Efficient Synthesis of *peri*-Hydroxylated 9,10-Anthracenedione Ethers via Alkylation of Cesium Phenolates

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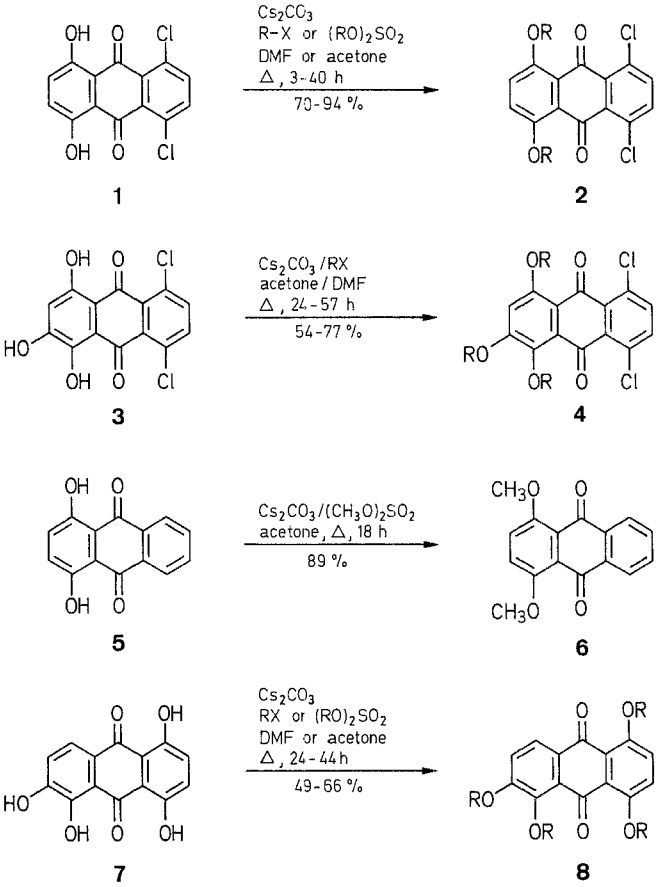
A comparison of the reaction of the potassium and cesium phenolates of a series of *peri*-hydroxylated 9,10-anthracenediones with a range of alkylating agents is described. Cesium phenolates promote accelerated reaction rates, give higher product yields, and provide for the introduction of a wider range of alkyl groups.

During the course of research directed toward the preclinical development of the anthrapyrazoles, a novel class of highly active DNA-binding anticancer agents,[1] we required a general and high-yielding method for the synthesis of alkyl ethers of several *peri*-hydroxylated 9,10-anthracenedione precursors. Such ethers are generally more difficult to synthesize than standard phenolic ethers because of the delocalization of charge of the derived phenolate onto the quinone carbonyl function, resulting in lowered reactivity to alkylation. The classical method for their synthesis is via the alkylation of sodium or potassium phenolates[2] and this was generally suitable for most of our applications, especially ethers of 1,4-dichloro-5-hydroxy-9,10-anthracenedione[3] and 1,4-dichloro-5,8-dihydroxy-9,10-anthracenedione (**1**),[4] precursors for three anthrapyrazole clinical candidates.[5] However, extension of this methodology to the synthesis of hindered ethers of these substrates or simple ethers of more highly hydroxylated congeners was problematic.

In this paper we compare the reaction times and yields for a series of ethers derived from the alkylation of the potassium and cesium phenolates of *peri*-hydroxylated 9,10-anthracenediones **1**, **3**, **5** and **7**. Our interest in evaluating cesium phenolates was spurred by an earlier report which compared several Group I metal carboxylates in the preparation of medium- to large-ring macrocyclic lactones.[6] Superior yields were derived from cesium salts. This was attributed to the greater polarizability and the reduced solvation of the cesium cation, which stems from its low charge-to-surface area ratio. By analogy, we reasoned that for our quinone substrates, cesium phenolates would be more reactive than potassium phenolates.

The ethers **2**, **4**, **6** and **8** that we synthesized are listed in the Table together with their physical and spectral data. The data show that the alkylation of cesium phenolates with a wide range of alkyl halides or dialkyl sulfates resulted in a marked reduction of reaction times and gave product yields that were comparable to or better than those for corresponding potassium salts. This was especially apparent for the trihydroxylated substrate **3** and tetrahydroxylated substrate **7** (quinalizarin) in which the potassium salts either reacted sluggishly or not at all with simple alkylating agents. Noteworthy also is the ease of synthesis of isopropyl ethers **2b**, and **4b** via cesium phenolates and the marked effect of solvent on both reaction time and yield of **2b** and **2d**. In general we found acetone to be a preferred solvent for the dihydroxylated substrates **1** and **5** and the acetone/dimethylformamide combination for the more highly hydroxylated substrates **3** and **7**. One exception to this was the permethylation of quinalizarin (**7**) in which product **8a** was obtained in modest yield only in acetone. In the synthesis of diisopropyl ether **2b**, the use of dimethylformamide alone resulted in the shortest reaction time, but with a slight reduction in yield.



