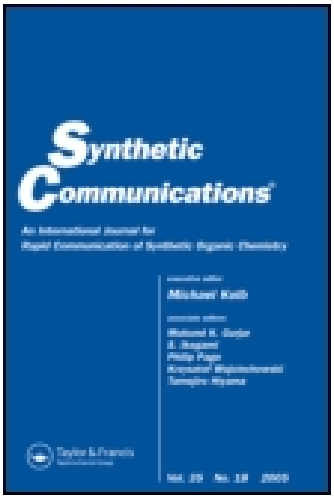

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Synthesis of Benzo[c][2,7]Naphthyridines by One-Pot Multicomponent Reaction Using Ceric(IV) Ammonium Nitrate

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SYNTHESIS OF BENZO[*c*][2,7]NAPHTHYRIDINES BY ONE-POT MULTICOMPONENT REACTION USING CERIC(IV) AMMONIUM NITRATE

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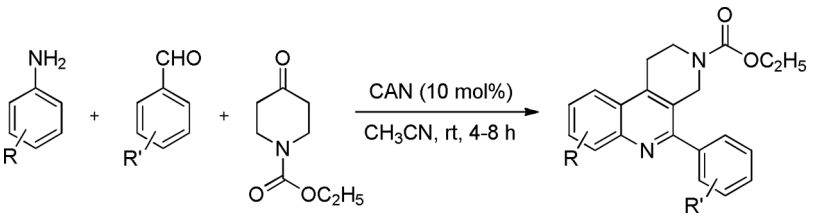
GRAPHICAL ABSTRACT



Abstract *A new, one-pot, three-component reaction for the synthesis of benzo[c][2,7]-naphthyridines has been achieved from aromatic amines, aromatic aldehydes, and N-carbethoxy-4-piperidone in the presence of a catalytic amount of ceric ammonium nitrate in good yields at room temperature. The advantages of this procedure are mild reaction conditions, low toxicity, and the use of inexpensive reagents. Apart from milder and environmentally benign conditions, this method involves a simple, reliable approach to give good yields of the desired products and is compatible with a wide range of functional groups.*

Keywords Ceric ammonium nitrate; multicomponent reaction; naphthyridines; one-pot synthesis

INTRODUCTION

Multicomponent reactions (MCRs) have emerged as a powerful synthetic strategy because of their efficiency, atom economy, high selectivity, and convenience in the construction of diverse chemical libraries of "drug-like" molecules.[1–3] MCRs are convergent reactions, in which three or more starting materials react to give a highly complex product in one pot. Typically, purification of products resulting from MCRs is also simple because all the organic reagents employed are consumed and incorporated into the target compound. The usefulness of MCRs is even greater if they provide access to "privileged medicinal scaffolds" such as naphthyridines.[4]

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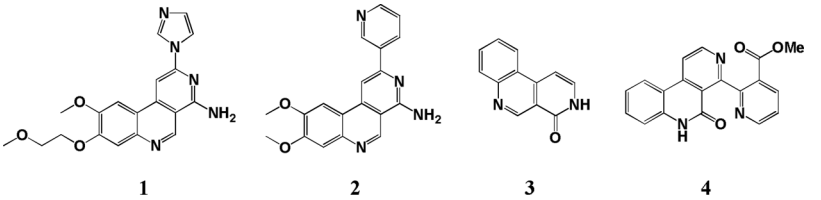
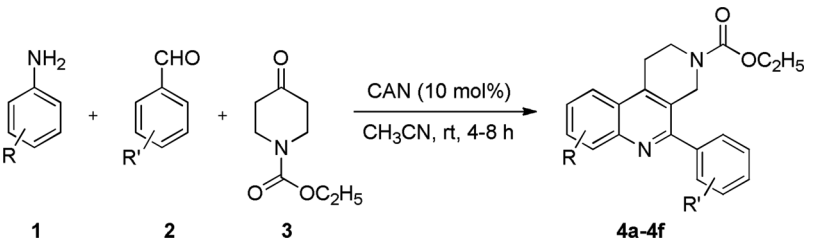


Figure 1. Pharmaceutical compounds and alkaloids containing benzo[*c*][2,7]naphthyridines.

