SHORT PAPER

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Regioselective alkylation of anthrone, 5,5-dimethyl-3-isoxazolidinone and 4-methylquinolone by phase transfer catalysis†

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Anthrone (**1**) can be alkylated selectively to give O-, C,O- or C,C-substituted compounds **2**, **4**, or **5**, respectively. Similarly, 5,5-dimethyl-3-isoxazolidinone (**6**) and 4-methylquinolone (**9**) yield N- or O-derivatives **7** and **8** or **10** and **11**, respectively. The product ratios can be influenced strongly sometimes by use of different phase transfer catalysts, but the sensitivity of each reaction towards the catalysts is unique.

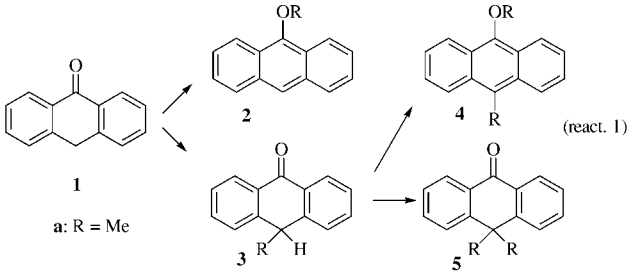
Keywords: anthrone, 5,5-dimethyl-3-isoxazolidinone, 4-methylquinoline, phase transfer catalyst

Influences of phase transfer catalyst (PTC) structure on regioselective alkylations of certain ambident anions have been reported before from our[1–6] and other groups (reviews[7–9]). These results can be summed up as follows: Sterically "accessible" onium cations (Q^+) and certain crown ether catalysts may direct alkylations to the "soft" end of the ambident anion, whereas large, highly delocalised cations may direct to the more electronegative atom of the anion. Other, more typical PTCs exhibited little selectivity. There were cases of unexpected special effects of singular catalysts as well as instances in which almost no catalyst influences were discernible. In this communication we present results on three more systems.

Anthrone (**1**) can be O- or C-alkylated in a first reaction step to give **2** or **3**, and **3** will result in O- and C-products in a second step (Scheme 1). Quantitative PTC O-alkylation of **1** was observed by Willner and Halpern[10] with 32 % aq. NaOH / CH_2Cl_2 / Me_2SO_4 / room temperature using benzyltriethylammonium chloride (TEBA) as catalyst. In contrast, similar conditions gave mostly C,C-dialkylation products (**5**) with allylic and propargylic bromides in the hands of Majumdar *et al.*[11]

Table 1 lists our results on the methylation of **1** with methyl iodide in dichloromethane /50% aq. NaOH. Only C-alkylated compound **5a** was obtained in the absence of a catalyst or in the presence of benzo-15-crown-5. On the other hand, all other investigated catalysts gave none or very little of **5a** along with varying mixtures of **2a** and **4a**. Obviously, there is a competition between a catalytic and a non-catalytic process - presumably at the interphase. A closer inspection shows that the net O-/C-alkylation ratio of the first step can vary between 0 and 1.06. In the second step, this ratio can be between 8 (for NMe_4^+) and a few hundredfold to even larger (for most other catalysts). A similar, but not as dramatic difference in selectivities of consecutive reaction steps was found previously in PTC reactions of 2-indanone.[3]

Competitive N- vs. O-benzylations of 5,5-dimethyl-3-isoxazolidinone (**6**) [reaction (2)] with tetrabutylammonium bromide as PT catalyst gave a 85: 15 mixture of **7** and **8** in earlier work by Ly, Dou *et al.*[12] Our results are shown in Scheme 2 and Table 2. A solid/liquid system with crushed NaOH and dichloromethane was applied. Here, almost no blind reaction occurs in the absence of catalyst. The ratio of N-/O-alkylation varies between 2 and 3 with most of the normal, symmetrical cation catalysts over ≈6–7 ($AsPh_4^+$, PPh_4^+, 15-crown-5) to



