

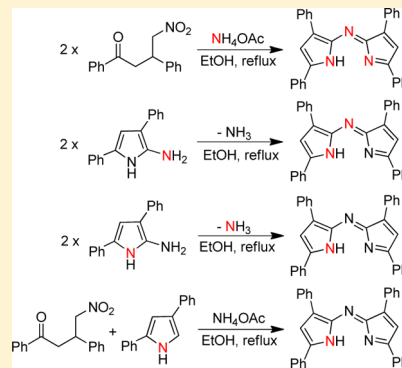
Mechanistic Insight into the Formation of Tetraarylazadipyrromethenes

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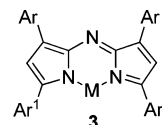
Supporting Information

ABSTRACT: The tetraarylazadipyrromethene chromophore class has gained increasing attention in the past decade for a diverse set of scientific interests and applications. The most direct synthetic route available for their generation is heating of 4-nitro-1,3-diarylbutan-1-ones with an ammonium source in an alcohol solvent. Despite the practical simplicity, the reaction pathway(s) for these conversions are lengthy and unclear. To gain insight into the steps involved, ^{15}N labeling experiments with MS and NMR analysis were utilized for conversion of 4-nitro-1,3-diphenylbutan-1-one **1** into tetraphenylazadipyrromethene **2** with $^{15}\text{NH}_4\text{OAc}$. To permit examination of later stages of the reaction sequence to **2**, the ^{15}N -labeled potential intermediate 3,5-diphenyl-1H-pyrrol-2-amine **10** was synthesized. A study of the dimerization pathway utilizing ^{15}N -labeled **10** revealed an unprecedented nitrogen rearrangement in the final stages of the pathway involving a ring-opening/closing of a pyrrole ring. Utilizing ^{15}N labeling experiments we have shown that 2,4-diphenylpyrrole **8** can also react under the reaction conditions with 3,5-diphenyl-2H-pyrrol-2-imine **7** (from oxidation of **10**) to produce **2**. Overall in the conversion of **1** into **2**, two related pathways are ongoing concurrently; the first involves a dimerization of 3,5-diphenyl-2H-pyrrol-2-imine **7**, and the other a reaction of **7** with 2,4-diphenylpyrrole **8**.



INTRODUCTION

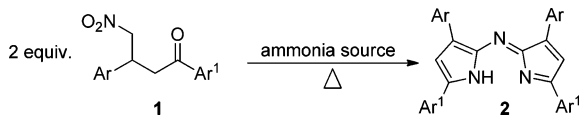
Use of isotope-labeled compounds in conjunction with mass spectrometry and NMR is a powerful tool for studying reaction pathways as well as metabolic patterns.¹ In this report, the stable isotope ^{15}N labeling was combined with tandem mass spectrometry (MS/MS) experiments and NMR data to gain insight into the formation of *N*-(3,5-diaryl-2H-pyrrol-2-ylidene)-3,5-diphenyl-1H-pyrrol-2-amine (tetraarylazadipyrromethenes) **2** (Scheme 1). Tetraarylazadipyrromethenes **2** were



M = BF₂, B(OR)₂, Ni, Co, Cu, Zn, Au, Ag

Figure 1. Chelated tetraarylazadipyrromethenes **3**.

Scheme 1. Synthesis of Tetraarylazadipyrromethenes **2**



first reported by M. Rogers in the early 1940s as unexpected deep blue colored products obtained from the treatment of diaryl- γ -nitro ketones **1** with various ammonia sources.² Using the limited analytical techniques available at the time, it was proven that the blue chromophore obtained from the reaction of 2 equiv of the relatively simple substrate **1** was the nitrogen-bridged dipyrrole structure **2**.

A renewed interest in this compound class has rapidly grown in recent years following our reports on their BF₂ and B(OR)₂ chelates **3** (Figure 1).³ These boron-chelated derivatives have

high fluorescence quantum yields in the near-infrared spectral region and have been adapted toward applications as fluorochromes,⁴ sensors/energy transfer cassettes,⁵ nanoparticle conjugates for real-time fluorescence imaging,⁶ and donor/acceptor conjugates for solar cell applications.⁷ Additionally, they have been further modified to act as highly effective light-activated therapeutics,⁸ and the d-block metal chelates have been proposed as supramolecular architecture building blocks as well as medical chemical agents (Figure 1).⁹

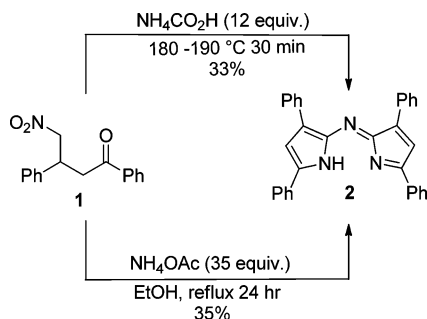
RESULTS AND DISCUSSION

Despite their growing importance, a mechanism of formation of **2** starting from diaryl- γ -nitro ketones remains elusive. In Roger's original paper, **1** (Ar, Ar¹ = Ph) was heated neat (no solvent) with an excess of ammonium formate at 180 °C for 15

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min and then at 190 °C for a further 15 min. After cooling, the product **2** was isolated by trituration with methanol in a 33% yield (Scheme 2).^{2a} Work from our own laboratory has shown

Scheme 2. Reaction Conditions for the Synthesis of **2**

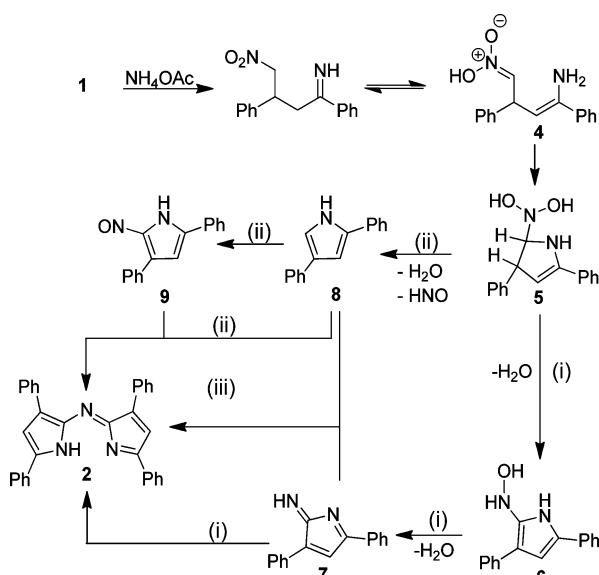


that a comparable 35% yield can be obtained under the milder conditions of reflux in ethanol for 24 h in the presence of 35 equiv of ammonium acetate.^{3b}

Insight into the route(s) by which **2** is formed is clearly of interest, but the overall reaction sequence or sequences contain numerous intermediates along the pathway. Despite this, **2** equiv of **1** are clearly incorporated into the final product **2** and while the origin of the carbon skeleton in **2** is evident, the same cannot be stated for the nitrogens.