Naphthyridines are a class of heterocyclic compounds that exhibit a broad spectrum of biological activities. Substituted benzo[*c*][2,7]naphthyridine derivatives have been described to exhibit anti-inflammatory[5] and antimalarial[6] activities. Dialkoxybenzo[*c*][2,7]naphthyridines,[7] exemplified by the imidazole substituted derivative **1** and the pyridyl substituted derivative **2**, were potent inhibitors of PDK-1 (Fig. 1). Among the vast number of alkaloids isolated from living organisms, until now only two tricyclic benzo[*c*][2,7]naphthyridines have been described, namely perlolidine **3** from the perennial ryegrass (*Loliumperenne*)[8] and the 4-pyridylbenzo[*c*][2,7]naphthyridine subarine **4** from a singaporean ascidian[9] (Fig. 1). Keeping in mind the important properties of naphthyridines, we describe here a detailed report of the synthesis of benzo [*c*][2,7]naphthyridines.

Lewis acid–catalyzed multicomponent organic transformations are gaining increasing popularity because of their economic and ecological efficacy.[10] Ceric(IV) ammonium nitrate (CAN) is a convenient and widely used reagent for a wide array of synthetic transformations because of its many advantages such as solubility in organic solvents, low toxicity, high reactivity, ease of handling, and commercially availability. Besides, CAN is able to catalyze various organic transformations not only based on its electron transfer capacity but also with its lewis acidic property in C–C bond forming reaction.[11,12]

The synthesis of napthonaphthyridines using iodine as catalyst under reflux conditions with prolonged reaction time was reported.[13] Herein, we report a new one-pot, three-component reaction for the synthesis of ethyl 5-aryl-1, 2-dihydrobenzo[*c*][2,7]naphthyridine-3(*4H*)-carboxylate derivatives **4** by the reaction of aromatic amines, aromatic aldehydes, and N-carbethoxy-4-piperidone in the presence of CAN as catalyst in good yield in relatively short reaction time at room temparature (Scheme 1). The present method offers a highly efficient method under mild reaction conditions with good yields. To the best of our knowledge, there are no reports on the synthesis of these compounds *via* MCR using CAN as the catalyst.



Scheme 1. Synthesis of substituted benzo[*c*][2,7]naphthyridines **4a–4f**.

Table 1. Screening of reaction conditions using catalysts[a]

Entry	Catalyst	Time (h)	Yield[b] (%)
1	No catalyst	24	0
2	$AlCl_3$	6	61
3	$BiCl_3$	6	70
4	$FeCl_3$	6	57
5	$ZrCl_4$	6	72
6	$Sc(OTf)_3$	6	66
7	$ZnCl_2$	6	69
8	AcOH	24	45
9	*p*-TsOH	24	50
10	**CAN**	**5**	**84**

[a]Reaction conditions: The reaction was performed with aniline (1 mmol), benzaldehyde (1 mmol), N-carbethoxy-4-piperidone (1 mmol), and catalyst (10 mol%) in acetonitrile (5 mL) at room temperature.
[b]Isolated yields after column chromatography.

RESULTS AND DISCUSSION

The catalyst played an important role in the formation of substituted benzo[*c*][2,7]naphthyridine. Initially, aniline, benzaldehyde, and N-carbethoxy-4-piperidone were selected as representative substrates to investigate the reaction conditions. Without the catalyst, it was observed that no conversion to product was obtained even after 24 h (Table 1, entry 1). Then, we focused our attention on using various Lewis and Brønsted acid catalysts, which might help to reduce the reaction time and improve the yields of the target compounds. The common Lewis acids such as $AlCl_3$, $BiCl_3$, $FeCl_3$, $ZrCl_4$, $Sc(oTf)_3$, and $ZnCl_2$ (Table 1, entries 2–7) and Brønsted acid catalysts such as AcOH and *p*-TsOH (Table 1, entries 8 and 9) afforded the desired product but only in moderate yields. Among the Lewis and Brønsted acid catalysts tested, we observed that CAN could efficiently catalyze the reaction to afford the desired product **4a** in good yield in relatively short reaction time at room temperature (Table 1, entry 10).

