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Dithiocarbamates: Reagents for the Removal of Transition Metals from Organic Reaction Media

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S Supporting Information

ABSTRACT: Dithiocarbamates (DTCs) are ligands known to chelate with Cu and other transition metals to form insoluble complexes. Wastewater treatment protocols have utilized DTCs to remove trace (ppb) metals from waste streams. We have extended the applicability of DTCs to a protocol that readily enables control of the residual Cu in isolated material in a quick and cost-effective manner. Formation of the chelate complex typically results in purging of Cu and a variety of other metals in an array of reaction media to ≤10 ppm. Furthermore, the simplicity of the method makes it very attractive for large-scale applications late in a synthetic sequence because of the low toxicity and efficient removal of the metal complex by filtration.

INTRODUCTION

In pharmaceutical process research, final products must meet strict purity requirements, and thus, impurity removal becomes an essential task. The favored industrial-scale techniques for rejecting impurities are crystallization and extraction, but these approaches are not always viable. In the laboratory, chromatography offers a functional solution to many impurity problems, but on an industrial scale, it is rather time-demanding and expensive.

The increasing use of organometallic reagents and homogeneous catalysts in pharmaceutical synthesis has made the removal of trace metal impurities[1] a high priority. Unlike heterogeneous[2] catalysis, where the metal can simply be filtered away, homogeneous processes are burdened with soluble metal impurities or byproducts. For example, copper catalysis[3] is employed in ring expansions, Castro−Stevens (Sonogashira) couplings,[4a] Huisgen azide−alkyne cycloadditions,[4b] and Ullmann reactions.[3b] Other metal-catalyzed coupling reactions have also become increasingly utilized to make advanced intermediates or final products.[5] Since the coupling conditions can tolerate a high degree of complexity, the metal-catalyzed reaction is often positioned late in the synthetic scheme, thus restricting opportunities for impurity rejection.[6] Because of the high enantioselectivity achieved, homogeneous catalytic hydrogenation has become a chosen method for preparing enantiopure intermediates on a large scale. In addition, removal of trace metal impurities can be further complicated by the existence of the metal as two or more different species, often as a result of multiple oxidation states. We have recently found an attractive and broadly applicable method for removing trace metals from organic reaction media and have demonstrated its effectiveness on a large scale with an Ullmann coupling.

RESULTS AND DISCUSSION

In the synthesis of a key intermediate for an HIV attachment inhibitor, we recently encountered a process necessitating the removal of Cu^+/Cu^{3+} from an Ullmann coupling. Furthermore, the product could participate in a Cu-catalyzed oxidative dimerization, thus lowering the yield of the desired material (Scheme 1).

The Ullmann coupling presumably proceeds through a Cu^+/Cu^{3+} catalytic cycle.[7] On a lab scale, typical workup upon reaction completion involved opening the system to air followed by washing with EDTA, which provided oxidative conditions to form the needed Cu^{2+} species. As the process was scaled up, the amount of O_2 needed varied depending on the scale, and thus, our process to provide the oxidative conditions to remove the Cu was inconsistent. Our experimental data showed that the formation of the undesired side product **4** required the combination KOH, O_2, and Cu. We hypothesized that if we could effect Cu removal under low O_2 levels, the formation of **4** could be minimized.[8] We then examined a variety of methods to remove Cu from our process stream (Table 1). A variety of solid-supported reagents[9] were tested, but the results were highly variable. Metal hydroxides have been used to precipitate transition metals, but these methods caused further degradation of **3**. The formation of metal sulfides has been used, but with our system, further degradation was seen.

A literature search revealed that dithiocarbamates (DTCs) have been utilized in the water treatment industry to remove trace (ppb) amounts of heavy metals[10] for more than 30 years. DTCs form stable complexes with most transition metals, independent of oxidation state.[11] Scheme 2 shows a variety of DTCs that are readily available in bulk quantities in solid form and as aqueous solutions. DTCs are air-stable solids that possess high water solubility,[12] which makes removal of any residual DTC from the reaction train straightforward, in contrast to solid-phase adsorbents,[13] which could require specialized equipment for their use. DTCs are generally stable at pH 7.0 or above, but at lower pH they can degrade to their parent amine and CS_2.

