A CONVENIENT SYNTHESIS OF AZAANTHRAQUINONES *VIA* POLAR ADDITION TO HETARYNE INTERMEDIATES. USE OF CARBANIONS DERIVED FROM 3-CYANO-1(3H)-ISOBENZOFURANONES

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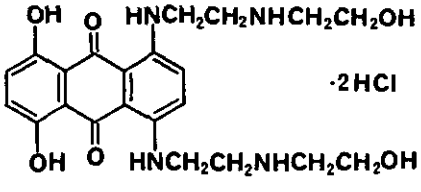
Abstract - A convenient synthesis of 2-azaanthraquinones using the reaction of carbanions derived from 3-cyano-1(3H)-isobenzofuranones which serve as 1,4-dipole equivalents and hetaryne intermediates generated from bromopyridines and lithium diisopropylamide is reported.

INTRODUCTION

Mitoxantrone (1) and related anthraquinones are of considerable interest in cancer chemotherapy. Mitoxantrone has been shown to be an intercalant[1a] to DNA, and, on the basis of a theoretical model[1b-d] for intercalation, it was predicted that azaanthraquinone analogues of **1** would be very effective intercalants. Thus their study as potential antitumor agents is of considerable interest. Several synthetic strategies[2] for the synthesis of azaanthraquinones have been applied. Most of these involve a Friedel-Crafts approach[2a], the most important being the cycloaddition of an azanaphthoquinone with an appropriate diene.[2b-h] Amidine derivatives of anthraquinone of the general formula **2** exhibit antiprotozoal activities and were found to be active against Entamoeba histolytica infections in experimental animals.[3,4] In connection with studies on novel amoebicides, several new heterocyclic quinones of the type **3** similar to anthraquinones **2** were synthesized.[5] For



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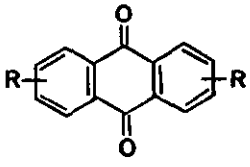

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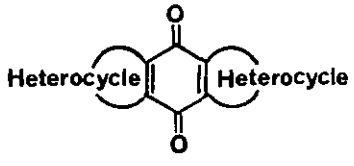
R = $CH_2N\langle^{R_1}_{R_2}$



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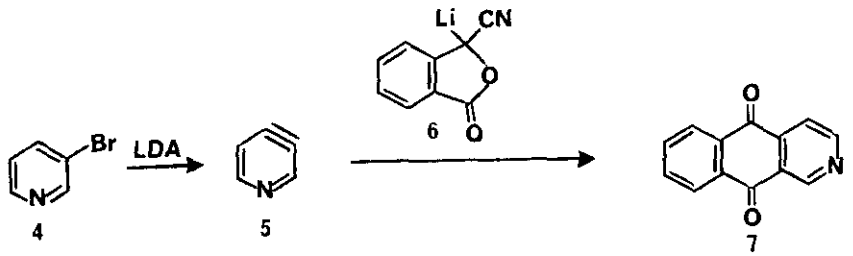
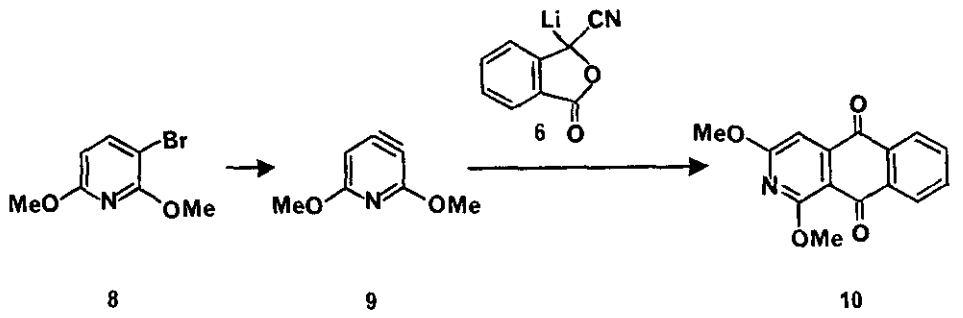
example, pyrazolo[3,4-g]quinoxalinequinone, isoxazolo[4,5-g]quinoxalinequinone and pyrrolo[3,4-g]quinoxalinequinone were synthesized using dipolar cycloaddition reactions of quinoxalinequinones. Recently, we[6,7] demonstrated that arynes, generated from haloarenes and lithium diisopropylamide in tetrahydrofuran, react regioselectively with lithiated 3-cyano-1-(3H)-isobenzofuranones (hereafter referred to as 3-cyanophthalides) affording the corresponding anthraquinones in good to moderate yields. Several anthraquinones, including methyl ethers of naturally occurring ones such as pachybasin, chrysophanol, zieganien, helminthosporin, islandicin, didigitopurpone, catenarin etc. and certain precursors used in the synthesis of 4-demethoxydaunomycinone and daunomycinone were synthesized[7] in a rapid and efficient way. We have extended the aryne annulation method to the synthesis of azaanthraquinones *via* the addition of carbanions derived from 3-cyanophthalides to certain hetarynes, the results of which are reported herein.