	R		R
2a	CH_3O	**4a**	$PhCH_2O$
2b	$i\text{-}C_3H_7O$	**4b**	$i\text{-}C_3H_7O$
2c	$PhCH_2O$	**6**	CH_3O
2d	$2,5\text{-}Me_2C_6H_3CH_2O$	**8a**	CH_3O
2e	$2,4,6\text{-}Me_3C_6H_2CH_2O$	**8b**	$PhCH_2O$

Several attempted alkylations of cesium phenolates of related 9,10-anthracenediones were unsuccessful, giving only recovered starting materials. Notable in this regard was the attempted alkylation of **1** with *tert*-butyl chloride in dimethylformamide, 1,2,4-trihydroxy-9,10-anthracenedione (purpurin) with dibromomethane in acetone/dimethylformamide, and 1,5-dihydroxy-4,8-dinitro-9,10-anthracenedione[7] with benzyl bromide in acetone/dimethylformamide.

In summary, we have compared the alkylation of the potassium and cesium phenolates of a number of *peri*-hydroxylated 9,10-anthracenediones, and find that the latter promote accelerated

Table. Comparison of Alkylation of Potassium and Cesium Phenolates of *peri*-Hydroxylated 9,10-Anthracenediones

Starting Material	Reaction Conditions				Product	Yield[c] (%)	mp (°C)[d] (solvent)	Molecular Formula[e]	IR (KBr)[f] ν (cm^{-1})	^{1}H-NMR[g] δ, J (Hz)
	Alkylating Agent	Base	Solvent[a,b]	Time (h)						
1	$(CH_3O)_2SO_2$	K_2CO_3	Acetone	64	**2a**	84	320–325[h]	313.5[8]	–[i]	–[i]
		Cs_2CO_3	Acetone	15		94	330[h]			
			Acetone	40		70	310–320[h] (aq. H_2SO_4)			
1	*i*-PrI	K_2CO_3	Acetone/DMF	–[j]	**2b**	–[j]		$C_{20}H_{18}Cl_2O_4$ (393.3)	2979, 1684, 1590, 1562, 1473, 1381, 1265, 1212, 1136, 1107	1.37 (d, 12H, J = 6); 4.48 (septet, 2H, J = 6); 7.18 (s, 2H); 7.50 (s, 2H)
			DMF	> 30		< 20				
		Cs_2CO_3	Acetone	> 120		< 20				
			Acetonitrile	–[j]		–[j]				
			DMF	3		72	151–153			
			Acetone/DMF	18		83	155–156 (2-propanol)[k]			
1	$PhCH_2Br$	K_2CO_3	Acetone	120	**2c**	79	190–194	$C_{28}H_{18}Cl_2O_4$ (489.4)	–[i]	–[i]
		Cs_2CO_3	Acetone	22		86	187–190 (DMF)			
1	2,5-$Me_2C_6H_3CH_2Cl$	K_2CO_3	Acetone	–[j]	**2d**	–[j]		$C_{32}H_{26}Cl_2O_4$ (545.5)	1692, 1592, 1574, 1458, 1291, 1264, 1208, 1135, 1049	2.34 (s, 1, 12H); 5.17 (s, 4H); 7.07–7.08 (m, 4H); 7.19 (s, 2H); 7.37 (s, 2H); 7.55 (s, 2H)
			Acetone/DMF	27		60	183–187			
		Cs_2CO_3	Acetone/DMF	26		78	198–202 (EtOAc)			
1	2,4,6-$Me_3C_6H_2CH_2Cl$	K_2CO_3	Acetone/DMF	27	**2e**	81	259–261	$C_{34}H_{30}Cl_2O_4$ (573.5)	1692, 1615, 1572, 1472, 1415, 1381, 1264, 1205, 1133, 1015	2.03 (s, 6H); 2.13 (s, 12H); 4.88 (s, 4H); 6.63 (s, 4H); 7.09 (s, 2H); 7.28 (s, 2H)
		Cs_2CO_3	Acetone/DMF	24		84	257–263 (MeOH)[k]			
3	$PhCH_2Br$	K_2CO_3	Acetone/DMF[l]	72	**4a**	52	171–175	$C_{35}H_{24}Cl_2O_5$ (595.5)	1682, 1672, 1580, 1568, 1498, 1455, 1340, 1210, 1140, 1040	5.09 (s, 2H); 5.15 (s, 2H); 5.20 (s, 2H); 7.22–7.58 (m, 18H)
		Cs_2CO_3	Acetone/DMF	24		77	171–174 (EtOAc)			
3	*i*-PrI	Cs_2CO_3	Acetone/DMF	57	**4b**	54	141–142 (cyclohexane)[k]	$C_{23}H_{24}Cl_2O_5$ (451.4)	2985, 1687, 1584, 1559, 1475, 1377, 1367, 1302, 1201, 1106	1.30–1.44 (m, 18H); 4.32–4.77 (m, 3H); 6.71 (s, 1H); 7.51 (s, 2H)
5	$(CH_3O)_2SO_2$	K_2CO_3	Acetone	72	**6**	95	169–172	170–171[10]	3000, 1670, 1590, 1568, 1480, 1433, 1328, 1268, 1250, 1185	4.01 (s, 6H); 7.36 (s, 2H); 7.72 (dd, 2H, J = 3.3, 5.8); 8.18 (dd, 2H, J = 3.3, 5.8)
		Cs_2CO_3	Acetone	18		89	169–171 (2-propanol)[k]			
7	$(CH_3O)_2SO_2$	K_2CO_3[m]	Acetone/DMF[n]	192	**8a**	–[o]	198–200 (toluene)	202[12]	2944, 1675, 1575, 1480, 1408, 1328, 1269, 1242, 1197, 1060	3.94 (s, 9H); 4.00 (s, 3H); 7.15 (d, 1H, J = 8.6); 7.20–7.28 (m, 2H); 7.91 (d, 1H, J = 8.6)
		Cs_2CO_3	Acetone	44		49[p]				
			Acetone/DMF	> 168		–[q]				
7	$PhCH_2Br$	Cs_2CO_3	Acetone/DMF	24	**8b**	66	160–161 (2-propanol/acetone, 2 : 1)[k]	$C_{42}H_{32}O_6$ (632.7)	1675, 1575, 1498, 1450, 1410, 1380, 1323, 1270, 1238, 1058	5.19 (s, 2H); 5.23 (s, 6H); 7.20–7.71 (m, 23H); 7.95 (d, 1H, J = 8.6)