A plausible start of the reaction pathway(s) to **2** could involve generation of enamine intermediate **4** from **1** and ammonia followed by nucleophilic addition to the *aci*-nitro tautomer to generate **5** from which several potential pathways may be considered (Scheme 3). Route i evokes an elimination

Scheme 3. Alternative Route Outlines to **2**



of water and tautomerization to *N*-(3,5-diphenyl-1*H*-pyrrol-2-yl)hydroxylamine **6** and subsequent further dehydration to generate 3,5-diphenyl-2*H*-pyrrol-2-imine **7** (Scheme 3, pathway i).¹⁰ From **7**, a formal dismutation, dimerization, and loss of ammonia could provide **2** (Scheme 3).¹¹ Alternatively, route ii has been postulated by others, in which an elimination of water and HNO could generate 2,4-diphenylpyrrole **8** followed by a partial in situ conversion to 2-nitroso-3,5-diphenyl pyrrole **9**

and subsequent condensation with nonconverted **8** to generate **2** (Scheme 3, pathway ii).¹² The means by which **8** is partially converted into **9** is not discussed. While we anticipated that pathway i would be plausible, a further alternative pathway iii could also be considered in which 2,4-diphenylpyrrole **8** is produced within the reaction mixture but reacts with **7** to generate **2** (Scheme 3). In this report we describe our efforts to gain insight into potential routes i and iii with a focus on 3,5-diphenyl-2*H*-pyrrol-2-imine intermediate **7** and the pathways by which it can produce **2**.

At the outset, a series of ¹⁵N labeling studies were carried out in an effort to shed some light on the overall pathway. The use of this isotope allowed the employment of mass spectrometry and ¹⁵N NMR techniques to characterize the labeled products. On the basis of the outline of pathway i, it would be a plausible expectation that by utilizing a ¹⁵N-labeled source of ammonia, the label would be incorporated into the two pyrrole nitrogen positions leaving the bridging nitrogen unlabeled. With this goal in mind, 4-nitro-1,3-diphenylbutan-1-one **1** was heated with ¹⁵NH₄OAc (35 equiv) in ethanol under reflux for 24 h, and the product, which precipitated from the reaction, was analyzed by ¹⁵N NMR and electrospray ionization mass spectrometry (ESI-MS) in the positive ion mode. The ¹⁵N NMR results were initially inconclusive (*vide infra*), as three signals were observed with chemical shifts of −86.2, −175.7, and −176.2 ppm (Figure S, spectrum A). The positive mode ESI-MS of **2** from the ¹⁴N ammonium acetate gave the expected [M + H]⁺ ion peak of *m/z* 450 and peaks of lesser abundant ions at *m/z* 451 and *m/z* 452 arising from the natural abundance of ¹³C (Figure 2A). In contrast, the ESI-MS data of **2** generated using ¹⁵NH₄OAc had an obvious absence of a peak at 450 *m/z* with a distribution of peaks from 451 to 455 *m/z* (Figure 2B). The most abundant was that of the trileveled species (peak 453 *m/z*) followed by dilabeled species (peak 452 *m/z*) and monolabeled (peak 451 *m/z*). The composition of

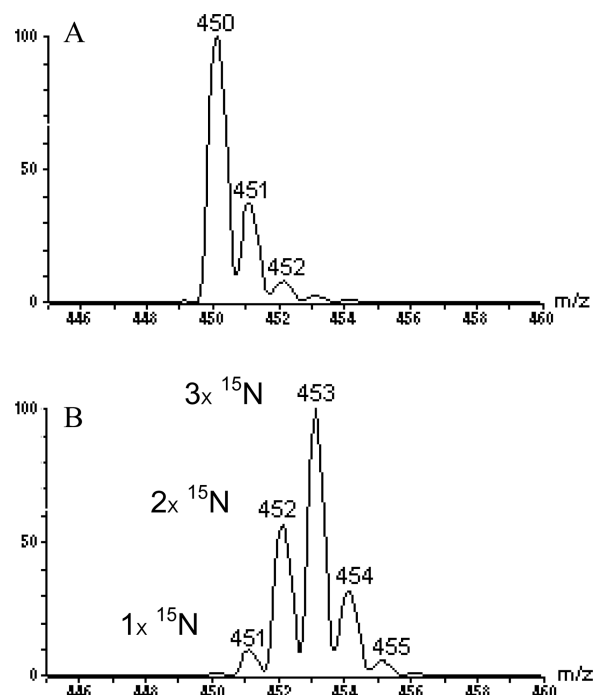


Figure 2. A: Positive mode ESI-MS of **2** generated with NH₄OAc. B: ESI-MS of **2** generated with ¹⁵NH₄OAc.

the isotopologue mixture from the mass spectrum as shown in Figure 2B was calculated by relative peak height to give a ratio of 9:6:1 of the tri:di:mono labeled species, respectively (Figure 3).

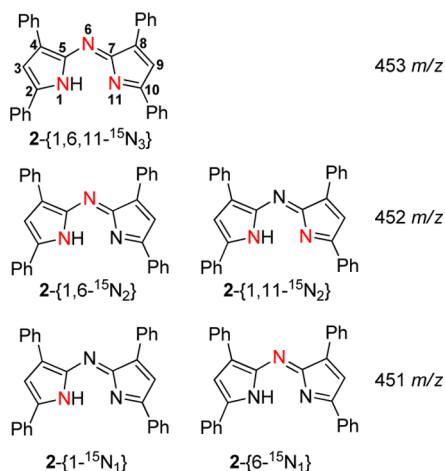


Figure 3. All possible ^{15}N (red color) isotopologues and isotopomers of **2** with calculated positive mode m/z values.

