Pergamon

Tetrahedron Letters, Vol. 37, No. 42, pp. 7615-7618, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01675-9

Regiospecific Free Radical Annulation Reactions of Diethylbenzylmalonate with Unsymmetrical 1,4 - Naphthoquinones: A Direct Approach to Ring A Aromatic Angucyclinones

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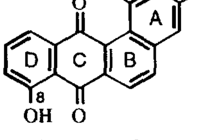
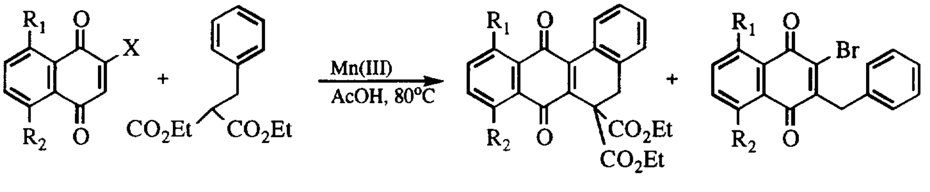
Abstract: *The regiospecific formation of the C-8 oxygenated benz[a]anthraquinones was achieved by a bromine directed Mn (III) initiated oxidative free radical reaction of diethylbenzylmalonate (DBM) with quinones. The regioisomeric benz[a]anthraquinone was obtained when the isomeric quinone was employed. The novel Mn(OAc)$_3$ induced C - benzylation of bromoquinones with diethylbenzylmalonate is described.* Copyright © 1996 Elsevier Science Ltd

Recently there has been considerable interest in the chemistry of the angucyclinones.[1,2] Many members of this rapidly growing class of antibiotics exhibit a wide variety of biological activities, including antitumour activity and enzyme inhibition.[1] Several elegant syntheses of the angucyclinones have been described.[2] One of the earliest syntheses of an angucylinone was achieved by Thompson *et al.*,[3] who applied Torsell's decarboxylative radical alkylation chemistry[4] as a key step in their synthesis of tetrangulol **1**, a ring A aromatic angucyclinone, which possesses the characteristic C-8 oxygen functionality. More recently Chuang *et al.*[5] described a Mn (III) initiated radical addition-cyclization between unsubstituted 1,4 - naphthoquinone and dimethylbenzylmalonates which afforded the benz[*a*] anthraquinone framework.



Tetrangulol **1**

Our objective was a regiospecific construct of the C-8 oxygenated nucleus of ring A aromatic angucyclinones. Previously we reported the regiospecific annulation of enaminoketones[6] and enaminoesters[7] to bromoquinones. We concluded that the orientation of free radical annulations to quinones could likewise be directed by quinonoidal bromine. We now report our preliminary results in this area.



(1)

2a-i
a:$R_1=R_2=X=H$
b:$R_1=R_2=H$, X=Br
c:$R_1=H$, $R_2=OMe$, X=H
d:$R_1=H$, $R_2=OMe$, X=Br
e:$R_1=OMe$, $R_2=H$, X=Br
f:$R_1=OAc$, $R_2=X=H$
g:$R_1=OAc$, $R_2=H$, X=Br
h:$R_1=H$, $R_2=OAc$, X = Br
i:$R_1=H=X$, $R_2=OH$

3a-e
a:$R_1=R_2=H$
b:$R_1=H$, $R_2=OMe$
c:$R_1=OMe$, $R_2=H$
d:$R_1=OAc$, $R_2=H$
e:$R_1=H$, $R_2=OAc$

4a-e
a:$R_1=R_2=H$
b:$R_1=H$, $R_2=OMe$
c:$R_1=OMe$, $R_2=H$
d:$R_1=OAc$, $R_2=H$
e:$R_1=H$, $R_2=OAc$

Table 1: Products from the Mn(III) Initiated Reactions of Naphthoquinones with DBM

Quinone	Product*,¶		Isolated yield (%)	
	3	4	3	4
2a	3a	-	59	-
2b	3a	4a	68	22
2c	3b	-	53	-
2d	3b	4b	48	37
2e	3c	4c	30	54
2f	3d, 3e	-	46#	-
2g	3d	4d	56	35
2h	3e	4e	45	29

* The dimer of DBM was also isolated in 5 - 30 % yield. ¶ Reactions were conducted in AcOH at 80°C for 8 hours. The molar ratio of $Mn(OAc)_3$: DBM: quinone was 5:2.1:1. # Isolated as a 2:3 inseparable mixture of regioisomers **3d** and **3e**.

Our results are summarised in Equation **1** and Table **1**. Consistent with our expectations, in all the cases we investigated, bromine regiospecifically directed initial carbon - carbon bond formation to the free quinonoid position. Thus, the C-8 oxygenated benz[*a*]anthraquinones **3b** and **3e** were obtained regiospecifically from the 2-bromonaphthoquinones **2d** and **2h**, respectively. Similarly, the isomeric C-11 oxygenated benz-[*a*]anthraquinones **3c** and **3d** were obtained regiospecifically from the 3-bromonaphthoquinones **2e** and **2g**, respectively. Interestingly, without the influence of bromine, the regiochemistry depended quite subtly on the nature of the substituents. Thus, O-methyljuglone, **2c**, provided **3b** exclusively, whereas O-acetyljuglone, **2f**, led to the formation of an inseparable mixture of regioisomers, **3d** and **3e**. In contrast, no reaction was observed when juglone **2i** was employed and is probably due to phenolic interaction with the $Mn(OAc)_3$.

