Efficient Syntheses and the Nucleophilic Substitution of Dibromo- and Tribromo-azulenequinones: Differences in Reactivity between Five- and Seven-membered Ring Moieties

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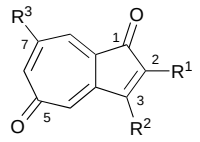
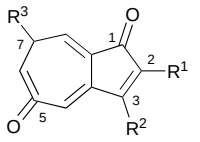
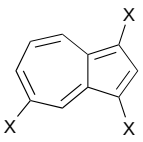
Efficient syntheses and the nucleophilic substitution of dibromoazulenequinones **5a** and **5b** and tribromoazulenequinones **6a** and **6b** were carried out: the five-membered ring portion of the molecule is proved to be more reactive than the seven-membered ring.

Azulenequinones (AzQs) are novel and one of the most interesting classes of nonbenzenoid quinones[1] and their chemical and physical properties are of particular interest in connection with benzenoid quinones.[2,3] As a general synthesis of monosubstituted AzQs, a one-pot synthesis of 3-bromo-1,5- and -1,7-AzQs **2a** and **2b** from azulene **3** and various 3-substituted 1,5- and 1,7-AzQs by a nucleophilic substitution reaction has been reported.[5–7] Concerning the general synthesis of disubstituted AzQs, a preliminary summary of our syntheses of 3,7-disubstituted 1,5- and 3,5-disubstituted 1,7-AzQs **7** and **8** from the corresponding dibromo-1,5- and -1,7-AzQs **5a** and **5b** has been given by one of us (N.T.) in a review.[5] **5a** and **5b** have been recorded as by-products in the synthesis of **2a** and **2b**.[6]







1a $R^1 = R^2 = R^3 = H$
2a $R^1 = R^3 = H$, $R^2 = Br$
5a $R^1 = H$, $R^2 = R^3 = Br$
6a $R^1 = R^2 = R^3 = Br$
7a $R^1 = H$, $R^2 = R$, $R^3 = Br$
8a $R^1 = H$, $R^2 = R^3 = R$
9a $R^1 = R^2 = Br$
10a $R^1 = Br$, $R^2 = R^3 = R$
11a $R^1 = R^2 = R^3 = R$

1b $R^1 = R^2 = R^3 = H$
2b $R^1 = R^3 = H$, $R^2 = Br$
5b $R^1 = H$, $R^2 = R^3 = Br$
6b $R^1 = R^2 = R^3 = Br$
7b $R^1 = H$, $R^2 = R$, $R^3 = Br$
8a $R^1 = H$, $R^2 = R^3 = R$
9b $R^1 = R^2 = Br$
10b $R^1 = Br$, $R^2 = R^3 = R$
11b $R^1 = R^2 = R^3 = R$

3 X = H
4 X = Br

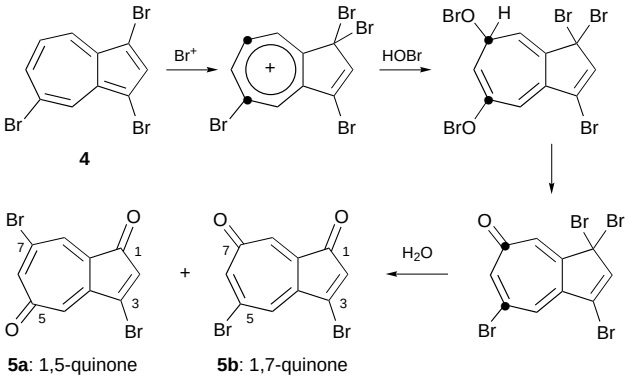
We report herein a detailed study of an efficient synthesis of **5a** and **5b** *via* 1,3,5-tribromoazulene **4**, and their nucleophilic substitution to afford **7a**,**7b** and **8a**,**8b**. The synthesis of 2,3,7-tribromo-1,5- and 2,3,5-tribromo-1,7-AzQs **6a** and **6b** by the regioselective bromination of **5a** and **5b**, respectively, and their nucleophilic substitution will be also described.

Azulene **3** was boiled with pyridinium tribromide (Py-HBr_3) in benzene to give 1,3,5-tribromoazulene **4** (86%).

In acetonitrile, acetic acid and water, **4** was treated with Py-HBr_3 to give 3,7-dibromo-1,5-AzQ **5a** (41%) and 3,5-dibromo-1,7-AzQ **5b** (23%). When this reaction was performed in aqueous THF and acetic acid,[6] the yield of **5a** and **5b** was lower (17%).

