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Synthesis of Pentacyclic 13-Azadibenzo[*a*,*de*]anthracenes via Anionic Cascade Ring Closure

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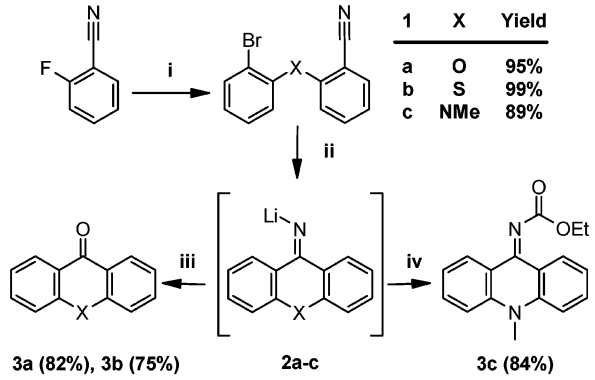
Abstract: Bromine−lithium exchange using *tert*-butyllithium at −78 °C initiates a cascade process whereby either xanthone derivatives or pentacyclic 13-azadibenzo[*a*,*de*]anthracenes are produced in high yields. The reaction proceeds via a sequential intramolecular trapping of organolithium intermediates.

The generation of a very reactive organometallic intermediate via metalation or halogen−metal exchange followed by an intramolecular ring closing reaction is a powerful way of constructing complex polycyclic molecules.[1] In this paper, we wish to report the design and execution of a new anionic cascade reaction giving access to pentacyclic 13-azadibenzo[*a*,*de*]anthracene derivatives via a sequential intramolecular trapping of organolithium intermediates. This class of compounds have been reported as potent telomerase inhibitors with potential applications within anti-cancer therapy.[2]

In connection with a recent program in our laboratories directed toward the synthesis of a new class of azaxanthones, we reported that a cyano group functions as an electrophile in the intramolecular trapping of metalated pyrazole derivatives.[3] In Scheme 1, the generalization of this approach to the synthesis of xanthone derivatives is outlined. Substrates **1a**−**c** were prepared in one step via nucleophilic aromatic substitution of the fluorine in 2-fluorobenzonitrile. 2-Bromophenol gave **1a** in 95% yield, and 2-bromothiophenol produced **1b** in 99% yield. 2-Bromoaniline gave **1c** in 89% yield via a one-pot SN_{AR}/alkylation procedure.[4] When **1a**−**c** were added to 2.1 equiv of *tert*-butyllithium[5] at −78 °C and the reaction

SCHEME 1. Synthesis of Xanthone Derivatives 3a−c[a]



[a] Key: (i) **1a**: 2-bromophenol, K_2CO_3, DMF, 100 °C, 48 h; **1b**: 2-bromothiophenol, K_2CO_3, DMF, 100 °C, 24 h; **1c**: (1) 2-bromoaniline, KO^{t}Bu, DMSO, rt, (2) MeI; (ii) (1) *t*-BuLi, THF, −78 °C to rt; (iii) 4 N HCl, 70 °C, 12 h; (iv) EtOCOCl.

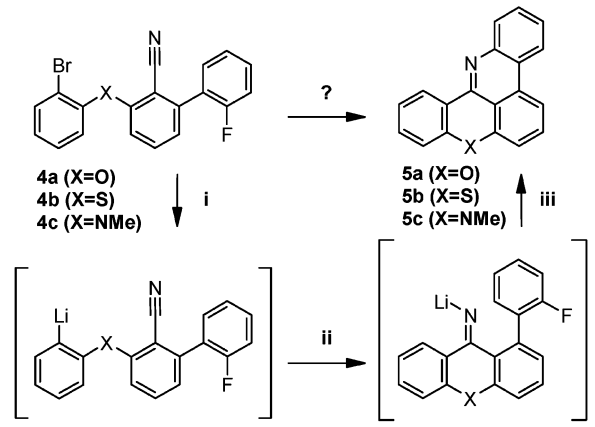


FIGURE 1. Proposed cascade process. Key: (i) Br−Li exchange, (ii) intramolecular addition to CN, (iii) intramolecular SN_{AR}.

mixture was allowed to warm to room temperature, the intermediate cyclic lithio-imines **2a**−**c** were formed via bromine−lithium exchange followed by an intramolecular attack on the cyano group.[6] Subsequent hydrolysis of **2a** and **2b** gave xanthone **3a** and thioxanthone **3b** in 82% and 75% yield, respectively. Imine **2c** proved extremely sluggish toward hydrolysis, and instead **2c** was reacted with ethyl chloroformate to give **3c**[7] in 84% yield.

