



The molecular diversity of three-component reactions of 4-dimethylamino- or 4-methoxypyridine with acetylenedicarboxylates and arylidene cyanoacetates



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ABSTRACT

The three-component reactions of 4-dimethylamino- or 4-methoxypyridine with acetylenedicarboxylates and arylidene cyanoacetates showed very interesting molecular diversity. The polysubstituted 1,8,9,9a-tetrahydro-4H-1,4-ethanoquinolizines, 2H-pyran-2,3-dicarboxylates, and buta-1,3-diene-1,2,4-tricarboxylates derivatives can be formed in high yields and with good diastereoselectivity depending on the substrates and reaction conditions.

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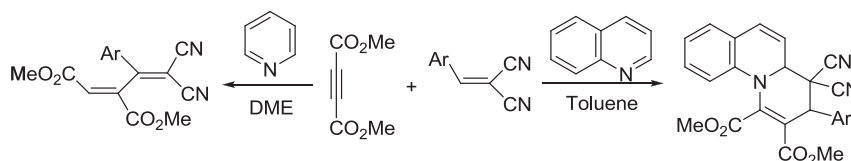
1. Introduction

In recent years more and more attentions have been given to the chemistry of Huisgen's 1,4-dipoles, which can be easily generated from addition reactions of the nucleophiles such as nitrogen-containing heterocycles, trialkylphosphines, and isocyanates to electron-deficient alkynes.^{1,2} The Huisgen's 1,4-dipoles can be trapped in situ by various electrophiles or nucleophiles to give numerous efficient synthetic procedures for the versatile carbocyclic and heterocyclic systems.^{3–7} We also successfully developed a series of multicomponent reactions by using Huisgen's 1,4-dipoles as key intermediates to construct the versatile heterocyclic skeletons.^{8–10} In these investigations we noticed that the Huisgen's 1,4-dipole derived from the addition of *p*-dimethylaminopyridine to electron-deficient alkynes showed very different reactivity to that generated from reaction of pyridine or quinoline to electron-deficient alkynes.^{9a,10} Against this background and in order to further demonstrate the potential applications of Huisgen's 1,4-dipoles in synthetic reactions, herein we wish to report the three-component reactions of *p*-dimethylaminopyridine, acetylenedicarboxylate, and arylidene cyanoacetates for the diastereoselective synthesis of the functionalized 1,8,9,9a-tetrahydro-4H-1,4-ethanoquinolizine derivatives.

2. Results and discussion

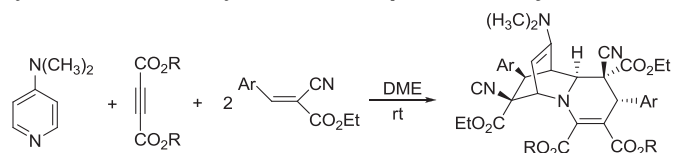
Nair and co-workers have reported that the three-component reaction of pyridine, dimethyl acetylenedicarboxylate, and benzylidene malonitrile in dimethoxyethane giving the polysubstituted buta-1,3-dienes. When quinoline was used in the three-component reaction, 4,4a-dihydro-3H-pyrido[1,2a]quinoline derivatives were produced in good yields (Scheme 1).¹¹ We wondered whether the similar reaction could be accomplished by replacing pyridine with 4-dimethylaminopyridine (DMAP). To test this new process, initially a dimethoxyethane solution of DMAP, dimethyl acetylenedicarboxylate (DMAD), and benzylidene cyanoacetate was stirred at room temperature overnight. After workup, we did not observe the expected polysubstituted buta-1,3-diene. Instead, the reaction afforded the functionalized 1,8,9,9a-tetrahydro-4H-1,4-ethanoquinolizine (**1a**) as main product, in which one DMAP and two moieties of benzylidene cyanoacetates were combined to construct the heterocyclic skeleton of 1,4-ethanoquinolizine. When 2 M benzylidene cyanoacetates were used in the reaction, the satisfactory yield (82%) of 1,8,9,9a-tetrahydro-4H-1,4-ethanoquinolizine (**1a**) was successfully obtained. Under similar reaction conditions various arylidene cyanoacetates were used in the three-component reactions and the corresponding functionalized 1,8,9,9a-tetrahydro-4H-1,4-ethanoquinolizines (**1b–1h**) were prepared in 75–91% yield (Table 1, entries 1–10). The similar reactions containing diethyl acetylenedicarboxylate also proceeded very smoothly to afford the products **1i** and **1j** in 85 and 82% yields,

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Scheme 1. Nair's three-component reactions containing pyridine and quinoline.

