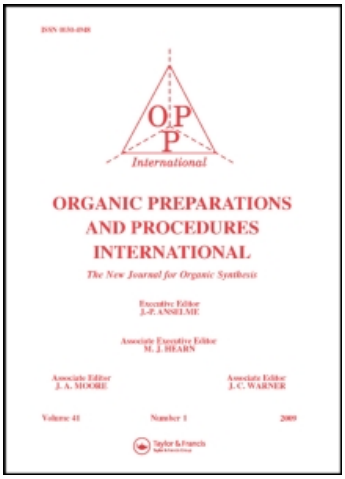

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

PREPARATION OF TRIAZAPHENAN THRENES

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To cite this Article Nutaitis, Charles F. and Brennan, Megan(2004) 'PREPARATION OF TRIAZAPHENAN THRENES', Organic Preparations and Procedures International, 36: 4, 367 — 370
To link to this Article: DOI: 10.1080/00304940409458681
URL: http://dx.doi.org/10.1080/00304940409458681

PREPARATION OF TRIAZAPHENANTHRENES

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(05/05/04)

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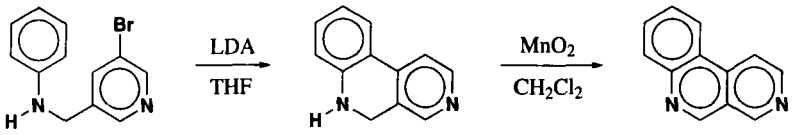
Aza and polyaza derivatives of polycyclic aromatic hydrocarbons (azaarenes or aza-PAH) have long been recognized as environmental pollutants and potential human carcinogens, yet have not been studied to the extent that carbocyclic PAH systems have been.[1] One of the prime reasons for this situation is a lack of versatile divergent synthetic protocols for the preparation of the numerous constitutional isomers possible for even a moderately complex PAH system containing one or more ring nitrogen atoms.

One method that holds great potential for the preparation of a variety of azaarenes is the intramolecular pyridyne cyclization strategy originally developed by Kessar[2] in 1976 and later modified by Nutaitis and coworkers.[3]

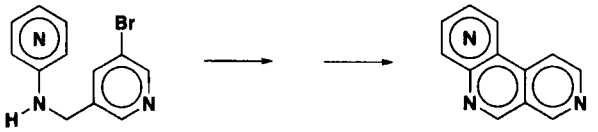


1 2 3

In the original procedure of Kessar, the pyridyne precursor **1** was prepared by the alkylation of aniline with 5-bromo-3-chloromethylpyridinium hydrochloride. This step, which required a five-fold excess of the aniline in order to minimize polyalkylation, resulted in cumbersome and capricious chromatographic purification to separate the unreacted excess aniline from the secondary amine product. In order to eliminate this drawback, we developed an alternate route in which the pyridyne cyclization precursors were obtained from 5-bromonicotinaldehyde and the requisite aniline *via* formation and subsequent reduction of the imine.[4] This alternate route utilizes the aniline and aldehyde in an equimolar ratio. Moreover, this new procedure should allow entry into a wider variety of azaarene systems. For example, it was envisioned that the combination of 5-bromonicotinaldehyde and an aminopyridine would afford triazaphenanthrene products. Utilization of anilines which possess an additional nucleophilic ring nitrogen with 5-bromo-3-chloromethylpyridinium hydrochloride is not feasible due to competing formation of alkyl pyridinium salts. Our modified procedure does not impose this limitation.

