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A modular approach toward the synthesis of 2,4-disubstituted pyridines

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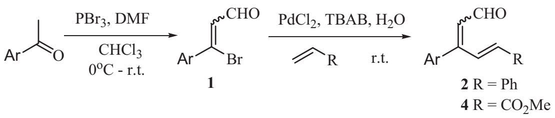
ABSTRACT

A number of 2,4-disubstituted pyridines have been synthesized using α,β,γ,δ-unsaturated aldehydes and ammonium chloride in the presence of triethylamine in acetonitrile solvent at 80 °C under air balloon.

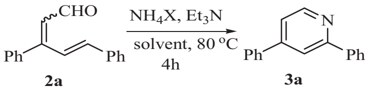
Heterocyclic compounds gradually become more attractive targets in organic and medicinal chemistry due to their great chemical and biological importance.[1]Among numerous heterocycles, pyridine moiety has always been one of the most important frameworks. Substituted pyridines are important constituents of a wide range of natural products, pharmaceutical drugs, and various kinds of functional materials.[2] As a consequence; different synthetic methods are reported in the literature from early days for the construction of pyridine rings. The traditional methods for the synthesis of pyridine rings are based upon condensation reactions of carbonyl compounds with amines, for example Hantzsch synthesis, and Guareschi synthesis.[3] However, from these methods, the high yields of single products are usually obtained for symmetrically substituted systems. Other classical methods are based upon thermal or metal-catalyzed cycloaddition reactions; but allow a specific location of the substituents in the pyridine core.[4]

Although a large amount of work has been devoted for their synthesis, versatile and flexible methodologies to construct unsymmetrically substituted pyridines using readily accessible starting materials are still of critical importance. In this communication we report the synthesis of a series of 2,4-disubstituted pyridines from a modular framework α,β,γ,δ-unsaturated aldehydes in a single step under mild reaction conditions. The final step involves three consecutive steps: imine formation,[5] electrocyclization,[6] and aerial oxidation.[3d,6b,7]



Scheme 1. Synthesis of α,β,γ,δ-unsaturated aldehydes.

Table 1
Screening of the reaction conditions*



Entry	Ammonium salt	Solvent	Temperature (°C)	Time (h)	Yield** (%)
1	NH_4Cl	EtOH	80	6	64
2	NH_4Cl	Toluene	80	6	61
3	NH_4Cl	MeCN	80	4	82
4	NH_4Cl	DCE	80	4	79
5	NH_4Cl	DMF	80	4	80
6	NH_4OAc	MeCN	80	4	76
7	$(NH_4)_2CO_3$	MeCN	80	4	72
8	NH_4Cl	MeCN	60	24	56
9	NH_4Cl	MeCN	90	3	80

* Reaction conditions: **2a** (0.5 mmol), NH_4X (1.5 equiv), Et_3N (3 equiv), solvent (3 mL) refluxed under air balloon.
** Yields were calculated after purification of products.

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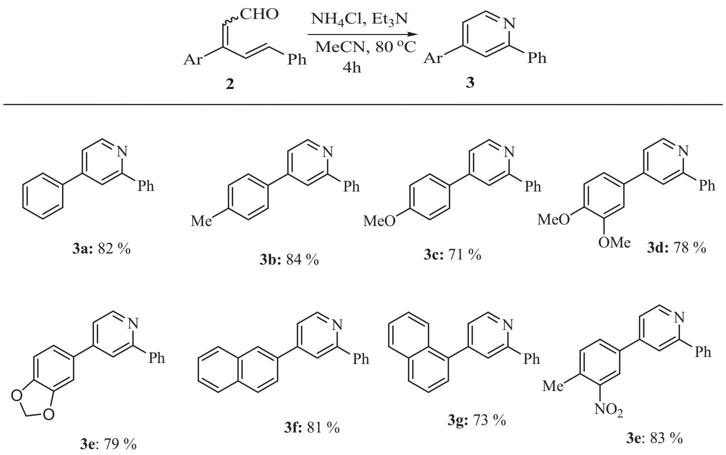
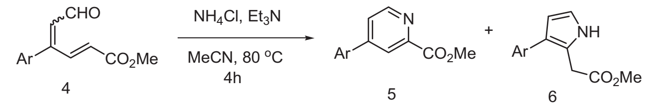
Table 2
Synthesis of 2,4-disubstituted pyridines[*]



3a: 82 %
3b: 84 %
3c: 71 %
3d: 78 %
3e: 79 %
3f: 81 %
3g: 73 %
3e: 83 %

[*] Yields were determined after purification of products by column chromatography.