This result shows that for the most abundant trilabeled isotopologue $2\text{-}\{1,6,11\text{-}^{15}\text{N}_3\}$, the nitrogen from the nitro group of **1** is not incorporated into the final product. To assign the labeled nitrogen position(s) in the di- and monolabeled species, two different isotopomers $2\text{-}\{1,6\text{-}^{15}\text{N}_2\}$, $2\text{-}\{1,11\text{-}^{15}\text{N}_2\}$ and $2\text{-}\{1\text{-}^{15}\text{N}_1\}$, $2\text{-}\{6\text{-}^{15}\text{N}_1\}$ must be considered for each case (Figure 3). To achieve this, we turned to ESI-MS/MS experiments with examination of the fragmentation patterns of the m/z 452 and 451 peaks. To be confident in the interpretation of MS/MS fragmentation results from the isotope mixture and to assign ^{15}N NMR resonances, authentic samples of the four differently labeled derivatives were first individually synthesized following our previously reported multistep route utilizing a pyrrole/nitrosopyrrole condensation.¹³

The ^{15}N -labeled pyrrole $8\text{-}\{1\text{-}^{15}\text{N}_1\}$ was generated by a Nef reaction on **1** to yield the corresponding keto-aldehyde (4-oxo-2,4-diphenylbutanal) followed by condensation with $^{15}\text{NH}_4\text{OAc}$ (Figure 4). Synthesis of the ^{15}N -labeled nitroso pyrroles $9\text{-}\{2\text{-}^{15}\text{N}_1\}$ and $9\text{-}\{1\text{-}^{15}\text{N}_1\}$ was achieved by reaction of the corresponding pyrroles **8** and $8\text{-}\{1\text{-}^{15}\text{N}_1\}$ with $\text{Na}^{15}\text{NO}_2$

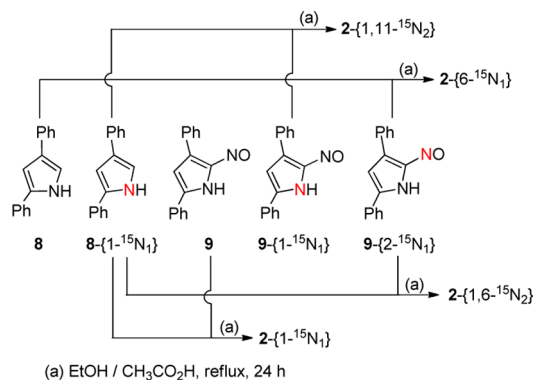


Figure 4. Rational syntheses of ^{15}N (red color) isotopologues and isotopomers of **2**.

and NaNO_2 , respectively.¹³ The systematic condensation of unlabeled and labeled 2,4-diphenylpyrroles **8** and $8\text{-}\{1\text{-}^{15}\text{N}_1\}$ with 2-nitroso-3,5-diphenylpyrroles **9**, $9\text{-}\{1\text{-}^{15}\text{N}_1\}$ and $9\text{-}\{2\text{-}^{15}\text{N}_1\}$ was performed in ethanol/acetic acid generating the four derivatives $2\text{-}\{1\text{-}^{15}\text{N}_1\}$, $2\text{-}\{6\text{-}^{15}\text{N}_1\}$, $2\text{-}\{1,6\text{-}^{15}\text{N}_2\}$, and $2\text{-}\{1,11\text{-}^{15}\text{N}_2\}$ (Figure 4).

^{15}N NMR for $2\text{-}\{1\text{-}^{15}\text{N}_1\}$, $2\text{-}\{6\text{-}^{15}\text{N}_1\}$, $2\text{-}\{1,6\text{-}^{15}\text{N}_2\}$, and $2\text{-}\{1,11\text{-}^{15}\text{N}_2\}$ were recorded in CDCl_3 using nitromethane as reference (Figure 5, spectra B–E, respectively). Monolabeled **2**

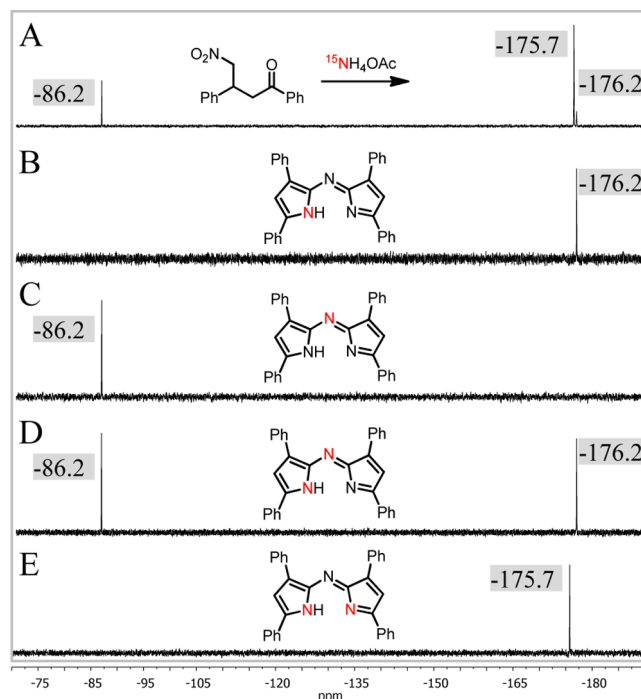


Figure 5. ^{15}N NMR spectra of A: product **2** generated with $^{15}\text{NH}_4\text{OAc}$. B–E: rationally synthesized isotopologues and isotopomers of **2**.

$\{1\text{-}^{15}\text{N}_1\}$ and $2\text{-}\{6\text{-}^{15}\text{N}_1\}$ gave single peaks with chemical shifts of -176.2 and -86.2 ppm which could be assigned to the pyrrole and bridging exocyclic nitrogens, respectively.¹⁴ Dilabeled compound $2\text{-}\{1,6\text{-}^{15}\text{N}_2\}$ which contains one pyrrole ^{15}N label and one exocyclic ^{15}N label recorded both chemical shifts of -176.2 and -86.2 ppm, respectively. Structurally revealing its dilabeled isotopomer $2\text{-}\{1,11\text{-}^{15}\text{N}_2\}$ gave the expected one ^{15}N pyrrole signal but with a chemical shift of -175.7 ppm which is marginally different from that of either $2\text{-}\{1,6\text{-}^{15}\text{N}_2\}$ or $2\text{-}\{1\text{-}^{15}\text{N}_1\}$. As **2** is a quasiaromatic system with N–H tautomerization making both pyrrole nitrogens equivalent, the different ^{15}N pyrrole chemical shifts can be attributed to a heavy atom equilibrium isotope effect on the averaged chemical shift resonances of $2\text{-}\{1,6\text{-}^{15}\text{N}_2\}$ and $2\text{-}\{1,11\text{-}^{15}\text{N}_2\}$.¹⁵ This subtle yet important difference allows the NMR differentiation of $2\text{-}\{1\text{-}^{15}\text{N}_1\}$, $2\text{-}\{1,11\text{-}^{15}\text{N}_2\}$, and $2\text{-}\{1,6,11\text{-}^{15}\text{N}_3\}$ by ^{15}N NMR even as label mixtures (Figure 5, spectra A, B, E).

