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Application of Oxathiazolidine-S-oxide Chemistry to the Large-Scale Single-Step Synthesis of an O-Arylethanolamine

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Abstract:

Alternative routes to the arylethanolamine subunit of a development drug have been investigated. The selected route, involving O-alkylation of a phenol using N-benzyloxathiazolidine-S-oxide, was developed to give a process used successfully for pilot plant manufacture.

Introduction

Zeneca Pharmaceuticals development candidate ZD2079 (**7**), a β-3 agonist intended for the treatment of non-insulin-dependent diabetes, entered development in 1991. Prior to entry into development, the route outlined in Scheme 1[1] (X = Br) had been used by chemists in our Research Department to prepare 230 g of **7**.

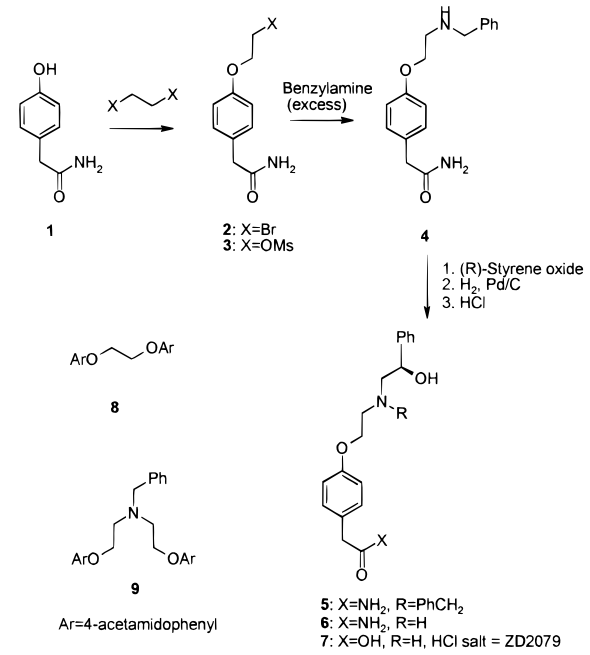
The majority of the process chemistry challenges posed by the synthesis of **7** were resolved relatively quickly. The selectivity of the opening of styrene oxide with amine **4** was optimised by selection of a sterically hindered alcohol as reaction solvent (methyl isobutylcarbinol). Furthermore, the intermediate **5** and product **6** were found to be crystalline, and hence they could be easily purified. The subject of this article is the preparation of the amine **4**, which necessitated a more fundamental investigation of process alternatives.

Results and Discussion

Early Manufacturing Campaigns. The approaches to **4** used for early development manufacture were based on that used in our Research Department, shown in Scheme 1 (X = Br). It was immediately apparent, based on previous work on an earlier development compound,[2] that large-scale reaction of dibromoethane with **1** would be unacceptable, as the toxic gas vinyl bromide is generated and cannot readily be removed by scrubbing on a plant scale.

For initial pilot plant manufacture, therefore, ethylene glycol dimesylate was used in place of dibromoethane. When phenol **1** was reacted with ethylene glycol dimesylate (1.7 equiv), the reaction was acceptable, but the physical form of product **3** was poor, and therefore plant filtration times were long. Mesylate **3** was then reacted with 7 equiv of benzylamine (lower charges of benzylamine gave rise to unacceptable levels of tertiary amine **9**, which could not be removed by downstream processing). The mixture was filtered to remove the bis-ether impurity **8** and diluted with water to precipitate product, and the product was filtered off. Again, on the plant scale there were major problems with rates of both the impurity screen and the product filtration, the latter taking up to 2 weeks on a 100-kg scale. Attempts to improve the physical form and filtration rates of **3** and **4** were unsuccessful. In view of the poor yields (9% over three stages) and lengthy processing times, as well as the inefficiency of using large excesses of reagents, it was decided that the route was unsuitable for further scale-up, and work to develop an alternative route to **4** was initiated.

