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DBU-CATALYZED HIGHLY EFFICIENT SYNTHESIS OF 1,4-DIHYDROPYRIDINE DERIVATIVES FROM ARYLIDENEMALONONITRILES AND *β*-ENAMINO IMIDES

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Abstract – Various 1,4-dihydropyridine derivatives were efficiently synthesized from arylidenemalononitriles and *β*-enamino imides using DBU (3 mol%) as the catalyst at room temperature. This mild, straightforward high-yielding protocol was atom-economy, time-economy, with a low catalyst load, and without the need for reflux.

Among the numerous *N*-heterocyclic compounds in existence, 1,4-dihydropyridine derivatives play an important role in drug discovery, biochemistry, medicinal chemistry, and organic synthesis.[1–7] The 1,4-dihydropyridine skeleton exists in various natural products and pharmaceuticals such as the antianginal and antihypertensive agents amlodipine and barnidipine (Figure 1).[8,9] Moreover, introducing another heterocyclic moiety into the one molecule is a popular means of generating new bioactive compounds. For example, citriquinochroman, a natural product bearing multiple heterocycles in its skeleton, is cytotoxic against the murine lymphoma L5178Y cell line, with an IC_{50} value of 6.1 μM.[10] Quinolactacide, which is isolated from *Penicillium citrinum*, shows 88% mortality against green peach aphids.[11] A12B4C3 is an inhibitor of human polynucleotide kinase/phosphatase (hPNKP).[12] Therefore, the development of efficient synthetic methods for generating various heterocycle-fused 1,4-dihydropyridine derivatives is very significant in organic synthesis and pivotal to drug discovery.

The synthesis of 1,4-dihydropyridine derivatives using arylidenemalononitriles and *β*-enamino imides provides a straightforward, convenient method for facilitates the simultaneous introduction of a succinimide skeleton which is derived from the *β*-enamino imide starting material. Since the succinimide skeleton is the backbone of numerous bioactive compounds,[13] the aforementioned method provided an efficient means of generating succinimide-fused pharmaceuticals and bioactive 1,4-dihydropyridine derivatives.

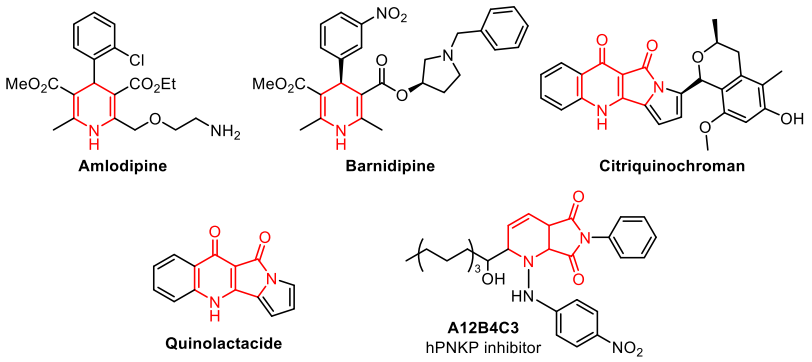


Figure 1. Bioactive 1,4-dihydropyridines and multiple heterocyclic compounds

To date, there are only three reported methods for the synthesis of 1,4-dihydropyridine derivatives from arylidenemalononitriles and *β*-enamino imides. In 2014, Mashaly *et al*. reported a piperidine-catalyzed protocol for this reaction,[14] whereas Yan *et al*. reported a triethylamine-catalyzed three-component reaction for the synthesis of succinimide-fused 1,4-dihydropyridine derivatives in 2016.[15] Although, Khan *et al*. vastly improved the above mentioned three-component protocol in 2019, a high catalyst load (10 mol% of DMAP) and harsh refluxing conditions are still necessary.[16]

In comparing with the bases used in reported methods, DBU is also commercially available, cheap, and has been used as a base catalyst in many organic reactions due to its stronger basicity. Thus, we proposed DBU can accelerate this reaction more smoothly by promoting the proton shift step (Figure 2). As a result, a more rapid and mild protocol for preparing 1,4-dihydropyridine derivatives will be achieved.

