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Convenient One-Step Synthesis of Benzo[*c*]phenanthridines by Three-Component Reactions of Isochromenylium Tetrafluoroborates and Stilbenes in Acetonitrile

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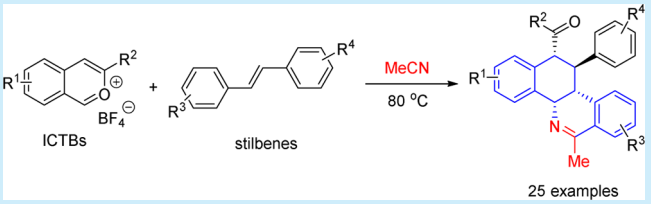
Supporting Information

ABSTRACT: A new type of three-component reaction of air-stable isochromenylium tetrafluoroborates with electron-rich stilbenes in acetonitrile has been developed under catalyst-free conditions in this work. This cascade multibond-formation reaction is initiated by an intermolecular oxa [4 + 2]-cycloaddition, relayed with a nucleophilic addition of acetonitrile, and terminated by an intramolecular Friedel–Crafts reaction, affording the corresponding benzo[*c*]-phenanthridine analogues in one step.



The benzo[*c*]phenanthridine core commonly exists in bioactive alkaloids[1−4] and other related natural products,[5] such as sanguinarine, chelerythrine, and chelamine[6,7] (Figure 1). Because of these products' diverse biological properties

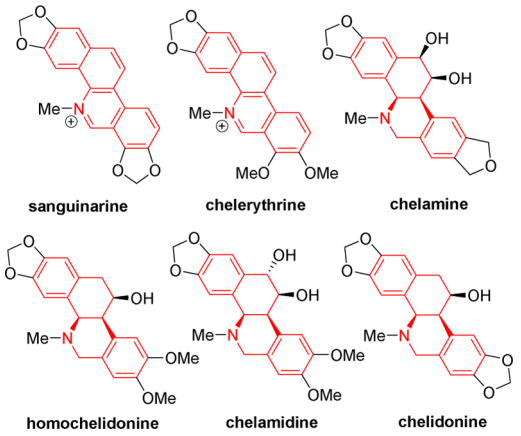


Figure 1. Representative bioactive benzo[*c*]phenanthridine derivatives.

(especially antibiotic and antitumor[8]), great efforts have been devoted to the synthesis of natural and unnatural benzo[*c*]-phenanthridines using multistep approaches.[9−13] Recently, the Clement and Blache groups reported two concise syntheses of this type of alkaloids and their derivatives, using strong base-promoted condensation of 2-methylbenzonitrile with aromatic aldehydes[14] and $Pd(OAc)_2$-catalyzed oxidative C–N bond formation reaction,[15] respectively.

Our recent investigations of isochromenylium tetrafluoroborates (ICTBs),[16,17] a class of air-stable reactive organic salts having nonclassical Hückel aromaticity,[18] have revealed that they were able to smoothly react with either nucleophiles at the C-1 position[19−22] or electron-rich olefins via [4 + 2]-cycloaddition pathways[23−26] under mild metal-free conditions. In addition, three-component reactions of ICTBs, enols (in situ derived from aliphatic aldehydes), and nitriles/aldehydes provided various amino- and hydroxyl-functionalized tetrahydronaphthalenes and dihydronaphthalenes.[27] In this work, we report a new three-component reaction[28,29] of ICTBs, stilbenes, and acetonitrile which delivers benzo[*c*]phenanthridines within a single operation (Figure 2). This new method represents an alternative convenient one-step entrance to the diverse benzo[*c*]phenanthridine derivatives.

Our previous work showed that stilbene **3a** could react with ICTB **1a** (a representative isochromenylium tetrafluoroborate) in MeCN at 80 °C to afford the dihydronaphthalene derivative **5a** through formal [4 + 2]-cycloaddition and proton elimination (Figure 2).[16] On the basis of our understanding

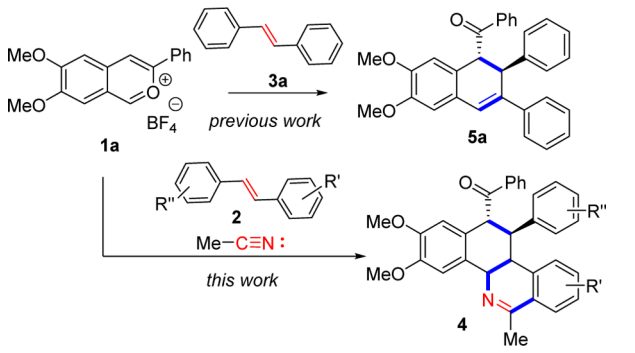


Figure 2. New one-step synthesis of benzo[*c*]phenanthridines.

