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Preparation of ABNO on Scale and Analysis by Quantitative Paramagnetic NMR

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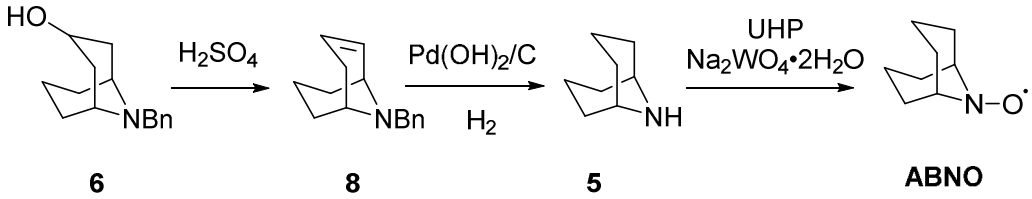


6 **8** **5** **ABNO**

ABSTRACT

A practical, safe, and scalable synthesis of the stable nitro-oxide radical catalyst, ABNO, was developed. This process is chromatography free and avoids the Wolff-Kishner reduction. Proton NMR of this paramagnetic compound was obtained that allows assessment of its chemical purity. Impact sensitivity test data of solid ABNO is also reported.

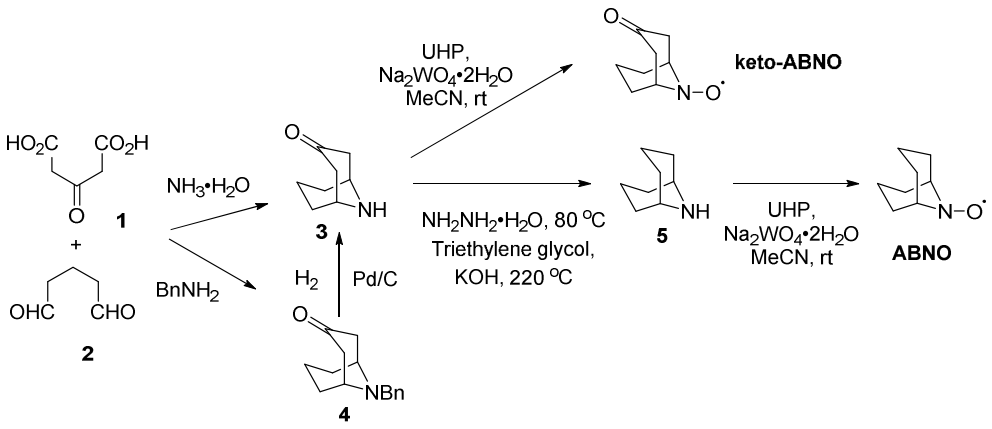
KEYWORDS

ABNO, keto-ABNO, nitroxyl radical, paramagnetic NMR

TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl) and related nitro-oxide radicals are an important class of catalysts for the oxidation of alcohols. Aerobic oxidation of alcohols to ketones and aldehydes is particularly attractive for large scale reactions because of the potential to reduce cost and minimize waste. ABNO (9-azabicyclo[3.3.1]nonane-N-oxyl) and keto-ABNO (9-azabicyclo[3.3.1]nonane-3-one-N-oxyl) are the most effective catalysts for such reactions.[1,2] Typically, 1-10 mol% of the catalyst is employed, which would represent significant quantities on scale. Due to their rather limited commercial availability, we were required to prepare kilogram quantities to support our ongoing efforts to prepare drug candidates.