We consider the reaction mechanism to be that presented in Scheme 1.

We tried further bromination of **5a** and **5b**. When **5a** was treated in THF with Py-HBr_3 and 48% aqueous HBr, a regioselectively brominated compound, 2,3,7-tribromo-1,5-AzQ **6a** was obtained (89%). **5b** was also converted into **6b** (93%).

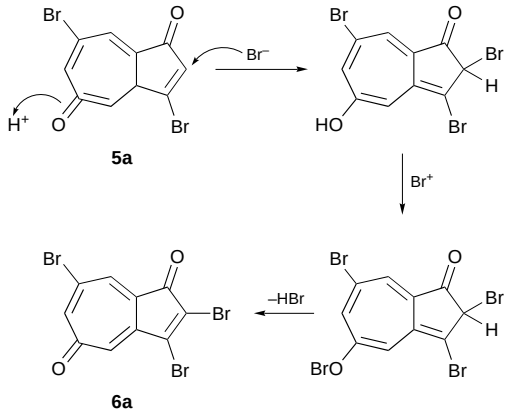


5a: 1,5-quinone **5b**: 1,7-quinone

Scheme 1

The reaction mechanism for this further bromination is shown in Scheme 2.

The results of nucleophilic substitution of **5a** and **5b** with various nucleophiles are shown in Table 1. In methanol, **5a** or **5b** was treated with a catalytic amount of K_2CO_3 to afford monomethoxy-AzQ (at the C-3 position) together with recovered starting material (Entries 1 and 2). In contrast, dimethoxy-AzQs were obtained by using NaOMe as a more reactve nucleophile (Entries 3 and 4). When Et_2NH was used in THF at room temperature, 3-diethylamino-AzQs were obtained but in ethanol bis(diethylamino)-AzQs were produced under refluxing conditions in the presence of an excess of the reagent (Entries 5 to 8).



5a

6a

Scheme 2

*To receive any correspondence.

Table 1 Nucleophilic substitution of **5a** and **5b**

Entry	Substrate	Reaction conditions (mol equiv.)	R	Yield[a] (%) **7**	**8**
1	**5a**	K_2CO_3 (0.1)/MeOH/r.t	OMe	47[b]	—
2	**5b**	K_2CO_3 (0.1)/MeOH/r.t	OMe	47[b]	—
3	**5a**	NaOMe (10)/MeOH/r.t.	OMe	—	81
4	**5b**	NaOMe (10)/MeOH/r.t.	OMe	—	68
5	**5a**	Et_2NH (3)/THF/r.t.	NEt_2	87	—
6	**5b**	Et_2NH (3)/THF/r.t.	NEt_2	86	—
7	**5a**	Et_2NH (20)/EtOH/reflux	NEt_2	—	83
8	**5b**	Et_2NH (20)/EtOH/reflux	NEt_2	—	56
9	**5a**	Pr^nNH_2 (3)/THF/r.t.	NHP^n	85	—
10	**5b**	Pr^nNH_2 (3)/THF/r.t.	$NHPr^n$	81	—
11	**5a**	*p*-Toluidine (3)/THF/r.t.	NHC_6H_4-*p*-Me	80	—
12	**5b**	*p*-Toluidine (3)/THF/r.t.	NHC_6H_4-*p*-Me	94	—
13	**5a**	*p*-Nitrophenol (3)/DABCO (2)/THF/r.t.	OC_6H_4-*p*-NO_2	93	—
14	**5b**	*p*-Nitrophenol (3)/DABCO (2)/THF/r.t.	OC_6H_4-*p*-NO_2	88	—
15	**5a**	Ethanolamine (3)/THF/r.t.	$NH[CH_2]_2OH$	80	—
16	**5b**	Ethanolamine (3)/THF/r.t.	$NH[CH_2]_2OH$	92	—
17	**5a**	Azulene (1.2)/AcOH–THF/r.t.	azulen-1-yl	14	—
18	**5b**	Azulene (1.2)/AcOH–THF/r.t.	azulen-1-yl	45	—
19	**5a**	Benzenethiol (1.5)/THF/r.t.	SPh	53	27
20	**5b**	Benzenethiol (1.5)/THF/r.t.	SPh	56	37
21	**5a**	Et_4NCl (20)/1,4-dioxane/100 °C	Cl	—	88
22	**5b**	Et_4NCl (20)/1,4-dioxane/100 °C	Cl	—	79
23	**5a**	NH_4OAc (3)/THF/r.t.	OH[c]	10[b]	—
24	**5b**	NH_4OAc (3)/THF/r.t.	OH[c]	21[b]	—

[a]Isolated yield. [b] Substrates were recovered. [c]These compounds were generated from their acetates.