[a] All reactions run at reflux, except at 70 °C for DMF and MeCN as solvent.
[b] Acetone/DMF (3 : 1), unless otherwise noted.
[c] Yield of isolated pure product.
[d] Uncorrected.
[e] Satisfactory microanalyses obtained: C, H, Cl ± 0.4.
[f] Recorded on Digilab FTS-14 or Nicolet MX-1 spectrometers.
[g] Recorded on Varian XL-200 spectrometer in $CDCl_3$ except for 5% DMSO-d_6 in $CDCl_3$ for **2e**.
[h] With decomposition.
[i] Spectrum identical to that previously recorded.[9]
[j] No reaction; presence of starting material only after 24–48 h reaction time.
[k] With trituration.
[l] Acetone/DMF (2 : 1).
[m] Utilized 4.5 equivalents.
[n] Acetone/DMF (4 : 1).
[o] 2-Methoxy-1,5,8-trihydroxy-9,10-anthracenedione[11] isolated in 59% yield.
[p] Product slowly decomposes under reaction conditions.
[q] Complex mixture containing trace of **8a**.

reaction rates, generally give higher product yields, and provide for the introduction of a wider range of alkyl groups. The application of this methodology to the synthesis of ethers of polyhydroxylated benzoic acids will be the subject of a future report.

1,4-Dichloro-5,8-bis(1-methylethoxy)-9,10-anthracenedione (2b); Typical Procedure:

A three-necked flask equipped with an overhead stirrer, reflux condenser, and nitrogen inlet is charged with 1,4-dichloro-5,8-dihydroxy-9,10-anthracenedione (**1**;[4] 6.2 g, 20 mmol), 2-iodopropane (6 mL, 60 mmol), acetone (80 mL), and dimethylformamide (26 mL). The vigorously stirring suspension is purged with N_2 for 30 min, treated with anhydrous Cs_2CO_3 (29.4 g, 90 mmol), and refluxed for 20 h. The hot olive-colored suspension is filtered over Celite and the pad is thoroughly rinsed with acetone. The filtrate is concentrated to give a dark solid that is triturated in boiling petroleum ether. After standing at 5 °C overnight, the solids are collected by filtration to afford **2b**; yield: 6.53 g (83%); mp 155–156 °C (Table).

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