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Simple and efficient syntheses of novel benzo[4,5]imidazo[1,2-*a*]pyridine derivatives

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ABSTRACT

A novel series of benzo[4,5]imidazo[1,2-*a*]pyridine derivatives is synthesized through the reaction of 2-(1*H*-benzo[*d*]imidazol-2-yl)acetonitrile and different ethyl 2,4-dioxo-4-arylbutanoate derivatives in the presence of piperidine in refluxing EtOH. All the products are easily prepared within 25–45 min in good to excellent yields.

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Benzimidazole is a vital structural motif in a variety of biologically active compounds,[1] and plays an important role in drug discovery developments.[2] Among various benzimidazoles, fused frameworks, especially azino-fused cyclic derivatives possess an extensive array of biological properties such as anticancer,[2–4] antimalarial,[5] antifungal,[6] antibacterial,[7] and antiviral.[8] Benzo[4,5]imidazo[1,2-*a*]pyridines bearing a cyano group at the 4-position possess valuable properties (compounds **A**,[3] **B**,[4] **C**,[5] **D**,[6] and **E**;[8] Fig. 1) have attracted the attention of medicinal chemists as well as synthetic organic chemists, and consequently significant efforts have been devoted to develop efficient methods for the synthesis of this fused system. In spite of their versatile biological properties, there are few reports in the literature on practical library-based synthetic procedures for the construction of cyanobenzimidazopyridines.

There are numerous synthetic approaches for the preparation of benzo[4,5]imidazo[1,2-*a*]pyridines and some of them have opened new horizons in the synthesis of benzimidazopyridines. For example, the synthesis of benzimidazopyridines via intramolecular copper-catalyzed N-arylation of cyclic amidines,[9] photo-stimulated cyclization of 2-(2-halophenylamino)pyridines in liquid ammonia,[10] metal-catalyzed coupling of *o*-haloanilines and *o*-halopyridines,[11,12] intramolecular C–H amination of *N*-arylpyridin-2-amines,[13–15] fusing 1*H*-benzimidazole-2-acetonitrile with β-ketoesters,[16,17] metal-catalyzed cyclization of *o*-alkynylaldehydes and substituted benzenediamines,[18] [3+3] cyclocondensation of dianions of 2-methyl and 2-cyanomethyl benzimidazoles with α-oxoketene dithioacetals,[19] palladium-mediated cyclization of *N*-benzyl-2-aminopyridines,[20] twofold or fourfold amination of N-substituted amidines,[21] and condensation reactions of 1*H*-benzimidazol-2-ylacetonitrile with 3-substituted chromones.[22]

In view of our long-standing interest in the synthesis of novel heterocycles[23–25] herein, we describe a simple, rapid, and versatile procedure for the preparation of benzo[4,5]imidazo[1,2-*a*]pyridines **3** (Scheme 1).

Initially, the desired starting materials, including 2-(1*H*-benzo[*d*]imidazol-2-yl)acetonitrile (**1**) [prepared from *o*-phenylenediamine (**4**) and ethyl cyanoacetate (**5**)] and ethyl 2,4-dioxo-4-arylbutanoates **2** [prepared from acetophenones **6** and diethyl oxalate (**7**)] were synthesized by conventional methods according to the literature (Scheme 1).[26,27] Next, the reaction of compound **1** and ethyl 2,4-dioxo-4-phenylbutanoate (**2a**) was studied comprehensively as a representative example. To access product **3a**