RESULTS AND DISCUSSION

Reaction of 3-cyanophthalide with 3,4-didehydropyridine and 2,6-dimethoxy-3,4-didehydropyridine. The reaction of 3-lithio-3-cyanophthalide (**6**) with 3,4-didehydropyridine (**5**) and 2,6-dimethoxy-3,4-didehydropyridine (**9**) were first studied since these reactions would give a single product regardless of the orientation of **6** to the respective hetaryne. Thus, the reaction of **6** with 3,4-didehydropyridine itself (**5**) gave 2-azaanthraquinone[8] (**7**) in 65% yield.

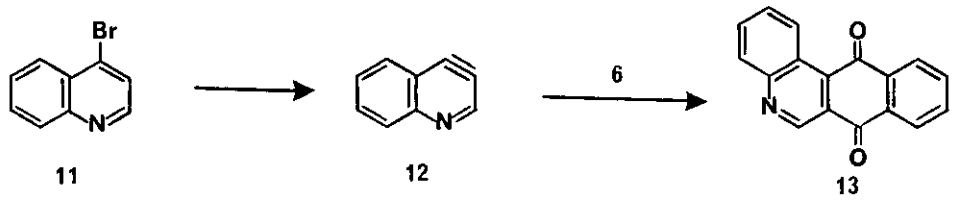


Similarly, the reaction of 3-bromo-2,6-dimethoxypyridine (**8**) with 3-cyanophthalide (**6**) and LDA gave 1,3-dimethoxy-2-azaanthraquinone (**10**) in 55% yield *via* hetaryne **9**.



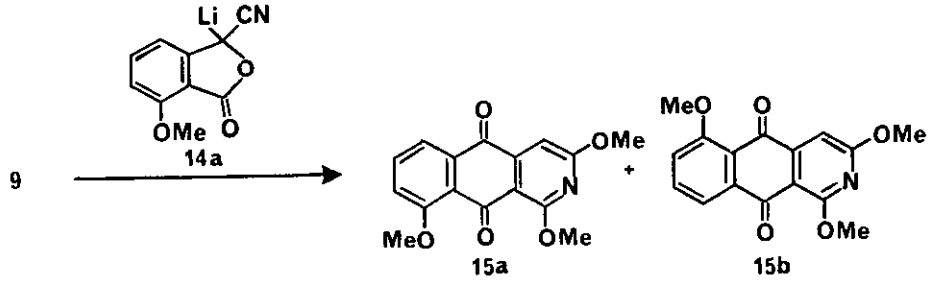
Reaction of Bicyclic didehydropyridine with 3-cyanophthalide.

Reaction of 4-bromoquinoline with 3-cyanophthalide (**6**) and LDA was then studied. In case of bicyclic systems nucleophiles have greater tendency to undergo nucleophilic addition reaction.[9] Benz[d]-2-azaanthraquinone (**13**) was prepared in good yield (60%) by reacting 4-bromoquinoline (**11**) with **6** and LDA.