To screen the effectiveness of DTCs in our system, we carried out the Ullmann coupling, and upon completion the

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Scheme 1. Cu-catalyzed Ullman coupling

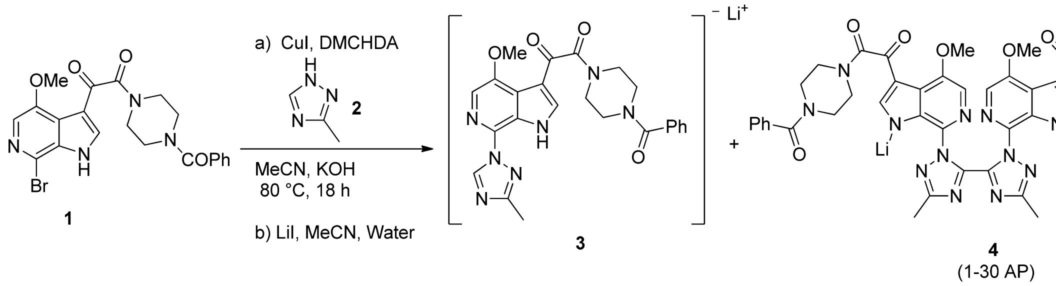


Table 1. Initial screening of Cu scavengers (15 g scale)

reagent	amount of reagent	Cu level[a] in rich organic phase
SiliaMetS Thiol	30 g	900 ppm + **4**
SiliaMetS Thiourea	60 g	850 ppm + **4**
KOH	10 equiv wrt Cu	3500 ppm + **4**
EDTA	6 equiv wrt Cu	500−3500 ppm + **4**
Na_2S	10 equiv wrt Cu	750 ppm + **4**

[a] The starting level was 3600 ppm.

Table 2. Initial use of DTCs for Cu removal

DTC	scale	Cu level in rich organic phase (ppm)	**4**[b]
NaDMDTC	15 g	86	0.10
NaDEDTC	15 g	85	0.10
APDTC	15 g	75	0.10
APDTC (optimized)	15 g	20[a]	0.10
APDTC (optimized)	100 g	20[a]	0.10
APDTC (optimized)	20 kg	20[a]	0.10
APDTC (optimized)	90 kg	24[a]	0.10
APDTC (optimized)	156 kg	3[c]	0.10

[a] After filtration through a 1 μm polish filter at 50 °C. [b] These values are HPLC area percentages. [c] The filtration was carried out at 30 °C through a 1 μm polish filter.

reaction mixture was cooled to 50 °C.[14] An excess of each DTC was added as a solid under an atmosphere of N_2, and a dark solid precipitated immediately. The slurry was filtered, and the rich organics were analyzed for Cu content. We found that in each case the amount of Cu was reduced to <100 ppm, and no product degradation was observed. Experimental results and knowledge from single-crystal X-ray studies showing that DTC−metal complexes are primarily dimeric in structure[15] led us to use 2.2 equiv of DTC with respect to (wrt) the amount of CuI used. We found that the addition of solid DTC led to faster filtering of the material[16] compared with the addition of an aqueous solution of DTC. With the optimized conditions[17] in hand, APDTC[18] was demonstrated to control Cu levels to less than 25 ppm on scales from 15 g to 156 kg (Table 2). We were also pleased that we had control of **4** once the Cu was removed from the system. On scale, the filtration setup was critical for consistent removal of the solids, as we needed to filter at 1 μm porosity[19] to remove the formed small particles. We utilized a nutsche filter with a Celite bed to remove a majority of the DTC complex[20] followed by an in-line polish filter (1 μm).

