Organic LETTERS

Letter

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Convergent Synthesis, Resolution, and Chiroptical Properties of Dimethoxychromenoacridinium Ions

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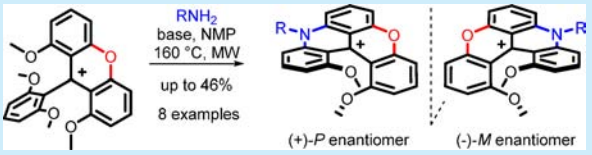
Supporting Information

ABSTRACT: Cationic azaoxa[4]helicenes can be prepared in a single step from a common xanthenium precursor by addition of nucleophilic amines under monitored conditions (160 °C, 2 min, MW). The (−)-(*M*) and (+)-(*P*) enantiomers can be separated by chiral stationary-phase chromatography. Determination of the absolute configuration and racemization barrier ($\Delta G^{\ddagger}$ (433 K) 33.3 ± 1.3 kcal·mol^{-1}) was achieved by VCD and ECD spectroscopy, respectively.



Cationic helicenes related to the family of triangulene dyes and fluorophores are investigated for their unusually high stability under basic conditions and for applications in the fields of chirality, physical organic chemistry, catalysis, photophysics and biology.[1,2] Two families of derivatives have been reported so far, the [4] and [6]helicenes respectively (Figure 1). They

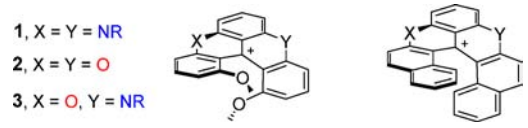


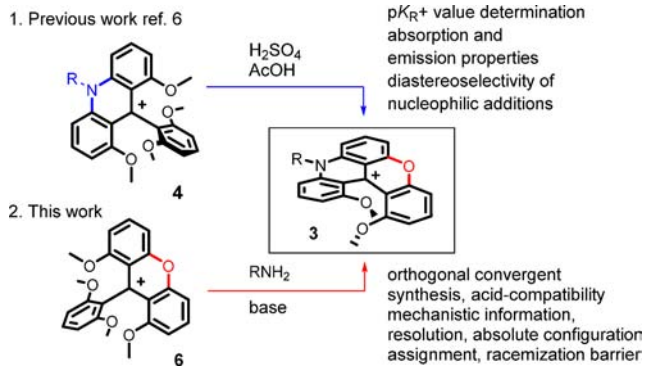
Figure 1. Cationic [4]- and [6]helicenes (*P* enantiomers shown). X, Y = O, NR.

are characterized by a (formally) central positive charge flanked by two neighboring donor heteroatoms that tame the reactivity of the electrophilic center. While two nitrogen, two oxygen or a combination of both atoms can be relatively easily introduced into the [6]helicene framework,[3] achieving such a diversity in the [4]helicene series has been less trivial. Diaza derivative **1** was for a long time the only known member of the [4] family;[4] dioxa **2** [4l,5] and azaoxa **3**[6] being reported quite later.[7]

In fact, the synthesis of dimethoxychromenoacridinium ions **3** was reported only recently by Laursen and collaborators (Scheme 1, eq 1).[6] Several acridiniums **4** were prepared by reactions of tris(2,6-dimethoxybenzene)methyl cation **5** (Scheme 2) with primary amines.[4a,b] Then, treatment in concentrated H_2SO_4/AcOH afforded the targeted azaoxa[4]-helicenes in moderate to excellent yields. Compounds **3** were characterized by their pK_R^+ value (13.0). Absorption and emission properties were also examined and discussed. The reactivity toward nucleophiles such as hydrides ($NaBH_4$) or organolithium reagents (MeLi) was investigated demonstrating good levels of facial selectivity in the nucleophilic attacks to the central carbon.

Herein, in a complementary study, we present a chemically orthogonal and convergent procedure for the preparation and

Scheme 1. Preparation of Dimethoxychromenoacridinium Ions 3



isolation of chromenoacridinium ions **3** (Scheme 1, eq 2). Xanthenium salt **6** is used as a common precursor for all derivatives **3**. Under optimized conditions (rapid RNH_2 addition, chemo- and stereoselective reduction, novel photochemical reoxidation), salts **3** are isolated in yields up to 46% for four combined steps. Interestingly, this procedure is amenable to acid-sensitive residues and some important mechanistic information is afforded by the isolation in high yields of initial leuco intermediates. Compound **3a** (R = Pr) was furthermore separated into single enantiomers by chiral stationary phase (CSP) chromatography. The *P* and *M* enantiomers were identified by vibrational circular dichroism (VCD) and they present a rather large barrier of racemization ($\Delta G^{\ddagger}$ 33.3 ± 1.3 kcal·mol^{-1} at 433 K).

