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Synthesis of Polysubstituted Dihydropyridines by Four-Component Reactions of Aromatic Aldehydes, Malononitrile, Arylamines, and Acetylenedicarboxylate

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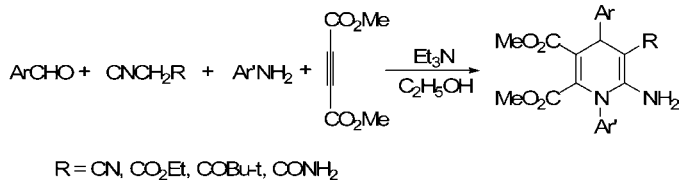
ABSTRACT



A practical and efficient procedure for the preparation of the polysubstituted dihydropyridines was developed through a unique four-component reaction of aromatic aldehydes, malononitrile, arylamines, and acetylenedicarboxylate in ethanol in the presence of triethylamine as a base promoter. This four-component reaction is atom-efficient, high-yielding, and applicable to a wide variety of four-component reactions.

In a Huisgen 1,4-dipolar addition, the intermediate formed in situ by the addition of nitrogen heterocycles to electron-deficient alkynes and reacted with different dipolarophilic reagents leading to a considerable number of heterocyclic compounds.[1,2] In the past years, extensive interest has been given to these interesting 1,4-dipoles, and a number of carbon−carbon bond formation reactions and heterocyclic constructions have been established.[3] Recently, these potential 1,4-dipoles have been also widely used in multicomponent reactions to develop more atom-economic and environmental synthetic methods. A series of three-component and four-component reactions involving nitrogen heterocycles, the activated acetylenes and electrophiles or dipolarophiles have been developed by several research groups such as Nair[4] and Yavari[5] as well as others.[6−8] Quite recently, this protocol has been broadened to employ primary and secondary amines to replace nitrogen heterocycles to generate the 1,4-dipolar intermediates.[9−11] The multicom-

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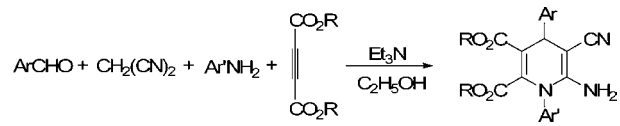
ponent reactions containing primary amine, acetylenedicarboxylate, and the third component as well as others provide new elegant procedures for the clean synthesis of polysubstituted N- and N,O-heterocycles.[12,13] In this letter, we wish to report an efficient and practical synthesis of polysubstituted dihydropyridines via the four-component reactions of aromatic aldehydes, arylamines, acetylenedicarboxylate, and acetonitrile derivatives.

In an exploratory experiment, the reaction conditions of the four-component reaction of benzaldehyde, malononitrile, *p*-toluidine, and dimethyl acetylenedicarboxylate were examined, which included base catalyst, solvents, temperature, and adding sequences of substrates. The best result was obtained by stirring the solution of benzaldehyde, malononitrile, and triethylamine in ethanol for 10 min and then adding a solution of acetylenedicarboxylate and *p*-toluidine in ethanol to it, which produced **1a** in 82% yield (Table 1, entry 1). Other solvents such as methanol and acetonitrile and bases such as DABAO were also examined. If no base was added, the reaction did not yield the expected product. Afterword, with the optimized conditions in hand, we turned our attention to examine the scope of the reaction. At first, various aromatic aldehydes were employed, and the reaction proceeded very well to give the corresponding polysubstituted dihydropyridines **1b**−**1j** in 80−96% yields (Table 1, entries 2−10). Benzaldehydes with both stronger electron-donating and electron-withdrawing substituents all afforded the desired products in very satisfactory yields. Then, other arylamines and diethyl acetylenedicarboxylate were also used in the reaction (Table 1, entries 11−24). Arylamines with versatile substituents at *o*-, *m*-, and *p*-positions of the amino group afforded the expected dihydropyridines (**1k**−**1x**) in very good yields. Diethyl acetylenedicarboxylate also showed very high reactivity. These results indicated that this four-component reaction is quite general and has very broad substrate scopes. The polysubstituted dihydropyridines **1a**−**1x** were fully characterized by ^{1}H and ^{13}C NMR, MS, and IR spectra and elemental analysis, and their structures were confirmed by single-crystal X-ray diffraction studies performed for three representative componds **1i**, **1r**, and **1x**. In ^{1}H NMR spectra, the 2-amino group usually displays one singlet at about 4.00 ppm, and the proton at the 4-position of dropyridine appears at 4.60 ppm. It should be pointed out that ^{1}H NMR spectra of compound **1v**, **1w**, and **1x** showed that they existed in two stereoiosmers, which might be due to sterical hindrance of the *o*-methylphenyl and the α-naphthyl groups in the molecules. As shown in Figure 1, the rotation of the α-naphthyl group is restricted by 2-amino and 6-methoxycarbonyl groups. The 4-*p*-chlorophenyl group and *N*-α-naphthyl group existed in the diastereomeric position.