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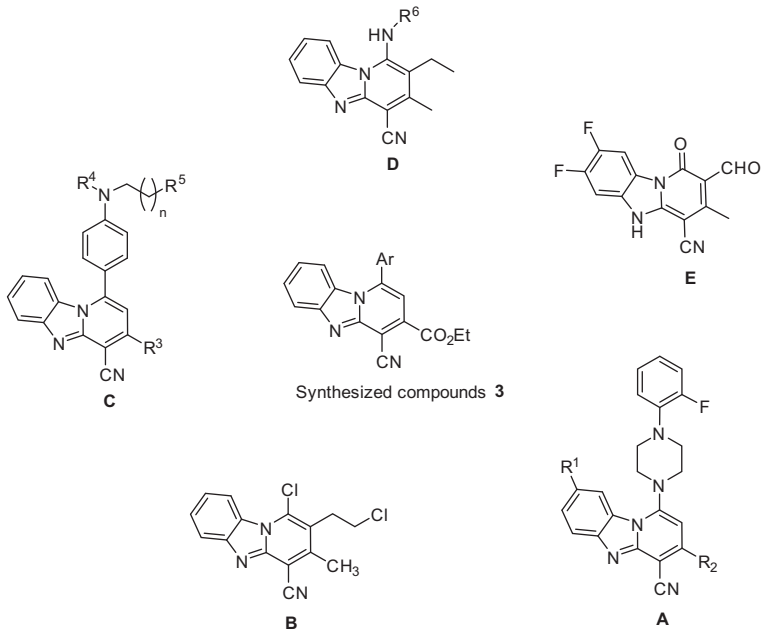
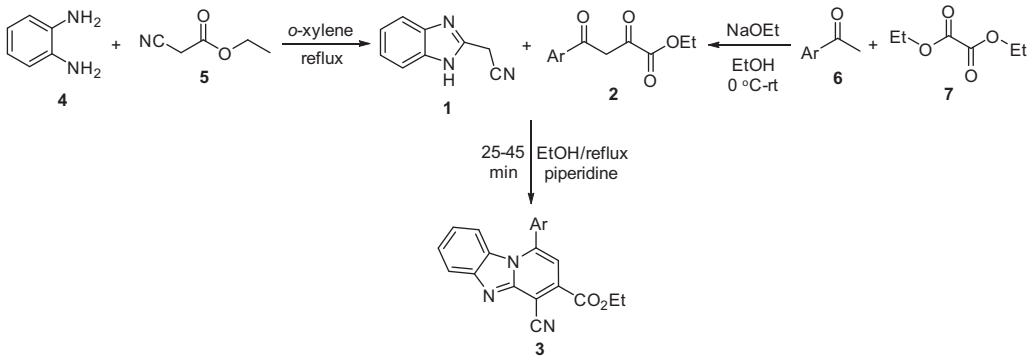
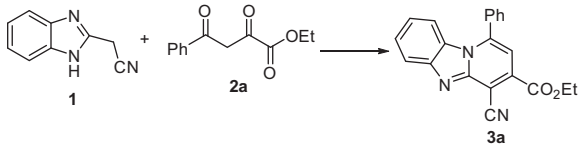


Figure 1. Structures of bioactive cyano-benzo[4,5]imidazo[1,2-*a*]pyridines **A**–**E**, and synthesized compounds **3**.



Scheme 1. Synthesis of novel benzo[4,5]imidazo[1,2-*a*]pyridines **3**.

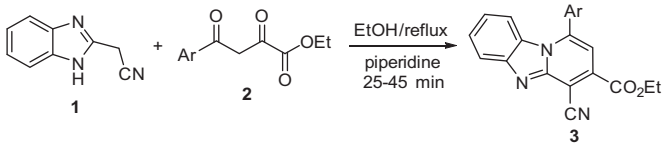
Table 1
Investigation of various conditions for the reaction of **1** and **2a** to obtain the corresponding product **3a**



Entry	Solvent	Base	Temp	Time	Yield[a] (%)
1	EtOH	Piperidine	rt	12 h	20
2	EtOH	Piperidine	Reflux	40 min	90
3	EtOH	K_2CO_3	Reflux	5 h	35
4	EtOH	KOH	Reflux	5 h	45
5	EtOH	Et_3N	Reflux	5 h	65
6	EtOH	I_2	Reflux	5 h	65
7	EtOH	*p*-TSA	Reflux	5 h	40
8	H_2O	Piperidine	Reflux	12 h	15
9	CH_3CN	Piperidine	Reflux	3 h	70
10	MeOH	Piperidine	Reflux	3 h	90
11	$PhCH_3$	Piperidine	Reflux	12 h	45

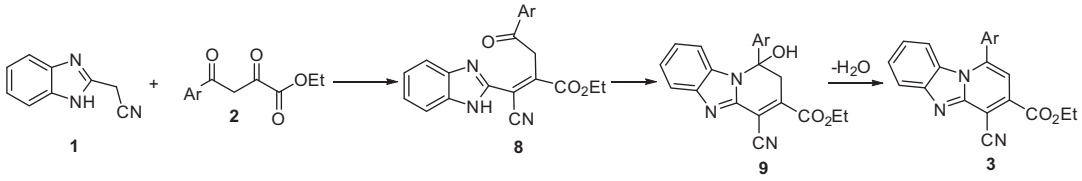
[a] Isolated yield.

