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Aza-Henry Reactions of 3,4-Dihydroisoquinoline

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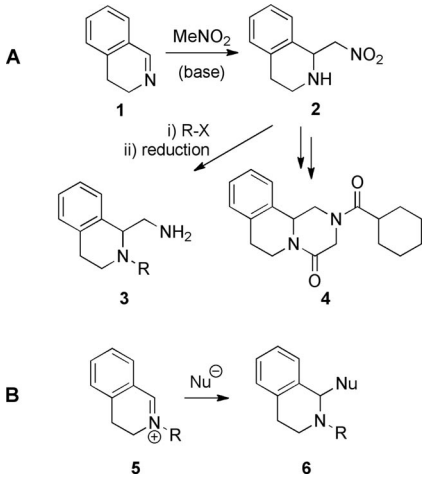
The aza-Henry reaction of 3,4-dihydroisoquinoline is reported. The reaction is favourable in excess nitromethane under ambient conditions. Isolation of the unstable reaction product is achieved by acylation or alkylation, allowing the synthesis of Reissert-like compounds in good yields from a one-pot, three-component coupling. The rates of reaction for dihydroisoquinoline and the corresponding benzylisoquinolinium ion have been investigated in the presence and absence of base. The reaction with dihydroisoquinoline probably proceeds via an azinic acid tautomer of nitromethane, a reaction pathway unavailable to the isoquinolinium ion. The traditionally problematic reduction of two of the resulting β-nitroamine derivatives was achieved, providing access to a number of new chiral vicinal diamines.

Introduction

The chemistry of quinoline derivatives remains central to heterocyclic chemistry, but less is known of the chemistry of 3,4-dihydroisoquinoline (3,4-DHIQ, **1**, see part A of Scheme 1) than the parent isoquinoline or tetrahydroisoquinoline motifs.[1] The aza-Henry (nitro-Mannich) reaction of 3,4-DHIQ with nitromethane to give the corresponding 1-(nitromethyl)tetrahydroisoquinoline (**2**) has never been reported and is of interest for four reasons. Firstly, a simple alkylation-reduction sequence of **2** would rapidly generate diverse novel chiral vicinal diamines (**3**), of wide synthetic and catalytic utility.[2] Secondly, the aza-Henry reaction has recently been shown to be catalysed asymmetrically by a wide range of inexpensive ligands, which would permit the generation of novel enantio-enriched diamines.[3] Thirdly, the reaction represents a promising new synthetic approach to the potent anthelmintic praziquantel (PZQ, **4**), the drug of choice for the tropical disease schistosomiasis, and for which analogues and an inexpensive, enantioselective synthesis are urgently needed.[4,5] Finally, there is a near-ubiquitous use in the literature of electron-deficient imines (involving, e.g., *N*-Boc or *N*-PMP protection) for the aza-Henry reaction, an inaccessible strategy for 3,4-DHIQ; thus the successful demonstration of the aza-Henry reaction with 3,4-DHIQ would broaden the scope of this important reaction, potentially leading to future asymmetric examples. In this report the feasibility and rate of the aza-Henry reaction of 3,4-DHIQ are examined, the unstable product of the reaction is isolated via alkylation and acylation, and two of these reaction products are elaborated into the corresponding diamine derivatives.



Scheme 1. The aza-Henry reaction with 3,4-DHIQ (A) in the synthesis of chiral diamines (**3**) and praziquantel (**4**), and (B) the comparison with traditional Reissert-type reactions.

The literature contains numerous examples of the reaction of imines with organometallic reagents,[6] or the reaction of alkylated or acylated (Reissert-like) isoquinolines with (frequently reactive, metallated) nucleophiles (**5** to **6**, see Scheme 1, B).[7–9] Recent examples of the reaction of isoquinolines with non-organometallic species include Shibasaki's catalytic, asymmetric cyanation of isoquinolines,[10] Jorgensen's intramolecular organocatalytic annulation reaction of an enamine with an alkyliminium ion in the synthesis of 1,2-dihydroisoquinoline derivatives,[11] and Jacobsen's organocatalyzed acyl nitro-Mannich reaction between isoquinolines and silyl ketene acetals.[12,13] Reports of similar

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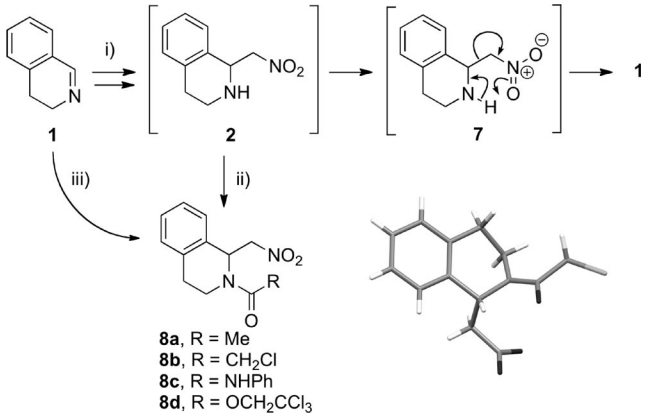
reactions with dihydroisoquinolines rather than quinolines are fewer in number, but, besides the synthesis of Reissert-type compounds,[14] include intramolecular[15] and intermolecular[16] attack of enolates on alkyldihydroisoquinolinium salts, enolate addition to a chiral acyldihydroisoquinolinium salt,[17] enantioselective metal-catalyzed addition of malonates and alkenylzirconocenes to acyldihydroisoquinolinium salts,[18] and 1,3-dipolar cycloadditions of the azomethine ylides derived from Reissert compounds.[19] It is typical for the dihydroisoquinoline to be covalently "activated" by alkylation or acylation (or via formation of the *N*-oxide[20]) prior to nucleophilic attack, but in some cases this is not necessary. It has been shown that "unactivated" dihydroisoquinolines can react with active methylene compounds (e.g. dimedone)[21] and naphthols,[22,23] to give stable products and this reaction type will be considered again below. Despite all the reports of C–C bond formation with dihydroisoquinolines, and the extensive literature on the aza-Henry reaction itself,[3,24] the employment of nitroalkanes as coupling partners with 3,4-DHIQ and its derivatives is rare. To the best of our knowledge there are only two examples: the reaction between a nitroalkane and an alkyldihydroisoquinolinium salt (generated in situ) reported by Perkin in 1925[25] and Robinson in 1927.[26,27] More recently it has been shown that access to β-nitroamine products similar to those of interest here, but through a different mechanism, is possible via a cross-dehydrogenative coupling reaction via the formation of an (non-isolated) Reissert-like dihydroisoquinolinium ion derived from an in situ oxidation.[28]

