Selectivity in Alkylation of Phenols with 1-Bromo-3-chloropropane Using Phase-Transfer Catalysis

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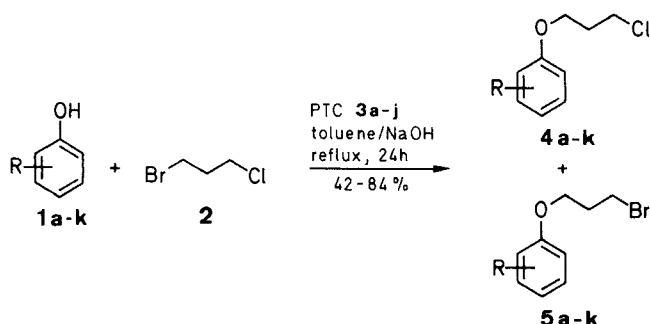
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Dedicated to Prof. H.J. Bestmann on the occasion of his 65th birthday

The use of various phase-transfer catalysts in the alkylation of phenol and substituted phenols with 1-bromo-3-chloropropane was investigated. When a quarternary ammonium salt of the general formula $R'_4N^+ X^-$, where R' = alkyl with a minimum chain length of 4 was used, a mixture of 1-aryloxy-3-chloropropane and 1-aryloxy-3-bromopropane resulted. The effect of counterion, added potassium bromide, and catalysts other than quarternary ammonium salts were assessed for the halopropylation of 2,5-dimethylphenol.

A three-carbon chain linked between a phenol and a hetero-substituent is a structural element of frequent use in drug synthesis. 1-Aryloxy-3-halopropanes are normally synthesized by alkylation of phenols with 1,3-dihalopropanes, with potassium carbonate or sodium hydroxide as the base, with a ketone as the solvent.[1] The use of 1-bromo-3-chloropropane (2) avoids the danger of dialkylation and usually yields 1-aryloxy-3-chloropropanes as the major product. The preparation of the corresponding bromo-derivatives would enable or accelerate the reaction using unreactive substrates. Formation of 1-aryloxy-3-bromopropanes by haloalkylation of phenols with 2 has been reported but without experimental details.[2]

We have investigated the haloalkylation of phenols (1) by 1-bromo-3-chloropropane (2) using phase transfer catalysis. Initially we examined the use of benzyltriethylammonium bromide (3a) as catalyst in the haloalkylation of 2,5-dimethylphenol (1b), which gave the expected chloro-compound 4b in 71% yield. We then examined the optimization of this reaction using other catalysts. When tetrabutylammonium bromide (3b) was used as the catalyst, surprisingly we obtained a mixture of chloro/bromo-compounds 4b/5b in a ratio of approximately 2:1. This finding was unexpected, as when 3b

was used in the alkylation of purines with 2, the sole products were the chloropropyl compounds.[3] The reaction of 2 with cyanide using Aliquat 336 also gave only the chloro compound.[4] Such remarkable effects of phase-transfer catalysts have already been cited in the literature for other types of reactions.[5-10] Hence the influence of phase transfer catalysts (PTC) on the alkylation of phenols with 2 was investigated further.

In the first series of experiments, the results of benzyltriethylammonium bromide (3a) and tetrabutylammonium bromide (3b) as catalysts in the haloalkylation of substituted phenols 1a-k with 1-bromo-3-chloropropane (2) are compared. The results are shown in Table 1.

Table 1. Halopropylation of Phenol Derivatives 1 with 1-Bromo-3-chloropropane (2)

Phenol	PTC	Yield (%) 4 + 5	Ratio 4/5	mp (°C) or bp (°C)/Torr	Molecular Formula[a] or Lit. Data[b]
1a	3a	71	24.9	133–136/15	127–129/13[11]
	3b	80	1.9		
1b	3a	71	24.6	150–152/15	145–148/10[12]
	3b	75	1.9		
1c	3a	73	24.6	108–110/0.01	106/0.017[13]
	3b	80	2.4		
1d	3a	73	34.7	125–130/15	$C_9H_{10}Cl_2O$
	3b	84	1.9		(205.1)
1e	3a	76	30.3	140–142/15	130–131/10[14]
	3b	79	1.9		
1f	3a	68	46.6	130–134/12	oil[15]
	3b	76	1.9		
1g	3a	71	48.0	127–131/11	$C_9H_{10}ClNO_3$
	3b	81	1.8		(215.6)
1h	3a	66	79.1	35–37	37–39[15]
	3b	84	2.5		
1i	3a	71	29.4	108–110/0.01	105/0.02[13]
	3b	73	1.8		
1j	3a	60	44.3	90–93/0.01	95–103/0.06[16]
	3b	78	3.3		
1k	3a	41	100	97–100	$C_{14}H_{15}ClO_3$
	3b	79	1.9		(266.7)