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(4) Full experimental details are given in the Supporting Information.

(5) A side product arising from the competing addition of the organolithium to the nitrile could be detected in the crude products. Other alkyllithiums, solvents, and temperatures were tested, but we found that the best results were obtained using inverse addition of the substrate to a solution af *tert*-butyllithium in THF at −78 °C. See the following references for the use of *tert*-butylllithium in halogen−lithium exchange reactions: (a) Seebach, D.; Neumann, H. *Chem. Ber.* **1974**, *107*, 847. (b) Bailey, W.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404. (c) Negishi, E.-I.; Swanson, D. R.; Rousset, C. J. *J. Org. Chem.* **1990**, *55*, 5406.

(6) GC-MS analysis of quenched aliquots showed full conversion of the starting aryl bromides **1a**−**c** and formation of the corresponding imines as the major products.

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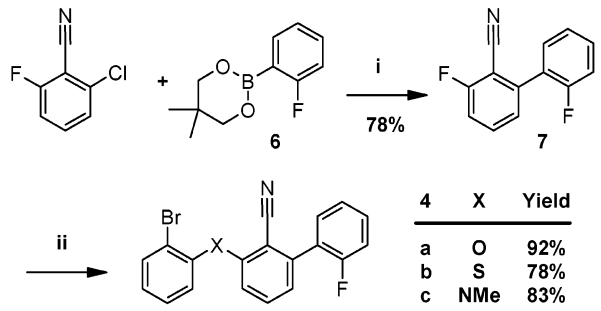
SCHEME 2. Synthesis of Substrates 4a−c for Anionic Ring Closure[a]



4	X	Yield
a	O	92%
b	S	78%
c	NMe	83%

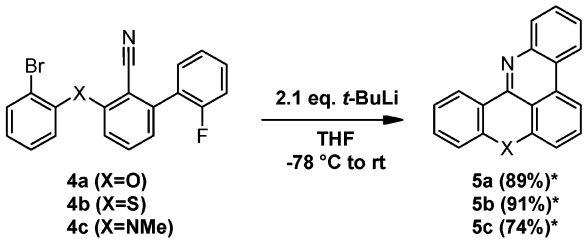
[a] Key: (i) $Pd(PPh_3)_4$, 2 M K_2CO_3, EtOH/toluene, 80 °C, 63 h; (ii) see the Supporting Information.

This demonstrated that the intermediate lithio-imines could be trapped with electrophiles. We speculated that if this observation was combined with our recently reported protocol for the synthesis of 6-substituted phenanthridines via *intra*molecular trapping of imine-anions,[8] this could lead to the pentacyclic systems **5a**−**c** from **4a**−**c** via the cascade process indicated in Figure 1.

The required substrates **4a**−**c** were prepared in two steps, as summarized in Scheme 2. Suzuki−Miyaura coupling[9] of commercially available 2-chloro-6-fluorobenzonitrile with 2-fluoroarylboronic ester **6**[10] gave biaryl **7** in 78% yield. Subsequent regioselective nucleophilic aromatic substitution of the fluorine ortho to the activating cyano group, using the conditions developed for the synthesis of **1a**−**c**, gave **4a**−**c** in 78−92% yield.

With the key substrates in hand, we set out to test the hypothesis; see Scheme 3. Addition of **4a**−**c** to 2.1 equiv of *tert*-butyllithium in THF at −78 °C followed by warming to room temperature did indeed induce the proposed sequence in Figure 1. Thus, the pentacyclic 13-azadibenzo[*a*,*de*]anthracenes **5a**−**c** were isolated in 74−91% yield.

SCHEME 3. Synthesis of 13-Azadibenzo[*a*,*de*]-anthracene 5a−c via Anionic Cascade Ring Closure[a]



[a] Key: *isolated yield. Average of two runs.

In conclusion, we have developed a novel approach to the synthesis of 13-azadibenzo[*a*,*de*]anthracene derivatives via an anionic cascade ring-closing reaction. Previous methodologies rely on Grade−Uhlmann thermolysis of benzotriazole derivatives at reflux in diphenyl ether and other radical cyclizations.[11] Our synthetic approach proceeds in three steps from readily available starting material in over all 48−65% yield and should offer rapid access to substituted derivatives inaccessible via previously reported methodologies. We are currently exploring the scope of the reaction with respect to the incorporation of heterocycles in the pursuit of pyridoacridine alkaloid analogues.[12]

Supporting Information Available: Detailed experimental procedures and characterization of compounds **1a**−**c**, **3a**−**c**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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