ORGANIC LETTERS

2009
Vol. 11, No. 20
4676−4679

Transformation of Reactive Isochromenylium Intermediates to Stable Salts and Their Cascade Reactions with Olefins

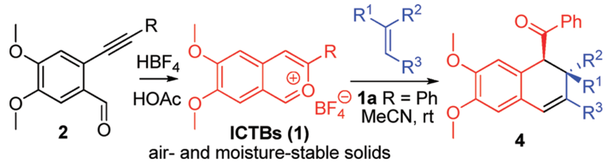
Zhi-Long Hu,[†] Wen-Jian Qian,[†] Sheng Wang,[‡] Shaozhong Wang,[‡] and Zhu-Jun Yao*[,†,‡]

State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China, and Nanjing National Laboratory of Microstructures, School of Chemistry and Chemical Engineering, Nanjing University, 22 Hankou Road, Nanjing, Jiangsu 210093, China

yaoz@mail.sioc.ac.cn; yaoz@nju.edu.cn

Received August 23, 2009

ABSTRACT



Transformation of reactive isochromenylium intermediates to the corresponding storable and stable reagents has been achieved, and a number of isochromenylium tetrafluoroborates (ICTBs, 1) have been conveniently prepared and characterized. Direct metal-free treatment of isochromenylium tetrafluoroborate 1a with olefins afforded a variety of polycyclic frameworks 4 via mild cascade reactions. Starting from the prefunctionalized *o*-alkynylbenzaldehydes, a one-pot metal-free procedure of intramolecular cascade annulation to 2,3-dihydrophenanthren-4(1*H*)-one derivatives was also developed.

Isochromenyliums, a type of reactive intermediate, have attracted great attention of organic chemists in recent years.[1−3] They are commonly produced *in situ* as inseparable intermediates in the treatment of *o*-alkynylbenzaldehydes with certain metal catalysts (AuX_3,[4] AgX,[5] CuX_2,[6] PdX_2,[7] W,[8] PtX_2,[9] etc.) or some electrophiles (IPy_2BF_4, I_2,[10] TfOH,[11]

[†] Chinese Academy of Sciences.

[‡] Nanjing University.

(1) (a) Zhang, Y. -C.; Lebeau, E.; Gillard, J. W.; Attardo, G. *Tetrahedron Lett.* **1993**, *34*, 3841–3844. (b) Mutter, R.; Campbell, I. B.; Martin de la Nava, E. M.; Merritt, A. T.; Wills, M. *J. Org. Chem.* **2001**, *66*, 3284–3290. (c) Kueny-Stotz, M.; Isorez, G.; Chassaing, S.; Brouillard, R. *Synlett.* **2007**, 1067–1070. (d) Peter, L. *Synlett* **2007**, 1016–1025.

(2) (a) Zhu, J. L.; Germain, A. R.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2004**, *43*, 1239–1243. (b) Qian, W.-J.; Wei, W. -G.; Zhang, Y.-X.; Yao, Z.-J. *J. Am. Chem. Soc.* **2007**, *129*, 6400–6401. (c) Wei, W.-G.; Zhang, Y.-X.; Yao, Z.-J. *Tetrahedron* **2005**, *61*, 11882–11886. (d) Marsini, M. A.; Gowin, K. M.; Pettus, T. R. *Org. Lett.* **2006**, *8*, 3481–3483. (e) Zhu, J. L.; Grigoriadis, N. P.; Lee, J. P.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2005**, *127*, 9342–9343.

(3) (a) Wei, W.-G.; Yao, Z.-J. *J. Org. Chem.* **2005**, *70*, 4585–4590. (b) Yao, Y.-S.; Yao, Z.-J. *J. Org. Chem.* **2008**, *73*, 5221–5225.

