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Design and synthesis of angucyclinone AB-pyrido[2,3-*d*] pyrimidine analogues

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Abstract

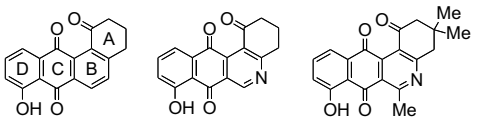
The preparation of two pyrimido[4,5-*c*]isoquinoline-7,10-quinones from acylhydroquinones and 1,3-dimethyl-5-aminouracil and their cycloadditions with 1-trimethylsilyloxybutadiene and 1-dimethylamino-3-methyl-1-azabutadiene is described. The remarkable regiocontrol of these cycloadditions that yield stable 1:1 cycloadducts is discussed on the basis of steric interactions into the pyrimido[4,5-*c*]-isoquinoline-7,10-quinones. The access to angucyclinone AB-pyridopyrimidine analogues from Diels–Alder adducts and preliminar evidences on their antitumour activities are also reported.

Keywords: Quinones; Michael addition; Diels–Alder reaction; Regioselectivity

The substitution of a nitrogen atom for an aromatic CH group in anticancer drugs (e.g., ametantrone and 11-deoxydoxorubicin),[1,2] which provides active antitumour N-analogues, has shown to be an effective strategy to design new potential antitumour compounds. These N-heterocyclic aromatic congeners could potentially retain the planar shape of the drug chromophore necessary for molecular recognition of the host. Furthermore, the basic and electron-withdrawing properties of the N-heterocycles seem to improve the affinity for the biological target and/or the generation of reactive oxygen species (ROS) through redox cycling.[3,4] The synthesis of aza-congeners of the benz[*a*]anthraquinone chromophore **1** of angucycline and angucyclinones[5,6] has received relatively little attention[7] despite the antitumour activity of several members of this family of antibiotics.

Recently, we have reported the regioselective synthesis of angucyclinone 5-aza-analogues (i.e., **2** and **3**) from acylhydroquinones and enaminones through an efficient Michael addition–heterocyclization, Diels–Alder and oxidative aromatization reaction sequence.[8] Preliminary screening of angucyclinone 5-aza-analogues showed their potent antitumour activities compared to a structurally related benz[*a*]anthraquinone.[8]

These results support the design of new antitumoural chemotypes resulting by the bioisosteric replacement of the carbocyclic B-ring in the anthraquinone chromophore **1** for a pyridine ring.



1 **2** **3**

Encouraged in this result we embarked on a programme to synthesize new angucyclinone aza-analogues designed by the replacement of the AB carbocyclic rings of chromophore **1** by the biologically relevant pyrido[2,3-*d*]pyrimidine moiety.[9–11]

We now report our findings which show that pyridopyrimidine-containing quinones can be efficiently obtained via a sequence of ionic [3+3] process, cycloaddition and oxidative aromatization reactions.

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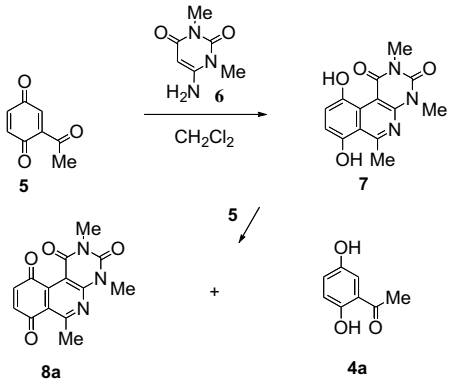
Based on a recent result on the reaction of activated benzoquinones with cyclic enaminones that provides access to dihydroxyphenanthridines,[8] we planned to apply this reaction for the synthesis of dihydroxy-pyrimidoisoquinolines from activated 1,4-benzoquinones and 5-amino-1, 3-dimethyluracil. Quinone **5**, prepared from 2,5-dihydroxyacetophenone **4a**, was reacted with 1 equiv of aminouracil **6** to afford a mixture of dihydroxypyrimidoisoquinoline **7**, pyrimidoisoquinoline-quinone **8a** and acylhydroquinone **4a** (Scheme 1).

This result shows that aminouracil **6** undergoes a Michael addition across the activated 2,3-double bond of acylquinone **5** to give the corresponding addition product which by a subsequent heterocyclization afforded heterocycle **7**. Further redox reaction between **7** and **5** provides quinone **8a** and hydroquinone **4a**.