Results and Discussion

a) Reaction between 3,4-Dihydroisoquinoline and Nitromethane

It was not known whether the aza-Henry reaction with nitromethane could be performed directly on dihydroisoquinoline (**1**). Accordingly, dihydroisoquinoline was mixed with nitromethane (as solvent) and triethylamine as base at room temperature for 16 hours (Scheme 2). TLC clearly indicated a reaction was occurring, but attempts to purify the reaction mixture by chromatography returned only starting material. It was assumed the product **2** of the reaction was reverting to starting material via **7**; retroaddition of β-nitroamines is a standard problem encountered during their purification.[24,29] A simple work-up of this reaction with no purification removed the excess nitromethane in vacuo and produced a clean ^{1}H NMR spectrum for this unstable material (Figure 1). Reversion of **2** to starting material was monitored by ^{1}H NMR spectroscopy over time. A plot of the ratio of the integrals of the signal corresponding to the proton at position 1 (the stereogenic centre) plus the signal corresponding to the adjacent methylene vs. the emerging signal corresponding to the methyl group of nitromethane indicated compound **2** decomposes rapidly at room temperature. The asymptote here is approximately 1.1, indicating a position of equilibrium for the decomposition giving 54% product. The rate constant for the decomposition under these conditions is approximately 0.04 h^{-1} (see Supporting Information).



Scheme 2. Decomposition, and acylation, of unstable β-nitroamine **2**. Reagents and conditions: i) nitromethane, triethylamine; ii) for **8a**: acetyl chloride, for **8b**: chloroacetyl chloride and 2,2,6,6-tetramethylpiperidine; iii) One-pot protocol: nitromethane, acylating agent (1.1 equiv.), triethylamine (1.1 equiv.), 45 °C, 2 h. Inset: crystal structure for **8b**.

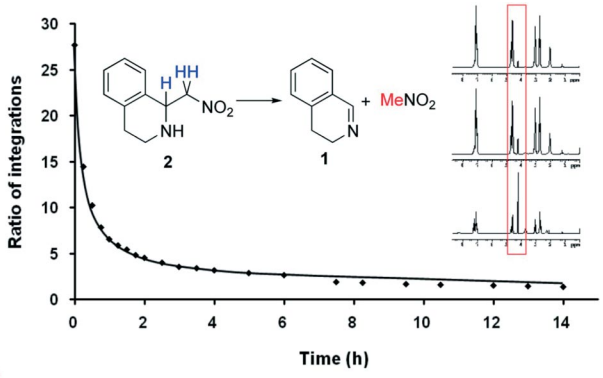


Figure 1. Kinetic study on the instability of β-nitroamine **2** and the corresponding ^{1}H NMR spectra at the following times: (i) 0 min (top); (ii) 15 min (middle) and (iii) 14 h (bottom). The ratio calculated is the integral of the signals for the three protons marked blue in the nitroamine (**2**) vs. the signals for the protons marked red for the nitromethane produced by the decomposition reaction (linear scale of NMR spectra in inset is 0 to 8 ppm).

Attempts to reduce compound **2** in situ to the corresponding amine rapidly, with e.g. samarium iodide,[29] were unsuccessful. Thus while the aza-Henry reaction could be observed to occur, synthesis of chiral vicinal diamines by this route required the isolation of a more stable derivative. None of these reaction conditions gave any reaction when isoquinoline was employed in place of dihydroisoquinoline.

b) Synthesis of Alkylated/Acylated β-Nitroamines by the aza-Henry Reaction

1) Acylation

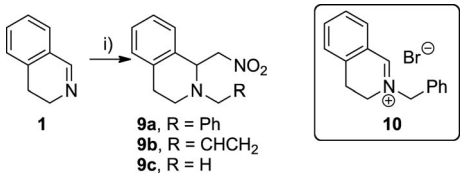
Acylation of the unstable β-nitroamine was found to be an effective means of isolating a stable product. Thus reac-

tion to generate the β-nitroamine, followed by immediate addition of the relevant acylating agent gave the novel compounds **8a** and **8b** (ca. 50% for two steps). Product **8b** could be easily purified by trituration from ethyl acetate and hexane and its structure was confirmed by X-ray crystallography (Scheme 2) – a process that was otherwise complicated by the presence of a 3:1 mixture of rotamers in the ^{1}H NMR spectrum. It was found that a simple one-pot reaction was a more convenient experimental procedure for the preparation of these acylated products. When 3,4-DHIQ and chloroacetyl chloride were mixed with nitromethane and triethylamine for two hours at 45 °C, product **8b** was isolated by recrystallisation in a 61% unoptimised yield. The same one-pot approach was employed in the rapid synthesis of the urea **8c** (84% yield) and carbamate **8d** (64%) indicating that a range of acylating agents is compatible with this reaction. The mechanism of this process, with regards whether attachment of nitromethane or the acyl derivative occurs first, is discussed below.

The experiments in this paper were conducted with nitromethane that had not been dried. While the issue of dry vs. wet nitromethane was not exhaustively studied here, a comparison was performed for the synthesis of compound **8c**. Thus wet nitromethane (used from the supplier bottle with no anhydrous precautions) was compared with dry nitromethane (stored over calcium chloride for 16 hours, followed by filtration through molecular sieves (3 Å). When these preparations of nitromethane were used for the synthesis of compound **8c**, no differences in the yield or speed of the reaction could be observed.

2) Alkylation

Another method of trapping the intermediate species **2** via an alkylation was explored. Such a route, after reduction of the nitro moiety, would permit access to a range of synthetically useful chiral vicinal diamines. Accordingly 3,4-DHIQ was mixed with nitromethane as before, and the reaction was quenched by the addition of benzyl bromide (Scheme 3). This one-pot process successfully gave the novel *N*-benzyl derivative **9a** in 55% isolated yield and the *N*-allyl derivative **9b** in 63% yield using the same conditions used for the acylated products. The *N*-methylated derivative **9c** could not be obtained through a one-pot process and was only successfully obtained (in 66% yield) by addition of methyl iodide prior to the addition of nitromethane in a two-step process.



