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N- vs O-Alkylation in 2(1H)-quinolinone derivatives

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Abstract

N- vs O-alkylation reactions of 8-benzyloxy-2(1H)-quinolinone have been investigated using both classical and phase transfer conditions. The influence of reaction solvents/conditions was found to have a dramatic effect on selectivity, with opposite trends to that observed for 2-pyridone alkylation.

Key words: Alkylation, quinolinones, phase transfer

As part of an ongoing study[1] aimed at synthesising dendroid peptide (conotoxin) mimetics we selected 8-hydroxy-2(1H)-quinolinone as a potential core (not least because 2(1H)-quinolinone derivatives are themselves of biological interest[2]). The synthesis requires two successive alkylations, first at the 8-hydroxyl group and then on nitrogen. This first alkylation can be achieved selectively following a modified literature procedure[2c] to give 8-benzyloxy-2(1H)-quinolinone.[3] The second alkylation, however, involves an ambident anion and can be expected to yield a mixture of N- and O-alkylated products.

N- vs O-alkylation of 2-pyridone[4] and other heterocyclic ambident anions[5] has been extensively investigated. Selectivity depends on solvent, cation and alkylating agent. In the case of 2-pyridone,[4a] alkylation of the sodium salt with benzyl bromide in DMF leads to selective N-

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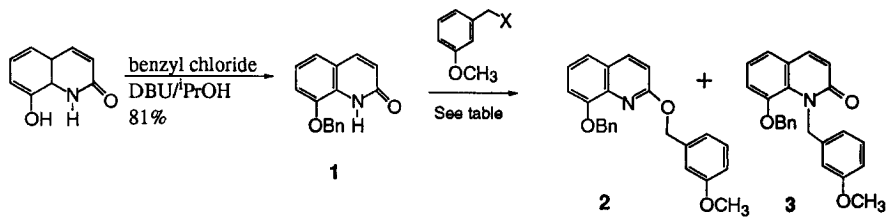

Entry	X	Solvent/base	Catalyst	Temperature (time)	2 : 3[a]
1	Cl	DMF/NaH	-	rt (24h) then 55°C (22h)	2.6 : 1 (71%:26%)
2	Cl	Toluene/water/NaOH	TEBA	55°C (66h) then reflux (4h)	1 : 1 (39%:47%)
3	Cl	Toluene/KOH	TBAB	rt (22h) then 55°C (5h)	1 : 1.3 (43%:54%)
4	Br	DMF/NaH	-	rt (18h)	1.6 : 1
5	Br	Toluene/water/NaOH	TEBA	55°C (24h) then 90°C (22h)	1 : 1.5
6	Br	Toluene/KOH	TBAB	rt (19h)	1 : 2.8
7	Br	CH_2Cl_2/KOH	TBAB	rt (19h)	1 : 1.1
8	Br	CH_3CN/KOH	TBAB	rt (19h)	1 : 1.2
9	Br	Ether/KOH	TBAB	rt (92h)	1 : 2.1
10	Br	Benzene/KOH	TBAB	rt (19h)	1 : 2.2
11	Br	Toluene/KOH	TBAI	rt (19h)	1 : 3.6
12	Br	Toluene/KOH	TEBA	rt (6 days)	1 : 2.6

[a] ratio based on ^1H NMR spectroscopy of the product mixture. Yields in parentheses refer to isolated products (column chromatography). (TEBA = benzyltriethylammonium chloride, TBAB/I = tetrabutylammonium bromide/iodide).

alkylation (97:3) whereas using the silver salt in benzene leads exclusively to the O-alkylated product. Phase transfer conditions are often employed in such alkylations and have been reported to favour the formation of N-alkylated products (and in certain cases only N-alkylation is observed).[5] Alkylation of 2-pyridone using liquid-liquid phase transfer conditions was found to result in preferential N-alkylation (N:O = 4:1). This ratio is essentially unaffected by change of organic solvent, temperature or alkylating agent.[4b] Selective O-alkylation of 2-pyridone has been achieved using Mitsunobu conditions.[4c]

Our first attempt to alkylate 8-benzyloxy-2(1H)-quinolinone using "classical" conditions (3-methoxybenzyl bromide, DMF, NaH) gave the unwanted O-alkylated material as the major product.[6] Different reaction conditions were therefore systematically investigated in order to find a set of conditions which would favour N-alkylation. The results are summarised in the table.[7] It can be seen that a number of factors control N- vs O-alkylation in this reaction. "Classical" conditions (DMF, NaH) favour O-alkylation with selectivity most pronounced when the rate is slowed through use of a benzyl chloride as alkylating agent. It is interesting to note that this selectivity contrasts the observations for alkylation of 2-pyridone. Liquid-liquid phase transfer conditions offer no selectivity (chloride) or moderate selectivity in favour of N-alkylation (bromide). Solid-liquid phase transfer conditions, however, resulted in preferred N-alkylation. The selectivity was extremely sensitive to the reaction solvent. Use of TBAI in toluene (KOH base) was found to give the highest selectivity of 3.6:1 in favour of N-alkylation[8] (in this case the alkylating agent is likely to be a mixture of benzyl bromide and iodide with concomitant increased reaction rate).

