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A Selective Process for *N*-Alkylation in Competition with *O*-Alkylation: Boric Acid, Borax, and Metaborate as a Cheap and Effective Protecting Group Applicable for Industrial-Scale Synthetic Processes

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Abstract:

This paper describes a selective process for the *N*-alkylation of substrates that contain 1,2-diol groups. The developed approach utilises temporary protection of the diol groups by boric acid, Borax, or metaborate. The introduction of the boron-containing groups into the substrate may provide, in addition to affording the intended protection of the hydroxyl groups that may otherwise act as nucleophilic sites, the advantages of improved solubility of the substrate in water that is used as solvent. Moreover the *N*-alkylation and the deprotection of the diols are performed in one pot, and the formation of undesired *O*-alkylated by-products is significantly reduced. The paper gives examples from the synthesis of several X-ray contrast agents used in medical imaging diagnostics: iohexol (Ominipaque, Nycomed Imaging); iopentol (Imagopaque, Nycomed Imaging); iodixanol (Visipaque, Nycomed Imaging); ioversol (Optiray, Mallinckrodt).

Introduction

Hydrophilic X-ray absorbing agents for examination of the cardiovascular system constitute a major class of contrast agents in the field of medical imaging diagnostics. The synthetic preparation of such compounds often requires linear multistep syntheses where different side chains, such as carboxylic acid, carboxamide, hydroxy, ether, and sugar moieties, are successively introduced to the core substrate containing the X-ray-absorbing moiety, the tri-iodinated benzene. The motivation for the introduction of such functionality is to modify the lipophilic−hydrophilic properties to achieve the desired and optimised pharmacokinetic profile of the final drug product. Since more nucleophilic sites are introduced into the X-ray-absorbing substrate as the synthesis progresses the major challenge becomes promoting the desired alkylation reaction over competing side-reactions. Such a situation occurs in several organic processes, leading to pharmaceutical chemicals used as X-ray imaging diagnostics such as iohexol (Ominipaque, Nycomed Imaging), iopentol (Imagopaque, Nycomed Imaging), iodixanol (Visipaque, Nycomed Imaging), ioversol (Optiray, Mallinckrodt). The actual reaction step involved is an *N*-alkylation using a reagent of general formula R^2-CH_2-X, where X is the leaving group. Under these reaction conditions, competing *O*-alkylation reactions may also proceed since the side chains of the substrate **1** and target molecule (TM) **2** contain both primary and secondary hydroxyl groups (see Scheme 1). The alkylation reaction may proceed on the primary hydroxyl group according to reaction paths *(c)* + *(e)* and *(b)* + *(g)* resulting in the formation of the by-product **6**. Alkylation of the secondary hydroxyl groups may take place following the routes *(a)* + *(d)* and *(b)* + *(f)* leading to the by-product **4**. The *O*-alkylated impurities **4** and **6**, frequently called *"over-alkylated by-products"*, often have properties similar to those of TM **2** and may thus cause severe purification problems.

A major challenge in process R&D and synthetic procedure industrialisation is optimising the process conditions to obtain a high conversion, while maintaining the selectivity of the desired reaction by suppression of possible side reactions. This may be performed by fine-tuning the experimental conditions[1,2] of the designed synthetic route and optimising the properties of the reagents.[3] However, both of these methods can also be combined with introduction of auxiliary or protecting groups, which may (1) suppress or block the undesired reaction(s), (2) promote the desired reaction, and (3) improve solubility of the substrate and the reagent.

In synthetic route discovery one attempts to avoid applying synthetic transformations that require the use of protective groups[4,5] since this implies introduction of at least two more reaction steps: application and removal of the protecting groups. Furthermore, additional steps such as solvent exchange and workup procedures may also be required. In organic process R&D it is therefore evident that the application of protective group methodologies is even less desirable. Exceptions can be found in cases where a concatenated process may be established when the protection, the desired synthetic transformation, and the deprotection are performed in a one-pot procedure with cheap reagents and a simple workup.