(4) (a) Asao, N.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 12650–12651. (b) Asao, N.; Nogami, T.; Lee, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 10921–10925. (c) Asao, N.; Aikawa, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 7458–7459. (d) Dyker, G.; Hildebrandt, D.; Liu, J. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4399–4402. (e) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395–3442. (f) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266–3325. (g) Li, Z. G.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239–3265. (h) Jin, T. N.; Yamamoto, Y. *Org. Lett.* **2007**, *9*, 5259–5262. (i) Shen, H. C. *Tetrahedron* **2008**, *64*, 7847–7870. (j) Li, G. T.; Huang, X. G.; Zhang, L. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 346–349. (k) Kim, N.; Kim, Y.; Park, W.; Sung, D.; Gupta, A. K.; Oh, C. H. *Org. Lett.* **2005**, *7*, 5289–5291.

(5) (a) Beeler, A. B.; Su, S.; Singleton, C. A.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 1413–1419. (b) Pale, P.; Chuche, J. *Eur. J. Org. Chem.* **2000**, 1019–1025. (c) Patil, N. T.; Pahadi, N. K.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 4564–4565.

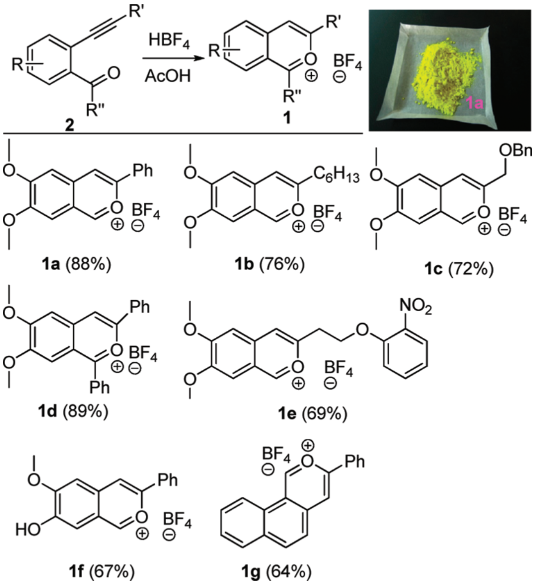
(6) (a) Asao, N.; Kasahara, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 3504–3506. (b) Ezquerra, J.; Pedregal, C.; Lamas, C. *J. Org.*

10.1021/ol9019524 CCC: $40.75

etc.). Roles of the catalysts or promoters are thought to activate the alkyne and initiate the subsequent intramolecular cyclization by the oxygen of a carbonyl group. However, few have been involved in deeply understanding the chemical properties of isochromenyliums (salts or intermediates) including their physical characterizations. Although the present *in situ* protocols of generating isochromenyliums with assistance of metal catalysts or promoters simplify the experimental operations in many successful reactions, uses of the reactants and reagents are usually inaccurate in stoichiometry and highly dependent on the experience of researchers. In some multistep cascade transformations involving isochromenyliums, optimization of conditions in those unsatisfactory cases is rather difficult. Therefore, thorough understanding of isochromenyliums is of great value for broadening their further applications in organic synthesis. Undoubtedly, acquirement of isochromenylium intermediates as a stable and storable form will be a shortcut to resolve all of these questions. Unfortunately, such storable isochromenyliums have remained challenging for several decades.[12] In this work, we report our recent achievement on the air- and moisture-stable isochromenylium salts, including their preparation and full characterizations as well as their use in the cascade reactions with variously substituted olefins.

