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Technical Notes

Heavy-Metal-Free Reduction Methodology for Large-Scale Synthesis Applicable to Heterocyclic and Arylhydrazines†

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Abstract:

A green chemistry methodology that uses a heavy-metal-free reduction in aqueous medium is described to produce 5-hydrazinoquinoline [1-(quinolin-5-yl)hydrazine] (6a) as the anhydrous dihydrochloride salt at large scale. The process is entirely aqueous and utilizes L-ascorbic acid to reduce the diazonium salt (2a) derived from 5-aminoquinoline [quinolin-5-amine] (1a).

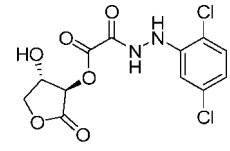
Introduction

During the scale-up and design phase of a drug candidate[1] the key starting material selected for the synthesis was 5-hydrazinoquinoline (**6a**). This compound was originally prepared from 5-aminoquinoline (**1a**) by diazotization followed by reduction with tin and hydrochloric acid or stannous chloride and mineral acid.[2] The product obtained from the tin reduction protocol was not clean enough for pharmaceutical use as it was typically contaminated with tin residues and colored side products. Old literature[3] indicated that ascorbic acid could be reacted with diazonium salts to form a number of products including arylhydrazines. This was used as the starting point for the design of a large-scale process to manufacture 5-hydrazinoquinoline, which had previously only been reported as prepared by the tin reduction method.

Laboratory Results and Discussion

The reaction and the intermediates potentially involved in the transformation from aryl amine to aryl hydrazine were evaluated using the following aryl amines: 2-bromoaniline (**1b**), 2-chloroaniline (**1c**), 2,5-dichloroaniline (**1d**), and the target molecule 5-aminoquinoline (**1a**). Scheme 1 shows the probable (and later verified) intermediates suspected in the reaction sequence after the diazonium salts **1a**−**d** are allowed to react with L-ascorbic acid (**3**).

The proposed lactone intermediate **4** was the most difficult of the intermediates to isolate in pure form due to the labile nature of this class of lactones caused by hydrolysis in acidic or basic media. It turned out to be possible to isolate and purify lactone **4d** derived from 2,5-dichloroaniline (**1d**) by ensuring the reaction between the diazonium salt (**2d**) and **3** was carried out below 0 °C in dilute aqueous reaction media with the minimal practical amount of hydrochloric acid needed to form the nitrous acid used for diazonium salt formation. The initial crude product isolated contained 20−25 mol % of oxalic acid intermediate **5d**; this was reduced to 6−7 mol % on trituration with isopropyl acetate. This enabled NMR evidence to be measured[4] which supported the lactone structure **4d**. The L-threo stereochemistry is inferred from the earlier work and claims of Weidenhagen et al.[5] who demonstrated that **4d** has optical activity. See also the Erlbach paper on the D-erythrophenyl analogue.[6]



4d

Oxalic acid derivatives **5a**−**d** were isolated and identified. The results are noted in Table 1. Intermediates **5a**−**d** are quite stable and can be isolated from their reaction media, dried, and stored at room temperature, unlike the lactone intermediates **4a**−**d** which are readily hydrolyzed by mineral acid. The oxalic acid derivatives **5a**−**d** provided a possible purification gate to facilitate synthesis of very pure hydrazine dihydrochloride salts. Some derivatives, though usually >95% pure by main band assay, were colored; in one case, **5d** was red! This could be removed by treatment with activated charcoal. Alternatively, the process can be telescoped, and the suspension of **5a**−**d**

† This contribution is made to celebrate the life and work in chemical science of Dr. Christopher Schmid.

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(1) Lambert, J. F.; Norris, T. Preparation of Sodium-Hydrogen Exchanger Type I Inhibitors. Patent Application WO 02/44133 A1, 2002.
(2) Dufton, S. F. *J. Chem. Soc.* **1892**, 782–787.
(3) Weidenhagen, R.; Wegner, H.; Lung, K. H.; Nordstrom, L. *Chem. Ber.* **1939**, *72B*, 2010–2020.

(4) ^{1}H NMR (DMSO-d_6) δ 7.94 (broad s, 1H), 7.76 (d, J = 8.6 Hz, 1H), 7.67 (dd, J = 2.5, J = 8.6 Hz, 1H), 7.41 (d, J = 2.5 Hz, 1H), 7.12 (broad s, 1H), 5.67 (broad s, 1H), 4.64 (s, 1H), 4.40 (dd, J = 3.7 Hz, J = 6.0 Hz, 1H), 4.26 (dd, J = 6.0 Hz, J = 9.5 Hz, 1H), 3.96 (dd, J = 3.7 Hz, J = 9.5 Hz, 1H).

