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A Regiospecific Synthesis of 2-Azaanthraquinon-3-ones via a Hetero Diels-Alder Reaction with Bromonaphthoquinones

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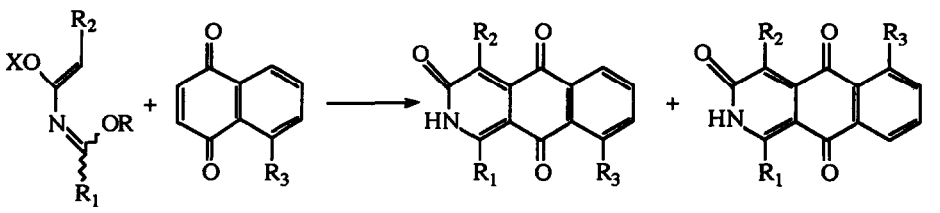
Abstract The Diels-Alder reaction between 2-azadienes and 2- or 3-bromo-5-substituted naphthoquinones (R_3=OH, OAc, OMe) led to a regiospecific synthesis of the corresponding 2-azaanthraquinon-3-ones The results indicate that the bromine atom exerts a stronger regiochemical control in these cycloadditions than the 5-substituent.

The usefulness of 2-aza-1,3-butadienes in the Diels-Alder synthesis of pyridones and piperidones derivatives has been well established [1] In order to obtain some polysubstituted 2-azaanthraquinon-3-ones of biological interest, we had investigated the cycloadditions of 2-azadienes **1** upon 5-substituted naphthoquinones **2** [2,3] A mixture of the regioisomeric 2-azaanthraquinon-3-ones **3** and **4** was then obtained (Scheme 1) The cycloadditions were more regioselective with juglone **2** (R_3=OH) and its methyl ether than with acetyl juglone

Scheme 1



1 **2** **3** **4**

R = Et, i-Pr , R_1, R_2 = H, Me , R_3 = OH, OAc, OMe , X = t-BuMe_2Si

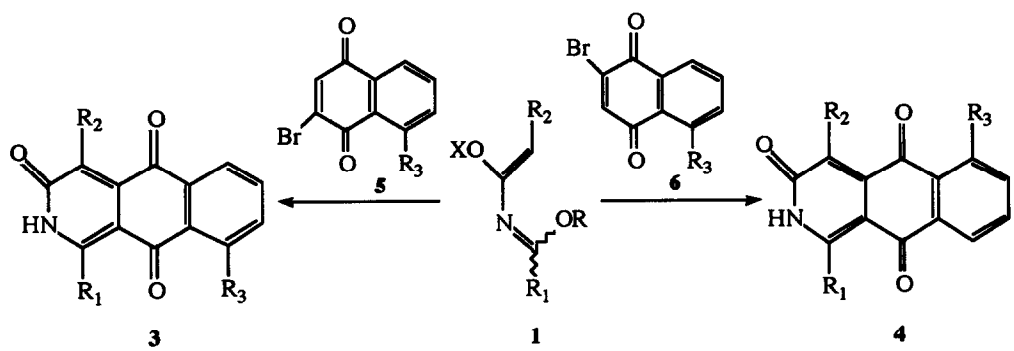
In the case of **2** (R_3=OH), the structures of the major regioisomers **3** were in good agreement with the known directing effect of the 5-hydroxy group [4] Starting with methyljuglone, formation of compounds **4** as the major products can be accomodated by the donor effect of the methyl group The poor and the opposite regioselectivity generally observed with **2** (R_3=OAc) is also in accord with the literature [5]

These cycloadditions being generally unsatisfactory in terms of yields and separation of the regioisomers, we turned our attention to the use of 2- or 3-bromo-5-substituted naphthoquinones **5** and **6** (R_3=OH, OAc, OMe) As these compounds are more electron deficient than quinones **2**, they should be more reactive towards azadienes **1** Furthermore, the bromine atom would exert a stronger regiochemical control in these cycloadditions than the 5-substituent (R_3=OH, OMe) since the electron-rich end of a transoid diene is known to add exclusively at the unsubstituted carbon of bromonaphthoquinones [6-8]