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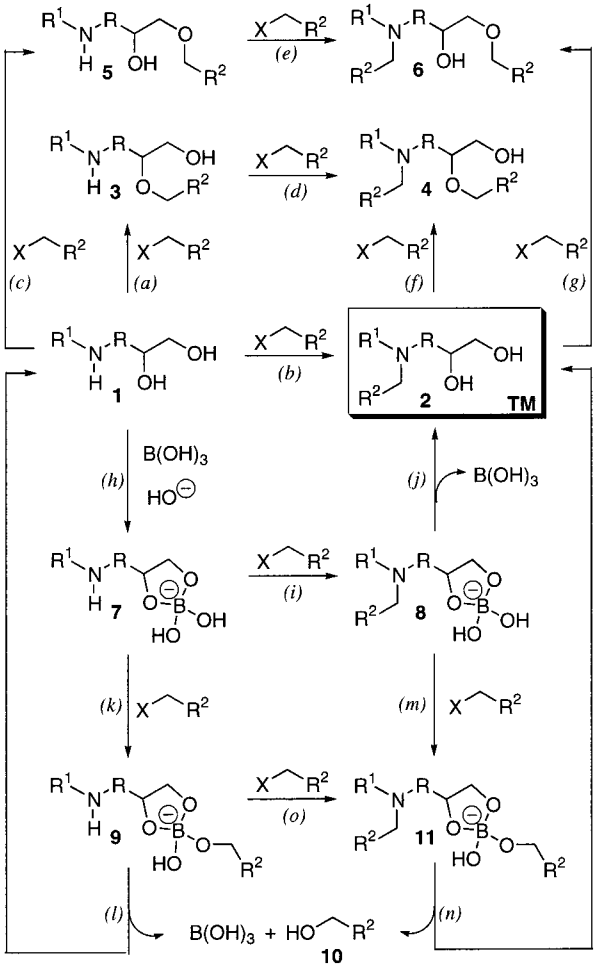
Scheme 1

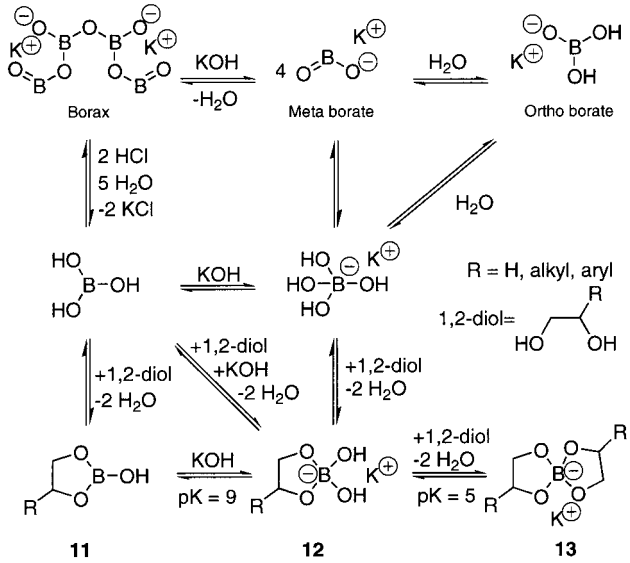


The present paper presents results from a case in which the protecting group methodology was used to improve the chemoselectivity of an *N*-alkylation reaction for substrates containing 1,2-diols in addition to the *N*-nucleophilic site. Besides the requirements for improvements in chemoselectivity, other parameters for a good process design were also required, including that the final process should be cheap and of course "green enough" for large-scale production.

Methods and Results

Several methods exist for the protection of hydroxylic groups, for example, transformation into ethers, esters, and carbonates. Furthermore 1,2- and 1,3-diols can be protected as cyclic ethers, for example, acetonides, or cyclic esters, for example, polystyrylboronic acid esters,[6] or phenyl−boranates,[7] although the later are unstable in water and alcohols.[8] Moreover, boronic acid residues[6] have already been used for protection of diols. Methylation of ribonucleosides by trimethyl phosphate or dimethyl sulphate was performed in the presence of boric acid.[9] Oi, Takeda, and Kakihana[10] have esterified boric acid with 1,2-propanediol, 3-amino-1,2-propanediol, and 3-(dimethylamino)-1,2-propanediol.

Scheme 2



Boric acid, a weak monovalent acid[11] that can be esterified to form alkoxy−borate complexes **12** or **13** (Scheme 2), was brought to our attention as a possible protecting group for large-scale syntheses since (1) the hydroxyl groups are easily transformed temporarily into borates[12] of many types, (2) the cost of boric acid is low, (3) the borate ester is compatible with water as solvent, and (4) it has low toxicity.

