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Very Important Publication

γ-Functionalization of α,β-Unsaturated Nitrile in Mild Condition: Versatile Synthesis of 4-Aryl-2-Bromopyridines

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Abstract: This report describes the synthesis of 4-aryl-2-halopyridines *via* γ-functionalization of α,β-unsaturated nitriles, which were obtained by the HWE reaction with the corresponding ketones. The key features of our methods involve a conjugated γ-enamine formation of α,β-unsaturated nitrile (enamino nitrile), followed by consecutive intramolecular cyclization, resulting in heteroaromatic compounds like 2-halopyridines, α-pyrone, etc.

Keywords: γ-functionalization; 2-halopyridine; α-pyrone; α,β-unsaturated nitrile; vinylogus enaminonitrile

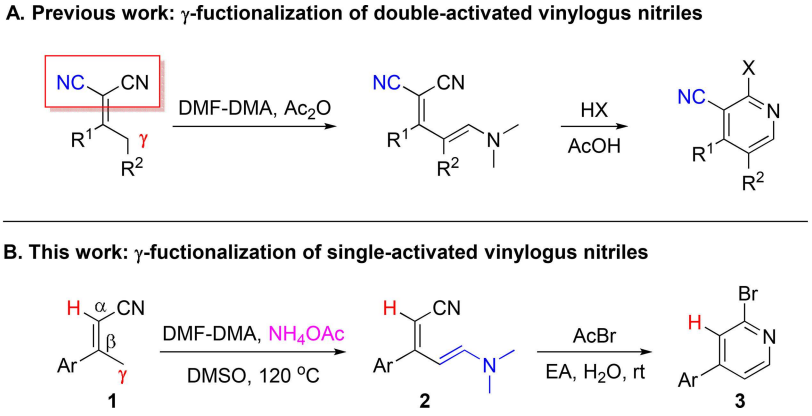
Introduction

Pyridine containing heterocyclic compounds receive significant attentions because of their privileged role in various biological activities, and their presence in pharmaceuticals and various important molecules.[1] For example, they are present in niacin (vitamin B_3), pyridoxine (vitamin B_6), nicotine, etc.[2] From a pharmaceutical perspective, pyridines have been at the forefront of drug development such as atazanavir for HIV, and imatinib mesylate for chronic myelogenous leukemia, etc,.[3] In addition, this moieties are also used as chelating agents in coordination chemistry;[4] as catalysts, directing groups, and bases in organic chemistry;[5] as herbicides and insecticides in agrochemistry,[6] and so on.[7–9] Consequently, tremendous efforts have been made on the synthesis of functionalized pyridines by several groups over the past few decades.[10]

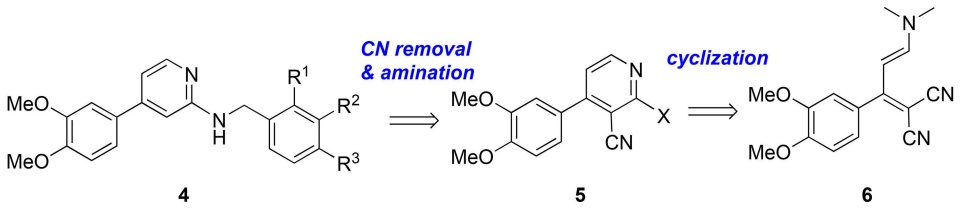
The synthesis of halide-containing pyridine is one of the most fascinating phenomena, mainly due to their interesting characteristics and potential for further functionalization. In particular, the synthesis of 2-halopyridine has been important for medicinal chemistry purposes.[11]

In this context, several groups were able to achieve synthesis of the vinylogus enamino malononitriles from alkylidenemalononitrile, which were easily transformed into the desired 2-bromonicotinonitriles after sequential reactions (Scheme 1A, X = Br).[12,13] Even though much progress has been achieved, *two EWG groups* were crucial to obtain the requisite precursor for designated cyclization in previously described methods.[12–14] Moreover, removal of residual nitrile proved to be very difficult. During the course of our continuing studies directed toward the synthesis of potent inhibitors of melanogenesis,[15] we have been interested in the versatile synthesis of CGA (chlorogenic acid) derivatives **4** possessing pyridine moiety (Scheme 2). However, it was concluded that all attempts to remove unnecessary nitrile group of the cyclized product **5** failed.