The ESI-MS of the dilabeled isotopomers $2\text{-}\{1,6\text{-}^{15}\text{N}_2\}$ and $2\text{-}\{1,11\text{-}^{15}\text{N}_2\}$ gave the expected molecular ion peaks at 452 m/z . Encouragingly, ESI-MS/MS of the two isotopic isomers showed differing fragmentation patterns such that $2\text{-}\{1,6\text{-}^{15}\text{N}_2\}$ gave $218/219\text{ m/z}$ and $232/233\text{ m/z}$ fragments, whereas $2\text{-}\{1,11\text{-}^{15}\text{N}_2\}$ fragmented to 219 m/z and 232 m/z (Figure 6,

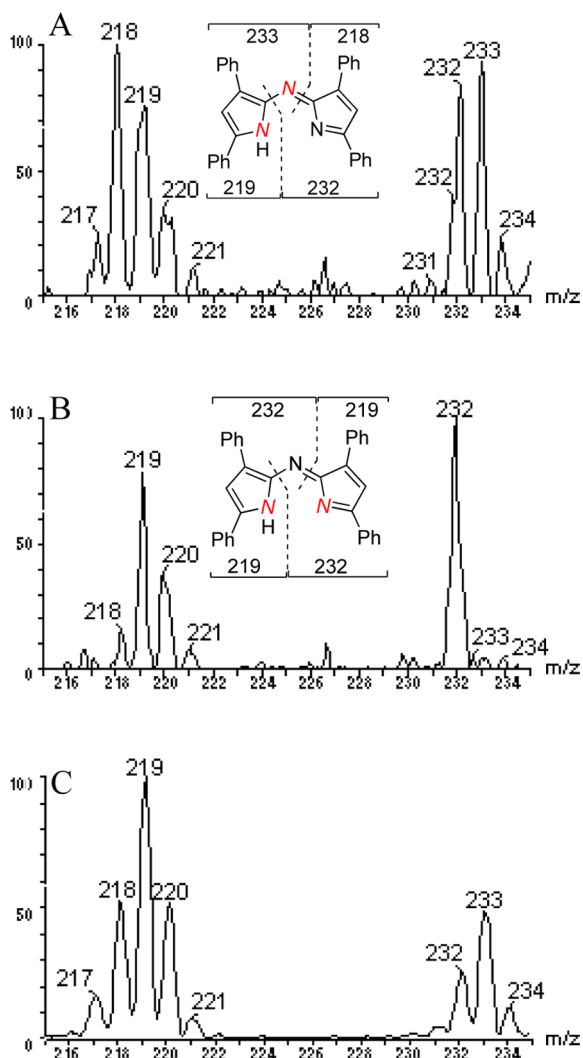


Figure 6. A: Positive mode ESI-MS/MS for 2-{1,6- $^{15}\text{N}_2$ }. B: ESI-MS/MS for 2-{1,11- $^{15}\text{N}_2$ }. C: ESI-MS/MS for the 452 m/z peak of labeled products obtained from reaction of **1** with $^{15}\text{NH}_4\text{OAc}$.

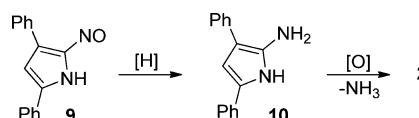
spectra A and B). This is consistent with the unsymmetrical labeling pattern of 2-{1,6- $^{15}\text{N}_2$ } (one pyrrole ^{15}N and one bridging ^{15}N) and the symmetrical labeling (both pyrrole ^{15}N) of 2-{1,11- $^{15}\text{N}_2$ }. Investigation of the MS/MS fragmentation pattern for the m/z 452 peak for the product from the reaction of labeled ammonium acetate and **1** showed it to be a mixture of both isotopomers 2-{1,6- $^{15}\text{N}_2$ } and 2-{1,11- $^{15}\text{N}_2$ } (Figure 6C). Taken with the ^{15}N NMR data, these results illustrated that scrambling of nitrogen positions occurred during the reaction sequence for the formation of the dilabeled species.

In a similar fashion, monolabeled 2-{1- $^{15}\text{N}_1$ } and 2-{6- $^{15}\text{N}_1$ } could be distinguished by their fragmentation peaks at 218/219, 231/232, and 218/232 m/z , respectively (Figure S1, Supporting Information). The main findings from these initial ^{15}N labeling experiments were that the nitro group of the starting material in **1** was not found in over 50% of the isolated product, and exchanging of the nitrogen positions could be observed in the dilabeled product, as both isotopomers could be detected.

To probe the later stages of the formation of **2**, the reactivity of 3,5-diphenyl-1H-pyrrol-2-amine **10** was selected for further investigation. In addition to the synthetic approaches to **2** outlined above, **10** is also known to generate **2** when exposed

to air oxidation (Scheme 4).^{2a,16} As a formal oxidation of amino-pyrrole **10** equates to **7**, a potential advanced

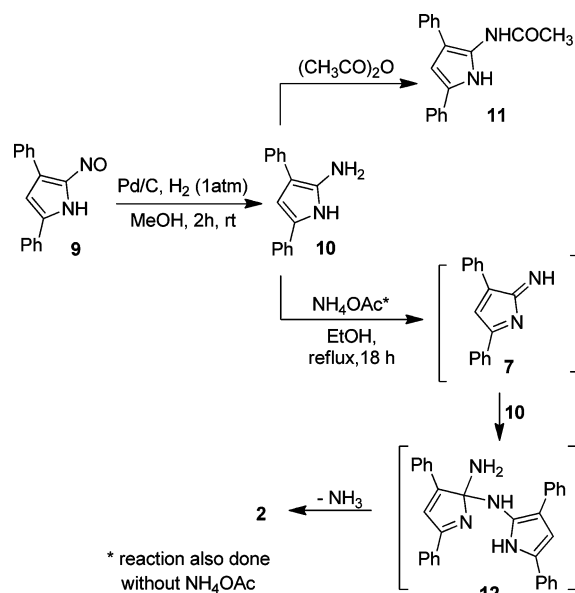
Scheme 4. Synthetic Route to **2** via 3,5-Diphenyl-1H-pyrrol-2-amine **10**



intermediate of the reaction sequence as shown in Scheme 2, an examination of its conversion into **2** offered an opportunity to probe potential final stages of the reaction sequence. Synthetic access to **10** could be achieved by reduction of the available 2-nitroso-3,5-diphenylpyrrole **9** (Scheme 4). This route was previously shown to be viable by reduction of **9** with Adam's catalyst producing a solution of **10** which, without isolation, underwent air oxidation leading to dimerization with loss of ammonia to give **2**.^{2a}

