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Synthesis of imidazo[1,5-*a*]pyridines from 1,1-dibromo-1-alkenes

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ABSTRACT

An efficient method is developed for the synthesis of imidazo[1,5-*a*]pyridine from the reaction of 1,1-dibromo-1-alkenes with 2-aminomethylpyridines. The reaction requires an inorganic base, such as Na_2CO_3, and moderate heating in DMF to proceed. Moderate to good yields are obtained. As demonstrated by the authors and others, 1,1-dibromo-1-alkenes are employed as synthons for activated carboxyl groups.

Fused heteroaromatic compounds containing ring-junction nitrogen atoms are important for the preparation of biologically active molecules.[1] One such heteroaromatic class of compounds, imidazo[1,5-*a*]pyridines have been found in antibiotic cribrostatin-6 isolated from blue marine sponge[2] and in important synthetic bioactive molecules.[3]

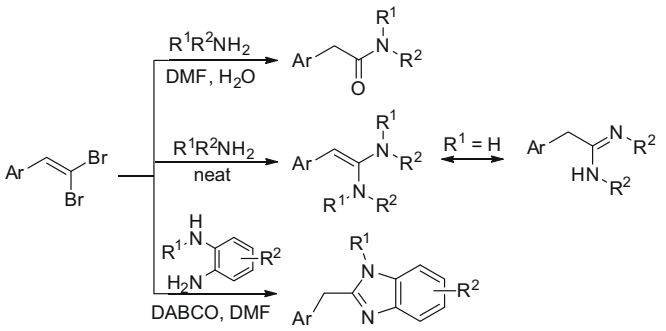
The most common synthesis of imidazo[1,5-*a*]pyridines employs a two-step sequence of acylation or thioacylation of 2-aminomethylpyridines, followed by cyclization.[4] An efficient one-pot procedure with propane phosphoric acid anhydride was recently reported.[5] Another general route for the preparation of imidazo[1,5-*a*]pyridines involves condensation of 2-aminomethylpyridines with aldehydes under oxidative conditions.[6] Another multistep preparation of imidazo[1,5-*a*]pyridines is also reported, such as sequential van Leusen/intramolecular Heck reactions,[7a] benzotriazole-mediated reaction,[7b] and ammonium acetate-mediated condensation of pyridyl ketones with aldehydes.[7c]

These preparations of imidazo[1,5-*a*]pyridines often employ either toxic, strongly acidic, corrosive reagents, or involve multistep syntheses. Therefore alternative methods are still of interest to organic and medicinal chemists. Previously in our laboratory, 1,1-dibromo-1-alkenes were found to be versatile intermediates[8] in the synthesis of isocoumarins,[8a] trisubstituted alkenes, unsymmetrical alkynes,[8b,d] and 1,3-dialkynes.[8c] More recently, we and others reported that 1,1-dibromo-1-alkenes could be employed as synthons for activated carboxylic acids, to prepare amides[9] and amidines[10] in excellent yields from 2-aryl-1,1-dibromoethenes and alkyl amines under mild reaction conditions (Scheme 1). This versatility of 1,1-dibromo-1-alkenes was further demonstrated in the preparation of benzimidazoles.[11] We now report an effective synthesis of imidazo[1,5-*a*]pyridines from 1,1-dibromo-1-alkenes under mild basic conditions.

Initially, the optimized reaction conditions for benzimidazole preparation[11] were applied to the reaction of methyl 4-(2,2-dibromovinyl)benzoate (**1a**) and 2-aminomethylpyridine (**2a**), as shown in Scheme 2. However, only low yield (15%) of methyl 4-(imidazo[1,5-*a*]pyridin-3-ylmethyl)benzoate (**3a**) was isolated, along with low yields of amide (**4a**) and amidine (**5a**).