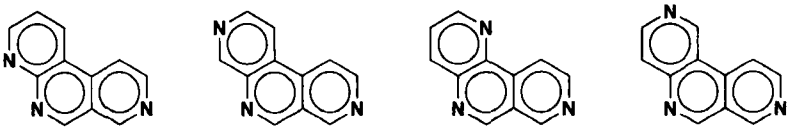
An exhaustive literature search revealed that of the sixty different triazaphenanthrene isomers theoretically possible, only nineteen of the parent, unsubstituted ring systems had been previously synthesized and twenty-one of the triazaphenanthrene ring systems are unknown. Employment of the three different aminopyridine isomers in the synthetic sequence should, in theory, afford four different triazaphenanthrenes **5**. None of the parent ring systems depicted in **5** had been previously reported, and two of the systems, 2,5,8-triazaphenanthrene (**5d**) and 3,5,8-

triazaphenanthrene (**5b**), were unknown. We now report the results of our investigations on the condensation and subsequent cyclization of 5-bromonicotinaldehyde with the three aminopyridine constitutional isomers in order to prepare the parent triazaphenanthrene ring systems **5**.



4 5

Condensation and subsequent reduction of 5-bromonicotinaldehyde with an excess of an aminopyridine affords the desired pyridyne cyclization precursors **4**. Although 5-bromonicotinaldehyde was previously reported to require only an equimolar amount of an aniline, it was found that, with the aminopyridines, an excess quantity doubles the overall yield. Unfortunately, all attempts to completely purify the products by flash chromatography failed due to co-elution of **4** with the unreacted aminopyridine used as starting materials. Nevertheless, when the partially purified materials were subjected to the cyclization step by treatment with excess LDA followed by oxidation with manganese dioxide, the triazaphenanthrenes **5** were obtained. Once again flash chromatography proved quite troublesome due to the presence of unreacted amine **4** and/or the starting aminopyridine left over from the first step of the synthesis. However, advantage was taken of the different oxidation states of the nitrogen atoms at this stage of the synthesis. Treatment of the mixture with excess propionyl chloride followed by hydrolysis with aqueous sodium hydroxide converted any unreacted primary and secondary amine contaminants to amides while leaving the triazaphenanthrene products unchanged; these compounds now displayed a sufficient difference in mobility on silica gel to allow efficient separation. When 2-aminopyridine served as starting material 3,6,7-triazaphenanthrene (**5a**) was obtained in 13% overall yield, while incorporation of 3-aminopyridine into the synthesis resulted in formation of 3,5,8-triazaphenanthrene (**5b**) in 11% overall yield. While both final products were homogeneous by thin layer chromatrography and clean by proton NMR, they darkened considerably upon standing and upon recrystallization. As a result, all attempts to secure adequate elemental analyses failed. Although 3-aminopyridine could, in theory, also provide 1,5,8-triazaphenanthrene (**5c**), no evidence of **5c** was observed by proton NMR, suggesting that the pyridyne cyclization occurs regioselectively. The fourth possible isomer in this series, 2,5,8-triazaphenanthrene (**5d**), could not be synthesized by this methodology due to the high insolubility of 4-aminopyridine in either benzene or toluene. As a result, attempts to synthesize the imine were unsuccessful.



5a 5b 5c 5d

In summary, two different ring systems in the azaarene class have been synthesized. Of these, 3,5,8-triazaphenanthrene (**5b**) represents a completely new ring system, while for 3,6,7-triazaphenanthrene (**5a**) only a single compound, in the form of a pyridone, had been reported previously.[5] Additionally, the pyridyne cyclization strategy described herein has been extended to incorporation of heterocyclic amines as condensation substrates. Studies are currently underway in our laboratories to explore the scope and limitations of this protocol for the preparation of a wide variety of azaarenes.

Acknowledgements.- We thank Lafayette College for supporting this work and the mass spectrometry facility at Michigan State University for providing the high resolution mass spectral data.

EXPERIMENTAL SECTION

All reactions were performed in oven-dried glassware (120°C), and all lithiation reactions were performed under nitrogen. Lithium diisopropylamide (LDA) was prepared by standard procedures from diisopropylamine and *n*-butyllithium. Tetrahydrofuran was distilled from sodium/benzophenone. Thin layer chromatography was performed on precoated (0.25 mm) silica gel 60 F_{254} plastic sheets and was visualized with 254 nm ultraviolet light. Flash chromatography was performed with silica gel 60 (200-400 mesh).[6] Proton and carbon NMR spectra were recorded on a Jeol Eclipse400 FT-NMR spectrometer; chemical shifts are reported in parts per million relative to internal-TMS (proton) or the solvent chloroform-d (carbon). Melting points were determined in open capillary tubes with a Mel-Temp Laboratory Devices apparatus and are uncorrected.

