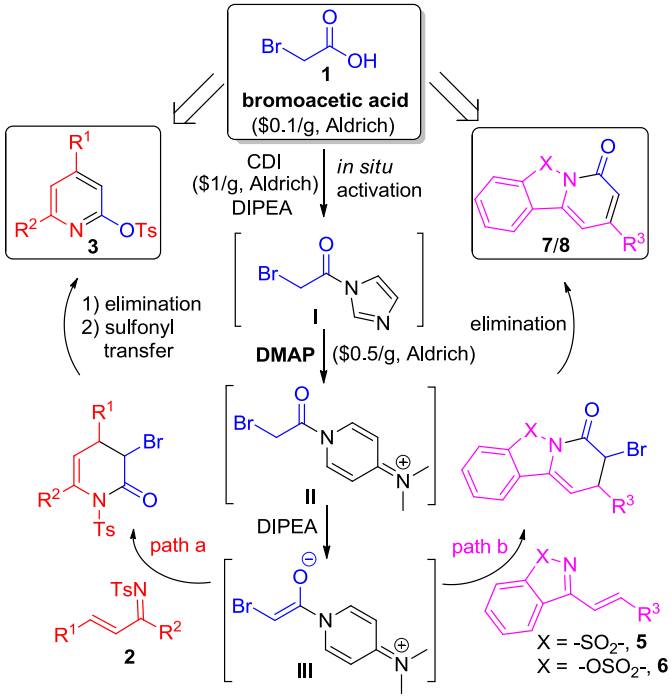
and *N*-sulfonyl-1-azadienes (Scheme 1, eq c). For these methods, *N*-sulfonyl-1-azadienes are used as the nitrogen source[3b,3f,7] to combine with diverse 2-carbon synthon precursors for the construction of the pyridine motif under different organocatalytic conditions. However, there are still some limitations for these methods, such as expensive or not commercially available substrates or catalysts.

In order to develop simple and practical synthetic protocols from readily accessible starting materials and catalysts for rapid access to pyridines, we reason that bromoacetic acid, a low-cost commercially available reagent ($0.1/g, Aldrich), may be used as the potential 2-carbon synthon precursor to combine with *N*-sulfonyl-1-azadienes via an organocatalyst-promoted in situ activation strategy. Herein, we reported 4-dimethylaminopyridine (DMAP)-promoted in situ activation of bromoacetic acid **1** for facile synthesis of 2,4,6-trisubstituted pyridines **3** from 1-azadienes **2**, which can be easily prepared through the condensation of α,β-unsaturated enones with 4-methylbenzenesulfonamide[8] (Scheme 2, path a). In addition, this protocol proved to be equally applicable for the synthesis of fused pyridin-2-ones **7**/**8** from cyclic 1-azadienes **5**/**6**[9] (Scheme 2, path b). For these reactions, imidazole-bound acyl intermediate **I** derived from in situ activation of bromoacetic acid by CDI/DIPEA is unreactive. So, the more reactive DMAP-bound acyl intermediate **II** is formed by nucleophilic substitution of **I** with DMAP to facilitate the reaction. The subsequent deprotonation of **II** with DIPEA affords the key DMAP-bound enolate **III**, which undergoes formal [4+2] cycloaddition with acyclic 1-azadienes **2** or cyclic azadienes **5**/**6** to afford the corresponding (fused) 2-bromo pyridin-2-one intermediates. For acyclic 1-azadiene substrates, the 2-bromo pyridin-2-one intermediates undergo a tandem HBr elimination/*N*- to *O*- sulfonyl transfer process to afford 2,4,6-trisubstituted pyridines **3**. For cyclic 1-azadiene substrates, the fused 2-bromo pyridin-2-one intermediates only undergo HBr elimination to give fused pyridin-2-ones **7**/**8**.