As just mentioned, helical dimethoxychromenoacridinium ions have been recently reported by the group of Laursen.[6] In this study, compounds **3** were prepared in two main steps by reactions of tris(2,6-dimethoxybenzene)methyl cation **5** with

Received: June 11, 2014
Published: July 7, 2014

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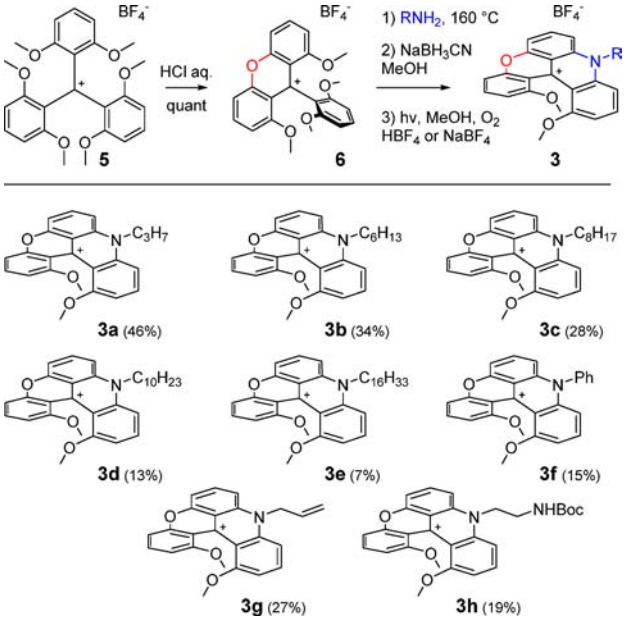
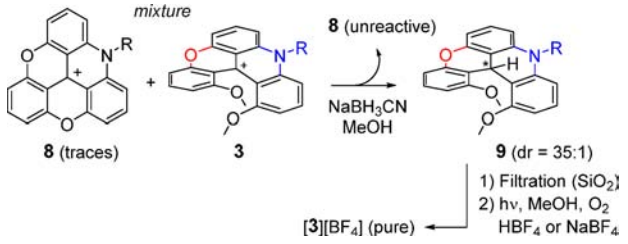
Scheme 2. Convergent Synthesis of Azaoxa[4]helicenes 3



primary amines and then treatment of the resulting acridinium salts **4** in strongly acidic conditions (Scheme 1, eq 1). Despite the efficiency of this method,[8] we saw an advantage in developing of an alternative protocol which would be convergent and allow the use of acid-sensitive side chains (e.g., NHBoc, allyl). This approach would use xanthenium salt [**6**][BF_4] as a common precursor for all derivatives **3** (Schemes 1 and 2). We considered that **6** ought to react with primary amines under controlled conditions and afford the dimethoxychromenoacridinium ions by nucleophilic aromatic substitutions of two neighboring MeO substituents by the aza-nucleophiles.

In practice, [**6**][BF_4] was prepared using conditions described by Martin and Smith.[9] A solution of [**5**][BF_4] in aqueous HCl was heated at reflux for 12 h to obtain, after workup and acidification with HBF_4, salt [**6**][BF_4] in quantitative yield. Then, solutions in dry NMP of primary amines and [**6**][BF_4] were heated at 160 °C in a microwave apparatus. Care was taken to use a short reaction time (2 min) and a relatively modest quantity of amine (3 equiv) since large amounts of base and prolonged reaction times provoke further reactions and favor the formation of triangulene products.[10] To our satisfaction, analysis of the reaction crude revealed the rapid consumption of **6** (see the mechanistic discussion) and the formation of desired products [**3**][BF_4] which were extracted from the organic layers after the addition of EtOAc and brine, along with traces of the corresponding ADOTA adducts **8** (typically 1−10%, ADOTA = azadioxatriangulenium ions, Scheme 3). While it was impossible to separate **3** from **8** by column chromatography or precipitation, a chemo and stereoselective reduction afforded a rapid solution to the problem.[11] Treatment of the mixtures with $NaBH_3CN$ led to the exclusive reduction of **3** (Scheme 3).[12] Resulting neutral triarylmethanes **9** were then easily separated from cationic **8** by filtration over silica gel plugs. Of interest, compounds **9** were isolated in quite better diastereomeric ratios (35:1, HPLC) using $NaBH_3CN$ as hydride source instead of $NaBH_4$ (10.1:1).[6] Clearly, the milder nature of the cyano-containing reagent is beneficial; the higher selectivity being then possibly the result of