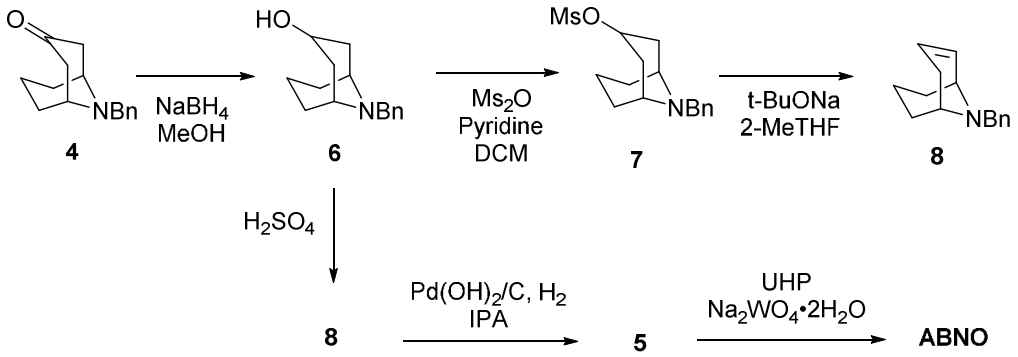
We initially evaluated the literature procedure for preparation of these compounds, which is shown in scheme 1.[1] The shortest route to access ABNO and keto-ABNO is through compound **3** which can be made directly from **1** and **2** via Mannich reaction followed by decarboxylation. Keto-ABNO is made from compound **3** in one step by oxidation. ABNO is made from compound **3** after deoxygenation of the ketone via Wolff-Kishner reduction followed by a similar oxidation step. While these sequences were reported for the preparation of gram quantities of ABNO and keto-ABNO, direct scale-up to kilogram quantities pose serious process challenges and grave process-safety concerns. Herein, we report significant modifications to the synthetic sequence and process parameters that make the process readily amenable for scale up. We also developed analytical methods for determining the purity of the final products, which are challenging to characterize by conventional methods. Operational safety for handling ABNO and keto-ABNO will also be discussed.

Scheme 1.



Evaluation of the literature procedure revealed several deficiencies that made it impractical to run on scale.[1] The Mannich reaction between compounds **1**, **2**, and ammonia was performed in water, and the product is highly water soluble and thus cannot be easily extracted into organic solvents for isolation and purification. In the Wolff-Kishner reduction sequence, a very high temperature (220 ^{o}C) was required, which in the presence of excess hydrazine was unsafe, and the extreme water solubility of the hydrazone intermediate made it impractical to isolate.[1,3] For the oxidations of amines **3** and **5** to keto-ABNO and ABNO, respectively, we observed that the use of acetonitrile as reaction solvent following the reported procedure resulted in incomplete conversion. Finally, practical crystallization procedures for purification of ABNO and keto-ABNO besides chromatography or sublimation were needed.

Scheme 2.



The need for purification of compound **3** was driven by the fact that very often diacid **1** is prone to decomposition so the reaction to form **3** from **1** and **2** can form a substantial amount of tar. As an alternative to making compound **3** directly from **1**, **2**, and ammonia, the reaction of benzylamine with **1** and **2** gave compound **4**, which can be extracted into organic solvents and offers purification opportunities. Compound **4** can then be deprotected under hydrogenolysis conditions to give **3**.[1b] To avoid the use of a large excess of hydrazine at high temperature in the Wolff-Kishner reduction, we evaluated different routes for deoxygenation of ketones **3** and **4**. Ketone **4** can be readily reduced to alcohol **6** with sodium borohydride in quantitative yield.[1b] We then found that alcohol **6** can be converted to mesylate **7** and subsequently transformed into olefin **8** with sodium t-butoxide. More directly, alcohol **6** can be dehydrated with sulfuric acid to olefin **8**. Under hydrogenation conditions, the olefin was reduced with simultaneous benzyl group deprotection, cleanly generating compound **5**. This new three-step sequence from compound **4** to **5** via **8** has the same number of chemical transformations as the previous method but is more economical, much simpler to execute, avoids the hazardous use of hydrazine, and is more amenable for large scale. The details of each step of the new route will be discussed in the following sections.