For our investigation of this pathway, alternative reducing conditions of catalytic Pd/C and H_2 (1 atm) in MeOH for 2 h at rt proved optimal (Scheme 5). In general, the isolation of

Scheme 5. Route to **2** via Dimerization of **10**



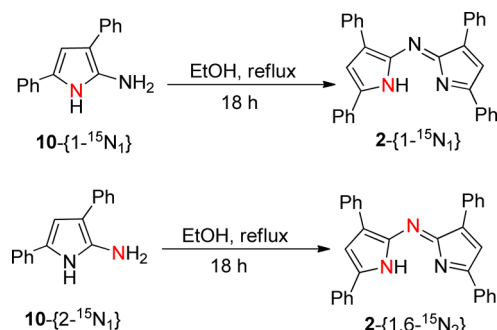
amino-pyrroles is often problematic due to their air sensitivity.¹⁷ As such, following reduction of **9**, the solution of **10** was rapidly filtered to remove the Pd and directly treated with acetic anhydride, and the product isolated following silica gel chromatography. Analysis of the product was consistent with the expected C-2 amido-substituted pyrrole structure **11** (Scheme 5). In subsequent attempts it was found that with careful exclusion of air during workup, the C-2 amino-pyrrole **10** could be isolated and characterized with HRMS and NMR. In addition, following reduction of isotopomers 9-{1- $^{15}\text{N}_1$ } and 9-{2- $^{15}\text{N}_1$ }, the ^{15}N NMR analysis of 10-{1- $^{15}\text{N}_1$ } and 10-{2- $^{15}\text{N}_1$ } showed single signals at -240.0 and -337.1 ppm, respectively, which are consistent with ^{15}N -labeled pyrrole and amino nitrogens.^{17b,18}

Heating an air-exposed ethanolic solution of **10** and NH_4OAc under reflux for 18 h provided the azadipyrromethene

2 in a 56% yield. In the absence of NH_4OAc , **2** was also formed but in a lower 8% yield. These conversions would be consistent with an oxidation of **10** to **7**, subsequent in situ condensation with a second equivalent of **10**, and loss of ammonia via an intermediate **12** yielding **2** (Scheme 5).¹⁹ A similar mechanism with structurally related intermediates has also been evoked in the formation of phthalocyanines starting from phthalonitriles and of methylene blue.²⁰

To investigate the possibility of nitrogen interchange during the conversion of **10** into **2**, the oxidative/dimerization of ^{15}N -labeled amino-pyrroles **10**-{1- $^{15}\text{N}_1$ } and **10**-{2- $^{15}\text{N}_1$ } were studied (Scheme 6). Remarkably, following heating of **10**-

Scheme 6. ^{15}N Rearrangement upon Oxidative Dimerization of **10**

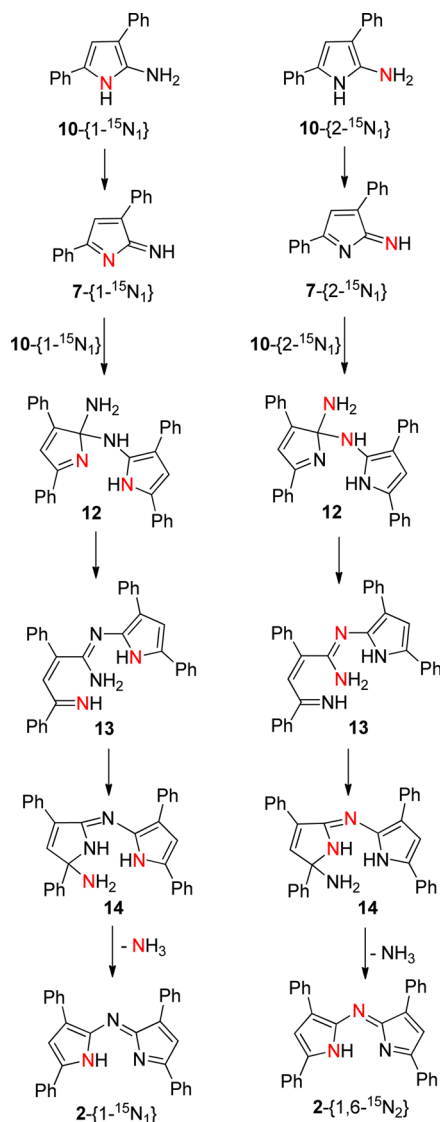


{1- $^{15}\text{N}_1$ } (pyrrole nitrogen labeled) under reflux in EtOH (without NH_4OAc), the ESI-MS and ^{15}N NMR analysis revealed that only a mono- ^{15}N -labeled product was obtained. This indicated that a pyrrole-labeled nitrogen had been exchanged, and comparison of the ^{15}N NMR chemical shift (-176.2 ppm) proved that the isotopomer formed was 2-{1- $^{15}\text{N}_1$ }. This rearrangement was confirmed by repeating the same reaction conditions with **10**-{2- $^{15}\text{N}_1$ } (amino nitrogen labeled) which gave a dilabeled product by MS and two ^{15}N signals in the NMR spectrum (-86.2 and -176.2 ppm) corresponding to the isotopomer 2-{1,6- $^{15}\text{N}_2$ } containing one label in a pyrrole ring and a labeled bridging nitrogen (Scheme 6).