Scheme 3. Chemoselective Reduction and Photochemical Reoxidation of Neutral Adducts 9

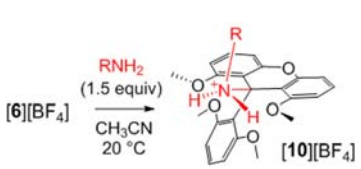


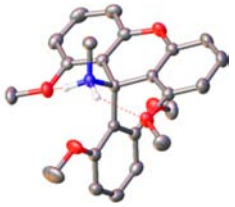
the reactivity−selectivity principle under kinetic control.[13] Finally, reoxidation of compounds **9** to salts [**3**][BF_4] was afforded by a photochemical irradiation of MeOH solutions in the presence of air and of $NaBF_4$ or HBF_4.[14,15]

With this procedure in hand, a variety of side chains were introduced. Yields are low to moderate, from 7 to 46%, but they correspond to the combined yields of four consecutive steps—the last three being performed in a row. Alkyl residues from propyl to hexadecyl are introduced readily; yields of the corresponding cations **3a** to **3e** decreasing however constantly with the longer side-chains. The reason for the decrease is unknown at the moment. Less nucleophilic aniline reacted nevertheless to afford **3f** in 15% yield. To our satisfaction, it was possible to introduce acid-sensitive allylamine and *tert*-butyl (2-aminoethyl)carbamate. The corresponding tetrafluoroborate salts [**3g**][BF_4]and [**3h**][BF_4] were isolated in 27% and 19% respectively.

At that stage, to shed some light on the mechanism, it was decided to investigate further the addition of amines to salt [**6**][BF_4]. Reactions were performed in CH_3CN at 20 °C. In all instances (Table 1), a rapid discoloration was achieved and

Table 1. Isolation of the Triarylammonium salts [10][BF_4][a]





entry	compd	R	yield (%)
1	**10a**	propyl	95
2	**10b**	hexyl	80
3	**10c**	octyl	70
4	**10d**	decyl	69
5	**10e**	hexadecyl	70

[a]Anisotropic displacement ellipsoids plot of the crystal structure of [**10a**][BF_4]. Thermal ellipsoids are drawn at 50% probability. For clarity, most hydrogen atoms have been removed and the propyl side chain was truncated.

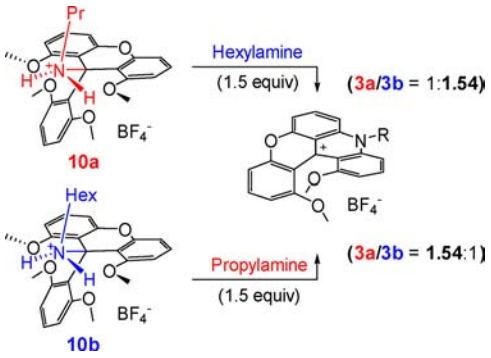
NMR spectroscopic analyses revealed the predominant formation of 1:1 adducts between **6** and the amines. These *leuco* products were isolated by precipitation upon addition of Et_2O and a further cooling to 4 °C. Only a motif with an ammonium moiety bound directly to the central carbon atom was consistent with the ^1H, ^{13}C, IR, and MS analyses; the motif was confirmed by the X-ray diffraction study of [**10a**][BF_4] (see Table 1 and the Supporting Information).[16] Interestingly and a bit surprisingly, these ammonium salts are highly stable as

dx.doi.org/10.1021/ol501692r | *Org. Lett.* 2014, 16, 3800−3803

evidenced by their lack of reactivity when heated to 160 °C in solution in NMP (MW, 2 min). In fact, the reactions remain essentially colorless and salts [**10**][BF_4] are recovered quantitatively.[17]