Scheme 3. Aza-Henry reaction with alkylation. Reagents and conditions: i) as for one-pot procedure, Scheme 2; **9c** synthesized by a two-step process.

3) Mechanistic Studies

Two aspects of the mechanism of these reactions are of interest:

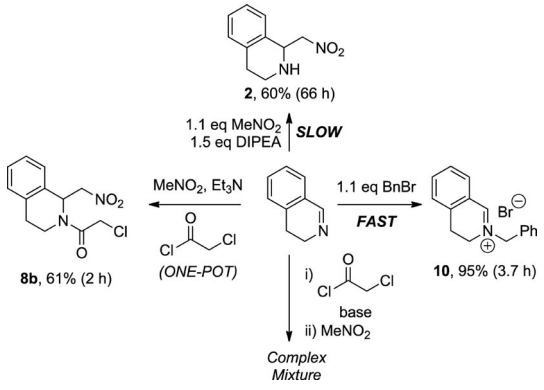
1) Which reaction step (alkylation/acylation or attack of nitromethane) is faster?

2) What is the role of the base?

i) Rates of Alkylation/Acylation vs. Attack of Nitromethane

Initial investigation of the rates of the two processes occurring in these reactions began with the removal of a series of aliquots over time from the reaction between 3,4-DHIQ and nitromethane. Alkylation of each aliquot with benzyl bromide for several minutes was carried out followed by analysis of the resulting crude samples with ^{1}H NMR spectroscopy. Unexpectedly, none of these spectra showed the presence of any *N*-alkylated product **9a**. Instead another compound was formed that was not starting material. A downfield peak at δ = 10.6 ppm in the ^{1}H NMR spectrum suggested that this species was **10**, the *N*-alkyliminium ion formed from direct alkylation of the dihydroisoquinoline. The ionic representation (as opposed to the covalent structure where the bromide has attacked the acyliminium ion) [30] is supported by a singlet for the benzylic methylene group in the NMR spectrum, as opposed to the pronounced AB quartet observed for this methylene in the aza-Henry reaction product **9a**.

Repeated isolation of **10** in these experiments has significant implications for the mechanism of the aza-Henry reaction on dihydroisoquinoline. Presumably the alkylation is fast, and promotes the slower attack of the nitromethane. To verify this, several NMR experiments were performed to monitor the reaction between dihydroisoquinoline and nitromethane/benzyl bromide (Scheme 4). In the first case the nitromethane was a reagent (1.1 equiv.), and the NMR spectrum was performed in $CDCl_3$. By monitoring the disappearance of the N=CH starting material proton (δ =8.3 ppm) and the appearance of the signal for the same proton at 4.6 ppm for the product, it could be seen that the reaction was slow: after 66 hours (when monitoring was stopped) the reaction was only 60% complete. In the second case mixing 3,4-DHIQ with benzyl bromide under the same



Scheme 4. Investigations into the mechanism of the quenched aza-Henry reaction of dihydroisoquinoline.

conditions and monitoring by NMR spectroscopy indicated clean production of **10** in 78% yield after 50 min, increasing to 95% after 220 min.

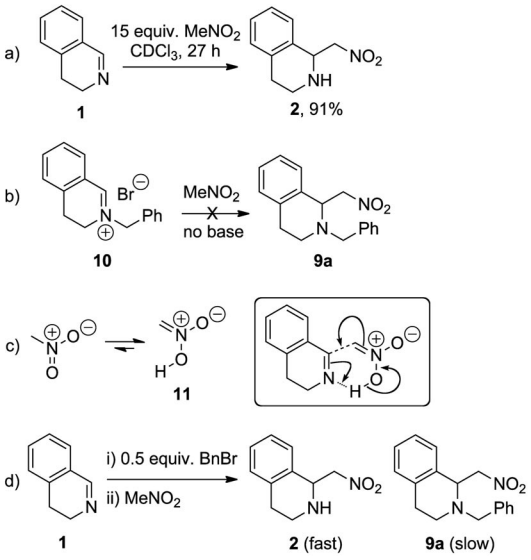
The implication is that the reaction between dihydroisoquinoline and nitroalkanes is slow, but may be promoted by alkylation or acylation of the ring nitrogen, as in standard Reissert-like chemistry. The direct reaction between 3,4-DHIQ and nitromethane occurs rapidly when the nitroalkane is in excess (i.e. as the solvent) since quantitative formation of this product was observed by ^{1}H NMR spectroscopy (above). This knowledge was applied to the attempted synthesis of the acylated product **8b** where the order of reagents was reversed from that used above, i.e. acylating agent first, followed by nitromethane. This experiment required performing the acylation of dihydroisoquinoline in a solvent other than nitromethane (here dichloromethane), followed by removal of the solvent from the intermediate and immediate resuspension in nitromethane (with added base) for the second step. Only a complex mixture was obtained containing no product in the crude ^{1}H NMR spectrum, implying the acyliminium ion intermediate reacted with other species in the reaction mixture.[31] Thus the one-pot reactions described above gave good yields of the desired products presumably because the nitromethane was present in excess and throughout.

ii) Role of the Base

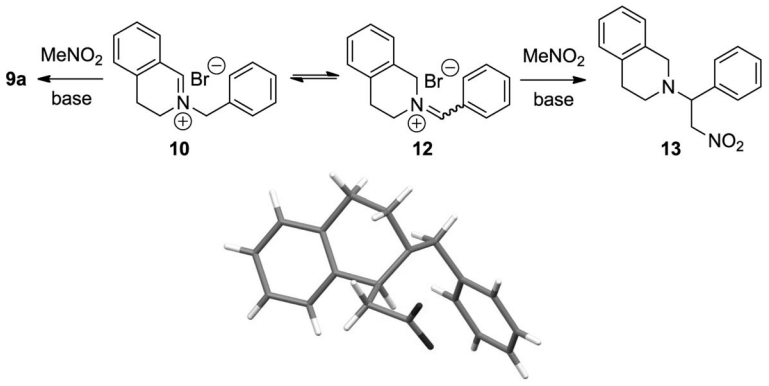
Base is not necessary for the reaction between 3,4-DHIQ and nitromethane: when these reagents were mixed (15 equiv. of CD_3NO_2 in $CDCl_3$) the NMR spectra of the mixture clearly indicated the expected reaction was occurring, giving the product in 59% yield after three hours and 91% yield after 27 hours (Scheme 5, a). On the other hand, when 3,4-DHIQ and benzyl bromide were first mixed [to give the salt (**10**)] and nitromethane subsequently added *without* base then no further reaction was observed (Scheme 5, b). It appears base is only necessary for reaction between 3,4-DHIQ and nitromethane when the 3,4-DHIQ is alkylated.

