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Removal of Palladium from Organic Reaction Mixtures by Trimercaptotriazine

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Abstract:

In an effort to remove residual palladium from a drug candidate prepared by palladium-catalyzed indolization, many treatments were examined. The most effective treatment was to precipitate palladium from solution using 2,4,6-trimercapto-*s*-triazine (TMT), which reduced palladium levels from 600−650 ppm to 20−60 ppm in an isolated indole intermediate. Subsequent crystallizations routinely afforded active pharmaceutical ingredient with <1 ppm of palladium. TMT treatment should prove useful to reduce the concentration of residual palladium in other reactions.

Palladium-mediated reactions provide the organic chemist with a rich selection of tools. Examples include the Heck reaction,[1] cross-coupling reactions,[2] carbon monoxide insertions,[3] hydrogenation over heterogeneous catalysts,[4] Wacker-type oxidation,[5] amination,[6] indole formation,[7] and others.[8] Palladium catalysis is widely used in the chemical industry.[9] In the literature, removal of palladium from reactions has usually not been considered; however, removing palladium from an active pharmaceutical ingredient (API) can be a major purity concern.

Many approaches have been undertaken to reduce the level of residual palladium in organic processes. One key is to efficiently recycle the palladium within the reaction, thereby allowing the smallest charge possible and thus decreasing the burden of palladium removal. In the extreme, there are stories (possibly apochryphal) of dedicated reactors with sufficient metals embedded in the surface of the reactor walls so that no catalyst charging is necessary. The removal of even small amounts of catalyst can prove troublesome. The classic approach for removing impurities by selective crystallization of the organic product often fails to reduce impurities down to the parts per million level, which is highly desirable or even essential for the preparation of the API. Palladium-catalyzed reactions have been repositioned from the final step to earlier in the synthetic sequence, with the anticipation that processing of subsequent intermediates will also aid in reducing the level of residual palladium in the final product.[10,11]

Methodology for reduction of residual palladium has been addressed in the literature. Most, if not all, of these studies are related to the remediation of contaminated sites. Nuclear and fossil-fueled power plants generate a large volume of waste that contains toxic metals. Approaches for palladium removal can be divided into two categories: (1) extraction and precipitation treatments and (2) solid phase treaments. Although some of these applications are inappropriate for the purification of reactive fine chemicals, the references highlighted below may provide future applications for use in organic synthesis.

Extraction and Precipitation Methods for Removal of Palladium. An extensive review has been prepared on solvent extraction of metals into organic solvents using β-hydroxy ketones, 8-hydroxyquinoline, 8-mercaptoquinoline, oximes, hydroxylamines, sodium diethyldithiocarbamate, and others.[12] An *N*,*N*-dimethyldithiocarbamoylethoxy-substituted calix[4]arene is an effective extractant for palladium.[13] Sulfur-based extraction reagents, e.g., nonylthiourea, dodecylthiourea, and triisobutylphosphine sulfide,

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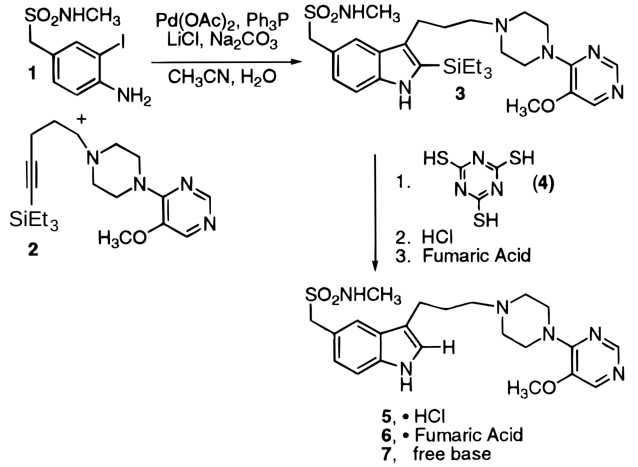
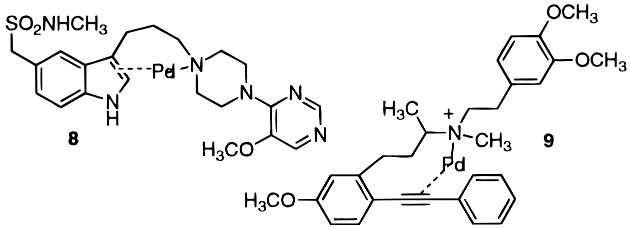
extract palladium as $PdCl_4^{2-}$ from aqueous HCl solutions.[14] A solvated complex is formed between palladium(II) and [[*N*,*N*-bis(2-ethyl-1-hexyl)amino]methyl]phosphonic acid from acidic chloride media.[15] Selective extraction of palladium(II) with thiocrown ethers from aqueous chloride−nitrate waste solutions has been demonstrated.[16] Hydrazine was shown to be highly effective for the precipitation of palladium in a nitric acid solution.[17]

