Nucleophilic Substitution Reactions of 2-Chloropyridine with Polymethylenediols Using Phase-Transfer Catalysis: Selective Formation of Mono- or Diethers

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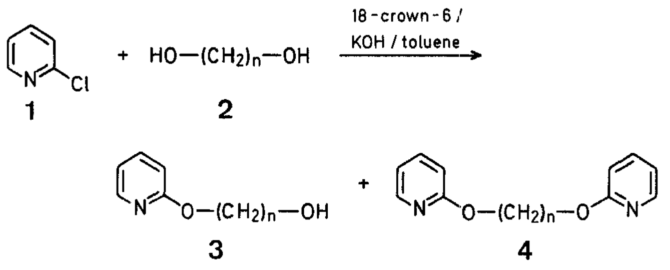
We have examined the phase-transfer catalyzed (PTC) nucleophilic substitution reaction of 2-chloropyridine (**1**) with polymethylenediols (**2**) using potassium hydroxide as a base and 18-crown-6 as a catalyst[1]. In the presence of a sufficient amount of base, the reaction would lead to either mono- (**3**) or diether (**4**) depending upon which reagent (the chloride **1** or the diol **2**) is present in excess[2]. However, we have now found that even if the ratio of the chloride and diol is kept constant, the amount of potassium hydroxide (relative to the diol) exerts a crucial influence upon whether the product is the mono- or diether.



The effect of the proportion of potassium hydroxide to the diol upon the course of reaction was examined under the following conditions: 1.0 mmol of 2-chloropyridine (**1**) and 5.5 mmol of the diol **2a–d** in the presence of 0.4 mmol of 18-crown-6 in 50 ml of toluene. After addition of potassium hydroxide, the mixture is refluxed until the disappearance of **1** which is complete within 5–26 h in all cases.

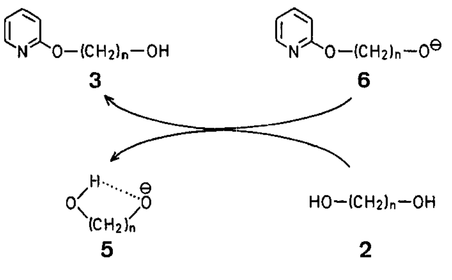
Addition of 2.0 mmol or less of potassium hydroxide in the above system (Method A) resulted in an almost exclusive formation of the monoether **3a–d**, while addition of 20 mmol or more of the base (Method B) afforded the diether **4a–d** predominantly[3]. The results obtained are almost the same irrespective of the diol employed[4] (Table 1).

0039-7881/82/0632-0465 $ 03.00

Table 1. Preparation of Mono- (3) and Diethers (4) from 1 and Diols 2a-d

Diol 2 used No.	n	Method	Reflux time	Yield [%] of 3	of 4
2a	2	A	26 h	71	6.6
2b	3	A	7.5 h	78	1.9
2c	4	A	5 h	81	1.1
2d	6	A	6.5 h	75	3.5
2a	2	B	12 h	0.7	94
2d	6	B	5 h	25	59

Though detailed investigations to clarify the origin of this selectivity have not been done as yet, the following two assumptions seem to be valid. Firstly, since the mono-alkoxide ion **5** of the diol **2** is stabilized appreciably by intramolecular hydrogen bonding, the alkoxide ion **6** of the monoether **3** would not be formed in any significant amount under the conditions of Method A where a lot of the free diol is present in the system. Secondly, when the free diol can no longer be present in the system as in Method B, the alkoxide ion **6** can exist as such and hence react further with the chloride **1** to form the diether **4**. In this case (Method B), the nucleophilicity of **6** would be much stronger than that of **5**, because the latter is hydrogen-bonded intramolecularly, and hence the substitution via the former ion **6** should occur in preference to that via the latter ion **5**.



While more detailed investigations are necessary to confirm the above idea, the present procedure may be applicable to phase-transfer-mediated Williamson ether synthesis[5] using a diol as an alcohol and thus provide a selective route to either the mono- or the diether without using one reactant (halide or diol) in a large excess.