Several trials directed to the preparation of compound **7** were carried out. However, the fast redox reaction of **5** with the nascent [3+3] product **7** cannot be avoided. Then we decided to apply our recently reported one-step procedure for the synthesis of phenanthridinquinones from acylhydroquinones **4**, enaminones and silver(I) oxide.[8] The treatment of hydroquinones **4a**,**b**, uracil **6** and silver (I) oxide in dichloromethane afforded the expected pyrimidoisoquinolinequinones **8a**,**b**[12] in 86% and 61% isolated yields (Scheme 2).

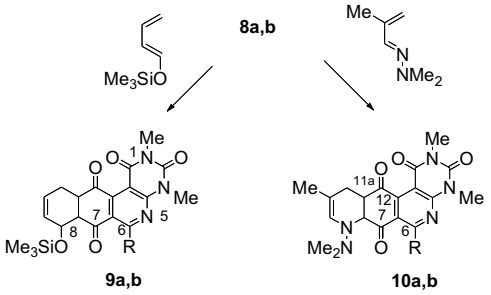
After synthesizing pyrimidoisoquinoline-7,10-quinones **8a**,**b** we explored their dienophilic reactivity on cycloaddition reactions with the 1-(*E*)-trimethylsilyloxybuta-1, 3-diene. The reaction of quinones **8a**,**b** with the diene proceeded smoothly in dichloromethane at room temperature to yield the corresponding adducts **9a**,**b** in high yields (Scheme 3). It is interesting to point out that no regioisomer was detected (TLC, ^{1}H NMR) in the reaction mixtures.

The structures of adducts **9a**,**b** were assigned on the basis of the HMBC spectrum of **9b** that shows $^3J_{C,H}$ couplings between the C-7 carbon (δ 196.9 ppm) with the protons at C-6 (δ 9.29 ppm) and C-8 (δ 4.54 ppm). This result indicates that the carbonyl group at C-7 in dienophiles **8a**,**b** provides the control on the regiochemistry of these cycloaddition reactions.



Scheme 1. Reaction of quinone **5** with aminouracil **6**.

Scheme 2. One-pot synthesis of quinones **8a**,**b**.



Scheme 3. Cycloaddition reactions of quinones **8** with polarized dienes (**a**. R = Me, **b**. R = H).

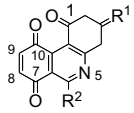
To verify the scope of the remarkable behaviour of quinones **8** in cycloaddition reactions with polarized dienes, we studied the Diels–Alder reaction of **8a**,**b** with 1-dimethylamino-3-methyl-1-azabutadiene. The reactions, that were performed in dichloromethane at room temperature, gave the stable cycloadducts **10a**,**b** in 99% and 65% yields, respectively (Scheme 3). We did not observe the formation of any regioisomers in these cycloaddition reactions. It is interesting to point out that the isolation of the stable adducts **10** is unusual taking into account that cycloaddition reactions of 1,4-quinones with 1-dimethylamino-3-methyl-1-azabutadiene usually afforded the corresponding 1,4-dihydro and/or aromatized cycloadducts, due to the tendency of the primary cycloadducts to liberate dimethylamine.[13]

The structure of adducts **10a**,**b** was established on the basis of the HMBC spectrum of **10b** that showed $^2J_{C,H}$ of the carbon at C-12 (δ 193.9 ppm) with the proton at C-11a (δ 3.63 ppm) and $^3J_{C,H}$ of the carbon at C-7 (δ 192.4 ppm) with the proton at C-6 (δ 9.23 ppm).

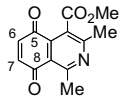
The cycloaddition reactions of quinones **8a**,**b** with the unsymmetrical dienes demonstrates that the carbonyl group at C-7 provides the control on the attack of the nucleophiles end, of the polarized dienes, to the C-9 atom of dienophiles **8**. It interesting to note that we have observed similar regiochemical behaviours to that of quinones **8a**,**b** for the cycloaddition of phenanthridinquinones **11a**,**b**[8] with trimethylsilyloxydiene. In this case, theoretical calculation of the HOMOdiene–LUMOdienophile interactions of the primary orbitals indicates that cycloadditions of the Diels–Alder partners proceeds in an opposite manner to that predicted by FMO theory.

