Organic Process Research & Development **2008,** *12,* 116–119

Sulfur Contamination Due to Quenching of Halogenation Reactions with Sodium Thiosulfate: Resolution of Process Problems via Improved Quench Protocols

Yanqiao Xiang, Pierre-Yves Caron, Brett M. Lillie, and Rajappa Vaidyanathan*

Development Science and Technology, Pfizer Inc., Eastern Point Road, Groton, Connecticut 06340, U.S.A.

Abstract:

Many metal-mediated cross-couplings involve the use of organic halides, which are usually accessed by halogenation reactions. Cross-couplings are sensitive to the presence of impurities in the halides. This paper describes the origin of one such problematic impurity (sulfur) during the synthesis of organic halides and proposes alternatives to minimize or eliminate its formation.

Introduction

Metal-mediated cross-couplings have gained widespread use in organic synthesis, particularly in the pharmaceutical industry.[1] These reactions typically involve coupling of an organic halide with the appropriate coupling partner in the presence of a catalytic amount of metal and ligand. Since very small quantities of catalysts are used in these types of reactions, the presence of trace amounts of catalyst poisons in the reaction mixture can have a deleterious effect on the reaction rate and outcome. It is therefore important to ensure that the coupling partners in these cross-coupling reactions are of acceptable purity.

Most of the organic halides used in cross-coupling reactions are synthesized via a halogenation reaction. Generally, the workup of halogenation reactions involves the use of a reducing agent to quench the excess halogen source. In addition to choosing an effective quench, it is important to pay due attention to the byproduct of the quench, since small amounts of residues could have an impact on subsequent transformations of the halogenated compounds. This paper describes the identification of a catalyst poison arising from a reductive quench and proposes alternative approaches to minimize or eliminate its formation.

Background

Axitinib (**1**), a potent inhibitor of the vascular endothelial growth factor (VEGF), is currently under investigation for the treatment of a variety of tumors. The synthetic route to this active pharmaceutical ingredient (API) is depicted in Scheme 1. The first step in the synthesis is a Migita coupling reaction between commercially available 6-iodoindazole (**2**) and 2-mercapto-*N*-methylbenzamide (**3**) in the presence of $Pd_2(dba)_3$ and xantphos to afford **4**. Iodination of **4** followed by a Heck reaction with 2-vinylpyridine furnishes the desired API **1**.[2]

During efforts to develop the manufacturing process for **1**, it was found that the Migita coupling reaction of **2** with **3** was capricious. While some batches of 6-iodoindazole (**2**) purchased from external vendors underwent the desired coupling using 1 mol % catalyst loading, other batches required significantly higher catalyst loadings (up to 4 mol %). Surprisingly, the HPLC potencies and purity profiles of the good and offending batches of **2** were comparable, and there was no discernible difference between the batches by routine analytical methods (^{1}H NMR, GC, HPLC, ROI, and heavy metals assay). However, it was found that the presence of an event at ca. 115 °C in the differential scanning calorimetry (DSC) thermogram of **2** correlated with poor performance in the coupling reaction. All of the offending batches of **2** that required a higher catalyst loading exhibited a DSC event at 115 °C, whereas the good batches did not.

Assuming that **2** is synthesized via a Sandmeyer reaction (Scheme 2),[3,4] it would be safe to surmise that a reducing agent was used to quench the iodination reaction. The most common quenching agents used for such reactions are sulfur-based reductants, usually sodium thiosulfate or sodium bisulfite. On the basis of known melting points, it was hypothesized that the event at 115 °C could be due to the presence of either iodine (mp = 113 °C) or elemental sulfur (mp = 112–120 °C depending on the allotropic form). Small quantities of iodine and elemental sulfur (ca. 0.2 wt %) were separately spiked into the Migita coupling reaction with a good batch of **2** in order to determine if one of these compounds led to stalled or slow reactions. It was found that the reactions with iodine proceeded to completion with the usual 1 mol % charge of catalyst, whereas the reactions spiked with sulfur required the addition of excess catalyst. An HPLC method was quickly developed for the detection and quantitation of elemental sulfur in **2** (vide infra). It was found that all of the offending lots contained >0.2 wt % sulfur, while the good lots contained <0.01 wt % sulfur. Based on further experimentation, appropriate specifications for sulfur levels in **2** were set in order to ensure robust performance in the Migita coupling step.