Table 2
Synthesis of benzo[4,5]imidazo[1,2-*a*]pyridine derivatives **3**

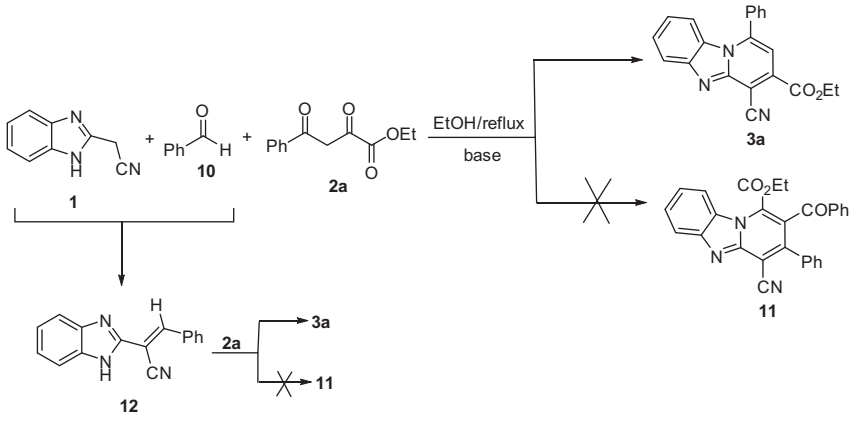


Entry	Ar	Product	Yield[a] (%)
1	Ph	**3a**	90
2	4-F-C_6H_4	**3b**	80
3	2-Cl-C_6H_4	**3c**	85
4	4-Cl-C_6H_4	**3d**	85
5	2,4-Cl_2-C_6H_3	**3e**	95
6	4-Br-C_6H_4	**3f**	80
7	3-Me-C_6H_4	**3g**	65
8	4-Me-C_6H_4	**3h**	70
9	4-MeO-C_6H_4	**3i**	80
10	3,4-MeO_2-C_6H_3	**3j**	87

[a] Isolated yield.



Scheme 2. Mechanism for the formation of benzo[4,5]imidazo[1,2-*a*]pyridines **3**.



Scheme 3. Attempted three-component reaction of compounds **1**, **2a**, and benzaldehyde (**9**).

in a rapid and efficient manner, different solvents and reagents were examined (Table 1). As shown in Table 1, the expected product was obtained in the presence of piperidine in refluxing EtOH (Table 1, entry 2). It was found that half an equivalent of the base was sufficient and higher amounts did not improve the yield of the reaction.

With these results in hand, different benzo[4,5]imidazo[1,2-*a*]pyridine derivatives **3a**–**j** were prepared using various ethyl 2,4-dioxo-4-arylbutanoates **2** (Table 2).[28] Substrates possessing electron-rich as well as electron-poor substituents underwent the piperidine-promoted cyclization reaction to give the products **3** in short reaction times (25–45 min) and typically good yields were achieved. All the products were characterized by IR and NMR spectroscopy as well as by mass spectrometry. The obtained data confirmed the structures of the synthesized compounds.

The mechanism is shown in Scheme 2. The process begins with the Knoevenagel condensation reaction of compounds **1** and **2** to give intermediate **8**. Intramolecular nucleophilic attack of the nitrogen on the carbonyl group followed by the loss of water leads to the formation of benzo[4,5]imidazo[1,2-*a*]pyridines **3**.

Following these successful experiments, we expanded our approach to an attempted three-component reaction of 2-(1*H*-benzo[*d*]imidazol-2-yl)acetonitrile (**1**), ethyl 2,4-dioxo-4-arylbutanoate derivatives **2**, and aromatic aldehydes. Hence, the reaction of compounds **1**, **2a**, and benzaldehyde (**10**) was investigated in an attempt to prepare the corresponding benzo[4,5]imidazo[1,2-*a*]pyridine **11** (Scheme 3). Although this reaction was conducted under different conditions to those outlined in Table 1, product **11** could not be obtained, and all attempts led to the formation of product **3a**. Clearly, benzaldehyde did not participate in the reaction. In an attempt to overcome this problem, 2-(1*H*-benzo[*d*]imidazol-2-yl)-3-phenylacrylonitrile (**12**) was prepared and its reaction with ethyl 2,4-dioxo-4-phenylbutanoate (**2a**) was investigated. Our results revealed that product **3a** was the main product and product **11** could not be obtained (Scheme 3).