It is interesting to point out that the regiochemistry of the cycloaddition reactions of the polarized dienes with

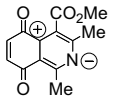
isoquinolinquinone **12**, which is structurally related to **8** and **11**, proceed in accord with that predicted by the FMO and electronic resonance theories.[14] Therefore, the electron withdrawing effect of the nitrogen atom in **12**, showed in structure **13**, makes the C-5 carbonyl group more electron deficient directing the nucleophile C-4 end of the polarized dienes, to attack the C-7 carbon of quinone **12**.



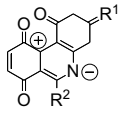
11a. R^1 = H,H, R^2 = Me
b. R^1 = Me,Me; R^2 = H



12



13



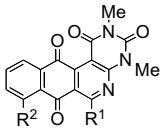
14

Since the electron withdrawing effect of the nitrogen atom in dienophiles **8** and **11** (i.e., structure **14**) does not have influence on the regiochemistry of the cycloadditions the regioselectivity control could be determined by steric interactions between the C-1 and C-10 carbonyl groups into these dienophiles.

An inspection of the molecular model of **8b** (Fig. 1) shows a significant inhibition to the coplanarity of the C-10 carbonyl group with respect to the quinone double bond, due to its steric interaction with the carbonyl groups at C-1.

This steric interaction twists the carbonyl double bond at C-10 and prevents the enone system activation by conjugation. Therefore, it seems reasonable to assume that the carbonyl group at C-7 provides the regiochemical control on the cycloaddition of the polarized dienes across the quinone double bond of dienophiles **8**. This assumption could be considered to explain the regioselectivity observed in the cycloaddition of a phenanthrenequinone with 1-trimethylsilyloxybutadiene reported in the literature.[15]

Diels–Alder adducts **9a**,**b** were converted into the corresponding aromatized compounds **15a**,**b** by reaction with hydrochloric acid. On the other hand, mild hydrolysis of adducts **9a**,**b** with hydrochloric acid followed by oxidation with PCC of the alcohol intermediaries, yielded the corresponding benzo[*g*]pyrimido[4,5-*c*]isoquinolinequinones **15c**,**d**.



15a. R^1 = Me, R^2 = H
b. R^1 = R^2 = H
c. R^1 = Me, R^2 = OH
d. R^1 = H, R^2 = OH

To get preliminary information on the cytotoxic activity of the novel angucyclinone N-congeners, they were evaluated against human AGS gastric adenocarcinoma cells. The screening showed that congeners **15b** and **15d** displayed major potencies (IC_{50}: 3.5; 5.9 μM, respectively) than analogues **15a** and **15c** (IC_{50}: 19.0; 70.0 μM, respectively). Furthermore, the N-analogues **15a**, **15b**, and **15d** were more potent than 6,8-dihydroxy-1,2,3,4-tetrahydrobenz[*a*]anthra-7,12-quinone used as an angucyclinone-type drug reference (IC_{50}: 41.6 μM).[8]

These results support our approach to entry into new potentially cytotoxic agents based on the replacement of the AB-carbocyclic rings of the benz[*a*]antraquinone chromophore **1** by a pyrido[2,3-*d*]pyrimidine system.

In conclusion, we have described a simple strategy to prepare angucyclinone AB-heterocyclic congeners. The reported synthesis involves easily available precursors and an efficient Michael addition–heterocyclization, Diels–Alder and oxidative aromatization reaction sequence. Taking into account the accessibility to acylhydroquinones by photo-Friedel–Crafts acylation of 1,4-quinones with aldehydes,[16,17] this approach may be used to make a variety of angucyclinone AB-pyrido[2,3-*d*]pyrimidine analogues for biological evaluation. In ongoing studies, this method will be applied to the synthesis of a broad range of members of this new class of N-heterocyclic quinones and their cytotoxic activity on a panel of cancer cells will be studied.

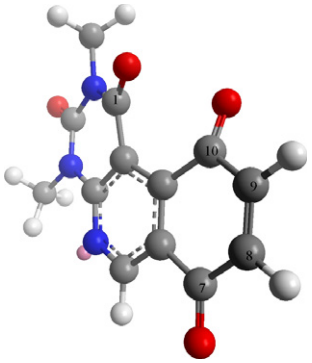


Fig. 1. Molecular model of quinone **8b**.

Acknowledgements

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Supplementary data

Experimental procedures, spectroscopic and physical characterization data of compounds **8a**, **9a**, **10a**, **15a**, and **15c**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.133.

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