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An optimized method for the synthesis of 2,6-diaminoanthracene

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ABSTRACT

The reduction of 2,6-diaminoanthraquinone to 2,6-diaminoanthracene was examined under a variety of conditions. Direct reduction using zinc powder gave a mixture of the target product and 9,10-dihydro-2,6-diaminoanthracene under all the conditions examined. Protection of the starting amine, followed by borohydride reduction and deprotection, gave the target product in 14–50% yield. Finally, tin powder was used to reduce the anthraquinone to 2,6-diaminoanthrone in quantitative yield. This compound was further reduced to the target 2,6-diaminoanthracene in 55–65% yield.

Anthracenes and larger acenes continue to be the subject of extensive research in the field of organic semiconductors.[1–3] In the course of our research in this field, we recently identified 2,6-diaminoanthracene (**2**) as a key intermediate for the production of several acene platforms. Surprisingly, even though the corresponding 2,6-diaminoanthraquinone (**1**) is inexpensive and readily available, there are very few reports describing the preparation of **2**.

Although Criswell reported the reduction of a number of substituted anthraquinones using sodium borohydride, the amino-substituted quinones were not examined.[4] Another study suggested that compound **2** had been prepared from either borohydride or zinc in aqueous ammonia, but did not provide spectral evidence for its formation.[5] Yanagimoto et al. reported that reduction using zinc in aqueous ammonia gave 2,6-diamino-9,10-dihydroanthracene (**3**),[6,7] while Rabjohns reported that compound **2** could be prepared using powdered zinc in aqueous hydroxide.[8] Because of the potential importance of compound **2**, and because of our need for larger quantities of this material, we wished to optimize the reduction of anthraquinone **1** to anthracene **2** (Scheme 1).

In our initial efforts, we found compound **1** to be unreactive toward sodium borohydride in isopropanol at reflux temperatures. We, therefore, turned to the reduction of compound **1** using powdered zinc as a reducing agent. We found the zinc reduction in aqueous ammonia to be very sluggish, typically yielding 0–10% conversion to a mixture of **2** and **3** after 24 h at reflux temperatures. We examined the reduction under a number of other solvent conditions, including water, aq acetic acid (5–50%), aq ammonium chloride (1 M), and aq ammonium sulfate. We examined both classical heating and microwave methods. None of these yielded significant amounts of the product.

We then turned to the procedure of Rabjohns et al., who reported the synthesis of **2** in 40% yield by heating compound **1** to reflux in 2.5 M aq sodium hydroxide with 9 equiv of zinc for 24 h, followed by filtration and separation from the residual zinc using Soxhlet extraction.[8] While we found this procedure to be significantly improved over other methods, in our hands these conditions gave a mixture of compounds **2** and **3** in a ratio of 40:60 with 40% combined yield. It is postulated that differences in the activity of zinc may account for the discrepancies between our results and the literature reports.

In order to optimize this synthesis, we examined the effects of reagent ratio, solvent, and temperature on the ratio of compounds **2** and **3** formed. We found a minimum of 4 equiv of zinc was necessary to drive the reaction to completion,[‡] and that the formation of side product **3** was observed under all ratios examined (Table 1, entries 1–4). Although we had postulated that the over-reduction to compound **3** might be favored at higher temperatures, we found that reducing the temperature did not improve the ratio of **2**:**3** (Table 1, entries 4–5). Finally, we examined the role of solvent composition on the rate. While we did not find a strong correlation between the solvent components and the product ratio, we did note that (a) the reaction goes to completion much more quickly in 50% ethanol than in 10% ethanol and (b) the reaction did not go to completion when ethanol was raised to 80% (Table 1, entries 4, 6 and 7).

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[‡] Qualitatively, the completion of this reaction is evidenced by a color change from deep red to bright yellow.

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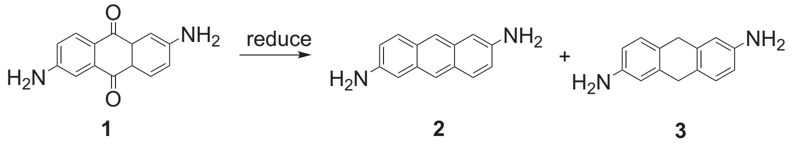


Scheme 1. Reported reduction products of 2,6-diaminoanthraquinone.