Scheme 1

Table 1 O- *vs* C- methylation of anthrone (**1**) using different PT catalysts

Catalyst	**2** (%)	**3** (%)	**4** (%)	**5** (%)	O/C ratio, 1st step (**2**/**3**+**4**+**5**)
None	0	0	0	100	0
NMe_4Cl	50.5	0	44.0	5.5	1.02
NEt_4Cl	45.1	0	54.8	0.1	0.82
NBu_4Br	36.7	0	63.3	0	0.58
$NPen_4Br$	48.1	0	51.9	0	0.93
$[Et_3NCH_2\text{-}Ph]$ Br	42.7	0	57.3	0	0.74
PPh_4 Cl	51.5	0	48.5	0	1.06
$[Ph_3P{=}N{=}PPh_3]$ Cl	47.3	0	52.6	0.1	0.90
benzo-15-crown-5	0	0	0	100	0

10-27 (benzo-15-crown-5, 18-crown-6 and its dibenzo analogue). The different behaviour of the smaller, more hydrophilic crowns (*c.f.* 12-crown-4 = 3.3 !) is quite remarkable. In the group of symmetrical NR_4^+ cations, the N-/O-ratio decreases with size which might be due to the intermediacy of ion pairs that become looser and looser. A peculiar effect, however, is found with NEt_4^+ and NBu_4^+ both of which give much higher N-/O-values than expected. This type of discontinuity in performance is also present in the series of benzyl catalysts $PhCH_2\text{-}NR_3^+$. Such 'special effects' are found occasionally in PTC.[7–9] In such cases, catalyst behaviour in new reactions is rather unpredictable and this includes enantioselective PTC in particular. Apparently very specific interactions between catalyst cation and reagent anion prevail.

The benzylation of 4-methyl-2-quinolone (**9**) ([reaction (3)],Table 2) exhibits somewhat less differences among the catalysts. Again there is a negligible blind reaction, and dibenzo-18- crown-6 and 18-crown-6 direct most strongly towards N. The sterically accessible Q^+, NMe_4^+, $C_{16}H_{33}NMe_3^+$,and $PhCH_2\text{-}NMe_3^+$ behave similarly, although

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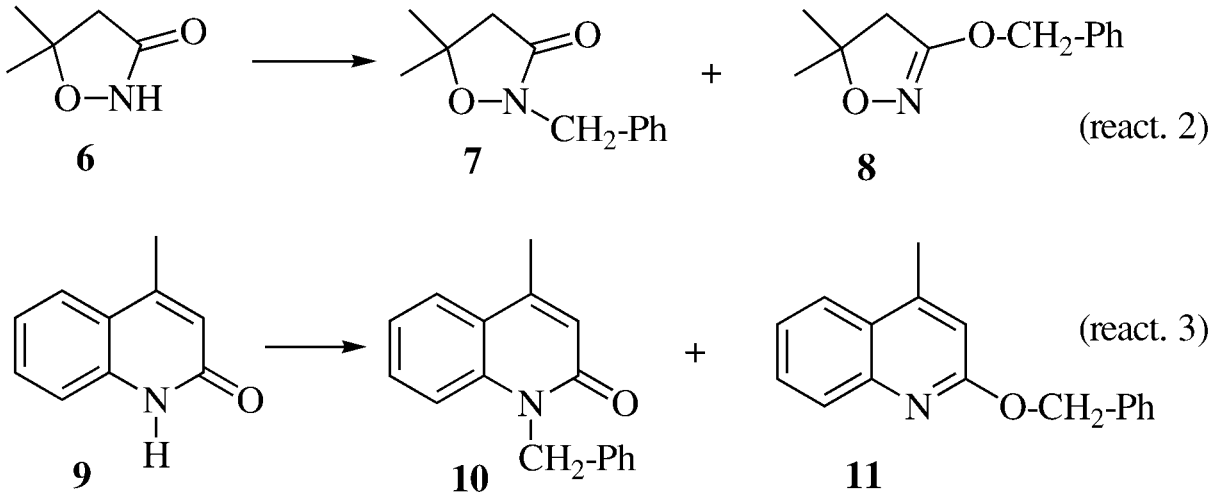
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*



Scheme 2

Table 2 N-*vs* O-benzylation of 5,5-dimethyl-3-isoxazolidinone (**6**) and of 4-methyl-2-quinolone (**9**) using various PT catalysts.