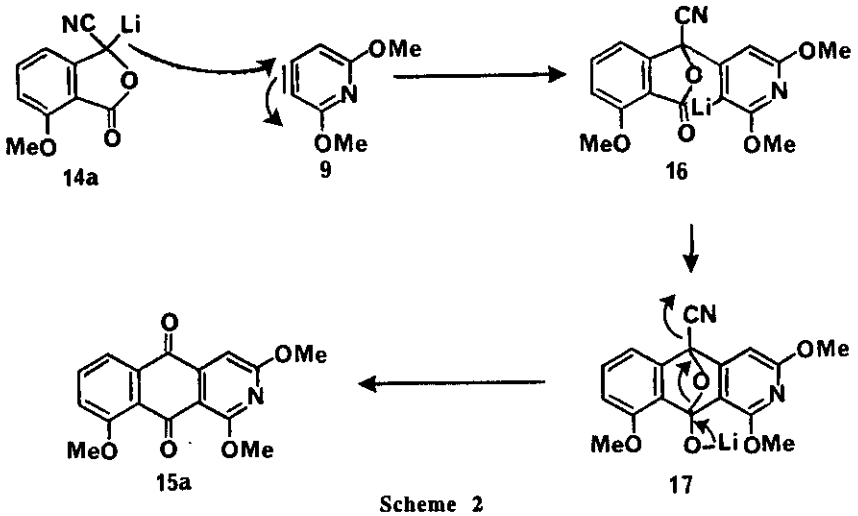
Reaction of substituted 3-cyanophthalides with 3,4-didehydropyridine and substituted 3,4-didehydropyridines.

The presence of a substituent either on 3-cyanophthalide or 3,4-didehydropyridine can affect the orientation of addition to the hetaryne. An example of this is shown in the reaction of 2,6-dimethoxy-3,4-didehydropyridine (**9**) with 7-methoxy 3-lithio-3-cyanophthalide (**14a**) which gave a 9:1 mixture of 2-azaanthraquinones **15a** and **15b** from the two possible orientations of the addition of lithiocyanophthalide **14a** to **9** in overall yields of 35% as shown in Scheme 1 with the major product



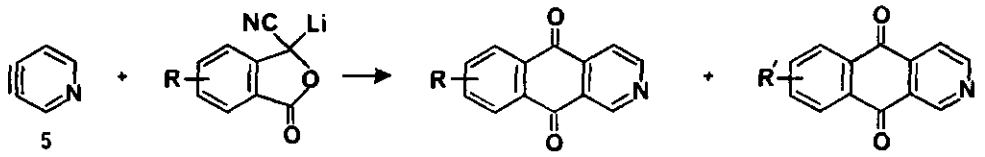
Scheme 1

being formed by the addition of **14a** to the 4-position of **9**. The major product was obtained in the pure state by flash column chromatography. Scheme **2** illustrates the mechanism and regioselectivity of this hetaryne-annulation reaction using the preparation of **15a** as a typical example. Accordingly, **14a** adds to **9** affording preferentially adduct **16**. Nucleophilic attack by the lithio-site on to the carbonyl group yields intermediate **17** which then is converted to product



Scheme 2

15a by the concomitant loss of cyanide ion. The reaction of 3,4-didehydropyridine (**5**) with substituted 3-cyanophthalides was then carried out and the results are shown in Scheme 3. These reactions gave *ca* 2:1 mixtures of 2-azaanthraquinones.



14a R = 7-Meo **18a** R = 9-MeO **19a** R' = 6-MeO

14b R = 4,6-di-MeO **18b** R = 6,8-di-MeO **19b** R' = 7,9-di-MeO

Scheme 3

The isomer yields were determined from the pure products isolated by flash column chromatography. The major products are formed from that being addition at the 4-position of **5** which is in agreement with theoretical calculations[10] that nucleophiles add preferentially to the 4-position of 3,4-didehydropyridine (**5**).

In conclusion, we have shown that hetaryne-annulation reaction is a convenient way to prepare 2-azaanthraquinones. Presently, we are investigating the use of this reaction for the preparation of diazaanthraquinones.