Thus, it was necessary to devise a γ-functionalization of the single-activated substrate (e.g **1**, Scheme 1B) rather than that of the double-activated substrate (e.g. **1q**). To the best of our knowledge, synthetic methods for enamino nitriles with just *one*



Scheme 1. Previous work and our approach for synthesis of 2-bromopyridine.



Scheme 2. Our retrosynthetic representation for synthesis of 4-aryl-2-amino pyridine derivatives.

EWG have not been reported (Scheme 1).[16] Herein, we describe our efforts to develop γ-functionalization of α,β-unsaturated nitriles. Salient features of our present method are an efficient γ-enamine formation of single-activated α,β-unsaturated nitriles, followed by intramolecular cyclization using a halogen source.

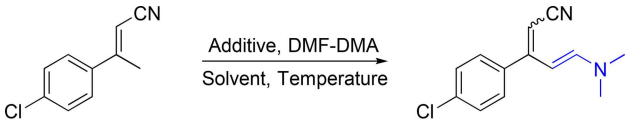
Result and Discussion

The starting material **1i** was easily obtained from the acetophenone via HWE reaction with corresponding phosphonate in high yield as a *E/Z* mixture (see S.I). With the key substrate for further transformation in hands, we attempted to explore the optimal reaction condition (Table 1). We used alkylidene nitrile **1i** (1.0 equiv.) and DMF–DMA (*N,N*-dimethylformamide dimethyl acetal, 5.0 equiv.) as an initial condition. When we performed the reaction at room temperature, without any additives, no enamino nitrile **2i** was observed, while we were delighted to obtain 39% yield at 120 °C after 24 h (entry 1).[17] We next attempted Mcquade's reaction conditions (Ac_2O, DCM),[13] which did not afford the desired product (entry 2). Later, to activate nitrile and/or DMF–DMA we used acid or base as an additive, which proved to be not helpful (entry 3).

Delightfully, the reaction with ammonium acetate at room temperature afforded the desired enamine **2i** in 43% yield (entry 4). We assumed that the acetate ion could efficiently activate DMF–DMA to generate the active electrophile species. (see the mechanism, Scheme 5). The yield increased to 55% at 120 °C under neat conditions after 2 h. Switching conditions from neat to DMSO solvent showed superior performance and the highest yield of 97% was observed in just 20 min (entry 6) mainly due to the increased solubility of acetate in DMSO. Screening of various amount of additive or other solvents resulted in inferior outcomes and took longer reaction time to complete (entries 7–10). With other acetate sources, the reactions didn't show any significant improvement on the yields. For example, when we used CsOAc, NaOAc, KOAc, or LiOAc instead of NH4OAc, they gave the similar yields (52~60%, entry 11). We also screened different ammonium additives and notably, ammonium carbonate gave comparable yield of **2i** at 95%, while using ammonium chloride and sodium carbonate led to a dramatic decrease in yields (entries 12–14); suggesting that both ammonium and acetate ions could be essential for this transformation.

With the optimal reaction condition for the γ-enamine formation in hands, we next attempted to explore intramolecular cyclization. On the basis of extensive experimentation, it was eventually concluded that using acetyl bromide as a bromide source in EA: H_2O (3:1) was most effective, in terms of yield (84% yield, see S.I). Therefore, the described conditions were used to further explore the scope of the substrates (Table 2). As expected, when we applied optimized conditions to various substrates possessing both elec-

Table 1. Optimization of Reaction Conditions for the Enamine [a].