Catalyst	**7** (%) (from **6**)	**8** (%)	N/O ratio (**7**/**8**)	**10** (%) (from **9**)	**11** (%)	N/O ratio (**10**/**11**)
None	Trace	Trace	–	Trace	Trace	–
NMe_4Cl	79.4	20.6	3.87	85.0	15.0	5.67
NEt_4Br[*)]	80.6	19.4	4.22	80.0	20.0	4.00
NPr_4Br	71.5	28.5	2.49	80.4	19.6	4.11
NBu_4Br	81.8	18.2	4.51	77.3	22.7	3.41
$NPen_4Br$	78.4	21.6	3.70	73.7	26.3	2.80
$NHex_4Br$	75.7	24.3	3.20	82.9	17.1	4.86
$NHep_4Br$	76.1	23.9	3.20	79.6	20.4	3.90
$NOct_4Br$	72.5	27.5	2.65	82.1	17.9	4.57
$PhCH_2NMe_3Br$[a]	72.4	26.6	2.63	85.1	14.9	5.71
$PhCH_2NEt_3Br$[a]	76.7	23.3	3.30	79.5	20.5	3.88
$PhCH_2NPr_3Cl$	65.7	34.3	2.01	80.2	19.8	4.05
$PhCH_2NBu_3Cl$	70.2	29.8	2.39	78.7	21.3	3.69
PPh_4Br[a]	87.5	12.5	7.00	Trace	Trace	–
PBu_4Br	77.7	22.3	3.62	80.9	19.1	4.22
$[Ph_3P{=}N{=}PPh_3]Cl$	82.9	17.1	4.88	55.0	45.0	1.22
$AsPh_4Cl$	85.2	14.8	5.77	70.0	30.0	2.33
$AsBu_4Br$	79.4	20.6	3.85	82.2	17.8	4.63
$C_{16}H_{33}NMe_3Br$	69.6	30.4	2.30	82.4	17.6	4.68
$C_{16}H_{33}NEt_3Br$[a]	74.2	25.8	2.88	80.6	19.4	4.37
12-crown-4	76.9	23.1	3.34	70.6	29.4	2.41
15-crown-5	87.4	12.6	6.95	79.4	20.6	3.86
benzo-15-crown-5	91.5	8.5	10.80	78.1	21.9	3.56
18-crown-6	90.9	9.1	10.05	89.5	10.5	8.50
dibenzo-18-crown-6	95.9	4.1	26.60	92.0	8.0	11.43

[a]Catalyst chloride instead of bromide used in alkylation of **9**.

Table 3 Influence of branching in the catalyst cation on the N-/O-ratio of reaction (2)

Unbranched catalyst	N/O ratio (**7**/**8**)	Branched catalyst	N/O ratio (**7**/**8**)
$MeNBu_3I$	3.72	$MeNiso\text{-}Bu_3I$	3.66
Me_2NBu_2I	4.06	$Me_2Niso\text{-}Bu_2I$	2.79
$PhCH_2NMeBu_2Br$	3.87	$PhCH_2N(Me)iso\text{-}Bu_2Br$	3.38
$NEtMeBu_2I$	3.96	$NEt(Me)iso\text{-}Bu_2I$	3.14

to a lesser extent. In this reaction, the two catalysts $AsPh_4^+$ and $[Ph_3P{=}N{=}PPh_3]^+$ are the ones with strongest steering towards O, as could be expected from some of our previous results, but not from the other two reactions of this study.

PTC effects of stronger branching in the alkyl groups of the catalysts have not been investigated systematically. Therefore, a series of Q^+ salts containing isobutyl groups along with other residues was prepared and tested relative to Q^+ salts with *n*-butyl groups for the reactions (2) and (3).[13] One might have expected that the sterically more demanding cations would give less tight ion pairs and therefore more O-alkylation. This is indeed the case for reaction (2). Selected results are shown in Table 3 for the benzylation of **6**. It can be noticed that the effects are relatively small. Virtually no influence of "crowding in the catalyst cation" can be observed in the benzylation of **9**.[13]

Overall, these results support our earlier conclusions as mentioned in the first paragraph: Certain specific catalysts (most likely onium ions $RNMe_3^+$, benzo-15-crown -5 and dibenzo-18- crown-6) foster attack at the softer position, presumably because these "hard" cations attach preferentially to the "harder" place of the ambident and thus shield this location. Conversely, large and sterically demanding cations provide for less tight ion pairs leaving the more electronegative position more free for alkylation. It must be stressed again that these effects vary among the reactions considered. Although

no general predictions can be made, the observed trends may be used as a rule of thumb in planning new PTC reactions.