To obtain a stable isochromenylium salt for NMR measurements, our initial attempts focused on the optimiziation of the literature conditions. However, the known procedures[2b,c,3] could not afford a qualified sample for a clean NMR spectrum. Instead, rather complicated mixtures were often indicated by the corresponding ^{1}H NMRs. To improve the stablility of reactive isochromenylium species, introduction of a suitable counterion was thus considered. Treatment of *o*-alkynylbenzaldehyde **2a** with Brønsted acids HCl, TFA, and $HClO_4$ were examined, respectively. Unfortunately, all of the produced solid precipitations were unstable when they were exposed to the air at room temperature. Because tetrafluoroborate (BF_4^-) has been frequently used as a counterion to stabilize oxoniums in some chemically stable reagents, for example, Me_3OBF_4,[13] tetrafluoroboric acid was thus employed to our experiments. To our delight, simple treatment of *o*-alkynylbenzaldehydes **2a** with tetrafluoroboric acid in acetic acid gave a yellow solid **1a** in a high yield (Scheme 1). This solid is considerably stable in the open air and can be stored in the laboratory for more than a year at room temperature. No decomposition and other transformations have been observed when exposured to air even at 60−100 °C (either in the solution or in the solid state) after one day. Its ^{19}F NMR shows a typical signal of BF_4^- at −151.2 ppm, and its ^{1}H NMR unambiguously indicates an identical isochromenylium structure. Isochromenylium tetrafluoroborate (ICTB) **1a** was further characterized by ^{13}C NMR, IR, mass spectrum, and elemental analysis, and finally confirmed by the X-ray crystallographic analysis (see Supporting Information).[14]

Scheme 1. Preparation of Stable Isochromenylium Tetrafluoroborates **1**



To examine the structural scope, a number of other isochromenylium tetrafluoroborates with different substituents were accordingly prepared. Using the substrates (**2a**−**2e**) bearing 3,4-dimethoxyl functionalities on their corresponding phenyl ring, satisfactory yields of the expected salts (**1a**−**1e**) were achieved (Scheme 1). In all these examples, the nature of alkyne-substituent of substrates **2** affects little on the corresponding results. A naphthalene-derived substrate **2g** also afforded good yield of isochromenylium salt **1g**. Existence of a phenol hydroxyl group (**2f**) does not affect the formation of the corresponding salt **1f**. Advantageously, all of these isochromenylium tetrafluoroborates could be

---

Chem. **1996**, *61*, 5804–5812. (c) Hiroya, K.; Itoh, S.; Sakamoto, T. *J. Org. Chem.* **2004**, *69*, 1126–1136.

(7) (a) Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 764–765. (b) Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*; Pergamon: New York, 2000.

(8) (a) Kusama, H.; Funami, H.; Shido, M.; Iwasawa, N. *J. Am. Chem. Soc.* **2005**, *127*, 2709–2716. (b) Maeyama, K.; Iwasawa, N. *J. Am. Chem. Soc.* **1998**, *120*, 1928–1929. (c) Bruneau, C.; Dixneuf, P. H. *Acc. Chem. Res.* **1999**, *32*, 311–323.

(9) (a) Hildebrandt, D.; Hüggenberg, W.; Kanthak, M.; Dyker, G. *Chem. Commun.* **2006**, 2260–2261. (b) Kusama, H.; Ishida, K.; Funami, H.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4903–4905.

(10) (a) Barluenga, J.; Vázquez-Villa, H.; Ballesteros, A.; González, J. M. *J. Am. Chem. Soc.* **2003**, *125*, 9028–9029. (b) Barluenga, J.; Vázquez-Villa, H.; Ballesteros, A.; González, J. M. *Adv. Synth. Catal.* **2005**, *347*, 526–530. (c) Barluenga, J.; Vázquez-Villa, H.; Merino, I.; Ballesteros, A.; González, J. M. *Chem.—Eur. J.* **2006**, *12*, 5790–5805. (d) Waldo, J. P.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 9643–9647.

(11) (a) Singh, V.; Krishna, U. M.; Vikrant, V.; Trivedi, G. K. *Tetrahedron* **2008**, *64*, 3405–3428. (b) Tovar, J. D.; Swager, T. M. *J. Org. Chem.* **1999**, *64*, 6499–6504. (c) Goldfinger, M. B.; Crawford, K. B.; Swager, T. M. *J. Am. Chem. Soc.* **1994**, *116*, 7895–7896.