1i **2i**

Entry	Additive (1.2 equiv.)	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]
1	–	–	120	24	39
2	Ac_2O[c]	DCM	RT/reflux	24	NR
3	Acid or Base[d]	–	120	24	NR
4	NH_4OAc	–	RT	24 h	43
5	NH_4OAc	–	120	2 h	55
6	**NH_4OAc**	**DMSO**	**120**	**20 min**	**97**
7	NH_4OAc[c]	DMSO	120	24	60
8	NH_4OAc[e]	DMSO	120	2	80
9	NH_4OAc	DMF	120	24	48
10	NH_4OAc	Benzene	120	24	59
11	Other acetates	DMSO	120	3	52~60
12	NH_4Cl	DMSO	120	24	14
13	$(NH_4)_2CO_3$	DMSO	120	3	95
14	Na_2CO_3	DMSO	120	3	47

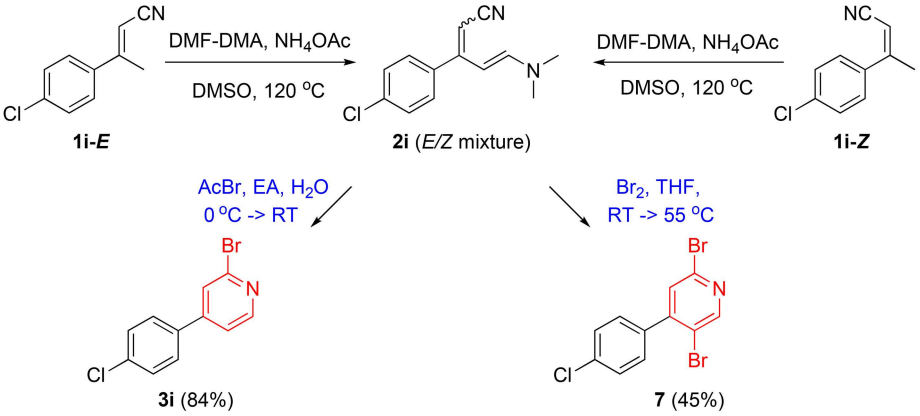
[a] Reaction conditions: **1i** (0.2 mmol, 1.0 equiv.), DMF–DMA (5.0 equiv.), solvent (1.0 M).
[b] Determined by GC using mesitylene as an internal standard.
[c] 20 mol% additive was used,
[d] Acetic acid, NaOMe, DBU and K_2CO_3.
[e] 3.0 equiv. of additive was used, RT = Room Temperature, NR = No Reaction.

tron donating and withdrawing groups in the acetophenones, they were well tolerated and delivered the corresponding products in good to high yields (Table 2). The substrates containing alkyl in *ortho*, *meta* and *para* positions of the aromatic ring afforded the expected products in very high yields (Table 2, **3b–d**). Similarly, methoxy substituents proceeded smoothly and afforded the products in good yields (**3e–f**). Methylenedioxy and methyl sulfide also delivered, the bromo pyridines in excellent yields (**3g–h**). Next, we tested the halogen substituted acetophenones, which were perfectly tolerated and afforded excellent yields (**3i–j**). We concluded that the electron withdrawing groups had no significant negative influence on this reaction as we obtained very good yields (**3k–m**).

Moreover, 2-acetylnaphthalene afforded product **3n** in high yields. Acetyl thiophene also reacted with this condition and rendered the expected product **3o** in 66% yield. Importantly, we synthesized 2-bromonicotino nitrile derivatives by modification of SM. 1-Cyanoacetophenone after three consecutive reactions provided **3p** in 74% yield. On the other hand, all substrate (**1p**, **1q** and **1s**) possessing active methylidene proceeded effectively with our optimized condition afforded the desired products (**3p**, **3q**[13c] and **3s**) in comparable yield.[18] This same method was amenable with α-tetralone, and the initially synthesized dinitrile was successfully converted into the corresponding product **3r**[13c] in 53% yield. Notably, DCM in place of DMSO at room temperature also gave **3p**, **3q** and **3s** in good yields. However, alkyl and aryl substrates at the γ-position of **1** showed the less favorable results. For example, propiophenone did not provide the desired enamine product, while 2-phenylacetophenone gave low yield of the corresponding enamine in less than 20% yield.