In conclusion, we have demonstrated that novel benzo[4,5]imidazo[1,2-*a*]pyridines could be easily prepared via the reaction of 2-(1*H*-benzo[*d*]imidazol-2-yl)acetonitrile and various ethyl 2,4-dioxo-4-arylbutanoates in short reaction times (25–45 min). Numerous benefits such as the absence of a catalyst, an easy work-up, and no requirement for time-consuming purification steps should make this method useful for chemists interested in developing novel benzimidazopyridine-based drugs.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.12.099.

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28. *Synthesis of benzo[4,5]imidazo[1,2-a]pyridine derivatives* **3**. General Procedure: A mixture of 2-(1*H*-benzo[*d*]imidazol-2-yl)acetonitrile (**1**) (1 mmol), ethyl 2,4-dioxo-4-arylbutanoate **2** (1 mmol), and piperidine (0.5 mmol) in EtOH (8 mL) was heated at reflux for 25–45 min. After completion of the reaction (monitored by TLC), the mixture was cooled to room temperature, and pure product **3** was obtained as yellow crystals. The product was isolated by filtration and oven-dried at 50–60 °C. *Ethyl 4-cyano-1-phenylbenzo[4,5]imidazo[1,2-a]pyridine-3-carboxylate* (**3a**). Yield: 90%; yellow crystals; mp 270–272 °C; IR (KBr): 2989, 2231, 1717, 1632, 1535 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ_H = 1.53 (t, *J* = 7.2 Hz, 3H, CH_3), 4.57 (q, *J* = 7.2 Hz, 2H, OCH_2), 6.68 (d, *J* = 8.0 Hz, 1H, H6), 7.14 (td, *J* = 8.0, 1.2 Hz, 1H, H8), 7.33 (s, 1H, H2), 7.54 (td, *J* = 8.0, 1.2 Hz, 1H, H7), 7.64–7.61 (m, 2H, Ph), 7.75–7.67 (m, 3H, Ph), 8.10 (d, *J* = 8.0 Hz, 1H, H9). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 14.1, 63.2, 102.1, 111.1, 113.7, 115.0, 121.1, 122.8, 126.9, 128.5, 129.3, 129.5, 131.2, 132.7, 135.0, 144.8, 145.9, 147.1, 162.9. MS: *m*/*z* (%) = 341 $[M]^+$ (100), 313 (62), 267 (29), 241 (20), 140 (12), 102 (10), 76 (16). Anal. Calcd for $C_{21}H_{15}N_3O_2$: C, 73.89; H, 4.43; N, 12.31. Found: C, 73.64; H, 4.24; N, 12.18. *Ethyl 4-cyano-1-(4-fluorophenyl)benzo[4,5]imidazo[1,2-a]pyridine-3-carboxylate* (**3b**). Yield: 80%; yellow crystals; mp 303–306 °C; IR (KBr): 2992, 2228, 1732, 1632, 1498 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ_H = 1.51 (t, *J* = 7.1 Hz, 3H, CH_3), 4.55 (q, *J* = 7.1 Hz, 2H, OCH_2), 6.70 (d, *J* = 8.0 Hz, 1H, H6), 7.14 (t, *J* = 8.0 Hz, 1H, H8), 7.27 (s, 1H, H2), 7.39 (t, *J* = 8.5 Hz, 2H, H3′, H5′), 7.50 (t, *J* = 8.0 Hz, 1H, H7), 7.68 (m, 2H, H2′, H6′), 8.02 (d, *J* = 8.0 Hz, 1H, H9). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 14.1, 63.2, 102.1, 113.6, 114.8, 116.7, 117.0, 121.1, 123.0, 126.9, 128.7 (d, J_{C-F} = 3.7 Hz), 129.1, 130.9 (d, J_{C-F} = 8.5 Hz), 134.8, 143.7, 145.7, 146.9, 162.7, 164.2 (d, J_{C-F} = 251.2 Hz). MS: *m*/*z* (%) = 359 $[M]^+$ (100), 313 (60), 286 (22), 259 (11). Anal. Calcd for $C_{21}H_{14}FN_3O_2$: C, 70.19; H, 3.93; N, 11.69. Found: C, 70.33; H, 4.18; N, 11.48.