ORGANIC LETTERS

2013
Vol. 15, No. 16
4090–4093

A One-Step, Versatile Synthesis of Dibenzo [*n*.2.2] Macrobicyclic Compounds via a Conformation-Directed Macrocyclization Reaction

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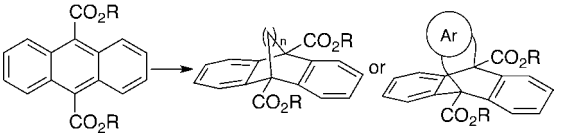
Received June 13, 2013

ABSTRACT



A series of dibenzo [*n*.2.2] bicyclic compounds (*n* = 2−20) were prepared in one step and good yields starting from dimethyl anthracene-9, 10-dicarboxylate. Reduction of the aromatic diester using lithium/naphthalene led to a *bis*-enolate that was cyclized with a variety of *bis*-electrophiles. The ease of the cyclization is probably due to the puckered conformation of the intermediate formed after the first alkylation step, in which the newly introduced chain that will become the bridge portion occupies a pseudoaxial position, positioning the leaving group close to the enolate nucleophile in the macrocyclization step.

From a synthetic point of view the preparation of medium- and large-sized carbocycles is not a trivial task. The numerous strategies envisioned for the construction of these types of meso- and macrocycles can be grouped in three general approaches: cycloadditions, cyclization reactions, and transformations of pre-existing rings (fragmentation of bicycles and ring expansion reactions).

Medium-sized rings[1] are especially hard to prepare efficiently by conventional cyclization approaches due to both disfavoring entropic and enthalpic factors. The ease (or lack thereof) of their preparation has been shown to be very sensitive to changes in the makeup of the ring (presence of heteroatoms and substituents). Ionic and radical fragmentation processes, as well as ring-expansion reactions,[2] have been used for the preparation of 7- to 10-membered rings. Ring closing olefin metathesis (RCM), on the other hand, has been successfully applied for the synthesis of medium-sized rings in systems that present some sort of conformational constraint (such as additional rings or stereoelectronic effects), as well as for the synthesis of macrocycles where the presence of a polar functional group has shown to be more important than the ring size for the success of the reaction.[3]

Macrocyclization methods[4] include carbocyclization,[5] macrolactonization,[6] and macrolactamization[7] reactions. Probably the most general and direct approach for the

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10.1021/ol4016767
Published on Web 08/05/2013

preparation of macrocycles consists in the ring-closure reaction[8] of a bifunctional flexible chain possessing a nucleophile and an electrophile at each end, although this is usually a low yielding process since polymerization can be an efficient competing reaction. That is the reason why the majority of the synthetic approaches for the preparation of macrocycles usually require high dilution conditions.[9] Alternative strategies to improve the yield of the macrocyclization step basically rely on the incorporation of a rigid group to restrict rotation in the chain, on some kind of conformational preorganization[10] or, more often, on the presence of a metal ion around which the molecule preorganizes the two reacting centers in a productive conformation (the template effect).[11]

We describe herein the preparation of different dibenzo [*n*.2.2] bicyclic compounds, where *n* varies from 2 to 20, usually in good yields, almost regardless of the ring size (small, medium, or large), starting from an anthracene dicarboxylate. No high dilution conditions are required, and neither a template effect nor the presence of a rigid group appears to be responsible for the efficiency of this transformation.

We have previously reported[12] the successful coupling of a dearomatization reaction of aromatic and heteroaromatic diesters with a *bis*-alkylation reaction to prepare fused [6,5], [6,6], and [6,7] bicyclic compounds. The reaction was applied to benzene, pyridine, naphthalene, furane, thiophene, and benzofurane dicarboxylates. Mechanistically, the reaction is initiated by anionic tin nucleophiles to give, via a stanna-Brook rearrangement, a *bis*-enolate intermediate that can be easily alkylated and cyclized by reaction with different *bis*-electrophiles. In some cases these *bis*-alkylative cyclizations could also be performed with sodium metal as a substitute for the tin anions (for the generation of the intermediate *bis*-enolates). We now disclose that this type of cyclizations also occurs with anthracene derivatives substituted by carboxylate groups at positions 9 and 10, but in this case the products are not fused, but bridged bicyclic compounds instead. When diisopropyl anthracene-9,10-dicarboxylate (**1a**) was treated with Me_3SnLi in THF at −78 °C followed by 1,3-dibromopropane, the crude reaction ^1H NMR showed the presence of only one product, identified as the bridged bicyclic compound **2a**, which could be isolated in 92% yield (see Scheme 1). This encouraging result prompted us to explore the scope of this reaction with different electrophiles. When the *bis*-alkylation of the intermediate bis-enolate was carried out with 1,4-dibromobutane or *cis*-1, 4-dichlorobutene the bridged bicyclic compounds **3a** and **12a** were isolated in 53% and 92% yield, respectively.