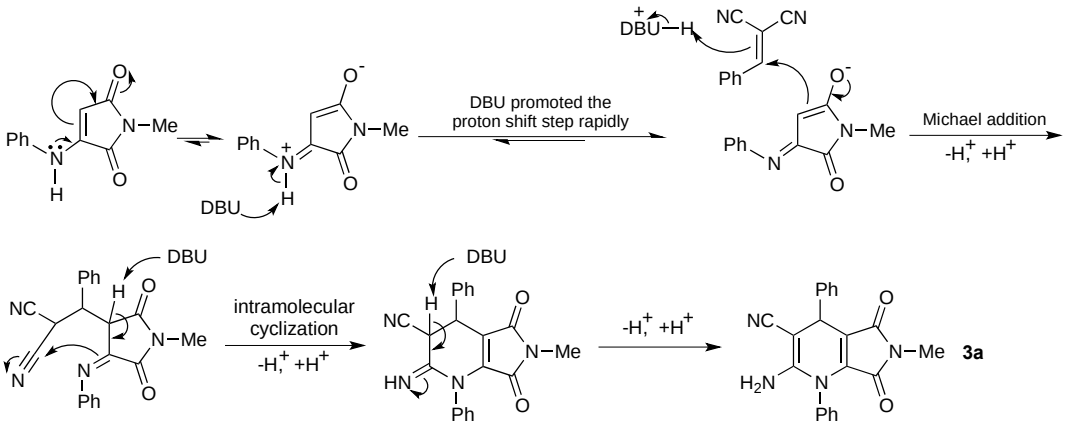
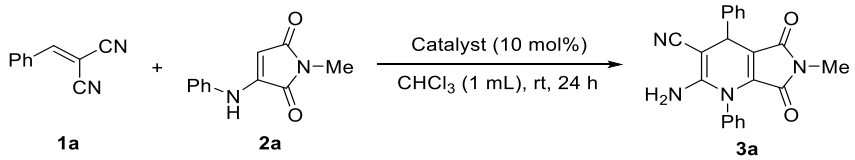


Figure 2. Proposed reaction mechanism with the effect of DBU

Recently, we reported the facile synthesis of 1,4-dihydropyridine derivatives using arylidenemalononitriles and cyclic enaminones in DMSO.[17] As a continuation of our work on the synthesis of this valuable building block, a strategy for the rapid synthesis of 1,4-dihydropyridine derivatives from arylidenemalononitriles and *β*-enamino imides is reported herein. Our method offers the advantage of a low catalyst load (only 3 mol% DBU) and can be conducted at room temperature.

While considering the solubility of *β*-enamino imides,[18] we initially attempted the reaction between benzylidenemalononitrile **1a** (0.1 mmol) and the enamino imide **2a** (0.12 mmol) in $CHCl_3$ at room temperature in the presence of various basic catalysts (Table 1). Using commercially available bases (10 mol%) such as piperidine, pyrrolidine, Et_2NH, and Et_3N yielded the corresponding 1,4-dihydropyridine derivative **3a** in 65%, 89%, 48%, and 43% yields respectively, after a reaction time of 24 h (Entries 1–4). The primary amine $^nBuNH_2$ was unsuitable for this reaction (Entry 5). The strongly basic catalysts DBN and DBU completed the reaction within 1 h and produced **3a** in 87% and 94% yields respectively (Entries 6, 7). Moreover, the reaction proceeded smoothly to give the desired product in 91% yield using 3 mol% of DBU after a reaction time of 1 h (Entry 8). Thus, we decided that 3 mol% of DBU was the optimal catalyst load for this reaction.

