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An Efficient Method for Removal of Residual Palladium from Organic Solution of Faropenem Sodium in the Pd(II)-Catalyzed Cleavage of Allyl Faropenem

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Abstract:

An improved palladium(II)-catalyzed cleavage of the allyl group in allyl faropenem 2 into faropenem sodium 1 is described. The development of an efficient method for the removal of palladium impurities from the crude product 1 upon treatment with polystyrene-bound 2,4,6-trimercapto-*s*-triazine (polystyrene-bound TMT) led to a drastic decrease of residual palladium level from 1500−1600 ppm to less than 10 ppm in the final isolated product. The palladium(II)-catalyzed cleavage and palladium removal process demonstrated on 10 kg scale are highly convenient and efficient.

Introduction

As part of an ongoing faropenem and its analogues research program in our laboratory,[1] the cleavage of allyl group in **2** was identified as a key step for the preparation of **1**, a penem antibiotic with β-lactamase stablility and broad-spectrum antibacterial activity.[2] To date, although several palladium catalysts have been documented in the literature for the deprotection of the allyl groups of **2** into **1**,[3] the most common method for this cleavage in industry involves the use of $Pd(PPh_3)_4/PPh_3$/base catalytic system. However, a moderate yield was achieved when repeating the cleavage conditions on 2-L scale, and the high levels of residual Pd (>1500 ppm) identified in the isolated **1** did not meet the demand for heavy metals content, which is generally below 10 ppm for an active pharmaceutical ingredient (API).[4] Therefore, the development of an efficient and convenient cleavage of the allyl group in **2** and removal of residual palladium from the reaction mixture is of great importance in the preparation of **1** on large scale. Herein, an expedient and high-yielding method for the cleavage of the allyl group of **2** into **1** catalyzed by $PdCl_2(PPh_3)_2/PPh_3$/base as well as efficient removal of residual Pd from crude **1** using polystyrene-bound TMT as scavenger is being disclosed.

Results and Discussion

At the outset, the cleavage of the allyl group in **2** was repeated in our laboratory using $Pd(PPh_3)_4/PPh_3$ as catalyst system in the presence of sodium 2-ethylhexanoate and CH_2Cl_2/EtOAc/H_2O following the reported procedure.[3a] This method was not viable for large-scale preparation because it required a difficult chromatographic separation. Hence, an improvement more amenable to the manufacture of **1** was sought. To our surprise, the deprotection proceeded smoothly to provide desired **1** in 86.5% yield and avoided chromatograph by employing $PdCl_2(PPh_3)_2/PPh_3$ as catalyst system in the presence of sodium 2-ethylhexanoate, EtOAc, and 2.5 equiv of H_2O (Scheme 1). Under the same reaction system, other conventional palladium catalysts such as $Pd(PPh_3)_4$, $Pd(OAc)_2$, and $PdCl_2$ were carried out to give **1** in 64%, 65%, and 73% yield, respectively. Moreover, the deprotection procedure was performed using Pd/C as catalyst, maintaining 5−50 kg pressure of hydrogen gas to furnish **1** in 20−43% yield in the presence of sodium bicarbonate, water, and ethyl acetate following the literature.[3d] Unfortunately, the levels of palladium in all isolated products **1** using different catalysts were too high (1500−1600 ppm) to attain acceptable residual limit (less than 10 ppm), We therefore turned our efforts to reduce the palladium content of crude product **1**.

A considerable body of literature describing the methods for removing residual palladium from pharmaceutical intermediates as well as APIs is presented and involves a review.[4] These common methods for reducing the level of Pd to acceptable levels divide into four categories: adsorption, extraction, crystallization, and distillation. Adsorption is the most commonly utilized technique. By adsorbing palladium to a solid scaffold, the palladium complex is filtered out to leave a non-palladium reaction mixture (supposing a solvent is employed in which the scaffold is insoluble); or by complexing palladium to a liquid phase, the resulting palladium complex can become more solube in the solvent system, and then the desired compound is crystallized to leave the palladium complex in the mother liquor.[5] Extraction is usually used when there is a significant solubility difference between the palladium compound and the