Absorption of Palladium by Solid Phase Treatments. Iminodiacetic acid resins selectively bind divalent cations, and at pH 5 (acetate buffer) Chelex 100 has a greater affinity for Pd(II) than even for Cu(II).[18] The macroreticular cation exchange resin Dowex M-33[19] and a thiourea-modified resin[20] are also known to have a high affinity for Pd(II). An anion-exchange resin containing benzimidazoles and quaternary benzimidazolium species has been successfully employed for the removal of palladium ions from a nitric acid medium.[21] Carbonaceous pyropolymers have been identified for effective removal of palladium from aqueous solutions, by reducing the palladium ion to the zero valent state with concurrent plating of the metal onto the carbonaceous pyropolymer.[22] A magnetic chelating resin with a high content of sulfur and nitrogen atoms was shown to be effective for the removal of palladium ions under acidic conditions.[23] A tertiary pyridine-type anion-exchange resin was developed and shown to have a good affinity for removal of palladium under acidic conditions.[24] The use of bacteria immobilized in a tubular membrane reactor for palladium recovery has also been developed with success.[25] A chemically active ceramic composite material containing thiol and amine moieties has been developed for removal of metal ions.[26] A few novel techniques utilizing natural resources have recently been developed for palladium extraction, including the use of chicken feathers,[27] chicken eggshell membrane,[28] wool and silk,[29] and the roots of sunflower plants, terrestrial turf grasses, and members of the family Brassicaceae.[30]

Scheme 1. **Preparation of 6**



Scheme 2. **Possible organopalladium complexes**



Preparation of 6 Containing Low Levels of Palladium. Using a palladium-catalyzed indolization, the antimigraine candidate 4-(5-methoxy-4-pyrimidinyl)-1-[3-[5-[[(methylamino)sulfonyl]methyl]-1*H*-indol-3-yl]propyl]piperazine (**6**)[31] was prepared from the silylated indole **3**[32,33] (Scheme 1). The level of palladium in isolated **5** was typically 600−650 ppm, and multiple recrystallizations reduced the levels to 25−30 ppm in isolated **6**. An additional recrystallization of **5** from water to further reduce the concentration of residual palladium was not desirable, due to the cost of possible yield losses from such additional handling. With the goal of routinely producing API containing no more than 5 ppm palladium, additional treatments were examined in order to reduce the palladium levels in **6**.

Filtration of solutions of **7** through 0.22 μm filters did not effectively remove the palladium, even when the solutions were first treated with diatomaceous earth or charcoal−

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Table 1. **Removing palladium from 7 by resin treatment**

resin	soln[a] pH	treatment mode[b]	treatment time (20 °C)	[Pd], μg/g of **7**[c]	comments
Chelex 100	4.3	column	1 pass through bed	36.6	
	4.3	column	5 passes through bed	35.1	
	4.9	column	1 h recycle	58.1	
	4.9	column	2 h recycle	45.0	
	4.9	column	3 h recycle	44.1	
	4.9	column	4 h recycle	41.5	
	4.85	batch	7 h stirring	<15	85% **7** recovered from resin
	4.0	batch	3 days stirring	9.9	
Dowex M-33	4.0	column	10 passes through bed	32.3	
	4.9	column	1 h recycle	46.0	
	4.9	column	2 h recycle	43.5	
	4.9	column	3 h recycle	35.5	
	4.9	column	4 h recycle	37.0	
	4.85	batch	7 h stirring	29.4	90% **7** recovered from resin
	4.0	batch	3 days stirring	6.7	