Since we are utilizing DTCs in the preparation of active pharmaceutical agents, we need to pay attention to their toxicity, as trace levels of these impurities could be present in our isolated material. NaDMDTC has been extensively studied[21] and is considered to be a genotoxic impurity (GTI), whereas the NaDEDTC[22] has been found to be Ames-negative. We recently tested APDTC and found it to be Ames-negative, and thus, it is not considered to be a GTI.

Since we had success with Cu removal, we postulated that DTCs could be utilized to remove other thiophilic metals from organic media. Initially, we looked at several different metals that are soluble in organic solvents. Because of their availability and low toxicity, NaDEDTC and APDTC were chosen for further study. The solvent composition and oxidation state of the metal were varied. We initially made solutions containing 4000 ppm metal. At 20 °C,[23] the solid DTC (2.2 equiv wrt metal) was added, followed by water. After 1 h of stirring, the solutions were filtered and analyzed. Our initial results indicated that homogeneous Pd, Cu, Al, Fe, Ni, and Ru[24] could be removed to less than 10 ppm (Tables 3 and 4).[25] We also prepared a select few examples containing 100 ppm metal (Table 5). After DTC treatment and filtration, the metal was removed to ≤10 ppm in each case.

The competition with various ligands was also considered. In the Ullmann coupling, we utilized a diamine ligand that did not interfere with the DTC complexation. 1,1′-Bis(diphenylphosphino)ferrocene (dppf)[26] is a ligand that is known to bind to Pd very well. With dppf in THF, treatment with APDTC resulted in complete removal of the ligand from the THF solution. When $Pd^{II}(dppf)Cl_2$ was used, we were able to remove the palladium and the dppf from the organic solvent (Table 6).

Having demonstrated the ability to remove the metals in an isolated environment, we next looked at several different metal-catalyzed reactions to see whether the DTC was as efficient in removing a variety of metals from other complex reaction media. We performed a borylation, a Heck coupling,[27] a Sonogashira coupling, a Rh-catalyzed hydrogenation, and a

Scheme 2. Types of commercially available DTCs

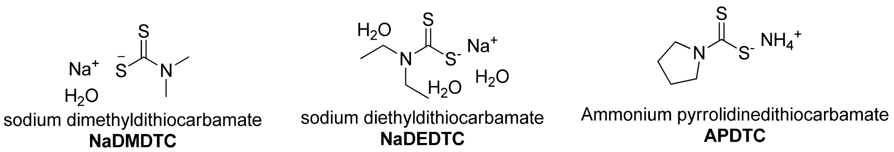


Table 3. Use of APDTC with a starting concentration of 4000 ppm in solution

metal	solvent	final metal content (ppm)
$Pd(OAc)_2$	THF	<10
	MeCN	<10
	DMF	<10
$PdCl_2(MeCN)_2$	THF	<10
	MeCN	<10
	DMF	<10
Pd_2dba_3	THF	<10
	MeCN	<10
	DMF	<10
$Cu(OAc)_2$	MeCN/MeOH	<10
DIBALH	THF	<10
	MTBE	<10
	PhMe	<10
$Co(acac)_2$	MeCN	140
	DMF	104
$Fe(OAc)_2$	NMP	<10
	MeCN/MeOH	<10
$Ni(acac)_2$	DMF	<10
	THF	<10
$NiCl_2(PPh_3)_2$	MeCN	<10
	DMF	<10
RuO_2	NMP	<10
	MeCN	<10
$Rh(COD)_2BF_4$	MeCN	<10
$RhCl(PPh_3)_3$	THF	70
	DMF	70
$Rh(CO)(PPh_3)_3$	THF	16
	DMF	15