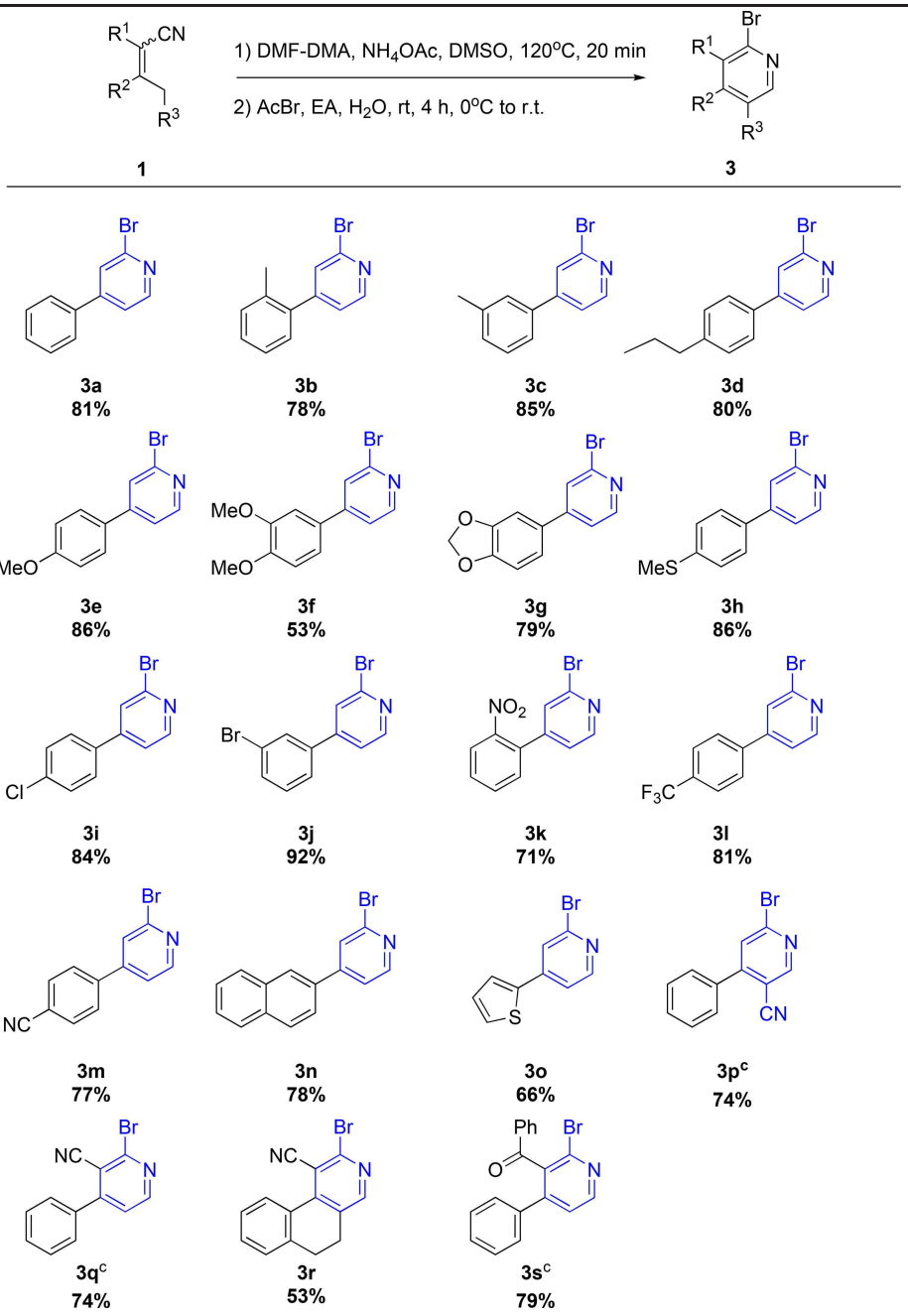
We have successfully isolated both *E* and *Z* isomer alkylidene nitrile of **1i** after the HWE reaction, and did separate enamino nitrile synthesis, which fortunately provided **2i** as *E/Z* mixture (Scheme 3). The reaction with bromine provided dibromo derivative **7** in 45%, and using our optimized condition delivered the expected product **3i** in 84% yield.

