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An improved synthesis of 4-aminobutanenitrile from 4-azidobutanenitrile and comments on room temperature stability

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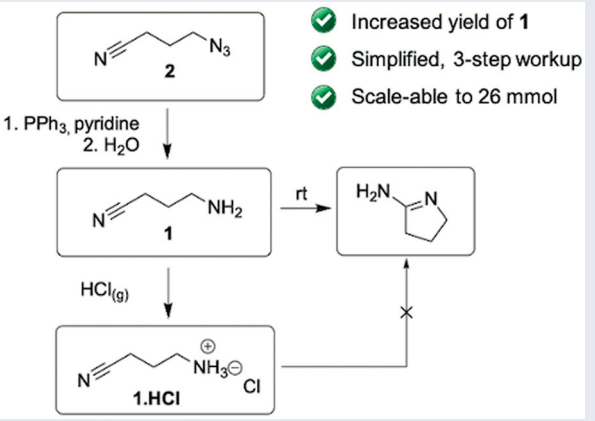
ABSTRACT

4-Aminobutanenitrile (**1**) is an important synthetic intermediate for neurological disorder therapeutics including Parkinson's and Alzheimer's diseases, and is an industrial precursor to pyrroline and pyrrolidine. Synthesis of **1** by Co(II) catalyzed reduction of 4-azidobutanenitrile (**2**) with $NaBH_4$, or by a one-pot Staudinger reduction of **2** in THF, was low yielding. ^{1}H-NMR analysis of the Staudinger reduction revealed the formation of iminophosphorane intermediate (**3**) after 22 h at rt, and that increasing the reaction temperature from rt to 40 °C promoted hydrolysis of **3** to **1**. A modified Staudinger reduction of **2** involving pyridine as solvent, addition of water 3 h after triphenylphosphine, and a temperature increase to 40 °C, gave rise to **1** in 69% yield. **1** is unstable at rt, thus the hydrochloride salt of **1** (**1**·**HCl**) was prepared by bubbling $HCl_{(g)}$ through a solution of **1** in chloroform. **1**·**HCl** is stable at rt and is hence the preferred form for storage.

GRAPHICAL ABSTRACT



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Introduction

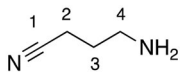
Aminonitriles are common structural features in a wide range of bioactive compounds, as was recently reviewed by Fleming et al.[1] Specifically, 4-aminobutanenitrile (**1**, see Fig. 1) is an important synthetic intermediate of neurological disorder therapeutics including those treating Parkinson's and Alzheimer's diseases,[2] and in the industrial production of pyrroline and pyrrolidine.[3,4] Furthermore, **1** is commonly used in epoxy resins or as an oil additive,[5] and the characteristic spectroscopic signature of its component nitrile (infrared and Raman spectroscopy bands in the 2250–2230 cm^{-1} range)[6,7] provides an opportunity for spectroscopic identification. For example, **1** can be used to functionalize carboxylic acid decorated nanomaterials *via* amide bond formation, with the nitrile available for spectroscopic validation of functionalization (unpublished work in our laboratory).

In this article, we investigate the synthesis and subsequent stability of 4-aminobutanenitrile (**1**). Its synthesis has been reported previously by reduction of the corresponding azide, 4-azidobutanenitrile (**2**). A Staudinger reduction of **2** to **1** was reported by Yuan and Silverman in 2006,[2] while Fringuelli et al.[8] reported a cobalt(II) catalyzed reduction of **2** to **1** with $NaBH_4$ in water. In our hands, these procedures were not reproducible, with little to no product formation observed. Furthermore, in the cases when **1** was obtained, we found it to be unstable at rt in the laboratory, with pure samples forming a complex mixture over 2–3 days. Here, we discuss these issues in detail and report an improved Staudinger reduction of **2** to provide **1**, including formation of the hydrochloride salt, **1**·**HCl**.