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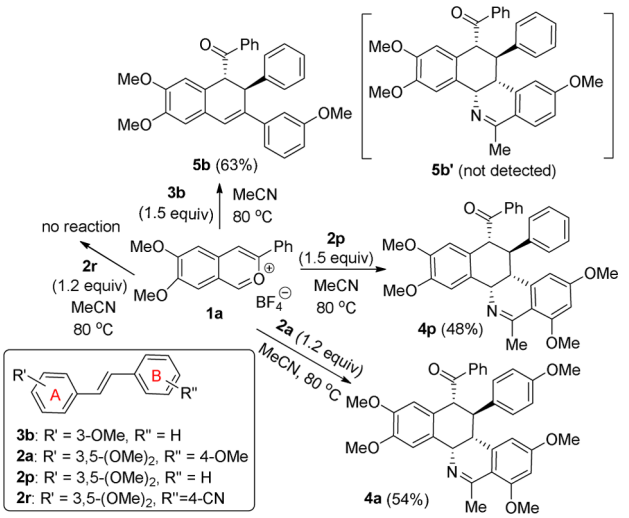
of the mechanism, immediate capture of the cationic intermediate (after the [4 + 2]-cycloaddition) with an external nucleophile would be a potential method to generate more diverse products. It also would be a meaningful expansion of the application scope of these air-stable ICTBs. Acetonitrile (MeCN) is an economically available and widely applied polar aprotic solvent. Since it contains a lone electron pair on its nitrogen, acetonitrile has occasionally been applied as a weaker nucleophile and nitrogen source in organic synthesis, such as Ritter reactions.[30] To favor the insertion of MeCN into the above-mentioned ICTB reaction, proper adjustment of the electronic density of the stilbene (to keep the cationic intermediate in the reaction for a longer lifetime) was considered. Therefore, the reaction behaviors of ICTB in MeCN were examined through tuning the substituents of the stilbenes (Scheme 1).

Scheme 1. Examination of the Reactions of ICTB 1a with Stilbenes 2a,p,r and 3b



The reaction of ICTB **1a** and stilbene **3b** was carried out in MeCN at 80 °C, affording a dihydronaphthalene derivative **5b** in 63% yield, and the expected tricyclic product **5b′** was not detected[16] (Scheme 1). Clearly, acetonitrile could not take part in this reaction, while the reaction of stilbene **2p**, in which the benzene ring A was equipped with two electron-donating methoxyl groups, provided the expected product **4p** in 48% yield under the same conditions. It indicated that the more electron-rich phenyl ring A of the stilbene substrate favored trapping acetonitrile into the reaction. With 3,5-dimethoxyl groups fixed on the phenyl ring A of the stilbenes, additional reactions were investigated by varying the substituent(s) of phenyl ring B. The reaction with stilbene **2r** (having an electron-withdrawing cyano group on ring B) did not take place, while the reaction with **2a** (bearing an electron-donating methoxyl group) smoothly afforded the corresponding product **4a**. According to this evidence, we speculate that electron-rich characters of both phenyl rings A and B of the stilbene are crucial to favor the three-component reaction.

Next, the reaction between ICTB **1a** and stilbene **2a** was applied as a platform for optimization of the conditions. Owing to the poor solubility of **1a** in either THF or DCE, the reaction did not happen, even with small amounts of MeCN as the cosolvent (Table 1, entries 1 and 2). MeCN was proven to be

Table 1. Optimization of Reaction Conditions of ICTB 1a with Stilbene 2a

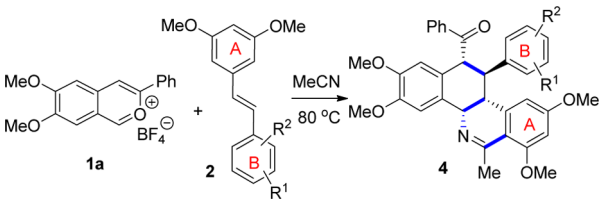
entry[a]	solvent	2a (equiv)	temp (°C)	concn (M)	time (h)	4a[b] (%)
1[c]	THF	1.0	60	0.1	48	NR
2[c]	DCE	1.0	60	0.1	48	NR
3	MeCN	1.0	25	0.05	36	NR
4	MeCN	1.0	40	0.05	24	trace
5	MeCN	1.0	80	0.05	18	39
6	MeCN	1.5	80	0.05	12	64
7	MeCN	2.0	80	0.05	10	65
8	MeCN	1.5	80	0.025	9	57
9	MeCN	1.5	80	0.1	15	46

[a]All reactions were performed under nitrogen atmosphere. [b]Isolated yields. [c]MeCN (5.0 equiv of **1a**) was used as a reagent.

the most suitable solvent. In other words, MeCN played dual roles as both a reactant (the nitrogen source) and the solvent in the reaction. Higher temperature could accelerate the reaction and improve the efficiency (entries 3–5). Raising the amounts of substrate **2a** (based on 1 equiv of ICTB **1a**) also favored this reaction, and 1.5 equiv of **2a** was considered to be a suitable and economic choice (entries 5–7). The best reaction concentration was proven to be 0.05 M (entries 6, 8, and 9). Finally, entry 6 (1.5 equiv of **2a**, 0.05 M in MeCN, 80 °C) was selected as the standard conditions for further study.