These results show that a rearrangement has taken place that exchanged one pyrrole nitrogen for the exocyclic bridging nitrogen. While the exact sequence by which this occurs remains as yet uncertain, this would require a pyrrole opening and reclosing to take place during the final stages of the reaction pathway (Scheme 7). A plausible pyrrole ring-opened intermediate **13** is akin to the intermediate generated in the pyrrole synthesis from the reductive ring contraction of 1,2-pyridazines.²¹ Reclosing to a five-membered ring would give **14**, which upon elimination of ammonia would generate products 2-{1- $^{15}\text{N}_1$ } or 2-{1,6- $^{15}\text{N}_2$ } depending upon the position of the ^{15}N label in the starting material (Scheme 7).²² This unprecedented rearrangement can account for the formation of both dilabeled isotopomers 2-{1,6- $^{15}\text{N}_2$ } and 2-{1,11- $^{15}\text{N}_2$ } in the reaction of **1** with $^{15}\text{NH}_4\text{OAc}$ as described in Scheme 3 but does not necessarily explain the fact that trilabeled 2-{1,6,11- $^{15}\text{N}_3$ } is the major isotopologue obtained.

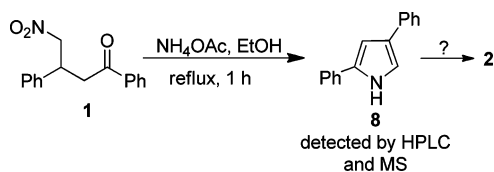
To explore the potential for intermolecular nitrogen exchange during the conversion of **10** into **2**, the oxidative dimerization of **10**-{2- $^{15}\text{N}_1$ } in EtOH/ $^{14}\text{NH}_4\text{OAc}$ was carried out. Revealingly, the MS product analysis showed a mixture of mono- and dilabeled isotopologues obtained in an approx-

Scheme 7. ^{15}N Rearrangement upon Oxidative Dimerization of **10**-{1- $^{15}\text{N}_1$ } and **10**-{2- $^{15}\text{N}_1$ }



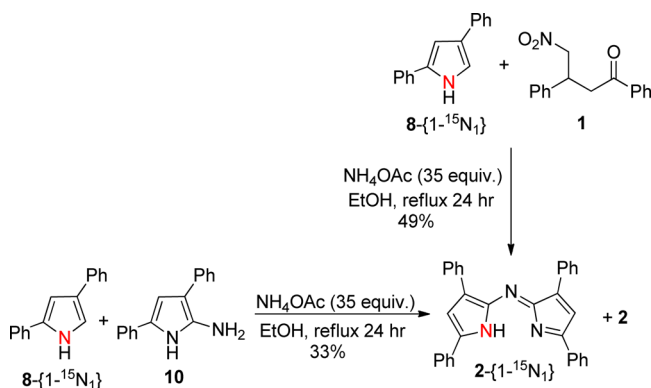
imately 40:60 ratio (^{15}N NMR analysis showed a scrambling of label positions) in contrast to the dilabeled 2-{1,6- $^{15}\text{N}_2$ } alone being obtained in the absence of an external ^{14}N source. This shows that even at the later stages of the reaction sequence, intermolecular nitrogen exchange can occur, with intermediate **7** being the most likely candidate for exchange.²³ This exchange could account for trinitrogen-labeled **2** being the predominant labeled species obtained from the reaction of **1** with $^{15}\text{NH}_4\text{OAc}$.²⁴

Attempts to directly detect formation of pyrrole intermediates in the conversion of **1** into **2** by TLC were unsuccessful presumably because of their low concentration. More sensitive MS and HPLC techniques revealed the presence of diphenylpyrrole **8** in the reacting mixture after 1 h (Scheme 8). In situ MS observation of other pyrrole intermediates was not achieved, but this could be attributed to their lower stability preventing direct observation. The observation of **8** in the reaction mixture, though it is not obtained in any significant quantities at the end of the reaction, pointed toward the existence of an additional pathway, which could proceed concurrently with pathway i (Scheme 3). For this to be the

Scheme 8. Direct Evidence for the Formation of **8** from **1**

case, two possibilities must exist for the intermediate **5** in which it can either advance to **7** or to the diphenylpyrrole **8**. As shown above, **7** can dimerize to form the product **2** (route i), but two possibilities could be envisaged for the conversion of **8** into **2** (Scheme 3, routes ii or iii). We considered route ii which requires in situ conversion of **8** into **9** less likely, with reaction of **8** and **7** (route iii) more probable.

To investigate the reaction pathway in which **7** and **8** combine to produce **2**, two experiments were carried out using ^{15}N -labeled diphenylpyrrole **8**- $\{1\text{-}^{15}\text{N}_1\}$. Reaction of equal molar equivalents of **8**- $\{1\text{-}^{15}\text{N}_1\}$ and amino-pyrrole **10** in EtOH/ NH_4OAc provided the monolabeled isotopomer **2**- $\{1\text{-}^{15}\text{N}_1\}$ and unlabeled **2** in a 1:1 ratio, illustrating that the two pathways i and iii are operating concurrently (Scheme 9). One

Scheme 9. Trapping of in Situ-Generated **7** from **1** or **10**

pathway in which **10** is in situ oxidized to **7** and trapped by **8**- $\{1\text{-}^{15}\text{N}_1\}$ generating **2**- $\{1\text{-}^{15}\text{N}_1\}$, and the other in which **10** reacts with **7** to produce unlabeled **2**.²⁵ This result indicated that it may be possible to intercept the intermediate **7** as it is being produced from the diphenylnitroketone **1**. When **8**- $\{1\text{-}^{15}\text{N}_1\}$ was included as a reagent in the typical reaction conditions of **1**/ NH_4OAc /EtOH, the result was most revealing (Scheme 9). Following reflux in NH_4OAc /EtOH, the two substrates provided **2**- $\{1\text{-}^{15}\text{N}_1\}$ as the only isotopologue showing that **8**- $\{1\text{-}^{15}\text{N}_1\}$ could efficiently react with **7** as it was generated from **1**. In contrast to the result described above, predominantly **2**- $\{1\text{-}^{15}\text{N}_1\}$ was formed with very little unlabeled **2** observed. This can be explained by the fact that at any one time only a low concentration of **7** is being generated in the presence of a larger excess of pyrrole **8**- $\{1\text{-}^{15}\text{N}_1\}$, thereby biasing toward pathway iii and away from the dimerization of **7** via pathway i. This result has added importance, as it offers a new synthetic approach to tetraarylazadipyrromethenes containing differing aryl substituents on each pyrrole ring (without the need to synthesize nitroso-pyrroles as shown in Figure 4) by the reaction of a diarylnitroketone with a diarylpyrrole containing different aryl groups.²⁶