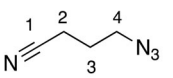
Results and discussion

Synthesis design and optimization

The key starting material 4-azidobutanenitrile (**2**) was obtained from 4-bromobutanenitrile on reaction with sodium azide (see Supplementary Information),[2] and subsequent reduction to **1** was attempted under a variety of conditions as shown in Table 1 (reactions Cobalt #1–#3). Attempted reduction with a cobalt(II) chloride hexahydrate catalyst and $NaBH_4$, in water at rt, gave rise to a quantitative recovery of **2**, contrary to the literature report[8] of a 98% yield of **1** after 10 min (Scheme 1, top route). Extension of the reaction time up to 1 h did not result in any formation of **1**. The addition of surfactant cetyltrimethylammonium bromide (CTABr), as described in the original manuscript[8] for use with hydrophobic azides (**2** is insoluble in water), also returned starting material **2** without evidence of amine **1**. Finally, cobalt(II) catalyst crushed into a fine powder with a mortar and pestle was used in the reduction to provide increased catalyst surface area, however, this reaction also returned **2** only.



4-aminobutanenitrile (**1**)

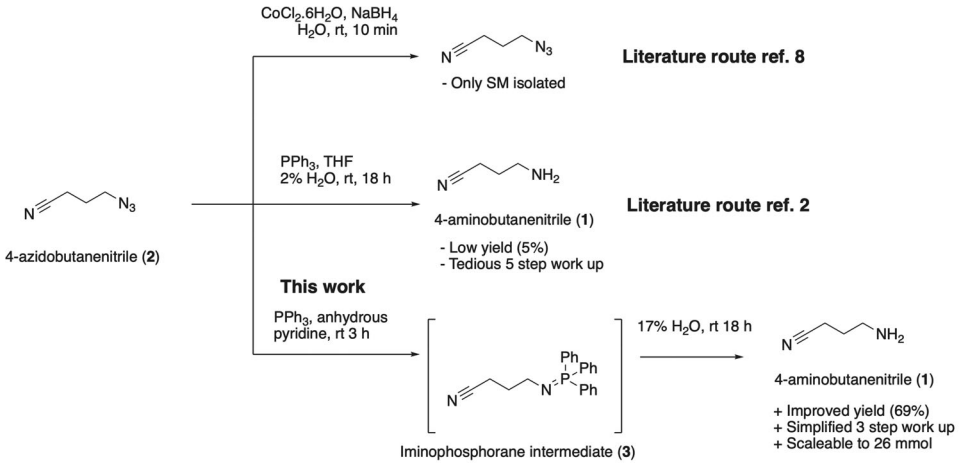


4-azidobutanenitrile (**2**)

Figure 1. Structures of 4-aminobutanenitrile (**1**) and key starting material 4-azidobutanenitrile (**2**) with carbon atoms numbered.

Table 1. Summary of the literature reactions attempted to reduce 4-azidobutanenitrile (**2**) to 4-aminobutanenitrile (**1**).

Reaction	Conditions	Result
Cobalt #1 (as per literature)[8]	$NaBH_4$ (2 equiv.), $CoCl_2.6H_2O$ (0.1 equiv.), water, rt, 10 min to 1 h	Recovered starting material (**2**)
Cobalt #2	$NaBH_4$ (2 equiv.), $CoCl_2.6H_2O$ (0.1 equiv.), CTABr (0.1 equiv.) water, rt, 10 min	Recovered starting material (**2**)
Cobalt #3	$NaBH_4$ (2 equiv.), $CoCl_2.6H_2O$ (0.1 equiv., crushed into a fine powder), water, rt, 10 min	Recovered starting material (**2**)
Staudinger #1 (as per literature)[2]	Triphenylphosphine (1 equiv.), water (2% v/v), THF, rt, 18 h	5% yield of **1**



Scheme 1. Reduction reactions of 4-azidobutanenitrile (**2**) to 4-aminobutanenitrile (**1**). Co(II) catalyzed reaction resulted in recovery of **2**, while the Staudinger reduction in THF was repeatedly low yielding and required a tedious workup. New conditions were developed for the Staudinger reduction in anhydrous pyridine to obtain product **1** in $>$ 69% yield. The new conditions contain a simplified work up and have been scaled up to 26 mmol of starting material **2**.

Next, the Staudinger reduction of **2** to **1** was attempted as per literature conditions (Table 1, entry Staudinger #1 and Scheme 1, central route).[2] Azide **2** was stirred in THF with 2% (v/v) water and 1 equiv. of triphenylphosphine at rt overnight. The literature work up was followed, with solvent removed and the residue taken up in ethyl acetate, followed by extraction of the organic layer with 1 M HCl, adjustment of the aqueous layer to pH 12 with 1 M NaOH, and extraction with ethyl acetate, then finally solvent removal to isolate **1** in only 5% yield. The fact that **1** was obtained, albeit in low yield, prompted further investigation of the reaction progress.