Although we had established over the years that tin compounds are very useful reagents in dearomatization–*bis*-alkylation reactions, their inherent toxicity and high cost are drawbacks serious enough to compel us to find alternative reagents for these transformations.

As anthracene dicarboxylate **1** is an electron-deficient aromatic molecule, we considered that it could be reduced under modified (ammonia-free) Birch[13] conditions, and if the reaction were carried out in the absence of a proton source, a *bis*-enolate should be obtained as the reaction intermediate, which could then be efficiently *bis*-alkylated. To this end we chose lithium as the metal and naphthalene as the electron carrier.[14] In practice, the reaction of dimethyl anthracene-9,10-dicarboxylate (**1b**) with excess lithium and naphthalene (ca. 5:1) in THF, followed by 1,3-dibromopropane, gave the bridged bicyclic compound **2b** in 95% yield (see Scheme 1).

We then decided to study the ability of this dianionic system to react with different electrophiles to give rise to bicyclic rings of different bridge sizes. When the solution obtained by reduction of anthracene diester **1b** was quenched with 1,4-dibromobutane, the [4.2.2] bridged compound **3b** was obtained in 52% yield, a very good yield based on the difficulty in forming rings of this particular size (eight-membered ring). However, when 1,5-dibromopentane was used as the electrophile we could not isolate the corresponding nine-membered ring **4b** under any of the reaction conditions tested. At low temperature a mixture of mono- and dialkylated (one electrophile coupled with two nucleophiles) products and dihydroanthracene-9,10-dicarboxylate was obtained, while the bisalkylated (one nucleophile alkylated with two electrophiles) product was isolated at higher temperatures. No cyclized product was observed when the monoalkylated product was isolated and then treated with LDA. Although disappointing, this was not a very surprising result as it is well-known that the ease of carbocyclization depends on the ring size, with eight- and nine-membered rings being the most difficult to form.

Better results were obtained when *bis*-electrophiles with longer chains were used. Thus, with 1,6-dibromohexane and 1,7-dibromoheptane the corresponding 10- and 11-membered rings **5b** and **6b** were isolated in 41% and 72% yield, respectively.

The synthesis of macrocyclic compounds was shown to be very easy for this system, as 1,9-dibromononane allowed

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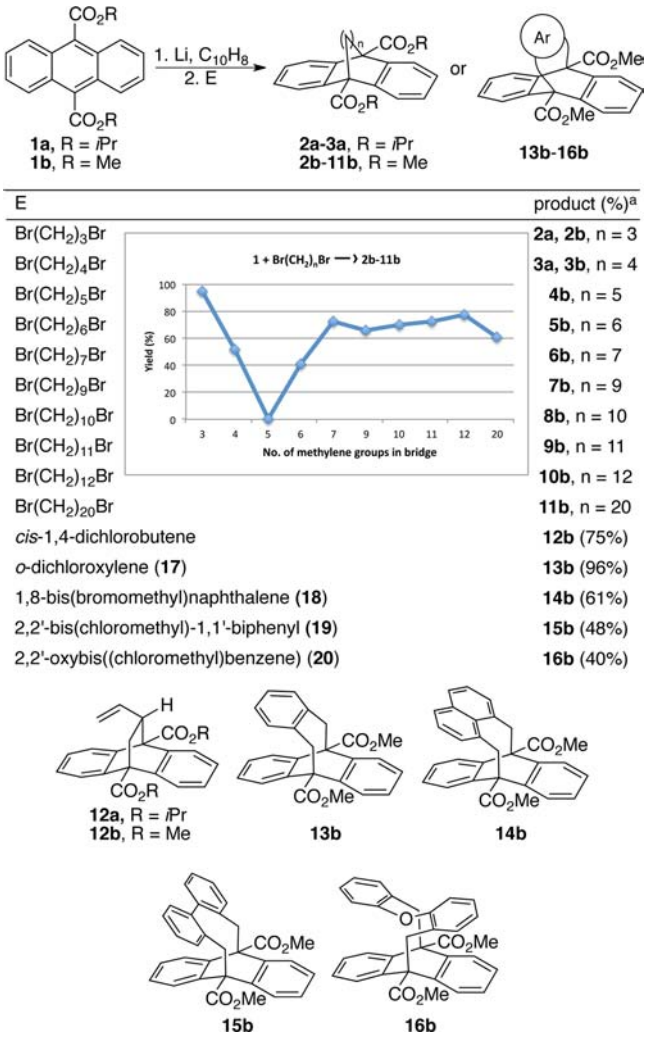
Scheme 1. Synthesis of Bridged [*n*.2.2] Bicyclic Compounds