Preparation of compound 4: In the reported literature procedure,[1b] benzylamine hydrochloride was used in the reaction with **1** and **2** in water in the presence of sodium acetate buffer. After

initial condensation reaction at room temperature, the reaction mixture was heated for decarboxylation. We evaluated the combination of benzylamine with different acids such as acetic acid, sulfuric acid, phosphoric acid; only sulfuric acid gave comparable results to the HCl salt, while other acids gave inferior reaction profiles. We chose sulfuric acid over hydrochloric acid to minimize the halide-containing waste. The reaction solvent was changed to a mixture of water and methanol to alleviate the agitation problem caused by the tar formed during the reaction. The maximum reaction temperature was also reduced from the reported 50 ^{o}C to 30 ^{o}C to minimize tar formation and to alleviate safety concerns for the decarboxylation step (CO_2 evolution). After reaction and adjustment to low pH, the reaction mixture was extracted with MTBE to remove any organic soluble impurities, and the product was extracted into heptane under basic conditions. We found this crude product mixture was much more stable in heptane than in MTBE, although, pure **4** was stable in both solvents. This heptane solution was filtered through a small amount of silica gel and the solvent distilled off to give the crude **4**, which was used in the next step without purification. The purity at this stage was typically 90-95% by HPLC and the isolated yield was 53%. Although the yield is modest, this process has proven to be reproducible at over 100 kg scale.

Preparation of compound 5 through compounds 6 and 8: The sodium borohydride reduction of **4** in methanol was straightforward and resulted in essentially quantitative yield. This alcohol **6** was extracted into MTBE from the reaction after acid quench and basification. The crude product was used in the subsequent elimination directly after removal of solvent. Treatment of alcohol **6** with 70% sulfuric acid at 100 ^{o}C resulted in a clean elimination to the desired olefin **8**. After pH adjustment, the product was extracted into ethyl acetate. The assay yield and purity by HPLC was 97%. The crude product was solvent switched into isopropanol for hydrogenation

using palladium hydroxide on carbon as catalyst to give **5** in high yield and purity. Product **5** is fairly volatile and some loss of product to the distillates may occur if distillation of solvent is required.

Preparation of ABNO: The reported method used acetonitrile as solvent for oxidation of **5** with urea hydrogen peroxide and catalytic $Na_2WO_4 \cdot 2H_2O$.[1b] Under these conditions, we observed sluggish conversion and a large excess of urea hydrogen peroxide was required to drive the reaction to completion. It was also observed that $Na_2WO_4 \cdot 2H_2O$ was not completely soluble. This prompted us to investigate mixtures of water and organic solvents such as methanol, isopropanol, and acetone. Use of methanol resulted in up to 30% of the formamide of **5**, but in water/isopropanol or water/acetone mixtures, the reaction was clean and proceeded to completion. We chose a mixture of isopropanol and water because isopropanol was used in the previous hydrogenation step. It is critical to charge the urea hydrogen peroxide complex to the reaction over time to control decomposition and associated release of oxygen gas in this step. This slow, controlled addition also allowed for more efficient use of the hydrogen peroxide and thus better conversion. After the reaction, the product was extracted into dichloromethane and crystallized from dichloromethane and heptane to ABNO in 99.5% GC area percent purity and 70% isolated yield.

Preparation of keto-ABNO: Compound **4** was hydrogenated over palladium on carbon in methanol to cleave the benzyl protecting group to give compound **3**. The same oxidation procedure was used in the preparation of keto-ABNO from compound **3**, except the reaction solvent was mostly water with low levels of methanol that was carried over from the previous step. The same workup and crystallization from dichloromethane/heptane gave keto-ABNO in 67% isolated yield and 98.5% HPLC area percent purity.

Safety considerations for the handling of ABNO and keto-ABNO: Both compounds exhibit a large exotherm on DSC with an onset temperature of *ca.* 80 ^{o}C. The exotherms for ABNO and keto-ABNO are approximately 960 J/g and 1100 J/g, respectively, over a temperature range of 80-220 ^{o}C. These are potentially large exotherms at rather low onset temperatures, which are serious concerns from a process safety perspective. Shock sensitivity evaluation indicated that solid ABNO gave positive fall-hammer results (explosions) in 3 out of 8 drops at an impact energy level of 30 J, but 0 out of 8 drops at 20 J. ABNO solid is thus considered potentially impact sensitive so proper precaution is required when handling solid ABNO. The fall-hammer test result for keto-ABNO is 0 out of 8 positive at 50 J, so keto-ABNO solid is not considered to be impact sensitive for normal handling. Although exotherms measured on DSC for the process solution streams containing ABNO and keto-ABNO are very modest, process temperature was kept below 45 ^{o}C as a precaution.