To extend the utility of this domino reaction, the reactivity of ethyl cyanoacetate was also explored. Under similar reaction conditions, the four-component reaction of aromatic

Table 1. Synthesis of Polysubstituted Dihydropyridines from Reactions of Malononitrile



entry	compd	Ar	Ar′	R	yield (%)
1	**1a**	C_6H_5	*p*-$CH_3C_6H_4$	Me	82
2	**1b**	*p*-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$	Me	87
3	**1c**	*p*-i-PrC_6H_4	*p*-$CH_3C_6H_4$	Me	85
4	**1d**	*p*-$(CH_3)_3CC_6H_4$	*p*-$CH_3C_6H_4$	Me	84
5	**1e**	*p*-$CH_3OC_6H_4$	*p*-$CH_3C_6H_4$	Me	80
6	**1f**	*p*-FC_6H_4	*p*-$CH_3C_6H_4$	Me	88
7	**1g**	*m*-ClC_6H_4	*p*-$CH_3C_6H_4$	Me	95
8	**1h**	*p*-ClC_6H_4	*p*-$CH_3C_6H_4$	Me	95
9	**1i**	*p*-BrC_6H_4	*p*-$CH_3C_6H_4$	Me	94
10	**1j**	*m*-$NO_2C_6H_4$	*p*-$CH_3C_6H_4$	Me	96
11	**1k**	*p*-$CH_3OC_6H_4$	C_6H_5	Me	82
12	**1l**	*p*-ClC_6H_4	*m*-$CH_3C_6H_4$	Me	87
13	**1m**	C_6H_5	*p*-$CH_3OC_6H_4$	Me	88
14	**1n**	*p*-$CH_3C_6H_4$	*p*-$CH_3OC_6H_4$	Me	81
15	**1o**	*p*-ClC_6H_4	*p*-$CH_3OC_6H_4$	Me	87
16	**1p**	*p*-$CH_3OC_6H_4$	*o*-ClC_6H_4	Me	80
17	**1q**	*p*-ClC_6H_4	*m*-ClC_6H_4	Me	91
18	**1r**	*p*-ClC_6H_4	*p*-ClC_6H_4	Me	84
19	**1s**	*p*-$CH_3OC_6H_4$	*p*-$CH_3OC_6H_4$	Et	76
20	**1t**	*p*-$CH_3OC_6H_4$	*m*-ClC_6H_4	Et	85
21	**1u**	*p*-$CH_3OC_6H_4$	*p*-ClC_6H_4	Et	81
22	**1v**	*p*-ClC_6H_4	*o*-$CH_3C_6H_4$	Me	85
23	**1w**	*p*-$CH_3OC_6H_4$	*o*-$CH_3C_6H_4$	Et	80
24	**1x**	*p*-ClC_6H_4	α-Naph	Me	96

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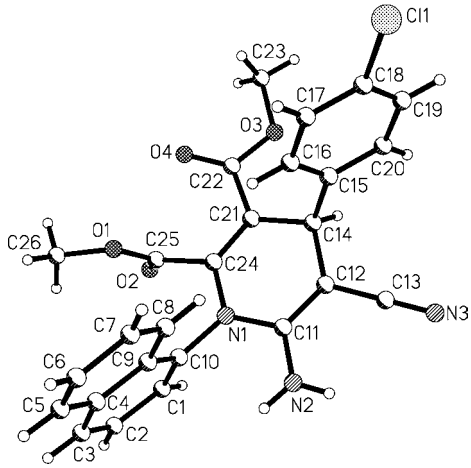
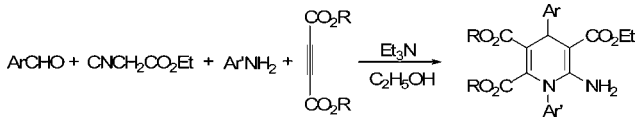


Figure 1. Molecular structure of dihydropyridine **1x**.

aldehydes, ethyl cyanoacetate, arylamine, and acetylenedicarboxylate gave the corresponding polysubstituted dihydropyridines (**2a**−**2v**) in 75−94% yields (Table 2). This

Table 2. Synthesis of Polysubstituted Dihydropyridines from Reactions of Ethyl Cyanoacetate