However, additions of 1.5 equiv of base (Et_3N, $^iPr_2NEt$, DBU, or the primary amines themselves) to the NMP solutions of salts [**10**][BF_4] result in an immediate red color. After heating (MW, 160 °C, 2 min) and workup, the corresponding [**3**][BF_4] salts can be isolated (yields 11−15%). To characterize this transformation, salts [**10a**][BF_4] (R = Pr) and [**10b**][BF_4] (R = Hex) were reacted with hexylamine and propylamine, respectively (1.5 equiv). In both experiments (Scheme 4),

Scheme 4. Evidence for a Dissociative Intermolecular Mechanism



products [**3a**][BF_4] and [**3b**][BF_4] were obtained in a statistical mixture; the ratios reflecting the stoichiometry between the propyl and hexyl components in each crude. Clearly, these results indicate that a base is required to transform ammonium derivatives [**10**][BF_4] into products **3** and that a dissociative intermolecular mechanism is at play.[18]

With these results in hand, the resolution of **3a** was tackled. The enantiomeric separation was, however, performed by CSP chromatography on neutral compound **9a** rather than on the charged moiety; the high diastereomeric purity of **9a** (dr 35:1) obviously helped the separation process. In fact, the resolution of *rac*-**9a** was achieved on a semipreparative scale using a Chiralpak IC column and a mixture of *n*-hexane:*i*-PrOH 99:1 as eluent. From 50 mg of *rac*-**9a**, after several runs, two major separated fractions were afforded, 9 mg (*ee* > 99%, 18%) of (−)-**9a** and 9 mg (*ee*>99%, 18%) of (+)-**9a** (see the Supporting Information for details). Upon photochemical oxidation (Scheme 3), the corresponding enantiopure salts (−)-[**3a**][BF_4] and the (+)-[**3a**][BF_4] were afforded. Electronic circular dichroism (ECD) spectra display totally symmetrical curves in the 250−650 nm domain. The spectra are reported in Figure S2 (Supporting Information).

The absolute configuration of helicene **3a** was established by vibrational circular dichroism (VCD).[19] IR absorption and VCD spectra were measured for solutions (CD_2Cl_2) of both (+)- and (−)-[**3a**][BF_4] and compared to the most stable conformer of (*P*)-**3a** (Figure 2), thus accounting for about 90% according its Boltzmann weight. Overall, a good agreement between the experimental and theoretical spectra is observed allowing the assignment of a *P* and *M* configurations for the carbenium ion in salts (+)- and (−)-[**3a**][BF_4] respectively.

With the enantiopure salt in hand, the determination of the kinetic barrier for the interconversion between the enantiomers of **3a** was examined. The determination of the racemization

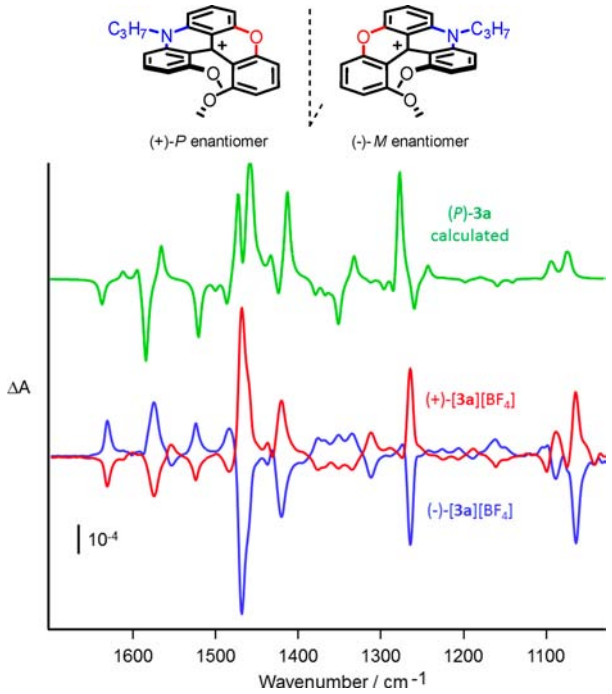


Figure 2. Experimental VCD spectra (CD_2Cl_2, 298 K) of (−)-[**3a**][BF_4] (blue) and (+)-[**3a**][BF_4] (red). Calculated spectrum of (*P*)-**3a** (green).