Table 1
Optimization of conditions for zinc reduction

Entry	Conditions[a]	Solvent ratio aq OH^-:EtOH	Product[b] (%)	
			2	**3**
1	4 equiv zn, reflux, 24 h	3:5	60	40
2[c]	6 equiv zn, reflux, 24 h	1:1	64	37
3[c]	8 equiv zn, reflux, 24 h	1:1	66	35
4[c]	10 equiv zn, reflux, 24 h	1:1	69	31
5	8 equiv zn, 60 °C, 16 h	1:1	50	50
6	8 equiv zn, reflux, 24 h	4:1	58	42
7	8 equiv zn, reflux, 24 h	1:4	64	32[d]

[a] All reactions shown run under inert atmosphere, using 2.5 M NaOH as aqueous component.

[b] Percentage of compound in the mixture determined by ^1H NMR in DMSO-d_6 (while slightly soluble in chloroform, we found that compound **2** gives a complex NMR spectrum in $CDCl_3$, which resolves into the simple, predicted spectrum in DMSO-d_6. This presumably is due to concentration-dependent aggregation effects in chloroform. As a result, all quantitative studies were conducted in DMSO-d_6).

[c] Average of 2 runs.

[d] In entry 7, 4% starting compound **1** was also present.

We next examined the time required for this reaction. We suspected that compound **2** was the initially formed product, and that it underwent a subsequent 2-electron reduction to produce **3**. In light of this, we postulated that shorter reaction times might enhance our production of compound **2**. We therefore ran a series of experiments in which we monitored the reaction progress as a function of time (Fig. 1). Surprisingly, we found that the rate of formation of **3** is strongly dependent on the concentration of starting material and the percentage of **3** changes very little after the starting material has been consumed. Further, when we combined pure compound **2** with 6 equiv of zinc for 24 h under refluxing conditions, we found that no compound **3** was formed. These results suggest that the primary mechanism for over-reduction of **1** to **3** does not involve compound **2** as an intermediate. Under all conditions of zinc reduction tested, we found the production of compound **3** to be competitive with the formation of compound **2**.

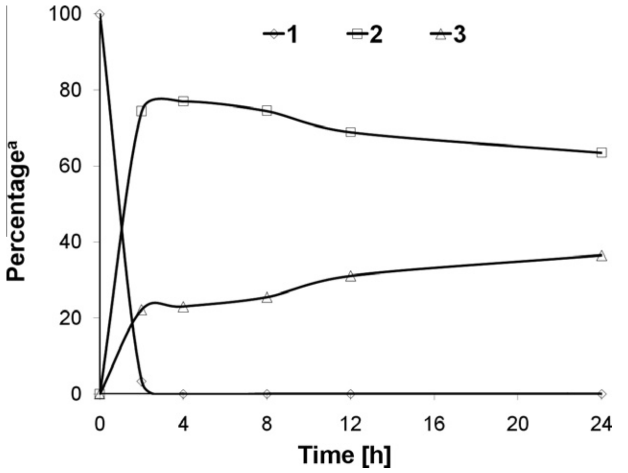


Figure 1. Percentages of compounds **1**, **2**, and **3** in reaction mixture as a function of time. Reaction conditions: 6 equiv zinc, solvent = 1:1 10% aq NaOH:ethanol, reflux temperatures, inert atmosphere.

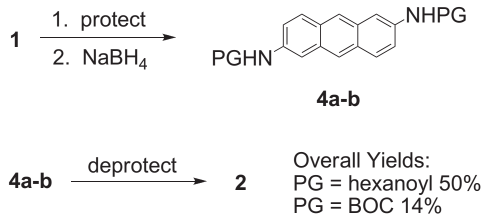
Concurrent with the study of one-step reduction conditions described above, we also explored several protection–reduction–deprotection schemes to access compound **2**. While compound **1** is very resistant to borohydride reduction (presumably due to the strongly electron-donating amine groups), we found that if the amine was protected by either an acyl or a BOC protecting group, the borohydride reduction went smoothly. Deprotection then gave the purified target in 50% overall yield using hexanoyl or 14% overall yield using BOC protecting groups (Scheme 2).[§]