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(1) Zhang, H.; Chen, F. E.; Chen, M. Q. *Acta. Crystallogr., Sect. E* **2007**, *63*, o3099.
(2) Suntory Ltd. *Drugs Future* **1993**, *18*, 525−528.
(3) (a) Han, H. N.; Liu, J.; Hu, L. X.; Wu, Y. B. *Chin. J. Pharm.* **2001**, *32*, 339–341. (b) Han, H. N.; Jin, X. F.; Jin, J.; Liu, J. *Chin. J. New Drugs* **2001**, *10*, 350–352. (c) Suntory Ltd., EP 0199446, 1986. (d) Andrew, G.; Sivasankaran, V.; Veeramani, G.; Senthilkumar, U. P. WO/2008/035153 A2, 2008.
(4) Garrett, C. E.; Prasad, K. *Adv. Synth. Catal.* **2004**, *346*, 889–900.
(5) (a) Rosso, V. W.; Lust, D. A.; Bernot, P. J.; Grosso, J. A.; Modi, S. P.; Rusowicz, A.; Sedergran, T. C.; Simpson, J. H.; Srivastava, S. K.; Humora, M. J.; Anderson, N. G. *Org. Process Res. Dev.* **1997**, *1*, 311–314. (b) Ishihara, K.; Nakayama, M.; Kurihara, H.; Itoh, A.; Haraguchi, H. *Chem. Lett.* **2000**, *10*, 1218–1219. (c) Urawa, Y.; Miyazawa, M.; Ozeki, N.; Ogura, K. *Org. Process Res. Dev.* **2003**, *7*, 191–195. (d) Prashad, M.; Bin, H.; Har, D.; Repič, O.; Blacklock, T. J. *Adv. Synth. Catal.* **2001**, *343*, 461–472. (e) Anson, M. S.; Leese, M. P.; Tonks, L.; Williams, J. M. J. *J. Chem. Soc., Dalton Trans.* **1998**, 3529–3538. (f) Galaffu, N.; Man, S. P.; Wilkes, R. D.; Wilson, J. R. H. *Org. Process Res. Dev.* **2007**, *11*, 406–413. (g) Flahive, E. J.; Ewanicki, B. L.; Sach, N. W.; O'Neill-Slawecki, S. A.; Stankovic, N. S.; Yu, S.; Guinness, S. M.; Dunn, J. *Org. Process Res. Dev.* **2008**, *12*, 637–645. (h) Pink, C. J.; Wong, H.; Ferreira, F. C.; Livingston, A. G. *Org. Process Res. Dev.* **2008**, *12*, 589–595.

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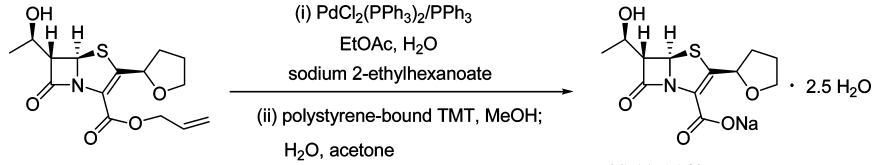
Scheme 1. **Cleavage of allyl group by palladium catalyst and scavenging of residual palladium**



Yield: 64 %
Residual palladium: 3 ppm

desired drug substance in water or organic solvent.[6] Crystallization is usually used when the desired compound is insoluble in the solvent, while the palladium is soluble and is reserved in the mother liquor.[7] Distillation is usually used when the desired organic product can be distilled out at normal laboratory distillation temperatures and pressures, while the nonvolatile palladium compound is retained in the distillation residue. In conclusion, the purification technique for APIs will alter greatly, depending on their properties, reaction conditions, and the state of residual palladium [typically Pd(0), Pd(II), or colloidal Pd].[4]

Initial work focused on the purification of the crude product **1** through precipitation from an aqueous solution by addition of aectone. This provided **1** in 74.4% yield with Pd levels down to 1200 ppm.

