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Technical Note

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The Development of a Scalable, Chemoselective Nitro Reduction

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Supporting Information

ABSTRACT: We have demonstrated a scalable chemoselective reduction of a nitro functional group in the presence of an aryl imine using $(NH_4)_2S$/EtOH or hydrogenation (Sponge Nickel) to afford the corresponding amino-imines in moderate to excellent yields. Other reducible groups such as aryl halides, styryl olefins, and ether linkages survived as well.

INTRODUCTION

The reduction of nitro compounds to amines is a useful synthetic transformation for which vast arrays of reagents and reaction conditions have been developed.[1] Typically employed methods utilize iron,[2] zinc,[3] or tin[4] and reductions using catalytic hydrogenation.[5] However, selectivity versus the reduction of other sensitive functionalities in the substrate remains a challenge in modern[6] synthetic methodology.

During the development work for a recent drug candidate, we had a need to develop an efficient, chemoselective method for the reduction of nitro functionality in the presence of other reducible functional groups (Scheme 1). Limitations associated with the reduction of the nitro functionality in **1**[7] were the acid-sensitive/reductive nature of an imine, an aryl ether linkage, and the presence of two aryl halides. Nevertheless, there exist at least two examples of such a transformation. Levacher[8] has demonstrated that $Na_2S \cdot H_2O$ selectively reduced a nitro group in the presence of an aldimine. However, our system was not tolerant of these conditions, as concomitant ether cleavage occurred.[9] Similarly, Lemaire[10] utilized a Pd-catalyzed hydrogenation to perform a nitro reduction; however, when **1** was subjected to these conditions, uncontrolled reduction leading to a mixture of **2**−**5** occurred (Scheme 1).

RESULTS AND DISCUSSION

Subsequently, we screened a variety of reduction protocols under basic or neutral conditions. See Table 1 which shows promising results of this initial screen. The use of sodium dithionite[11] or Zn/NH_4OH[12] afforded reduction to aniline **2** with variable amounts of the hydroxylamine **3** produced. Efforts to further reduce the hydroxylamine **3** were unsuccessful. Sulfur (S_8) can be a mild reductant[13] but failed with our system. Transfer[14] hydrogenation yielded, as expected, over-reduction products **4** and **5**. $FeSO_4/NH_4OH$[15] afforded the desired aniline **2** in 85% yield with only a few impurities (<1%), but purity was dependent on the batch/source of $FeSO_4$.[16]

Our best procedures were promising in that the only impurity remaining was hydroxylamine **3**. As **3** could not be easily purged or further reduced under the reaction conditions, we considered the use of sequential $FeSO_4/Na_2S$ to address the half-reduced substrate. Following reduction with $FeSO_4/NH_4OH$ to produce a 7:1 mixture of aniline **2**/hydroxylamine **3**, the batch was treated with Na_2S to further reduce hydroxylamine **3** to aniline **2**, producing consistent yields of 65−68%[17] after isolation. Higher yields (75−80%) were possible in a $TiCl_4/Mg^0$ system[18] with <1% hydroxylamine or over-reduction products remaining. However, due to the large excess of $TiCl_4$ required, this method was not considered practical due to slow filtration of the inorganic salts encountered during the isolation.

A scalable method was developed by the use of $(NH_4)_2S$.[19] When a 40 wt % $(NH_4)_2S$ solution in water was added to **1** in IPA at 80 °C, gas rapidly evolved, and the reaction was complete after ~3 h. To minimize the hazard of gassing, we observed that simply stirring the suspension of the reaction mixture for 2 h at 20 °C[20] afforded a 4:1 mixture of hydroxylamine **3** and aniline **2**. Once the nitro compound was consumed, the reaction was heated to 70 °C for 2.5 h to complete the reduction of the hydroxylamine **3**. The reaction was diluted with water, cooled to 20 °C, and filtered, and upon recrystallization, 75−80% of the desired aniline **2** was obtained in >98% purity (Scheme 2). Disappointingly, at >20-kg scale the yield fell to 53% as the reduction was highly dependent on the particular batch and source of $(NH_4)_2S$.

As it seemed we had sufficiently explored low-valent elements for reduction, we began a more in-depth investigation of transition metal catalyzed hydrogenation conditions using Pd,[21] and Pt[22] or Rh [23] and Ni[24] catalysts with varying pressures of H_2, temperatures and solvents. Unfortunately, we did not observe a selective reduction to aniline **2** using Pd, Pt, or Rh. Of general interest is that Pd/C in EtOAc afforded the benzhydryl-aniline **4** exclusively[25] in 90% yield and >99% purity.

