Organic Process Research & Development **2002**, *6,* 811−813

Technical Notes

Development of a Manufacturing Route to 1-Hydroxy-4-(3-pyridyl)butan-2-one Using Heck Methodology

Debra Ainge* and Luis-Manuel Vaz

AstraZeneca, Process Research & Development Department, Charnwood, Bakewell Road, Loughborough, Leicestershire, LE11 5RH, UK

Abstract:

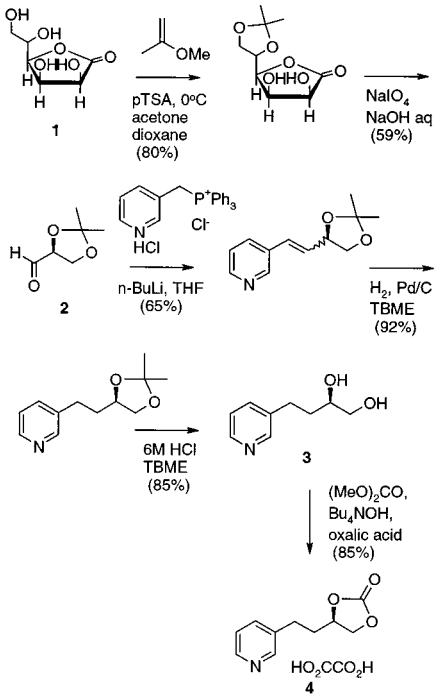
The optimisation and scale-up of a manufacturing route to a key intermediate, 1-hydroxy-4-(3-pyridyl)butan-2-one, utilising the Heck coupling of 3-bromopyridine and 3-butene-1,2-diol, is described.

A manufacturing route to pyridine diol **3**, a key intermediate in a candidate drug, was required. The route had to be capable of supplying **3** in >1000 kg/annum at <£500/kg. Previously, the compound had been prepared using the route identified by Medicinal Chemistry, as detailed in Scheme 1.[1] This route was successfully optimised and scaled up in collaboration with a contract manufacturer and provided a total of 84 kg of the cyclic carbonate **4** in batches of 15−20 kg. However, it was recognised that this route would be unsuitable for the long-term supply of **3**. The aldehyde **2** is known to be unstable[2] with respect to racemisation and polymerisation, and this instability became problematic during scale-up of this route. This severely limited the window of time available to carry out the subsequent step and further scale-up of the route would have resulted in unacceptable processing times, leading to significant degradation of **2**. In addition, the cost of the starting material gulonolactone **1** (£350/kg) contributed to an unacceptably high cost of **4** (estimated at >£5000/kg). With this in mind, other potential routes were investigated.

Many alternative synthetic routes were investigated. The second synthesis that was carried out at scale is detailed in Scheme 2 and relied on the enzymatic resolution of the racemic α-hydroxy ester **5**. This route was successfully carried out by a contract manufacturer and provided 19 kg of **4**. Initial calculations predicted this route could supply **3** at a suitable cost. However, the initial calculated cost was not realised, partly because of the cost associated with the hydrogenation catalyst and enzymatic resolution step.

Previous research had demonstrated that asymmetric reduction of ketone **6** furnished the diol **3** in high yield and enantiomeric excess, Scheme 3. To exploit this finding, an efficient synthesis of ketone **6** was required. The ketone was

Scheme 1. **First-generation synthesis**



initially prepared using a low-yielding, multistep synthesis. Of many alternative approaches, the Heck coupling of 3-bromopyridine with 3-butene1,2-diol was the most attractive. Use of literature conditions[3] resulted in poor ratios of ketone **6** to unsaturated diol **7**, along with small amounts of **8**.