EXPERIMENTAL

General Aspects: Proton nuclear magnetic resonance spectra (^{1}H nmr) were measured in $CDCl_3$ solution on a WP 200-SY Bruker spectrometer. All chemical shifts are reported in parts per million downfield from internal tetramethylsilane. Infrared spectra (ir) were recorded on a Perkin-Elmer 283 grating spectrometer. Mass spectra (70eV) were obtained on a Hewlett-Packard Model 5988A chromatograph/mass spectrometer. Microanalyses were performed on a Carlo ERBA

strumentazione instrument. E. Merck silica gel 9385 (230-400 mesh) was used for flash chromatography. Reported boiling points are uncorrected; melting points were determined on an electrothermal apparatus and are uncorrected. All reactions were carried out in flame-dried flasks under nitrogen atmosphere.

Starting Materials. 3-Cyanophthalides were available from a previous study.[6] 3-Bromopyridine,3-bromoquinoline, n-butyllithium, and diisopropylamine were purchased from Aldrich Chemical Co. 3-Bromo-2,6-dimethoxypyridine was prepared by brominating 2,6-dimethoxypyridine. All liquids were dried and distilled prior to use.

General Procedure for the Reaction of Bromoheteroarenes with Cyanophthalides: LDA was prepared in a flamed-dried flask flushed with nitrogen by adding diisopropylamine (18 mmol) into a -78° C solution of n-BuLi (15 mmol, 2.5M in hexame) in THF (25 ml) under nitrogen atmosphere (using septum cap technique). After stirring the solution for 10 min at -78° C, the appropriate cyanophthalide (5 mmol) in THF (25 ml) was added dropwise over 20 min at -40° C. A solution of heteroarene (5 mmol) in THF (25 ml) was added dropwise over 20 min. at 140°C. The reaction mixture was stirred for 10 more additional minutes, then the dark reddish brown solution was quenched with saturated aqueous ammonium chloride solution and allowed to warm to room temperature. The solvent was then removed (rotatory evaporator), and the residue extracted with methylene chloride (3x50 ml). The combined methylene chloride extracts were washed with brine, dried (Na_2SO_4), and concentrated (rotatory evaporator) to yield crude reaction mixture. Purification of the products was accomplished by flash column chromatography using a mixture of hexane/EtOAc [9:1 or 19:1, depending on the polarity of the azaanthraquinone] as eluant. In those reactions in which isomeric product mixtures were obtained, the isomers were isolated by flash column chromatography. The products were identified on the basis of elemental analysis, ^1H nmr, C-13 nmr spectroscopy, and mass spectrometry.

2-Azaanthra-5,10-quinone (7): Yellow needles (from EtOAc/hexane); mp 181-183° (lit[12] 178-180°C); ^1H nmr ($CDCl_3$) δ 7.89 (m, 2H, C_7 and C_8-H), 8.11 (d, J = 5 Hz, 1H, C_4-H), 8.34 (m, 2H, C_6 and C_4-H), 9.14 (d, J = 5 Hz, 1H, C_3-H), 9.6 (s, 1H, C_1-H); ir ν_{max} ($CHCl_3$) cm^{-1} 1670 (anthraquinone); ^{13}C nmr ($CDCl_3$) δ 119.03, 126.28, 127.40, 133.07, 134.62, 135.04, 138.53, 149.68, 155.30, 182.04, 182.49. Anal. calcd for $C_{13}H_7O_2N$: C, 74.64; H, 3.37; N, 6.69. Found: C, 74.61; H, 3.25; N, 6.74.