However, Sponge Nickel[26] in 2-MeTHF produced a mixture of aniline **2** as the major product (99%), with hydroxylamine **3** (<1%) as a minor impurity. A variety of solvents were screened and were found to be less optimal than 2-MeTHF (CH_2Cl_2, EtOAc, toluene, and THF). Optimization led us to the following conditions: 2-MeTHF (10 mL/g), 125 mg/g·LR[27] Sponge Nickel, 40 °C, and 25 psig H_2. To attenuate[28] the activity of the catalyst, the commercial Sponge Nickel was washed sequentially with 5% AcOH, water, and MeOH. The water washes ensure that any residual acid is gone, as its presence could induce imine hydrolysis. The sponge Nickel[29] obtained after this wash sequence was then utilized under the

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Scheme 1. Desired selective reduction of a nitro group

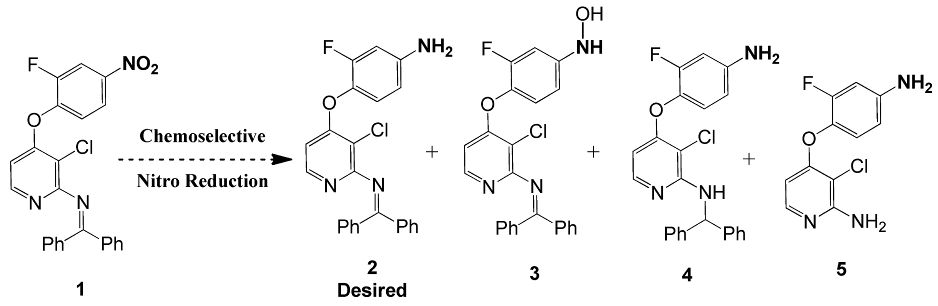


Table 1. Initial screen of reductants

entry	reductant	yield (%)[a]	2:3:4:5[b]
1	$Na_2S_2O_4$	65	1:1:0:0
2	Na_2S	53	1:0:0:0
3	Pd/C NH_4HCO_2	67	0:0:1:1
4	Zn/NH_4Cl	68	3:1:0:0
5	Zn/NaOH	72	2:1:0:0
6	$FeSO_4/NH_4OH$	85	7:1:0:0
7	$FeSO_4/NH_4OH$ then Na_2S	65	1:0:0:0
8	$TiCl_4/Mg^0$	75	1:0:0:0
9	$(NH_4)_2S$	90	1:0:0:0

[a] Isolated yields of mixtures. [b] HPLC ratios.

Table 2. Summary of processes

process	scale (kg)	yield (%)	comments
$FeSO_4/$ NH_4OHNa_2S	2	65	problematic filtration
aq $(NH_4)_2S$/IPA	25	53	yield dependent on batch of $(NH_4)_2S$
Sponge Nickel (A-5001)	22	88	reproducibly performed with various lots of sponge nickel

optimized conditions which completed the reaction after ~8 h at 25 °C. The benzhydryl-aniline **4** would form after prolonged reaction times (>48 h), but only after the complete consumption of hydroxylamine **3**. Using the optimized conditions **B** (Scheme 2) with the commercially available Sponge Nickel A-5001[28] (from Johnson-Matthey), we successfully carried out a 22-kg campaign[30] in 88% yield. While different batches of $FeSO_4$, and $(NH_4)_2S$ had led to variable reductions, all lots (four separate lots) of Sponge Nickel (type A-5001) performed identically (Table 2). Lab-scale (<25 g) experiments have demonstrated that the catalyst could be reused up to five times (filtered off catalyst and recharged to a separate flask) with no loss in reactivity or chemoselectivity. Further exploration of recycling the Sponge Nickel is needed to demonstrate the reproducibility and scalability.

■ GENERALITY OF REDUCTION METHODOLOGY

With both the Sponge Nickel hydrogenation and sulfide ($(NH_4)_2S$ or Na_2S) conditions in hand, we screened a variety of substrates to test the scope of our protocols (Scheme 3). Utilizing either Na_2S, $(NH_4)_2S$, or Sponge Nickel, aryl ketimines as well as aryl aldimines[31] survived the reduction sequence to exclusively afford the corresponding imino-anilines with high selectivity. Remarkably, little to no reduction[32] of vinyl, alkynyl, and halogen substituents were observed, and the products were isolated in 48−86% yields.

