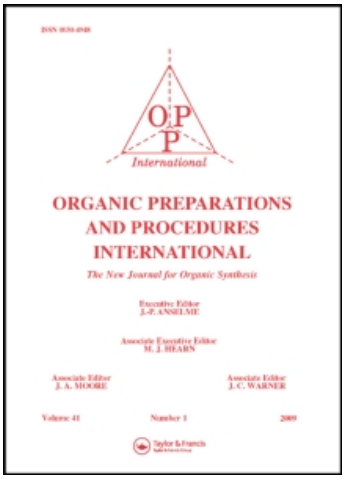

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PHASE-TRANSFER CATALYZED ALKYLATION OF HYDROXY 9,10-ANTHRAQUINONES

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11. D. Dumez, J. M. Armstrong, M. Allely, L. Patmore and P. Ferrandon, *J. Cardiovasc. Pharm.*, **14**, 184 (1989).

12. H. Frances, *Pharmacol. Biochem. Ber.*, **31**, 37 (1988).

13. A. Sacha, *Acta Polonia Pharm.*, **37**, 511(1980); *Chem. Abs.*, **95**, 150586w (1981).

14. T. Matsuda, K. Saito, A. Baba, H. Aona, A. Tobe, Y. H. Seong, T. Kanda and H. Iwata, *Eur. J. Pharmacol.*, **170**, 75 (1989).

15. I. V. Komissarov, N. A. Kharin, V. N. Voschula, S. V. Tolkunov, A.V. Kibalyni, Y. A. Nikolyukin, O. E. Obraztsova, A. N. Talalayenko and V. I. Dulenko, *Khimika-farmatsevtichesk II. Zh.*, **25**, 40 (1991); *Chem. Abs.*,**115**, 105837z (1982).

16. H. Fukushi, H. Mabuchi, K. Itah, Z. Tereshita, K. Nishikawa and H. Sugihara, *Chem. Pharm. Bull. Jpn*, **42**, 541 (1994).

17. H. Fukushi, H. Mabuchi, Z. Terashita, K. Nishikawa and H. Sugihara, *ibid.*, **42**, 551 (1994).

18. J. Seginko, P. Dobrocky and B. Caganova, *Pharmazie*, **50**, 368 (1995).

19. L. M. Gross, D. H. Blank and W. M. Welch, *J. Org. Chem.*, **58**, 2104 (1993).

20. E. B. Merkushev, *Synthesis*, 923 (**1988**).

21. Z. Wu and J. S. Moore, *Tetrahedron Lett.*, **35**, 5539 (1994).

22. J. S. Moore, E. J. Weinstein and Z. Wu, *ibid.*, **32**, 2465 (1991).

23. A. Disli and Y. Yildirir, *Org. Prep. Proced. Int.*, **30**, 349 (1998).

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PHASE-TRANSFER CATALYZED ALKYLATION OF HYDROXY 9,10-ANTHRAQUINONES

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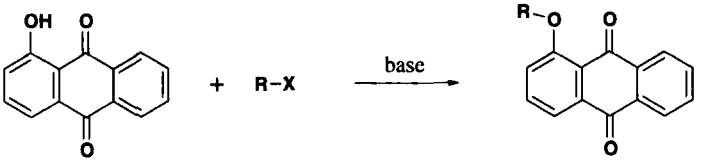
Substituted 9,10-anthraquinones have wide applications as dyes and in electron-transfer studies. Reduction of these compounds provides the corresponding substituted anthracenes[1] which also find numerous uses, for example as fluorescent probes. We were interested in 1-alkoxy and 1,8-

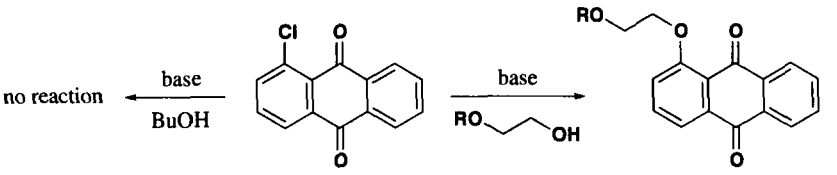
dialkoxy derivatives as intermediates in the synthesis of non-linear optical chromophores.[2,3] While examples of these aromatic ethers are known in the literature, their synthesis is problematic. Although the alkylation of 1-hydroxy-9,10-anthraquinones and related compounds seems a simple reaction, simple alkyl halides surprisingly fail to react under standard conditions (K_2CO_3, acetone or MEK reflux); only very aggressive alkylating reagents such as methyl sulfate were effective. Primary tosylates can be used under forcing conditions, but in our experience, harsh conditions lead to substantial decomposition with attendant difficulties in purifying the desired ether.



