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Technical Notes

A Synthesis of Atenolol Using a Nitrile Hydration Catalyst

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Abstract:

The synthesis of atenolol is described using a platinum containing homogeneous catalyst for the conversion of a nitrile to an amide. The catalytic reaction may be employed as the final step in the synthesis or in the preparation of the intermediate 4-hydroxyphenylacetamide. The structure of the nitrile intermediate, 1-(4′-cyanomethylphenoxy)-2-hydroxy-3-isopropylaminopropane, has been determined by X-ray crystallography.

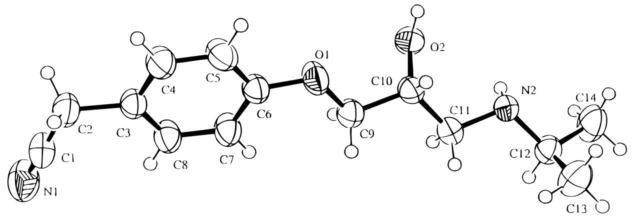
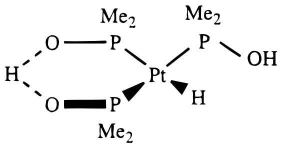


Figure 1. **Molecular Structure of 3b showing the atomic numbering.**

Introduction

Atenolol (**3a**) is a widely used β-blocker which contains an amide group. The usual industrial route to atenolol uses the reaction of 4-hydroxyphenylacetamide (**1a**) with epichlorohydrin followed by ring opening of the epoxide **2a** with isopropylamine (see Scheme 1).[1]

An alternative synthesis using the nitrile **1b** as starting material and converting the nitrile **3b** to atenolol (**3a**) as the final step has been proposed by Rosenberg.[2] We recently reported that bis(dimethylphosphinous acid-κP)dimethylphosphinyl-κP-hydridoplatinum(II) (**4**) is a catalyst for the hydrolysis of nitriles to amides.[3]



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The catalyst converts a nitrile to an amide within the coordination sphere of the platinum atom, from which the amide is then released and, therefore, is not hydrolyzed further to the acid. We decided to test whether the catalyst could be used in the presence of other functional groups, in particular those involved in the conversion of **3b** to atenolol (**3a**).

Results and Discussion

The conversion of the phenol **1b** to the ether **2b** by reaction with epichlorohydrin has been described by Rosenberg,[2] Rietzel et al.,[4] and Lindner and co-workers.[5] This superficially simple reaction proceeds via a Payne rearrangement,[6] so that the carbon atom initially bonded to chlorine in epichlorohydrin becomes the terminal atom of the epoxide group in **2b**. We carried out the reaction between **1b** and epichlorohydrin to give **2b** with a piperidine catalyst using a modification of the procedure given by Barrett et al.[7] for the amide **2a**. Ring opening of the epoxide **2b** to the amino alcohol **3b** was carried out as described by Rietzel and coworkers[4] by reaction with a large excess of isopropylamine in methanol at room temperature and atmospheric pressure. We found this to be simpler and more satisfactory than the use of a sealed tube at 110 °C as described by Barrett et al.[7]

As there are some discrepancies (see Experimental Section) in the literature concerning the melting point of **3b**, and as we had good quality crystals available, we decided to carry out an X-ray structure determination of this nitrile. Figure 1 shows an ORTEP drawing of **3b** and the numbering scheme. The bond lengths are normal, and the main item of interest is the intermolecular hydrogen bonding between the hydroxy group O2−H and the amine nitrogen N2 of a neighbouring molecule which occurs around a centre of symmetry, giving a dimeric unit.

The isolation of amides by the hydrolysis of nitriles is often difficult because of the tendency for further hydrolysis to the acid to occur.[8] One method of obtaining the amide is to use very concentrated acid for the nitrile hydration,

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(4) Rietzel, C.; Knauf, H.; Mutschler, E.; Volger, K.-D. GB Pat. Appl. 2,155,-923 A, 1985. Equivalent to: Belgian Pat. Appl. 901850; *Chem. Abstr.* **1985**, *103*, 178279.

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(6) March, J. *Advanced Organic Chemistry,* 4th ed.; J.Wiley: New York, 1992; p 391. Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819.

(7) Barrett, A. M.; Carter, J.; Hull, R.; Le Count, D. J.; Squire, C. J. US Patent 3,836,671, 1974. Equivalent to: Ger. Offen. 2007751; *Chem. Abstr.* **1970**, *73,* 120318.