(5) See ref 3, p 2017.
(6) Erlbach, H. *Chem. Ber.* **1935**, *68*, 534–539.

(7) NMR data supporting the structure of compounds **5a**, **5b**, and **5c** are contained in the Supporting Information.

(8) The hydrazines in the table are all known compounds and were characterized by comparison to authentic reference samples using IR.

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Scheme 1. **Aryldiazonium salts reaction sequence with L-ascorbic acid to form arylhydrazines**

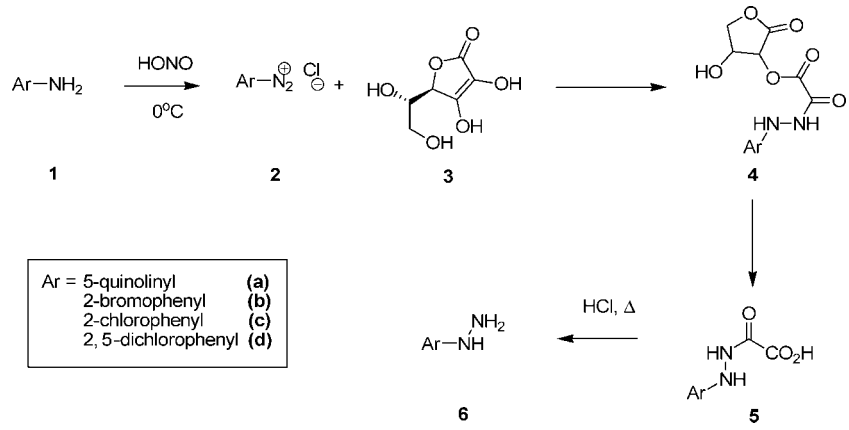

Table 1. **Oxalic acid derivatives (5a−d) yield and purity data (scale > 0.1 mol)**

$ArNH_2$	$ArNHNH\cdot CO\cdot CO_2H$	yield (%)	comments
1a	**5a**	68.4	isolated as mono HCl salt, HPLC purity 99.7%
1b	**5b**	69	pale brown solid, HPLC purity 99%
1c	**5c**	62.5	yellow solid, HPLC purity 99%
1d	**5d**	73 (crude)	off-white solid. Color prior to C treatment red. HPLC purity before C treatment 96.2%
		25 (decolorized)	HPLC purity after C treatment 98.4%

Table 2. **Laboratory runs exemplifying aniline to hydrazine hydrochloride conversion: $ArNH_2$ (1a−d) → crude wet $ArNHNH\cdot CO\cdot CO_2H$ (5a−d) → $ArNHNH_2\cdot xHCL\cdot yH_2O$ (6a−d)**

$ArNH_2$	$ArNH_2$ (mol)	ascorbic acid (mol)	$NaNO_2$ (mol)	$ArNHNH\cdot CO\cdot CO_2H$ dec conds. °C (h)	molar yield hydrazine (%) **1** → **6**	HPLC main band $ArNH\cdot NH_2$ (%)
1a	0.347	0.363	0.42	80 (0.33)	66	98.6
1b	0.058	0.058	0.07	80 (2)	57	96.3
1c	0.15	0.15	0.18	70 (6)	64	94.5
1d	0.123	0.129	0.148	90 (2)	71	98.3

process intermediates can be directly hydrolyzed by heating in hydrochloric acid to form hydrazines **6a**−**d**. Quinoline derivative **5a** was isolated as a monohydrochloride salt due to the presence of the basic quinoline nitrogen atom. The other derivatives, **5b**−**d**, were isolated as $ArNHNH\cdot CO\cdot CO_2H$ compounds.

A number of experiments were carried out to get an understanding of the formation of the diazonium salts **2a**−**d** and their subsequent reaction with L-ascorbic acid **3** which was always initiated at ∼0 °C and carried out in water and ending at room temperature ∼25 °C. It appeared that the optimum level of **3** was near 1.00−1.05 mol relative to anilines **1a**−**d**. This resulted in the formation of oxalic acid derivatives **5a**−**d** that yielded the hydrazines **6a**−**d** when treated with hydrochloric acid at elevated temperature between 70−90 °C. At the lower end of the treatment temperature longer reaction times were required: 6 h at 70 °C for **5c** → **6c**. The shortest reaction time was observed for **5c** → **6c** in 1/3 h at 80 °C. $NaNO_2$ was used at 1.2 mol relative to the aniline **1a**−**d** for all evaluations. Table 2 summarizes the results obtained in the laboratory for conversion of anilines **1a**−**d** into hydrazines **6a**−**d**. In these experiments the oxalic acid intermediates **5a**−**d** were isolated as crude wet solids and directly converted into hydrazines **6a**−**d** by treatment with aqueous hydrochloric acid at elevated temperature, and **6a**−**c** were isolated as hydrochloride hydrates The overall molar yield range was 57−71% for the conversion of **1a**−**d** into **6a**−**d**. Hydrazines **6b** and **6c** were isolated as hydrochloride monohydrates, **6a** as a dihydrochloride salt, and **6d** as monohydrochloride, ∼2.5−2.6 hydrate.