The use of extraction and precipitation methods for removing palladium impurities from palladium-catalyzed reactions has become quite common in the pharmaceutical industry.[4] n-Bu_3P was shown to be highly effective for complexing and solubilizing palladium in the organic phase.[7a] We first examined this phosphine reagent for removing residue palladium from crude **1**. Thus, n-Bu_3P (40 equivs vs $PdCl_2(PPh_3)_2$) was added to a suspension of aqueous crude **1** in EtOAc and stirred at room temperature for 13 h. The organic layer containing Pd-phosphine complex was removed. The aqueous layer was washed with EtOAc. The precipitation of **1** from the aqueous layer was then carried out by adding acetone and provided **1** in 45% yield with a palladium content was 679 ppm.

Adsorption and complexation of palladium from organic solutions using polystyrene-bound TMT received extensive attention as an effective method for complexing palladium in solution.[5b] The ability of polystyrene-bound TMT to remove palladium from our crude **1** was therefore tested. In preliminary experiments, crude **1** was treated with low loading polystyrene-bound TMT (0.30 mmol TMT unit/g resin) in methanol and stirred at ambient temperature for 15 h. After filtration, the filtrate was concentrated and the residue was dissolved in a minimum of deionized water (near saturation) to effect crystallization of **1** by slow addition of acetone, affording **1** in a 75% yield with 55 ppm of pd. Next, the optimization of the complexing agent was also investigated. As seen from the Table 1, both prolonging the treatment time and increasing the amount of resin showed a slight effect on the reduction of residual palladium when using low loading resin (0.30 mmol TMT unit/g resin) as adsorbent (entries 1, 2 and 3). In contrast, in the presence of the high loading resin (0.58 mmol TMT unit/g resin), a significant decrease was observed by extending the complexing time 15 to 32 h with no improvement with the longer 46 h exposure time (entries 4 to 6). Doubling the amount of high loading resin allowed us to attain the acceptable limit for palladium content (<10 ppm) (entry 7), and keeping on extending the complexing time scarcely reduced the palladium content (entry 8).

The present method for the cleavage of the allyl group in allyl faropenem **2** and the decrease of residual palladium level in the final product **1** to less than 10 ppm has proven reliable on a 10 kg scale-up in the pilot plant.

Conclusions

In summary, an improved and convenient deprotection of **2** into **1** that is amenable to scale-up has been accomplished in 86.5% yield by using $PdCl_2(PPh_3)_2/PPh_3$ as the catalyst system without chromatographic purification. An efficient method for reducing the residual palladium level from 1500−1600 ppm to <10 ppm from a methanolic solution of product **1** has been developed with the use of polystyrene-bound TMT as scavenger, providing Pd-free product **1** in 64% overall yield.

Experimental Section

General Procedures. All commercially available substrates, reagents, and solvents were used without further purification. Polymer-supported TMT was prepared following the procedure reported by Ishihara, et al.[5b]^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra was recorded on a Bruker Avance 400 spectrometer in D_2O using tetramethylsilane (TMS) as internal standard. Optical rotation is recorded on a JASCO P1020 digital polarimeter. HPLC analysis is performed by a standard method on a Kromasil 100-5 C_{18} column, 250 mm × 4.6 mm (5 μm), λ = 230 nm; mobile phase: disssolve 4.8 g of potassium dihydrogenphosphate, 5.4 g of disodium hydrogen phosphate dodecahydrate, and 1.0 g of tetra-*n*-butyl ammonium bromide in water to make 1000 mL; to 870 mL of this solution is added 130 mL of acetonitrile. Quantitative analysis of residual Pd is carried out by inductively coupled plasma mass spectrometry (ICP-MS) using a Perkin-Elmer SCIEX Elan DRC-II instrument.

Preparation of Faropenem Sodium. To a stirred solution of of sodium 2-ethylhexanoate (5.10 kg) in deionized water (1.38 L) at ambient temperature was added a solution of allyl (1′*R*,2″*R*,5*R*,6*S*)-6-(1′-hydroxyethyl)-2-(2″-tetrahydrofuranyl)-penem-3-carboxylate (**2**) (10 kg, 30.8 mol) in 40 L of ethyl

(6) (a) Villa, M.; Cannata, V.; Rosi, A.; Allegrini, P. WO/98/51646, 1998. (b) Prashad, M.; Liu, Y.; Repič, O. *Adv. Synth. Catal.* **2003**, *345*, 533–536. (c) Chen, C. Y.; Dagneau, P.; Grabowski, E. J. J.; Oballa, R.; O'Shea, P.; Prasit, P.; Robichaud, J.; Tillyer, R.; Wang, X. *J. Org. Chem.* **2003**, *68*, 2633–2638. (d) Bullock, K. M.; Mitchell, M. B.; Toczko, J. F. *Org. Process Res. Dev.* **2008**, *12*, 896–899.