The mechanism of the aza-Henry reaction traditionally involves the nucleophilic attack of a nitronate onto an imine. A consideration of the p*K*a values of nitromethane (10.2) and product (ca. 9) and the pKa_H value of triethylamine (11) suggest this mechanism is unrealistic in the present case.[32] Simplistically, the excess of nitromethane promotes the bulk reaction by Le Chatelier's principle, but an alternative mechanism is needed to explain the data above. When present in excess, there is presumably a fair quantity of the methylideneazinic acid tautomer **11** present (Scheme 5, c). This species would be able to hydrogen bond with the starting material, and form the C–C bond via a cyclic mechanism; indeed this mechanism is implied by the principle of microscopic reversibility if the decomposition mechanism in Scheme 2 is correct. A similar atom-economic mechanism has been suggested by others in related cases.[22,23,33] An *intermolecular* reaction of the azinic acid tautomer in a more usual Reissert fashion must therefore be comparatively slow since the salt **10** is unable to coordinate the azinic acid, but the C–C bond forming reaction may be accelerated through the addition of a base. Experimentally, addition of base to **10** at the same time as the nitromethane gave the expected reaction product **9a**.

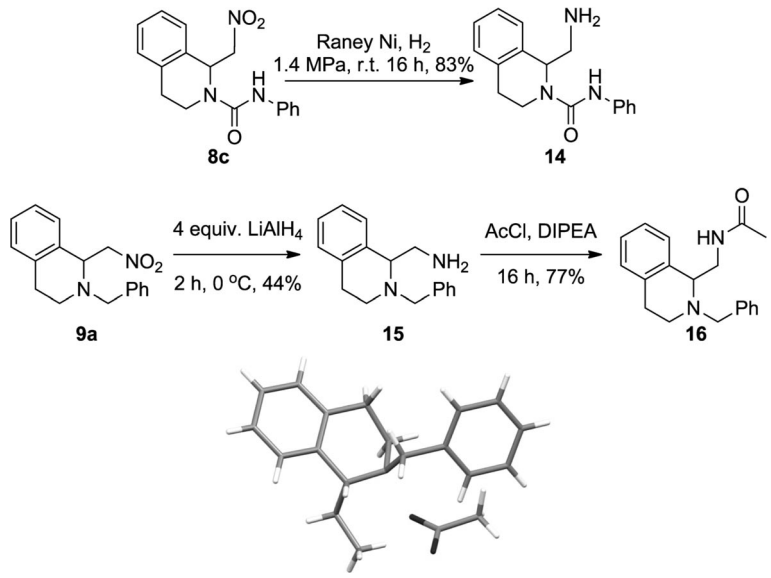
In a competition experiment (Scheme 5, d) 3,4-DHIQ was mixed with 0.5 equiv. of benzyl bromide, generating a



Scheme 5. Experiments towards understanding the mechanism of the aza-Henry reaction between 3,4-DHIQ and nitromethane.



Scheme 6. Potential tautomerism in **10**, and crystal structure of the isolated product **9a**.



Scheme 7. Reductions of nitro compounds **8c** and **9a**, and X-ray crystal structure of **15**·OAc.

1:1 mixture of **1** and **10** observed by NMR spectroscopy. This mixture was treated with nitromethane in the absence of base. The NMR spectrum showed that the dihydroisoquinoline was being consumed faster than the alkylated salt, suggesting the reaction mode depicted in Scheme 5 is significant. However, this experiment was also designed to test whether the isoquinoline itself could act as a competent base in an intermolecular aza-Henry reaction with the alkylated intermediate **10** (thereby giving consumption of the salt faster than the 3,4-DHIQ), but the low rate of consumption of **10** suggested this mode of reaction was not occurring or slow.

Note that in these reactions it is possible that a tautomer of the isoquinolinium ion could form (**12**, Scheme 6), which would lead to product nitroamine **13** upon reaction with nitromethane. The identity of the product (which gave a clean ^{1}H NMR spectrum, indicating a single product was being formed) was established as **9a** with X-ray crystallography suggesting that a tautomerisation, if it occurred, did not interfere with the reaction giving the desired product.

c) Reductions of β-Nitroamines/Amides to the Corresponding Amines

Reduction of the nitroalkyl group in a number of products to the corresponding amine with a range of reducing conditions (including samarium iodide and Pd/C-catalysed hydrogenation) was unsuccessful, giving either no reaction or mixtures of products. *N*-Substituted tetrahydroisoquinolines were frequently isolated, presumably arising from in situ reduction of the iminium ion derived from retroaddition of the nitromethane; this product was observed for example when the combination of triethylamine and formic acid was employed under hydrogen atmosphere with Pd/C catalyst.[34] Reduction of β-nitroamines is a reaction with remarkably few reliable general procedures in the literature.[35] An interesting report[36] by Anderson describing the use of Al/Hg amalgam was investigated but was not successful with substrates **8a**,**b** and **9a**, generating a mixture of products.

Raney nickel-catalysed hydrogenation conditions were finally identified as effective reducing conditions for **8c** to give the novel amine **14** in good yield (Scheme 7). Similar conditions have since also been used by us for the reduction of related nitro compounds derived from *N*-phenyltetrahydroisoquinolines.[28c] On the other hand, $LiAlH_4$ was found to be effective for the reduction of the *N*-benzyl derivative **9a**, yielding the reduced product **15** in 44% yield. This diamine has been reported only once in the primary research literature, but with minimal characterization.[37] Fortunately, the first X-ray crystal structure of this compound could be obtained; the crystal actually contained the acetate salt of the expected product, presumably due to adventitious production of acetic acid during the workup. The free amine could be reacted further with acetyl chloride to functionalise the primary amine (to give **16**), suggesting a synthetic route to a range of new derivatives of these isoquinoline-derived chiral vicinal diamines that may now be explored for their potential as ligands in catalysis.