Results and Discussion

It is well-known that elemental sulfur can poison transition metal catalysts. It is well-documented but seldom recognized that sodium thiosulfate decomposes to elemental sulfur under

---

* To whom correspondence should be addressed. Email: rajappa.vaidyanathan@pfizer.com.

(1) Dugger, R.; Ragan, J.; Ripin, D. *Org. Process Res. Dev.* **2005**, *9*, 253–258.

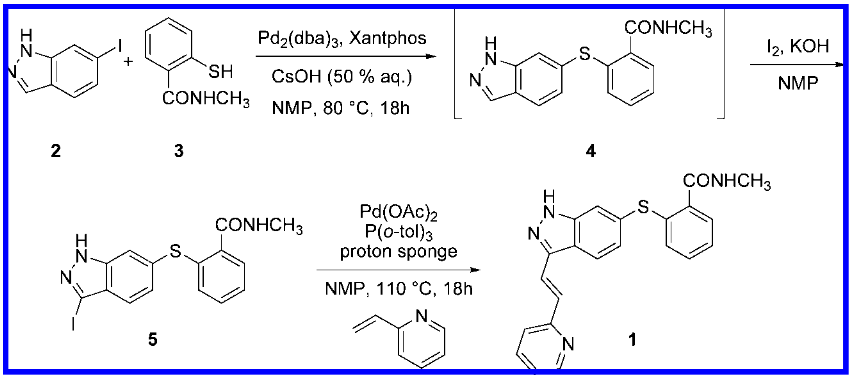
(2) Flahive, E.; Ewaniki, B.; Yu, S.; Higginson, P. D.; Sach, N. W.; Inaki, M. *QSAR Comb. Sci.,* **2007**, *26*, 679–685.

(3) Edwards, L.; Isaac, M.; Maddaford, S.; Slassi, A.; Xin, T. WO 2001005758, 2001.

(4) Foloppe, N.; Fisher, L. M.; Francis, G.; Howes, R.; Kierstan, P.; Potter, A. *Bioorg. Med. Chem.* **2006**, *14*, 1792–1804.

10.1021/op700227p CCC: $40.75

Scheme 1



Scheme 2

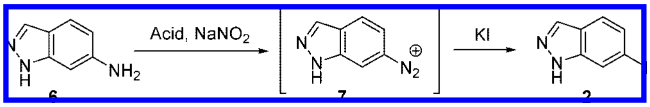
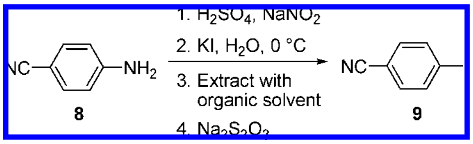


Table 1. **Dependence of sulfur levels on extraction solvent**



entry	extraction solvent	yield	wt % S	solubility of water in solvent (w/w %)
1	2-MeTHF	98	12.9	4.3
2	MTBE	97	4.4	1.4
3	EtOAc	91	2.6	3.3
4	CH_2Cl_2	89	0.2	0.2
5	$PhCH_3$	91	0.07	0.04

acidic conditions (eq 1).[5–7] Nevertheless, a cursory survey of the literature reveals that thiosulfate is one of the most commonly used reducing agents to quench iodination reactions. Indeed, the suppliers of **2** later confirmed that they were using the Sandmeyer reaction and a thiosulfate quench in the manufacture of **2**. Since iodination reactions generate the precursors for many metal-mediated couplings, it is important to understand the factors that contribute to unacceptable levels of sulfur in these compounds. Furthermore, it is critical to identify protocols that minimize or eliminate this pesky contaminant. Sulfur contamination may not be a problem in small-scale syntheses, where the iodinated compounds are typically purified by chromatography prior to use in the subsequent step, but could be an issue for large-scale manufacture, where crystallization is the preferred isolation and purification method.