[a] **7** was dissolved in deionized water (1 g/60 mL) and acidified with glacial acetic acid. [b] Resin loading was 0.1 g/g of **7**. [c] Initial [Pd] was 55 μg/g of **7**.

diatomaceous earth admixtures. The palladium may have been solubilized either as complex **8**, similar to the proposed palladium−acetylene complex **9**[10] (Scheme 2), or by salt formation with reagents or byproducts from the indolization. Without attempts to purge oxygen from the solutions, residual palladium is expected to be found in the Pd(II) state (reduction potential $+0.623$ V). An attempt to remove palladium by reductively plating Pd(0) onto carbon electrodes was not successful.

Treating dilute aqueous solutions of **7** with either Chelex or Dowex M-33 resins gradually reduced the palladium levels (Table 1). These resin treatments were not examined for inputs of **7** with higher levels of palladium, as would be necessary for the development of a plant-worthy process. In the hope of finding more time-efficient means of removing palladium from preparations of **6**, other treatments were investigated.

Treatment of **7** as a solution in MeOH−aqueous HCl with triphenylphosphine, potassium iodide, oxalic acid, or sodium metabisulfite reduced the palladium burden from 55 ppm to only 20−30 ppm. Under these acidic conditions hydroxylamine hydrochloride reduced the palladium level from 55 ppm to <5 ppm, but these low levels were not reached when solutions of **7** with higher concentrations of palladium were treated with hydroxylamine hydrochloride. Hydrogen sulfide treatment reduced the palladium burden from 55 ppm to <5 ppm; however, the toxicity of hydrogen sulfide precluded further development. Treatment with poly-DMAP resin (methyl isobutyl ketone−MeOH) or Deloxan THP II resin did not reliably reduce the concentration of palladium in **7**.

2,4,6-Trimercapto-*s*-triazine (TMT, **4**) was demonstrated to be the superior agent for removing palladium from preparations of **6**. TMT has been used to precipitate heavy metals from wastewaters,[34] flue gases,[35] and soils[36] and has exhibited high affinity for cupric ion.[37] TMT is available as the un-ionized trithiol **4**, the solid trisodium salt (TMT-Na$_3$ undecahydrate, TMT 55), and a 15% aqueous solution of TMT-Na$_3$ (TMT 15). Studies have shown that TMT and TMT-Na$_3$ have low toxicity towards humans and animals.[38] Since many agents which bind Cu(II) often bind Pd(II),[12] TMT was examined.

Table 2. **Variation of typical palladium levels in isolated 5 and 6 due to TMT treatment of unisolated 3**

stream[a]	TMT treatment	typical [Pd],[b] ppm **5**	**6**
prepn of **3**, mixed phases	none	600−650	25−30
prepn of **3**, organic phase	none	180−300	4−5
prepn of **3**, organic phase	yes	10	not investigated[c]
prepn of **3**, mixed phases	yes	20−60	<1−4

[a] At completion of indolization the reaction mixture is heterogeneous, with solids, an organic phase, and a small amount of an aqueous phase (ca. pH 9.1). All preparations of **3** above were subjected to Darco treatment, with or without TMT treatment, before conversion to **5** and then to **6**. [b] Palladium assays by ICP-MS. [c] 8% of **3** was lost to the TMT cake, and this processing variation was not investigated further.