Extension of this reaction using 5-benzylated Meldrum's acid as an alternative to DBM was investigated. Only recovered starting material was obtained. This result is consistent with the proposed mechanism of radical formation which is believed to involve a cyclic intermediate between Mn(lll) and the oxidised 1,3-dicarbonyl substrate.[8] In the case of 5-benzyl Meldrum's acid, it is not structurally possible to form such an intermediate.

The regiochemistry of the tetracycle **3d**, not readily determined by nmr, was established by X-ray analysis,[9] (Figure 1). The other products, **3b**,**3c**, and **3e**, were then related to **3d** by nmr.

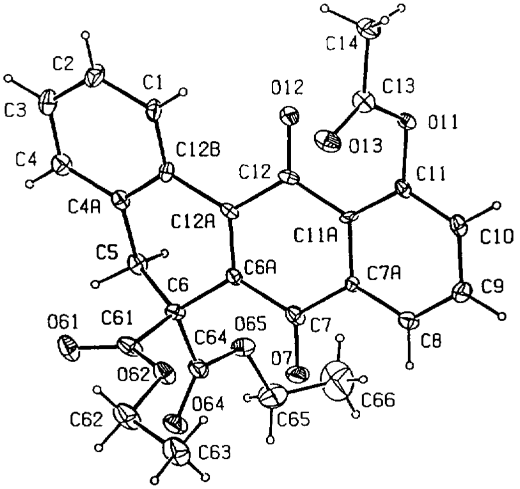
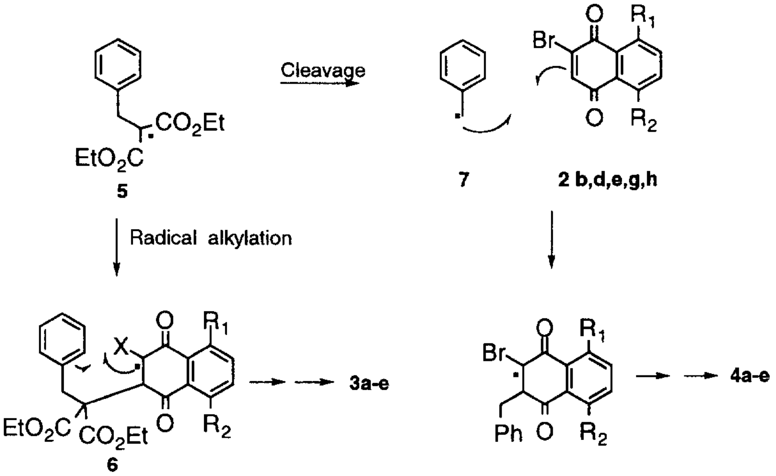


Figure 1: A view of tetracycle **3d** showing the regiochemistry and the crystallographic numbering scheme.

Scheme 1



Of additional interest is the formation of the benzylated products,**4a-e**.[10] The use of $Mn(OAc)_3$ in the formation of the adducts of type **4** is unprecedented. This reaction remains to be investigated in detail. The proposed mechanism for the formation of products **3** and **4** is outlined in scheme **1**. The initially formed radical **5** may either attack the bromoquinone **2** with preferential formation of the bromine stabilised[11] radical intermediate **6**, undergo dimerisation as is observed in all reactions (see Table), or fragment[12] to the benzyl radical **7**[13].

Subsequent bromine directed attack by the benzyl radical **7** on the bromoquinone, ultimately leads to the formation of **4.** Since benzylated quinone products **4a-e** were observed only with bromoquinone substrates, presumably the rate of alkylation of the non - brominated quinones by **5** is such that the cleavage of **5** to give the benzyl radical **7** is not a competitive route.

In summary we report the regiospecific annulation of quinones **2b-h** by means of a bromine directed radical alkylation, which is followed by a cyclisation to afford the tetracycles **3a-e**. This methodology should prove a powerful means of accessing the C-8 oxygenated ring A aromatic angucyclinones. Furthermore a novel regiospecific method of benzylation of quinones with $Mn(OAc)_3$ is described. Further studies involving the application of this chemistry to natural product synthesis including angucyclinones and kinamycins are underway.

Acknowledgements This work was partly supported by Eolas/Forbairt, the Irish Science and Technology Agency and University College, Cork. GF thanks NSERC (Canada) for research grants.

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9. Crystals of **3d** are triclinic, space group P-1 with 2 molecules of $C_{26}H_{22}O_8$ in a unit cell of dimensions a = 9.449(3), b = 11.837(3), c = 12.315(4)Å. V = 1139.8(6)$Å^3$, F(000) 284, $\mu = 0.10\ mm^{-1}$. Some 2106 reflections were measured of which 839 had I > 2(sigma)I. Structure solved by direct methods using SHELXS86 (Sheldrick, G.M. A program for the solution of crystal structures, University of Gottingen, Germany) using all 2106 measured reflections and SHELXL93*(idem, ibid.)*. H atoms allowed for as riding atoms and non-H atoms allowed anisotropic motion. Final R-factors on the 839 "observed" data are R=0.0619, wR(Fsquared) = 0.1212. The molecular geometry is entirely in accord with expectations: full details available in Crystallographic Information File (CIF) format from the authors; these details have also been deposited with the Cambridge Crystallographic Data Centre.
10. All new compounds reported gave satisfactory spectroscopic and analytical data.
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12 Cleavage of **5** has not been recorded previously. Although the reaction conditions combined with the structure of **4a-e** are consistant with the formation of a benzyl radical[13], the nature of the DEM residue - possibly a Fischer Mn-stabilised carbene complex - remains unknown.
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(*Received in UK* 24 *July* 1996; *revised* 16 *August* 1996; *accepted* 23 *August* 1996)