Table 1. Optimization of the catalysts[a]



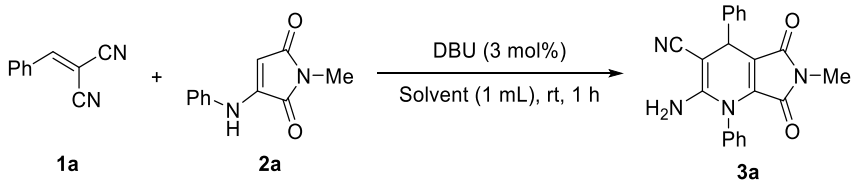
Entry	Catalysts	Yield /%[b]
1	piperidine	65
2	pyrrolidine	89
3	Et_2NH	48
4	Et_3N	43
5	$^nBuNH_2$	2
6[c]	DBN	87
7[c]	DBU	94
8[c,d]	DBU	91

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), and catalysts (10 mol%) in $CHCl_3$ (1 mL) at rt for 24 h. [b]Isolated yield. [c]Reaction time = 1 h. [d]3 mol% DBU was used. DBN = 1,5-diazabicyclo[4.3.0]non-5-ene. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

Next, we tested other reaction conditions, and the results were summarized in Table 2. Solvents containing the chloro-atom, such as $CHCl_3$, CH_2Cl_2, and $ClCH_2CH_2Cl$ produced high yields of **3a** in a reaction time of 1 h (Entries 1–3). In particular, the highest quantitative yield was achieved in CH_2Cl_2 (Entry 2). Various solvents were investigated, including the nonpolar solvent toluene, as well as polar aprotic and protic solvents such as THF, DMSO, DMF, MeOH, and EtOH, moderate or poor yields were

obtained in these cases (Entries 4–9).[19] Given these results, we chose CH_2Cl_2 as the best solvent for this transformation. We also sought to optimize the amount of enamino imide used. Here, we noted that using 0.11 mmol of enamino imide provided **3a** in excellent yields of 99% (Entry 10). When the amount of enamino imide **2a** was reduced to 0.1 mmol, the yield of **3a** decreased to 83% (Entry 11). Overall, the optimized reaction conditions were determined as follows: **1a** (0.1 mmol), **2a** (0.11 mmol), and DBU (3 mol%) in CH_2Cl_2 (1.0 mL) at room temperature for 1 h.

Table 2. Optimization of the solvents[a]



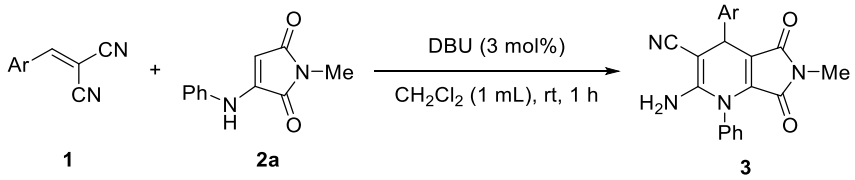
Entry	Solvent	Yield /%[b]
1	$CHCl_3$	91
2	CH_2Cl_2	100
3	$ClCH_2CH_2Cl$	91
4	toluene	60
5	THF	69
6	DMSO	27
7	DMF	42
8	MeOH	46
9	EtOH	28
10[c]	CH_2Cl_2	99
11[d]	CH_2Cl_2	83

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), and DBU (3 mol%) in solvent (1 mL) at rt for 1 h. [b]Isolated yield. [c]**2a** = 0.11 mmol. [d]**2a** = 0.1 mmol.