Experimental

The starting materials were commercially available (**1**) or were prepared using known methods (**6**: m.p.70–71°C, lit.[14] 70°C; **9**: m.p. 223–225°C, lit.[15] 220–222°C). All reaction products are known compounds. For spectral comparison and analytic purposes, authentic samples were prepared as described: **2a**[10], **3a**[16], **4a**[17], **5a**[18], **7**[12], **8**[12], **10**[19], **11**[20]. The PT catalysts are also known compounds except for the following which were prepared by quaternisation of the apropriate amines with MeI or $PhCH_2Br$: *Diisobutyldimethylammonium iodide*, m.p. 182°C, calcd. for $C_{10}H_{24}IN$: C 42.11, H 8.48, N 4.91; found: C 42.26, H 8.11, N 4.70. *Benzyldiisobutylmethylammonium bromide*, m.p. 194°C, calcd. for $C_{16}H_{28}BrN$: C 61.14, H 8.98, N 4.46; found: C 61.06, H 9.18, N 4.66.

Reactions were run until the starting materials were consumed. Analyses of the mixtures were performed by integration of the relevant NMR signals of the components. Reaction (1): **1**: δ 4.23 (s, H-10), **2**: δ 8.22 (s, H-10), 4.15 (OCH_3); **3**: δ 4.18 (q, H-10), 1.50 (d, C-CH_3); **4**: δ 4.12 (OCH_3), 3.05 (C-CH_3); **5**: δ 1.63 (2 × C-CH_3).- Reaction (2): **7**: δ 4.68 (NCH_2Ph); **8**: δ 5.14 (OCH_2Ph).- Reaction (3): **10**: δ 6.69 (H-3), 2.50 (CH_3); **11** δ 6.82 (H-3), 2.61 (CH_3). There was no interference by foreign peaks as the catalysts remained in the aqueous phase or were removed as described below. All values given in the tables are means of double determinations.

(1):5.0 mmol of **1**, 15 mmol of MeI, and 1.0 mmol of catalyst were dissolved in 25 ml of CH_2Cl_2. 25 ml of 50 % aq. NaOH were added, and the mixture was stirred for 15 h at r.t. It was diluted with 50 ml of water and acidified (HCl). Phases were separated, and the aqueous one was extracted five times with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4) and concentrated to dryness. The residue was dissolved in $CDCl_3$ and analysed.

(2):4.34 mmol of **6**, 8.7 mmol of benzyl bromide, and 0.43 mmol of catalyst were dissolved in 25 ml of CH_2Cl_2 , and 2.5 g of crushed solid NaOH were added. The mixture was stirred for 15 h at r.t., then diluted with 25 ml of water. Phases were separated, and the organic one was extracted thrice with 15 ml of dichloromethane. The combined organic layers were dried (Na_2SO_4), and the solvent was removed. The oily residue was distilled in a Kugelrohr (0.2 mbar at 100°C [air bath temperature]), then dissolved in $CDCl_3$ for analysis.

(3):5.0 mmol of **9**, 0.5 mmol of catalyst, and 10.0 mmol of benzyl bromide were dissolved in 15 ml of dichloromethane, and 25 mmol of 50 % aq. NaOH were added. The mixture was stirred for 18 h at r.t., then diluted with 30 ml of water. The aqueous phase was extracted twice with 20 ml of CH_2Cl_2, and the combined extracts were dried (Na_2SO_4), whereafter the solvent was removed. The residue was taken up in 50 ml of *tert*-butyl methyl ether and filtered through a column (5.5 × 2 cm) of silica gel. The product mixture was eluted with 3 × 30 ml of further *tert*-butyl methyl ether. Then the solvent was removed *in vacuo*, and the residue was dissolved in $CDCl_3$ for analysis.

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