(12) (a) Dorofeenko, G. N.; Safaryan, G. P.; Kuznetsov, E. V. *Chem. Heterocycl. Compd.* **1970**, *6*, 941–942. (b) Birchall, G. R.; Galbraith, M. N.; Gray, R. W.; King, R. R.; Whalley, W. B. *J. Chem. Soc. C: Org.* **1971**, 3559–3563.

(13) Me_3OBF_4 is a commercial available reagent. Tetrafluoroborate anion was frequently utilized as counterion to stabilize the oxoniums and ammoniums.

(14) Crystal sample of **1a** for X-ray single crystallographic study was obtained from a mixed solvent of acetonitrile and petroleum ether.

conveniently prepared at room temperature in a scale up to 100 g. Simple filtration and solvent washes (to remove the unreacted substrates and excess reagents) in the open air are sufficient to afford the qualified samples for analyses. However, under the same conditions, those substrates **2** having electron-withdrawing group(s) and/or halogen(s) on their phenyl ring failed to provide the corresponding isochromenylium salts; instead, a dimerization reaction happened. In those metal-catalyzed reactions with olefins, the substrates bearing electron-withdrawing group(s) also could not afford corresponding products.[4−6,8] Fortunately, the phenol and/or phenol methyl ethers existing in the above stable ICTBs would make future further transformations (of the obtained products after their reactions) possible to more diverse functionalities including the carboxylic ester, amide, aniline, cyanid, and aryl halide through the corresponding intermediates ArOTf.

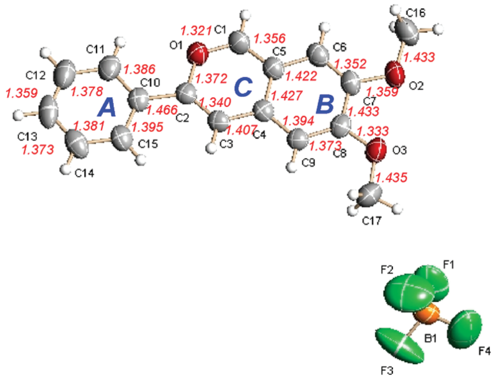
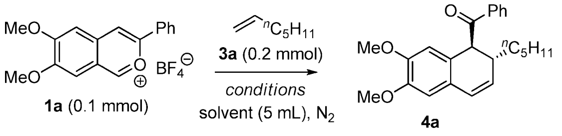


Figure 1. ORTEP drawing of isochromenylium tetrafluoroborate **1a** and the bond lengths (red digitals).

The crystal structure of ICTB **1a** (Figure 1) shows that all three rings A/B/C are approximately in the same plane so that the positive charge of the oxygen (O1) could be delocalized to the best extent. This provides a large electronic conjugated system and makes ICTB **1a** sufficiently stable. Unsymmetrical distribution of carbon−carbon bonds in the pyrylium ring B of crystal **1a** indicates that it is an unusual aromatic system.[15] Ring C is also affected by ring B. The lengths of C2−C3 and C1−C5 are more close to a double bond, while the lengths of C3−C4 and C4−C5 show the tendency to a single bond. The difference of bond lengths of O1−C1 (1.32 Å, ring B) and O1−C2 (1.37 Å) suggests that C1−O1 is more likely an activated carbonyl group. The contact forces are also found between different layers of ICTB **1a** in the crystal. Complex inter- and intramolecular hydrogen bonding networks are observed in the crystal cell parameters (for a summary, see Supporting Information). Such interactions of hydrogen bondings not only help to stabilize energetic compounds substantially but also help to pile up the molecules orderly and thus increase the crystal density markedly. In addition, fluorines of tetrafluoroborate anions are found to serve as the hydrogen bonding acceptors in the crystal.

Because ring B presents weak Hückel aromaticity in crystal **1a**, ICTBs **1** are likely suitable oxa-dienes for the [4 + 2] cycloadditions. A simple olefin 1-heptene (**3a**) was thus chosen as the substrate to examine the corresponding reaction with ICTB **1a** (Table 1). Screening of reaction conditions showed that MeCN was the best solvent. Under the optimized conditions, 1,2-dihydronaphthalene **4a** was afforded in 75−76% yield in shorter reaction times (Table 1, entries 7−8).