In particular, azide **1** and 1 equiv. of triphenylphosphine were dissolved in $CDCl_3$ (700 µL) and the ensuing reaction was monitored by ^{1}H NMR spectroscopy at rt over three days (Fig. 2 and Table 2). The ^{1}H NMR spectrum after 18 h revealed two new resonances at δ 3.20 and 1.84 ppm (Fig. 2, blue), when compared to that of **2** (Fig. 2, purple, top) and **1** (Fig. 2, red, bottom). These new resonances are attributed to the iminophosphorane intermediate (**3**, see Scheme 1), a known intermediate in the Staudinger reduction.[9–11] Partial consumption of starting material **2** was

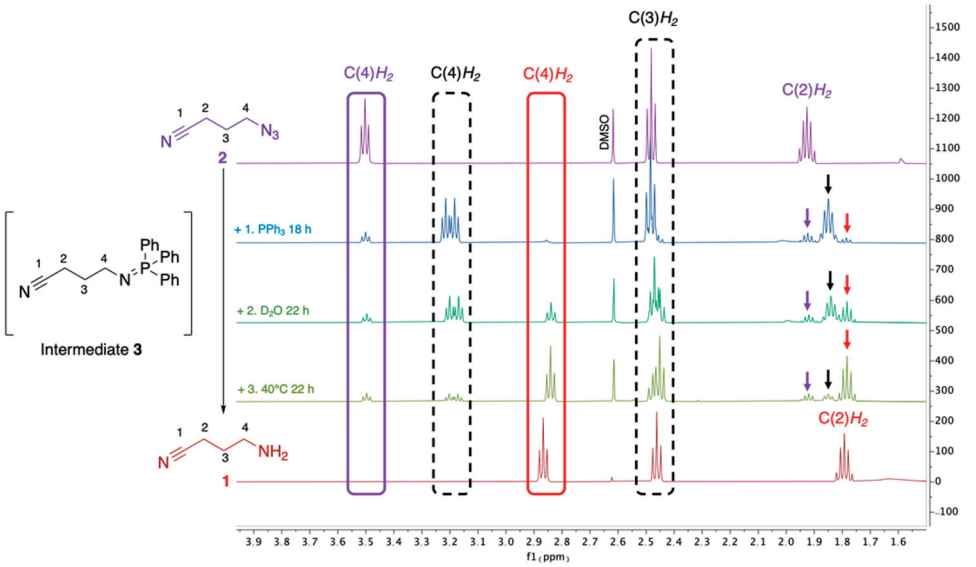


Figure 2. ^{1}H NMR spectra following the reduction reaction of 4-azidobutanenitrile (**2**) with triphenylphosphine in $CDCl_3$. From top to bottom: **2** (purple), 18 h at rt after triphenylphosphine addition (blue), 22 h after D_2O addition (green), 22 h after heating at 40 °C (yellow), and pure 4-aminobutanenitrile (**1**) (red). Signals in solid boxes correspond to the C(4)H_2 signal for **2** (purple), and **1** (red). The C(4)H_2 signal for the iminophosphorane intermediate (**3**) and C(3)H_2 signal for all compounds are marked by black dashed boxes. Changes to the C(2)H_2 signal are marked by colored arrows, where the arrow for **2** is purple, intermediate **3** is black, and **1** is red.

Table 2. Summary of the reduction of 4-azidobutanenitrile (**2**) to 4-aminobutanenitrile (**1**) followed by ^{1}H NMR spectroscopy in $CDCl_3$ at key intervals.

Conditions	Result
Azide **2** (1 equiv.), triphenylphosphine (1 equiv.), and $CDCl_3$ (700 µL), rt, 18 h	Iminophosphorane intermediate **3** observed by ^{1}H NMR
D_2O (2% v/v) added, rt, 22 h	**1** and **3** observed in a 2:5 ratio by ^{1}H NMR
Reaction increased to 40 °C, 22 h	**1** and **3** observed in a 4:1 ratio by ^{1}H NMR

observed by the lower integration of its assigned C(4)H_2 and C(2)H_2 resonances at δ 3.50 and 1.90 ppm, respectively, compared to the integration of the new resonances assigned to **3** (δ 3.20 and 1.84 ppm). A minor resonance was also observed at δ 2.85 ppm (Fig. 2, blue), consistent with the production of a small quantity of **1**.

