

Efficient Synthesis of Octahydrophenanthrene Derivatives with Mild Cascade Reactions of Isochromenylium Tetrafluoroborates and Bifunctional Styrenes

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Supporting Information



ABSTRACT: A highly efficient catalyst-free cascade reaction of air-stable isochromenylium tetrafluoroborates and bifunctional styrenes containing a 1,3-diketone moiety has been developed, affording the corresponding single diastereomeric octahydrophenanthrene derivatives (21 examples, up to 86% yield). A cascade process of [4 + 2]-cyclization and subsequent intramolecular nucleophilic addition is proposed to generate the three new C–C bonds diastereoselectively in the reactions.

Octahydrophenanthrene is a frequently observed core structure of many biologically important molecules, including steroids¹ and a number of biologically interesting quinone-fused heterocycles² (Figure 1). Consequently, great

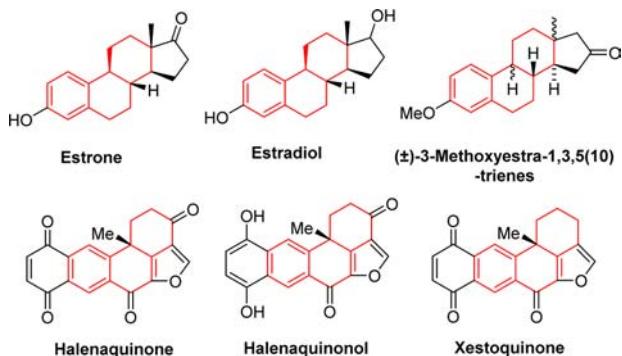


Figure 1. Several biologically important molecules containing a octahydrophenanthrene core (shown in red).

effort has been devoted to the concise synthesis of this type of skeleton, among which Bronsted acid or Lewis acid promoted Friedel–Crafts-type reactions are one major methodology.^{3,4} Most of these syntheses took a number of steps and resulted in unsatisfactory or low efficiency.

Isochromenyliums (or isobenzopyryliums) have been recently proven to be a type of useful reactive species that have attracted great attention from organic chemists.^{5–7} For the unique oxonium 10π -electron Huckel aromaticity, a variety of new transformations based on the isochromenyliums have been developed and applied to the syntheses of natural and unnatural

molecules.^{8–10} In 2009, our group prepared a number of air-stable crystalline isochromenylium tetrafluoroborates (ICTBs), in which tetrafluoroborate anion was applied (as the counterion) to stabilize the reactive oxonium.¹¹ However, such ICTBs were found to recover high reactivity in organic solvents such as MeCN , DCM , and DCE . They could quickly react with various heteroatom-based nucleophiles, electron-rich olefins, and arenes without any assistance of catalysts or promoters under very mild conditions.¹² Diverse reactivities of ICTBs, which were previously observed in the reactions with various types of nucleophiles and olefins, enable us to design suitable multistep cascade reactions for generating useful polycyclic compounds using proper reactants^{12a} (Figure 2). Herein, we report a new highly efficient cascade reaction between ICTBs and bifunctional styrenes containing a 1,3-dicarbonyl functionality, which could conveniently construct the functionalized octahydrophenanthrenes in a one-step fashion.

Our previous works have shown that ICTBs were able to smoothly react with styrenes¹¹ and 1,3-diketones,^{12c} respectively. Further analysis indicates that inter- or intramolecular reaction of ICTBs with the substrate(s) having these two functionalities might be a quick access to octahydrophenanthrene derivatives. To examine such a proposal, we tested several reactions at first (Scheme 1). Both 1,3-dicarbonyl compound **2** (1 equiv) and styrene (**4**, 2 equiv) were found to well react with ICTB **1a** in MeCN at rt, giving the expected products **3** and **5**, respectively. However, combined use of these two substrates (**2** and **4**, 1 equiv each) under the same reaction