Preparation of 3-bromo-2,6-dimethoxypyridine (8): A mixture of 2,6-dimethoxypyridine (7 mmol) and pyridinium hydrobromide perbromide (7.5 mmol) in dry CCl_4 (150 ml) was stirred at room temperature for overnight and then refluxed for 2h. The solution was cooled and water was added to the reaction mixture. The organic layer was separated, washed with brine, and then dried over Na_2SO_4. After removal of the solvent, the residue was purified by vacuum distillation. Pure product **8** was obtained in 30% yield; bp 80°/0.9 mm; ^1H nmr ($CDCl_3$) δ 3.92 (s, 3H, OMe), 4.01 (s, 3H, OMe), 6.25 (d, J = 8.3 Hz, 1H, C_5-H), 7.65 (d, J = 8.3 Hz, 1H, C_4-H). In addition to the monobromo compound **8**,

15% of 2,6-dimethoxypyridine was recovered (bp 82-85°C/0.9 mm) and 3,5-dibromo-2,6-dimethoxypyridine was obtained from the residue in 15% yield; white solid; mp 84-85°C; ^{1}H nmr δ 4.0 (s, 6H, C_2 and C_6-OMe), 7.86 (s, 1H, C_4-H).

1,3-Dimethoxy-2-azaanthra-5,10-quinone (10): Yellow needles (from EtOAc); mp 206-208°C; ^{1}H nmr ($CDCl_3$) δ 4.03 (s, 3H, C_3-OMe), 4.16 (s, 3H, C_1-OMe), 7.17 (s, 1H, C_4-H), 7.74-7.84 (m, 2H, C_7 and C_8-H), 8.23 (dd, J = 7.5 and 1.3 Hz, 1H, C_9-H), 8.33 (dd, J = 7.5 Hz and 1.3 Hz, 1H, C_6-H); ir ν_{max}($CHCl_3$) cm^{-1} 1670 (anthraquinone); ms, m/z 269 ($M^{+\cdot}$). Anal. calcd for $C_{15}H_{11}O_4N$: C, 66.85; H, 4.11; N, 5.2. Found: C, 66.83; H, 4.17; N, 5.21.

Benz[d]2-azaanthra-7,12-quinone (13): Yellow needles (from benzene); mp 200-202°C; ^{1}H nmr (($CDCl_3$) δ 7.21 (dd, J = 8.3 and 1.5 Hz, 1H, C_3-H), 7.8-7.91 (m, 4H, C_3, C_4, C_9 and C_{10}-H), 8.2-8.32 (m, 2H, C_8 and C_{11}-H), 9.58 (dd, J = 8.3 and 1.5 Hz, 1H, C_6-H), 9.82 (s, 1H, C_1-H); ir ν_{max}($CHCl_3$) cm^{-1} 1670 (anthraquinone); ms, m/z 259 ($M^{+\cdot}$). Anal. calcd for $C_{17}H_9O_2N$: C, 78.75; H, 3.49; N, 5.40. Found: C, 78.83; H, 3,42; N, 5.47.

1,3,9-Trimethoxy-2-azaanthra-5,10-quinone (15a): *The reaction of 2,6-dimethoxy-3-bromopyridine (8) with* 7-methoxy-3-cyanophthalide (**14a**) under the hetaryne forming conditions (as described in the general procedure) furnished a mixture of 1,3,9-trimethoxy-2-azaanthra-5,10-iquinone (**15a**) and 1,3,6-trimethoxy-2-azaanthra-5,10-quinone (**15b**) in overall yield of 35% after purification by flash column chromatography (approximate ratio of **15a**:**15b** 9:1). Pure product **15a** was obtained by preparative thin layer chromatography as yellow solid; mp 171-175°C; ^{1}H nmr ($CDCl_3$) δ 4.01 (s, 3H, OMe), 4.05 (s, 3H, OMe), 4.15 (s, 3H, OMe), 7.04 (s, 1H, C_4-H), 7.35 (m, 1H, C_8-H), 7.64 (t, 1H, C_7-H), 7.85 (dd, J = 8.1 and 1.3 Hz, 1H, C_6-H); ir ν_{max}($CHCl_3$) cm^{-1} 1670 (anthraquinone), 1590 (Ar-CH); ms, m/z 299 ($M^{+\cdot}$). Anal. calcd for $C_{16}H_{13}O_5N$: C, 64.21; H, 4.37; N, 4.68. Found: C, 64.11; H, 4.32; N, 4.61.