These poor results prompted us to optimize the reaction conditions for the formation of (**3a**, Table 1). Contrary to previously reported reaction conditions for the synthesis of amides[9a] or benzimidazoles,[11] organic bases (Table 1, entries 1 and 2) were not suitable for this transformation.[12] On the other hand, heating the reaction with anhyd $NaHCO_3$ in DMF gave a good yield of the desired product (**3a**) based on HPLC analysis. This led us to examine other inorganic bases, and it was found that aq Na_2CO_3 in DMF gave the best yield. The product (**3a**) was partially hydrolyzed at 90 °C (Table 1, entry 6), and that problem could be overcome with lower reaction temperature (Table 1, entry 8).

With the optimized reaction conditions, the scope of the reaction was examined, and the results are summarized in Table 2. The reaction is sensitive to steric hindrance (Table 2, entry 1). A significant amount of amide (**4b**) was formed. When the reaction



Scheme 1. 2-Aryl-1,1-dibromoethenes as equivalents to activated carboxylic acids.

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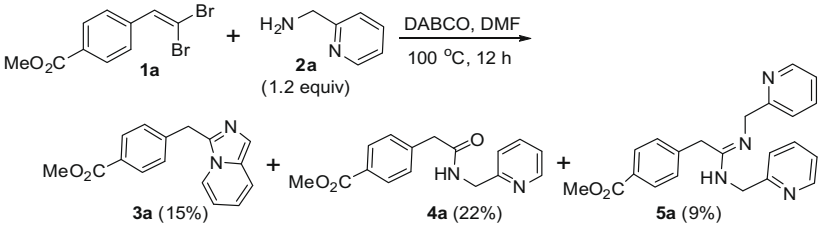
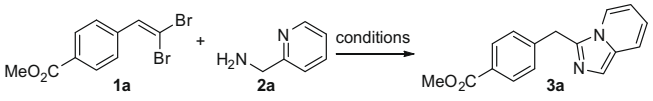


Scheme 2. Synthesis of imidazo[1,5-*a*]pyridine **3a** with DABCO base.

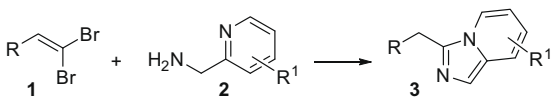
Table 1
Optimization of reaction conditions[a]

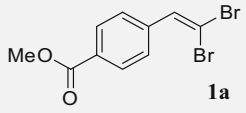
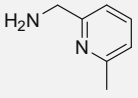
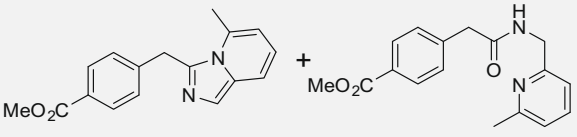
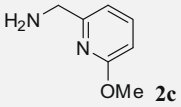
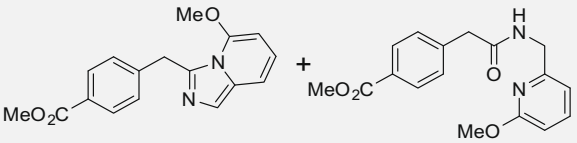
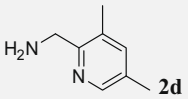
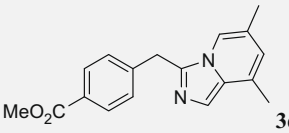


Entry	Solvent	Base (equiv)	*T* (°C), *t* (h)	Yield[b] (%)
1	DMF	DIEA (3)	90, 12	23[c]
2	DMF	DABCO (3)	90, 6	37[c]
3	DMF	$NaHCO_3$ (3)	90, 6	54
4	DMSO	$NaHCO_3$ (3)	90, 6	49
5	DMF	Na_2CO_3 (2)	90, 6	79
7	DMF	K_2CO_3 (2)	90, 6	21
6	DMF	Na_2CO_3 (2, 1.0 M, aq)	90, 6	72, 9 (acid)[d]
8	DMF	Na_2CO_3 (2, 1.0 M, aq)	80, 20	86 (69%)[e]

[a] Reaction conditions: **1a** (0.50 mmol), **2a** (0.60 mmol), solvent (2.5 mL). After **1a** was consumed, 4-phenyl-2-cyanopyridine (0.0 mmol) was added to the mixture as an internal standard, and the reaction mixture was analyzed by HPLC–MS.
[b] Yield was calculated based on HPLC analysis with 4-phenylpyridine as the internal standard.
[c] Small amount of amide **4a** was also detected by LC–MS.
[d] Aqueous solution of Na_2CO_3 (2.0 M) was used, and the corresponding acid was detected from HPLC–MS analysis.
[e] Yield in parentheses (69%) is the isolated yield.