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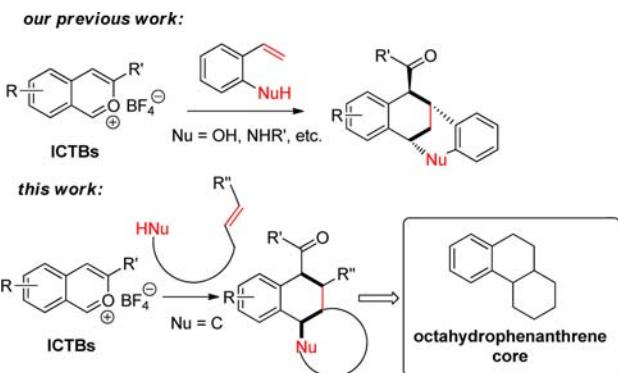
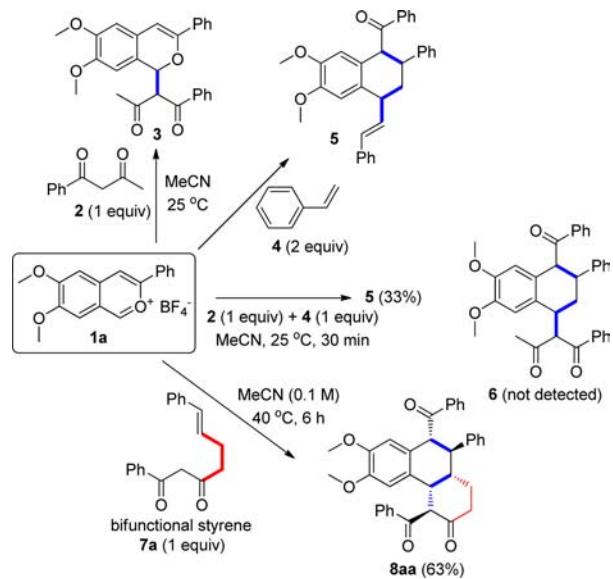


Figure 2. Design of ICTB reaction for the synthesis of octahydrophenanthrene skeleton.

Scheme 1. Reactions of ICTB 1a with Styrene (4) and/or 1,3-Dicarbonyl Substrate 2 and with Bifunctional Substrate 7a



conditions did not afford the expected product **6**. Instead, a lower yield of **5** (33%) was isolated. The results showed that ICTB **1a** preferred to react with styrene (**4**), and termination of the cationic reaction with the 1,3-dicarbonyl species was unfavorable by such an intermolecular protocol. Reaction of bifunctional substrate **7a**, in which styrene and 1,3-dicarbonyl functionalities were both introduced with a short hydrocarbon linker, was then attempted with ICTB **1a**. To our delight, this reaction underwent smoothly and could be carried out in MeCN under mild conditions, affording the corresponding target octahydrophenanthrene **8aa** (63%).

Optimization of the reaction conditions was then conducted upon the reaction of **1a** and **7a** (Scheme 1). First, a variety of solvents were examined. Only a trace amount of the product **8aa** was obtained in either DCE or toluene owing to poor solubility of the ICTB (Table 1, entries 1 and 2). Using MeCN as the solvent, higher temperatures would shorten the reaction times but could not improve the yields (entries 3–5). Raising the equivalents of substrate **7a** (based on 1 equiv of **1a**) also sped up the reaction (entries 3, 6, and 7), and 1.5 equiv of **7a** was proved to be the most economic choice (entry 6). No further improvements were achieved by raising or lowering the