Scheme 1



N-Benzyloxathiazolidine-S-oxide (10). A more promising synthon for the two-carbon unit provided by ethylene glycol in the above approach appears to be N-benzylethanolamine (NBEA), which is inexpensive and readily available. However, activation of the hydroxyl group leads to formation of N-benzylaziridine, which is both toxic and unreactive towards nucleophiles.

It was envisaged that a cyclic derivative of benzylethanolamine such as **10** could provide activation of the oxygen towards nucleophilic attack while preventing intramolecular attack by nitrogen. While there are a few reports of this ring

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(2) Lee, S.; Robinson, G. *Process Development: Fine chemicals from grams to kilograms*; Oxford University Press: Oxford, UK, 1995; Chapter 9.

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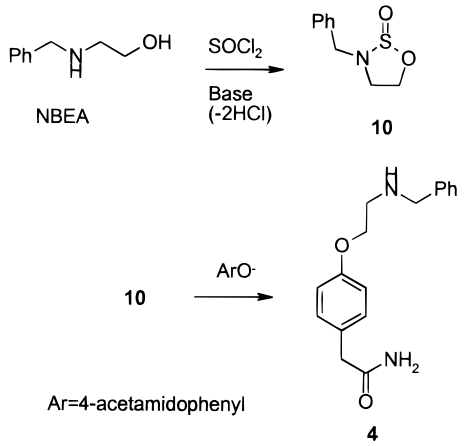
Scheme 2



system in the literature,[3−5] a paper describing its exploitation in synthesis has only recently been published.[6] The corresponding S,S-dioxide analogues have generally received more attention.[7,8] In initial laboratory investigations, **10** was prepared by reaction of NBEA with thionyl chloride and triethylamine[9] and isolated after an aqueous workup. Ring opening using the potassium salt of **1** then gave a 64% yield of **4**. However, stability trials showed that **10** was both thermally and hydrolytically[10] unstable, decomposing rapidly in contact with aqueous acid or base and more slowly when held at 70 °C in *N*-methylpyrrolidine (NMP). It was decided that the oxathiazolidine was not sufficiently stable to withstand the time scales or temperatures of plant-scale aqueous workup or a distillative solvent swap, and it followed that a process which avoided the isolation of **10** was necessary. After a range of reaction solvents were investigated, NMP was selected, a critical factor being its ability to dissolve both **1** and its sodium salt.

Laboratory Process Development. Accordingly, NBEA in NMP was treated with sodium hydride (2.0 equiv) followed by thionyl chloride.[11] Reaction to give **10** was efficient but did not proceed via the dianion of NBEA; one equivalent of sodium hydride reacted on addition, while the second equivalent did not react until thionyl chloride was added. On a laboratory scale, this simple and convenient process presented no problem, but on pilot plant scale the co-evolution of acidic gases, which required scrubbing, and flammable hydrogen, which required venting, could not be accommodated safely. Further attempts to form the dianion of NBEA using NaH and other bases were unsuccessful.

Table 1

	oxathiazolidine-S-oxide		
	ethylene glycol approach	sodium hydride approach[14]	N-methyl-morpholine approach[15]
no. of stages	3	1	1
yield (%)	9	59	44
output (g/L)	−	56	16.5
environmental load factor[12]	300	32	63.1
typical total related substances (%)	12.2	5.0	2.9

The problem of unreacted sodium hydride could be overcome if a second equivalent of NBEA was used. The second equivalent effectively acted as an inert base and was lost entirely to the mother liquors on workup. Addition of 2 equiv of the monoanion of NBEA (itself generated with sodium hydride) to thionyl chloride, followed by addition of the sodium salt of **1** at room temperature, gave fair yields of **4** (71% chemical yield, 47% after crystallisation). The isolated yield was increased to 59% (see Table 1) when the formation of **10** was performed between −10 and 0 °C. However, concerns still remained over the possible co-evolution of acid gases and hydrogen using this approach, and for this reason an alternative process was sought for the forthcoming plant campaign.