1 2

2a) R = CH_3 **2b)** R = $CH(CH_3)_2$ **2c)** R = $(CH_2)_3CH_3$
2d) R = $(CH_2)_5CH_3$ **2e)** R = $CH_2C_6H_5$ **2f)** R = $(CH_2)_{17}CH_3$

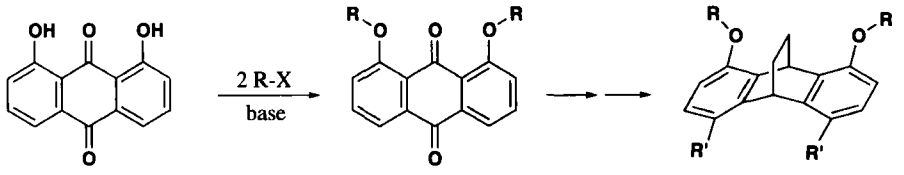
This problem was recognized by Gokel *et al.*[4-6] who disclosed that this kind of structure could be synthesized by aromatic nucleophilic substitution on the readily available 1-chloroanthracenes. However, this reaction only works in the special case of "podand" alkoxides, and fails completely for simple alkoxides. Although Gokel *et al.* mention that the podands can be further displaced by other alkoxides, in our hands, this procedure did not give satisfactory yields.



R = CH_3 or $CH_3OCH_2CH_2O$

As part of an effort to prepare dibenzobarrelane derivatives for nonlinear optical applications, we required 1,8-dialkoxyanthraquinones as intermediates.[2,3] Inasmuch as this scheme necessitated *two* difficult alkylations of 1,8-dihydroxy-9,10-anthraquinone (**3**), an improved synthetic method was necessary. Gokel *et al.* had suggested that the poor nucleophilicity of 1-hydroxy-9,10-anthraquinones could be explained by ion pairing effects. We reasoned that tight ion pairing might be averted through the use of organic counter ions such as tetraalkylammonium ions. Such species are conveniently generated using phase-transfer catalysis, a common procedure to enhance reaction rates of anionic species.[7,8] The resulting looser ion pair should be especially reactive when free of a solvent shell. This paper describes a simple phase-transfer catalyzed procedure for accomplishing this alkylation, which works well for primary alkyl bromides and iodides.

We discovered that hydroxy 9,10-anthraquinones can be alkylated readily with simple primary halides using a two-phase procedure and a phase-transfer catalyst. For example, reaction of 1,8-dihydroxy-9,10-anthraquinone (**3**) with butyl iodide in the presence of 0.05 eq of tetrabutyl-



3 4

4a) R = $(CH_2)_3CH_3$ **4b**) R = $(CH_2)_5CH_3$
4c) R = $(CH_2)_2OC(CH_3)_3$

ammonium bromide in a two-phase mixture of aqueous potassium hydroxide and chlorobenzene gave after 40 h of reflux an 86% yield of pure 1,8-dibutoxy-9,10-anthraquinone (**4b**). In contrast, the same product could be obtained in 50% yield by refluxing the bisphenol with excess butyl tosylate and potassium carbonate in *o*-dichlorobenzene *for 6 days,* and then removing the solvent by steam distillation. Extensive purification of the crude product by column chromatography was required when using the latter method. In addition, it was necessary to synthesize and use butyl tosylate because butyl iodide reacts too slowly even under these vigorous conditions.

The phase-transfer procedure is especially convenient. One simply stirs mechanically a heterogeneous mixture of the hydroxy anthraquinone, alkyl halide, quaternary ammonium salt, aqueous potassium hydroxide, and chlorobenzene while heating the mixture at gentle reflux. The reactants become a two phase fluid after a short time. Progress of the reaction can be monitored by observing the disappearance of the deep purple or red color of the phenoxide, and the appearance of the light yellow color of the product. Typical reaction times are 12-40 h. The product is isolated by cooling the reaction mixture, and then separating and concentrating the organic layer. The yields (calculated assuming pure product) and approximate purities (estimated by GC or HPLC) of the products are shown in Table 1.