TMT treatment was incorporated before desilylation of **3**. Upon completion of the palladium-catalyzed indolization, precipitates had been routinely removed by filtration. By inserting a TMT treatment prior to this filtration, process operations were minimized. For optimal removal of palladium, the aqueous acetonitrile mixture of **3** and salts was stirred with **4**, charcoal, and diatomaceous earth. After cooling to 0−5 °C, the palladium-containing precipitates were removed by filtration. Protodesilylation and salt formation from the filtrates routinely afforded **6** with 1 ppm of palladium (range 1− 4 ppm, Table 2). By processing streams of **3** to **5** and to **6**, TMT treatment did not reduce

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Table 3. **Solubilities of 4 and TMT 55 in selected solvents**

solvent	solubility of **4**,[a] %	solubility of TMT 55, calcd as **4**,[b] %
water	<0.1	820 g/L of H_2O[c]
toluene	0.02	<0.01
diethyl ether	0.8	not examined
acetonitrile		<0.01
methyl acetate	0.85	0.1
acetone	0.9	0.7
methyl ethyl ketone	1	<0.01
methanol	1.1	18.3
ethanol	2.2	4.3
dioxane	3.7	0.05
2-methoxyethanol	10	12.4
tetrahydrofuran	19	1.0
dimethyl sulfoxide	20	21.2

[a] Data from ref 37. Solubility of **4** in acetonitrile was not included. [b] Solubilities were determined by reverse-phase HPLC assay. HPLC conditions: YMC-Pack phenyl column, A 403−5, 250 × 4.6 mm i.d., 5 μm, 120 Å; eluted at room temperature at 1.0 mL/min with 40:60 acetonitrile/0.05 M ammonium dihydrogen phosphate; 210 nm. Approximate TMT retention time: 8 min. This sytem was used only to determine the solubility of TMT 55. [c] Reference 37.

the overall yield of **6**. TMT was not detected in batches of **5** or **6** (HPLC limit of detection 0.03 wt %). This treatment proved reliable on a 12 kg scale in the pilot plant, producing **6** with palladium levels averaging less than 1 ppm (range <0.1−2.2 ppm).

Few options for TMT treatment of intermediates leading to **6** were examined, due in part to the success of the simple treatment outlined above. In removing palladium, adding solid **4** was found to be more effective than adding solid TMT-Na_3, probably due to the increased solubility and hence availability of **4** in organic solvents (see Table 3). Successive extractions of organic solutions of **5** with aqueous solutions of TMT-Na_3 (adjusted to pH 12.6 for the biphasic mixture) reduced the palladium content, but less conveniently than did the single treatment with solid TMT. Some water was necessary during the TMT treatment of reactions of **3** to minimize the loss of **3** to the precipitates (Table 2). Adjusting the pH may influence the precipitation of palladium and other metals with TMT.

This simple TMT treatment has effectively reduced the concentration of palladium in other drug candidates. The use of TMT-Na_3, which has been shown to decrease levels of heavy metals in aqueous streams, may also prove to be effective for the removal of metals from organic reactions.

Conclusions. In an effort to remove residual palladium from drug candidate **6**, many treatments were examined in addition to recrystallization. The most effective process was to precipitate palladium from solution using TMT and then recrystallize to afford API. In other drug candidates prepared by palladium-catalyzed reactions, TMT treatment has effectively removed residual palladium. TMT treatment should prove useful in other reactions to reduce the concentration of palladium and other metals.

Experimental Section

Reduction of Palladium Burden in Streams of 3. A suspension of **1** (30.0 g, 63.5 mmol), **2** (22.5 g, 69 mmol), Na_2CO_3 (24.3 g, 229 mmol), triphenylphosphine (3.3 g, 12.6 mmol), lithium chloride (3.5 g, 82.6 mmol), and $Pd(OAc)_2$ (1.4 g, 6.2 mmol) in acetonitrile (55 mL) and deionized water (128 mL) was refluxed with vigorous agitation until the reaction was complete (6−9 h) and cooled to 20−25 °C. Acetonitrile (250 mL), **4** (3.0 g, 16.9 mol), and Darco G-60 decolorizing charcoal (6.0 g) were added, and the mixture was stirred at 20−25 °C for 1 h. Hy-Flo filter aid (3.0 g) was optionally added, and the mixture was stirred at 0−5 °C for 1 h. The precipitates were removed by suction filtration through filter paper and washed with acetonitrile (125 mL). The aqueous phase (ca. pH 9.1) of the combined filtrates was removed by phase separation. The organic phase, containing **3**, was processed to **5** and **6** by protodesilylation and salt formations.[33]

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