To gain a deep insight into the reaction pathway, we have done several control experiments. Considering that the reaction of **1i** with NaOMe did not give any conversion under neat conditions (Table 1, entry 3), we



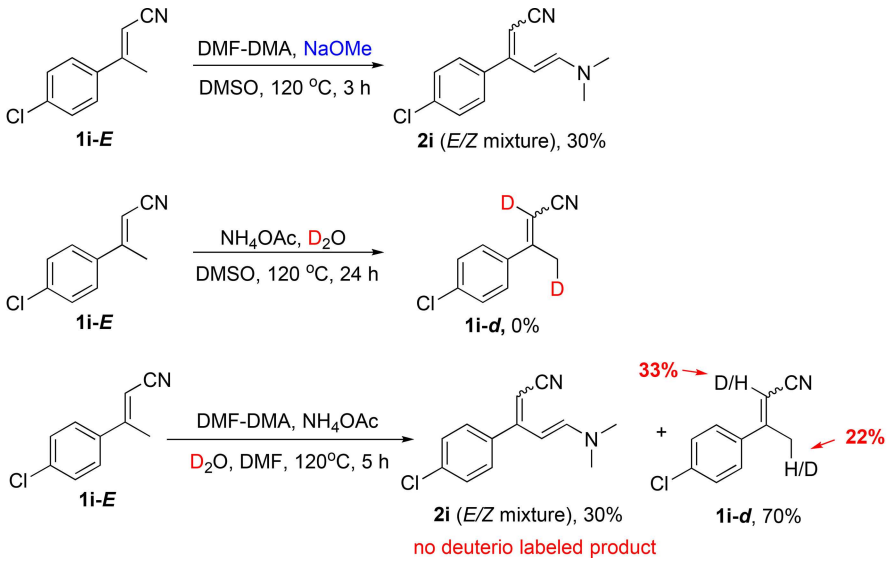
Scheme 3. Control Experiments A.

Table 2. Synthesis of 2-Bromopyridine Derivatives [a], [b].

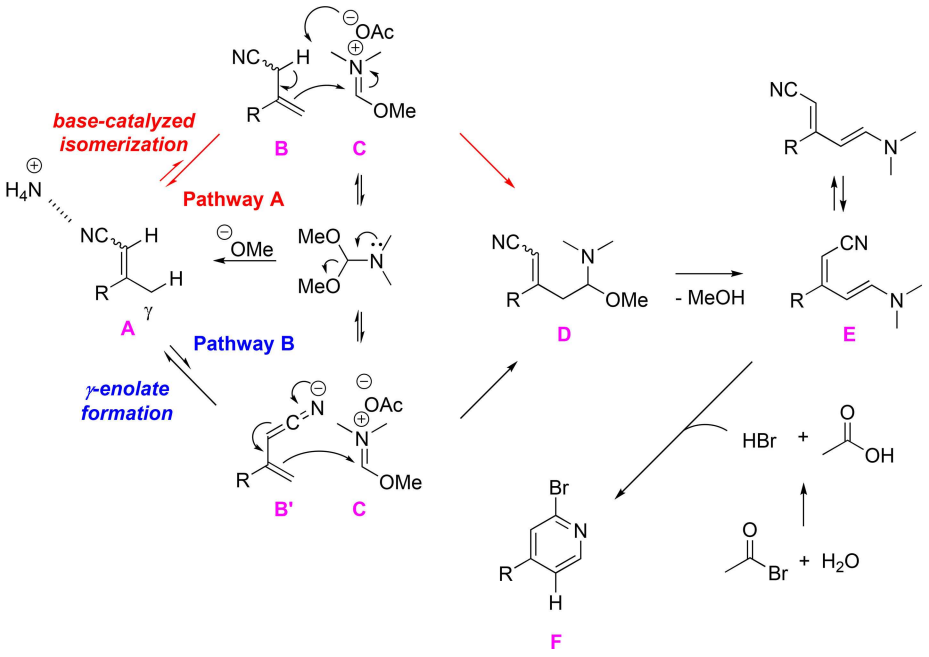


[a] Reaction condition: see supporting information for details.
[b] Isolated yield after two steps.
[c] Only changes using solvent DCM.