Purity analysis of ABNO and keto-ABNO: Because ABNO and keto-ABNO are paramagnetic, characterization by NMR is not straightforward. When we analyzed ABNO by GC/EI-MS, the mass spectrum showed $[m]^{+}/z = 140$ as the most abundant peak but higher than expected intensity of the M+1 peak ($[m]^{+}/z = 141$), which caused us concern that this may be the co-eluting hydroxylamine intermediate as an impurity. Our attempt to screen GC conditions to separate the presumed hydroxylamine impurity proved fruitless. However, when an acidic eluent was used with LC/ESI-MS, two chromatographically resolved peaks were observed. One peak exhibits a mass spectrum similar to that observed on GC-MS for ABNO but with a higher than expected M+1 peak ($[m]^{+}/z = 141$), while the other exhibits a mass spectrum consistent with the corresponding hydroxylamine ($[m]^{+}/z = 142$ for M+H). This appears to indicate that the hydroxylamine seen by LC-MS and GC-MS is an artifact, presumably caused by

disproportionation of ABNO during the analysis. Similar acid catalyzed disproportionation of related compound TEMPO to the corresponding hydroxy amine and the oxoammonium cation was known.[4a] Fortunately, we were able to confirm the purity of ABNO by quantitative NMR, a gentler and non-destructive technique, that showed typical batches were made with less than 0.2% hydroxylamine. Figure 1 shows the proton NMR of a typical sample of ABNO with peak assignments that were determined from density functional theory (DFT) calculations of chemical shifts (see Supporting Information for calculation details).[4b] Since the compound is paramagnetic, a high concentration (ca. 200 mg/mL) of ABNO was dissolved in CD_3CN to improve T_2 relaxation, and the spectral region was increased to -100 to +250 ppm. The sharpest resonance of ABNO at 26.2 ppm was used for quantitation versus the impurity signals. To determine the identity of impurity peaks, 2D NMR experiments (i.e., COSY, HSQC, HMBC, and NOESY) were performed on a narrow spectral region from -1 to 14 ppm using standard acquisition parameters. This NMR technique allowed us to assertain the purity of the prepared ABNO in conjunction with GC analysis.

For keto-ABNO, the hydroxylamine peak on HPLC was resolved and identified by LC-MS. The hydroxylamine in the isolated solid keto-ABNO was present at 0.2% by HPLC. Similar proton NMR was also observed for keto-ABNO.