DIBALH reduction on a lab scale. After the reactions were taken to completion, the reaction mixtures were treated with APDTC and filtered (1 μm), and the rich organic phases were analyzed for metal content.[28] Upon completion of the borylation and Heck coupling reactions (Scheme 3), the treatment with DTC (2.2 equiv) followed by filtration afforded a product-rich organic stream with <10 ppm Pd. The Sonogashira coupling[29] was chosen to demonstrate that two different metals could be removed simultaneously (Scheme 4). Upon treatment with APDTC, solids precipitated immediately from the reaction medium. Analysis of the rich organic phase indicated that both Pd and Cu were removed to ≤10 ppm. Upon completion of the Rh-catalyzed hydrogenation,[30] APDTC treatment generated a rich organic stream that contained <20 ppm Rh and <10 ppm Fe.

Finally, we examined a DIBALH reduction, a process that has a large excess of metal present. Typically, after quenching of the residual DIBALH, aqueous washes are applied to remove the Al. These washes can be problematic because of the formation of emulsions that can be very challenging on a large scale. Once the DIBALH reduction was complete and the residual DIBALH was quenched, we added APDTC, and a solid precipitated immediately. After filtration of the solids, the rich organic stream contained <20 ppm Al.

Table 4. Use of NaDEDTC with a starting concentration of 4000 ppm in solution

metal	solvent	final metal content (ppm)
$Pd(OAc)_2$	THF	<10
	MeCN	<10
	DMF	<10
$PdCl_2(MeCN)_2$	THF	<10
	MeCN	<10
	DMF	<10
Pd_2dba_3	THF	<10
	MeCN	<10
	DMF	<10
$Cu(OAc)_2$	MeCN/MeOH	<10
DIBALH	THF	<10
	MTBE	<10
	PhMe	<10
$Co(acac)_2$	MeCN	140
	DMF	160
$Fe(OAc)_2$	NMP	<10
	MeCN/MeOH	<10
$Ni(acac)_2$	DMF	<10
	THF	<10
$NiCl_2(PPh_3)_2$	MeCN	<10
	DMF	<10
RuO_2	NMP	<10
	MeCN	<10
$Rh(COD)_2BF_4$	MeCN	<10
$RhCl(PPh_3)_3$	THF	85
	DMF	80
$Rh(CO)(PPh_3)_3$	THF	16
	DMF	20

Table 5. Use of APDTC with a starting concentration of 100 ppm in solution

metal	solvent	final metal content (ppm)
$Pd(OAc)_2$	THF	<10
	MeCN	<10
	DMF	<10
$PdCl_2(MeCN)_2$	THF	<10
	MeCN	<10
	DMF	<10
Pd_2dba_3	THF	<10
	MeCN	<10
	DMF	<10
$Cu(OAc)_2$	MeCN/MeOH	<10

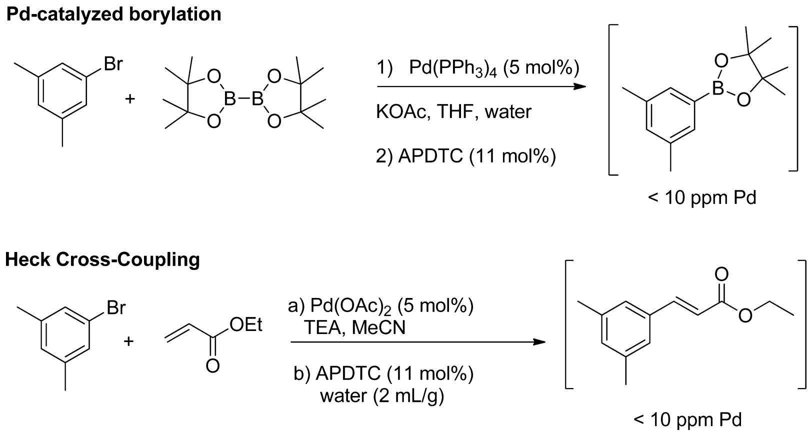
Table 6. Ligand competition experiment

reagent	equiv of APDTC	rich organic analysis
dppf	2.2	<10 ppm Fe
$Pd(dppf)Cl_2$	4.4	<10 ppm Pd <10 ppm Fe