first attempted the same reaction in DMSO to afford the desire product **2i** in 30% yield. We surmised that DMF–DMA initially dissociates into both alkoxyiminium cation and methoxide ion, which acts as a base to abstract γ-hydrogen. The product formation is mainly dependent on alkoxyiminium cation's stabilization. For instance, when the reaction was carried out with NaOMe instead of NH_4OAc, diminished yield was observed at 30%, this may be due to the low stabilization ability of NaOMe than NH_4OAc. Finally, when D_2O was used as a proton source to find out whether the reaction pathway is an ene type or an enolate type reaction, mixture of products containing deuterium exchanged products **1i**–***d*** was obtained in 70% yield, along with 30% of the desired product **2i**. The above results clearly demonstrate that both are



Scheme 4. Control Experiments B.



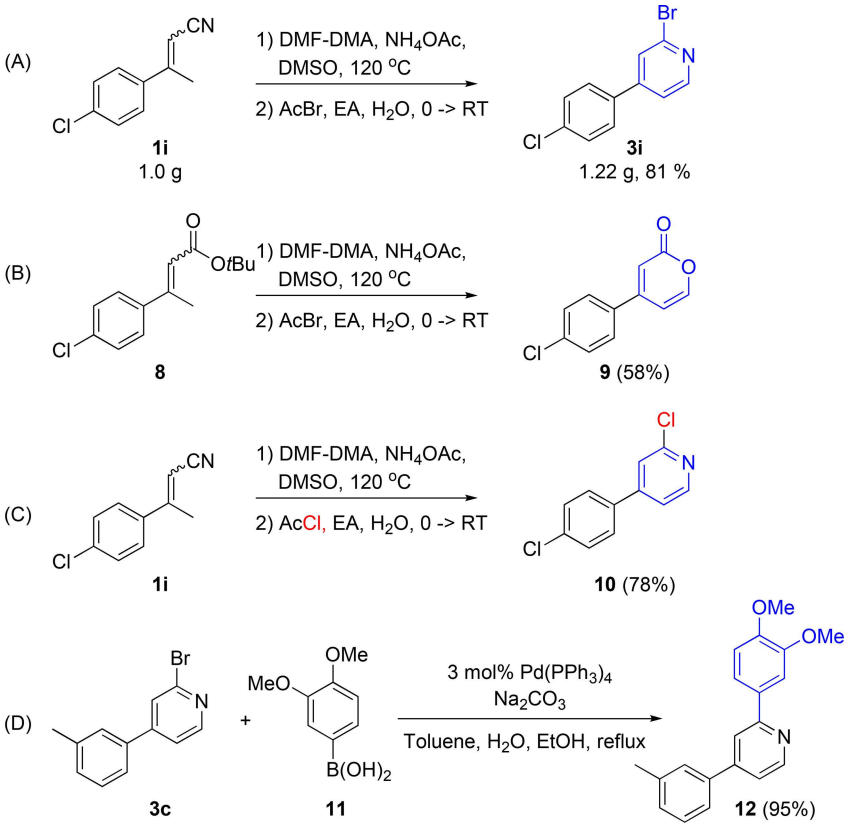
Scheme 5. Plausible Reaction Mechanism.

possible ways to produce the product. Moreover, this also reveals that both of DMF–DMA and NH_4OAc are very essential for this reaction, and without these, no deuterated product **1 i**–***d*** is obtained.