D_2O (2% v/v) was next added to the NMR tube to hydrolyze **3** to the desired product **1**, and the reaction mixture stood at rt for a further 22 h. The ^{1}H NMR spectrum was recorded to reveal resonances occurring again at δ 3.20 and 1.84 ppm due to C(4)H_2 and C(2)H_2 of **3,** respectively (Fig. 2, green). Two new resonances were observed at δ 2.85 and 1.80 ppm and were assigned to C(4)H_2 and C(2)H_2 of product **1,** respectively. The product **1** and intermediate **3** were present in a ratio of 2:5 based on integration of the C(4)H_2 resonances of **1** and **3**.

Finally, the NMR tube reaction was heated at 40 °C for 22 h in an attempt to complete hydrolysis of **3** to **1** (Fig. 2, yellow). This gave rise to further **1**, with **1** and **3** now present in a ratio of 4:1. However, it should be noted that some of azide **2** remained

unreacted, as shown by the presence of the C(2)H_2, C(3)H_2, and C(4)H_2 resonances for **2** in all spectra through the course of the NMR reaction study.

Based on the results of the NMR spectroscopy study, in a separate reaction, azide **2** was first stirred in anhydrous THF with triphenylphosphine (1 equiv.) for 3 h, then 2% v/v H_2O added and the reaction mixture heated at 40 °C for 18 h. This was done in order to separate the iminophosphorane formation and hydrolysis steps, as was done in the NMR study. NMR analysis on this reaction mixture, prior to work up, revealed the presence of **1** in a 2:5 ratio to **2**. Further water, up to a final concentration of 8% v/v was added and the reaction heated at 40 °C over 72 h in an attempt to complete hydrolysis of **3** to **1**. The reaction mixture was cooled to rt and worked up by the literature procedure described earlier,[2] to give **1** in 13% yield.

Next, the Staudinger reduction was repeated, using anhydrous pyridine instead of anhydrous THF, based on the authors' prior experience with Staudinger reductions performed on similar substrates. Azide **2** was stirred with triphenylphosphine (1.15 equiv.) in anhydrous pyridine for 3 h, then water was added at 17% v/v and the reaction mixture stirred at rt overnight (Scheme 1, bottom route). In this instance, the reaction mixture was worked up by dilution with water, then **1** separated from the triphenylphosphine oxide by-product by washing the aqueous mixture with ethyl acetate. Water was removed under reduced pressure to give **1** in a 69% yield. This compares to a yield of 5% using the reported literature Staudinger conditions.[2] The new workup removes the need for the aqueous extraction, basification, and organic extraction required in the literature workup.[2]

This new Staudinger reduction of **2** was next carried out on a larger 26 mmol scale, given the importance of **1** as a precursor to pyrroline and pyrrolidine. The 14-fold increased reaction scale required only a 3.3-fold increase in ethyl acetate for work up, with **1** isolated in 71% yield. A purity of 94% was calculated by qHNMR using the "*100% method*" as described by Pauli et al.[12] (see Supplementary Information Fig. S3), without the need for chromatographic purification.

Stability of 1

A sample of thus prepared **1** (an oil) was stored on the bench for one week at rt, then the ^{1}H NMR spectrum was collected to reveal multiple new resonances, with those at δ 3.51, 2.34, and 1.89 ppm consistent with 2-aminopyrroline (Fig. 3, red arrows).[13] We propose that **1** cyclizes to give 2-aminopyrroline as has been previously reported for **1** (and the related compound 1,4-butanediamine) under nickel catalyzed hydrogenation,[3,4,14] however, to the best of our knowledge, this is the first report of its occurrence at rt. The original sample of **1**, still dissolved in $CDCl_3$, was re-analyzed by ^{1}H NMR after one week and the resultant spectrum was unchanged relative to the first spectrum obtained (Fig. 3). This sample had thus not cyclized, likely due to the formation of the hydrochloride salt of **1** due to residual HCl in the $CDCl_3$ (Scheme 2).