Conclusions

The aza-Henry reaction may be performed directly on dihydroisoquinolines to generate the novel β-nitroamine **2**. The reaction operates in an excess of nitromethane, without conversion to an "activated" or Reissert compound, presumably by an in situ activation of the nitrogen by the methylideneazinic acid tautomer. The resultant β-nitroamine is not thermodynamically stable with respect to starting materials, but may be alkylated or acylated to give stable compounds. Alkylation of the isoquinoline nitrogen is

faster than the C–C bond forming reaction, and standard Reissert chemistry operates when nitromethane is not in excess. Effective reducing conditions were found that convert two of the nitro compounds to the corresponding novel vicinal diamine derivatives. Exploration of the catalytic properties of these new compounds is currently underway.

Experimental Section

General: All reagents and solvents were purchased from Aldrich or Lancaster, except for 3,4-dihydroisoquinoline which was a gift from SamiLabs, Bangalore, India. Reagents were used without further purification. Nitromethane was not dried before use. Flash column chromatography was performed using Merck Kieselgel 60 silica gel (SiO_2, 0.040–0.063 mm). Thin-layer chromatography (TLC) was carried out with Merck Kieselgel 60 silica gel precoated aluminum sheets (0.2 mm). Melting points were measured on Gallenkamp melting point apparatus. ^{1}H nuclear magnetic resonance spectra were recorded on a Bruker Avance spectrometer at a frequency of 300.13 MHz (unless otherwise stated) at 300 K. Signals are reported in the order chemical shift (ppm downfield with respect to internal TMS), multiplicity, integration, coupling constants J (Hz) and assignments. For AB quartets the separation of the midpoints of the two doublets is given as $\Delta\nu$ in Hertz. ^{13}C Nuclear Magnetic Resonance spectra were recorded on a Bruker Avance 300 spectrometer at a frequency of 75.47 MHz (unless otherwise stated) at 300 K. NMR spectra were acquired in $CDCl_3$ unless otherwise stated. Raw NMR spectroscopic data are available in the Supporting Information as jcamp.dx files that may be viewed by processing programs such as Jspecview. Infra-red spectra were measured on a Shimadzu Model 8400 FT-IR, and the samples deposited as a thin film on NaCl plates with dichloromethane. Low-resolution electrospray ionization mass spectra were determined on a ThermoQuest Finnigan LCQ Deca ion trap mass spectrometer. High resolution mass spectroscopy was performed on a Bruker Fourier Transform Ion Cyclotron Resonance (FT-ICR) spectrometer in electrospray mode with a 4.7 T superconducting magnet by Dr. Keith Fisher at the Australian National University, Canberra, Australia.

1,2,3,4-Tetrahydro-1-(nitromethyl)isoquinoline (2): To 3,4-dihydroisoquinoline (0.890 g, 6.79 mmol) was added nitromethane (90 mL). The solution was allowed to stir for 5 min. Triethylamine (0.949 g, 1.30 mL, 9.38 mmol, 1.50 equiv.) was added to the reaction and stirring was continued for 16 h. Water (90 mL) was added, the reaction layers were separated and the aqueous layer extracted with dichloromethane (3 × 70 mL). The combined organic layers were dried with magnesium sulfate and concentrated under reduced pressure and in vacuo to afford **2** as a pale yellow solid (1.25 g, 96%). ^{1}H NMR: δ = 2.71 (m, 2 H, H^4), 2.94–3.15 (m, 2 H, H^3), 4.55–4.59 (m, 2 H, H^9), 4.63–4.73 (m, 1 H, H^1), 7.11 (m, 4 H, Ar) ppm. Further characterization was not performed as this compound is unstable with respect to starting materials.

1-[3,4-Dihydro-1-(nitromethyl)isoquinoline-2(1*H*)-yl]ethanone (8a): To 3,4-dihydroisoquinoline (0.077 g, 0.58 mmol) was added nitromethane (3.9 mL). The solution was allowed to stir for 5 min. Triethylamine (62 mg, 0.085 mL, 0.61 mmol, 1 equiv.) was added and stirring was continued for 16 h. Acetyl chloride (0.099 g, 90 μL, 1.27 mmol, 2 equiv.) was added, and stirring was continued for 2 h before water (10 mL) was added and the reaction layers were separated. The aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried with magnesium sulfate and concentrated under reduced pressure and in vacuo to afford a brown oil which was purified by flash column chromatography (EtOAc) to give **8a** as pale yellow crystals (0.061 g, 45%). R_F (EtOAc) = 0.54; m.p. 110–112 °C. ^{1}H NMR: Approx. 2.5:1 ratio of rotamers. Major rotamer: δ = 2.20 (s, 3 H, H^{11}), 2.70–3.15 (m, 2 H, H^3), 3.58–3.89 (m, 2 H, H^4), 4.61–4.90 (m, 2 H, H^9), 6.25 (apparent t, 1 H, J = 5.8 Hz, H^1), 7.10–7.30 (m, 4 H, Ar); minor rotamer: δ = 2.18 (s, 3 H, H^{11}), 2.70–3.15 (m, 3 H, 2 H^3 and 1 H^4), 4.61–4.90 (m, 3 H, 1 H^4 and 2 H^9), 5.68 (dd, J = 10.2, 5.2 Hz, 1 H, H^1), 7.10–7.30 (m, 4 H, Ar) ppm. ^{13}C NMR Major rotamer: δ = 22.3, 29.2, 41.9, 51.7, 78.6, 127.6, 127.7, 128.6, 129.4, 132.1, 134.7, 170.7 ppm; minor rotamer: δ = 21.5, 27.8, 35.6, 56.1, 78.8, 127.0, 127.3, 129.0, 130.5, 131.2, 135.7, 170.2 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 1549, 1643 cm^{-1}. MS (ES): m/z (%) = 257.1 (100) [MNa$^+$], 235.0 (72) [MH$^+$]. HRMS (ESI): calcd. for $C_{12}H_{14}N_2NaO_3$ [MNa$^+$]: 257.090210, found 257.089256; $C_{12}H_{14}N_2O_3$ (234.2512): calcd. C 61.53, H 6.02, N 11.96; found C 61.24, H 6.07, N 11.78.