The desired *N*-alkylation reaction of substrate **1** can be performed with an alkylation reagent of general formula R^2-CH_2-X. The reaction may be carried out with water as solvent, which is advantageous for environmental as well as economical reasons. Moreover, with water as solvent the free hydroxyl groups of the side chain of substrate **1** can easily be temporarily transformed into a borate ester **7** following path *(h)* of Scheme 1. This may be very advantageous for two reasons: (1) substrates of type **1** with poor aqueous solubility may become more soluble, and (2) the hydroxyl groups will be protected from participating in undesired *O*-alkylation reactions as shown in the routes *(a)*, *(c)*, *(f)*, and *(g)* of Scheme 1. The synthetic route to target molecule **2** is thus composed of three synthetic steps: (1) protection of the diol, **1** → **7**, (2) alkylation of the borate ester **7** giving the *N*-alkylated borate ester **8**, and finally (3) removing the borate ester group under acidic hydrolytic workup conditions to obtain TM **2**. The complete reaction sequence **1** → **7** → **8** → **2** can thus be performed in a one-pot process. Schemes 3 and 4 follow this reaction path and show the reaction schemes for the synthesis of iohexol, iodixanol, iopentol, and ioversol all of which are used as X-ray imaging diagnostic agents. The alkylation reagent R^2-CH_2-X may, however, also react with the borate ester **7**

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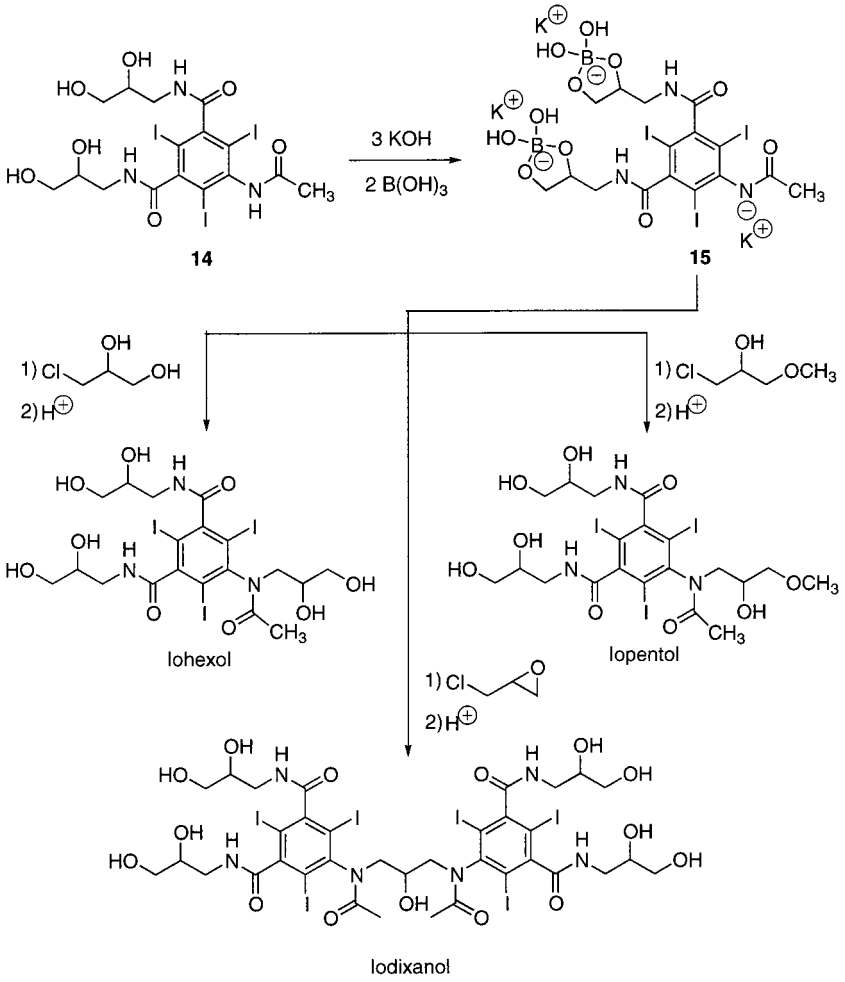
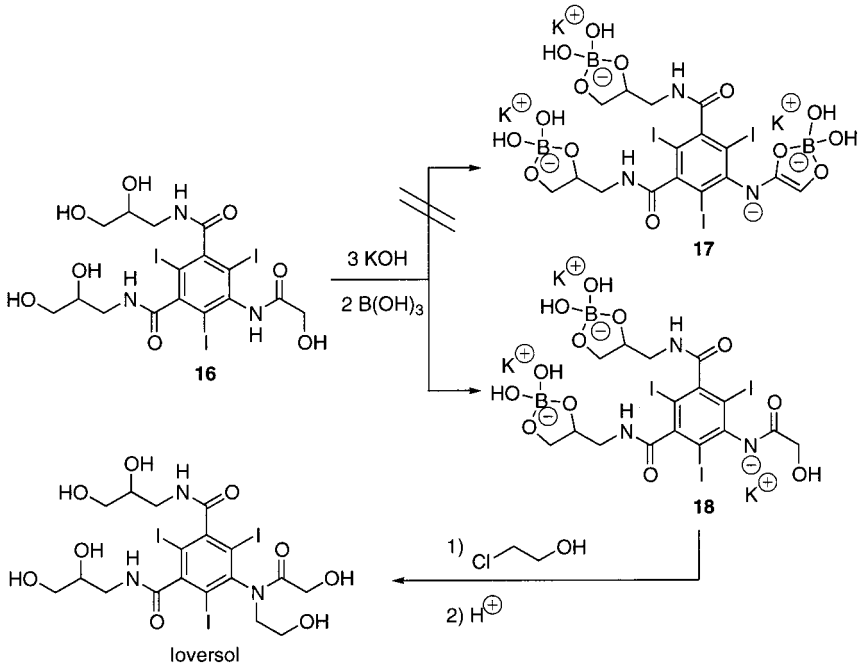
Scheme 3



