

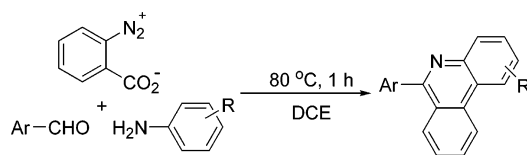
Cascade Approach to Substituted 6-Aryl-phenanthridines from Aromatic Aldehydes, Anilines, and Benzenediazonium-2-carboxylate

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Received August 8, 2006



Aromatic aldehydes reacted with anilines and benzenediazonium-2-carboxylate to afford 6-aryl-phenanthridines. The reaction furnishes a rapid and direct construction of substituted phenanthridine rings from readily available starting materials via a one-pot cascade process.

Substituted phenanthridines are an important class of heterocyclic compounds in material science¹ and in medicinal chemistry due to their significant biological activities.² The Bischler–Napieralski cyclization has been used extensively to synthesize phenanthridine derivatives.³ It is usually performed in the presence of P₄O₁₀, POCl₃, or PCl₅ at elevated temperatures, thereby limiting the kind of functional groups that can be tolerated. Although several other synthetic routes to substituted phenanthridines have been developed, most of them require multi-step syntheses, strictly anhydrous conditions, and/or metal catalysts.⁴ Thus, there is a need for more efficient, versatile, and simpler synthetic methods of creating phenanthridines. As one promising approach, we were particularly interested in cascade reactions⁵ since this methodology can form several

bonds in one operation without isolating the intermediates and adding further reagents and has exhibited high efficiency in the synthesis of complex organic building blocks from easily available starting materials.⁶ Herein, we report a new cascade reaction of benzyne with aromatic aldehydes and anilines, which furnishes a rapid and versatile synthesis of 6-aryl-phenanthridines.

Benzynes are highly reactive intermediates that have found numerous applications in organic synthesis.⁷ The dienophilic nature of the benzynes has been exploited in [2 + 2] and [4 + 2] cycloaddition reactions with enes and dienes.⁸ It is reported that the reaction between benzyne and imines, such as *N*-benzylideneanilines, gave 1,2-diarylbenzazetidines,⁹ *N*-(*o*-anilino-benzhydryl)-aniline, and 5,6-dihydro-5,6-diphenylphenanthridines¹⁰ as well as acridines¹¹ via [2 + 2] and/or [4 + 2] cycloaddition reactions. In our initial experiment, we found that the in situ generated benzyne from benzenediazonium-2-

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SCHEME 1. Three-Component Cascade Synthesis of Phenanthridine 6a

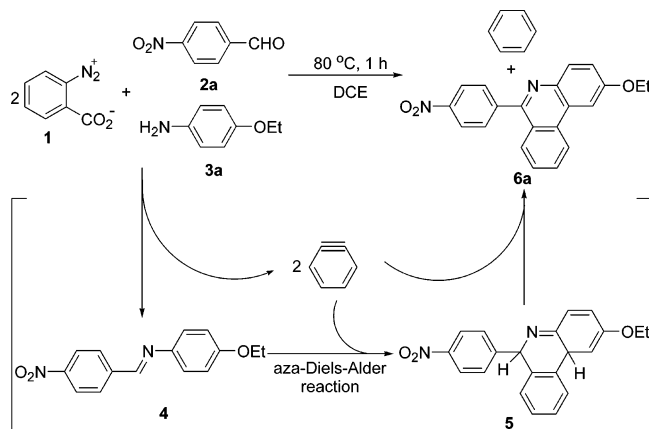


TABLE 1. One-Pot Synthesis of 6-Arylphenanthridines 6

entry	Ar	R	product	isolated yield (%)
1	4-O ₂ NC ₆ H ₄ (2a)	4-OEt (3a)	6a	95
2	2a	4-Me (3d)	6b	75
3	2a	H (3c)	6c	65
4	C ₆ H ₅ (2b)	3a	6d	35
5	3,4-Me ₂ C ₆ H ₃ (2c)	3a	6e	31
6	2c	4-OMe (3b)	6f	32
7	4-BrC ₆ H ₄ (2d)	3d	6g	38
8	4-ClC ₆ H ₄ (2e)	3d	6h	40
9	4-FC ₆ H ₄ (2f)	3d	6i	45
10	4-(EtO ₂ C)C ₆ H ₄ (2g)	3a	6j	78
11	2g	3b	6k	75
12	2f	3b	6l	65
13	2e	3b	6m	62
14	2f	3a	6n	66
15	2e	3a	6o	64
16	2d	3b	6p	58
17	2d	3a	6q	59
18	2b	3b	6r	43
19	2a	3b	6s	94
20	2-naphthyl (2h)	3a	6t	54
21	2h	3b	6u	55
22	2-HOC ₆ H ₄ (2i)	3a	6v	58
23	2i	3b	6w	57
24	2-HO,5-BrC ₆ H ₃ (2j)	3a	6x	65
25	2j	3b	6y	67
26	2j	3d	6z	43
27	2b	4-Cl (3e)		trace

carboxylate (1)¹² could react with 4-nitro-benzaldehyde (2a) and 4-ethoxy-aniline (3a) to give 6-aryl-phenanthridine (6a) in a one-pot process (Scheme 1). When the reaction was performed in 1,2-dichloroethane (DCE) at 80 °C for 1 h, almost quantitative conversion was obtained. The reaction is believed to involve a cascade imine and benzyne formation/[4 + 2] cycloaddition/dehydrogenation sequence as shown in Scheme 1.