With the optimized reaction conditions in hand, we investigated the substrate scope of the arylidenemalononitriles **1** (Table 3). Substrates bearing halogen-atoms, as well as electron-deficient and electron-rich functional groups substituted at the *para*-position, provided the corresponding products **3b-3i** in excellent yields (Entries 2–9), except the NO_2 group substituted arylidenemalononitrile, due to an unclear side reaction in this case (Entry 5). Moreover, the substituent position at the phenyl ring influenced this reaction slightly and products **3i-3k** were obtained in high yields (Entries 9–11). However, substituting the free hydroxy and the dimethylamino groups on the *para*-position of substrates gave poor

results (Entries 12–13). Arylidenemalononitriles derived from heteroaromatic aldehydes, 2-naphthaldehyde, and isatin were well tolerated, affording the corresponding products **3n-3q** in high to excellent yields (Entries 14–17). Unfortunately, using aliphatic aldehyde (cyclohexanecarboxaldehyde) was unsuccessful (Entry 18).[20]

Table 3. Substrate scope of arylidenemalononitriles[a]



Entry	Ar	Product **3**	Yield /%[b]
1	Ph	**3a**	99
2	4-ClC_6H_4	**3b**	97
3	4-BrC_6H_4	**3c**	100
4	4-CNC_6H_4	**3d**	97
5	4-$NO_2C_6H_4$	**3e**	54
6	4-$AcOC_6H_4$	**3f**	100
7	4-$CO_2MeC_6H_4$	**3g**	100
8	4-$MeOC_6H_4$	**3h**	93
9	4-MeC_6H_4	**3i**	98
10	3-MeC_6H_4	**3j**	91
11	2-MeC_6H_4	**3k**	91
12	4-HOC_6H_4	**3l**	0
13	4-$NMe_2C_6H_4$	**3m**	30
14	2-furyl	**3n**	88
15	2-thienyl	**3o**	95
16	2-naphthyl	**3p**	98
17	isatyl	**3q**	99
18	Cy	**3r**	0

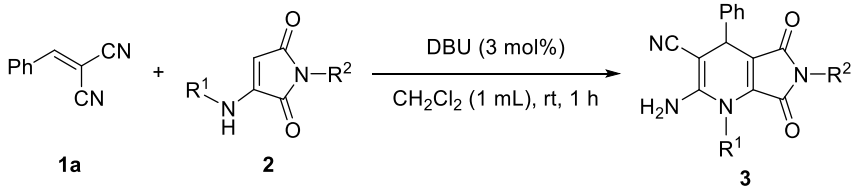
[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.11 mmol), and DBU (3 mol%) in CH_2Cl_2 (1.0 mL) at rt for 1 h. [b]Isolated yield.

Next, we studied the substrate scope of the *β*-enamino imides (Table 4). All screened *β*-enamino imides **2** generally reacted very well with **1a** to give the respective 1,4-dihydropyridine derivatives **3s-3z** in good

to excellent yields under the optimized reaction conditions (Entries 1– 8).

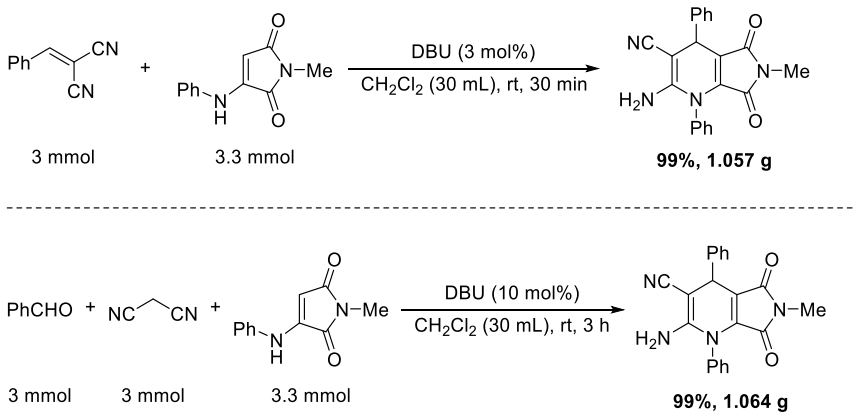
With the optimized reaction conditions, the gram-scale synthesis of 1,4-dihydropyridine derivatives was completed in only 30 min in 99% yield (Scheme 1a). It is worth noting that three-component reaction was also achieved in 99% yield after a reaction time of 3 h, even though the reaction time was extended to compensate for the slow Knoevenagel condensation step (Scheme 1b).