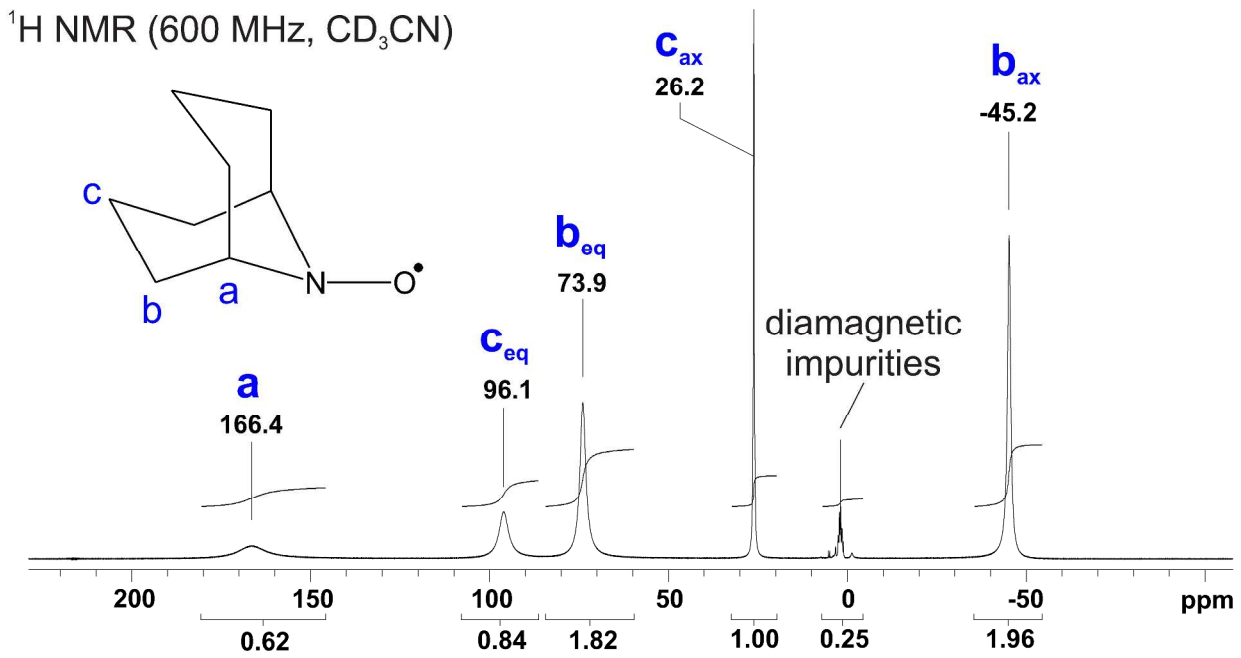


Figure 1. NMR spectrum of a typical batch of ABNO. Note that diamagnetic impurities include the HDO and residual acetonitrile-d_2 peaks as the largest signals.

In summary, a scalable process was developed for the preparation of ABNO and keto-ABNO and the process steps have been scaled up either on pilot plant or several hundred gram scale. Quantitative proton and 2D NMR of ABNO allows for structure confirmation and purity analysis. The potential for impact sensitivity should be taken into consideration when handling ABNO, especially in its solid form.

EXPERIMENTAL

All reagents and solvents were used as purchased as reagent grade or better except otherwise noted. Purity of isolated products are reported as LCAP (liquid chromatography area percent), GCAP (gas chromatography area percent), or wt% (weight %). Reference standards used to determine wt% were assigned purity based on LCAP or GCAP minus residual moisture by KF titration and residual solvents by GC confirmed by quantitative NMR when possible.

9-Benzyl-9-azabicyclo[3.3.1]nonan-3-one (4)[1b] To a mixture of water (388 g) and benzylamine

(100 g, 0.93 mol, 0.9 eq.) at 0-10 ^{o}C was added 18% sulfuric acid (364 g, 0.67 mol, 0.65 eq.) while maintaining the reaction mixture at 0-10 ^{o}C. The reaction flask was protected from light as a general precaution. Then 50% glutaraldehyde (**2**, 205.5 g, 1.03 mol, 1.0 eq.) was added followed by acetone dicarboxylic acid (**1**, 150 g, 1.03 mol, 1.0 eq.) while maintaining the reaction mixture at 0-10 ^{o}C. Then 9% sodium acetate (363 g, 0.40 mol, 0.4 eq.) solution was added over 4 h. The reaction mixture was aged at 0-10 ^{o}C for 10 h and then 20-30 ^{o}C for 29 h. Slow gas evolution was observed during the reaction. A sample analyzed by HPLC indicated complete consumption of acetone dicarboxylic acid but 10/90 ratio of benzylamine to product. Additional 18% sulfuric acid (132 g) was added at 20-30 ^{o}C to adjust the batch pH to 2. The batch was extracted with MTBE (3 x 884 g). Then heptane (3.42 kg), silica gel (150 g) were added to the aqueous layer followed by 20% Na_2CO_3 (450 g) to adjust the pH to 8 (Caution: gas evolution!). The batch was filtered and cake washed with 2.4 L heptane. The layers were separated, and the organic layer concentrated under vacuum and solvent switched to methanol (about 1.66 kg). A solution of **4** in methanol at about 15 wt% was obtained with an assay amount of 114 g (53% yield) and 94% LCAP. A pure sample was obtained by silica gel column purification using ethyl acetate/heptanes as eluent, which resulted in a white solid with mp 72.4 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45-7.38 (m, 2H), 7.38-7.31 (m, 2H), 7.31-7.25 (m, 1H), 3.94-3.90 (m, 2H), 3.32 (br. s, 2H), 2.74 (dd, *J* = 6.6, 16.6 Hz, 2H), 2.27 (d, *J* = 16.7 Hz, 2H), 2.02-1.89 (m, 2H), 1.61-1.46 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 211.59, 139.20, 128.35, 128.28, 127.11, 57.03, 53.49, 42.81, 29.30, 16.53. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{15}H_{20}NO$ 230.1539; Found 230.1540.