Work advanced by screening a range of bases (NEt_3, proton sponge, 1,2,2,5,5-pentamethyl piperidine, $^iPrNEt_2$, DBU, DABCO, K_2CO_3), ligands (PBu_3, P(o-tolyl)$_3$, dppm, dppe, and dppf), catalysts ($Pd(OAc)_2$ and $Pd_2(dba)_3$) and solvents (THF, toluene, and DME) to find the optimal conditions for the formation of **6**. The standard reaction conditions to test various components employed 5 vols of solvent (relative to 3-bromopyridine), 3-bromopyridine (1 equiv), 3-butene-1,2-diol (1.25 equiv) at reflux for 16−24

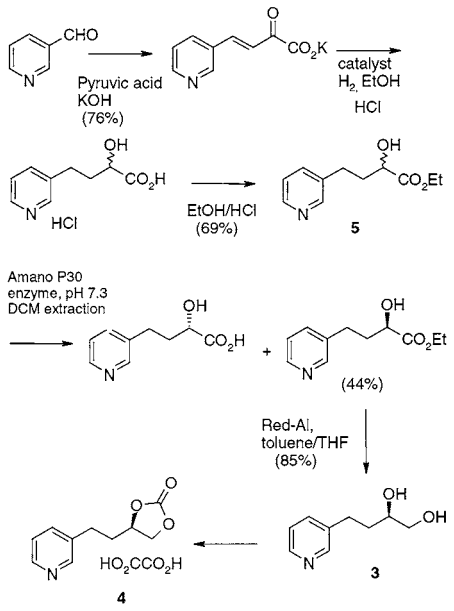
(1) Cheshire, D.; Cladingboel, D.; Hardern, D.; Stocks, M. PCT Int. Appl.; CODEN: PIXXD2, WO 9720815 A1 970612, p 146.

(2) Leonard, J.; Mohialdin, S.; Swain, P. *Synth. Commun.* **1989**, *19*, 3529 and references therein; Hubschwerlen, C. *Synthesis* **1986**, 962.

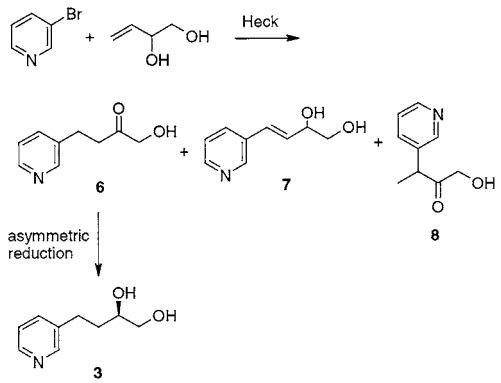
(3) Reetz, M. T.; Westermann, E.; Lohmer, R.; Lohmer, G. *Tetrahedron Lett.* **1998**, *39*, 8449; Reetz, M. T.; Lohmer, G.; Schwickardi, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 481; Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10; Jeffery, T. *Tetrahedron Lett.* **1994**, *35*, 3051.

10.1021/op0255736 CCC: $22.00
Published on Web 10/10/2002

Scheme 2. **Second-generation synthesis**



Scheme 3. **Third-generation synthesis**



h. A catalyst loading of 0.3 mol % and 1.25 or 2 equiv of base were employed in initial experiments. Over 50 sets of conditions were examined. The crude reaction mixtures were analysed by NMR, and the conversion and ratio of products were calculated. No attempt was made to isolate products from these reactions.

The choice of base had a dominant effect on the reaction selectivity and conversion. Proton sponge and 1,2,2,5,5-pentamethyl piperidine gave the best ketone:diol ratios, although the best conversion was obtained with the simple bases, NEt_3 and $^iPrNEt_2$. With the except of K_2CO_3, all bases gave some product. Use of 2 equiv of base compared to 1.25 equiv gave lower conversions. The ligand had less of an influence on the reaction. With the except of PBu_3, all ligands gave some product. Dppf favoured the formation of the ketone and gave the highest conversions. The affect of the catalyst was less straightforward, $Pd_2(dba)_3$ giving marginally better ketone selectivity. Toluene was the best solvent in terms of conversion and selectivity, although this effect may be attributed to differences in reaction temperature, as reactions were run at reflux for each solvent.