$$S_2O_3^{2-} + H^+ \rightarrow HSO_3^- + S(s) \qquad (1)$$

The conversion of 4-aminobenzonitrile (**8**) to 4-iodobenzonitrile (**9**) via the corresponding diazonium salt[8] was chosen as the test reaction, in an effort to garner a better understanding of the factors that lead to sulfur precipitation during the reductive workup. It was hypothesized that the levels of sulfur in the product could be controlled by varying the solvent used for the extractive workup or by modifying the pH of the reaction mixture prior to the thiosulfate quench. Alternatively, the precipitation of sulfur could be eliminated by avoiding the use of thiosulfate to quench the halogenations. The results of our experiments are described below.

The dependence of sulfur levels on the extraction solvent was studied first. Five identical Sandmeyer reactions were set up starting with **8**. After the iodination reactions were deemed complete by HPLC, the acidic reaction mixtures were extracted with different solvents (Table 1). The organic layers were washed with a 20% w/w solution of aqueous sodium thiosulfate (3×). During each wash, the layers were stirred for 45 min at room temperature and then separated. This was done in order to simulate the long stir/settle times that would be encountered upon scale-up. The organic layers were concentrated to dryness[9] and analyzed for sulfur content. Although all of the experiments afforded the product in comparable yields and purities by ^{1}H NMR, there was a significant difference in the levels of sulfur in the samples (Table 1). Interestingly, the extractions with methylene chloride and toluene led to the lowest amounts of sulfur in the product, while 2-MeTHF provided the highest amount of sulfur. In general, the sulfur levels seemed to correlate with the solubility of water in the solvents used for extractions. Extractions with solvents in which water has a higher solubility led to more sulfur in the isolated product than with solvents in which water is less soluble.[10,11] It is unclear whether this trend is due to the amount of aqueous acid trapped in the organic layer prior to the thiosulfate wash or the relative solubilities of elemental sulfur in these organic solvents.[12]

The next parameter investigated was the pH of the reaction mixture prior to the reductive quench. Typically, the reaction

---

(5) Cooke, J.; Bright, R.; Coleman, M.; Jenkins, K. *Org. Process Res. Dev.* **2001**, *5*, 383–386.

(6) *Quantitative Chemical Analysis*, 6th ed.; Harris, D. C.; W. H. Freeman and Company: New York, 2003.

(7) Souza, F. E. S.; Sutherland, H. S.; Carlini, R.; Rodrigo, R. *J. Org. Chem.* **2002**, *67*, 6568–6570.

(8) Brown, S. J.; Clark, J. H.; Macquarrie, D. J. *J. Chem. Soc. Dalton Trans.* **1988**, 277–280.

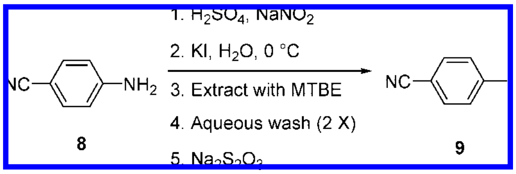
(9) The product was isolated by concentrating the solution to dryness and not by crystallization. This was done in order to avoid any removal of sulfur by crystallization and to determine the true amount of sulfur in the sample.

(10) *The Pilot Plant Real Book*; McConville, F. X.; FXM Engineering and Design: Worcester, MA, 2002.

(11) Stephenson, R. M. *J. Chem. Eng. Data* **1992**, *37*, 80–95.

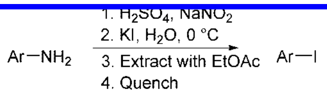
(12) Unfortunately, experimental data on the solubility of elemental sulfur in these organic solvents was not readily available in the literature.