Scheme 4



in an *O*-alkylation side reaction at the boron-bound hydroxyl groups following path (*k*) with formation of the borate ester **9**. Under the acidic hydrolytic workup conditions, the borate ester **9** decomposes to the starting material **1**, which can be recycled, boric acid, and hydrolysed alkylation agent **10**. The reaction sequence **7** → **9** → **1** shows how valuable starting

material can be recovered from *over-alkylated by-products* and thus contribute to improving the selectivity of the process. Another *O*-alkylation side reaction may also take place at the boron-bound hydroxyl groups of the *N*-alkylated borate ester **8** with formation of the borate ester **11**. Under the slightly acidic hydrolytic workup conditions, the borate ester **11** is cleaved to the target product **2**, boric acid, and the hydrolysed form of the alkylation agent **10**. The reaction sequence **8** → **11** → **2** shows how the valuable target product **2** can be obtained from *over-alkylated by-product*s. *N*-alkylation of the borate ester **9** following path (*o*) will also give the desired product **2**, hydrolysed reagent **10**, and boric acid. As a result of this concatenated synthetic route the *N*/*O*-alkylation ratio can be improved considerably compared with the corresponding reaction with the unprotected substrate **1** following path *(b)* of Scheme 1.

Stability of the Alkylation Reagent. Another problem to be overcome in the current process development is the hydrolytic degradation of the alkylation reagent R^2-CH_2-X. In aqueous basic media a competing basic hydrolysis[13] of the reagent (the electrophile E) can take place. King et al.[14] have studied such reactions and derived a general model, eq 1, that describes the pH_{max} as the pH that gives the highest yield of the product (P) of the reaction of a nucleophile (Nu) with a hydrolysable electrophile (E) in water:

$$pH_{max} = \frac{1}{2}\left[\log\left(\frac{k_w}{k_{OH}}\right) + pH_w + pH_a\right] \quad (1)$$

The parameters k_w and k_{OH} of eq 1 refer to the water- and hydroxide-promoted hydrolysis of E, K_w is the autoprotolysis constant of water and K_a is the acid dissociation constant of NuH^+, the conjugate acid of Nu. pH_{max} thus depends on a property of E (namely k_w/k_{OH})[15] and a property of Nu (the pK_a of NuH^+), but not on the rate constant for the reaction of E with Nu or the concentration of Nu. Several studies[16−20] have been reported using this model for both alkylation and acylation in water. The current process development takes account of this aspect in the design of the procedures for the *N*-alkylation of the boric acid esters **7**.

Formation and Stability of the Boric Acid Ester: The Protected Substrate. Many studies of borates have been reported including those investigating structure and stability[21] as a function of pH.[22] Borate esters[23] of carbohydrates and related compounds in aqueous media have been studied by ^{11}B and ^{13}C NMR spectroscopy. Borate esters of vicinal diols, such as **12** or **13**, were observed at pH > 7 (see Scheme 2). The pH-dependent stability of esters of boric acid and borate has been formulated in a general rule of thumb:[24] "esters of boric acid and borate with dihydroxy compounds in aqueous medium show the highest stability at that pH where the sum of the charges of the free esterifying species is equal to the charge of the ester".

Thus, to ensure that the proposed protection steps of the process of Scheme 1 occur, *N*,*N*′-bis-(2,3-dihydroxypropyl)-5-(2-hydroxy-acetylamino)-2,4,6-triiodo-isophthalamide **16** (Scheme 4) was reacted with boric acid in basic media, the product was isolated, and the ^1H-, ^{13}C-, and ^{11}B NMR spectra were measured in D_2O/NaOD/boric acid solution.