9-Benzyl-9-azabicyclo[3.3.1]nonan-3-ol (6).[1b] To a stirred solution of **4** (48.4 g in 458 g methanol, 0.21 mol, 1.0 eq.) at 5-15 °C under nitrogen was added $NaBH_4$ (50 g, 1.32 mol, 6.3 eq.) in portions over 1 h while maintaining the batch temperature at 10 °C. The batch was stirred at 25 °C for 1 h until HPLC analysis indicated completion of reaction. The batch was then cooled to 5 °C and quenched by slow addition of 10% hydrochloric acid (511 g over 1 h) to get the batch pH to 5-6 (Caution: hydrogen gas evolution was removed by steady nitrogen sweep). The batch was concentrated under vacuum (<50 ^{o}C) to about 10 L and cooled to 5 °C and then mixed with MTBE (286 g). Then 20% NaOH solution (73 g) was added at 10 °C to adjust the pH to 11-12. The batch was filtered to remove the solids formed, and the cake was washed with

MTBE (72 g). The layers were separated, and the aqueous layer extracted with MTBE (144 g). The combined organic layer was washed with 4% aqueous $NaHCO_3$ solution (200 g), concentrated under reduced pressure at below 40 °C to remove all solvents. Crude compound **6** was obtained as a thick oil (51.0 g), which was used directly in the next step without purification. A pure sample was obtained by silica gel column purification with ethyl acetate/heptanes as eluent, which yielded a white solid with mp 70.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39-7.31 (m, 4H), 7.29-7.23 (m, 1H), 4.36-4.25 (m, 1H), 3.82 (s, 2H), 3.11-3.04 (m, 2H), 2.46-2.36 (m, 2H), 2.31-2.17 (m, 1H), 2.03-1.87 (m, 3H), 1.60-1.52 (m, 1H), 1.42-1.34 (m, 2H), 1.18-1.11 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 140.45, 128.14, 128.09, 126.60, 64.13, 55.85, 49.60, 35.49, 25.00, 14.53. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{15}H_{22}NO$ 232.1696; Found 232.1696.

9-Benzyl-9-azabicyclo[3.3.1]non-3-ene (8) A solution of crude **6** from the previous step (50 g, theoretical 0.21 mol, 1.0 eq.) in 70% aq. H_2SO_4 (500 g, 3.6 mol, 17 eq.) was heated to 100 °C and stirred for 20 h until >99% conversion by HPLC. The batch was slowly quenched into a solution of NaOH (288 g in 1200 g water) while maintaining the quench batch temperature at or below 30 °C (The end pH was 7-8). The batch was then extracted with 3x1L ethyl acetate, and the combined organic layer was washed with 300 mL water. The organic layer was concentrated to remove all solvents to give 52.7 g oil residue which contained 43.8 g **8** by HPLC assay and 96.8% LCAP in 97.3% overall yield for two steps. Pure **8** was obtained as a light yellow oil via silica gel column purification with ethyl acetate/heptanes as eluent. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35-7.28 (m, 2H), 7.27-7.19 (m, 2H), 7.19-7.12 (m, 1H), 5.95 (td, J = 3.5, 10.1 Hz, 1H), 5.56-5.39 (m, 1H), 3.66-3.54 (m, 2H), 3.07 (br. s, 1H), 2.91-2.84 (m, 1H), 2.37 (ddd, J = 3.0, 4.3, 18.8 Hz, 1H), 1.82-1.57 (m, 4H), 1.45-1.29 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 140.16, 128.69, 128.04, 127.86, 127.12, 126.57, 57.79, 52.48, 50.55, 33.38, 28.37, 25.70, 16.09. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{15}H_{20}N$ 214.1590; Found 214.1588.