2-(Chloroacetyl)-1,2,3,4-tetrahydro-1-(nitromethyl)isoquinoline (8b): To 3,4-dihydroisoquinoline (0.890 g, 6.79 mmol) was added nitromethane (90 mL). The solution was allowed to stir for 5 min. Triethylamine (0.949 g, 1.31 mL, 9.38 mmol, 1.38 equiv.) was added and stirring was continued overnight before water (50 mL) was added. The reaction layers were separated and the aqueous layer was extracted with dichloromethane (3 × 70 mL). The combined organic layers were dried with magnesium sulfate and concentrated under reduced pressure and in vacuo to afford crude β-nitroamine that was immediately dissolved in dry dichloromethane (40 mL). 2,2,6,6-Tetramethylpiperidine (1.909 g, 13.52 mmol, 1.99 equiv.) was added followed by chloroacetyl chloride (1.177 g, 10.42 mmol, 1.53 equiv.). The resulting solution was stirred for 2 h, water (40 mL) was added and the layers were separated. The aqueous phase was extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried with magnesium sulfate and concentrated under reduced pressure to give a brown oil. This oil was triturated from ethyl acetate and hexane to afford **8b** as pale orange plates (0.845 g, 46%). R_F (3:1 hexane/EtOAc) = 0.13; m.p. 98–103 °C. ^{1}H NMR ($CDCl_3$): Approx. 3:1 ratio of rotamers: Major rotamer: δ = 2.92 (dt, J = 16.2, 4.4 Hz, 1 H, H^{4a}), 3.02–3.18 (m, 1 H, H^{4b}), 3.72 (ddd, J = 13.3, 9.7, 4.4 Hz, 1 H, H^{3a}), 3.93 (dt, J = 13.3, 5.0 Hz, 1 H, H^{3b}), 4.17 (ABq, J = 12.4 Hz, 2 H, $\Delta\nu$ 21.3, H^{11}), 4.67–4.93 (m, 2 H, H^9), 6.19 (apparent t, J = 6.3 Hz, 1 H, H^1), 7.17–7.30 (m, 4 H, Ar) ppm; minor rotamer: δ = 2.79 (br. d, J = 15.4 Hz, 1 H, H^{3a}), 2.99–3.18 (m, 2 H, H^{3b} and H^{4a}), 4.22 (ABq, J = 12.4 Hz, 2 H, $\Delta\nu$ 80.6, H^{11}), 4.67–4.93 (m, 3 H, H^{4b} and H^9), 5.75 (dd, J = 9.9 Hz, 1 H and 3.8, H^1), 7.17–7.30 (m, 4 H, Ar) ppm. ^{13}C NMR: Major rotamer: δ = 29.0, 41.5, 41.7, 52.3, 78.4, 127.6, 127.6, 128.8, 129.5, 131.3, 134.5, 166.8 ppm; minor rotamer: δ = 27.6, 36.6, 41.3, 55.5, 77.8, 127.1, 127.4, 129.1, 130.3, 130.7, 135.1, 166.4 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 1553, 1659 cm^{-1}. MS (ES): m/z (%) = 293.1 (44) [MNa$^+$], 291.1 (100) [MNa$^+$]. HRMS (ESI): calcd. for $C_{12}H_{13}ClN_2NaO_3$ [MNa$^+$]: 291.051240, found 291.050601. $C_{12}H_{13}ClN_2O_3$ (268.6962): calcd. C 53.64, H 4.88, N 10.43; found C 53.72, H 4.89, N 10.43.

CCDC-634262 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

One-Pot Procedure: 3,4-Dihydroisoquinoline (1.000 g, 7.624 mmol) was dissolved in nitromethane (4.5 mL, 84 mmol, 11 equiv.). To this clear pale yellow solution, chloroacetyl chloride (0.67 mL, 8.39 mmol, 1.1 equiv.) was added followed by triethylamine (1.2 mL, 0.85 g, 8.4 mmol, 1.1 equiv.). The mixture was stirred at

45 °C for 2 h and allowed to cool to room temp. Water (100 mL) was added and the reaction mixture was extracted with dichloromethane (1 × 50 mL, 2 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The crude product was recrystallised with hexane and ethyl acetate (ca. 1:1) yielding the isoquinoline derivative as a brown crystalline solid (1.250 g, 61%) spectroscopically identical to the product from the two-step procedure above.

1-(Nitromethyl)-*N*-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxamide (8c): By employing the same conditions as the general one-pot procedure (above), a yellow solid was obtained which was recrystallized (Et_2O) to give **8c** as a colourless solid (0.400 g, 84%). R_F (2.3:1 hexane/EtOAc) = 0.45; m.p. 143–144 °C. ^{1}H NMR (200 MHz): δ = 2.85 (ddd, J = 16.3, 4.4, 4.4, Hz, 1 H, H^{4a}), 3.14 (ddd, J = 16.4, 9.6, 5.1 Hz, 1 H, H^{4b}), 3.46 (ddd, J = 12.4, 9.4, 4.6 Hz, 1 H, H^{3b}), 4.10 (ddd, J = 12.4, 5.1, 4.7 Hz, 1 H, H^{3a}), 4.73 (dd, J = 12.9, 5.1 Hz, 1 H, H^{9a}), 4.93 (dd, J = 12.8, 8.9 Hz, 1 H, H^{9b}), 5.97 (dd, J = 8.6, 5.1 Hz, 1 H, H^1), 7.02–7.43 (m, 9 H, Ar) ppm. ^{13}C NMR: δ = 28.0, 39.4, 54.6, 79.1, 120.5, 123.7, 127.4, 129.3, 129.8, 131.7, 135.5, 139.0, 155.6 (one Ar and C=O peak obscured) ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3333, 1651, 1543 cm^{-1}. MS (ES): m/z (%) = 312.1 (100) [MH^+]. HRMS (ESI): calcd. for $C_{17}H_{17}N_3O_3$ [MH^+]: 312.13482, found 312.13406.

