Further studies of regioselective alkoxydehalogenation of 2,4-dichloroquinolines, 2,6-dichloropyridine and 2,4-dichloronitrobenzene

J. Chem. Research (S), 2002, 4
J. Chem. Research (M), 2002, 0124–0148

Alan G. Osborne*, Galya T. Dimitrova, Paul Galbally, David D. Hughes, Clare Jones, Anthony L. Lipman and Nicola Wilstead

Department of Biological Sciences, University of Essex, Wivenhoe Park, Colchester, Essex CO3 4SQ, UK

A comparison of regioselective (solid sodium alkoxide/toluene) and standard (alcoholic alkoxide solution) alkoxydehalogenation reactions with a series of 2,4-dichloroquinolines and with 2,6-dichloropyridine and 2,4-dichloronitrobenzene, with product analysis by NMR spectroscopy, is reported.

Keywords: nucleophilic substitution, quinolines, pyridines, regioselection in S_NAr, alkoxydehalogenation

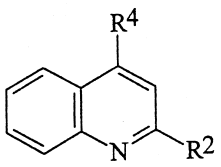
We have previously reported[1] the use of solid sodium alkoxide in toluene for regioselective alkoxydehalogenation (RA) of 2,4-dihaloquinolines **1a** and **2a** (see Table 1). In this study the scope of the reaction has been further extended and the results compared with those from the standard (alcoholic alkoxide solution)[8] alkoxydehalogenation (SA) method.

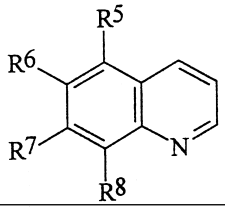
In the RA reactions 2,4-dichloroquinolines **1a–1k** gave the corresponding 2-alkoxy-4-haloquinolines **6** and **7** (Table 2); only **1g** showed any significant steric effect. The SA reaction (Table 3) gave mainly the 2,4-dialkoxy substituted compounds **3**–**5**. In the presence of additional 5-, 6- and 7-methyl substituents some 2-alkoxylation occurred to give the appropriate compounds **6** or **7**. In complete contrast, when an 8-substituent was present a significant amount of 4-alkoxylation took place to produce the corresponding derivatives **10** or **12**.

RA reactions with 2,6-dichloropyridine **13** (Table 5) showed α-regioselectivity to give the 2-chloro-6-alkoxy compounds **15**, **16** exclusively. The SA reactions with **13** and with 2,4-dichloronitrobenzene **20** gave the expected dialkoxy substituted products.[3–6] In the benzenoid series, the RA reaction with **20** was a total failure, which confirmed that initial interaction between a basic heterocyclic nitrogen lone pair and the alkoxide surface was the prime requisite for success.

^1H and ^{13}C NMR (Tables 6 - 8) were used for identification and product composition analysis, the signals for H-3 and C-3 being particularly characteristic for each series. Use of Cl/Me and OMe/Me (Table 10) *peri*-proximity effects[7] were necessary for accurate and reliable estimation of ^{13}C chemical shifts for the 4,5-disubstituted compounds (series **b** and **h**).

Table 1 List of quinoline derivatives studied





	R^2	R^4		R^5	R^6	R^7	R^8
1	Cl	Cl	**a**	H	H	H	H
2	Br	Br	**b**	Me	H	H	H
3	OMe	OMe	**c**	H	Me	H	H
4	OEt	OEt	**d**	H	H	Me	H
5	OPr	OPr	**e**	H	H	H	Me
6	OMe	Cl	**f**	H	H	H	Et
7	OEt	Cl	**g**	H	H	H	CMe_3
8	OMe	Br	**h**	Me	H	H	Me
9	OEt	Br	**j**	H	Me	H	Me
10	Cl	OMe	**k**	H	H	Me	Me
11	OPr	Cl	**m**	H	H	Cl	H
12	Cl	OEt					

Techniques used: ^1H and ^{13}C NMR spectroscopy

Schemes: 2

Tables: 13

Table 2: Results of RA reactions with 2,4-dichloroquinolines

Table 3: Results of SA reactions with 2,4-dichloroquinolines

Table 4: List of 2,6-disubstituted pyridines

Table 5: Reactions with 2,6-dichloropyridine

Tables 6–9: ^1H and ^{13}C NMR of quinolines

Table 10: *peri*-Proximity effects (p.p.m.) for the quinoline series

Table 11: NMR spectra of 2,6-disubstituted pyridines

Tables 12-13: Prepared quinoline products; yields, properties, analyses

Received 25 July 2001; accepted 24 September 2001
Paper 01/998

References cited in this synopsis

1 A.G. Osborne and L.A.D. Miller, *J. Chem. Soc., Perkin Trans.* 1, 1993, 181.
3 H.J. Den Hertog and J.P. Wibaut, *Rec. Trav. Chim.*, 1936, **55**, 122.
4 D.S. Noyce and J.A. Virgilo, *J. Org. Chem.*, 1973, **38**, 2660.
5 L. Testaferri, M. Tiecco, M. Tingoli, D. Bartoli and A. Masoli, *Tetrahedron*, 1985, **41**, 1373.
6 A.F. Holleman and DeMeoy, *Rec. Trav. Chim.*, 1916, **35**, 15.
7 A.G. Osborne, *Magn. Reson. Chem.*, 1989, **27**, 348.
8 A.G. Osborne, J.F. Warmsley and G.T. Dimitrova, *J. Nat. Prods.*, 1992, **55**, 589.

* To receive any correspondence.