Preparation of 3,5,8-Triazaphenanthrene (5b).- A magnetically stirred solution of 5-bromonicotinaldehyde (0.594 g, 3.19 mmol), 3-aminopyridine (1.37 g, 14.5 mmol), and *p*-toluenesulfonic acid monohydrate (0.01 g, 0.053 mmol) in benzene (50 mL) was refluxed for 24 hrs with water removal *via* a Dean-Stark Trap. The benzene was removed *in vacuo*, the oily residue was dissolved in methanol (50 mL), and sodium borohydride pellets (2.4 g, 63 mmol) were added over 1 hr. The resulting mixture was stirred magnetically at room temperature for 24 hrs. The methanol was removed *in vacuo* and the yellow solid was partitioned between ethyl acetate (50 mL) and water (50 mL). The aqueous layer was further extracted with ethyl acetate (1 x 50 mL) and the combined organic layers were dried with anhydrous sodium sulfate, filtered and concentrated and dried *in vacuo* to afford an orange oil. A solution of the oil in dry THF (10 mL) was added over a period of 2 min, by means of a syringe, to a magnetically stirred solution of LDA (15.8 mmol) in dry THF (25 mL) at -78°C under nitrogen. The resulting mixture was allowed to warm to room temperature and stirred for 24 hrs. The dark brown reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (3 x 50 mL). The combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The resulting dark oil was dissolved in methylene chloride (25 mL), manganese dioxide (1.40 g, 16.1 mmol) was added and the mixture was stirred magnetically for 48 hrs. The manganese dioxide was removed

by filtering the reaction mixture through Celite and the Celite was washed with acetone (50 mL), and the filtrate was concentrated *in vacuo*. To a magnetically stirred solution of the resulting orange-brown solid in methylene chloride (25 mL) was added propionyl chloride (2.0 mL, 23 mmol) over a period of 1 min. The mixture was stirred for 24 hrs then 10% aqueous sodium hydroxide (25 mL) was added. The layers were separated, the aqueous phase was extracted further with methylene chloride (1 x 25 mL), and the combined extracts were dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo* with adsorption onto silica gel. Flash chromatography (acetone) gave 3,5,8-triazaphenanthrene (**5b**) as a yellow solid, mp. 203-206°C, which darkened on standing (0.065 g, 11%). ^{1}H NMR($CDCl_3$): δ 9.62 (s, 1H), 9.53 (s, 1H), 9.50 (s, 1H), 9.08 (d, 1H), 8.90 (d, 1H), 8.40 (d, 1H), 8.34 (d, 1H); ^{13}C NMR($CDCl_3$): δ 153.9, 153.7, 152.5, 150.0, 146.5, 140.5, 135.8, 127.2, 122.4, 115.76, 115.75; HRMS (FAB^+)

Anal. Calcd for $C_{11}H_8N_3$: 182.0718. Found: 182.0717

3,6,7-Triazaphenanthrene (5a) was prepared analogously from 5-bromonicotinaldehyde and 2-aminopyridine (13%) as an orange solid, mp. 217-219°C, which darkened on standing. ^{1}H NMR($CDCl_3$): δ 9.62 (s, 1H), 9.47 (s, 1H), 9.18 (dd, 1H), 8.98 (d, 1H), 8.89 (dd, 1H), 8.35 (d, 1H), 7.68 (dd, 1H); ^{13}C NMR($CDCl_3$): δ 156.0, 155.1, 153.7, 152.5, 149.6, 137.8, 132.3, 123.0, 121.3, 117.2, 115.4; HRMS (FAB^+)

Anal. Calcd for $C_{11}H_8N_3$: 182.0718. Found: 182.0719

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