[a] Satisfactory microanalysis obtained: C ±0.25, H ±0.40, N ±0.30, Cl ±0.30.

[b] Data given for the chlorides 4.

1	R	1	R	1	R
a	H	g	3-O$_2$N	k	
b	2,5-Me$_2$	h	4-O$_2$N		
c	2-MeO	i	4-MeO		
d	2-Cl	j	2,6-Me$_2$		
e	4-Me				
f	3-Me				

In all cases 3a yielded chloro compounds 4a–k, with only minor contamination by bromo compounds 5a–k. However, 3b uniformly rendered 4 and 5 in a ratio of 2:1, with the exception of 1j, which produced a ratio of 3.3:1.

In a second series of experiments, we studied the influence of other phase transfer catalysts on the haloalkylation of 2,5-dimethylphenol (1b). The results are shown in Table 2.

Table 2. Influence of Phase-Transfer Catalyst on the Ratio of Products **4b/5b**

PTC	3	Yield (%) 4b + 5b	Ratio 4b/5b
Et₃BnN⁺Br⁻	a	71	24.6
Bn₄N⁺Br⁻	b	75	1.9
TDA-1	c	62	30.6
Et₄N⁺Cl⁻	d	60	26.2
BnBu₃N⁺Cl⁻	e	76	2.5
Me₃BnN⁺Cl⁻	f	58	25.6
Bu₄N⁺HSO₄⁻	g	72	2.1
(n-C₈H₁₇)₄N⁺Br⁻	h	63	2.1
(n-C₆H₁₃)₄N⁺Br⁻	i	56	2.3
18-crown-6	j	64	33.7

Table 3. Influence of the Anion of the PTC in the Ratio of Product **4b/5b** Formed

PTC	R'₄N⁺X⁻		Yield (%) 4b + 5b	Ratio 4b/5b
	R'₄	X		
3a	BnEt₃	Br	71	24.6
3a	BnEt₃	Br	60ᵃ	22.1
3b	Bu₄	Br	75	1.9
3b	Bu₄	Br	61ᵃ	1.1
3k	BnEt₃	Cl	68	49.4
3l	Bu₄	Cl	71	2.4

ᵃ One equivalent of KBr added.