The hydrochloride salt of amine **1** (**1·HCl**) was prepared by bubbling HCl gas through a solution of **1** (obtained by the new Staudinger reduction conditions) in chloroform, to give a white precipitate (see Supplementary Information). A gravimetric titration of **1·HCl** with $AgNO_3$ revealed it to be the mono-hydrochloride salt, rather

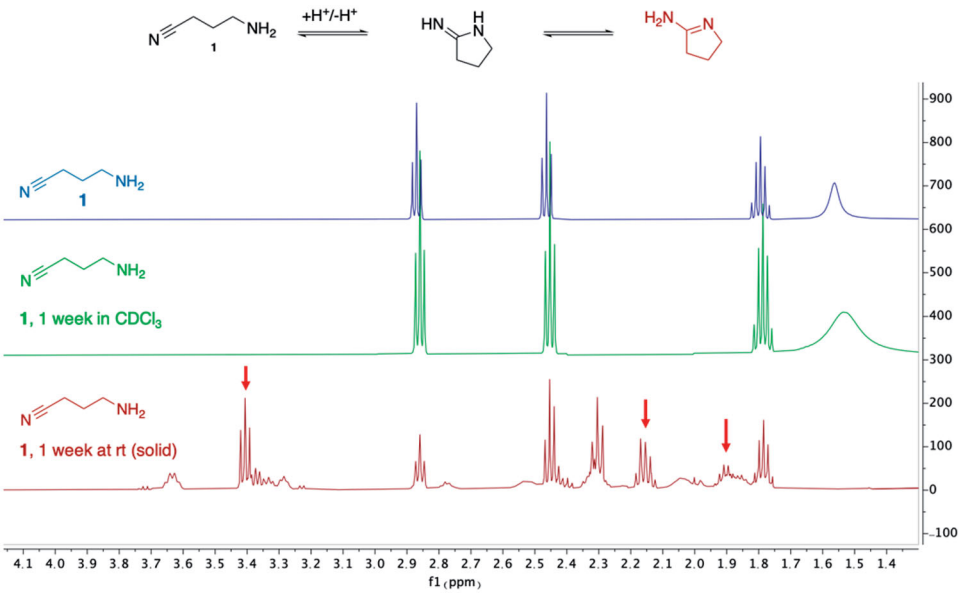
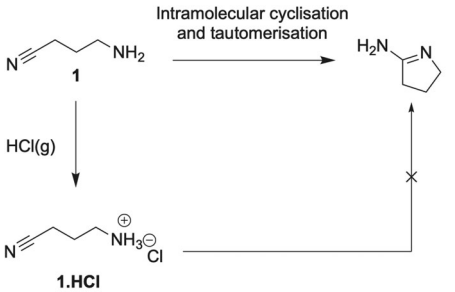


Figure 3. Top; Production of 2-aminopyrroline from 4-aminobutanenitrile (**1**). Bottom; NMR in $CDCl_3$ of **1** freshly synthesized (blue), after a week in $CDCl_3$ solution (green), and after a week on the lab bench at ambient conditions (red). Peaks corresponding to 2-aminopyrroline[13] are marked by red arrows.



Scheme 2. Proposed cyclization of 4-aminobutanenitrile (**1**) to 2-aminopyrroline, and synthesis of the corresponding hydrochloride salt (**1·HCl**).

than the di-hydrochloride salt (see Supplementary Information). **1·HCl** was also characterized by ^{1}H NMR (Fig. 4, blue), where a broad singlet was observed at δ 8.2 ppm and assigned to the $^+NH_3$ group. The methylenes at the C2, C3, and C4 positions were observed to have shifted downfield relative those of **1**. The C(4)H_2 resonance for **1·HCl** (2.85 ppm) was also more complex compared to that of **1** (2.55 ppm, see Fig. 4 purple and blue).

Finally, the stability of **1·HCl** was investigated by leaving a sample (solid) exposed to air over 7 days at rt. The sample was analyzed by ^{1}H NMR, with no changes observed (Fig. 4, green). The **1·HCl** thus has improved stability compared to the free amine and is as such the preferred method of storage (Scheme 2). The free amine **1** is liberated on treatment with a base such as triethylamine.