The results obtained in Tables 1 and 2 were used as a guide to finalize a laboratory process model suitable for scale-up of **6a**. Aniline **1a** was the limiting reagent, and the levels of the other reagents used to produce **5a** were as follows: $NaNO_2$ (1.1−1.2 equiv), L-ascorbic acid (**3**) (1.05−1.15 equiv), 32% HCl (∼8.8 equiv) and for the conversion **5a** → **6a**, 32% HCl (∼11 equiv). Experiments were carried out to determine the reaction heat[9] or enthalpy (ΔH), heat capacity (C_p) and adiabatic temperature rise (ΔT) for the five key operations where reactions were occurring. These data are shown in Table 3.

The proposed procedure had three operations where exothermic events were possible and needed careful control. These were the acid/base reaction between **1a** and concentrated HCl, the formation of the diazonium salt **2a**, and the reduction reaction of **2a** with **3**. The decomposition of **5a** by hydrolysis was endothermic and provided no potential problem. It was also observed that, when solid **3** was added portionwise to the diazonium salt, effervescence was observed and during the formation of the diazonium salt **2a** red fumes of NO_x were formed. It turned out that yield was adversely affected by the NO_x fumes, and it was important to clear these prior to commencement of the reduction phase using a nitrogen flow through the reactor train. The effervescence observed during solid addition of **3** to **2a** during the reduction phase indicated that it was best to add the cold diazonium salt suspension **2a**

Table 3. **Thermal chemistry data measured for conversion (1a → 6a)**

operation	ΔH (kJ)	C_p (J/kg K)	ΔT (°C)
Addition of **1a** to conc. HCl			
run 1	78.8	2417	27.3
run 2	82.7	2406	28.8
Addition of aq $NaNO_2$ to **1a** suspended in conc. HCl			
run 1	86.8	2625	23.1
run 2	90.8	2619	24.2
Addition of **2a** to **3** suspended in conc. HCl			
run 1	164.8	2909	33.5
Addition of **3** to **2a**			
run 1	149.4	2397	38.2
run 2	142.0	2289	38.2
Decomposition of **5a** into **6a**			
run 1	−643.1	4228	−91.5

into a solution of **3** maintained at 15−20 °C. This knowledge was taken forward to the scale-up stage.

Large-Scale Operations

This section describes the first scale-up used to produce 16 kg of 5-hydrazinoquinoline dihydrochloride. The main equipment required for this operation consisted of two jacketed glass-lined reactors equipped with heating and cooling services, a nitrogen system, an overhead condenser, and a receiver system. A filter dryer was also required. All charging operations were performed under a nitrogen atmosphere, and personnel were fully protected with appropriate chemical handling suits and respirators. Vacuum and vacuum lines were broken with nitrogen inflow. These are industry standard practices for all aqueous and solvent-based processes since all chemical operations have an intrinsic need for containment and exposure control even when using green chemistry protocols and processes. The process reactions and isolations are entirely aqueous. The only solvent used is methanol which is used as a displacement wash on the product cakes. This is done to facilitate more rapid drying times and thus reduce the process cycle time. The total quantity of methanol used for both steps to produce 16 kg of **6a** dihydrochloride was 50 or 3.125 L kg^{-1} **6a**. It was further envisaged that the two steps used for forming **5a** and **6a** could eventually be telescoped in the next process improvement iteration, as was demonstrated in the laboratory development work. The conservative approach was taken for the first trials at plant scale, and intermediate **5a** was dried and fully analyzed before final conversion into **6a**.

The reaction conditions used in the large-scale work were similar to those in the trials noted in Table 2. The diazotization reactions were carried out in the range −2−2 °C, aniline **1a** was the limiting reagent, $NaNO_2$ was used at ∼1.1 equiv, and 10.2 M or 32% aqueous HCl ∼7.4 equiv. Once the diazonium salt was formed, the reaction with L-ascorbic acid (∼1.04 equiv) was carried out in the temperature range 15−20 °C; this was accomplished by slowly adding the cold diazonium salt suspension into the aqueous L-ascorbic acid in a reaction vessel with a temperature-controlled jacket system. The molar yield from **1a** to **5a** obtained at scale was 81% better than that obtained in some laboratory-scale models where temperature control was not as precise, but was equal or slightly below the best laboratory pilot run.