RESULTS AND DISCUSSION

Thus, azadienes **1** reacted at reflux of chloroform with bromoquinones **5** and **6** to give regiospecifically the corresponding 2-azaanthraquinon-3-ones **3** and **4** (Scheme 2 and Table 1)

Scheme 2



The reactivity of bromonaphthoquinones **5** and **6** towards azadienes **1** is higher comparatively to quinones **2** [2,3] A high yield increase in compounds **3** or **4** is particularly observed with the 5-acetoxy (**5b** or **6b**) and the 5-methoxy (**5c** or **6c**) bromonaphthoquinones As examples 32% of a mixture of **3bb+4bb** was obtained with quinone **2** (R_3=OAc), while starting with **5b** or **6b** the yields in **3bb** or **4bb** were respectively 82% and 88% , similarly, 51% of a mixture of **3ac+4ac** was obtained from **2** (R_3=OMe) whereas the yields in **3ac** or **4ac** were respectively 90% and 95% when bromonaphthoquinones **5c** or **6c** were used Furthermore, due to the elimination of hydrogen bromide from the primary adduct, hydrolysis of the 3-silyloxy group occurred without addition of hydrofluoric acid

Table 1 Experimental conditions and yields of 2-azaanthraquinon-3-ones **3** and **4**

Azadiene	R	R_1	R_2	Quinone	R_3	Reflux time (h)	Yield %	Product
1a	i-Pr	H	H	**5a**	OH	2	91	**3aa**[2]
1b	Et	Me	H	**5a**	OH	2 5	92	**3ba**[2]
1c	i-Pr	H	Me	**5a**	OH	4 5	64	**3ca**[2]
1d	Et	Me	Me	**5a**	OH	2 5	85	**3da**[2]
1a	i-Pr	H	H	**5b**	OAc	3	83	**3ab**[2]
1b	Et	Me	H	**5b**	OAc	3	82	**3bb**[2]
1c	i-Pr	H	Me	**5b**	OAc	4	70	**3cb**[2]
1d	Et	Me	Me	**5b**	OAc	3	68	**3db**[2]
1a	i-Pr	H	H	**5c**	OMe	4	90	**3ac**[3]
1b	Et	Me	H	**5c**	OMe	5	74	**3bc**
1c	i-Pr	H	Me	**5c**	OMe	5	72	**3cc**
1d	Et	Me	Me	**5c**	OMe	3	59	**3dc**
1a	i-Pr	H	H	**6a**	OH	4	80	**4aa**[2]
1b	Et	Me	H	**6a**	OH	2 5	68	**4ba**[2]
1c	i-Pr	H	Me	**6a**	OH	2	91	**4ca**[2]
1d	Et	Me	Me	**6a**	OH	3	79	**4da**[2]
1a	i-Pr	H	H	**6b**	OAc	4 5	79	**4ab**[2]
1b	Et	Me	H	**6b**	OAc	4 5	88	**4bb**[2]
1c	i-Pr	H	Me	**6b**	OAc	6	87	**4cb**[2]
1d	Et	Me	Me	**6b**	OAc	5	77	**4db**[2]
1a	i-Pr	H	H	**6c**	OMe	5	95	**4ac**[3]
1b	Et	Me	H	**6c**	OMe	8	92	**4bc**[3]
1c	i-Pr	H	Me	**6c**	OMe	6 5	49	**4cc**
1d	Et	Me	Me	**6c**	OMe	3 5	71	**4dc**

Concerning the regiochemistry of the cycloadditions, compounds **3** and **4** are obtained as a single regioisomer A structural elucidation of compounds **3** or **4** (R_3=OH) was previously[2] supported by the known directing effect of the 5-hydroxy group of juglone and by the ^{1}H-NMR spectral data of the mixture of **3** and **4**