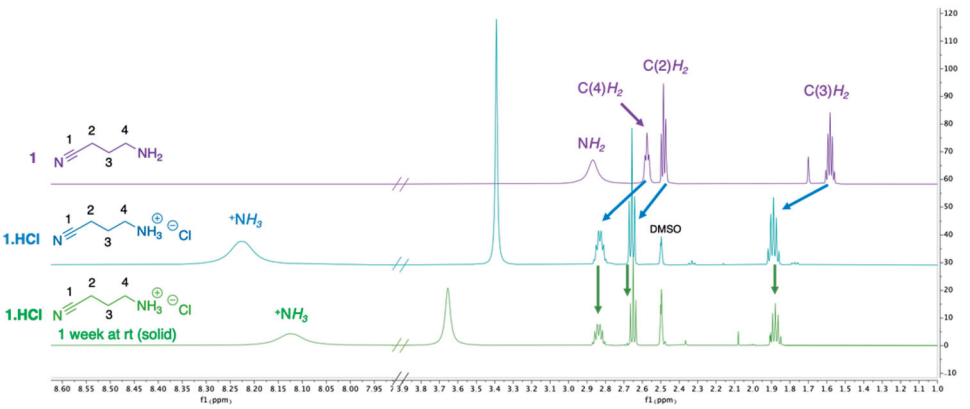


Figure 4. ^{1}H NMR spectra in DMSO-d_6 for 4-aminobutanenitrile (**1**) as synthesized (purple), with changes in chemical shift on hydrochloride salt formation highlighted (**1·HCl**, blue). **1·HCl** remains stable for one week on the lab bench under ambient conditions (green). A $-^{+}NH_3$ resonance was observed for freshly synthesized **1·HCl** (blue) and after one week (green) at 8.1–8.3 ppm, shifted from 2.8 ppm for the $-NH_2$ resonance in **1** (purple). There is a break in the *x*-axis between 3.9 and 7.9 ppm, with no resonances observed in this range.

Experimental

Synthesis of 4-aminobutanenitrile (1)

Compound **2** (200 mg, 1.82 mmol, 1 equiv.) was dissolved in anhydrous pyridine (3.64 mL) under a nitrogen atmosphere. Triphenylphosphine (548 mg, 2.09 mmol, 1.15 equiv.) was added and the reaction stirred at rt for 3 h. Water (0.58 mL) was added and the reaction mixture stirred for a further 16 h at rt. The reaction mixture was diluted with water (15 mL) and the aqueous mixture was washed with ethyl acetate (3 × 10 mL). The solvent was removed under reduced pressure to yield **1** as a colorless oil (106 mg, 69%). ^{1}H NMR in $CDCl_3$ was consistent with literature[2]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.86 (t, $J = 6.7$ Hz, 2H), 2.45 (t, $J = 7.1$ Hz, 2H), 1.87 − 1.74 (m, 2H) ppm. ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.61 (t, $J = 6.7$ Hz, 2H), 2.52 (t, $J = 7.2$ Hz, 2H), 1.61 (p, $J = 6.9$ Hz, 2H) ppm. ^{13}C NMR (151 MHz, DMSO-d_6) δ 120.81, 40.00, 28.34, and 13.64 ppm. FTIR (ATR mode): 3370 (N–H), 3297 (N–H), 3183 (N–H), 2939 (C–H), 2870 (C–H), 2245 (CN), 1599 (N–H) cm^{-1}. HRMS (ESI+) expected $[M + H]^{+}$ 84.0690 for $C_4H_8N_2$, found 84.0687.

Conclusion

In conclusion, we report an improved synthesis of 4-aminobutanenitrile (**1**), from 4-azidobutanenitrile (**2**). The reaction involves treating **2** with triphenylphosphine in pyridine rather than THF, with the reaction stirred for 3 h to allow for the formation of the iminophosphorane intermediate (**3**) prior to the addition of water (17% v/v). The optimum workup involves dilution with water and washing with ethyl acetate to give a 69% yield of **1**. This compares to a yield of 5% using the reported literature Staudinger conditions.[2] We show that this new procedure is amenable to scale up to 26 mmol of **2**, to give **1** in 71% yield at 94% purity without chromatographic purification (qHNMR,

100% method). Finally, we have also shown that **1** cyclizes to 2-aminopyrroline at rt over a period of several days. The corresponding hydrochloride salt **1**·**HCl**, prepared by bubbling HCl(g) through a solution of **1** is however stable and is the preferred form for storage.

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