Pergamon

Tetrahedron Letters, Vol. 38, No. 26, pp. 4717-4720, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01006-X

A Very Efficient Synthesis of 1,8-Diazaanthraquinones.

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Abstract. The reaction between 1-dimethylamino-1-azadienes and 2,6-dibromobenzoquinone gave excellent yields of the corresponding double hetero Diels-Alder cycloadducts. 3-Substituted azadienes directly gave aromatic 1,8-diazaanthraquinone derivatives, while 4-substituted azadienes led to 1,8-dimethylamino-1,4,5,8-tetrahydro-1,8-diazaanthraquinones, which were aromatized under thermal conditions. © 1997 Elsevier Science Ltd.

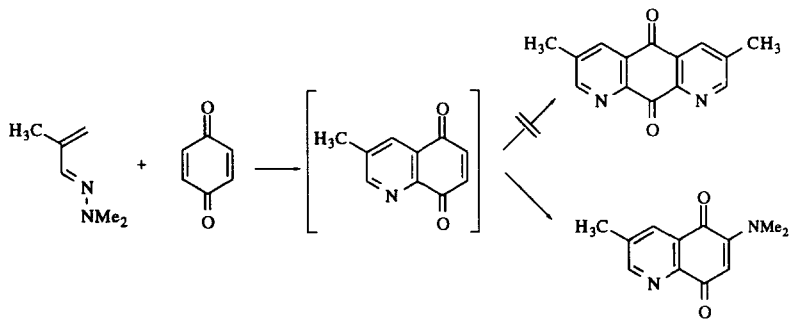
Anthraquinones are a very important class of antitumour compounds. Natural products that bear a 9,10-diazaanthracenedione moiety and show interesting antitumour properties include the anthracyclines,[1] the pluramycins[2] and some of the enediyne antibiotics, like dynemicin A and deoxydynemicin A.[3] Some of these compounds have been employed as leads for systematic structural manipulation, leading, among other analogues, to mitoxantrone[4] and related molecules.

The antitumour activity of these quinones is probably due to multiple mechanisms, normally initiated by DNA intercalation. Formation of DNA damaging anion-radical intermediates by reduction of the quinone unit is probably involved in their cytotoxicity, at least in the case of the anthracyclines.[5] In this respect, replacement of one or more carbons of the benzene rings by nitrogen atoms should afford compounds with geometries similar to those of the parent compounds and hence capable of intercalation, but with sites suitable for hydrogen bonding or ionic interactions and therefore with and increased affinity for DNA. Additionally, the electron-withdrawing properties of the heterocyclic rings would facilitate the formation of anion-radicals. For these reasons, the preparation of azaanthraquinones as potential antitumour agents is an active field of research.[6]

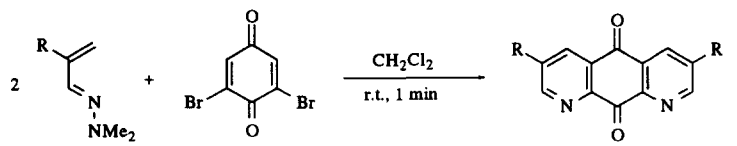
Although the considerations outlined above would apply particularly well to diazaanthraquinones, these compounds have receive little attention, which can be partially attributed to limitations in the existing synthetic methodology. In the case of 1,8-diazaanthraquinones, two main strategies are currently available. One of them[7] gives the unsubstituted 1,8-diazaanthraquinone system in 28 % yield from *N,N*-diethylpyridine-2-carboxamide and 2-bromopyridine-2-carbaldehyde through tandem *ortho*-directed metallation/metal-halogen exchange, followed by cyclization and air oxidation. A second approach[8] consists of treatment of quinolinequinones with 1-dimethylamino-1-azadienes, and affords mixtures of the desired 1,8-diazaanthraquinones, as major products, and their 1,5-diaza- regioisomers. Neither of these methods is well suited for the preparation of a series of derivatives of the 1,8-diazaanthraquinone system for biological evaluation because of difficulties in the synthesis

of the required starting materials.