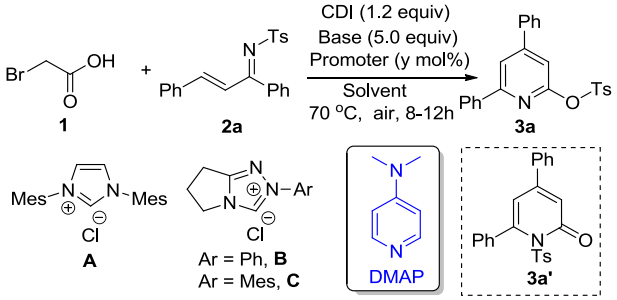


Scheme 2. Our pyridine and fused pyridine-2-one synthesis starting from bromoacetic acid.

2. Results and discussion

Our recent research focuses on the development of novel synthetic methodologies for quick construction of diverse heterocyclic frameworks with *N*-heterocyclic carbene (NHC) catalysis.[10] Since NHCs[11] have been successfully applied to generate NHC-bound enolates via in situ activation of carboxylic acids,[12] several NHC precursors were first employed to examine the reaction of bromoacetic acid **1** with 1-azadiene **2a** in the presence of CDI ($1/g, Aldrich), a low-cost commonly used peptide coupling reagent. As result, precursor triazolium salt **C** was found effective for the synthesis of pyridine **3a** in 37% yield (Table 1, entry 2). As DMAP is

Table 1
Optimization of the reaction conditions[a]



Entry	Promoter (y mol %)	Base	Solvent	Yield (%)[b]
1[c]	**A/B** (15)	NEt_3	1,2-DCE	Trace
2[c]	**C** (15)	NEt_3	1,2-DCE	37
3	DMAP (120)	NEt_3	1,2-DCE	64
4	DMAP (120)	Cs_2CO_3	1,2-DCE	28
5	DMAP (120)	NaH	1,2-DCE	43
6	***DMAP (120)***	***DIPEA***	***1,2-DCE***	***82***
7	DMAP (120)	DBU	1,2-DCE	78
8	DMAP (120)	DIPEA	toluene	49
9	DMAP (120)	DIPEA	CH_3CN	24
10	DMAP (120)	DIPEA	1,4-dioxane	14
11	DMAP (120)	DIPEA	DME	18
12	DMAP (80)	DIPEA	1,2-DCE	62
13	DMAP (40)	DIPEA	1,2-DCE	41

Bold entry aims to highlight that this is the optimal reaction condition.

[a] All reactions were performed in a 25 mL round-bottom flask on a 0.3 mmol scale with 1.2 equiv of **1**, 1.0 equiv of **2a**, 1.2 equiv of CDI, 5.0 equiv of a base, in an anhydrous solvent (3 mL) at 70 °C for 8–12 h in air.

[b] Isolated yields based on **2a**.

[c] The reactions were carried out under N_2. CDI=*N*,*N*′-Carbonyldiimidazole; DBU=1,8-diazabicyclo[5.4.0]-undec-7-ene; Mes=2,4,6-$(CH_3)_3C_6H_2$; DIPEA=*N*,*N*-diisopropylethylamine.

frequently used for facilitating the peptide coupling reactions, we then used stoichiometric amount of DMAP to promote this reaction. It was found that product **3a** was obtained in 64% yield when the reaction was heated at 70 °C in the presence of 1.2 equiv of DMAP (entry 3). Notably, unlike the NHC-catalyzed reaction usually carried out under inert gas shielding, this reaction is not air-sensitive which makes it more simple and practical. Then, an array of bases and solvents were used to further optimize the reaction conditions using DMAP as the promoter. DIPEA and 1,2-DCE were finally established as the optimal base and solvent, respectively (entry 6). Unfortunately, lowering DMAP loading resulted in significantly decreased yield (entries 12 and 13). Considering the low cost of DMAP ($0.5/g, Aldrich), the optimal reaction conditions were established as that in entry 6 affording **3a** in 82% yield. Notably, *N*-Ts pyridin-2-one intermediate **3a**′ was observed under lower temperature (40 °C), and it was converted to products **3a** under higher temperature with prolonged reaction time.

With the optimized conditions established, the substrate scope and generality of the reaction were probed (Scheme 3). Generally,