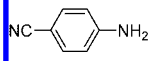
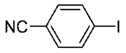
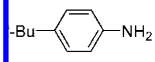
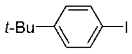
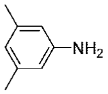
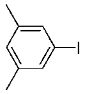
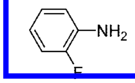
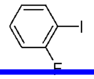
Table 2. **Correlation between sulfur levels and pH prior to quench**



entry	aq washes	wt % S
1		4.4
2	H_2O	2.2
3	satd $NaHCO_3$	0.36
4	20% K_2HPO_4	0.06
5	1 N NaOH	0.02

Table 3. **Dependence of sulfur levels on the quenching agent**[a]



Substrate	Product	$Na_2S_2O_3$		$NaHSO_3$		L-Ascorbic Aci	
		Yield	% S	Yield	% S	Yield	% S
		91	2.6	88	n.d.	88	n.d.
		89	1.2	90	n.d.	96	n.d.
		74	3.3	77	n.d.	74	n.d.
		79	3.6	78	n.d.	81	n.d.

[a] n.d.: not detected.

mixture at the end of the Sandmeyer reaction is acidic, and it is known that sodium thiosulfate decomposes under acidic conditions to produce sulfur (eq 1). We hypothesized that sulfur precipitation could be suppressed by controlling the pH of the reaction mixture before quenching with thiosulfate. Again, five identical reactions were set up as before. Upon reaction completion, the aqueous reaction mixture was extracted with MTBE. This solvent was chosen because it led to a moderate amount of sulfur in the experiments depicted in Table 1. The organic layers were washed twice with different aqueous solutions (Table 2) and then washed with 20% w/w sodium thiosulfate solution (3×). During each thiosulfate wash, the layers were stirred for 45 min prior to separation. The organic layers were concentrated to dryness and analyzed. It is evident from the results in Table 2 that the amount of sulfur in the isolated product decreased when the organic layer was washed with more basic solutions prior to the thiosulfate quench. Washing with a mild base such as sodium bicarbonate led to a significant decrease in the amount of sulfur compared to the baseline case without the extra washes (entry 3 vs entry 1, Table 2). Interestingly, the use of a more basic wash (sodium hydroxide) led to a more dramatic drop in sulfur levels (entry 5 vs entry 1, Table 2).

While basification of the reaction mixture before the thiosulfate quench drastically reduces the amount of sulfur in the product, it does not completely eliminate the formation of sulfur. Thus, alternative quenches were evaluated. We chose to examine another commonly used sulfur-based reductive quench (sodium bisulfite), and a sulfur-free quench (L-ascorbic acid).[7,13] Four different anilines were subjected to the Sandmeyer reaction. For each substrate, three separate reactions were set up. When the iodination was deemed complete, each of the reactions was washed with a different quenching agent ($Na_2S_2O_3$, $NaHSO_3$, and L-ascorbic acid). As before, the washes were stirred for 45 min. The organic layers were then concentrated to dryness and analyzed (Table 3). As expected, the products isolated from the thiosulfate quench contained significant quantities of sulfur, while the bisulfite and L-ascorbic acid quenches did not produce any sulfur. On the basis of these results, it would be prudent to avoid the use of thiosulfate to quench iodination reactions.

The same set of experiments was repeated using 6-aminoindazole (**6**) with very similar results. Whereas 6-iodoindazole (**2**) isolated from the thiosulfate quench required the addition of excess catalyst in the Migita coupling, reactions using crude 6-iodoindazole isolated from the bisulfite and L-ascorbic acid quenches proceeded to completion with the usual catalyst loading (1 mol %).

Conclusions

It has been established that the use of sodium thiosulfate to quench iodination reactions leads to the precipitation of elemental sulfur. This contaminant has the potential to poison transition metal catalysts. While the Sandmeyer reaction was used as the test case in this study, it is conceivable that the quench of most other halogenation or oxidation protocols with thiosulfate would lead to similar problems. Although the level of sulfur in the product can be mitigated by solvent choice and careful pH control during the workup, it cannot be completely eliminated. Alternative quenches such as sodium bisulfite and L-ascorbic acid did not lead to the precipitation of sulfur. Therefore, these quenches should be considered instead of sodium thiosulfate for quenching halogenation reactions.