Based on the above experiments we depict a plausible mechanism in Scheme 5. In the reaction pathway A, nitrile group of the **A** could be activated by ammonium ion and methoxide evolved from DMF–DMA was initiate base-catalyzed isomerization to give both Ene isomer **B** as well as iminium ion **C**. Much reactive isomer **B** then could react with **C** to deliver **D**. Intermediate **D** subsequently eliminate methanol affords enaminonitrile **E**. It is then an intramolecular Pinner cyclization with *in-situ* generated HBr gave the final 2-bromopyridine **F**.[13]

In the pathway B, extended conjugated enolate **B'** was induced by the methoxide obtained from DMF–DMA. **B'** then attacks the iminium ion **C** to produce **D**.

To check the feasibility of this reaction condition, we also tested this with gram scale synthesis which produced 81% overall yields of 2-bromo pyridine **3 i**



Scheme 6. Gram-Scale Reaction and Applications.

after two steps (Scheme 6). Meanwhile we introduced *t*-butylester **8** as EWG instead of CN, which converted into *α*-pyrone **9** in good yield. The reaction scope was extended to the synthesis of 2-chloro pyridine **10**. At the final intramolecular cyclization, using acetyl chloride instead of acetyl bromide provided the above product in high yield.[19] Finally, the synthesized bromo–pyridine **3 c** successfully underwent Suzuki-Miyaura coupling and afforded the corresponding coupling product **12** with excellent yield of 95%.

Conclusion

In conclusion, we have developed a novel method for 4-aryl-2-halopyridines by employing *γ*-enamine formation of *α,β*-unsaturated nitriles, followed by Pinner cyclization. Compared with the previous reports which used the activated alkylidene dinitriles, this method offers several advantages like mild reaction condition, simplicity of operation and atom-ecomomic process. We also demonstrated that this protocol can be applied to *α*-pyrone synthesis, as well as gram-scale reaction. Efforts toward various *γ*-functionalization of *α,β*-unsaturated EWGs with other electrophiles are currently underway, and a full account of application to the heteroaromatic compounds will be reported in due course.

Experimental Section

General procedure for the 1st step: To a solution of substituted *α,β*-unsaturated nitriles **1 a–s** (0.65 mmol, 1.0 equiv.) and NH_4OAc (0.78 mmol, 1.2 equiv.) in DMSO (0.65 mL), DMF–DMA (3.25 mmol, 5.0 equiv.) was added. The resulting reaction mixture was heated under 120 °C until reaction was completed as monitored by TLC. The reaction mixture was subsequently allowed to cool to room temperature, diluted with water and extracted with chloroform. The combined organic layers were washed with a saturated NaCl solution, dried over anhydrous $MgSO_4$ and evaporated. The resulting enamines **2** were taken to next reaction without any further purification.

General procedure for the 2nd step: To a solution of enamines **2** (0.65 mmol, 1.0 equiv.) in ethyl acetate (1.3 mL) and H_2O (0.4 mL), AcBr (13.0 mmol, 20.0 equiv.) was added slowly drop wise at 0 °C in ice bath. The ice bath was removed and the resulting mixture was warmed up to room temperature and stirred for 4 hours. After the reaction was complete as monitored by TLC, it was quenched with a saturated aqueous solution of $NaHCO_3$. After separation of the organic layer, the resulting mixture was extracted with ethyl acetate and the combined organic phase was dried over anhydrous $MgSO_4$. After filtration and evaporation of the solvent, the crude residue was purified by chromatography (silica gel, 4–10% ethyl acetate in hexanes) to afford the 2-bromopyridine derivatives **3**.

Acknowledgements

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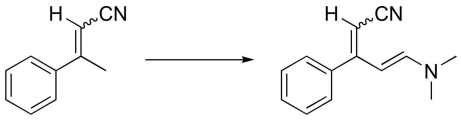
[16] When we used the below structure in the Sci-Finder search, no results were found. Similarly, we also searched some of the common key words which are related to our reactions, the obtained results show that two EWGs were involved rather than just one EWG as ours.



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UPDATES

γ-Functionalization of *α,β*-Unsaturated Nitrile in Mild Condition: Versatile Synthesis of 4-Aryl-2-Bromopyridines

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