In summary, the reaction pathways involved in the conversion of diphenylnitroketone **1** and ammonium acetate

into the tetraphenylazadipyrromethene **2** have been investigated using ^{15}N labeling methods. The mixture of mono-, di-, and trileveled species obtained from this reaction indicated a more complicated process than might first be envisaged. Further insight into the reaction pathways was obtained by examination of the latter stages of the reaction sequence starting from ^{15}N -labeled 3,5-diphenyl-1*H*-pyrrol-2-amine **10**. This provided unique insight into its oxidative dimerization process with an unexpected exchange of a pyrrole nitrogen with an exocyclic nitrogen taking place in the final stages of the reaction pathway. To the best of our knowledge, this is the first illustration of this nitrogen positional rearrangement and may not be confined to this example alone.²⁷ This rearrangement provides an understanding of the original distribution of ^{15}N labels observed from the conversion of **1** into **2** using a ^{15}N ammonia source. A second concurrent pathway was also revealed by our study in which 2,4-diphenylpyrrole **8**, which can be detected in the reaction mixture, can react with the same intermediate **7**. While it is not unusual to observe different pathways in a multicondensation style heterocyclic synthesis in which the undesired pathway produces an impurity, in this case an atypical situation arises in which the divergent pathway produces a potential impurity **8** which does not accumulate but rebounds back into a complementary product reaction pathway as it is intercepted by **7**.

In conclusion, the use of ^{15}N labeling has shed light on the complex pathways that lead to tetraarylazadipyrromethenes from 4-nitro-1,3-diarylbutan-1-ones precursors. Evidence has been provided to support the presence of a key intermediate **7** which can dimerize with loss of ammonia to form **2** or react with 2,4-diphenylpyrrole **8**. Both pathways operate concurrently under the reaction conditions that convert **1** into **2**.

EXPERIMENTAL DETAILS

Proton-decoupled ^{15}N NMR spectra were recorded directly at 60.79 MHz using a 45° pulse width of 12.5 μs , a relaxation delay of 1 s, and acquisition time of 1.23 s with a spectral window of 26595.7 Hz (31.7 ppm to -405.7 ppm). Spectra were recorded at rt using nitromethane as internal standard. The ESI-MS and ESI-MS/MS were performed on a Quattro microtandem quadrupole instrument. The HRMS data were recorded on an LC-time of flight mass spectrometer.

N-(3,5-Diphenyl-2*H*-pyrrol-2-ylidene)-3,5-diphenyl-1*H*-pyrrol-2-amine **2 Using $^{14}\text{NH}_4\text{OAc}$.**^{3a} In a round-bottom flask, **1** (0.1 g, 0.37 mmol) and $^{14}\text{NH}_4\text{OAc}$ (1 g, 13 mmol) were dissolved in ethanol (5 mL) and heated under reflux for 24 h. During the course of the reaction, the product precipitated from the reaction mixture. The reaction was cooled to rt and filtered, and the solid was washed with cold ethanol (2×2 mL) to yield product **2** as a blue-black solid (29 mg, 35%): mp $288\text{--}290^\circ\text{C}$. ^1H NMR (400 MHz, CDCl_3) δ : 8.06 (d, $J = 7.4$ Hz, 4H), 7.96 (d, $J = 7.5$ Hz, 4H), 7.57–7.51 (m, 4H), 7.50–7.41 (m, 6H), 7.39–7.34 (m, 2H), 7.21 (s, 2H) ppm. ^{13}C NMR (100 MHz, CDCl_3) δ : 155.3, 149.8, 142.8, 133.9, 132.3, 130.2, 129.3, 129.2, 128.4, 128.2, 126.7, 115.1 ppm. ESI-MS: m/z [$\text{M} + \text{H}$] $^+$ 450.2 (100%); 451.2 (37%); 452.2 (8%).

Synthesis of N-(3,5-Diphenyl-2*H*-pyrrol-2-ylidene)-3,5-diphenyl-1*H*-pyrrol-2-amine **2 Using $^{15}\text{NH}_4\text{OAc}$.** In a round-bottom flask, **1** (0.1 g, 0.37 mmol) and $^{15}\text{NH}_4\text{OAc}$ (1 g, 13 mmol) were dissolved in ethanol (5 mL) and heated under reflux for 24 h. During the course of the reaction, the product precipitated from the reaction mixture. The reaction was cooled to rt, filtered and the solid was washed with cold ethanol (2×2 mL) to yield the ^{15}N -labeled product **2** (32 mg, 38%) as a mixture of ^{15}N -labeled isomers. ^1H NMR (600 MHz, CDCl_3) δ : 8.08–8.05 (m, 4H), 7.98–7.95 (m, 4H), 7.56–7.52 (m, 4H), 7.49–7.49 (m, 2H), 7.45–7.41 (m, 4H), 7.38–7.34 (m, 2H), 7.21 (s, 2H) ppm. ^{15}N NMR (60.8 MHz, CDCl_3) δ : -86.2 , -175.7 , -176.2 ppm, **2**- $\{1\text{-}^{15}\text{N}_1\}$ (-176.2 ppm); **2**- $\{6\text{-}^{15}\text{N}_1\}$ (-86.2 ppm); **2**-

{1,6-¹⁵N₂} (−176.2, −86.2 ppm); 2-{1,11-¹⁵N₂} (−175.7 ppm), 2-{1,6,11-¹⁵N₃} (−175.7, −86.2 ppm). ESI-MS: *m/z* [M + H]⁺ 451.2 (10%); 452.2 (57%); 453.2 (100%); 454.2 (32%); 455.2 (7%).

