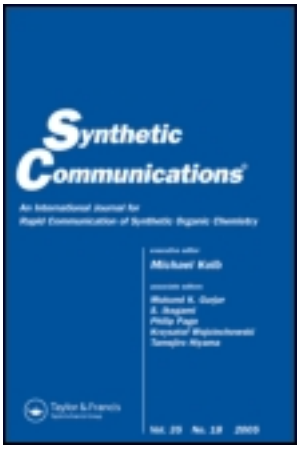

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ONE-POT MULTICOMPONENT REACTIONS FOR THE EFFICIENT SYNTHESIS OF HIGHLY FUNCTIONALIZED DIHYDROPYRIDINES

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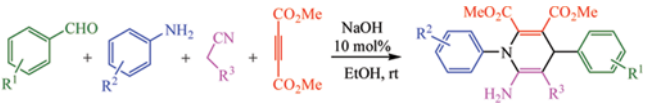
GRAPHICAL ABSTRACT



Abstract *An efficient, atom-economic, one-pot protocol has been developed for the synthesis of highly functionalized dihydropyridines via four-component reactions of aromatic aldehydes, arylamines, malononitrile, and dimethylacetylenedicarboxylate in the presence of sodium hydroxide in ethanol. This domino reaction proceeded smoothly in good to excellent yields and offered several advantages, including short reaction time, simple experimental procedure, and applicability to a broad range of substrates.*

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Keywords Aldehydes; amines; dihydropyridines; dimethylacetylenedicarboxylate; multicomponent reactions

INTRODUCTION

Synthesis of diverse heterocyclic molecules from the readily available starting materials in a cost and time effective manner is an enduring challenge for organic chemists.[1] Multicomponent reactions (MCRs), where three or more reactants are combined together in a single reaction flask to generate a product incorporating most of the atoms contained in the starting materials, are considered as an efficient tool for this challenge.[2] MCRs are suitable both from Green Chemistry and economic point of view considering its virtue such as pot, atom and step economy, consumption of less energy, less waste production and high selectivity. They allow rapid access to combinatorial libraries of complex organic molecules in a very short time. Thus MCRs have gained considerable interest in recent times.[3]

Dihydropyridines (DHPs) and their analogues represent an important class of nitrogen heterocycles, which is abundant in various natural products, synthetic

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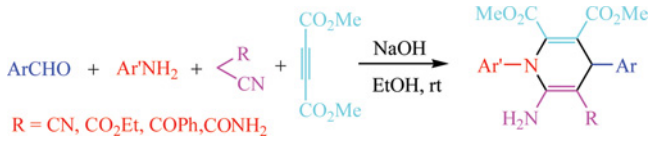


Scheme 1. Synthesis of highly substituted dihydropyridines. (Figure is provided in color online.)

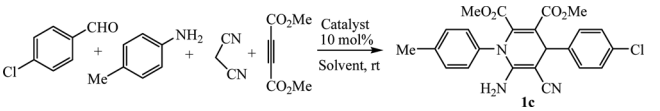
pharmaceuticals, and a wide variety of biologically active compounds.[4] Substituted dihydropyridines exhibit diverse range of biological activities like antihypertension,[5] antioxidant,[6,7] anticancer[8] and antitumor activity.[9] The remarkable drug activity of these compounds not only attracted many chemists to synthesize this heterocyclic nucleus but also became an active research area of continuing interest.

1,4-DHPs can be synthesized by various ways. The conventional way is the Hantzsch method from the cyclocondensation of an aldehyde, a β-ketoester and ammonia.[10] Regioselective [4 + 2] cycloaddition of 1-aryl-4-phenyl-1-azadienes and allenic esters for the synthesis of N-aryl-1,4-DHPs[11] and a multicomponent reaction of alkyl amines, ethyl propiolate, and benzaldehydes for the construction of N-alkyl-1,4-DHPs[12] are known in the literature. In continuation of our ongoing research to develop new synthetic methodologies for the synthesis of diverse heterocycles using multicomponent reactions, herein we report an efficient and practical synthesis of highly substituted dihydropyridines via the four-component reactions of aromatic aldehydes, arylamines, dimethylacetylenedicarboxylate, and malononitrile or its derivatives using sodium hydroxide as catalyst in ethanol as solvent at room temperature (Scheme 1).