(7) (a) Larsen, R. D.; King, A. O.; Chen, C. Y.; Corley, E. G.; Foster, B. S.; Roberts, F. E.; Yang, C.; Lieberman, D. R.; Reamer, R. A.; Tschaen, D. M.; Verhoeven, T. R.; Reider, P. J.; Lo, Y. S.; Rossano, L. T.; Brookes, S.; Meloni, D.; Moore, J. R.; Arnett, J. F. *J. Org. Chem.* **1994**, *59*, 6391–6394. (b) Königsberger, K.; Chen, G. P.; Wu, R.; Girgis, M. J.; Prasad, K.; Repič, O.; Blacklock, T. J. *Org. Process Res. Dev.* **2003**, *7*, 733–742. (c) Manley, P. W.; Acemoglu, M.; Marterer, W.; Pachinger, W. *Org. Process Res. Dev.* **2003**, *7*, 436–445.

Table 1. **Removal of palladium by polystyrene-bound TMT treatment**

entry	loading of TMT (mmol/g resin)[a]	ratio of resin and crude **1** (g/g)	time (h)	residual palladium in isolate **1** (ppm)[b]	yield (%)[c]
1	0.30	0.4	15	55	75
2	0.30	0.4	32	48	74
3	0.30	0.8	32	41	74
4	0.58	0.4	15	44	76
5	0.58	0.4	32	18	75
6	0.58	0.4	46	18	69
7	0.58	0.8	32	3.0	74
8	0.58	0.8	48	2.9	67

[a] The loading of TMT was estimated according to nitrogen content determined by elemental analysis. [b] Pd(II) determined by inductively coupled plasma mass spectroscopy (ICP-MS). [c] Isolated yield.

acetate, and then dichlorobis(triphenylphosphine) palladium (502 g, 716 mmol) and triphenylphosphine (938 g, 3.58 mol) were added under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 5 h. The precipitates were collected by suction filtration, washed with acetone (8 L), and dried to a constant weight in vacuo to give **1** (8.17 kg, 86.5%) as white solid, residual Pd: 1550 ppm. ^{1}H NMR (400 MHz, D_2O) δ 1.27 (d, 3H), 1.83−2.09 (m, 3H), 2.31−2.38 (m, 1H), 3.79−3.85 (m, 2H), 3.90−3.95 (m, 1H), 4.17−4.23 (m, 1H), 5.49 (t, 1H), 5.56 (d, 1H). ^{13}C NMR (100 MHz, D_2O) δ 20.05, 25.66, 33.15, 62.09, 64.74, 68.52, 69.56, 74.77, 124.77, 152.99, 166.22, 175.90.

Typical Procedure for Removal of Residual Palladium. To a stirred solution of crude faropenem sodium salt (8.17 kg, residual Pd 1550 ppm) in methanol (40 L) was added polystyrene-bound 2,4,6-trimercapto-*s*-triazine (6.54 kg, 0.58 mmol TMT unit/g resin). The mixture was then stirred at room temperature for 32 h. The resin was removed by suction filtration and washed with methanol (1 L). The filtrate was concentrated under vacuum at 25 °C, and the residue was dissolved in 24 L of deionized water. To the stirred aqueous solution was slowly added 120 L of acetone, and the mixture was then cooled to 0−5 °C. The precipitates were collected by filtration, washed with acetone (2 L × 2), and dried in vacuo for 12 h in an oven (35 °C, 0.1 Torr) to provide 6.05 kg of faropenem sodium hydrate as white crystals (yield: 74%, residual palladium: 3 ppm; HPLC: 99.9%; $[\alpha]_D^{20} = +146.7°$ (*c* 1.0, H_2O).

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