Considering all of the results obtained from this screen, the identified conditions were a combination of Pd_2dba_3, proton sponge, dppf, and toluene. This gave good conversion of starting materials (60−70%) and an excellent ratio of ketone:diol (13:1). However, further development and scale-up were not successful. Work aimed at improving the yield by achieving complete consumption of starting materials was not realised. We attributed this difficulty to the premature stalling of the reaction due to the trapping of starting materials in the proton sponge HBr salt that crystallises during the reaction. In addition, isolated yields were low (10−25%) due to difficulties in isolation. However, during this work we made an interesting observation. Quenching of the reaction mixture with Na_2CO_3 and extraction of the resulting aqueous phase with dichloromethane gave a 95:5 ratio of ketone:diol, regardless of the ratio of products in the aqueous phase. This prompted us to reevaluate our chosen reaction conditions.

Reinvestigation of our initial screen identified the NEt_3/P(*o*-tolyl)$_3$ system. Although not as selective for the ketone formation, these conditions gave consistently high conversion and also employed cheap, readily available reagents. To avoid the difficulty associated with the precipitation of the HBr salt of the base we opted to replace NEt_3 with NBu_3, whose HBr salt is soluble in toluene. We examined the NBu_3/P(*o*-tolyl)$_3$ system and showed it gave excellent conversion (+95%) with moderate ketone:diol selectivity (5:1). Further studies showed that Pd_2dba_3 could be replaced with $Pd(OAc)_2$ and the catalyst loading could be reduced to 0.1 mol %, although the reaction time was extended to 3 h.

Work then concentrated on development of an efficient workup. At the end of reaction, 1 M Na_2CO_3 was added to the reaction mixture to give two layers. The upper organic layer contained unreacted 3-bromopyridine, NBu_3, catalyst, and ligand, along with 1-hydroxybutan-2-one (isomerised 3-butene-1,2-diol). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 vols). The resulting aqueous layer contained unreacted 3-butene-1,2-diol, **7**, and residual amounts of **6** along with inorganic material. The organic extracts were combined with IPA (5 vols), and CH_2Cl_2 was removed by distillation. Oxalic acid in IPA (5 vols) was added to the resulting solution of the ketone. The oxalate salt precipitated. An antisolvent (EtOAc) was added to precipitate further oxalate. The product was isolated by filtration as an off-white solid in 60−65% yield and in 90% purity (HPLC). The product was recrystallised in 80−85% yield from MeOH/EtOAc to give **6** in 95% purity (HPLC) and low levels of residual Pd (>60 ppm).

Further optimisation established boundary conditions and incorporated some plant modifications into the method. The reaction has been shown to be sensitive to water. Anhydrous toluene (ex Aldrich, 30 ppm (w/v) H_2O) could be replaced with Fisher SLR (175 ppm (w/v) H_2O) without any detrimental effects. However, spiking toluene with 5% water (by volume) led to complete inhibition of the reaction. Further studies demonstrated that all unit operations (extractions, distillation, and precipitation) could be carried out in the same reaction vessel without prior cleaning.

To avoid an "all-in" reaction, we examined the viability of adding substoichiometric quantities of reagents at the beginning of the reaction to circumvent any potential

Table 1. **Summary of results**

scale[a]	yield (%)	purity (HPLC)[b]	Pd (ppm)[c]
20 g	53	93.0−95.0	2−60
200 g	53	93.0−95.0	2−60
3 kg	33	95.0	11.5

[a] With respect to 3-bromopyridine. [b] % area. [c] ICP.

runaway. Therefore, addition of 10% 3-butene-1,2-diol and 3-bromopyridine at the beginning of the reaction, followed by slow addition of the remaining 90% over 30 min, was examined. The reaction progressed as usual, and 61% of the crude oxalate was isolated. However, results from the safety department indicated that the reaction should not be problematic on the scale that we were working (max. 3 kg), and therefore this modification was not adopted.