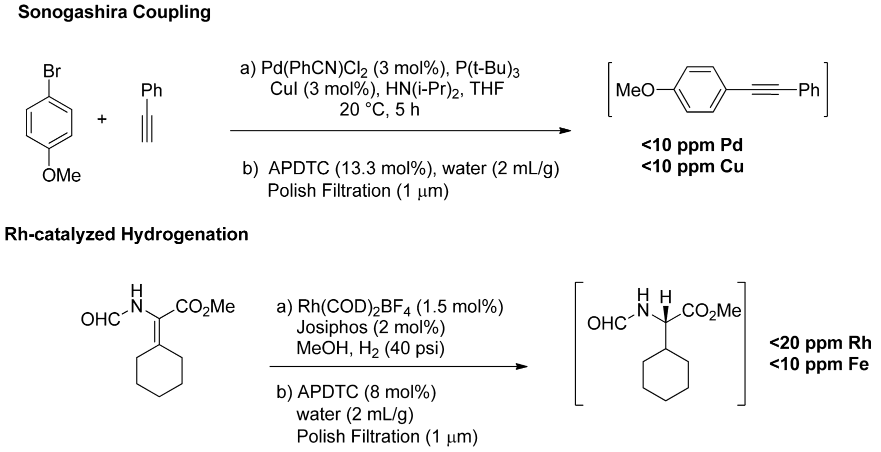
■ CONCLUSIONS

Our Ullmann process was optimized for the removal of Cu from the rich organic stream utilizing APDTC. We have shown that this protocol performed as expected up to a 156 kg scale while maintaining control of the dimer impurity **4**. We have demonstrated that DTCs can potentially be used to remove other metals to <10 ppm in a wide variety of reaction media. This protocol should allow the process scientist to control the residual metal in their isolated material in a quick and cost-effective manner. Furthermore, the simplicity of the method makes it very attractive for large-scale applications late in a synthetic sequence.

Scheme 3. Removal of a single metal with APDTC



Scheme 4. Removal of two metals simultaneously with APDTC



■ EXPERIMENTAL SECTION

General Methods. Reaction mixtures were stirred, and the reactions were monitored by HPLC. HPLC was performed[31] on an Agilent HPLC system with a Supelco Ascentis Express C18 column (150 mm × 3 mm, 2.7 μm particle size (part no. 53816-U). Yields refer to recrystallized and spectroscopically pure compounds, unless noted otherwise. Metal analysis was performed using ICP analysis (PerkinElmer Optima 8300 DV ICP-AES).

General Procedure for the Use of DTC on Lab Scale. Once the reaction was complete (TLC or HPLC), DTC (2.2 equiv wrt the metal) was added as a solid, followed by the addition of water (2 mL/g).[32] The reaction medium was held for 1 h at the desired temperature. The slurry was filtered through a 1 μm filter.