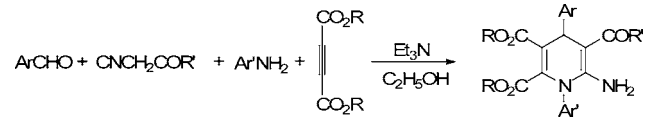


entry	compd	Ar	Ar'	R	yield (%)
1	**2a**	C_6H_5	p-ClC_6H_4	Me	86
2	**2b**	p-$CH_3C_6H_4$	p-ClC_6H_4	Me	82
3	**2c**	p-i-PrC_6H_4	p-ClC_6H_4	Me	87
4	**2d**	p-$(CH_3)_3CC_6H_4$	p-ClC_6H_4	Me	87
5	**2e**	p-$CH_3OC_6H_4$	p-ClC_6H_4	Me	86
6	**2f**	p-FC_6H_4	p-ClC_6H_4	Me	89
7	**2g**	m-ClC_6H_4	p-ClC_6H_4	Me	82
8	**2h**	p-ClC_6H_4	p-ClC_6H_4	Me	81
9	**2i**	p-BrC_6H_4	p-ClC_6H_4	Me	88
10	**2j**	m-$NO_2C_6H_4$	p-ClC_6H_4	Me	94
11	**2k**	p-ClC_6H_4	C_6H_5	Me	80
12	**2l**	p-ClC_6H_4	m-$CH_3C_6H_4$	Me	82
13	**2m**	p-$CH_3C_6H_4$	p-$CH_3C_6H_4$	Me	85
14	**2n**	p-ClC_6H_4	p-$CH_3OC_6H_4$	Me	87
15	**2o**	p-ClC_6H_4	m-ClC_6H_4	Me	84
16	**2p**	p-$(CH_3)_3CC_6H_4$	p-$CH_3OC_6H_4$	Et	78
17	**2q**	p-FC_6H_4	p-$CH_3OC_6H_4$	Et	79
18	**2r**	m-ClC_6H_4	p-$CH_3OC_6H_4$	Et	82
19	**2s**	p-ClC_6H_4	p-$CH_3OC_6H_4$	Et	75
20	**2t**	p-BrC_6H_4	p-$CH_3OC_6H_4$	Et	78
21	**2u**	m-$NO_2C_6H_4$	p-$CH_3OC_6H_4$	Et	92
22	**2v**	p-ClC_6H_4	α-Naph	Me	89

indicates that the substituents present on the *m*- and *p*-positions of the aromatic ring of aldehyde and amine have no obvious effects on the reactions. The more sterically hindered α-naphthylamine gave the expected dihydropyridine **2v** in 89% yields. However, its ^{1}H NMR spectra clearly indicated it existed in two diastereoisomers, which is due to the similar reason in compounds **1v**−**1x**. A total of 22 dihydropyridines were successfully prepared in satisfied yields. Their structures were fully characterized, and three representative single-crystal structures (**2l**, **2t**, **2v**) were determined by X-ray diffraction. This result showed that a domino reaction for the efficient synthesis of versatile functionalized *N*-aryl dihydropyridines has been successfully established.

Encouraged by these results, we turned our attention to study the reactivity of pivaloylacetonitrile and cyanoacetamide in this reaction. The four-component reaction involving pivaloylacetonitrile proceeded very slowly at room temperature and can be complete at the elevated temperature (60 °C) in about 24 h. Various aromatic aldehydes and amines behaved well to give the expected polysubstituted dihydropyridines **3a**−**3h** in good yields (63−82%, Table 3, entries

Table 3. Synthesis of Dihydropyridines from Reactions of Pivaloylacetonitrile and Cyanoacetamide



entry	compd	Ar	Ar′	R	R′	yield (%)
1	**3a**	p-ClC_6H_4	p-ClC_6H_4	Me	$C(CH_3)_3$	80
2	**3b**	p-BrC_6H_4	p-ClC_6H_4	Me	$C(CH_3)_3$	82
3	**3c**	p-t-BuC_6H_4	p-ClC_6H_4	Me	$C(CH_3)_3$	63
4	**3d**	p-FC_6H_4	p-ClC_6H_4	Me	$C(CH_3)_3$	80
5	**3e**	p-ClC_6H_4	p-$CH_3C_6H_4$	Et	$C(CH_3)_3$	73
6	**3f**	p-BrC_6H_4	p-$CH_3C_6H_4$	Et	$C(CH_3)_3$	75
7	**3g**	m-$NO_2C_6H_4$	p-$CH_3C_6H_4$	Et	$C(CH_3)_3$	65
8	**3h**	p-ClC_6H_4	p-ClC_6H_4	Et	$C(CH_3)_3$	78
9	**3i**	p-$CH_3C_6H_4$	p-$CH_3C_6H_4$	Me	NH_2	35
10	**3j**	p-ClC_6H_4	p-$CH_3C_6H_4$	Me	NH_2	46
11	**3k**	p-ClC_6H_4	p-$CH_3OC_6H_4$	Me	NH_2	51
12	**3l**	p-ClC_6H_4	m-$CH_3C_6H_4$	Me	NH_2	33
13	**3m**	p-ClC_6H_4	m-ClC_6H_4	Me	NH_2	38
14	**3n**	p-ClC_6H_4	p-ClC_6H_4	Me	NH_2	42
15	**3o**	m-$NO_2C_6H_4$	p-ClC_6H_4	Me	NH_2	45
16	**3p**	p-$CH_3C_6H_4$	p-BrC_6H_4	Me	NH_2	36