With this result in hand, we went on to study the scope of the methodology. Using the optimized reaction conditions, a variety of aromatic aldehydes and anilines were investigated.

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TABLE 2. One-Pot Synthesis of 6-Arylphenanthridines 7 and 8

entry	R	product	isolated yield (%)
1	H	7a	44
		8a	1 ^a
2	5-Br	7b	30
		8b	18

^a Determined by GC/MS.

As shown in Table 1, aniline and the electron-rich anilines afforded the desired 6-aryl-phenanthridines 6 in 31 to ~95% isolated yields (Table 1, entries 1 to ~26), while the electron-deficient anilines only gave trace products (Table 1, entry 27). Presumably because of steric effects, the asymmetry 3,4-dimethylaniline (3f) resulted in the less crowded compounds 7 as the major products (Table 2). Noteworthy, in all of our cases, we did not isolate 1,2-diarylbenzazetidines, which were previously reported to be the major products of [2 + 2] cycloaddition reactions of *N*-arylimines with benzyne generated in situ from benzenediazonium-2-carboxylate.⁹

Finally, the structures of products were characterized by IR, ¹H NMR, ¹³C NMR, MS, and HRMS spectra. The structure of compound 6d was unambiguously confirmed by X-ray crystallography (see Supporting Information).

In conclusion, we have demonstrated that the reaction of aromatic aldehydes with anilines and benzenediazonium-2-carboxylate afforded 6-aryl-phenanthridine derivatives 6. This three-component cascade reaction provides a rapid and direct construction of substituted 6-arylphenanthridine rings. Our method has several advantages including (1) a one-pot procedure with high bond-forming efficiency, (2) simple and easily available starting materials, and (3) metal-free and mild conditions. The scope and synthetic applications of this method are under investigation.

Experiment Section

General Procedure for the Synthesis of 6-Aryl-phenanthridine 6. To the solution of aromatic aldehyde 2 (1 mmol) and aniline 3 (1 mmol) in DCE (5 mL) was added a suspension of benzenediazonium-2-carboxylate¹¹ (2 mmol) in DCE (30 mL) at 80 °C over a period of 1 h. The solvent was evaporated in vacuum, and the residue was purified by silica gel column chromatography using hexane–EtOAc (15:1) as the eluant to afford pure 6, which was recrystallized from hexane–EtOAc.

2-Ethoxy-6-(4-nitrophenyl)phenanthridine (6a). Yellow crystal; mp 176–177 °C; IR (KBr) 1620, 1602, 1595, 1561, 1519, 1497, 1258, 1204 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 8.62 (d, *J* = 8.2 Hz, 1H), 8.39 (d, *J* = 8.2 Hz, 2H), 8.12 (d, *J* = 8.9 Hz, 1H), 7.96–7.93 (m, 2H), 7.90 (d, *J* = 8.2 Hz, 2H), 7.85 (t, *J* = 7.5

Hz, 1 H), 7.62 (d, $J = 7.5$ Hz, 1 H), 7.40 (t, $J = 7.2$ Hz, 1 H), 4.28 (q, $J = 6.8$ Hz, 2 H), 1.54 (t, $J = 6.8$ Hz, 3 H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ 158.6, 156.1, 148.1, 146.5, 139.1, 133.2, 133.1, 131.1, 130.7, 128.0, 127.8, 125.3, 124.8, 123.8, 122.8, 119.6, 103.9, 64.2, 15.1 ppm; MS (ESI): m/z 345 ($[\text{M} + \text{H}]^+$); HRMS (ESI): m/z calcd for $\text{C}_{21}\text{H}_{17}\text{N}_2\text{O}_3$ ($[\text{M} + \text{H}]^+$) 345.1234, found 345.1235.

2-Methyl-6-(4-nitrophenyl)phenanthridine (6b). Yellow solid; mp 168–169 °C; IR (KBr) 1597, 1520, 1347, 1323 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 8.73 (d, $J = 8.3$ Hz, 1 H), 8.43–8.41 (m, 3 H), 8.12 (d, $J = 8.3$ Hz, 1 H), 7.96 (d, $J = 8.2$ Hz, 1 H), 7.93–7.90 (m, 2 H), 7.87–7.86 (m, 1 H), 7.63–7.61 (m, 2 H), 2.67 (s, 3 H), ppm; ^{13}C NMR (125 MHz, CDCl_3): δ 157.9, 148.2, 146.5, 142.1, 138.0, 133.5, 131.2, 131.1, 131.0, 130.4, 128.6, 127.6, 124.8, 124.0, 123.9, 122.8, 121.9, 22.3 ppm; MS (ESI): m/z 315 ($[\text{M} + \text{H}]^+$); HRMS (ESI): m/z calcd for $(\text{C}_{20}\text{H}_{14}\text{N}_2\text{O}_2 + \text{H})$ 315.1128, found 315.1127.

Acknowledgment. This work was supported by the Specialized Research Fund for the Doctoral Program of Higher Education (20050335101), the Natural Science Foundation of Zhejiang Province (R404109), as well as the Teaching and Research Award Program for Outstanding Young Teachers in Higher Education Institutions of MOE, People's Republic of China.

Supporting Information Available: Experimental procedures; spectral data for other products; copies of ^1H and ^{13}C NMR spectra for all products; and X-ray structure details for compound **6d** (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO061648I