Use of APDTC on Scale: Removal of Cu from an Ullmann Coupling on a 20 kg Scale. A mixture of KOH (2.05 equiv, 4.88 kg), water (30 equiv, 23.2 kg), **2** (1.5 equiv, 5.30 kg), EtOH (237 L), *N,N′*-dimethyl-1,2-cyclohexanediamine (0.80 equiv, 4.83 kg), **1** (20 kg), and CuI (0.30 equiv, 2.43 kg) was placed under vacuum, and the reaction vessel was backfilled with N_2. This was completed three times. The reaction mixture was heated to 80 °C and held at that temperature for 20 h. Once the reaction was complete as determined by HPLC [<2 relative area percent **1**], the reaction mixture was cooled to 50 °C. A solution of KOH (0.68 equiv, 1.62 kg) in EtOH (29.0 L) was added, followed by APDTC (0.68 equiv, 4.99 kg). The mixture was stirred at 50 °C for 1 h and then filtered over a bed of Celite followed by an in-line polish filter (1 μm). The rich organic phase was then concentrated to half the volume by vacuum distillation. MeCN (120 L) was added, and a constant-volume distillation was performed using MeCN to achieve an end point of 2−3% EtOH and NMT 1% KF. At 50 °C, the solution was polish-filtered (1 μm) and transferred to a reactor. Water (0.30 L/kg, 6.00 L) was added, and the system was maintained at 50 °C. A solution of lithium iodide hydrate (1.05 equiv, 8.85 kg) and MeCN (2 L/kg, 40.00 L) was prepared, and 35% of this solution was added over 1 h. At this time, seeds of **3** (1 wt %, 0.200 kg) were added. At 50 °C, the remaining 65% of the solution was added over 12 h at 50 °C. The resulting slurry was cooled to 30 °C over 3 h. The slurry was filtered and washed with 97:3 MeCN/water (10 L/kg) and then a final rinse with 100% MeCN (10 L/kg). The solids were dried at 50 °C over 12 h to afford **3** (14.64 kg, 72% yield) as a yellow solid.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Solubility data for NADEDTC and APDTC and additional experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(8) The **3**:**4** ratio was determined by HPLC analysis.

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(12) Most DTCs display high water solubility, so they could simply be washed out of the rich organic stream prior to isolation if one wanted to remove residual DTCs.

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(14) 50 °C was chosen in order to maintain full solubility of the desired product **3**.

(15) X-ray analysis reported in the literature has shown that DTCs form dimeric structures with Cu. See: Giovagnini, L.; Sitran, S.; Montopoli, M.; Caparrotta, L.; Corsini, M.; Rosani, C.; Zanello, P.; Dou, Q. P.; Fregona, D. *Inorg. Chem.* **2008**, *47*, 6336−6343.

(16) Since the precipitation is rapid, it is difficult to control the particle size. Thus, small particles are obtained. When solid APDTC was used, the filtration flux was 1100 L m^{-2} h^{-1}. With an aqueous solution of APDTC, the filtration flux was 700 L m^{-2} h^{-1}.

(17) At least a 1 μm filter had to be used in order to remove all of the solids.

(18) Ammonium pyrrolidinedithiocarbamate (APDTC) was chosen for further development because of the quantity needed and the availability at the time. HPLC conditions were developed in order to analyze for residual APDTC in isolated materials.

(19) In the lab, we found that solids did pass through when 5 and 10 μm filter cloths were used.

(20) We utilized a cake wash to ensure that no product loss occurred. Analysis of the isolated APDTC−Cu complex showed no detectable amounts of the desired product **3**.

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(23) We utilized 50 °C for the initial Cu removal, but this was due to the low solubility of the product at 20 °C. Room temperature was chosen for ease of operation. Heating of the sample was not necessary for the DTC to form the metal complex.

(24) $Co(acac)_2$ was removed to only ~100 ppm. This system was not studied beyond these screens, and the solubility of the Co−DTC complex was not measured. Rh catalysts also were not purged completely, and the solubility of the Rh−DTC complex was not measured.

(25) We utilized 2.2 equiv of the desired DTC wrt the metal catalyst in all cases.

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(31) HPLC conditions: Buffer: 200 mM NH_4OAc. Mobile phase A: MeOH/buffer/water (2:1:7). Mobile phase B: MeCN/MeOH/buffer (7:2:1). Diluent: water/MeCN (2:8). Wavelength: 302 nm. Injection volume: 5 μL. Run time: 35 min. Flow rate: 0.4 mL/min. Column temperature: 30 °C. Gradient: 0 min, 0% B; 5 min, 20% B; 20 min, 25% B; 25 min, 100% B; 30 min, 100% B; 30.1 min, 0% B; 35 min, 0% B.

(32) Presumably water is the antisolvent for the formed metal−DTC complex. If water is excluded, the residual metal levels will be higher.