1−8). It is very interesting to find that the products **3c** and **3h** exist not in normal enamine form (C═C−NH_2) but in tautomerial imine form (C−C═NH), which might be caused by the larger *t*-butyl group in the molecule. The imino form of **3c** and **3h** can be converted to enamine form in refluxing ethanol for several hours. The molecular structures of **3e** in enamine form and **3h** in imine form were successfully determined by X-ray diffraction. On the other hand, the reaction of cyanoacetamide is very sluggish even in refluxing ethanol, and the expected dihydropydines **3i**−**3p** were prepared in 33−51% yields (Table 3, entries 9−16).

Lastly, the scope of this methodology was further broadened by using some diamines such as 4,4′-diamino-benzene, 4,4′-diaminobiphenyl, and 4,4′-diaminodiphenyl methane in the four-component reaction. A series of bis(dihydropyridines) **4a**−**4f** were obtained in satisfactory yields (Figure 2). The single-crystal structure of **4e** was also successfully determined by X-ray diffraction.

To explain the mechanism of this multicomponent reaction, we proposed a plausible reaction course (Scheme 1). Knoevenagel condensation of aldehyde with malononitrile

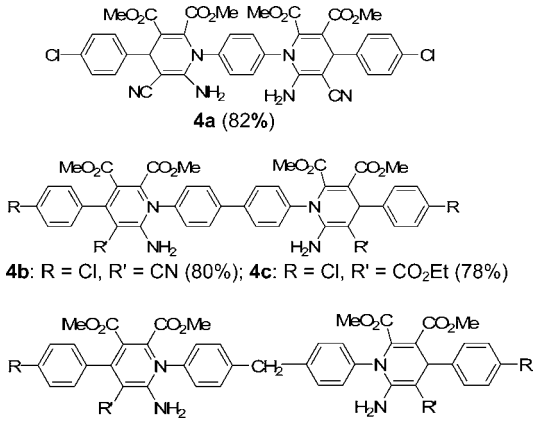
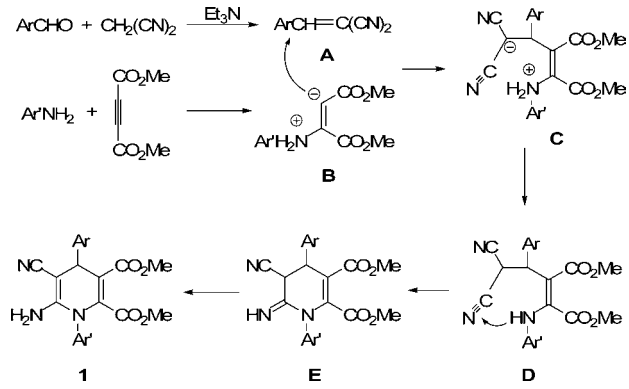


Figure 2. Synthesis of bis(dihydropyridines).

Scheme 1. Proposed Mechanism for the Four-Component Reaction



and triethylamine as base catalyst yielded arylidene malononitrile (**A**). Arylamine added to acetylenedicarboxylate to give the 1,3-dipole intermediate (**B**). Then, Michael addition of **B** to arylidene malononitrile **A** yielded the adduct **C**, which transformed to intermediate **D** through the migration of the hydrogen atom. In intermediate **D**, the intramolecular addition of the amino group to the C−N triple bond gave the cyclic intermediate (**E**). At last, the *N*-aryl dihydropyridine **1** was formed by the tautomerization of the imino group to the amino group.

In conclusion, a novel domino four-component reaction leading to selective and high-yielding polysubstituted dihydropyridines is developed from readily available starting materials involving aromatic aldehydes, arylamine, acetylenedicarboxylate, and substituted acetonitrile. Various aldehydes and amines as well as substituted acetonitrile are suitable for this four-component reaction. This protocol not only provides a novel and effective methodology for the preparation of functionalized dihydropyridines but also opens a brand new way for employing the 1,4-dipole intermediate to design new multicomponent reactions. Further expansion of the reaction scope and synthetic applications of this methodology are in progress in our laboratory.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds including crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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