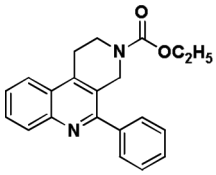
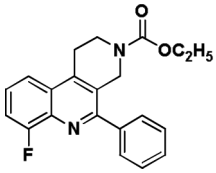
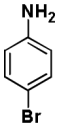
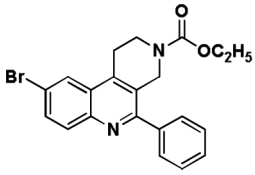
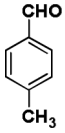
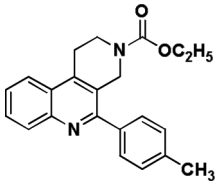
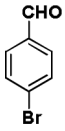
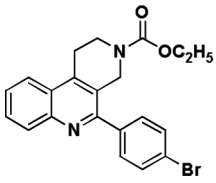
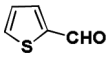
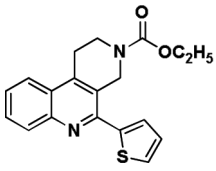
Table 2. Screening of reaction conditions using mol% and solvents[a]

Entry	Solvent	Mol (%)	Yield[b] (%)
1	CH_3CN	5	79
2	**CH_3CN**	**10**	**84**
3	CH_3CN	20	82
4	H_2O	10	0
5	CH_3OH	10	77
6	$CHCl_3$	10	74
7	CH_2Cl_2	10	65
8	C_6H_6	10	71
9	THF	10	73

[a]Reaction conditions: The reaction was performed with aniline (1 mmol), benzaldehyde (1 mmol), N-carbethoxy-4-piperidone (1 mmol), and CAN in the given solvent (5 mL) at room temperature for 5 h.
[b]Isolated yields after column chromatography.

To further improve the yield and to optimize the reaction conditions, the same reaction was carried out in the presence of 5, 10, and 20 mol% of CAN under similar conditions (Table 2, entries 1–3). Employing a lower percentage of CAN reduced the yield. A greater percentage loading of the catalyst slightly decreased the yield. The

Table 3. Synthesis of benzo[*c*][2,7]naphthyridines **4**[a]

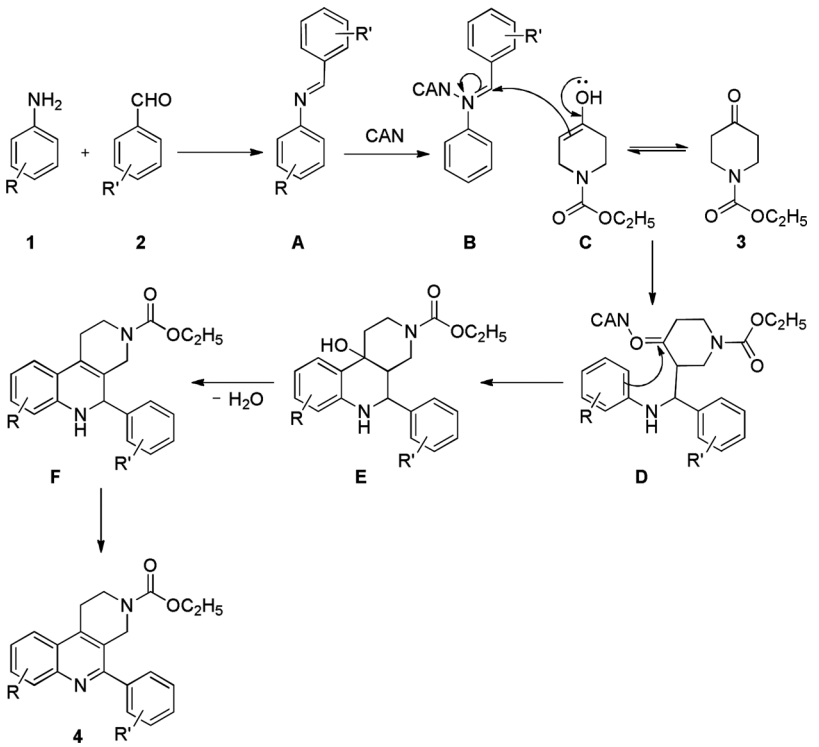
Entry	Amine	Aldehyde	Product		Time (h)	Yield[b] (%)
1				**4a**	5	84
2				**4b**	6	73
3				**4c**	6	75
4				**4d**	4	83
5				**4e**	6	77
6				**4f**	5	81