Under the optimized conditions, a variety of additional stilbenes **2b–s** were examined (Table 2). Most of the reactions could take place smoothly and afforded moderate to satisfactory yields of expected products when the phenyl ring B of substrate **2** has one or two electron-donating substituent(s). Compared with that of stilbene **2f** having one methoxyl substituent (giving

Table 2. Reactions of ICTB 1a with Stilbenes 2 in MeCN



entry[a]	2	time (h)	4[b] (%)
1	**2b** (R^1 = H, R^2 = 4-Me)	10	**4b** (57)
2	**2c** (R^1 = H, R^2 = 4-Cl)	14	**4c** (43)
3	**2d** (R^1 = 3-Me, R^2 = 5-Me)	17	**4d** (66)
4	**2e** (R^1 = 3-OMe, R^2 = 5-OMe)	12	**4e** (78)
5	**2f** (R^1 = H, R^2 = 3-OMe)	7	**4f** (67)
6	**2g** (R^1 = H, R^2 = 3-Me)	10	**4g** (58)
7	**2h** (R^1 = H, R^2 = 3-Cl)	12	**4h** (45)
8	**2i** (R^1 = 2-Me, R^2 = 3-Me)	16	**4i** (63)
9	**2j** (R^1 = H, R^2 = 2-OMe)	8	**4j** (66)
10	**2k** (R^1 = H, R^2 = 2-Me)	11	**4k** (55)
11	**2l** (R^1 = H, R^2 = 2-Cl)	15	**4l** (40)
12	**2m** (R^1 = 2-Me, R^2 = 4-Me)	13	**4m** (60)
13	**2n** (R^1 = 3-OMe, R^2 = 4-OMe)	11	**4n** (75)
14	**2o** (R^1 = 3-Me, R^2 = 4-Me)	18	**4o** (62)
15	**2q** (R^1 = H, R^2 = 4-NO_2)	48	NR
16	**2s** (R^1 = H, R^2 = 4-CF_3)	48	NR

[a]Reaction conditions: **1a** (1.0 mmol) and **2** (1.5 mmol) in anhydrous CH_3CN (20 mL) under nitrogen atmosphere at 80 °C. [b]Isolated yields.

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67% yield of product **4f**, entry 5), reaction with **2e** with two methoxyl substituents on ring B afforded compound **4e** in 78% yield (entry 4). This clearly indicated that more EDGs on ring B of **2** favored this type of three-component reaction. The reactions were also found to tolerate a halogen substituent on ring B, though lower yields of the products were given (entries 2, 7, and 11). However, when phenyl ring B of stilbene **2** has an electron-withdrawing group (such as nitro and CF_3 groups), the cascade reaction could not proceed (entries 15 and 16). Altering the position of substituent(s) on ring B of **2** did not significantly affect the reaction behaviors, and the reactions of substrates **2b**, **2g**, and **2k** afforded similar yields of products **4b**, **4g**, and **4k** (entries 1, 6, and 10). The relative configurations of representative product **4b** were determined by 1D and 2D NMR experiments, and other products were elucidated by spectral comparison accordingly.

A possible mechanism was suggested according to the comprehensive analysis of the results from this work (Figure 3).

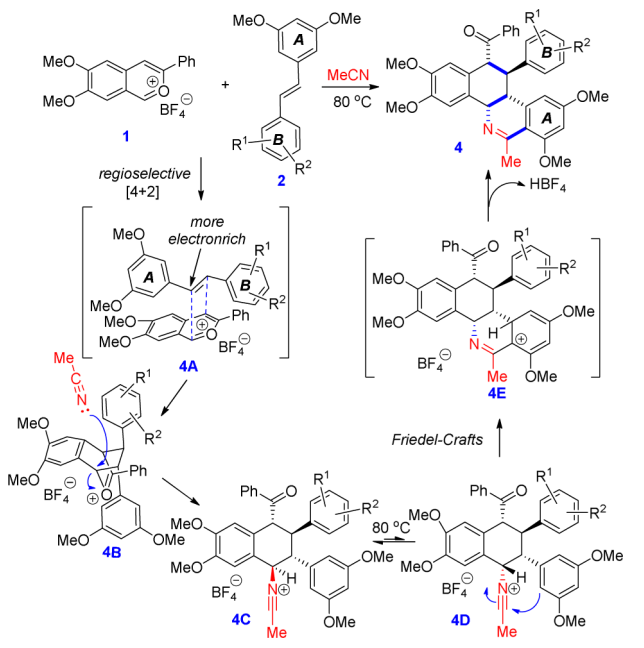
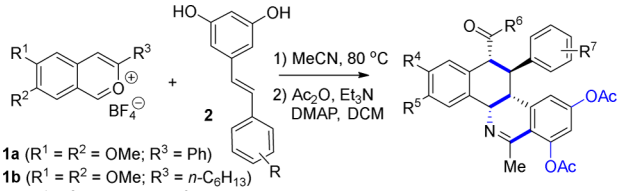


Figure 3. Proposed mechanism for the multistep cascade reaction.