9-Azabicyclo[3.3.1]nonane (5)[1b] A solution of **8** (10.0 g x 93.16 wt%, 44 mmol) in 50 mL isopropanol was purged with argon three times and mixed with $Pd(OH)_2$ on carbon (20 wt%) (2.0 g). The vessel was then purged with argon and pressurized with hydrogen at 40-50 psi and agitated at 40-50 °C for 48 h until complete reaction by GC. The catalyst was filtered off through Solka Floc, and the cake washed with 50 ml IPA. The filtrate contained 5.37 g (62.9 g x 8.53

wt%) product **5** by GC assay, 98% yield. A pure sample was obtained via silica gel column purification with ethyl acetate/heptanes as eluent, resulting in a light yellow solid, mp ~110 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.57 (br. s, 2H), 2.41-2.18 (m, 4H), 2.05-1.88 (m, 2H), 1.80-1.59 (m, 6H) ^{13}C NMR (101 MHz, $CDCl_3$) δ = 46.39, 27.05, 18.65. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_8H_{16}N$ 126.1277; Found 126.1279.

9-Azabicyclo[3.3.1]nonane-N-oxyl (ABNO)[1b] To a three-neck round bottom flask equipped with a thermometer, a mechanical stirrer, and a nitrogen inlet for slow sweep, was charged the solution of compound **5** (57.4 g x 8.53 wt% = 4.9 g, 39.1 mmol, 1.0 eq.) in IPA (13.6 vol.), 40 g of H_2O (40 mL) and 1.29 g (3.9 mmol, 0.1 eq.) of Na_2WO_4•$2H_2O$. The batch was cooled to 0-10 °C, and a pre-cooled solution of urea hydrogen peroxide (UHP, 12.5 g, 132.9 mmol, 3.4 eq.) in 40 g water (solution at 0 to 10 °C) was added drop-wise over 1 h. A sample was taken after another 0.5 h, and GC analysis indicated about 97% conversion. The batch was extracted with dichloromethane (DCM) (49 mL x 3). The combined organic layers were concentrated under reduced pressure at less than 10 °C until 12 mL and then solvent switched to n-heptane (100 mL x 2) to a final volume of 12 mL. The slurry was cooled to -10 to -5 °C and stirred overnight (18 h). Crude ABNO was collected by filtration. HPLC indicated 85% LCAP purity with significant amount of urea present. The wet cake was dissolved with 90 mL DCM, and the solution was washed with water (50 mL x 2). The aqueous layer was back-extracted with 30 mL DCM, and the combined organic layers were concentrated under reduced pressure to *ca.* 50 mL. The solution was then further azeotropically distilled with 100 mL n-heptane under reduced pressure to a final volume of 50 mL. The mixture was filtered and the cake dried in vacuum below 30 °C for 2 h. ABNO was obtained as a red solid, 3.84 g, 99.5% GCAP in 70% isolated yield. DSC showed two melting endotherms, 55 °C and 69 °C, indicating crystal form conversions. ^{1}H NMR (600 MHz, CD_3CN) δ 166.4 (br. s, 2H), 96.1 (br. s, 2H), 73.9 (br. s, 4H), 26.2 (br. s, 2H), -45.2 (br. s, 4H). More details on the peak assignments are available in the Supporting Information.

9-Azabicyclo[3.3.1]nonan-3-one (3)[1b] A hydrogenation vessel was charged with 112 g **4** (in about 1.05 kg solution in MeOH, 0.49 mol, 1.0 eq.). The vessel was purged three time with nitrogen, and 36.9 g of 10% Pd/C (0.035 mol, 0.07 eq.) was charged. The batch was agitated under H_2 (40 to 50 psi) and at 40 to 50 °C for 27 h until >99% conversion by HPLC analysis.