[a]Reaction conditions: The reaction was performed with anilines (1 mmol), aromatic aldehydes (1 mmol), N-carbethoxy-4-piperidone (1 mmol), and 10 mol% of CAN in acetonitrile (5 mL) at room temperature.
[b]Isolated yields after column chromatography.

best results were obtained with 10 mol% of CAN (Table 2, entry 2). We next performed the solvent effect on the outcome of the reaction. The model reaction was carried out with 10 mol% of CAN in solvents such as CH_3CN, CH_3OH, $CHCl_3$, CH_2Cl_2, C_6H_6, and THF at room temperature (Table 2, entries 2, 5–9). It was observed that acetonitrile was the most effective solvent, and the reaction proceeded smoothly, giving the maximum yield (Table 2, entry 2). It is noteworthy that when water was used as the solvent, no product was observed even after a prolonged reaction time (Table 2, entry 4).

To extend the range of substrates using the optimal reaction conditions, the reaction of aromatic amines and aromatic aldehydes with N-carbethoxy-4-piperidone were performed for the preparation of benzo[*c*][2,7]naphthyridines **4(a–f)** (Table 3, entries 1–6). Aromatic amines bearing substituents, such as 2-fluoro and 4-bromo, afforded the desired products **4b** and **4c** in good yields (Table 3, entries 2 and 3). The reactions of aromatic aldehydes containing substituents such as 4-methyl and 4-bromo groups reacted smoothly to provide the corresponding naphthyridines **4d** and **4e** in good yields (Table 3, entries 4 and 5).

However, in the case of an electron-withdrawing group such as nitro group the yield of the product was not satisfactory. This observation could be explained by the formation of more stable imine due to extra conjugation in the presence of nitro group. This stable imine is less reactive and inhibited the formation of corresponding



Scheme 2. Proposed mechanism for the synthesis of benzo[*c*][2,7]naphthyridines.

product. In addition to aromatic aldehydes, heterocyclic aldehyde such as thiophene-2-carboxaldehyde also furnished the expected product **4f** (Table 3, entry 6).

Mechanistically, first aniline **1** condenses with aldehyde **2** to give an imine **A**, which is activated by CAN to give intermediate **B**. Nucleophilic attack of the enol form **C** of N-carbethoxy-4-piperidone **3** on CAN activated intermediate **B** leads to the formation of intermediate **D**, which subsequently undergoes intramolecular cyclization to give intermediate **E**. On dehydration this intermediate results in tetrahydrobenzo[*c*][2,7] naphthyridine **F**. Finally, aerial oxidation of **F** affords the product **4** (Scheme 2).

EXPERIMENTAL

Typical Procedure for the Synthesis of Ethyl 5-Phenyl-1,2-dihydrobenzo[*c*][2,7]naphthyridine-3(*4H*)-carboxylate (4a)

CAN (10 mol%) was added to a mixture of aniline (1 mmol), benzaldehyde (1 mmol), and N-carbethoxy-4-piperidone (1 mmol) in acetonitrile (10 mL) at room temperature. The reaction mixture was allowed to stir, after completion of the reaction as indicated by thin-layer chromatography (TLC), and 10 mL of ethyl acetate was added and washed with brine (2×10 mL). The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give the crude product, which was purified by silica-gel column chromatography using ethyl acetate–hexane (1:10) as eluent, to afford the pure yellow oil product **4a**. Yield: 277 mg, 84%.