Other bases which gave a volatile byproduct on deprotonation of benzylethanolamine were investigated, with a view to removal of the byproduct by distillation prior to thionyl chloride addition. Sodium methoxide, sodium hydroxide, and tetramethylammonium hydroxide all failed to give acceptable reactions, probably due to incomplete removal of the water or methanol byproducts.

Plant Process and Manufacture. Attention was then turned to amine bases for the formation of **10**. Removal of the amine hydrochloride byproduct could then be carried out by filtration, again avoiding exposure of **10** to water or high temperature. N-Methylmorpholine (NMM) was selected, as its hydrochloride salt has very low solubility in NMP. A process was developed for the manufacturing campaign in which **10** was prepared by addition of thionyl chloride to NBEA in the presence of NMM (2 equiv). The NMM hydrochloride salt was removed by filtration, and the product solution was added to the sodium salt of **1**.

This process was used successfully to manufacture three batches of **4** on a 1000-L scale, yielding 75 kg of **4** in total, which was used satisfactorily to manufacture 40 kg of the drug substance.

The performances of the three processes (initial approach using ethylene glycol, best laboratory process using **10**, and plant process using **10**) are compared in Table 1. The latter two offer large advantages in yield, quality, and environmental impact[12] over the route originally employed. No significant new impurities were generated by the change of

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(9) White, G. J.; Garst, M. E. *J. Org. Chem.* **1991**, *56*, 3177. See also ref 3.
(10) Cox, S.; El Dusouqui, O. M. H.; McCormack, W.; Tillett, J. G. *J. Org. Chem.* **1975**, *7*, 949.
(11) Both thionyl chloride and sodium hydride react slowly with NMP. A full chemical hazard assessment of the process prior to manufacture showed that such side reactions did not render the process unsafe at the concentrations used.

(12) The environmental load factor is calculated as the ratio of total weight of materials used in the stage(s) to the weight of pure stage product. This is a quantitative measure of the environmental impact and does not take into account the varying environmental impact of different types of effluent.

route, and the quality of the derived drug substance was therefore not affected. Further work was in progress to render the preferred laboratory process suitable for plant accommodation, and to investigate further the mechanism of reaction,[13] when ZD2079 was withdrawn from development.

Conclusion

The relatively unexploited chemistry of the oxathiazolidine-S-oxide ring has been used to provide a single-step route to the O-arylethanolamine intermediate **4** of a development drug. A simple and convenient laboratory process was developed using sodium hydride as base throughout. Due to concerns about safety on scale-up, a modified process was used for plant manufacture, to give 75 kg of **4**; the process was shown to be robust and the product to be of acceptable quality. The process offered significant advantages over the original route, particularly in terms of reduced number of stages and improved operability.

Experimental Section

General. Solvents and raw materials were obtained from commercial suppliers and used without further purification. NMP used was anhydrous (<0.05% water).

The structure of the drug substance **7** has been confirmed unambiguously by a wide variety of physical measurements, proton and carbon NMR spectroscopy, mass spectrometry, and UV spectroscopy. Total levels of related substances in amine **4** cited in Table 1 and strengths cited in this section were determined by HPLC under the following conditions: eluent, 62.5% methanol, 37.5% aqueous 9.4 mM sodium lauryl sulphate solution; column, Spherisorb C8, 25 × 0.46 cm; UV detection at 210 nm; flow rate, 1.5 mL/min. All reactions were carried out under an inert atmosphere of either nitrogen or argon.