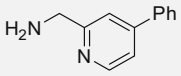
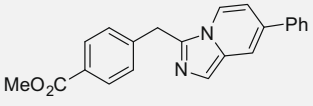
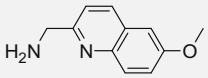
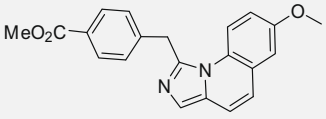
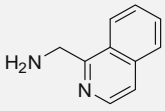
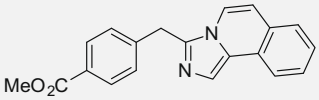
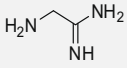
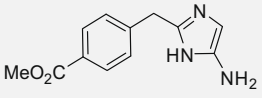
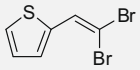
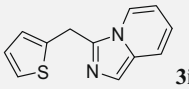
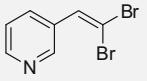
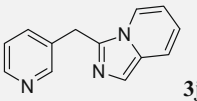
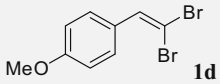
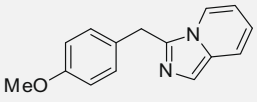
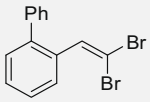
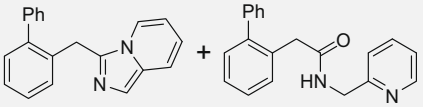
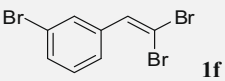
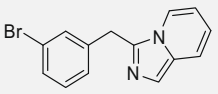
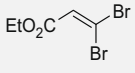
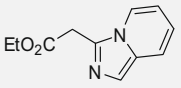
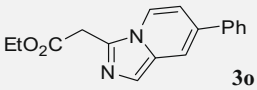
Table 2
Preparations of imidazo[1,5-*a*]pyridines[14]



Entry	Dibromide **1**	Amine **2**	Temp, time	Product	Yield (%)
1	 **1a**	 **2b**	80 °C, 20 h	 **3b** + **4b**	**3b** (36), **4b** (31)
2		 **2c**	80 °C, 20 h	 **3c** + **4c**	**3c** (0), **4c** (40)
3		 **2d**	80 °C, 20 h	 **3d**	**3d** (64)

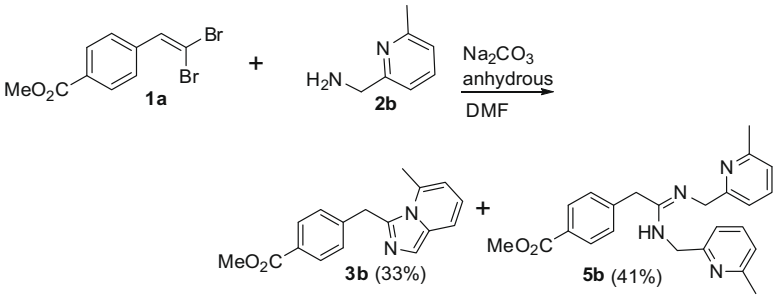
(*continued on next page*)

Table 2 (*continued*)

Entry	Dibromide **1**	Amine **2**	Temp, time	Product	Yield (%)
4		 **2e**	80 °C, 20 h	 **3e**	**3e** (52)
5		 **2f**	80 °C, 20 h	 **3f**	**3f** (51)
6		 **2g**	80 °C, 20 h	 **3g**	**3g** (43)
7		 **2h**	80 °C, 20 h	 **3h**	**3h** (0)
8	 **1b**	**2a**	80 °C, 20 h	 **3i**	**3i** (49)
9	 **1c**	**2a**	80 °C, 20 h	 **3j**	**3j** (59)
10	 **1d**	**2a**	80 °C, 20 h	 **3k**	**3k** (41)
11	 **1e**	**2a**	80 °C, 20 h	 **3b** + **4b**	**3l** (36), **4l** (19)
12	 **1f**	**2a**	80 °C, 20 h	 **3m**	**3m** (60)
13	 **1g**	**2a**	80 °C, 10 h	 **3n**	**3n** (46)
14		**2e**	80 °C, 10 h	 **3o**	**3o** (62)

was run with anhyd Na_2CO_3, the yield of the desired product (**3b**) did not improve, and instead of amide (**4b**), amidine (**5b**) was formed (Scheme 3).