In conclusion we have shown that N- vs O-alkylation in 8-benzyloxy-2(1H)-quinolinone can be controlled by careful choice of alkylation conditions. Selectivities up to 3.6:1 in favour of N-alkylation have been achieved using solid-liquid phase transfer conditions.

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References and notes

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3 **1**: mp 123.4-125.1°C. IR 3160, 1660, 1605 cm^{-1}; MS (EI) *m/z* 251 (20%, M^+); ^1H NMR ($CDCl_3$, 270MHz) δ 9.25 (brs, 1H), 7.71 (d, J= 9.6Hz, 1H), 7.35-7.45 (m, 5H), 7.02-7.17 (m, 3H), 6.65 (d, J= 9.6Hz, 1H), 5.17 (s, 2H); ^{13}C NMR δ 161.94, 144.53, 140.39, 135.60, 128.80, 128.66, 128.59, 127.87, 122.57, 122.15, 120.11, 119.84, 111.39, 70.98. Anal. Calcd for $C_{16}H_{13}NO_2$: C 76.48%, H 5.21%, N 5.57%; found C 76.48%, H 5.07%, N 5.51%.

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6 To a stirred solution of 8-benzyloxy-2(1H)-quinolinone (350 mg, 1.4 mmol) in dry DMF (10 ml) under N_2 was added NaH (1.15 equiv.). The mixture was stirred at r.t. for 1.5 h. 3-Methoxybenzyl chloride (283 mg, 1.3 equiv.) in DMF (1 ml) was added and the mixture was stirred at rt for 24 h, then at 55°C for 22 h. After cooling to rt, the mixture was poured onto water (50 ml) and extracted with ethyl acetate (3x30 ml). The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated to give a pale yellow oil (577 mg) which was purified by column chromatography (silica) eluting with ethyl acetate/petroleum ether 1:3 to give **2** as a viscous, colourless oil (which was distilled (bulb-to-bulb) at 200°C /0.01mm Hg) (367 mg, 71%) and **3** (135 mg, 26%) as white solid (mp 73.2-74.6°C).

2: IR 1610 cm^{-1}; MS (EI) *m/z* 371 (17%, M^+); ^1H NMR ($CDCl_3$, 300MHz) δ 7.93 (d, J= 8.8Hz, 1H), 7.55-7.57 (m, 2H), 7.07-7.39 (m, 9H), 6.96 (d, J= 8.8Hz, 1H), 6.81-6.85 (m, 1H), 5.57 (s, 2H), 5.31 (s, 2H), 3.73 (s, 3H); ^{13}C NMR δ 161.28, 159.92, 153.54, 139.17, 138.63, 137.75, 129.61, 128.64, 127.88, 127.37, 126.62, 124.16, 120.99, 120.52, 114.10, 113.63, 113.57, 112.64, 71.41, 67.63, 55.21 (CH_3). Anal. Calcd for $C_{24}H_{21}NO_3$: C 77.61%, H 5.7%, N 3.77%; found C 77.53%, H 5.61%, N 3.66%.

3: IR 1660, 1595 cm^{-1}; MS (EI) *m/z* 371 (34%, M^+); ^1H NMR ($CDCl_3$, 300MHz) δ 7.68 (d, J=9.5Hz, 1H), 7.26-7.30 (m, 3H), 7.01-7.19 (m, 6H), 6.78 (d, J= 9.5Hz, 1H), 6.66-6.70 (m, 1H), 6.46-6.51 (m, 2H), 5.91 (s, 2H),4.88 (s, 2H), 3.66 (s, 3H); ^{13}C NMR δ 163.72, 159.86, 147.49, 141.08, 140.13, 136.12, 130.94, 129.39, 128.74, 128.29, 127.77, 123.41, 123.03, 122.32, 122.05, 118.11, 115.27, 111.65, 111.58, 72.03, 55.06 (CH_3), 49.42. Anal. Calcd for $C_{24}H_{21}NO_3$: C 77.61%, H 5.7%, N 3.77%; found C 77.46%, H 5.71%, N 3.7%.

7 Control experiments were performed to ensure that the product distribution was not influenced by further equilibration (including Chapman rearrangement) under the reaction conditions.

8 KOH (powder, 1.8 equiv.) was added to a stirred mixture of 3-methoxybenzyl bromide (104 mg, 1.3 equiv.), 8-benzyloxy-2(1H)-quinolinone (100 mg, 0.4 mmol) and TBAI (29.4 mg, 0.2 equiv.) in dry toluene (8 ml) at rt under N_2. The mixture was stirred at rt for 19 h, poured onto water and extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4) and evaporated to give a pale yellow oil. ^1H NMR spectroscopy of the oil indicated that **2** and **3** were the only products present in a ratio of 1:3.6.