RESULTS AND DISCUSSION

Dimethylacetylenedicarboxylate (DMAD) is a versatile substrate for the synthesis of diverse N-heterocycles by multicomponent reactions.[13a–d] Most interestingly, the outcomes of the final products from the MCRs involving DMAD are substrate dependent. Therefore, we were interested to explore the virtue of this electron-deficient alkyne for the synthesis of highly substituted 1,4-DHPs using a very cheap and readily available catalyst. Initially, the reaction of 4-chlorobenzaldehyde (1.0 equiv.), 4-methylaniline (1.0 equiv.), malononitrile (1.0 equiv.), and dimethylacetylenedicarboxylate (1.0 equiv.) was tested in the presence of K_2CO_3 (10 mol%) in ethanol at room temperature. Interestingly, after 12 h, we ended with a four-component product **1c** in 50% yield. The compound was fully characterized by infrared (IR), ^1H and ^{13}C NMR, and elemental analysis. Encouraged by this result we were interested in optimizing the reaction condition by taking the same set of substrates in ethanol and changing the catalysts. Different base catalysts such as LiOH, Ln_2O_3, KOH, NaOH, PPh_3, Na_2CO_3, and $NaHCO_3$ were screened under the similar reaction conditions to find the optimum condition. The results are summarized in Table 1 (entries 2–9). Surprisingly, the LiOH provided a trace amount of the desired product, whereas NaOH was the most efficient catalyst of choice among all the screened catalysts for this transformation in terms of reaction time and yield obtained. In the absence of any catalyst, even after 24 h of stirring the desired

Table 1. Optimization of reaction conditions[a]



1c

Entry	Catalyst	Solvent	Time (h)	Yield (%)[b]
1	—	EtOH	24	0
2	K_2CO_3	EtOH	12	50
3	LiOH	EtOH	16	Trace
4	Ln_2O_3	EtOH	16	Trace
5	KOH	EtOH	8	66
6	PPh_3	EtOH	16	Trace
7	Na_2CO_3	EtOH	8	68
8	$NaHCO_3$	EtOH	8	70
9	**NaOH**	**EtOH**	**8**	**85**
10	NaOH	CH_3CN	8	68
11	NaOH	DMF	8	64
12	NaOH	CH_2Cl_2	8	Trace
13	NaOH	THF	8	63
14	NaOH	H_2O	8	20

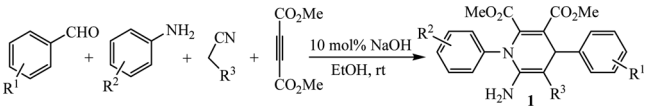
[a]All the reactions were carried out using 4-chlorobenzaldehyde, 4-methylaniline, malononitrile, and dimethylacetylenedicarboxylate in 1:1:1:1 ratio.
[b]Isolated yield.

product was not observed (Table 1, entry 1). To find the best solvent for this transformation, the four-component reaction in the presence of 10 mol% NaOH was also screened in various solvents such as CH_3CN, dimethylformamide (DMF), CH_2Cl_2, tetrahydrofuran (THF), and H_2O (Table 1, entries 10–14). Among all these solvents, EtOH was found to be the best solvent for this transformation, and dichloromethane was found to be an unsuitable solvent for this multicomponent reaction.

Under the optimized reaction conditions, a study on the substrate scope was carried out and the results are summarized in Table 2. It can be found from the results that a wide range of aromatic aldehydes and aromatic amines are suitable for this multicomponent reaction. Aromatic aldehydes tethered with both electron-donating and electron-withdrawing substituents afforded the desired products in very good yields. Similarly, arylamines with various substituents gave the expected dihydropyridines in very good yields. To extend the utility and generality of this method, malononitrile derivatives such as ethyl cyanoacetate and cyanoacetamide were also explored, and the corresponding highly substituted dihydropyridines **1o**–**1r** were obtained in good yields (Table 2, entries 15–18). Similarly, benzoylacetonitrile also afforded the corresponding four-component product **1s** in good yields.

Next we realized that this protocol is not so useful for aliphatic amines such as butyl amine, and in the case of benzylamine the reaction took longer time with moderate yield (**1t**, 50% in 24 h). Bulky amines such as α-naphthyl amine and β-naphthyl amine also underwent four-component reactions smoothly to provide **1u** and **1v** in good yields (Fig. 1).

Table 2. Synthesis of highly substituted dihydropyridines



Entry	R^1	R^2	R^3	Product	Time (h)	Yield (%)[a]	Mp[b] (°C)
1	H	H	CN	**1a**	10	78	161–163
2	H	4-Me	CN	**1b**	8	80	165–167[13c]
3	4-Cl	4-Me	CN	**1c**	8	85	186–188[13c]
4	4-Br	4-Me	CN	**1d**	7.5	89	185–187[13c]
5	3-Cl	4-Me	CN	**1e**	7	90	180–182[13c]
6	3-NO_2	4-Me	CN	**1f**	6.5	90	212–214[13c]
7	4-OMe	4-OMe	CN	**1g**	8	78	159–161
8	4-Cl	4-Cl	CN	**1h**	8	89	130–132[13c]
9	4-OMe	4-Me	CN	**1i**	8	83	168–170[13c]
10	3-NO_2	4-OMe	CN	**1j**	8	82	184–186
11	3-NO_2	4-Cl	CN	**1k**	8	92	195–197
12	4-Br	4-Cl	CN	**1l**	8	91	163–165
13	4-Br	4-OMe	CN	**1m**	9	80	165–167
14	3-NO_2	H	CN	**1n**	7	90	217–219
15	4-Cl	4-Cl	COOEt	**1o**	6	90	179–181[13c]
16	3-NO_2	4-Cl	COOEt	**1p**	8	88	186–188[13c]
17	4-Br	4-Cl	COOEt	**1q**	8	79	181–183[13c]
18	4-Cl	4-OMe	$CONH_2$	**1r**	24	55	221–223[13c]
19	4-Cl	4-Me	COPh	**1s**	10	70	184–186

[a]Isolated yields.
[b]Literature reference.