Table 1. Screening of Conditions for the Reaction of ICTB **1a** with 1-Hepatene **3a**[a]



entry	solvent	temp. (°C)	time (h)	yield (%)[b]
1	THF	25	48	<10
2	THF	60	48	16
3	toluene	25	48	<10
4	toluene	60	48	14
5	1,2-DCE	25	24	73
6	1,2-DCE	60	7	72
7	MeCN	25	2	76
8	MeCN	60	40 min	75

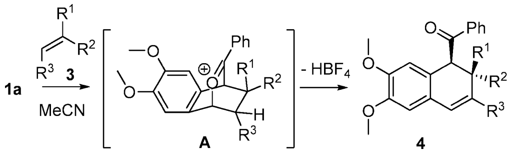
[a] Mixture of isochromenylium tetrafluoroborate **1a** (0.1 mmol) and 1-hepatene **3a** (0.2 mmol) was stirred in the indicated solvents (5 mL, anhydrous) at room temperature or at 60 °C. [b] Isolated yields of **4a**.

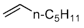
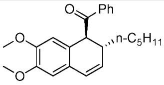
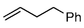
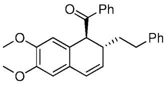
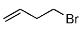
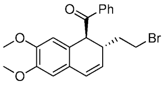
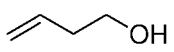
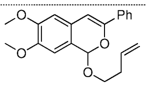
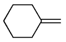
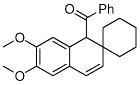
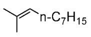
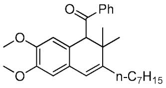
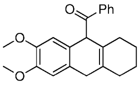
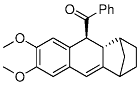
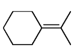
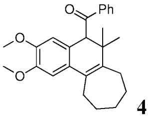
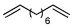
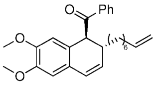
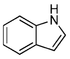
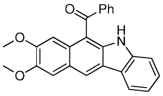
Under the optimized conditions, substrate scope of olefins **3** were further investigated (Table 2). Reactions of **1a** usually took place rapidly in MeCN at 25 °C with the monosubstituted, disubstituted, and trisubstituted olefins, as well as the cyclic olefins **3g** and **3h**, affording satisfactory yields of diverse 1,2-dihydronaphthalenes **4** (Table 2, entries 1−2 and 5−9). The relative configurations of products **4** were confirmed by corresponding NOESY experiments. However, reaction of **1a** with 3-buten-1-ol (**3d**), which contains both terminal olefin and hydroxyl functionalities, afforded the acetal product **4d** only. Obviously, reaction of the “unusual” carbonyl functionality of **1a** with the hydroxyl group of olefin substrate **3d** is much faster than the corresponding [4 + 2] reaction with terminal olefin of **3d** (entry 4). In the production of **4i** (entry 9), a 1,2-alkyl migration was involved prior to the final proton elimination. To our surprise, reaction of **1a** with α,ω-diene **3j** stopped at the mono-olefin addition stage (entry 10). It is inferred that further reactions with the second terminal olefin of **3j** are unfavorable by either intramolecular or intermolecular ways. Indole (**3k**) was also a good substrate for this cascade reaction, affording tetracyclic product **4k** in 43% yield (entry 11). Although indole was frequently used as the electron-donating agent, no addition of **3k** was detected to the C-1 position of **1a** in this reaction.

---

(15) In a typical aromatic ring system, each carbon-carbon bond length is almost equal due to the π-electron delocalization effects.