The batch was filtered through diatomite to remove catalyst. GC assay of the filtrate indicated 97.2% GCAP purity for **3** and quantitative yield. This solution was used in the next step without purification. NMR and MS data of the solid obtained after silica gel column purification matches the reported data. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.60 (br s, 2 H), 2.54-2.65 (m, 2 H), 2.36-2.45 (m, 2 H), 1.71-1.84 (m, 2 H), 1.61-1.71 (m, 3 H), 1.45-1.61 (m, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 211.00, 49.21, 47.40, 31.93, 16.67. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_8H_{14}NO$ 140.1070; Found 140.1072.

9-Azabicyclo[3.3.1]nonan-3-one-N-oxyl (keto-ABNO)[1b] A methanol solution of **3** from the last step (50.6 g, 0.36 mol in 765.1 g solution, 1.0 eq.) was concentrated under reduced pressure below 40 °C and solvent switched to water to a final volume of 650 mL. GC analysis indicated residue MeOH in the mixture was 3.39 wt%. The batch was cooled to 0-10 °C, and Na_2WO_4•$2H_2O$ (6 g, 0.018 mol, 0.05 eq.) was charged. In another vessel, urea hydrogen peroxide (UHP, 102.6 g, 1.09 mol, 3.0 eq.) was added in portions to 500 mL cold water at 0-10 °C. This UHP solution was then added drop-wise to the batch at 0-10 °C over 1.5 h. After aging for another 0.5 h, HPLC analysis indicated the levels of amine **3**/hydroxylamine/keto-ABNO to be 0% / 1.1% / 87.5% (Caution: prolonged aging for 18 h resulted in partial conversion of keto-ABNO back to hydroxylamine from 1% to 6%). The batch was twice extracted with 500 mL DCM (500 mL x 2). Assay of the DCM layer indicated purity of keto-ABNO was 96.1% LCAP, 44.2 g, 79% assay yield. The combined organic layers were concentrated under reduced pressure below 10 °C until 200 mL (Caution: it is critical to keep the batch temperature close to 0 ^{o}C, and the batch should not be stored at high concentration to minimize decomposition of keto-ABNO) and 750 mL n-heptane was added drop-wise at 0-5 °C over 4 h. The slurry was stirred at 0-5 °C for another 8 h and at -5 to 0 °C for 1 h. The batch was filtered, and the cake was dried on the filter under nitrogen flow. Keto-ABNO was obtained as a yellow solid, 34.2 g by assay (35.6 g x 96.0 wt %), and 98.5% LCAP in 61% yield. Mp by DSC (decomp.) ~110 °C. ^{1}H NMR (600 MHz, CD_2Cl_2) δ 130.8 (br. s, 2H), 98.5 (br. s, 2H), 55.8 (br. s, 2H), 52.0 (br. s, 1H), 15.1 (br. s, 1H), -32.5 (br. s, 2H), -53.1 (br. s, 2H). HRMS (ESI) m/z: $[M]^+$ Calcd for $C_8H_{12}NO_2$ 154.0868; Found 154.0861.

Supporting Information. HPLC or GC analysis conditions for each step, DSC of ABNO and keto-ABNO, and density functional theory (DFT) calculations of ^{1}H NMR chemical shifts for ABNO and keto-ABNO are included in the supporting information. This material is available free of charge via the internet at http://pubs.acs.org.

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5. One of the major challenges we faced for this step is the facile decomposition of acetone dicarboxylic acid **1**. Even the process of NMR sample preparation and analysis led to various extent of decarboxylation. Similar decarboxylation was also observed when **1** was analyzed by reverse phase HPLC. Due to the lack of analytical standard of this compound, the weight percentage purity of the material was not confirmed. We suspect the different reported yields of this step were largely due to the variable quality of the raw materials used. In our work we kept compound **1** refrigerated all the time except when needed for reaction.

6. Whenever possible, both ABNO and keto-ABNO solid should be stored refrigerated.

7. The mass spectrum for keto-ABNO and the corresponding hydroxylamine on GC/MS showed predominantly the positive molecular ion peak for each so they can be differentiated.