We believe the mechanism of the reaction goes via the Knoevenagel condensation of aldehyde and malononitrile in the presence of NaOH catalyst to yield arylidene malononitrile **I** (Fig. 2). Simultaneously aryl amine reacts with dimethylacetylenedicarboxylate to give the 1,3-dipole intermediate **II**. The next step

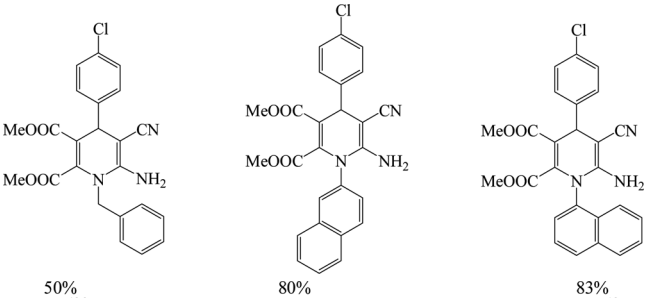


Figure 1. Highly substituted dihydropyridines obtained from benzyl and naphthyl amines.

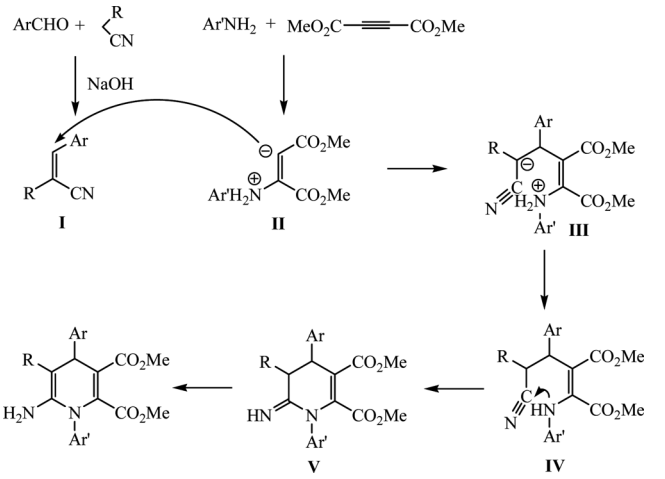


Figure 2. Proposed mechanism for the four component reaction.

is the Michael addition of **II** to arylidene malononitrile **I** to yield the adduct **III**. The migration of the hydrogen atom will provide the intermediate **IV** and subsequent intramolecular addition of the amino group to the C-N triple bond gave the cyclic intermediate (**V**), which tautomerizes to yield the final product *N*-aryl dihydropyridine.

CONCLUSION

In conclusion, we have developed a facile and efficient one-pot, four-component protocol for the synthesis of highly substituted dihydropyridines at room temperature in high yields. This domino reaction proceeded smoothly in good to excellent yields and offered several advantages including short reaction time, simple experimental procedure, and no toxic by-product. Due to the presence of NH_2 and CN functionality in ortho position of the molecules, further functionalization of these molecules is feasible, and work in this direction is ongoing in our laboratory and will be reported in due course.

EXPERIMENTAL

All reagents were purchased from commercial sources and used without further purification. IR spectra were recorded in Shimadzu FTIR spectrophotometer. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on Jeol/Bruker 500 and Brucker 400 MHz spectrometer in $CDCl_3$ using TMS as internal reference. Elemental analyses were carried out in a Perkin Elmer 2400 automatic carbon, hydrogen, and nitrogen analyzer. All unknown compounds were characterized by usual spectroscopic techniques and known compounds data were compared with the literature data and melting points.

General Procedure for the Preparation of Highly Functionalized Dihydropyridines

A solution of 4-chlorobenzaldehyde (1.0 mmol), malononitrile (1.0 mmol) and NaOH (0.1 mmol) were stirred in 3 mL of ethanol at room temperature. Then a solution of 4-methyl aniline (1.0 mmol) and dimethyl acetylenedicarboxylate (1.0 mmol) in 2 mL ethanol was added to it. The resulting mixture was stirred until the reaction was completed as indicated by thin-layer chromatography (TLC). The resulting precipitates were collected by filtration and washed with ethanol. The crude product was purified via recrystallization from hot ethanol/acetonitrile to give pure products. Complete experimental details are available online in the Supplementary Materials for this article.

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