TABLE 1. Phase-Transfer Catalyzed Alkylation

Phenol	R	X	Product	Yield[a] (%)	Purity[a,b] (%)
1	CH_3	I	**2a**	79	88
1	$(CH_2)_3CH_3$	I	**2b**	80	100
1	$CH(CH_3)_2$	I	**2c**	36	51
1	$(CH_2)_5CH_3$	Cl	**2d**	27	53
1	$(CH_2)_5CH_3$	Br	**2d**	58	96
1	$(CH_2)_5CH_3$	I	**2d**	71	97
1	$CH_2C_6H_5$	Br	**2e**	9	94
1	$(CH_2)_{17}CH_3$	I	**2f**	91	93
3	$(CH_2)_5CH_3$	I	**4a**	86	98
3	$(CH_2)_5CH_3$	I	**4b**	53	84
3	$(CH_2)_2OC(CH_3)_3$	Br	**4c**	87	94

a) After one crystallization of the crude product (see Table 3 for solvents). b) Estimated by GC or HPLC.

In most cases, the main impurity (as determined by HPLC/MS analysis) was unreacted starting phenol or, in the case of the bisphenol, **3**, monoalkylated material. One might anticipate that both the yields and product assays might be further improved by adjustment of the reaction conditions.

Examination of the data demonstrates that the phase-transfer procedure gives good results for ordinary primary iodides and bromides; the one exception is benzyl bromide, which inexplicably gave a low yield. The title reaction worked poorly in the cases of the one secondary iodide and one primary chloride examined, although probably yields in the latter case might be improved by iodide catalysis.

2-Hydroxyethyl aromatic ethers are particularly interesting compounds because they can be used to synthesize substituted derivatives including polymers. However, the phase-transfer catalyzed alkylation procedure described above does not work with 2-bromoethanol. When this halide was reacted with **3** under the title protocol, base was consumed but no product was isolated. Presumably, 2-bromoethanol reacts rapidly with base to form ethylene oxide, which then distills out of the reaction vessel. We found that protection of the alcohol with the *t*-butyl group made it possible to carry out the desired alkylation in a simple procedure. Thus, 2-bromoethanol was dissolved in chlorobenzene, a small amount of acidic ion exchange resin was added and isobutylene was bubbled through the stirred solution until all of the hydroxy groups had reacted. The resulting solution was filtered and used directly in the two-phase alkylation procedure with excellent results. The *t*-butyl protecting group can be cleaved readily with acid.

In conclusion, phase-transfer catalysis permits alkylation reactions of 1,8-dihydroxy-9,10-anthraquinone (**1**) and 1-hydroxy-9,10-anthraquinone (**3**) in an expeditious procedure. This method should be applicable to other isomers of hydroxy-anthraquinones, and to phenols, in general.

EXPERIMENTAL SECTION

^{1}H NMR spectra were recorded on a Varian VXR-300S spectrometer (300 MHz) in $CDCl_3$ solution, using the signal from the residual solvent protons as reference (δ 7.26). Field desorption-mass spectra (FD-MS) were obtained on a Varian MAT Model 731 instrument. Note that FD-MS usually detects the molecular ion (M^+) or protonated molecular ion (M^++1), with little or no fragmentation. The purity of the crude products was estimated by GC or HPLC analyses, and are reported in Table 1 as area percentages for the peaks observed. The HPLC instrument was a Hewlett Packard 1090 DR5, using a Hypersil BDS C-18, 4.6 x 150 mm column. A mixed solvent gradient elution technique was used, with Solvent A consisting of 50/50 (v/v) acetonitrile/2-propanol and Solvent B consisting of 0.01 M aqueous ammonium acetate. The gradient was from 10% (v/v) Solvent A/90% Solvent B to 100% Solvent A over 25 min, followed by 10 min of 100% Solvent A. The flow rate was 1.5 mL/min, and detection was by absorbance at 254 nm. The GC instrument was a Hewlett-Packard Model 5880, using a 15 m DB-5 capillary column, and a flame ionization detector. GC parameters were as follows: injection port: 225°; detector 300°; temperature ramp: 40° (hold for 1 min) to 320° at 20°/min. Elemental analyses were performed by Oneida Research Services, Inc. Elemental analyses for carbon were uniformly below theoretical values, presumably because of difficulty in fully combusting these highly aromatic fused ring compounds.