Due to the symmetry of the target ring system, we envisaged that a double hetero Diels-Alder approach from 1-dimethylamino-1-azadienes[9,10] and a benzoquinone derivative would provide a more efficient approach. However, the only literature antecedent of such a reaction was discouraging, since treatment of benzoquinone with methacrolein dimethylhydrazone gave no trace of double cycloaddition and the only product isolated was 6-dimethylamino-3-methylquinolinequinone.[8a] This shows that a single hetero Diels-Alder reaction occurs, followed by aromatization with concomitant release of dimethylamine, which then adds to the reaction product before the desired second cycloaddition takes place:



We reasoned that activation of the quinone by bromo substitution would accelerate the Diels-Alder reaction and it would also lead to liberation of hydrobromic acid from the cycloadduct, perhaps trapping dimethylamine and preventing its addition to quinones present in the reaction medium. In agreement with these expectations, treatment of azadienes **1a-c**[11] with the readily available[12] 2,6-dibromobenzoquinone **2** afforded the aromatic 1,8-diazaanthraquinones in a single operation and in good to excellent yields (Scheme 1). Polymerization of the starting 1-azadienes due the presence of traces of hydrobromic acid, as described by other workers,[10d] was not observed in our case, probably owing to their very rapid reaction with compound **2**.



Compound	R
1a	H
1b	CH_3
1c	C_2H_5

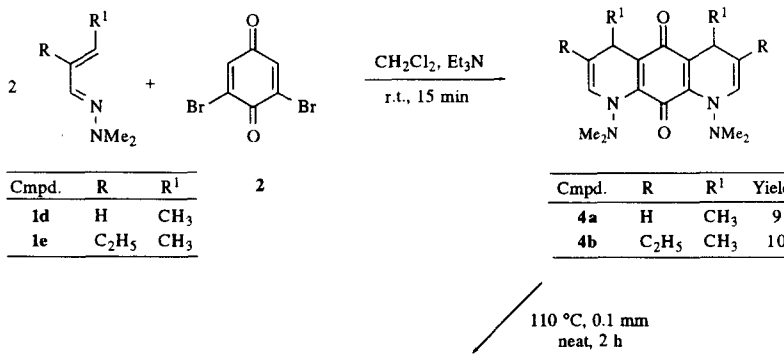
2

Compound	R	Yield, %
3a	H	85
3b	CH_3	94
3c	C_2H_5	66

Scheme 1

In our first experiments using 4-substituted azadienes (**1d,e**) we only isolated low yields of the 1,4,5,8-tetrahydro derivatives **4** (Scheme 2). Absence of spontaneous aromatization of compounds **4** to **3**, as observed for azadienes **1a,b**, was attributed to steric effects in 4,5-disubstituted aromatic 1,8-diazaanthraquinones.[13] Attempted aromatization of **4** by acid-catalized elimination of dimethylamine under several literature conditions[11,14] was unsuccessful and led to a complex mixture of decomposition products. This suggested that

these compounds are acid-labile and prompted us to carry out the Diels-Alder reaction in the presence of triethylamine as a scavenger of traces of hydrobromic acid. Under these modified conditions, compounds **4a,b** were obtained in nearly quantitative yields. Their aromatization to **3d,e** was finally accomplished under thermal conditions in excellent yields (Scheme 2).



Cmpd.	R	R^1
1d	H	CH_3
1e	C_2H_5	CH_3

2

Cmpd.	R	R^1	Yield, %
4a	H	CH_3	96
4b	C_2H_5	CH_3	100

Cmpd.	R	R^1	Yield, %
3d	H	CH_3	85
3e	C_2H_5	CH_3	80

Scheme 2

In conclusion, we have developed a very efficient synthesis of 1,8-diazaanthraquinones by double hetero Diels-Alder reaction between 2,6-dibromobenzoquinone and 1-dimethylamino-1-azadienes. Compounds **3** thus obtained have shown very promising antitumour properties in preliminary assays.

ACKNOWLEDGEMENTS

Financial support from CICYT (projects FAR 553-90 and PTR 0028-93) is gratefully acknowledged.

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(*Received in UK* 17 *April* 1997; *accepted* 23 *May* 1997)