Table 3
Synthesis of substituted pyridines and pyrroles



Entry	Substrate	Ar	Product	Yield[*] (%)	Ratio
1	**4a**	C_6H_5–	5a + 6a	37 + 24	60:40
2	**4b**	*p*-MeO-C_6H_4–	5b + 6b	25 + 38	40:60
3	**4c**	3,4-$(MeO)_2$-C_6H_3–	5c + 6c	30 + 32	48:52
4	**4d**	3,4-(CH_2O_2)-C_6H_3–	5d + 6d	28 + 38	42:58
5	**4e**	*m*-Me-C_6H_4–	5e + 6e	40 + 25	61:39
6	**4f**	naphthalen-2-yl–	5f + 6f	43 + 26	62:38

[*] Yield refers to the isolated yield after purification.

Attention was first focused on the synthesis of a suitably substituted starting framework α,β,γ,δ-unsaturated aldehydes and we have performed the task efficiently in two steps starting from a readily available starting material having a keto-methyl group. First we synthesized β-bromovinylaldehydes (**1**) by Vilsmeier–Haack type of reaction using PBr_3 and DMF as the reagent.[8] Then $PdCl_2$ catalyzed coupling reaction with styrene or methyl acrylate correspondingly, in water afforded the desired framework α,β,γ,δ-unsaturated aldehydes (**2** and **4**) (Scheme 1).[9]

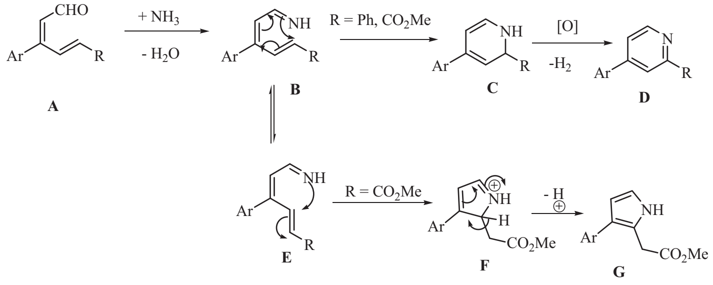
The initial experiment was carried out by heating a mixture of compound **2a** (1 equiv), NH_4Cl (1.5 equiv), and Et_3N (3 equiv) in ethanol solvent under air balloon at 80 °C for 6 h and it afforded 2,4-diphenyl pyridine (**3a**) in 64% yield. After getting success we used different ammonium salts and solvents to optimize the reaction conditions. The results are summarized in Table 1.

From Table 1, we concluded that the optimized reaction conditions were substrate (0.5 equiv), NH_4Cl (1.5 equiv), Et_3N (3 equiv), and acetonitrile (3 mL) refluxed under air balloon at 80 °C for 3–4 h. These optimized reaction conditions were then applied for the synthesis of different 2,4-disubstituted pyridines (Table 2).

The overall yields of compounds **3a–3g** (Table 2) were moderate to good. Now, for the substrates having an electron withdrawing group at δ-position, there is a possibility of nucleophilic attack at γ-carbon with respect to the aldehyde. Therefore two types of products are expected from the substrates α,β,γ,δ-unsaturated aldehydes bearing a methyl carboxylate as the functional group at δ-position and practically we got 2,3-disubstituted pyrroles along with the normal product, 2,4-disubstituted pyridines. The results are shown in Table 3.

From the above results (Table 3), we observed that the nucleophilic addition becomes more favorable for the electron rich aromatic rings (Table 3, entries 2–4) and hence gave pyrrole rings as the major product. Plausible rational for the formation of different products is shown in Scheme 2. In the presence of triethylamine, ammonium chloride releases ammonia which then forms an imine **B** intermediate by reacting with the substrate **A**. Intermediate **B** is a 6π-electron system; thus it undergoes an electrocyclization reaction under thermal condition and affords dihydropyridine intermediate **C**. Now our desired product 2,4-disubstituted pyridine is formed by the aerial oxidation of **C**.

On the other hand, intermediate **B** remains in equilibrium with its conformational isomer **E**. In the presence of an electron withdrawing group at δ-position, a nucleophilic addition occurs at γ-position by the lone pair electrons of imine nitrogen. Thus a cationic intermediate **F** forms which finally gives 2,3-disubstituted pyrroles **G** via bond rearrangement and loss of a proton.



Scheme 2. Plausible rational for the formation of products.

In conclusion, we have developed a modular and straight forward method for the synthesis of 2,4-disubstituted pyridines from readily available starting materials under mild reaction conditions.[10] In addition, 2,3-disubstituted pyrroles are also formed as important side products. The use of this methodology for the synthesis of a few natural products is under progress in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data (detailed experimental procedure and spectral data for the compounds **3a**–**g**, **5a**–**f** and **6a**–**f**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.06.092.

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10. General procedure for the synthesis of 2,4-disubstituted pyridines: The substrate (1 mmol) and NH_4Cl (1.5 equiv) were taken in a two-necked round bottomed flask fitted with a condenser. Then 3 mL of acetonitrile and Et_3N (3 equiv) were added and refluxed at 80 °C under air balloon for 3–4 h. After completion of the reaction, the reaction mixture was allowed to cool to room temperature, diluted with water, and extracted with ethyl acetate (3 × 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography using silica gel (60–120 mesh) and hexane/EtOAc (10:1) as eluent.