TABLE 2. Spectroscopic Data of **2a-f** and **4a-c**

Cmpd	^{1}H NMR (δ)			FD-MS
	Anthraquinone-H	Ar-OCH	Other CH	(m/e)
2a	7.35 (d, *J* = 8.6, 1 H) 7.75 (m, 3 H) 7.98 (d, *J* = 7.7, 1 H) 8.25 (m, 2 H)	4.06 (s, 3 H)		238
2b	7.32 (d, *J* = 8.6, 1 H) 7.7 (m, 3 H) 7.95 (d, *J* = 7.7, 1 H) 8.25 (m, 2 H)	4.74 (hept, *J* = 6.0, 1 H)	1.50 (d, *J* = 6.0, 6 H)	266
2c	7.32 (d, *J* = 8.4, 1 H) 7.7 (m, 3 H) 7.92 (d, *J* = 7.6, 1 H) 8.25 (m, 2 H)	4.16 (t, *J* = 6.5, 2 H)	1.02 (t, *J* = 7.4, 3 H) 1.60 (m, 2 H) 1.94 (m, 2H)	280
2d	7.32 (d, *J* = 8.4, 1 H) 7.7 (m, 3 H) 7.92 (d, *J* = 7.4, 1 H) 8.25 (m, 2 H)	4.16 (t, *J* = 6.7, 2 H)	0.93 (t, *J* = 6.9, 3 H) 1.4 (m, 4 H) 1.6 (m, 2 H) 1.95 (m, 2H)	308
2e	7.35 (d, *J* = 8.1, 1 H) 7.75 (m, 3 H) 7.98 (d, *J* = 7.7, 1 H) 8.25 (m, 2 H)	5.35 (s, 2 H)	7.4 (m, 3H) 7.62 (d, *J* = 7.4, 2 H)	314
2f	7.33 (d, *J* = 8.4, 1 H) 7.75 (m, 3 H) 7.95 (d, *J* = 7.7, 1 H) 8.25 (m, 2 H)	4.18 (*J* = 6.7, 2 H)	0.88 (t, *J* = 6.9, 3 H) 1.3 (m, 28 H) 1.6 (m, 2 H) 1.98 (m, 2H)	476
4a	7.25 (d, *J* = 8.0, 2 H) 7.56 (t, *J* = 8.0, 2 H) 7.78 (d, *J* = 7.6, 2 H)	4.11 (t, *J* = 6.4, 4 H)	0.99 (t, *J* = 7.4, 6 H) 1.6 (m, 4 H) 1.9 (m 4 H)	353
4b	7.26 (d, *J* = 8.5, 2 H) 7.57 (t, *J* = 8.0, 2 H) 7.80 (d, *J* = 7.7, 2 H)	4.12 (t, *J* = 6.6, 4 H)	0.92 (t, *J* = 6.9, 6 H) 1.38 (m, 8 H) 1.58 (m, 4 H) 1.92 (m 4 H)	408
4c	7.32 (d, *J* = 7.2, 2 H) 7.54 (t, *J* = 8.2, 2 H) 7.78 (d, *J* = 8.2, 2 H)	4.21 (t, *J* = 5.6, 4 H)	1.23 (s, 18 H) 3.81 (t, *J* = 5.6, 4 H)	440

1-Butoxy-9,10-anthraquinone (2c). Typical Procedure.- A mixture of 10.0 g (44.5 mmol) of 1-hydroxy-9,10-anthraquinone (**1**), 16.4 g (89.2 mmol) of *n*-butyl iodide, 1.4 g (4.4 mmol) of tetrabutylammonium bromide, 100 mL of chlorobenzene, and a solution of 5.0 g of potassium hydroxide dissolved in 100 mL of water was stirred mechanically at reflux for 18 h, after which time the initial red color had turned to yellow. The mixture was cooled to 23°, and 200 mL of ether was

added. The organic layer was separated, washed three times with water, dried ($MgSO_4$), and filtered. The solvent was stripped to deposit a yellow solid which was recrystallized from ethyl alcohol to give 10.0 g (80%) of **2c**.