Table 2. Reactions of ICTB **1a** with Olefins **3**[a]

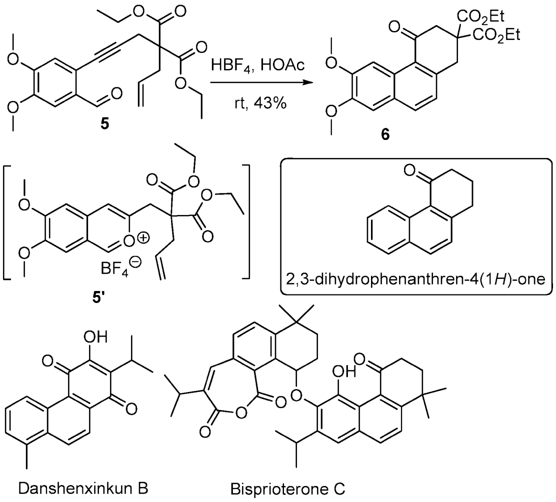


entry	olefins **3**	products **4**	yield (%)[b]
1	 **3a**	 **4a**	75
2	 **3b**	 **4b**	65
3[c][d][e]	 **3c**	 **4c**	67
4[f]	 **3d**	 **4d**	79
5	 **3e**	 **4e**	72
6[c]	 **3f**	 **4f**	78
7	 **3g**	 **4g**	69
8	 **3h**	 **4h**	56
9[c][g]	 **3i**	 **4i**	63
10	 **3j**	 **4j**	48
11[c]	 **3k**	 **4k**	43

[a] Mixture of isochromenylium tetrafluoroborate **1a** (0.1 mmol) and olefin **3** (0.2 mmol) was stirred in anhydrous MeCN (5 mL) at 25 °C for 1 h. [b] Isolated yields of **4**. [c] Reaction temperature is 60 °C. [d] Reaction time is 8 h. [e] Olefin **3** (4.0 equiv) was used. [f] Reaction time is 10 min. [g] Reaction time is 18 h.

With the above results (Table 2), we deduced that the cycloisomerizations would be possible using an intramolecular cascade reaction by direct treatment with HBF_4. A prefunctionalized acetylene-aldehyde substrate, 2-alkynylbenzaldehyde **5**, was thus prepared. To our delight, direct treatment of **5** with HBF_4 in acetic acid ar room temperature afforded 43% yield of the expected tricyclic product **6**. This provides a new straightforward metal-free access to the 2,3-dihydrophenanthren-4(1*H*)-one skeleton, which represents the tricyclic core structure of a number of biologically interesting natural products such as danshenxinkun B[16] and bisprioterone C.[17] Isochromenylium **5′** is thought to be the intermediate involved in this cascade process (Scheme 2).

Scheme 2. HBF_4-Promoted One-Pot Construction of 2,3-Dihydrophenanthren-4(1*H*)-one



In summary, a number of air- and moisture-stable isochromenylium tetrafluoroborates were conveniently prepared and characterized for the first time. These solid materials could be stored in the laboratory without any protection and used as regular laboratory reagents. Direct metal-free reactions of representative ICTB **1a** with olefins were studied, and a variety of multiple-ring-containing frameworks were afforded via efficient cationic cascade pathways. In addition, a one-pot procedure for the synthesis of 2,3-dihydrophenanthren-4(1*H*)-one derivatives under metal-free conditions was also developed in this work.

Acknowledgment. This project was financially supported by MOST (2010CB832200, 2009ZX09501), NSFC (20672128, 20621062), CAS (KJCX2-YW-H08), and SHMCST (08JC1422800, 07DZ22001). Y.Z.J. is a principle investigator of e-Institute of Chemical Biology of Shanghai Universities.

Supporting Information Available: Experimental details and charaterizations of new compounds, NMR copies of new compounds, and X-ray crystal data of **1a**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9019524

---

(16) Don, M.-J.; Shen, C.-C.; Syu, W.-J.; Ding, Y.-H.; Sun, C.-M. *Phytochemistry* **2006**, *67*, 497–503.

(17) Xu, J.; Chang, J.; Zhao, M.; Zhang, J.-S. *Phytochemistry* **2006**, *67*, 795–799.