At pH 13 and with a ratio **16**:boric acid = 1:3 (mol:mol) it was found that the hydroxyacetyl moiety did not react with boric acid to form the ester **17**. However, 72% of substrate **16** reacted with boric acid and formed mainly the diprotected compound **18** (94%) and a side product (6%) of the compound type **13**. The protection against *O*-alkylation in **18** is valid only for the diol groups. The last step of Scheme 4 shows how ioversol[25] [*N*,*N*′-bis-(2,3-dihydroxy-propyl)-5-[(2-hydroxy-acetyl)(2-hydroxy-ethyl)-amino]-2,4,6-triiodo-isophthalamide] is formed when the boric acid-protected substrate **18** is reacted with 2-chloro-ethanol.

The Different Elements Put Together To Give a New Selective Alkylation Process. The base is dissolved in water. Then the substrate **1** (1 equiv) is dissolved in this water solution and the boric acid then added. The optimal quantity (equiv) of boric acid (BA) to be added depends on the number of 1,2-diol groups, N_{diol}, present in the substrate. The quantity is given by eq 2

$$BA = N_{diol} \times f_{diol} \quad (2)$$

The factor f_{diol} has been determined to be in the range 0.5−2, where $f_{diol} > 1$ signifies a requirement for more boric acid equivalents than the number of diol groups; $f_{diol} < 1$ signifies a requirements for fewer boric acid equivalents than diol groups, and finally $f_{diol} = 1$ indicates an equimolar number of diol groups and boric acid.

The quantity of base OH (equiv) that should be used to adjust the optimum pH as described above is linked to (1) the quantity of boric acid, (2) the nature of the starting material, and (3) the alkylation reagent. For this purpose, we have derived the model given in eq 3, which can be used to estimate the quantity (equiv) of base OH:

$$OH = (BA + N_{N-H}) \times f + r \quad (3)$$

where BA = quantity of boric acid as described in eq 2 above; N_{N-H} = number of acidic N−H in the substrate; f is a correction factor for the quantity of base, it is preferably $f = 1$, but may vary in the interval $f = 0-2$; r is a reagent indicator variable, where $r = 0$ for epoxides or alkyl halides, $r = 1$ for halohydrins or for dialkyl sulphate alkylation

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(23) van Duin, M.; Peters, J. A.; Kieboom, A. P. G.; van Bekkum, H. *Tetrahedron* **1985**, *41*, 3411−3421.
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(25) Baily, A. R. et al. (Mallinckrodt Medical Inc.). U.S. Patent 5,489,708, 1996; Dunn, T. J. et al. U.S. Patent 5,648,536, 1997.

reagents, and finally $r = 2$ is used when base excess appears to give advantages.

The water volume is adjusted to a minimum, but a sufficient volume, 0.3−5 L/kg of substrate **1**, should be used to achieve a reaction mixture with a suitable viscosity. The mixing temperature is 20−50 °C, with a mixing time of 3−24 h, depending on the selected mixing temperature. The pH is monitored and if necessary adjusted to the desired value by addition of more base or boric acid. The optimal pH range depends on the pK_a of the nucleophile and hydrolytic rates of the alkylation reagent. The reaction temperature is adjusted in the range of 40−60 °C. The quantity (equiv) of alkylation reagent is given by eq 4

$$\mathrm{AR} = (N_{\mathrm{AR}})^{-1} + h \tag{4}$$

where the alkylation reagent variable $N_{\mathrm{AR}} = 1$ for mono-alkylating reagents and $N_{\mathrm{AR}} = 2$ for bis-alkylating reagents. The additive factor h is included to compensate for partial hydrolysis of the alkylation reagent, and for economic reasons this factor should be kept as small as possible. The alkylation reagent may be added in portions or continuously. The pH has to be continuously monitored and stabilized within the optimal pH range by addition of small amounts of base or boric acid. The reaction time depends on the reaction temperature and is typically 3−24 h. For working-up the reaction mixture, hydrochloric acid is added until pH < 5, whereby the boric acid precipitates. The suspension is cooled to a temperature of 0 °C and kept at that temperature for 1−3 h. The reaction mixture is then filtered while being kept cold. Reverse osmosis or ion exchange is used to remove the salts. The solution is evaporated to dryness in a vacuum and gives the crude product.

Conclusions

Using the synthetic strategy of Scheme 1 and by taking account of knowledge concerning the optimised pH adjustments for different alkylating reagents and the stability of the boronic acid esters, we have developed a general organic process with an improved chemoselectivity for the *N*-alkylation of polyhydroxy-containing substrates. Several X-ray contrast agents used for medicinal imaging diagnostics were synthesised using both the new process involving the protection of the diol groups and without the protecting steps to allow a comparison to be made. Table 1 shows the results. When the protection strategy was used in the processes to iohexol, iodixanol, iopentol and, ioversol (see Schemes 3 and 4), the *N*/*O*-alkylation ratios were substantially improved concomitant with a considerably increased yield of target molecule.