Furthermore, when 2-aminomethyl-6-methoxypyridine (**2c**) was used, no desired product (**3c**) but only amide (**4c**) was isolated (Table 2, entry 2). Significantly lower nucleophilicity of pyridyl 'N' (relative to pyridine) from 6-methoxy substitution,[13] in addition to the steric hindrance of 6-substitution, may be the reason for this observation. The steric sensitivity was further shown by dibromide **1e** (Table 2, entry 11). Even though the phenyl group is not immediately next to the reaction center, a significant amount of by-product amide (**4l**) was isolated. However, 2-aminomethyl-6-



Scheme 3. Influence of steric hinderance on the reaction.

methoxyquinoline (**2f**) afforded good yield of the desired product (**3f**) without the corresponding amide. Neutral substitutions at positions other than 'C-6' of 2-aminomethylpyridine are well tolerated (Table 2, entries 3, 4, 14).

Substitutions on the aryl ring of 2-aryl-1,1-dibromoethene are well tolerated, as both electron-donating (**1d**) and electron-withdrawing (**1a**, **1c**) substrates gave good yields of the corresponding products. Heteroaromatic substitutions (**1b**, **1c**) are also tolerated. Bromine substitution on aryl ring (**1f**) does not affect the reaction, while it may provide a handle for further manipulation of the resulting product (**3m**). Finally, an ester group in place of aryl ring gave good yields of products (entries 13 and 14). This would broaden the scope of this reaction.

In summary, a facile synthesis of imidazo[1,5-*a*]pyridines is described. This method employs a mild inorganic base and moderate heating, which are different from existing reaction conditions for the preparation of this class of compounds. Therefore, the method should complement the existing synthesis of imidazo[1,5-*a*]pyridines, and will find applications in both synthetic organic and medicinal chemistry.

Acknowledgments

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12. Besides di(isopropyl)ethylamine (DIEA) and DABCO, 4-methylmorpholine, DBU, tetramethylguanidine also failed to give good yields of the desired product.
13. The nucleophilicity of pyridinyl 'N' is parallel to its basicity: 2-Methoxypyridine is a significantly weaker base than pyridine or 2-methy pyridine (p*K*a's are 3.3 for 2-methoxypyridine, 5.2 for pyridine, and 6.0 for 2-methylpyridine): Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell: Oxford, 2000. Chapter 5.
14. Typical reaction procedure: A mixture of methyl 4-(2,2-dibromovinyl)benzoate (**1a**, 320 mg, 1.0 mmol) and 2-aminomethylpyridine (**2a**, 119 mg, 1.1 mmol) in DMF (5 mL) and Na_2CO_3 (1.0 M, 2.0 mmol) was heated at 80 °C for 20 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (80 mL), washed with water (10 mL) and brine (5 mL), dried over anhyd Na_2SO_4, and concentrated. The residue was subjected to silica gel chromatography using 10% methanol in dichloromethane to give methyl 4-(imidazo[1,5-*a*]pyridin-3-ylmethyl)benzoate (**3a**, 184 mg, 69%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.96 (d, J = 8.1 Hz, 2H),7.56 (d, J = 7.5 Hz, 1H), 7.44 (t, J = 4.4 Hz, 2H), 7.26 (d, J = 8.1 Hz, 2H), 6.66 (t, J = 7.8 Hz, 1H), 6.47 (t, J = 6.8 Hz, 1H), 4.49 (s, 2H), 3.90 (s, 3H); LC–MS (ESI+) m/z: 267 (M+H).