A 200-g lab batch of **6** incorporating all the plant modifications was prepared. The reaction yielded 64% of **6**. Recrystallisation gave **6** in 53% overall yield with HPLC purity of 92.8%, the major impurity being **7** (0.7% by HPLC), and a Pd level of 15 ppm.[4]

Finally, the procedure was transferred to the Large Scale Laboratories, and a 3-kg reaction was carried out. The reaction proceeded as expected, although consumption of 3-bromopyridine was somewhat lower than in the laboratory (80% vs <95% NMR). The decomposition of palladium catalysts in Heck reactions during scale-up has previously been reported,[5] although no explanation as to the cause is given. We suspected that premature catalyst decomposition due to water contamination was the cause. The water content of toluene was measured in the vessel prior to the addition of the other reagents and was found to be acceptable. A second KF measurement, after reflux was established, was not taken, and we suspect that water may have been incorporated at this point.[6] Further work was not carried out as it was decided not to advance the candidate drug. Workup and recrystallisation gave 33% overall yield of **2** in 95.0% purity (HPLC) with 11.5 ppm Pd. The results are summarised in Table 1.

In conclusion, we have demonstrated a short, efficient synthesis of **6** from inexpensive, readily available starting materials that is capable of supplying **3** at the target cost. Despite a 33% yield at pilot scale this route still represented a commercially viable synthesis.

(4) This material was suitable for use in the next step.
(5) Raggon, J. W.; Snyder, W. M. *Org. Process Res. Dev.* **2002**, *6*, 67.
(6) Further work was not carried out as it was decided not to advance the candidate drug.

Experimental Section

General. ^{1}H NMR spectra were recorded on a Bruker 300 MHz instrument. Chemical shifts for ^{1}H NMR are reported in ppm downfield relative to TMS as an internal standard in D_2O.

Palladium acetate (500 mg, 0.12 mmol) and tri-*o*-tolyl phosphine (1.60 g, 0.48 mmol) were added to a nitrogen-purged flask. Toluene (1 L) was added, and the solution was stirred for 1 h at ambient temperature. Tributylamine (380 mL, 1.58 mol), 3-bromopyridine (122 mL, 1.26 mol), and 3-butene-1,2-diol (133 mL, 1.58 mol) were combined and added to the catalyst to give a yellow solution which was heated to reflux for 3 h. HPLC of a sample after this time showed >95% conversion of 3-bromopyridine. During this time a palladium mirror forms on the surface of the vessel. The reaction mixture was cooled to below 80 °C, and 1 M aqueous sodium carbonate (1.5 l) was added. A small amount of effervescence was observed. Stirring was continued until the internal temperature had reached 32 °C (1 h). The two layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 1 L). The reaction flask was rinsed with water and then 2-propanol. The organic layers were combined in the reaction vessel with 2-propanol (1 L), and dichloromethane was removed by distillation. Oxalic acid (160 g, 1.26 mol) was dissolved in 2-propanol (1 L). This solution was warmed to ambient temperature and then added to the ketone at 40 °C. After addition ethyl acetate (1 L) was added; the temperature was allowed to cool to ambient, and the precipitate was stirred for 3 h. The white solid was collected by filtration and dried in a vacuum oven at 55 °C overnight. The solid (200 g) was dissolved in refluxing methanol (1 L). Ethyl acetate (1 L) was added, and the solution was allowed to cool to ambient. During this time the product precipitated. Ethyl acetate (1 L) was added, and the precipitate was stirred for 3 h at ambient temperature. The solid was collected by filtration and dried overnight in a vacuum oven at 55 °C. LC/MS AP 166, (MH^+). ^{1}H NMR (H_2O) 8.73 (1H, s); 8.67 (1H, d); 8.55 (1H, d); 8.04 (1H, dd); 4.39 (2H, s); 3.20 (2H, t); 3.03 (2H, t).

Acknowledgment

We thank Mel Giles and David Ennis of (PR&D Chemistry) for their helpful discussion and Tony Shephard (PR&D Analytical) for analytical support.

Received for review July 29, 2002.

OP0255736