barrier was performed by ECD, monitoring a single wavelength every second (410 nm, see the Supporting Information). It was necessary to heat DMSO solutions of (+)-[**3a**][BF_4] at 160 °C to start observing a relatively rapid decrease of the Cotton effect. After 1000 s, a 28% loss of enantiomeric purity was observed at that temperature. Samples were then heated at 170, 180, and 190 °C and analyzed for the same period of time. The kinetic constants were calculated (e.g., *k* (433 K) 1.75×10^{-4} s·mol^{-1}) and the activation parameters determined ($\Delta H^{\ddagger}$ (433 K) 24.9 ± 2.4 kcal·mol^{-1} and $\Delta S^{\ddagger}$ (433 K) −19.4 ± 2.5 cal·K^{-1}·mol^{-1}). Not surprisingly, the racemization barrier of [**3a**][BF_4] ($\Delta G^{\ddagger}$ (433 K) 33.3 ± 1.3 kcal·mol^{-1}) is lower than that of diaza[**1**][BF_4] ($\Delta G^{\ddagger}$ 41.3 kcal·mol^{-1}) and higher than dioxo [**2**][BF_4] ($\Delta G^{\ddagger}$ 27.7 kcal·mol^{-1}). Clearly, as observed before,[5,20] the presence of an oxygen atom at a bridging position causes a higher degree of flexibility leading to an easier racemization. Recently, Elm and co-workers reported a calculated estimation of 35.4 kcal·mol^{-1} for the racemization barrier of **3** showing a good agreement between experimental and theoretical values.[21]

In conclusion, using xanthenium ion **6** as precursor, a series of dimethoxychromenoacridinium ions **3** was afforded. This route is convergent and presents an interesting orthogonality to that reported by Laursen and co-workers.[6] Products **10** of initial addition of the amines to the central carbon atom of **6** were furthermore characterized and shown to be possible intermediates if treated under basic conditions. Upon resolution by CSP chromatography, single enantiomers were obtained of which racemization barriers and absolute configurations were determined by ECD and VCD spectroscopy, giving then a complete description of the chiroptical properties of this novel class of cationic helicenes.

dx.doi.org/10.1021/ol501692r | *Org. Lett.* 2014, 16, 3800−3803

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the University of Geneva and the Swiss National Science Foundation for financial support. We acknowledge the contributions of the Sciences Mass Spectrometry (SMS) platform at the Faculty of Sciences, University of Geneva.

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(8) The final ring closure under acid conditions can be particularly efficient (yield up to 92%). Together with the first step, combined yields range from 20 to 50%.

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(10) Typically, 25 equiv of RNH_2 is used for the formation of cationic diaza[4]- and -[6]helicenes. See refs 3 and 4a,c for details.

(11) We had initially considered using the procedure developed for the purification of dioxo[4]helicene **2**, i.e., the reduction with $NaBH_4$ of all cationic derivatives followed by a separation of the resulting neutral triarylmethane adducts (see reference 5). However, in our hands, a satisfactory separation of the reduced products could not be achieved.

(12) The chemoselectivity can be rationalized by the higher electrophilicity of cations **3** over **8** (pK_R+ 13 vs 14.5, respectively). This difference may be related to the skeleton deformation that occurs upon the addition of nucleophiles to the central carbon of the carbenium ions. This leads to change of hybridization from sp^2 to sp^3 and the resulting strain seems to be better accommodated by the helical framework of **3** than the rigid planar geometry of triangulene **8**.

(13) The relative configuration of compounds **9** was not determined in the course of this study but everything indicates that the major diastereoisomer obtained with $NaBH_4$ remains the same with $NaBH_3CN$. Its nature and the origin of the stereoselectivity are discussed in ref 6.

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(15) This procedure was preferred over the I_2 oxidation protocol that associates a triodide I_3^- anion to the cation; this colored anion then complicated the spectral analysis.

(16) For a related result on a compound of type **5**, see: Wada, M.; Watanabe, T.; Natsume, S.; Mishima, H.; Kirishima, K.; Erabi, T. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 3233−3240. The ammonium salts decompose however upon heating.

(17) Most probably, the strong bifurcated hydrogen bonding interactions that occur in the solid state between the $H-N^+$ bonds and the neighboring methoxy groups are also present in solution; those are the reasons for this stability.

(18) This experiment supports the cationic-driven S_NAr mechanism proposed previously (see ref 4a,b) and invalidates [1,3]-sigmatropic shifts as alternative hypotheses for the formation of products **3**.

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