Data

IR (KBr): 2981, 1692, 1598, 1474, 1433, 1380, 1319, 1237, 1171, 1118, 1067, 1015, 919, 817, 765 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.62–7.58(m, 1H); 7.46–7.32(m, 8H); 4.75–4.66(br s, 2H); 4.15 (q, $J = 7.3$ Hz, 2H); 3.81 (t, $J = 6.6$ Hz, 2H); 2.65 (t, $J = 6.6$ Hz, 2H); 1.34–1.19 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.0, 137.2, 134.3, 131.3, 130.0, 130.4, 129.4, 128.7, 128.2, 127.3, 114.9, 61.6, 44.8, 40.7, 14.7. ESI-HRMS: $[M+H]^+$, calcd. for $C_{21}H_{20}N_2O_2$: 333.1603, found: 333.1613.

CONCLUSION

In summary, we have described an efficient and simple three-component, one-pot approach for the synthesis of substituted benzo[*c*][2,7]naphthyridine derivatives from aromatic amines, aromatic aldehydes, and N-carbethoxy-4-piperidone in acetonitrile using CAN as the catalyst at room temperature via intramolecular cyclization step as the key reaction. All the products were obtained in good purity and good yields. We hope that this novel class of compounds will meet with success as biologically active substances.

FUNDING

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

REFERENCES

1. Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3168.
2. Zhu, J.; Bienaymé, H., Eds. *Multicomponent Reactions*; Wiley-VCH: Weinheim, Germany, 2005.
3. Dou, G. L.; Shi, C. L.; Shi, D. Q. *J. Comb. Chem.* **2008**, *10*, 810.
4. (a) Kumar, V.; Jaggi, M.; Singh, A. T.; Madaan, A.; Sanna, V.; Singh, P.; Sharma, P. K.; Irchhaiya, R.; Burman, A. C. *Eur. J. Med. Chem.* **2009**, *44*, 3356; (b) Andaloussi, M.; Moreau, E.; Masurier, N.; Lacroix, J.; Gaudreault, R. C.; Chezal, J. M.; Laghdach, A. El.; Canitrot, D.; Debiton, E.; Teulade, J. C.; Chavignon, O. *Eur. J. Med. Chem.* **2008**, *43*, 2505.
5. Görlitzer, K.; Bode, M.; Frohberg, P.; Drutkowski, G. *Pharmazie* **2004**, *59*, 15.
6. (a) Görlitzer, K.; Enge, C.; Jones, P. G.; Jomaa, H.; Wiesner, J. *Pharmazie* **2006**, *61*, 975; (b) Görlitzer, K.; Enge, C.; Jones, P. G.; Jomaa, H.; Wiesner, J. *Pharmazie* **2007**, *62*, 89.
7. Kim, K.; Wissner, A.; Floyd, M. B.; Fraser, H. L.; Wang, Y. D.; Dushin, R. G.; Hu, Y.; Olland, A.; Guo, B.; Arndt, K. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5225.
8. White, E. P.; Reifer, I. *New Zealand J. Sci. Technol.* **1945**, *27B*, 38.
9. Nilar, Sidebottom, P. J.; Carté, B. K.; Butler, M. S. *J. Nat. Prod.* **2002**, *65*, 1198.
10. (a) Dai, W. M.; Li, H. *Tetrahedron* **2007**, *63*, 12866; (b) Ghosh, R.; Maiti, S.; Chakraborty, A.; Chakraborty, S.; Mukherjee, A. K. *Tetrahedron* **2006**, *62*, 4059; (c) Church, T. L.; Byrne, C. M.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2007**, *129*, 8156.
11. Nair, V.; Deepthi, A. *Chem. Rev.* **2007**, *107*, 1862.
12. Sridharan, V.; Menendez, J. C. *Org. Lett.* **2008**, *10*, 4303.
13. Wang, X. S.; Li, Q.; Wu, J. R.; Yao, C. S.; Tu, S. J. *J. Heterocycl. Chem.* **2009**, *46*, 1229.