2-Oxo-3-phenylmethyl-1,2,3-oxathiazolidine (10). Intermediate **10** was not routinely isolated but was isolated for characterisation purposes by the reaction of NBEA in dichloromethane with thionyl chloride and triethylamine, followed by an aqueous workup at 0−5 °C. ^{1}H NMR: δ 3.3 (1H, m), 3.5 (1H, m), 4.0 (1H, AB), 4.4 (2H, AB + m), 4.8 (1H, m), 7.3−7.4 (5H, m). EI: *m/s* (relative intensity) 197 (M^+, 15), 133 (75), 120 (15), 104 (70), 91 (100).

4-[2-(Phenylmethylamino)ethoxy]phenyl Acetamide (4). *Laboratory Process.* To a suspension of sodium hydride (8.0 g of a 60% dispersion in mineral oil, 2.0 equiv) in NMP (57 mL) at −10 °C was added N-benzylethanolamine (28.4 mL, 30.2 g, 2.0 equiv) over a period of 50 min. The mixture was stirred at −4 °C for 65 min, and then thionyl chloride (7.2 mL, 11.5 g, 1.0 equiv) was added over 40 min. The solution was allowed to warm to room temperature and stirred overnight to give **10**. In a second flask, sodium hydride (4.0 g of a 60% dispersion in mineral oil, 1.0 equiv) was suspended in NMP (24 mL). To this was added a solution of 4-hydroxyphenylacetamide **1** (15.1 g, 1.0 equiv) in NMP (24 mL) over 45 min at 10 °C. After this solution was stirred at 10 °C for 70 min, the solution of **10** in NMP was added at room temperature over 15 min. The reaction mixture was then heated to 63−65 °C and stirred at this temperature overnight. After cooling, the mixture was drowned out into water (151 mL) containing sodium hydroxide (11.2 mL of a 17.5 M solution, 2.0 equiv) over 25 min, and the resultant slurry was stirred for 65 min at room temperature. The product was collected by filtration, washed with water, and dried overnight at 70 °C to give the title compound, 20.87 g dry weight, 81.7% w/w by HPLC analysis versus an authenticated external standard, as a beige-coloured solid. Corrected yield = 60%. ^{1}H NMR: δ 2.5 (1H, broad), 2.8 (2H, AA′BB′), 3.3 (2H, s), 3.7 (2H, s), 4.0 (2H, AA′BB′), 6.8 (2H, d), 7.2 (2H, d), 7.3−7.5 (7H, m). IR (KBr disk): ν 3380, 3150, 2900, 2800, 1640, 1520, 1240, 1040, 800, 740, 700. EI: *m/s* (relative intensity) 284 (M^+, 20), 134 (20), 120 (97), 91 (100).

Plant Process. To a solution of N-benzylethanolamine (26.6 kg, 176 mol) and N-methylmorpholine (NMM, 35.7 kg, 353 mol) in NMP (175 kg) at 10 °C was added thionyl chloride (20.9 kg, 176 mol). The mixture was stirred at 10 °C for 12−18 h to give **10** and then filtered to remove NMM hydrochloride salt. To a second vessel was charged sodium hydride (7.0 kg of a 60% dispersion in mineral oil (175 mol) and NMP (40 kg). To the resultant stirred slurry was added a solution of 4-hydroxyphenylacetamide (**1**, 26.6 kg, 176 mol) in NMP (40 kg) over 2.75 h at 10−15 °C. The mixture was stirred at this temperature for 1 h, the solution of **10** in NMP was added, and the mixture was heated to 65 °C for 12−18 h. The mixture was cooled and then drowned out into a solution of sodium hydroxide (30 kg of a 47% solution, 353 mol) in water (788 kg). The resultant slurry was stirred at 20 °C for 1 h, and then the product was collected by filtration, washed with water, and dried at 50 °C. The process yielded 26.0 kg of the title compound of strength 87.1% (w/w) and a yield of 44.4%.

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(13) Wudl, F.; Lee, T. B. K. *J. Am. Chem. Soc.* **1973**, *95*, 6349.
(14) Refers to laboratory process given in the Experimental Section.
(15) Refers to plant process given in the Experimental Section.