Table 1. Optimization of the Reaction Conditions

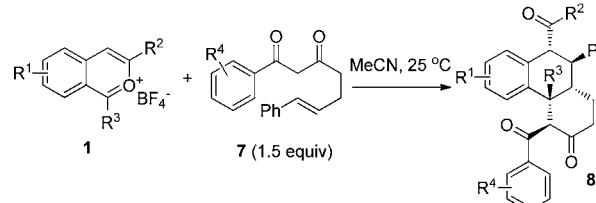
entry ^a	solvent	7a (equiv)	temp (°C)	concn (M)	time (h)	8aa ^b (%)
1	DCE	1.0	40	0.1	24	trace
2	toluene	1.0	40	0.1	24	trace
3	MeCN	1.0	25	0.1	20	72
4	MeCN	1.0	40	0.1	6	65
5	MeCN	1.0	reflux	0.1	1	63
6	MeCN	1.5	25	0.1	15	83
7	MeCN	2.0	25	0.1	13	84
8	MeCN	1.5	25	0.05	16	73
9	MeCN	1.5	25	0.2	8	57

^aUnless otherwise noted, all of the reactions were conducted under nitrogen atmosphere to avoid moisture. ^bIsolated yields.

reaction concentrations (entries 6, 8, and 9). Finally, entry 6 was chosen as the standard conditions (1.5 equiv of **7a**, 0.1 M in MeCN, 25 °C).

Under the optimized conditions, we examined a variety of ICTBs **1** using **7a** as the bifunctional reactant first (Table 2, entries 1–6). All of these reactions were carried out with good yields (entries 1–5, R³ = H) when R² is either a nude phenyl (entry 1) or a phenyl bearing an electron-withdrawing group (entry 5) or an electron-donating group (entries 3 and 4). Even when R² is an aliphatic group, this reaction could achieve 76% yield of the corresponding product (entry 2). Unfortunately,

Table 2. Reaction Scope Examination



entry ^a	1	7	time (h)	8 (yield, %) ^b
1	1b (R ¹ = 4,5-OCH ₂ O-; R ² = Ph; R ³ = H)	7a	14	8ba (81)
2	1c (R ¹ = 4,5-di-OMe; R ² = n-C ₆ H ₁₃ ; R ³ = H)	7a	11	8ca (76)
3	1d (R ¹ = 4,5-di-OMe; R ² = 4-MeC ₆ H ₄ ; R ³ = H)	7a	13	8da (86)
4	1e (R ¹ = 4,5-di-OMe; R ² = 4-MeOC ₆ H ₄ ; R ³ = H)	7a	14	8ea (84)
5	1f (R ¹ = 4,5-di-OMe; R ² = 4-NCC ₆ H ₄ ; R ³ = H)	7a	18	8fa (82) ^c
6	1g (R ¹ = 4,5-di-OMe; R ² = Ph; R ³ = Ph)	7a	48	NR
7	1a	7b (R ⁴ = 4-Br)	8	8ab (85)
8	1a	7c (R ⁴ = 3-Br)	10	8ac (77)
9	1a	7d (R ⁴ = 4-Me)	12	8ad (83)
10	1a	7e (R ⁴ = 3-Me)	6	8ae (84)
11	1a	7f (R ⁴ = 4-OMe)	9	8af (73)
12	1a	7g (R ⁴ = 3-OMe)	11	8ag (71)
13	1a	7h (R ⁴ = 4-CF ₃)	14	8ah (82)
14	1a	7i (R ⁴ = 3-CF ₃)	13	8ai (79)
15	1a	7j (R ⁴ = 2-Me)	17	8aj (67)

^aAll of the reactions were conducted using **1** (0.4 mmol) and **7** (0.6 mmol) in anhydrous MeCN (4 mL) under nitrogen atmosphere at 25 °C. ^bIsolated yields. ^cThe relative stereochemistry was confirmed by X-ray single crystallographic analysis (see the Supporting Information).

nothing happened when R^3 was a phenyl and resulted in the recovery of **1g** (entry 6). The relative configurations of the products **8** were determined by NMR methods and further confirmed by the single-crystal structure of representative product **8fa** (see the Supporting Information for more details). The scope of nucleophilic partners **7** was also examined in our study. No significant effects were observed on the reaction when the R^4 group of **7** is a phenyl bearing various substituents (such as Br, Me, OMe, and CF₃) (entries 7–15).