9-Methoxy-2-azaanthra-5,10-quinone (18a) and 6-methoxy-2-azaanthra-5,10-quinone (19a). The reaction of 3-bromopyridine (**4**) with 7-methoxy-3-cyanophthalide (**14a**) under the hetaryne forming conditions (as described in the general procedure) furnished a mixture of 9-methoxy-2-azaanthra-5,10-quinone (**18a**) and 6-methoxy-2-azaanthra-5,10-quinone (**19a**). This mixture was separated by flash column chromatography over silica gel using hexane/EtOAc (19:1) as eluant. The less polar compound was obtained in 15% yield and was identified as 6-methoxy-2-azaanthra-5,10-quinone (**19a**): light green needles (from EtOAc); mp 187-189°C; ^{1}H nmr ($CDCl_3$) δ 4.07 (s, 3H, C_6-OMe), 7.39 (d, J = 8.4 Hz, 1H, C_7-H), 7.79 (t, J = 8.3 Hz, 1H, C_8-H), 7.97 (dd, J = 7.8 Hz and 1.1 Hz, 1H, C_9-H), 8.061 (d, J = 5.1 Hz, 1H, C_4-H), 9.07 (d, J = 5.1 Hz, 1H, C_3-H), 9.48 (s, 1H, C_1-H); ir ν_{max}($CHCl_3$) cm^{-1} 1670 (anthraquinone), 1690 (Ar-CH); ms, m/z 239 ($M^{+\cdot}$); ^{13}C nmr ($CDCl_3$) δ 56.64, 118.33, 119.27, 119.81, 121.14, 125.62, 135.18, 135.98, 139.96, 149.11, 155.31, 160.64, 181.23, 182.69. The more polar compound obtained in 31% yield was identified[13] as 9-methoxy-2-azaanthra-5,10-quinone (**18a**): yellow needles (from EtOAc); mp 171-175°C; ^{1}H nmr ($CDCl_3$) δ 3.96 (s, 3H, C_9-OMe), 7.42 (d, J = 8.4 Hz, 1H, C_8-H), 7.73 (t, J = 7.8 Hz, 1H, C_7-H), 7.94 (dd, J = 7.6 and 1Hz, 1H, C_6-H), 7.99 (d, J = 5.1 Hz,

1H, C_4-H), 9.05 (d, J = 5.1 Hz, C_3-H), 9.53 (d, J = 0.6 Hz, 1H, C_1-H); ir $\nu_{max}(CHCl_3)$ cm^{-1} 1670 (anthraquinone), 1690 (Ar-CH); ms, m/z 239 ($M^{+\cdot}$); ^{13}C nmr ($CDCl_3$) δ 56.64, 118.17, 118.89, 119.88, 120.95, 127.56, 135.10, 135.50, 137.38, 149.95, 154.35, 160.57, 181.53, 182.99. Anal. calcd for $C_{14}H_9O_3N$: C, 70.29; H, 3.79; N, 5.85. Found: C, 70.21; H, 3.74; N, 5.80.

6,8-Dimethoxy-2-azaanthra-5,10-quinone (18b) and 7,9-dimethoxy-2-azaanthra-5,10-quinone (19b): The reaction of 3-bromopyridine (**4**) and 4,6-dimethoxycyanophthalide (**14b**) under the conditions as described in the general procedure furnished a mixture of 6,8-dimethoxy-2-azaanthra-5,10-quinone (**18b**) and 7,9-dimethoxy-2-azaanthra-5,10-quinone (**19b**) in approximate ratio[14] of 3:2 in overall yield of 45%. Separation of isomers **18b** and **19b** by either flash column chromatography or preparative thin layer chromatography was found to be difficult.

ACKNOWLEDGEMENT

We thank the Robert Welch Foundation for their generous financial support and Mrs. Anita S. Khanapure for performing microanalyses.

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13. The structures **15a** and **16a** were assigned on the basis of the ratio of the isolated pure products (2:1). The major product being formed by the addition of 4-position of 3,4-didehydropyridine which is in agreement with theoretical calculations.[9]

14. Ratio determined by ^{1}H nmr spectrum.

Received, 11th July, 1988