Experimental Section

Materials. The starting material 5-acetylamino-*N*,*N*′-bis-(2,3-dihydroxy-propyl)-2,4,6-triiodo-isophthalamide **14** was supplied by Nycomed Lindesnes Fabrikker (Norway). *N*,*N*′-Bis-(2,3-dihydroxy-propyl)-5-(2-hydroxy-acetylamino)-2,4,6-triiodo-isophthalamide **16** was prepared from 5-acetylamino-*N*,*N*′-bis-(2,3-dihydroxy-propyl)-2,4,6-triiodo-isophthalamide **14** and acetoxyacetyl chloride.[25] Reagents were purchased from commercial sources and used without further purification. All of the reaction products were known and were analysed by HPLC and by comparison with authentic samples that were either isolated from commercial products or from in-house production (Nycomed).

HPLC Analytical Methods.[26] The HPLC analyses were performed on an HPLC instrument equipped with a RP-18 Spheri-5 column (4.6 × 250 mm) from Brownlee Labs. The column was operated at room temperature. The detector was UV $\lambda = 254$ nm. The sample injection volume was 10 or 20 μL. The eluent system was composed of two different solvents A (a mixture of 50% water and 50% acetonitrile) and B (100% water). The eluent flow was 1 mL min^{-1}. The eluent program was: equilibration for 15 min A:B = 6:94, linear gradient starting at time = 0 min A:B = 6:94 to time = 29 min A:B = 20:80, followed by a concave gradient that started at time = 30 min with A:B = 20:80 that ended at time = 69 min with A:B = 100:0.

Sampling and Sample Preparation. A sample of 50 μL was withdrawn from the reaction mixture and diluted in a solution of concentrated HCl (50 μL) in water (14 mL). The prepared sample was injected (10 or 20 μL) on HPLC (RP-18).

Iodixanol. Substrate **14** (100 g) was dissolved in a solution of KOH (3.0 equiv, 22.53 g) in water (0.9 vol/wt **14**, 90 mL). Boric acid (2.0 equiv, 16.55 g) was added, and the solution was stirred for 48 h at 10 °C. Starting pH = 12.93. Epichlorohydrin (0.57 equiv, 7.046 g) was added to the stirred solution at 10 °C. The reaction mixture was stirred at 10 °C, and the pH was stabilized in the range 12.6−13. Samples were taken at 24 and 48 h and analysed by HPLC.

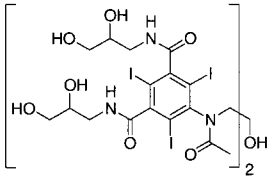
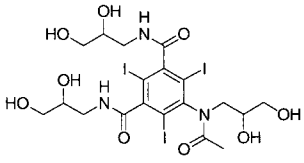
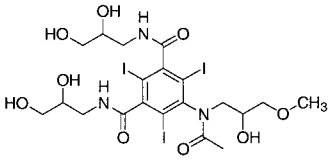
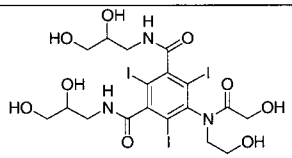
Substrate **14** (1 equiv, 100 g) was dissolved in a solution of Borax ($K_2B_4O_7{\cdot}4H_2O$) (2.0 boron-equiv, 20.45 g) in water (1.0 vol/wt **14**, 100 mL). KOH (2.0 equiv, 15.02 g) was added, and the solution was stirred for 48 h at 10 °C. Starting pH = 12.86. Epichlorohydrin (0.55 equiv, 6.80 g) was added to the stirred solution at 10 °C. The reaction mixture was stirred at 10 °C, and the pH was stabilized in the range 12.6−13 by addition of small amounts of boric acid or KOH. Samples were taken at 24 and 48 h and analysed by HPLC.

Substrate **14** (1 equiv, 100 g) was dissolved in a solution of potassium metaborate (KBO_2 H_2O) (2.0 boron-equiv, 26.75 g) in water (1.0 vol/wt **14**, 100 mL). KOH (1.0 equiv, 7.51 g or less) was added to the stirred solution until the pH was stabilized in the range 12.6−13. The solution was stirred for 48 h at 10 °C. Starting pH = 12.71. Epichlorohydrin (0.55 equiv, 6.80 g) was added to the stirred solution at 10 °C. The reaction mixture was stirred at 10 °C, and the pH was stabilized in the range 12.6−13 by addition of small amounts of boric acid or KOH. Samples were taken at 24 and 48 h and analysed by HPLC.