1,8-*bis*(2-*tert*-Butoxyethoxy)-9,10-anthraquinone (4c). Typical Procedure.- A mixture of 235 g (1.88 mol) of 2-bromoethanol , 500 mL of chlorobenzene, and 10 g of Amberlyst-15 acidic ion exchange resin was stirred at room temperature and treated with isobutylene *via* a fritted gas dispersion tube. The progress of the reaction was checked by ^1H NMR on aliquots of the solution. Conversion was complete in 11 h. The solution was filtered and then mixed with 200 g (0.83 mol) of 1,8-dihydroxy-9,10-anthraquinone (**3**), 26.8 g (0.083 mol) of tetrabutylammonium bromide, 20 g (0.12 mol) of potassium iodide, and a solution of 337 g (approx. 5 mol) of potassium hydroxide in 1500 mL of water. The resulting dark purple heterogeneous mixture was stirred mechanically and heated at reflux for 24 h, after which time a pale purple color persisted. An additional 88 g (0.70 mol) of 2-bromoethanol was treated with isobutylene as above, and the resulting bromoethyl *t*-butyl ether was added to the reaction mixture. Reflux was continued for 24 h, and the mixture turned light brown. The mixture was cooled to room temperature and extracted with dichloromethane. Addition of a little ammonium chloride to the extracting mixtures helped to promote phase separation. The combined extracts were dried and concentrated, and the residue was recrystallized from 30:70 (v:v) toluene/heptane, employing a small amount of silica gel as decolorant. The product (264 g, 87%) was obtained as yellow crystals.

TABLE 3. Mps and Combustion Analysis Data of **2a-f** and **4a-c**

Cmpd	mp[a] (°C)	lit mp. (°C)	Elemental analysis C	(Found) H
2a	169-170[b]	169,[9] 171,[10] 175-176[11]	75.62 (75.24)	4.23 (4.31)
2b	167-168[c]		76.68 (76.27)	5.30 (5.34)
2c	117-118[d]	116-6.5[6]	77.12 (77.01)	5.75 (5.78)
2d	99-100		77.90 (77.55)	6.54 (6.46)
2e	164-166	177-8,[6] 168-70[11]	80.24 (79.86)	4.49 (4.62)
2f	100-101		80.63 (80.39)	9.30 (9.16)
4a	120-122		74.98 (74.61)	6.86 (6.86)
4b	103-104		76.44 (76.15)	7.89 (7.77)
4c	124-125[e]		70.89 (70.77)	7.32 (7.22)

a) Purified by two recrystallizations from isopropanol unless otherwise noted. b) Two recrystallizations from 75:25 isopropanol/THF. c) Recrystallized from isopropanol, chromatographed on SiO_2 (CH_2Cl_2), recrystallized from isopropanol. d) Recrystallized from ethanol and then from isopropanol. e) Recrystallized from 30:70 toluene/heptane and then from isopropanol.

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REFERENCES

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1. T. R. Criswell and B. H. Klanderman, *J. Org. Chem.*, **39**, 770 (1974).

2. D. R. Robello, C. I. Martinez, A. B. Pangborn, J. Shi, E. J. Urankar and C. S. Willand, *Polym. Prepr.*, **35**, 124 (1994).

3. C. S. Willand, D. R. Robello, E. J. Urankar and A. Ulman, *US Patent* 5,501,821 (1996). This patent has not been indexed by Chem. Abstr.

4. T. Lu, H. K. Yoo, H. Zhang, S. Bott, J. L. Atwood, L. Echegoyen and G. W. Gokel, *J. Org. Chem.*, **55**, 2269 (1990).

5. H. K. Yoo, D. M. Davis, Z. Chen, L. Echegoyen and G. W. Gokel, *Tetrahedron Lett.*, **31**, 55 (1990).

6. J. P. Fang, T. Lu, H. Kim, I. Delgado, P. Geoffroy, J. L. Atwood and G. W. Gokel, *J. Org. Chem.*, **56**, 7059 (1991).

7. E. V. Dehmlow and S. S. Dehmlow, *"Phase-transfer Catalysis"*, Vol. 11, Verlag Chemie, Weinheim, West Germany, 1980.

8. M. Halpern, *"Phase-transfer Catalysis, Mechanisms and Syntheses"*, vol. 659, American Chemical Society, Washington, DC, 1997.

9. M. Fujita and T. Furuya, *Chem. Pharm. Bull. Jpn*, **9**, 967 (1961); Chem. Abstr., **57**, 1488d (1962).

10. M. M. Shemyakin, M. N. Kolosov, Y. A. Arbuzov, M. G. Karapetyan, E. S. Chaman and A. A. Onishchenko, *Zhur. Obshchei Khim.*, **29**, 1831 (1959); Chem. Abstr., **54**, 8753i (1960).

11. D. J. Dodsworth, M. P. Calcagno, E. U. Ehrmann, B. Devadas and P. G. Sammes, *J. Chem. Soc., Perkin Trans. 1*, 2120 (**1981**).

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