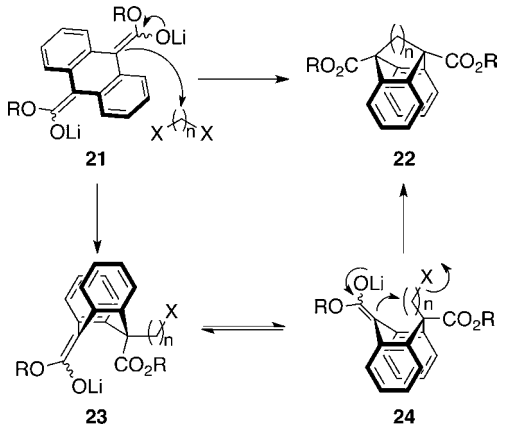


[a] Yields with aliphatic *bis*-electrophiles: **2b**, 95%; **3b**, 52%; **4b**, 0%; **5b**, 41%; **6b**, 72%; **7b**, 66%; **8b**, 70%; **9b**, 72%; **10b**, 77%; **11b**, 61%.

the preparation of bridged bicyclo [9.2.2] compound **7b** in 66% yield (13-membered ring), 1,10-dibromodecane yielded [10.2.2] bicyclic compound **8b** in 70% yield (14-membered ring), and 1,11-dibromoundecane and 1,12-dibromododecane led to the corresponding macrocycles **9b** and **10b** in 72% and 77% yield, respectively. Based on these results, it seemed as though macrocycles of almost any size could be prepared in high yield just by increasing the length of the methylene chain of the electrophile. To test this assertion we decided to prepare a 24-membered ring using the corresponding *bis*-electrophile, 1,20-dibromoicosane (the longest **1**,*ω*-dibromoalkane we could easily obtain), and thus [20.2.2] bicyclic compound **11b** was isolated in 61% yield. What is remarkable in this reaction is that there is no need to use high dilution conditions to obtain the

(15) The final concentration for most experiments (performed with 0.34 mmol of diester **1**) was 0.05 M due to experimental convenience, but when the reaction was performed at a higher scale, the final concentration was 0.1 M and the same yield was obtained.

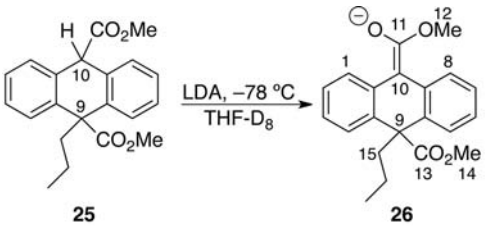
Scheme 2. Reactive Conformations of the Enolate Intermediate



macrocycles.[15] The trend observed for the propensity of the monoalkylated intermediates to cyclize (measured as the yield of the bridged product as a function of bridge size) (Scheme 1) roughly follows that observed by Illuminati and co-workers in their seminal kinetic study on macrocyclizations.[8d] As can be seen from the plot in Scheme 1, the ease of the cyclization goes through a minimum while trying to close a nine-membered ring (closing 8- or 10-membered rings is difficult but possible), a behavior clearly rooted in the importance of ring-strain factors in these types of macrocyclizations.[8b] To nullify the effect of this factor we decided to use *bis*-electrophiles that incorporate a rigid group to restrict rotation in the chain (**17**–**20**) in an attempt to favor the formation of medium sized rings. An excellent result was obtained when using *o*-dichloroxylene (**17**), as the eight-membered ring **13b** was isolated in 96% yield. The nine-membered ring **14b** could also be prepared in 61% yield when 1,8-*bis*(bromomethyl)naphthalene (**18**) was used as the electrophile. The corresponding 10- and 11-membered rings **15b** and **16b** were isolated in moderate yields when 2,2′-*bis*(chloromethyl)-1,1′-biphenyl (48%) and 2,2-oxy-*bis*[(chloromethyl)benzene] (40%) were used as *bis*-electrophiles, respectively. In these last two examples the lower yields of the bridged products do not appear to arise from difficulties in the cyclization step, but from a competing halogenation of the intermediate *bis*-enolates followed by rearomatization to the starting anthracene, which accounts for the balance of material in these reactions.