The cycloadditions being now regiospecific, we report in Table 2 the ^{1}H-NMR data of each pure regioisomer It is apparent from this Table that in compounds **3** (R_3=OH) the peri-OH and the NH signals are more deshielded comparatively to those of **4** Furthermore, the R_1 substituent (H or Me) in **3** is shifted to lower fields while in **4**, that is R_2 (H or Me) who is deshielded

The structure of the regioisomers **3** and **4** (R_3=OAc) is assigned after hydrolysis of the acetyl group by 5% aqueous NaOH Thus, the corresponding hydroxylated derivatives obtained have their ^{1}H-NMR spectral data identical with those of the hydroxylated compounds prepared respectively from bromojuglones **5** and **6**

On the other hand, since the NH and R_1 (H or Me) signals in the acetyl or methoxyl derivatives of **3** (R_3=OAc or OMe) are both shifted to the higher fields while the reverse occurred with the R_2 substituent (H or Me), we assign for these compounds the same regiochemistry

Finally, the fact that the regiospecificity observed is independent on the nature of the 5-substituent in naphthoquinones **5** and **6**, confirms the hypothesis that the nucleophilic end of these electron rich 2-azadienes adds exclusively at the unsubstituted carbon of the dienophiles **5** or **6**

Table 2. ^{1}H-NMR spectral data of 2-azaanthraquinon-3-ones **3** and **4** (300 MHz, DMSO-d_6, δ ppm)

Compound	NH	R_1 = H or Me	R_2 = H or Me	R_3 = OH, OAc or OMe
3aa	12 98	8 47	6 90	12 84
4aa	12 90	8 37	6 97	12 25
3ba	12 85	2 76	6 81	13 11
4ba	12 77	2 74	6 91	12 10
3ca	12 85	8 32	2 46	12 77
4ca	12 76	8 24	2 53	12 45
3da	12 75	2 74	2 42	13 08
4da	12 65	2 70	2 45	12 35
3ab	12 85	8 33	6 87	2 37
4ab	12 92	8 39	6 82	2 39
3bb	12 74	2 67	6 79	2 36
4bb	12 80	2 75	6 74	2 39
3cb	12 73	8 16	2 47	2 36
4cb	12 76	8 22	2 38	2 38
3db	12 59	2 61	2 39	2 35
4db	12 62	2 70	2 37	2 37
3ac	12 78	8 22	6 83	3 93
4ac	12 80	8 33	6 80	3 95
3bc	12 58	2 68	6 74	3 91
4bc	12 68	2 73	6 72	3 94
3cc	12 58	8 06	2 44	3 92
4cc	12 66	8 16	2 36	3 94
3dc	12 44	2 61	2 36	3 90
4dc	12 53	2 67	2 28	3 91

CONCLUSION

The use of 2-and 3-bromonaphthoquinones in the hetero Diels-Alder reaction of 2-aza-1,3-butadienes affords regiospecifically the 2-azaanthraquinon-3-ones **3** or **4** These results show that the bromine atom exerts a strong regiochemical control on the cycloadditions despite the directing effect of the 5-hydroxy or the 5-methoxy group

Furthermore, the use of this procedure enhanced substantially the yields of the cycloadditions

EXPERIMENTAL SECTION

Melting points were taken in capillary tube using a Büchi 510 apparatus. The infra-red spectra were performed on a Perkin-Elmer 1310 spectrophotometer ^{1}H-NMR spectra were recorded on a Bruker AM 300 spectrometer High resolution mass spectra were performed by direct ionisation (EI at 70 eV) on a AE1 MS 902 apparatus Elemental analysis were made at the Centre de Microanalyse du CNRS at Vernaison

Azadienes **1a**, **1b** and **1c** were prepared according to P Bayard procedure[9] while **1d** was described in reference [2] 3-Bromo-5-hydroxynaphthoquinone **5a** was prepared by treating juglone with bromine in glacial acetic acid [10] By this procedure we obtained also 13 % of the 2-bromo derivative **6a** which was eliminated by recrystallization from acetone The acetyl (**5b**)[10] and methyl (**5c**)[11] derivatives were prepared as described for quinones **2** (R_3=OAc, OMe) [12,13] 2-Bromo-5-acetoxynaphthoquinone **6b** was obtained by oxidation of 1,5-diacetoxynaphthalene with N-bromosuccinimide [8] Hydrolysis of **6b** gave **6a**[8] which was methylated into **6c** [11] The melting points of **5** and **6** are identical with the values reported in the literature [10,11]