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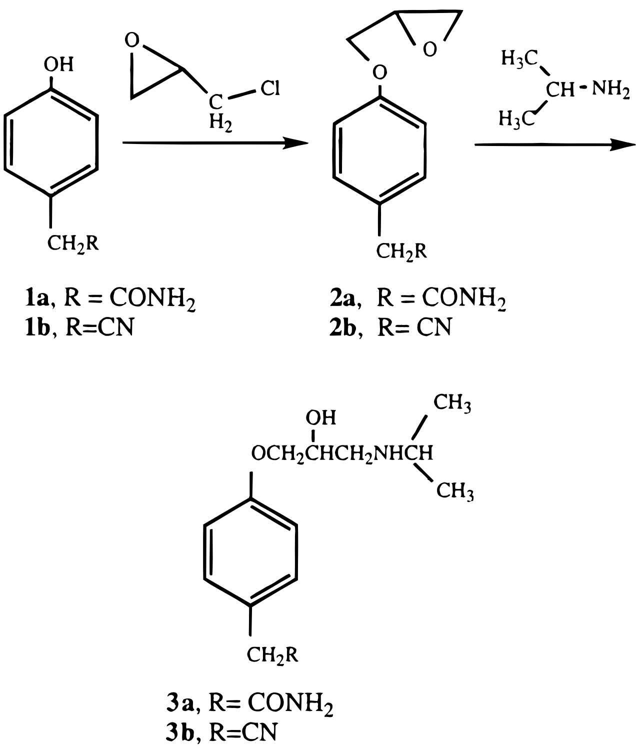
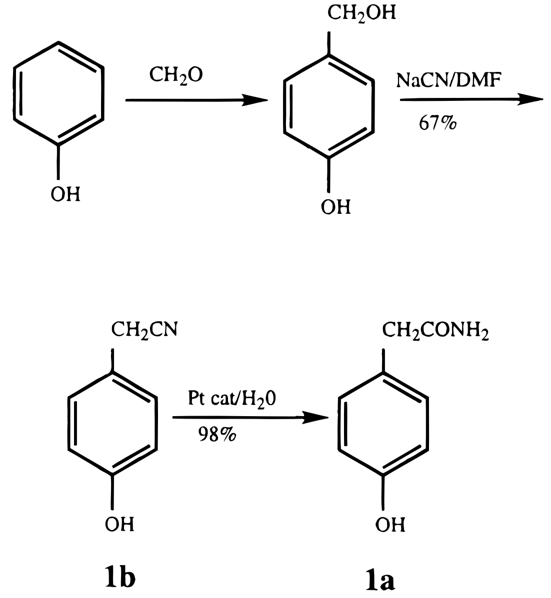
because under these conditions, the rate of hydrolysis of the nitrile to the amide is faster than that of the amide to the acid: in dilute solution the relationship is reversed.[9] In the case of the hydrolysis of **3b** to **3a**, Rosenberg[2] used concentrated hydrochloric acid saturated with gaseous hydrogen chloride in a pressure vessel at 50 °C to achieve the hydrolysis. As atenolol contains a basic amine group, 50% aqueous potassium hydroxide was needed to bring the pH to 12−13 and so liberate the product. Metal ion catalysts have clear advantages in homogeneous solution over simple acid or base catalysis. The other options which have been explored are heterogeneous metal[10] or metal oxide[11] catalysts and enzymes. The heterogeneous systems have been reviewed by Zil'berman[12] and enzymatic reactions involving nitriles have been surveyed by Sugai and co-workers.[13] The conditions required when using **4** as catalyst are mild, and we had no difficulty in executing the hydration step **3b** to **3a** using **4** as catalyst with a substrate/catalyst ratio of ∼740 in refluxing aqueous ethanol and obtained a yield of 93% in this step. Although the conversion of **3b** to **3a** proceeds satisfactorily using **4** as catalyst this is a difficult route to atenolol (**3a**). The intermediate nitriles **2b** and **3b** are low melting and not easy to crystallise but could be used as oils, as suggested by Rosenberg.[2]

A second approach which also employed the hydration catalyst was to use it to prepare 4-hydroxyphenylacetamide (**1a**), which is used in the industrial synthesis. Scheme 2 shows a very convenient route to **1a** starting from phenol, which is easily converted to 4-hydroxybenzyl alcohol. 4-Hydroxybenzyl cyanide (**1b**) can be made by an unusual reaction[14] involving displacement of the alcohol group by sodium cyanide in DMF. We found that the conversion of **1b** to **1a** can be achieved using **4** as catalyst with a substrate/catalyst ratio of ∼1000. This reaction proceeds very cleanly. Evaporation of the solvents gave a 98% yield of **1a** which had the correct melting point without recrystallisation, although it contained catalyst residues. The deficit of 2% probably arises from the impurities (especially water) in the commercial sample of **1b**.

Scheme 1



Scheme 2



Experimental Section

NMR spectra were measured at 360 MHz using a Bruker AM360 Spectrometer. The hydration catalyst, **4**, was prepared as described previously.[3] Reactions were carried out in air with no special precautions.