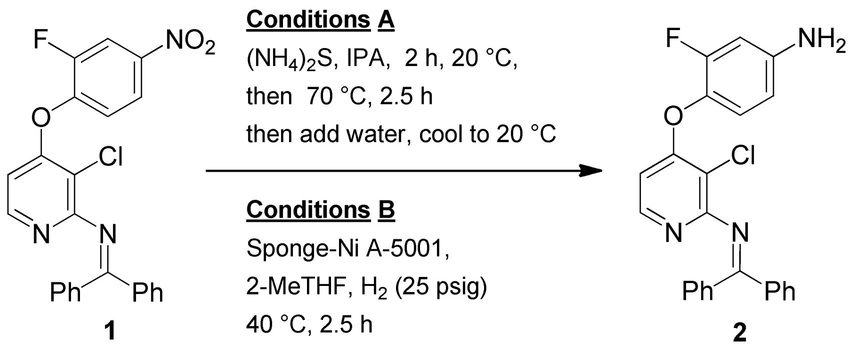
■ CONCLUSIONS

In summary, we have shown that a chemoselective reduction of a nitro group with Sponge Nickel (type A-5001) or sulfide can occur in the presence of an aryl imine, aryl fluorides and chlorides, and aryl ether functionalities. Both methods were scaled to >22 kg scale in good yield and selectivity. Reproducibly good yields and selectivity were obtained with both reagents for a variety of substrates, suggesting these will be useful for selective nitro group reduction in the presence of groups prone to reduction.

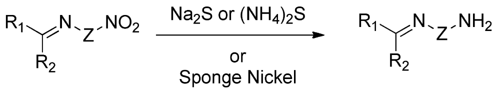
■ EXPERIMENTAL SECTION

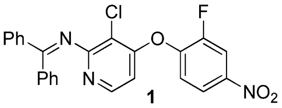
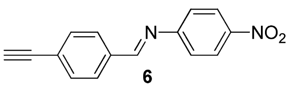
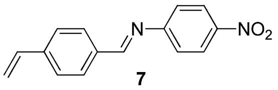
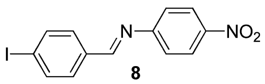
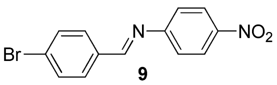
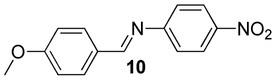
General Methods. Reagents were used as received, unless otherwise noted. Solvents were reagent grade. Reactions were stirred and monitored by HPLC. Yields refer to recrystallized and spectroscopically pure compounds unless noted otherwise. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. ^1H and ^{13}C were recorded

Scheme 2. Optimized $(NH_4)_2S$ protocol (A) and Sponge Nickel protocol (B)



Scheme 3. Chemoselective reduction of nitro functionality[a]



Nitro-imine	Reductant Na2S	 (NH4)2S	 Sponge Nickel
 **1**	**2**: 48%	**2**: 68%	**2**: 87%
 **6**	**11**: 55%	**11**: 62%	**11**: 80%
 **7**	**12**: 64%	**12**: 58%	**12**: 79%
 **8**	**13**: 71%	**13**: 58%	**13**: 82%
 **9**	**14**: 65%	**14**: 68%	**14**: 84%
 **10**	**15**: 52%	**15**: 55%	**15**: 79%

[a]All reactions are unoptimized, and all yields listed are of isolated material

on either a 400 or 500 MHz spectrometer. Chemical shifts are relative to either $CDCl_3$ (δ 7.26 for ^1H and δ 77.0 for ^{13}C) or d_6-DMSO (δ 2.50 for ^1H and δ 39.51 for ^{13}C).