Reference Experiment without Boric Acid. Substrate **14** (1 equiv, 100 g) was dissolved in a solution of sodium hydroxide (1.2 equiv, 6.43 g) in water (3.0 vol/wt **14**, 300 mL). The solution was stirred 24 h at 25 °C. Epichlorohydrin

(26) *Pharmacopoeial Forum Vol.* **2000**, *26*, 596−604.

Table 1. **Experimental results with and without the boric protection group**

Target Molecule	Experimental conditions[a] R eqv.	KOH eqv.	PG eqv.	*t* [h]	Responses[b] TM	S	O	B
 Iodixanol	EPI 0.57	3.0	**A** 2.0	24 48	80.3 83.4	6.9 2.5	5.1 5.2	7.5 8.9
	EPI 0.55	2.0	**B** 3.0	24 48	80.6 83.4	8.9 4.7	4.4 4.8	6.1 7.1
	EPI 0.55	1.0	**C** 2.0	24 48	79.8 83.3	8.7 3.8	4.7 5.1	6.8 7.8
	EPI 0.50	1.2[c)]	**N**	24	49.1	25.1	16.7	9.1
 Iohexol	CPD 1.10	4.5	**A** 2.5	24 48	78.3 86.8	19.2 10.5	2.5 2.6	– –
	GCD 1.03	3.5	**A** 2.5	24 48	72.7 78.6	23.8 16.9	3.5 4.4	– –
	CPD 1.10	2.0	**N**	24 48	65.5 67.1	23.1 17.6	9.5 14.1	– –
	GCD 1.03	1.0	**N**	24 48	55.3 54.2	25.3 28.2	18.5 15.4	– –
 Iopentol	GME 1.03	3.25	**A** 2.75	24 48	83.1 85.3	11.0 7.8	5.8 6.2	– –
	CMP 1.03	4.0	**A** 3.0	24 48	71.2 82.2	26.6 15.2	2.1 2.5	– –
	GME 1.03	0.5	**N**	24 48	67.0 67.9	22.7 20.3	9.4 10.9	– –
	GME 1.03	1.0	**N**	24 48	57.0 56.0	26.5 20.3	15.0 16.1	– –
	CMP 1.03	1.5	**N**	24 48	76.1 81.7	19.3 11.9	4.2 6.1	– –
	CMP 1.03	2.0	**N**	24 48	65.0 64.0	20.0 20.0	16.0 16.0	– –
 Ioversol	CLE 1.05	5.5	**A** 3.5	24 48	67.8 67.5	12.8 11.1	19.4 21.4	– –
	CLE 1.05	2.0	**N**	24 48	39.2 37.6	23.4 23.2	37.4 39.2	– –

[a] **R** = alkylating reagent (equivalents), EPI = epichlorohydrin, CPD = 3-chloro-1,2-propanediol, GCD = glycidol, GME = glycidyl methyl ether, CMP = 3-chloro-1-methoxy-2-propanol, CLE = 2-chloro-ethanol. **PG** (eqv) = type protection reagent (equivalents), **A** = $B(OH)_3$, **B** = $K_2B_4O_7 \cdot 4H_2O$, **C** = $KBO_2 \cdot H_2O$, **N** = no protection, *t* [h] = reaction time (h). [b] HPLC measurements of **TM** = target molecule, **S** = substrate, **O** = *O*-alkylated by-products, **B** = iohexol as by-product. [c] In this experiment was NaOH used as base.

(0.5 equiv, 6.181 g) was added to the stirred solution at 25 °C, and stirring continued. Samples were taken at 24 and 48 h and analysed by HPLC.

Iohexol. Substrate **14** (1 equiv, 100 g) was dissolved in a solution of KOH (4.5 equiv, 33.8 g) in water (1.0 vol/wt **14**, 100 mL). Boric acid (2.5 equiv, 20.69 g) was added, and the solution was stirred for 48 h at 10 °C. Starting pH > 14. 3-Chloro-1,2-propanediol (1.10 equiv, 16.28 g) was added to the stirred solution at 10 °C. The reaction mixture was stirred at 10 °C, and the pH dropped below 13. The pH was then stabilized in the range 12.6−13 by adding small amounts of boric acid (totally 0.14 equiv, 1.17 g). Samples were taken at 24 and 48 h and analysed by HPLC.