While these three-step sequences worked smoothly, we still felt that a reproducible, one-step reduction using an inexpensive metal should be possible. To this end, we postulated that a metal having a lower reduction potential might avoid the over-reduction and give product **2** more cleanly. When iron was substituted for zinc, no reduction was observed. However, when tin was used, the reduction was found to proceed smoothly to give 2,6-diaminoanthrone (**5**) as the only product in quantitative yield (Scheme 3).[**] Reduction of compound **5** using sodium borohydride in the presence of hydroxide then gives the target compound **2**, which is very easily and reproducibly isolated by vacuum filtration in 55–65% overall yield and >95% purity on a multi-gram scale reaction.[††]

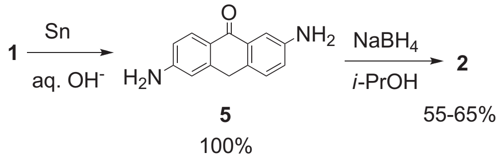
[§] See Supplementary data for experimental procedures and notes regarding these syntheses.

[**] *Optimized procedure for synthesis of 2,6-diaminoanthrone:* 2,6-Diaminoanthraquinone (10.0 g, 42 mmol), tin powder (100 mesh, 29.9 g, 252 mmol), 2.5 M aqueous NaOH (175 mL) and ethanol (200 mL) were combined in a 500 mL reaction flask and heated to reflux for 24 h under inert atmosphere. The hot reaction mixture was then poured into water (1 L) and stirred for 20 min. The resulting solid was filtered and dried in vacuo to give compound **5** (9.4 g, 100%) as a (color) solid. ^1H NMR (400 MHz, DMSO-d_6): δ 7.82 (d, J = 13.3 Hz, 1H); 7.27 (d, J = 2.3 Hz, 1H); 7.12 (d, J = 11.0 Hz, 1H); 6.80 (dd, J = 7.8, 2.3 Hz, 1H); 6.58 (dd, J = 8.7, 2.4 Hz, 1H); 6.49 (d, J = 1.8 Hz, 1H); 6.03 (s, 2H); 5.17 (s, 2H); 4.01 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 183.04, 153.93, 148.42, 144.71, 133.45, 129.85, 129.83, 128.65, 121.70, 120.02, 114.24, 111.52, 110.68, 32.97. HRMS (EI) calcd for $C_{14}H_{12}N_2O$: 224.0949, found 224.0949.

[††] *Optimized procedure for the synthesis of 2,6-diaminoanthracene* (**2**): Compound **5** (2.0 g, 8.9 mmol), $NaBH_4$ (2.7 g, 71 mmol), ethanol (40 mL) and aq NaOH (2.5 M, 40 mL) were combined and heated to reflux for 6 h. The hot reaction mixture was poured into water (200 mL) and stirred vigorously for 15 min. The resulting solid was filtered and dried to give compound **5** (1.05 g, 57%) as a yellow solid. ^1H, ^{13}C NMR, MS consistent with previously reported spectra.[8]



Scheme 2. Preparation of compound **2** through protection–reduction–deprotection sequences.



Scheme 3. Preparation of target compound **2** via a two-step Sn/$NaBH_4$ reduction sequence.

In conclusion, the literature presents several conflicting reports on the reduction products of 2,6-diaminoanthraquinone (**1**). In our laboratory, we found that this compound was resistant to reduction using sodium borohydride. While zinc effectively reduces the compound in basic aqueous solutions, we obtained a mixture of the target compound **2** and dihydro analog **3**. We found the over-reduction to the dihydro to be competitive with the reduction to anthracene under all conditions examined. On the other hand, reduction using powdered tin stops cleanly at anthrone **5**.

We found that target compound **2** could be most efficiently prepared through a two-step reduction involving tin, followed by sodium borohydride. While this method suffers from several drawbacks, including the toxicity of tin metal and the need for two reducing agents, we have found it to be the most reliable and high-yielding method for the preparation of this compound.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.07.106.

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