Table 2 Nucleophilic substitution of **6a** and **6b**

Entry	Substrate	Reaction conditions (mol equiv.)	R	Yield[a] (%) **9**	**10**	**11**
1	**6a**	K_2CO_3 (0.1)/MeOH/r.t.	OMe	39[b]	—	—
2	**6b**	K_2CO_3 (0.1)/MeOH/r.t.	OMe	46[b]	—	—
3	**6a**	NaOMe (10)/MeOH/r.t.	OMe	14	63	—
4	**6b**	NaOMe (10)/MeOH/r.t.	OMe	12	66	—
5	**6a**	Et_2NH (3)/THF/r.t.	NEt_2	59	—	—
6	**6b**	Et_2NH (3)/THF/r.t.	NEt_2	61	—	—
7	**6a**	Et_2NH (10)/EtOH/reflux	NEt_2	6	48	—
8	**6b**	Et_2NH (10)/EtOH/reflux	NEt_2	16[c]	44[c]	—
9	**6a**	Benzenethiol (1.5)/THF/r.t.	SPh	19[b]	—	38[b]
10	**6b**	Benzenethiol (1.5)/THF/r.t.	SPh	27[b]	3[b]	12[b]
11	**6a**	NH_4OAc (3)/THF/r.t.	OH[d]	54	—	—
12	**6b**	NH_4OAc (3)/THF/r.t.	OH[d]	24[b]	—	—

[a]Isolated yield. [b]Substrates were recovered. [c]2-Bromo-3-diethylamino-5-ethoxy-1,7-AzQ was obtained 25% yield. [d]These compounds were generated from their acetates.

Thus it is deduced that the reactivity of the five-membered ring moiety (at the C-3 position) is higher than that of the seven-membered one (at C-7 for **5a** or C-5 for **5b**). Therefore more severe conditions (high temperature, excess of nucleophile, more reactive reagent and polar solvent, *etc.*) should be needed to cause reaction at the C-5 or C-7 position. Ethanolamine, which contains two possible nucleophilic functional groups, reacted at a more reactve amino group (Entries 15 and 16). Azulene **3** also reacted with **5a** and **5b** (Entries 17 and 18). Because of the extremely high reactivity of benzenethiol, mono- and di-substituted-AzQs were obtained as a mixture in THF, even at room temperature (Entries 19 and 20). Dichloro-AzQs were produced by the reaction with Et_4NCl in 1,4-dioxane at 100 °C (Entries 21 and 22). NH_4OAc afforded 3-hydroxy-AzQs, which might be produced on the silica gel column by the hydrolysis of the 3-acetoxy derivatives formed as intermediates (Entries 23 and 24).

In Table 2, we show the results of nucleophilic substitution of **6a** and **6b**. The C-3 position of **6** was more reactive than the C-5 or C-7 position, as in the case of **5**. 2-Substituted-AzQs were formed only when benzenethiol was used as the nucleophile (Entries 9 and 10).

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Techniques used: ^1H and ^{13}C NMR, IR, UV–VIS, mass spectroscopy, elemental analysis, TLC

References: 8

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References cited in this synopsis

1 T. A. Turney, in *The Chemistry of Quinonoid Compounds*, ed. S. Patai, Wiley, New York, 1974, ch. 16; H. N. C. Wong, T. L. Chan and T. Y. Luh, in *The Chemistry of Quinonoid Compounds*, ed. S. Patai and Z. Rappoport, Wiley, London, 1988, ch. 26.
2 L. T. Scott, M. D. Rozeboom, K. N. Houk, T. Fukunaga, H. J. Lindner and K. Hafner, *J. Am. Chem. Soc.*, 1980, **102**, 5169.
3 L. T. Scott, in *The Chemistry of Quinonoid Compounds*, ed. S. Patai and Z. Rappoport, Wiley, London, 1988, ch. 24.
5 T. Nozoe and H. Takeshita, *Bull. Chem. Soc. Jpn.*, 1996, **69**, 1149.
6 T. Nozoe, H. Wakabayashi, K. Shindo, T. Kurihara, S. Ishikawa and M. Kageyama, *Chem. Lett.*, 1995, 25.
7 T. Nozoe, H. Wakabayashi, K. Shindo and S. Ishikawa, *Chem. Lett.*, 1995, 27.
8 J. Palou, *Chem. Soc. Rev.*, 1994, 357.