Table 4. Substrate scope of *β*-enamino imides[a]



Entry	R^1	R^2	Product **3**	Yield /%[b]
1	4-MeC_6H_4	Me	**3s**	100
2	4-$MeOC_6H_4$	Me	**3t**	100
3	4-ClC_6H_4	Me	**3u**	98
4	4-BrC_6H_4	Me	**3v**	98
5	Me	Me	**3w**	87
6	Bn	Me	**3x**	96
7	Ph	Bn	**3y**	99
8	Ph	Ph	**3z**	87

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.11 mmol), and DBU (3 mol%) in CH_2Cl_2 (1.0 mL) at rt for 1 h. [b]Isolated yield.



Scheme 1. An overview of the gram-scale (in this study) and the previously reported three-component reactions for the synthesis of 1,4-dihydropyridine derivatives

In summary, a highly efficient DBU-catalyzed protocol for preparing succinimide-fused 1,4-dihydropyridine derivatives from arylidenemalononitriles and *β*-enamino imides was developed herein. In contrast to the conventional methods previously reported, this procedure was achieved in extremely high yields, using a low catalyst load (3 mol%) and a short reaction time (within 1 h) without the need to apply reflux conditions. Moreover, the broad substrate scope of the arylidenemalononitriles and *β*-enamino imides were enabled to afford the desired products in high to excellent yields. The gram-scale and three-component reactions in this protocol were also successful for the synthesis of useful bioactive 1,4-dihydropyridine derivatives. Further studies on the synthesis of these valuable derivatives under mild reaction conditions are ongoing.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded in 500 MHz on a Bruker spectrometer. Chemical shifts are expressed in parts per million (δ-value) from TMS as an internal standard. IR spectra were recorded on a BRUKER TENSOR 27 spectrometer using KBr discs. Chromatographic separations were performed on a silica gel column using Wakogel® C-200. Thin layer chromatography was performed with Wakogel® B-5F. Commercially available materials and solvents were used without further purification. Without other notes, all reactions were carried out under open air condition.

Starting Materials. Arylidenemalononitriles **1**[21] and *β*-enamino imides **2**[22] were synthesized according to the literature procedures.

General Procedure for Synthesis of Products 3. To a mixture of arylidenemalononitiriles (0.1 mmol) and *β*-enamino imides (0.11 mmol) in CH_2Cl_2 (1.0 mL), DBU (0.45 mL, 3 mol%) was added at room temperature. After stirred for 1 h, the mixture was purified by thin-layer chromatography with hexane/EtOAc =1/1 to afford the corresponding 1,4-dihydropyridine derivatives **3**.

3a[16], **3h**[14], **3i**[16], **3s**[16], **3t**[16], **3u**[16], and **3v**[16] are known compounds.

SUPPORTING INFORMATION

Supplementary (synthesis of the starting materials, IR, ^{1}H and ^{13}C NMR, MS spectra, etc.) data associated with this article can be found, in the online version, at URL: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/27078/102/3.

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17. Our recently work: [Synthesis of *N*-Aryl-4-aryl-hexahydroquinoline Derivatives by the Reaction of Cyclic Enaminones with Arylidenemalononitriles in DMSO] in press.
18. *β*-Enamino imides dissolved readily in halogen solvents, especially in $CHCl_3$ and CH_2Cl_2.
19. The lower solubility of *β*-enamino imides in THF, MeOH, and EtOH may have effect on this reaction and led the poor results in these cases (Table 2, Entries 5, 8, and 9).
20. The acidic proton from the free hydroxy group (Table 3, Entry 12) or the *α*-position of the substrates (Table 3, Entry 18) may low the activity of DBU drastically and give the poor results.
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