To explain the ease of this meso- and macro-cyclization, almost independent of the ring size of the product, we have to consider the reactive conformation of the monoalkylated intermediate (see Scheme 2). Numerous studies[16] concerning the conformational analysis of 9-alkyl-9,10-dihydroanthracenes have shown the existence of a favored nonplanar conformation, with departure from planarity increasing with the bulkiness of the substituent. Moreover, it has been demonstrated that, in the preferred conformation, the substituent occupies a pseudoaxial position in a more or less flattened, boat-shaped conformation.[17] We propose that the distinctive facilitating element in this

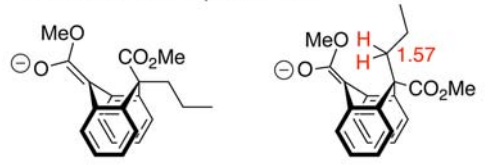
Scheme 3. NMR Data for Monoenolate **26** (δ in ppm)



25 26

26	1	8	9	10	11	12	13	14	15
^{1}H-NMR	8.14	7.84				3.54		3.61	1.57
$\Delta\delta^a$	0.70	0.40				0.03		0.2	-0.58
^{13}C-NMR	126.4	127.4	59.5	80.9	165.2	49.4	177.2	51.9	41.3
$\Delta\delta^a$	-3.7	-2.7	3.5	30.7	-8.1	-3.6	1.1	-0.9	-4.8

(a) $\Delta\delta$ = δ enolate **26** - δ protonated **25**



26-e **26-a**

newly described cyclization is the conformation of the intermediate monoenolate (see Scheme 2): a boat conformation with the alkyl chain bearing the leaving group disposed in a pseudoaxial position (in close proximity to the nucleophilic carbon of the enolate), which greatly facilitates the intramolecular alkylation.

To check this conformational hypothesis we prepared a model system of the key monoenolate intermediate (by reaction of dimethyl 9-propyl-9,10-dihydroanthracene-9,10-dicarboxylate, **25**, with LDA) and studied its structure and conformation by NMR (Scheme 3).[18] The ^{1}H NMR spectrum of propylated diester **25**, in THF-D_8 at −78 °C, shows the presence of a singlet at 5.30 ppm due to the C-10 proton and a multiplet at 2.15 ppm due to the CH_2 of the propyl group bound at C-9. When a solution of **25** in deuterated THF was added to an NMR tube containing a solution of LDA (210 mol %) at −78 °C, we observed the disappearance of the signal at δ 5.30 ppm in less than 30 min and the appearance of signals corresponding to the enolate (see Supporting Information and selected peaks in Scheme 3).

An NMR study of the deprotonation of 9-carboethoxy-9,10-dihydroanthracene performed by Rabideau's group[19] pointed out that the enolate is the preferred structure for the monoanion and thus the carbonyl π overlap forces some folding of the central ring. If the central ring adopts a boat conformation, as suggested by Rabideau, the chemical shift of the group in the pseudoaxial position should be affected by the cone-shape shielding zone of the enolate C−C double bond. Thus, if the propyl group preferentially exists in the pseudoaxial position, a sizable upfield displacement of the ^{1}H NMR signal should be observed (**26-a**; see Scheme 3). However, such a displacement should not be observed if the orientation of the propyl group in the enolate were preferentially pseudoequatorial, **26-e**. As can be seen in Scheme 3, the methylene group closest to the ester moiety experiences a considerable upfield shift ($\Delta\delta$ = −0.58 ppm), a value in agreement with the proposed boat conformation for the enolate and the pseudoaxial disposition for the propyl group. These observations lend credence to our proposal that a puckered conformation lies at the heart of the ease of this cyclization.

In conclusion, we have developed a highly efficient synthesis of bridged [*n*.2.2] bicyclic compounds based on the reductive alkylation of dimethyl anthracene-9,10-dicarboxylate with lithium and naphthalene. Under these conditions a stable *bis*-enolate was generated and then cyclized by reaction with a variety of *bis*-electrophiles, allowing the one-pot preparation of medium- and large-sized dibenzobicycles.

Bridgehead-substituted dibenzo [2.2.2] compounds have been used for the design and study of molecular devices.[20] We believe our approach could open the way for the preparation of analogous systems with more varied bicyclic cores. We are currently exploring further applications of this conformationally directed macrocyclization methodology toward this end.

Acknowledgment. This work was supported by the Ministerio de Economía y Competitividad of Spain (CTQ2011-22436) and Xunta de Galicia (PGIDIT10-PXIB209113PR, 10PXIB209155PR, and 2007/085).

Supporting Information Available. Full experimental procedures, characterization data, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.