At first, a [4 + 2]-cycloaddition (or a formal [4 + 2]-cyclization) takes place between the electron-deficient 2-oxa diene of the isochromenylium salt **1a** and the electron-enrich stilbene **2**, giving a bridged oxonium intermediate **4B**. This [4 + 2]-adduct is immediately attacked by the nitrogen atom of acetonitrile from the less steric direction. The resulting intermediate **4C** is then slowly converted into its diastereomer **4D** at reaction temperature (80 °C) to favor the subsequent intramolecular Friedel–Crafts reaction, completing the closure of the heterocycle. Final elimination of HBF_4 from the intermediate **4E** affords the observed multi-ring product **4**.

Based on our understanding of the above results, we further expanded the reactions to more ICTBs **1** and several additional electron-rich stilbenes containing free phenolic hydroxyl group(s), including natural resveratrol (**2t**) and pinosylvin (**2u**), in acetonitrile. Because of the high polarity of the products, these reactions were conducted in a two-stage process to improve the product purification (Table 3). The crude products from the first step (the three-component reaction) were fully acetylated with acetic anhydride, Et_3N, and a catalytic

Table 3. Reactions of ICTBs 1a–e with Stilbenes 2t–x



1a (R^1 = R^2 = OMe; R^3 = Ph)
1b (R^1 = R^2 = OMe; R^3 = n-C_6H_{13})
1c (R^1, R^2 = -OCH_2O-; R^3 = Ph)
1d (R^1 = OMe; R^2 = OH; R^3 = Ph)
1e (R^1 = OH; R^2 = OMe; R^3 = Ph)

entry[a]	1	2 (R =)	6[b] (yield, %)
1	1a	2t (4-OH)	6t (R^4 = R^5 = OMe; R^6 = Ph; R^7 = 4-OAc; 55)
2	1a	2u (3-OH)	6u (R^4 = R^5 = OMe; R^6 = Ph; R^7 = 3-OAc; 53)
3	1a	2v (H)	6v (R^4 = R^5 = OMe; R^6 = Ph; R^7 = H; 45)
4	1a	2w (2-Cl)	6w (R^4 = R^5 = OMe; R^6 = Ph; R^7 = 2-Cl; 38)
5	1a	2x (4-Cl)	6x (R^4 = R^5 = OMe; R^6 = Ph; R^7 = 4-Cl; 40)
6	1b	2t	6bt (R^4 = R^5 = OMe; R^6 = n-C_6H_{13}; R^7 = 4-OAc; 53)
7	1c	2t	6ct (R^4, R^5 = -OCH_2O-; R^6 = Ph; R^7 = 4-OAc; 60)
8	1d	2t	6dt (R^4 = OMe; R^5 = OAc; R^6 = Ph; R^7 = 4-OAc; 63)
9	1e	2t	6et (R^4 = OAc; R^5 = OMe; R^6 = Ph; R^7 = 4-OAc; 56)

[a]The procedure was described in the Supporting Information. [b]Isolated yields.

amount of DMAP in DCM, providing the corresponding acetates **6**. The results once again confirmed the above three-component cascade transformations, which worked well with various ICTBs **1a–e** and stilbenes containing free phenolic hydroxyl group(s). Slightly lower isolation yields in several cases might be caused by the material loss of the highly polar products on silica gel chromatography. The relative configurations of product **6t** were further confirmed by the X-ray single-crystal analysis (see the Supporting Information).

In summary, a new three-component cascade annulation of isochromenylium tetrafluoroborates, electron-rich stilbenes, and acetonitrile has been developed in this work, providing the corresponding benzo[*c*]phenanthridine analogues in a single operation with excellent diastereoselectivities. The mechanism of this cascade reaction was also discussed and proposed based on the results and experimental evidence. The new methodology is advantageous in its ease of operation and metal-free conditions and, thus, will be useful in future applications to the synthesis of biologically important natural and unnatural products having a benzo[*c*]phenanthridine core.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00010.

Experimental procedure and physical characterizations of the products; NMR copies of new compounds (PDF)
X-ray crystal data of **6t** (CIF)

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Notes

The authors declare no competing financial interest.

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