2,2,2-Trichloroethyl 1-(Nitromethyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (8d): By employing the same conditions as the general one-pot procedure (above), crude material was obtained and purified by flash column chromatography (95:5 hexane/EtOAc) to give **8d** as a pale yellow oil (0.470 g, 64%). R_F (9:1 hexane/EtOAc) = 0.75. ^{1}H NMR: δ = 2.74–2.79 (m, 1 H, H^{4a}), 2.80–2.98 (m, 1 H, H^{4b}), 3.38–3.52 (m, 1 H, H^{3a}), 4.06–4.13 (m, 1 H, H^{3b}), 4.50–4.90 (m, 4 H, $H^{9,10}$), 5.83–5.91 (m, 1 H, H^1), 7.13–7.18 (m, 4 H, Ar) ppm. ^{13}C NMR: δ = 28.2, 28.6, 39.4, 39.6, 54.3, 75.7, 77.7, 79.2, 127.8, 129.9, 131.4, 134.9, 135.0, 154.3 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 1705, 1560 cm^{-1}. MS (ES): m/z (%) = 389.1 (100) [MNa^+]. HRMS (ESI): calcd. for $C_{13}H_{13}{}^{35}Cl_3N_2NaO_4$ [MNa^+]: 388.98386, found 388.98331.

2-Benzyl-1,2,3,4-tetrahydro-1-(nitromethyl)isoquinoline (9a): By employing the same conditions as the general one-pot procedure (above), crude material was obtained that was purified by flash chromatography to give **9a** as yellow crystals (0.400 g, 55%). R_F (2.5:1 hexane/EtOAc) = 0.57; m.p. 62–64 °C. ^{1}H NMR: δ = 2.47–2.56 (m, 1 H, H^{3a}), 2.87–3.08 (m, 2 H, H^{3b}, H^{4a}), 3.14–3.25 (m, 1 H, H^{4b}), 3.78 (ABq, J = 13.3 Hz, 2 H, $\Delta\nu$ 23.2, H^{11}), 4.46 (dd, J = 11.3, 4.3 Hz, 1 H, H^{9a}), 4.54 (dd, J = 9.9, 4.3 Hz, 1 H, H^{9b}), 4.72 (dd, J = 11.3, 9.9 Hz, 1 H, H^1), 7.05–7.34 (m, 9 H, Ar) ppm. ^{13}C NMR: δ = 23.3, 42.2, 58.0, 60.1, 79.9, 127.0, 127.8, 128.0, 128.1, 128.8, 129.2, 130.1, 132.6, 135.7, 138.7 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1553 cm^{-1}. MS (ES): m/z (%) = 283.1 (26) [MH^+], 222.1 (100) [M^+ – CH_2NO_2]. HRMS (ESI): calcd. for $C_{17}H_{18}N_2O_2$: [MH^+]: 283.144650, found 283.144700. $C_{17}H_{18}N_2O_2$ (282.3370): calcd. C 72.32, H 6.43, N 9.92; found C 72.58, H 6.73, N 10.00.

CCDC-708674 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

2-Allyl-1,2,3,4-tetrahydro-1-(nitromethyl)isoquinoline (9b): By employing the same conditions as the general one-pot procedure (above), crude material was obtained that was purified by flash chromatography (1:3 EtOAc/hexane) to afford the product as a yellow oil (0.52 g, 65%). R_F (1:3 EtOAc/hexane) = 0.48. ^{1}H NMR: δ = 2.40–2.52 (m, 1 H), 2.83–3.00 (m, 2 H), 3.08–3.29 (m, 3 H), 4.40 (dd, 1 H, J = 11.1, 4.2 Hz, H^{9a}), 4.48 (dd, 1 H, J = 9.9, 4.2 Hz, H^1), 4.63 (dd, 1 H, J = 11.1, 9.9 Hz, H^{9b}), 5.02–5.07 (m, 1 H, H^{13a}), 5.09 (br. s, 1 H, H^{13b}), 5.66–5.81(m, 1 H, H^{12}), 6.95–7.30 (m, 4 H, Ar) ppm. ^{13}C NMR: δ = 23.5, 43.3, 56.9, 58.9, 79.9, 118.2, 126.9, 127.9, 128.1, 129.1, 130.0, 132.5, 135.7, 136.1 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1558 cm^{-1}. MS (ES): m/z (%) = 345.3 (100) [unidentified peak], 214.3 [M^+ – H_2O 52], 230.3 (17) [MH^+]. HRMS (ESI): calcd. for $C_{13}H_{16}N_2O_2$ [MH^+]: 233.12845, found 233.12886.

2-Methyl-1,2,3,4-tetrahydro-1-(nitromethyl)isoquinoline (9c): To 3,4-dihydroisoquinoline (0.500 g, 3.81 mmol) dissolved in diethyl ether (3 mL) was added methyl iodide (0.26 mL, 4.18 mmol, 1.1 equiv.). The resulting solution was stirred for 1 h and concentrated under reduced pressure. Nitromethane (5 mL) was added and stirring was continued for 5 min. To the solution was added triethylamine (0.58 mL, 4.16 mmol, 1.1 equiv.) and stirring was continued for a further 1 h before water (10 mL) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried with magnesium sulfate and concentrated in vacuo. The product was purified by flash chromatography (1:2 EtOAc/hexane) to afford **9c** as a yellow oil (0.52 g, 66%). R_F (EtOAc/hexane, 1:2) = 0.54. ^{1}H NMR: δ = 2.48 (s, 3 H, CH_3), 2.51–2.60 (m, 1 H, H^{4a}), 2.74–2.91 (m, 1 H, H^{4b}), 3.02–3.08 (m, 2 H, H^3), 4.28–4.41 (m, 2 H, H^9), 4.53–4.60 (m, 1 H, H^1), 6.98–7.10 (m, 4 H, Ar) ppm. ^{13}C NMR: δ = 24.1, 42.6, 46.0, 61.8, 79.9, 126.9, 127.8, 127.9, 129.9, 132.6, 135.5 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1540 cm^{-1}. MS (ES): m/z (%) = 146.1 (100) [M^+ – CH_2NO_2], 207.0 (80) [MH^+]. HRMS (ESI): calcd. for $C_{11}H_{14}N_2O_2$ [MH^+]: 207.112811, found 207.113068.