8-Acetoxy-2-aza-9,10-antraquinon-3-one, 3ab[14]

Azadiene **1a** (0 25 g, 1 01 mmol) and 5-acetoxy-3-bromonaphthoquinone **5b** (0 2 g, 0 67 mmol) were dissolved in anhydrous chloroform (4 ml) and the solution was heated to reflux for 3 h At the end of the reaction a yellow precipitate was formed After evaporation of chloroform, acetone (5 ml) was added to the residue and the mixture was heated to reflux for 2 h Compound **3ab** was recovered by cooling It was separated by filtration and washed twice with acetone (2 ml) and recristallized from this solvent. M p 305-310°C with decomposition, IR (KBr) ν 1765, 1690, 1670, 1655 (CO) cm^{-1}, ^{1}H-NMR (DMSO-d_6, 300 MHz) δ ppm 12 85 (br s, 1H, NH), 8 33 (s, 1H, H-1), 8 16 (d, 1H, J=7 2 Hz, H-8), 7 93 (dd, 1H, J=7 2 and 7 4 Hz, H-7), 7 64 (d, 1H, J=7 4 Hz, H-6), 6 87 (s, 1H, H-4), 2 37 (s, 3H, $COCH_3$)

5-Acetoxy-2-aza-9,10-anthraquinon-3-one, 4ab[14]

Following the procedure used to prepare **3ab**, compound **4ab** was obtained from azadiene **1a** and 5-acetoxy-2-bromonaphthoquinone **6b** M p 300-310°C with decomposition, IR (KBr) ν 1765, 1690, 1665, 1640 (CO) cm^{-1}, ^{1}H-NMR (DMSO-d_6, 300 MHz) δ ppm 12 92 (br s, 1H, NH), 8 39 (s, 1H, H-1), 8 18 (d, 1H, J=7 3 Hz, H-5), 7 98 (dd, 1H, J=7 3 and 7 4 Hz, H-6), 7 62 (d, 1H, J=7 4 Hz, H-7), 6 82 (s, 1H, H-4), 2 39 (s, 3H, $COCH_3$)

8-Methoxy-1-methyl-2-aza-9,10-anthraquinon-3-one, 3bc

Following the procedure used to prepare **3ab**, compound **3bc** was obtained from azadiene **1b** and 5-methoxy-3-bromonaphthoquinone **5c** M p >300°C, IR (KBr) ν 1680, 1650 (CO) cm^{-1}, ^{1}H-NMR (DMSO-d_6, 300 MHz) δ ppm 12 58 (br s, 1H, NH), 7 77 (dd, 1H, J=6 9 and 8 1 Hz, H-6), 7 72 (d, 1H, J=6 9 Hz, H-5), 7 58 (d, 1H, J=8 1 Hz, H-7), 6.74 (s, 1H, H-4), 3 91 (s, 3H, OCH_3), 2 68 (s, 3H, CH_3-1) Anal Calcd for $C_{15}H_{11}NO_4$, 0 2 H_2O C, 65 96, H, 4 17, N, 5 13 Found C, 66 26, H, 4 35, N, 5 04 HRMS Calcd for $C_{15}H_{11}NO_4$ 269 0688 Found 269 0694

8-Methoxy-4-methyl-2-aza-9,10-anthraquinon-3-one, 3cc

Following the procedure used to prepare **3ab**, compound **3cc** was obtained from azadiene **1c** and 5-methoxy-3-bromonaphthoquinone **5c** M p >300°C, IR (KBr) ν 1675, 1660, 1640 (CO) cm^{-1}, ^{1}H-NMR (DMSO-d_6, 300 MHz) δ ppm 12 58 (br s, 1H, NH), 8 06 (s, 1H, H-1), 7 81 (dd, 1H, J=7 2 and 8 2 Hz, H-6), 7 72 (d, 1H, J=7 2 Hz, H-5), 7 55 (d, 1H, J=8 2 Hz, H-7), 3 92 (s, 3H, OCH_3), 2 44 (s, 3H, CH_3-4) Anal Calcd for $C_{15}H_{11}NO_4$ C, 66 89, H, 4 12, N, 5 21 Found C, 66 83, H, 4 17, N, 5 20 HRMS Calcd for $C_{15}H_{11}NO_4$. 269 0688 Found 269 0698