Table 4. ¹H-NMR Spectroscopic Data of 1-Aryloxy-3-halopropanes **4/5** Prepared

Product	¹H-NMR (CDCl₃/TMS)ᵃ δ, J(Hz)
4a/5a	7.3 (m, 2H), 6.9 (m, 3H), 4.1 (t, 2H, J = 7), 3.8/3.7 (2t, 2H, J = 7), 2.25/2.15 (2q, 2H, J = 7)
4b/5b	7.0 (d, 1H, J = 7), 6.6 (m, 2H), 4.05 (t, 2H, J = 7), 3.7/3.6 (2t, 2H, J = 7), 2.3 (s, 3H), 2.25 (q, 2H, J = 7), 2.1 (s, 3H)
4c/5c	6.9 (m, 4H), 4.05 (t, 2H, J = 7), 3.85 (t, 2H, J = 7), 3.8/3.7 (2s, 3H), 2.2/2.1 (2q, 2H, J = 7)
4d/5d	7.15 (m, 4H), 4.15 (t, 3H, J = 7), 3.8/3.7 (2t, 2H, J = 7), 2.3/2.2 (2t, 2H, J = 7)
4e/5e	7.1 (d, 2H, J = 8), 6.8 (d, 2H, J = 8), 4.05 (t, 2H, J = 7), 3.8/3.65 (2t, 2H, J = 7), 2.25 (s, 3H), 2.2/2.15 (2q, 2H, J = 7)
4f/5f	7.2 (t, 1H, J = 7), 6.7 (m, 3H), 4.05 (t, 2H, J = 7), 3.75/3.65 (2t, 2H, J = 7), 2.3 (s, 3H), 2.2/2.15 (2q, 2H, J = 7)
4g/5g	7.6 (m, 4H), 4.2 (t, 2H, J = 7), 3.8/3.7 (2t, 2H, J = 7), 2.25/2.2 (2q, 2H, J = 7)
4h/5h	8.2 (d, 2H, J = 8), 7.2 (d, 2H, J = 8), 4.2 (t, 2H, J = 7), 3.8/3.7 (2t, 2H, J = 7), 2.3/2.2 (2q, 2H, J = 7)
4i/5i	6.9 (s, 4H), 4.0 (t, 2H, J = 7), 3.8/3.65 (2t, 2H, J = 7), 3.7 (s, 3H)
4j/5j	7.0 (m, 3H), 3.9 (t, 2H, J = 7), 3.85/3.7 (2t, 2H, J = 7), 2.25 (s, 6H), 2.15 (m, 2H)
4k/5k	7.65 (m, 1H), 6.9 (m, 2H), 4.15 (t, 2H, J = 7), 3.8/3.7 (2t, 2H, J = 7), 2.3/2.1 (2s, 6H), 2.25/2.2 (2q, 2H, J = 7)

ᵃ Recorded on a Bruker AC 250 spectrometer.

On the basis of these results, it is possible to divide the catalysts **3** into two classes. Catalysts with sterically more hindered ammonium ions (entries **3b**, **3e**, **3g**, **3h**, **3i**) yield **4/5** in a ratio of roughly 2:1, whereas sterically less hindered ammonium ions (entries **3a**, **3d**, **3f**) and non-ionic phase-transfer catalysts like TDA-1 (tris[2-(2-methoxyethoxy)ethyl]amine) and 18-crown-6 produce ratios of nearly 25:1.

To examine the effect of the counterion, we compared **3a** and **3b** with their corresponding chlorides **3k** and **3l**. The results are shown in Table 3. The catalyst-anion exercises only minor influence on the ratio **4b/5b**. Chloride **3k** also produces nearly exclusively **4b**, as does bromide **3a**; chloride **3l** produces a mixture of **4b/5b** in approximately the same ratio as bromide **3b**.

As indicated in Table 3 excess bromide has a clear effect on the ratio **4/5**. With **3a** as catalyst the ratio increases only slightly, whereas with **3b** the ratio increases significantly. Therefore it can be concluded, in this case, that **5b** is produced from **4b**, and that the sterically more hindered catalyst **3b** is a better catalyst for the reaction, to give **4b** as the major product.

All reagents were of commercial grade. The phenols **1a–k** were purchased from Aldrich Chemical Co. The phase-transfer catalysts were purchased from Fluka Chemical Co. Reagent quality solvents were used without further purification. The ratios of **4/5** were determined by gas chromatography with an HP 5 capillary column (10 m) recorded on an HP 5890. The retention time of the bromides was determined by comparison with a sample, synthesized independently from the corresponding phenol and 1,3-dibromopropane using the same conditions outlined below in the general procedure.

1-Aryloxy-3-halopropanes 4/5; General Procedure:
A mixture of the phase-transfer catalyst **3a–l** (0.01 mol, 0.1 equiv), 2 M NaOH solution (50 mL), toluene (50 mL), 1-bromo-3-chloropropane (**2**; 10.8 mL, 0.11 mol, 1.1 equiv) and the phenol **1a–k** (0.1 mol, 1 equiv) is refluxed with vigorous stirring for 24 h. After cooling to r.t. the organic layer is separated and the aqueous layer is extracted with toluene (25 mL). The combined organic layers are washed till neutral with water, dried (Na₂SO₄) and evaporated to dryness. The compounds are purified by vacuum distillation with the exception of **4h/5h** and **4k/5k** which are recrystallized from hexane.

All compounds gave satisfactory ¹H-NMR spectra (Table 4).

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