Use of $(NH_4)_2S$ as the Reductant. Preparation of 4-(4-Amino-2-fluorophenoxy)-3-chloro-*N*-(diphenylmethylene)pyridin-2-amine (2). To a reactor was added 3-chloro-*N*-(diphenylmethylene)-4-(2-fluoro-4-nitrophenoxy)pyridin-2-amine (**1**) (22.00 kg, 44.20 mol), isopropanol (200 L), and $(NH_4)_2S$ (60 L, 442 mol). This solution was allowed to stir at 20 °C for 1 h. This solution was then heated to 70 °C and held for 2.5 h. Water (200 L) was added, and the solution was cooled to 20 °C. After holding at 20 °C for 3 h, the slurry was filtered. The solids were dissolved into butyl acetate (110 L) by heating to 80 °C. At 80 °C, heptane (110 L) was added and the solution was cooled to 20 °C over 1 h. The slurry was aged for 2 h at 20 °C. The solids were filtered, washed with heptanes (110 L), and then dried (50 °C, 25 mmHg) to afford 4-(4-amino-2-fluorophenoxy)-3-chloro-*N*-(diphenylmethylene)pyridin-2-amine (**2**) (9.82 kg, 53% yield) as a yellow solid (mp =151−153 °C). ^1H NMR (500 MHz, DMSO-d_6) δ = 7.97 (d, J = 5.7 Hz, 1H), 7.81−7.15 (m, 10H), 6.96 (t, J = 9.0 Hz, 1H), 6.52 (d, J = 13.2 Hz, 1H), 6.43 (d, J = 8.5 Hz, 1H), 6.28 (d, J = 5.7 Hz, 1H), 5.52 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 170.5, 161.3, 160.9, 154.9, 152.9, 148.7, 147.4, 137.7, 135.6, 131.8, 129.3, 129.1, 128.5, 128.0, 123.5, 109.9, 107.9, 105.6, 101.4, 101.3. HRMS EI (m/z): [M + H] Calcd $C_{24}H_{18}ClFN_3O$, 418.1122; Found [M + H] 418.1127.

Use of Sponge Nickel (type A-5001) on a 22-kg-Scale Run. Preparation of 4-(4-Amino-2-fluorophenoxy)-3-chloro-*N*-(diphenylmethylene)pyridin-2-amine (2). To a 2000-L stainless-steel hydrogenator was added Sponge Nickel (type A-5001) (2.75 kg), 2-MeTHF (733 L) and 3-chloro-*N*-(diphenylmethylene)-4-(2-fluoro-4-nitrophenoxy)pyridin-2-amine (**1**) (22 kg, 49.12 mol). The vessel was purged with N_2 (30 psig, 3×), followed by purging with H_2 (30 psig, 3×). The vessel was pressurized with H_2 (25 psig) and was then heated to 25 °C. Once complete (6 h, HPLC analysis), the solution was filtered over Celite, followed by a cake wash of 2-MeTHF (180 L). The combined organics were passed through a 0.20 μm cartridge filter. The filtered organics were concentrated to approximately one-quarter volume. *n*-Butyl acetate (154 L) was added, heated to 80 °C, and held until complete dissolution was obtained. At 80 °C, heptane (154 L) was added over 3 h and then was cooled to 20 °C over 3 h. The slurry was aged for 15 h at 20 °C. The solids were filtered, washed with heptanes (75 L), and then dried (50 °C, 25 mmHg) to afford 4-(4-amino-2-fluorophenoxy)-3-chloro-*N*-(diphenylmethylene)-pyridin-2-amine (**2**) (17.42 kg, 85% yield) as a yellow solid. See above for spectroscopic data.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures for intermediates and copies of ^1H and ^{13}C NMR spectra for all new compounds. 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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(16) Each batch of $FeSO_4$ was analyzed with standard techniques, and no differences were observed.

(17) This protocol was scaled to 2 kg, but the filtration of the Fe salts proved to be extremely problematic on scale; thus, this system was not further studied.

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(25) See Supporting Information for experimental details.

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(27) mg/g·LR = mg per g of limiting reagent (LR).

(28) If the standard nickel was not treated with the wash sequence, variable amounts of hydroxylamine **3** (1−15%) were observed. This wash was applied to remove any residual NaOH.

(29) Sponge Nickel (A-5001 from Johnson-Matthey) is the commercially available form that is prewashed with washed with 5% AcOH, water, and then MeOH. It is supplied as a slurry in water.

(30) We utilized multiple lots of Sponge Nickel A-5001, and all lots performed as expected.

(31) When using aldimines, yields listed are for the isolated TFA-derivatives. The anilines were found to be unstable during isolation (they degraded to the bis-imine upon recrystallization or chromatography).

(32) LC/MS analysis of the crude reaction mixtures showed <5% of over-reduced impurities.