Substrate **14** (100 g) was dissolved in a solution of KOH (3.5 equiv, 26.29 g) in water (1.0 vol/wt **14**, 100 mL). Boric acid (2.5 equiv, 20.69 g) was added, and the solution was stirred for 48 h at 10 °C. Starting pH ≈ 12.4. Glycidol (1.03 equiv, 10.21 g) was added to the stirred solution at 10 °C. The reaction mixture was stirred at 10 °C, and the pH drifted towards 13. The pH was then stabilized in the range 12.6−13 by adding small amounts of boric acid (totally 0.34 equiv,

2.86 g). Samples were taken at 24 and 48 h and analysed by HPLC.

Reference Experiments without Boric Acid. Substrate **14** (10 g) was dissolved in a solution of KOH (2 equiv, 1.50 g) in water (1.0 vol/wt **14**, 10 mL). 3-Chloro-1,2-propanediol (1.10 equiv, 1.63 g) was added to the stirred solution at 10 °C. The reaction mixture was stirred at 10 °C. Samples were taken at 24 and 48 h and analysed by HPLC.

Substrate **14** (10 g) was dissolved in a solution of KOH (1 equiv, 0.75 g) in water (1.0 vol/wt 5410, 10 mL). Glycidol (1.03 equiv, 1.02 g) was added to the stirred solution at 10 °C. The reaction mixture was stirred at 10 °C. Samples were taken at 24 and 48 h and analysed by HPLC.

Iopentol. Substrate **14** (100 g) was dissolved in a solution of KOH (3.25 equiv, 24.41 g) in water (1.0 vol/wt **14**, 100 mL). Boric acid (2.75 equiv, 22.76 g) was added, and the solution was stirred for 48 h at 20 °C. Starting pH ≈ 11.7. Glycidyl methyl ether (1.03 equiv, 12.15 g) was added to the stirred solution at 20 °C. During the course of the reaction, the pH of the reaction mixture increased but not above 13. Samples were taken at 24 and 48 h and analysed by HPLC.

Substrate **14** (100 g) was dissolved in a solution of KOH (4.0 equiv, 30.04 g) in water (1.0 vol/wt **14**, 100 mL). Boric acid (3.0 equiv, 24.83 g) was added, and the solution was stirred for 48 h at 20 °C. Starting pH ≈12.4. 3-Chloro-1-methoxy-2-propanol (1.03 equiv, 17.17 g) was added to the stirred solution at 20 °C. During the course of the reaction, the pH of the reaction mixture decreased, but never below 10. Samples were taken at 24 and 48 h and analysed by HPLC.

Reference Experiments without Boric Acid. Substrate **14** (10 g) was dissolved in a solution of KOH (0.5 equiv, 0.38 g) in water (1.0 vol/wt **14**, 10 mL). Glycidyl methyl ether (1.03 equiv, 1.21 g) was added to the stirred solution at 20 °C. Samples were taken at 24 and 48 h and analysed by HPLC.

Substrate **14** (10 g) was dissolved in a solution of KOH (1.0 equiv, 0.75 g) in water (1.0 vol/wt **14**, 10 mL). Glycidyl methyl ether (1.03 equiv, 1.21 g) was added to the stirred solution at 20 °C. Samples were taken at 24 and 48 h and analysed by HPLC.

Substrate **14** (10 g) was dissolved in a solution of KOH (1.5 equiv, 1.13 g) in water (1.0 vol/wt **14**, 10 mL). 3-Chloro-1-methoxy-2-propanol (1.03 equiv, 1.72 g) was added to the stirred solution at 20 °C. Samples were taken at 24 and 48 h and analysed by HPLC.

Substrate **14** (10 g) was dissolved in a solution of KOH (2.0 equiv, 1.50 g) in water (1.0 vol/wt **14**, 10 mL). 3-Chloro-1-methoxy-2-propanol (1.03 equiv, 1.72 g) was added to the stirred solution at 20 °C. Samples were taken at 24 and 48 h and analysed by HPLC.

Ioversol. Substrate **16** (7.0 g) was dissolved in a solution of KOH (5.5 equiv, 2.83 g) in water (1.0 vol/wt **16**, 7 mL). Boric acid (3.5 equiv, 1.99 g) was added, and the solution was stirred 48 h at 20 °C. 2-Chloro-ethanol (1.05 equiv, 0.78 g, 0.644 mL) was added to the stirred solution at 20 °C. Sampling was performed at 24 and 48 h, and the samples were analysed on HPLC.

Reference Experiment without Boric Acid. Substrate **16** (7.0 g) was dissolved in a solution of KOH (2 equiv, 1.03 g) in water (1.0 vol/wt **16**, 7 mL). 2-Chloro-ethanol (1.05 equiv, 0.78 g, 0.644 mL) was added to the stirred solution at 20 °C. Samples were taken at 24 and 48 h and analysed by HPLC.

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