5-Methoxy-4-methyl-2-aza-9,10-anthraquinon-3-one, 4cc

Following the procedure used to prepare **3ab**, compound **4cc** was obtained from azadiene **1c** and 5-methoxy-2-bromonaphthoquinone **6c**. M p 160-165°C with decomposition, IR (KBr) ν 1675, 1645 (CO) cm^{-1}, ^{1}H-NMR (DMSO-d_6, 300 MHz) δ ppm 12 66 (br s, 1H, NH), 8 16 (s, 1H, H-1), 7 81 (dd, 1H, J=7.5 and 8 3 Hz, H-7), 7 70 (d, 1H, J=7 5 Hz, H-8), 7 53 (d, 1H, J=8 3 Hz, H-6), 3 94 (s, 3H, OCH_3), 2 36 (s, 3H, CH_3-4) Anal Calcd for $C_{15}H_{11}NO_4$, 0 33 H_2O C, 65 54, H, 4 27, N, 5 08 Found. C, 65 38, H, 4 07, N, 5 08 HRMS Calcd for $C_{15}H_{11}NO_4$ 269 0688 Found 269 0698

8-Methoxy-1,4-dimethyl-2-aza-9,10-anthraquinon-3-one, 3dc

Following the procedure used to prepare **3ab**, compound **3dc** was obtained from azadiene **1d** and 5-methoxy-3-bromonaphthoquinone **5c** M.p 185-195°C with decomposition, IR (KBr) ν 1665, 1645, 1630 (CO) cm^{-1}, ^{1}H-NMR (DMSO-d_6, 300 MHz) δ ppm 12 44 (br s, 1H, NH), 7 75 (dd, 1H, J=7 5 and 8 4 Hz, H-6), 7 61 (d, 1H, J=7 5 Hz, H-5), 7 51 (d, 1H, J=8 4 Hz, H-7), 3 90 (s, 3H, OCH_3), 2.61 (s, 3H, CH_3-1), 2 36 (s, 3H, CH_3-4) Anal Calcd for $C_{16}H_{13}NO_4$, 0 33 H_2O C, 66 43, H, 4 76, N, 4 84 Found C, 66 46, H, 4 96, N, 4 86 HRMS Calcd for $C_{16}H_{13}NO_4$. 283 0845 Found 283 0855

5-Methoxy-1,4-dimethyl-2-aza-9,10-anthraquinon-3-one, 4dc

Following the procedure used to prepare **3ab**, compound **4dc** was obtained from azadiene **1d** and 5-methoxy-2-bromonaphthoquinone **6c** M p >300°C with decomposition, IR (KBr) ν 1665, 1645, 1630 (CO) cm^{-1}, ^{1}H-NMR (DMSO-d_6, 300 MHz) δ ppm 12 53 (br s, 1H, NH), 7 77 (dd, 1H, J=7 7 and 8.4 Hz, H-7), 7 64 (d, 1H, J=7 7 Hz, H-8), 7 47 (d, 1H, J=8 4 Hz, H-6), 3 91 (s, 3H, CH_3O), 2 67 (s, 3H, CH_3-1), 2 28 (s, 3H, CH_3-4) Anal Calcd for $C_{16}H_{13}NO_4$. C, 67 82, H, 4 63, N, 4 95 Found C, 67 67, H, 4 72, N, 5 05 HRMS Calcd for $C_{16}H_{13}NO_4$. 283 0845 Found 283 0855

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14 The present work let us to assign the correct regiochemistry for **3ab** and **4ab**