Table 1
Synthesis of 1,8,9,9a-tetrahydro-4H-1,4-ethanoquinolizines^a **1a–1j**

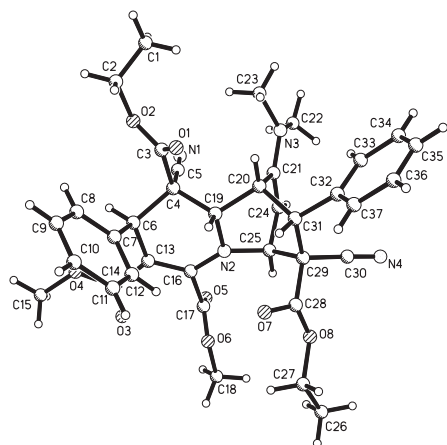


Entry	Compd	Ar	R	Yield ^b (%)
1	1a	C ₆ H ₅	CH ₃	82
2	1b	<i>p</i> -CH ₃ C ₆ H ₄	CH ₃	78
3	1c	<i>m</i> -CH ₃ C ₆ H ₄	CH ₃	83
4	1d	<i>p</i> -CH ₃ OC ₆ H ₄	CH ₃	75
5	1e	<i>p</i> -C(CH ₃) ₃ C ₆ H ₄	CH ₃	81
6	1f	<i>p</i> -ClC ₆ H ₄	CH ₃	91
7	1g	<i>m</i> -ClC ₆ H ₄	CH ₃	78
8	1h	<i>p</i> -BrC ₆ H ₄	CH ₃	80
9	1i	<i>p</i> -CH ₃ C ₆ H ₄	CH ₂ CH ₃	85
10	1j	<i>p</i> -ClC ₆ H ₄	CH ₂ CH ₃	82

^a Reaction condition: arylidene cyanoacetate (2.0 mmol), acetylenedicarboxylate (1.0 mmol), DMAP (1.0 mmol) in DME (10.0 mL), rt, 24 h.

^b Isolated yield.

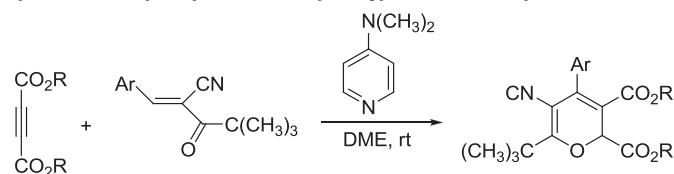
respectively (Table 1, entries 9 and 10). The structures of products **1a–1j** were established on the spectroscopic methods and confirmed by determination of the single crystal structures of compounds **1a** and **1i** (Fig. 1). Because there are several diastereoisomeric carbon atoms in the prepared polysubstituted 1,4-ethanoquinolizines (**1a–1j**), many diastereoisomers might exist in each product. ¹H NMR spectra clearly display one set of signs for the characterized groups in each molecule, which also showed that only one diastereoisomer usually exists in the prepared samples. It is known that the aryl group and cyano group exist in *cis*-position in the starting arylidene cyanoacetate. From the single crystal structures, it is clear to see that the aryl group and cyano group exist in the *exo*-position of the newly formed 1-aza-bicyclo[2.2.2]octene core



and exist in *trans*-position of the newly formed 1,2-dihydropyridyl ring. Thus, this domino reaction is both regioselective and diastereoselective reaction.

In order to explore the substrate scope, the arylidene malononitriles and arylidene pivaloylacetonitriles were also used in this domino reaction. It is very disappointed to find that the three-component reactions of DMAP, DMAD, and arylidene malononitriles in DME at room temperature or at elevated temperature resulted in a complicate mixture of products, from which no main product could be separated out. On the other hand the similar reactions of arylidene pivaloylacetonitriles afforded the poly-substituted 2H-pyran-2,3-dicarboxylates **2a–2i** in satisfactory yields (Table 2). Here the DMAP did not incorporate into the

Table 2
Synthesis of 4-aryl-5-cyano-6-*tert*-butyl-2H-pyran-2,3-dicarboxylate^a **2a–2i**



Entry	Compd	Ar	R	Yield ^b (%)
1	2a	C ₆ H ₅	CH ₃	76
2	2b	<i>p</i> -ClC ₆ H ₄	CH ₃	75
3	2c	<i>p</i> -(CH ₃) ₃ C ₆ H ₄	CH ₃	78
4	2d	<i>p</i> -CH ₃ OC ₆ H ₄	CH ₃	85
5	2e	<i>p</i> -BrC ₆ H ₄	CH ₃	78
6	2f	<i>p</i> -CH ₃ C ₆ H ₄	CH ₃	75
7	2g	<i>m</i> -ClC ₆ H ₄	CH ₃	73
8	2h	C ₆ H ₅	CH ₂ CH ₃	72
9	2i	<i>p</i> -ClC ₆ H ₄	CH ₂ CH ₃	75
10	2j	<i>p</i> -BrC ₆ H ₄	CH ₂ CH ₃	76

^a Reaction condition: arylidene pivaloylacetonitrile (2.0 mmol), acetylenedicarboxylate (2.0 mmol), DMAP (1.0 mmol) in DME (10.0 mL), rt, 6 h.

^b Isolated yield.

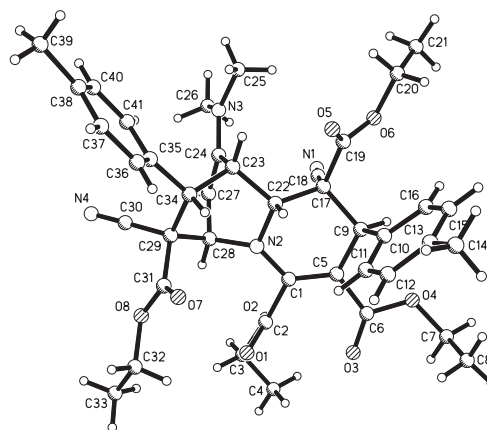


Fig. 1. Molecular structure of compounds **1a** and **1i**.

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