Experimental Section

General Procedure for Extraction Solvent and pH Screen Using 4-Iodobenzonitrile. Sulfuric acid (1.5 mL) was added dropwise to a suspension of 4-aminobenzonitrile (1 g, 1 equiv) in H_2O (20 mL) at 0 °C. The reaction mixture was stirred for 30 min. Acetone (8 mL) was then added to the slurry, and the mixture was stirred for another 15 min. A solution of $NaNO_2$ (3 equiv) in water (10 mL) was added dropwise, and the resulting solution was stirred for 60 min. A solution of KI (5 equiv) in water (10 mL) was added slowly to the reaction mixture. The resulting dark brown solution was allowed to warm to room temperature overnight. The reaction mixture was extracted with the appropriate solvent (3 × 10 mL). The combined organic layers were washed with 1 N HCl (1 × 20

---

(13) Verma, K. K.; Jain, A.; Verma, A. *Anal. Chem.* **1992**, *64*, 1484–1489.

mL) to remove any residual amine. The organic phase was washed with the appropriate aqueous solution (2 × 30 mL) and then washed with a 20% w/w aqueous solution of $Na_2S_2O_3$ (3 × 50 mL). During each $Na_2S_2O_3$ wash, the layers were stirred for 45 min at room temperature and then separated. This was done in order to simulate the long stir-settle times that would be encountered upon scale-up. The organic layer was washed with water (3 × 20 mL) and evaporated to dryness to afford 4-iodobenzonitrile.

General Procedure for the Synthesis of Aryl Iodides. Sulfuric acid (1.5 mL) was added dropwise to a suspension of the amine (1 g, 1 equiv) in H_2O (20 mL) at 0 °C. The reaction mixture was stirred for 30 min. Acetone (8 mL) was then added to the slurry, and the mixture was stirred for another 15 min. A solution of $NaNO_2$ (3 equiv) in water (10 mL) was added dropwise, and the resulting solution was stirred for 60 min. A solution of KI (5 equiv) in water (10 mL) was added slowly to the reaction mixture. The resulting dark brown solution was allowed to warm to room temperature overnight. The reaction mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with 1 N HCl (1 × 20 mL) to remove any residual amine. The organic phase was then washed with a 20% w/w aqueous solution of the appropriate quenching agent (3 × 50 mL). During each wash, the layers were stirred 45 min at room temperature and then separated. This was done in order to simulate the long stir-settle times that would be encountered upon scale-up. The organic layer was washed with water (3 × 20 mL) and evaporated to dryness to afford the desired iodo compounds.

HPLC Method for the Determination of Elemental Sulfur. Sample Preparation: A sample of the desired iodo compound (30.0 ± 1.0 mg) was weighed accurately and diluted to 10.0 mL with THF in a volumetric flask. This was analyzed against an external sulfur standard of known concentration (0.006 mg/mL). Injection volume: 10.0 μL. Column: Waters Symmetry C18 3.5 μm, 150 mm × 4.6 mm. Mobile phase: water/THF (40/60, v/v); isocratic run. Detection: UV at 254 nm. Flow rate: 0.8 mL/min. Run time: 15 min. Limit of detection for sulfur: 0.0001 mg/mL, i.e., 0.003 wt % for the sample preparation described above.

Acknowledgment

We thank Robert Singer, Robert McLaughlin, and Gregory Sluggett for helpful discussions during the course of this project. Jennifer Rutherford and John Lucas identified the correlation of poor performance in the Migita reaction with the extra event in the DSC thermogram. Analytical support from Gregg Tavares and Laurie Whipple is gratefully acknowledged. We thank the suppliers of **2** for providing information about the manufacturing process. A special word of thanks to Stéphane Caron and Nathan Ide for helpful suggestions in the preparation of this manuscript.

Received for review October 10, 2007.

OP700227P