Conversion of **5a** into **6a** was carried out in the temperature range 88−91 °C over 2 h with 32% aqueous HCl (∼11.5 equiv). **6a** was isolated as a dihydrochloride salt. This provided a molar yield for the acid decomposition step of 82% and an overall molar yield of 66% from **1a** → **6a** when run at scale for the first time. The details of the large-scale work are noted in the following two sections.

Pilot-Plant Production of 2-Oxo-2-(2-(quinolin-5-yl)hydrazinyl)-acetic Acid[10] Monohydrochloride (5a)

Example from First Run. Vessel A was charged with 32% aqueous HCl (75 L), and the contents were stirred and cooled from 17.5 to 0.5 °C over 1.75 h. 5-Aminoquinoline (**1a**) (15 kg) was added in four equal portions every 15 min. The exothermic reaction required active jacket cooling. The maximum temperature excursion allowed was limited to 25 °C. The final temperature at the end of this phase was noted as 5.7 °C. The vessel contents were then further cooled to 0 °C over 45 min to yield a suspension. Vessel B was charged with sodium nitrite (8 kg) and then purified water (15 L). The contents were stirred at 15−25 °C until a clear yellow-green solution was formed. Vessel A was actively cooled, and the contents of vessel B were metered slowly into the stirred cold suspension in vessel A over 2 h.The internal contents temperature of vessel A was not allowed to exceed 2 °C. After the addition was complete, the internal contents temperature was 1 °C. Active cooling was maintained for vessel A, and the contents were stirred in the range −2−2 °C for 1 h to allow the diazotization reaction to go to completion. Vessel A was then purged with nitrogen for 15 min to remove NO_x red fumes from the reactor headspace to the scrubber system. Vessel B was charged with L-ascorbic acid (19 kg) and then 32% aqueous HCl (30 L), the contents were stirred at 15−20 °C to form a homogeneous suspension. The cold stirred diazonium salt suspension in vessel A was transferred into vessel B over the period of 1 h. The vessel contents temperature of vessel B was maintained in the range 15−20 °C. When the transfer was completed, a followthrough wash of 32% aqueous HCl (4 L) was applied to vessel A and run into vessel B via the transfer pipe between the vessels to ensure complete transfer of the diazonium salt suspension. The final vessel B contents temperature after completion of the transfer was 16.5 °C. The reaction mixture was stirred for 20 min in the temperature range 15−20 °C and then in the range 35−45 °C for 3 h to complete the reaction; it was cooled to 15−20 °C and an IPC HPLC assay performed to confirm reaction completion. Purified water (41 L) was added to vessel B and the vessel contents cooled to −5−0 °C to form a product slurry which was granulated for 1.5 h prior to isolation. The

(9) Positive numbers indicate an exothermic event and negative numbers an endothermic event in the data presentation.
(10) Also named is [2-(5-quinolinyl)hydrazide]ethanedioic acid monohydrochloride.

product was washed with methanol (22.5 L) and dried under vacuum at ~40 °C. **5a**[11] yield 21.5 kg. Waste liquor 215 kg, pH = 0.

Pilot-Plant Production of 5-Quinolinyl-hydrazine dihydrochloride (6a)

Vessel B was charged with **5a** (21.5 kg), purified water (30 L), and 32% aqueous HCl (90 L). The content of vessel B was stirred and the suspension heated for 2 h at 88−91 °C. Cooled to 18−22 °C and granulated for 2 h, filtered, isolated, washed with methanol (22.5 L), and dried at 40−43 °C, **6a** yield was 16 kg of yellow solid. The product HPLC[12] main band assay was 99.3%, water content 0.14%, dihydrochloride salt and no detectable residual solvents were found by GC. Comparison of IR spectra with an authentic sample showed the following characteristic absorption peaks. IR (DRIFTS) ν_{max} cm^{-1}: 3897, 3843,1987, 1904, 1641, 1597, 1519, 1201, 1165, 1103, 1085, 1064. Waste liquor 180 kg, pH = 0.

(11) HPLC indicates that the end product **6a** is also present at this stage. This material is carried forward and does not impact overall yield or decomposition by hydrolysis of **5a**. The quantity varies from run to run.

(12) HPLC conditions for compounds **1a**, **3**, **5a**, and **6a**. Column, Zorbax RX-C_8, 4.6 mm × 250 mm; Column temperature, 40 °C; Mobile phase and dissolving medium, K_2HPO_4 40 mM containing TBAHS 20 mM (adjust to pH 6.8)/acetonitrile 85/15; Detection UV, 254 nm; Flow rate, 1 mL min^{-1}; Injection volume, 20 mL; Run time, ~40 min; Sample concentration, ~0.3 mg mL^{-1}. Typical RT: **3**, 2.88 min; **6a**, 5.88 min; **5a**, 6.35 min;**1a**, 8.32 min. An example chromatogram is contained in the Supporting Information.

Acknowledgment

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Supporting Information Available

NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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