A few more bifunctional styrene substrates **7** were further examined to react with ICTB **1a** (Table 3). Variously

Table 3. Examination of the Scope of Substrates **7**

entry ^a	7	<i>n</i>	R^5	R^6	time (h)	8 (yield, %) ^b
1	7k	2	4-BrC ₆ H ₄	H	12	8ak (67)
2	7l	2	4-MeOC ₆ H ₄	H	10	8al (86)
3	7m	2	4-CF ₃ C ₆ H ₄	H	30	8am (64)
4	7n	2	H	Ph	36	8aa (66)
5	7o	2	Ph	Me	13	NR
6	7p	0	Ph	H	48	NR
7	7q	1	Ph	H	14	8aq (67)
8	7r	3	Ph	H	16	8ar (57) ^c

^aAll the reactions were conducted using **1a** (0.4 mmol) and **7** (0.6 mmol) in anhydrous MeCN (4 mL) under nitrogen atmosphere at 25 °C. ^bIsolated yields. ^c21% yield of byproduct (see the Supporting Information).

substituted styrenes bearing either an electron-withdrawing or electron-donating group were all proven to be suitable reactants for this type of reaction (entries 1–3). Lowering the electron density of the styrene moiety would lead to longer reaction time and relatively lower yield (entry 3). Reaction of **1a** with the (*Z*)-olefin **7n** (entry 4) gave the same product **8aa** as that from the reaction with its (*E*)-olefin isomer **7a**. Unfortunately, the trisubstituted olefin **7o** could not react with the ICTB **1a** under the standard conditions (entry 5). The steric hindrance of trisubstituted olefins might be unfavorable for the crucial [4 + 2] cyclization (see Figure 3). We also tuned the length of the hydrocarbon linker for changing the size of ring C. Five to seven-membered rings could be easily achieved by this type of reaction (entries 1–4, 7, and 8), while the attempt to construct a four-membered ring failed (entry 6).

A possible mechanism was proposed according to the above results and observations (Figure 3). A cascade process of [4 + 2] cyclization and subsequent intramolecular nucleophilic addition is proposed to generate the three new C–C bonds diastereoselectively in the reaction. Considering *cis*-relative stereochemistries of C1 and C4 in the product **8**, we believe that a carbocation intermediate **B*** is likely generated to accept the attack by the enol after the crucial intermolecular [4 + 2] cyclization between the oxonium diene unit of ICTB and styrene olefin.

In summary, a highly efficient cascade reaction of isochromenylium tetrafluoroborates and bifunctional styrenes has been developed, providing octahydrophenanthrene deriv-

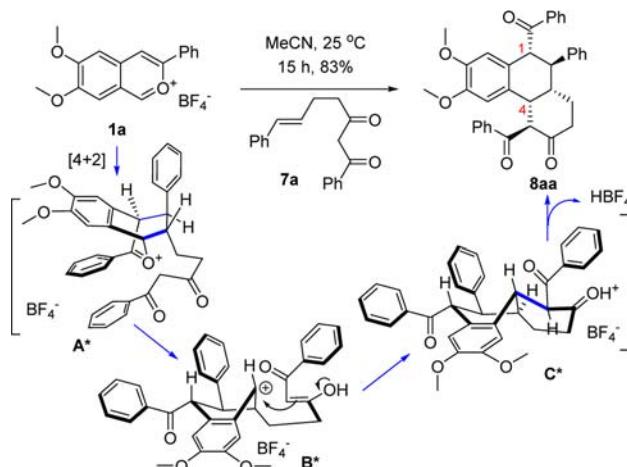


Figure 3. Proposed reaction mechanism.

atives with good yields under mild conditions. The newly developed cascade transformation diastereoselectively generates three new C–C bonds and thus exhibits great synthetic efficiency.

■ ASSOCIATED CONTENT

S Supporting Information

Typical experimental procedure, characterizations of new compounds, NMR copies of new compounds, and X-ray crystal data of **8fa** (CIF). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01532.

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Notes

The authors declare no competing financial interest.

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