Reaction of 2-Chloropyridine (1) with Polymethylenediols 2a-d; General Procedures:

Method A: A mixture of 2-chloropyridine (**1**, 1 mmol), polymethylenediol **2** (5.5 mmol), powdered potassium hydroxide (2 mmol), 18-crown-6 (0.4 mmol), and toluene (50 ml) is stirred rapidly under reflux. After 5-26 h, the reaction mixture is cooled and water (2 ml) is added. The mixture is extracted with dichloromethane (4 x 20 ml), the organic layer is dried with sodium sulfate, and concentrated in vacuo. Separation of the crude residue by column chromatography over silica gel (15 g) eluting with dichloromethane affords the diether **4** and then the monoether **3**. The latter fraction is followed closely by the recovered crown ether. Under these conditions, the monoethers **3** are formed almost exclusively. All of the monoethers are oils and form crystalline picrates which are recrystallizable from methanol (Table 2).

Method B: The same solution as used in Method A except for using 20 mmol of powdered potassium hydroxide is refluxed for 5-12 h. Work up as described in Method A affords **3** and **4**. Under these conditions, the diethers **4** are formed in predominance. All of the diethers except for **4c** are recrystallized from hexane/ether (Table 2).

Received: September 9, 1981

Table 2. Characterization of Mono- (3) and Diethers (4)

Product No.	n	m.p. [°C]	Molecular formula[a]	^{1}H-N.M.R. (CDCl$_3$/TMS)[b] δ [ppm] CH$_2$—O—Py	CH$_2$—OH	other —CH$_2$—
3a	2	108-110°[c]	$C_7H_9NO_2$ (139.2)	4.4-4.5 (m)	3.6-4.1 (m)	—
3b	3	141-142°[c]	$C_8H_{11}NO_2$ (153.2)	4.44 (t, J=6.0 Hz)	3.67 (br t, J=6.0 Hz)	1.95 (quin, J=6.0 Hz)
3c	4	82-83°[c]	$C_9H_{13}NO_2$ (167.2)	4.28 (br t, J=6.0 Hz)	3.67 (br t, J=5.6 Hz)	1.5-2.1 (m)
3d	6	73-74.5°[c]	$C_{11}H_{17}NO_2$ (195.3)	4.22 (t, J=6.0 Hz)	3.5-3.8 (m)	1.1-2.2 (m)
4a	2	68.5-69.5°	$C_{12}H_{12}N_2O_2$ (216.2)	4.61 (s)	—	—
4b	3	oil	$C_{13}H_{14}N_2O_2$ (230.3)	4.41 (t, J=6.4 Hz)	—	2.23 (quin, J=6.4 Hz)
4c	4	78-79°	$C_{14}H_{16}N_2O_2$ (244.3)	4.1-4.5 (m)	—	1.8-2.1 (m)
4d	6	80-82°	$C_{16}H_{20}N_2O_2$ (272.3)	4.26 (t, J=6.0 Hz)	—	1.2-2.3 (m)

[a] Satisfactory microanalyses (C ±0.30, H ±0.30, N ±0.20) and mass spectra obtained.

[b] Only CH$_2$ protons given. The ring protons give signals in the following regions: δ=6.5-6.9 (m, H—C-3, H—C-5): 7.4-7.5 (ddd, H—C-4, J=8.0 Hz, 6.8-7.2 Hz, 2.0 Hz); 8.0-8.05 ppm (ddd, H—C-6, J=4.8 Hz, 2.0 Hz, 1.0 Hz).

[c] Free bases are oils; m.p. of picrate given.

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[1] The first application of PTC conditions to heteroaromatic nucleophilic substitution employing alkoxide ions is reported by Duggan et al.: A. J. S. Duggan, E. J. J. Grabowski, W. K. Russ, *Synthesis* **1980**, 573.
See also, C. Kaneko, T. Naito, Y. Momose, H. Fujii, N. Nakayama, I. Koizumi, *Chem. Pharm. Bull.*, in the press.

[2] Reaction of naked acetate with ethylene dibromide was conducted under PTC conditions to yield either ethylene diacetate or predominantly 2-bromoethyl acetate depending upon which reagent is present in excess: C. L. Liotta, H. P. Harris, M. McDermott, T. Gonzalez, K. Smith, *Tetrahedron Lett.* **1974**, 2417.

[3] Use of potassium hydroxide in an amount between these two extremes showed decreased selectivity and both kinds of product (**3** and **4**) were obtained in comparable yields.

[4] Necessity for the exceptionally long period for the reaction of **1** with ethylene glycol under Method A seems to be noteworthy. This can be explained by assuming that the corresponding monoalkoxide ion of ethylene glycol (**5**; n=2) is very weak nucleophile due to its exceptionally strong intramolecular hydrogen bonding.

[5] H. H. Freedman, R. A. Dubois, *Tetrahedron Lett.* **1975**, 3251.