1-(Aminomethyl)-*N*-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxamide (14): 1-(Nitromethyl)-*N*-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxamide (**8c**, 0.320 g, 0.100 mmol) was taken in MeOH (50 mL). Aqueous ammonia (5 mL) was added and the mixture stirred until the starting material had dissolved. Raney Ni (1 mL solid in 5–6 mL slurry, ca. 0.6 g of catalyst[38]) was added and the mixture was degassed with H_2 [350 kPa (3.4 atm) × 2]. The reaction mixture was stirred at 1.4 MPa (13.6 atm) at room temp. for 16 h. Completion of reaction was monitored by TLC and LC-MS. The solvent was evaporated and the crude material was purified by flash chromatography to yield amine as colourless needles (0.240 g, 83%). R_F = 0.23 (9:1 DCM/MeOH); m.p. 132–135 °C. ^{1}H NMR: δ = 2.93–3.26 (m, 4 H, $H^{4,9}$), 4.14–4.25 (m, 2 H, H^3), 5.01–5.07 (m, 1 H, H^1), 6.90–7.05 (t, 1 H, J = 6.7 Hz, H^{12}), 7.05–7.50 (m, 8 H, Ar), 9.39 (br. s, 1 H, NH) ppm. ^{13}C NMR: δ = 29.0, 38.6, 47.7, 60.4, 119.4, 122.4, 126.7, 127.3, 127.4, 129.2, 129.4, 135.2, 136.0, 140.6, 157.7 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3342, 1664, 1547 cm^{-1}. MS (ES): m/z (%) = 281. 7 (100) [$(MH)^+$], 562.8 (42) [$(M_2\ H)^+$]. HRMS (ESI): calcd. for $C_{17}H_{20}N_3O$ [MH^+]: 282.16009, found 282.16013.

(2-Benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methanaminium Acetate (15·AcOH): To lithium aluminium hydride (0.056 g, 1.52 mmol, 4 equiv.) in tetrahydrofuran (3 mL) cooled to 0 °C, was added dropwise 2-benzyl-1,2,3,4-tetrahydro-1-(nitromethyl)isoquinoline (**9a**, 0.108 g, 0.38 mmol) in tetrahydrofuran (10 mL) under nitrogen. Stirring was continued at room temp. until completion of the reaction (2 h) as judged by TLC (ninhydrin stain). The reaction mixture was quenched with ethyl acetate (5 mL) and ice (ca. 1 g). The mixture was filtered through a celite pad with dichloromethane and the filtrate was concentrated in vacuo. The crude material was purified with a short plug of silica with a dichloromethane/methanol solvent system (1:0 rising to 9:1) to afford ninhydrin active fractions, which were concentrated under reduced pressure to afford a pink oil. This oil was triturated with dichloromethane and hexane (ca. 1:5) to afford the amine salt as pale yellow prisms (0.052 g,

44%). R_F (9:1 dichloromethane/methanol) = 0.42; m.p. 117–119 °C. ^{1}H NMR (CD_3COCD_3): δ = 1.85 (s, 3 H, OAc), 2.10–2.31 (m, 1 H, H^{4a}), 2.55–2.59 (m, 1 H, H^{4b}), 2.87–3.02 (m, 4 H, $H^{3,9}$), 3.23–3.30 (m, 2 H), 3.59–3.61 (m, 1 H), 3.72–3.82 (m, 2 H, H^{10}), 6.95 (br. s, 1 H, NH), 7.14–7.44 (m, 9 H, Ar) ppm. ^{13}C NMR (CD_3COCD_3): δ = 23.5, 25.1, 44.4, 44.9, 58.8, 61.5, 127.2, 127.6, 128.2, 129.4, 129.5, 130.2, 136.4, 137.1, 141.1, 170.1 (one Ar peak obscured) ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3302, 1651 cm^{-1}. MS (ES): *m*/*z* (%) = 253.3 (100) [$(MH)^+$]. HRMS (ESI): calcd. for $C_{17}H_{21}N_2$ [MH^+]: 253.16993, found 253.17018.

CCDC-707603 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

***N*-[(2-Benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl]acetamide (16):** To (2-benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methanaminium acetate (**15·AcOH**, 0.187 g, 0.592 mmol) in dichloromethane (10 mL) were added acetyl chloride (46 μL, 0.65 mmol, 1.1 equiv.) and diisopropylethylamine (150 μL, 0.9 mmol, 1.5 equiv.) and the reaction mixture was stirred for 16 h after which the reaction was judged complete by TLC (ninhydrin stain). The reaction mixture was diluted with water (20 mL) and dichloromethane (20 mL) the layers were separated and the aqueous phase extracted with further dichloromethane (20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude amide was washed with diethyl ether and triturated from dichloromethane and hexane (1:5) to afford **16** as pale yellow-brown prisms (0.136 g, 77%). R_F (1:1 ethyl acetate/hexane) = 0.58; m.p. 126–128 °C. ^{1}H NMR: δ = 1.88 (s, 3 H, Me), 2.56–2.62 (m, 1 H, H^4), 2.97–3.29 (m, 3 H), 3.67–3.82 (m, 3 H), 6.10 (br. s, 1 H), 7.15–7.40 (m, 9 H, Ar) ppm. ^{13}C NMR: δ = 23.7, 24.0, 43.5, 44.1, 57.9, 59.5, 126.8, 127.2, 127.8, 128.6, 128.9, 129.5, 134.8, 135.0, 139.6, 170.2 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 1651, 3302 cm^{-1}. MS (ES): *m*/*z* (%) = 295.5 (100) [$(MH)^+$]. HRMS (ESI): calcd. for $C_{19}H_{22}N_2O$ [MH^+]: 295.18049, found 295.18066. $C_{19}H_{22}N_2O$ (294.3908): calcd. C 77.52, H 7.53, N 9.52; found C 77.29, H 7.45, N 9.53.

Supporting Information (see also the footnote on the first page of this article): Copies of the ^{1}H and ^{13}C NMR spectra for all compounds, plus the derivation of the rate equation for the decomposition shown in Figure 1. JCAMP-DX files for all NMR spectra which may be opened by any NMR processing program, and the calculations for the derivation of the rate equation for Figure 1.

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