1-(4′-Cyanomethylphenoxy)-2,3 -epoxypropane (2b). A mixture of **1b** (2.0 g, 5 mmol), epichlorohydrin (5.9 cm^3, 75 mmol) and piperidine (3 drops) was heated at 95−100 °C for 6 h. The mixture was cooled and evaporated to give an oil, which was dissolved in hot methanol, treated with charcoal, filtered, and evaporated to give an oil. The oil was taken up in warm ethanol, diluted with hexane, and cooled to −20 °C to give the product as a waxy solid (1.36 g, 48%). Recrystallisation from 40−60 petrol/ethanol gave a free-flowing white powder (mp 47−48.5 °C). Lindner and co-workers[5] report a mp of 41-42 °C, but this appears to have been obtained by crystallisation of the oil. The NMR and IR spectra were in excellent agreement with those reported by Lindner and co-workers.

Anal. Found: C, 69.16; H, 5.63; N, 7.26. Calcd for C$_{11}$H$_{11}$NO$_2$: C, 69.83; H, 5.86; N, 7.40.

1-(4′-Cyanomethylphenoxy)-2-hydroxy-3-(isopropylamino)propane (3b). Compound **2b** (1.36 g, 7.2 mmol)

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was stirred with isopropylamine (6.1 cm^3, 72 mmol) in methanol (10 cm^3) at room temperature for 20 h. The solvent and excess of isopropylamine were removed by evaporation in vacuo, and the residue was crystallised from 2-propanol/hexane to give the product (1.03 g, 58%). Treatment with charcoal and recrystallisation from ethyl acetate gave white crystals (mp 70−72 °C, lit.[15] 70−72 °C). The NMR and IR spectra were in good agreement with those reported by Lindner and co-workers,[5] who crystallised their sample by stirring with petroleum and obtained a melting point of 77−78 °C. The crystal used for X-ray crystallography was crystallised from ethyl acetate/2-propanol.

Anal. Found: C, 67.65; H, 8.20; N, 11.31. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.72; H, 8.12; N, 11.28.

X-ray Crystallography. *Crystal data of **3b**:*[16] $C_{14}H_{20}N_2O_2$, triclinic, space group $P\bar{1}$, $a = 544.90(4)$, $b = 802.00(4)$, and $c = 1623.0(5)$ pm, $\alpha = 95.251(1)°$, $\beta = 96.573(1)°$, $\gamma = 94.912(1)°$, $V = 0.69850(7)$ nm^3, $Z = 2$, $D_x = 1.181$ Mg m^{-3}, λ(Mo Kα) = 71.073 pm, $\mu = 0.08$ mm^{-1}, $T = 298$ K.

Data collection and reduction: The colourless crystal 0.6 × 0.4 × 0.1 mm was mounted on a thin glass fibre using a fast setting epoxy resin. A total of 90 oscillation frames each of width 2° in ϕ and of 15 s exposure time were recorded using a Nonius $^{\text{Kappa}}$CCD diffractometer, with a detector to crystal distance of 25 mm. Crystals were indexed from the first 10 frames using the DENZO package[17] and positional data were refined along with diffractometer constants to give the final unit cell parameters; 6107 data to $2\theta_{\max} = 50°$ were collected, of which 2305 were used in the structure determination. Integration and scaling (DENZO, Scalepack[17]) resulted in unique data sets corrected for Lorentz and polarisation effects and for the effects of crystal decay and absorption by a combination of averaging of equivalent reflections and an overall volume and scaling correction.

Structure solution and refinement: The structure was solved by direct methods and refined using cycles of least squares and difference Fourier synthesis SHELXL-97[18] with the aid of the program RES2INS.[19] All non-hydrogen atoms were modelled anisotropically, while hydrogen atoms were placed in idealised positions, assigned an isotropic thermal parameter 1.2 times that of the parent atom (1.5 for terminal atoms) and allowed to ride on the atom to which they were attached. N−H and O−H hydrogen atoms were located experimentally and refined freely. All calculations were carried out with either a Silicon Graphics Indy 5000 workstation or an IBM-compatible PC. The final $wR(F^2)$ was 0.1267 for 172 parameters, conventional $R(F) = 0.0463$. $S = 1.04$; max $\Delta/\sigma = 0.001$; $\Delta\rho = 141$ e nm^{-3}.

Atenolol (3a). Compound **3b** (0.43 g, 1.7 mmol) in ethanol (5 cm^3) and water (5 cm^3) was heated under reflux with the platinum hydration catalyst **4** (1 mg, 2.3×10^{-6} mol) for 72 h. Concentration in vacuo gave **3a** (0.43 g, 93% yield), which was recrystallised from ethyl acetate to give white crystals (0.28 g), the NMR and IR spectra of which showed excellent agreement with those of a commercial sample of atenolol.

Conversion of 4-Hydroxybenzyl cyanide (1b) to 4-Hydroxyphenylacetamide (1a). Compound **1b** (1.00 g, 7.5 mmol) in ethanol (5 cm^3) and water (5 cm^3) was heated under reflux with the platinum hydration catalyst **4** (3.2 mg, 7.5×10^{-6} mol) for 18 h. Evaporation of the solvent gave **1a** (1.11 g, 98%) (mp 175−176, lit.[20] 175 °C).

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[16] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax, int.code+(1223) 336033; e-mail, teched@chemcrys.cam.ac.uk). Deposition number 101136.

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