2,4-Diphenyl-1H-pyrrole, 8-{1-¹⁵N₁}. A stirred suspension of **1** (0.5 g, 1.8 mmol) in MeOH (5 mL) was treated at rt with a solution of KOH (0.52 g, 9.3 mmol) in MeOH (20 mL). After 1 h, the clear solution was added dropwise to a solution of concentrated H₂SO₄ (3.8 mL) in MeOH (20 mL) at 0 °C, following which the solution was allowed to warm to rt and stirred for a further 1 h. Water (45 mL) and ice (45 g) were added, and the mixture was neutralized to pH 7 with aqueous 4 M NaOH. The stirred mixture produced a white solid which was filtered, washed with water, dried, and used for the following step without further purification. The solid was dissolved in acetic acid (9 mL), and ¹⁵NH₄OAc (0.35 g, 4.5 mmol) was added. The mixture was heated at 100 °C for 1 h, cooled to rt, poured in ice (100 g), and neutralized to pH 7 with 4 M NaOH. The precipitate was filtered, washed with water, and dried. The solid was triturated with Et₂O to yield 8-{1-¹⁵N₁} as a light pink solid (0.22 g, 56%): mp 173–175 °C. ¹H NMR (500 MHz, DMSO-*d*₆) δ: 11.42 (d, *J* = 95.7 Hz, 1H, ¹⁵NH coupling), 7.68 (d, *J* = 7.6 Hz, 2H), 7.61 (d, *J* = 7.5 Hz, 2H), 7.40–7.35 (m, 2H), 7.35–7.29 (m, 3H), 7.18 (t, *J* = 7.3 Hz, 1H), 7.12 (t, *J* = 7.3 Hz, 1H), 6.95 (bs, 1H) ppm. ¹³C NMR (125 MHz, DMSO-*d*₆) δ: 135.7 (d, *J* = 1.7 Hz), 132.6 (d, *J* = 2.2 Hz), 132.2 (d, *J* = 13.4 Hz), 128.6, 128.5, 125.6, 125.0, 124.7 (d, *J* = 3.5 Hz), 124.4, 123.4, 116.5 (d, *J* = 13.5 Hz), 103.2 (d, *J* = 4.0 Hz) ppm. ¹⁵N NMR (60.8 MHz, DMSO-*d*₆) δ: −227.3 ppm. HRMS (EI) calcd for C₁₆H₁₃¹⁵N [M]⁺ 220.1018, found 220.1010.

2-Nitroso-3,5-diphenyl-1H-pyrrole, 9-{1-¹⁵N₁}. To a stirred solution of 8-{1-¹⁵N₁} (0.15 g, 0.68 mmol) in EtOH (7 mL) was added concentrated HCl (0.13 mL), followed by a dropwise addition of aqueous NaNO₂ (54 mg, 0.78 mmol, in 1.3 mL of H₂O). The solution was stirred for 30 min and then cooled to 0 °C, and another portion of concentrated HCl (0.67 mL) was added. The solution was stirred for 1 h, and the resulting red solid was collected by filtration and washed with Et₂O. The solid was dissolved in minimal EtOH, an excess of aqueous NaOAc and ice was added, and the solution was stirred for 1 h. The resulting solid was collected by filtration, washed with water, dried, and purified by chromatography on alumina (EtOAc/cyclohexane). A green solid was obtained (0.11 g, 65%): mp 140–141 °C. ¹H NMR (400 MHz, CDCl₃) δ: 8.21–8.15 (m, 2H), 7.84–7.77 (m, 2H), 7.54–7.46 (m, 6H), 7.15 (d, *J* = 2.9 Hz, 1H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ: 163.1 (d, *J* = 11.6 Hz), 141.5, 132.0, 131.4, 129.8, 129.6, 129.5 (b), 129.0, 126.9 (b), 113.0 (b) ppm. ¹⁵N NMR (60.8 MHz, DMSO-*d*₆) δ: −248.8 ppm. HRMS (ES) calcd for C₁₆H₁₃¹⁴N¹⁵NO [M + H]⁺ 250.0998, found 250.0997.

2-Nitroso-3,5-diphenyl-1H-pyrrole, 9-{2-¹⁵N₁}. To a stirred solution of **8** (0.2 g, 0.91 mmol) in EtOH (9 mL) was added concentrated HCl (0.18 mL), followed by a dropwise addition of aqueous Na¹⁵NO₂ (74 mg, 1.05 mmol, in 1.8 mL of H₂O). The solution was stirred for 30 min and then cooled to 0 °C, and another portion of concentrated HCl (0.9 mL) was added. The solution was stirred for 1 h, and the resulting red solid was collected by filtration and washed with Et₂O. The solid was dissolved in minimal EtOH, an excess of aqueous NaOAc and ice was added, and the solution was stirred for 1 h. The resulting solid was collected by filtration, washed with water, dried, and purified by chromatography on alumina (EtOAc/cyclohexane). A green solid was obtained (0.165 g, 73%): mp 140–141 °C. ¹H NMR (400 MHz, CDCl₃) δ: 8.21–8.16 (m, 2H), 7.82–7.78 (m, 2H), 7.54–7.47 (m, 6H), 7.15 (s, 1H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ: 163.0 (d, *J* = 7.5 Hz), 148.2 (b), 141.6, 132.0, 131.4, 129.8, 129.7, 129.6, 129.4, 129.0, 127.0, 113.0 (b) ppm. ¹⁵N NMR (60.8 MHz, DMSO-*d*₆) δ: −326.0 ppm. HRMS (ES) calcd for C₁₆H₁₃¹⁴N¹⁵NO [M + H]⁺ 250.0998, found 250.0998.

N-(3,5-Diphenyl-2H-pyrrol-2-ylidene)-3,5-diphenyl-1H-pyrrol-2-amine, 2-{1-¹⁵N₁}. Compound 8-{1-¹⁵N₁} (5.0 mg, 0.227 mmol) and **9** (5.6 mg, 0.227 mmol) were dissolved in a mixture AcOH (0.1 mL) and EtOH (0.6 mL), and the solution was heated under reflux for 24 h. The solution was cooled to rt, and the precipitate was collected by filtration, washed with cold EtOH, and dried. The product was obtained as a dark blue solid (5.6 mg, 55%): mp 289–290 °C. ¹H

NMR (500 MHz, CDCl₃) δ: 8.08–8.05 (m, 4H), 7.98–7.94 (m, 4H), 7.57–7.52 (m, 4H), 7.50–7.41 (m, 6H), 7.39–7.34 (m, 2H), 7.22–7.20 (m, 2H) ppm. ¹⁵N NMR (60.8 MHz, CDCl₃) δ: −176.2 ppm. HRMS (ES) calcd for C₃₂H₂₄¹⁴N₂¹⁵N [M + H]⁺ 451.1941, found 451.1955.

N-(3,5-Diphenyl-2H-pyrrol-2-ylidene)-3,5-diphenyl-1H-pyrrol-2-amine, 2-{6-¹⁵N₁}. Compound **8** (5.0 mg, 0.0228 mmol) and **9**-{2-¹⁵N₁} (5.7 mg, 0.0228 mmol) were dissolved in a mixture AcOH (0.1 mL) and EtOH (0.6 mL), and the solution was heated under reflux for 24 h. The solution was cooled to rt, and the precipitate was collected by filtration, washed with cold EtOH, and dried. The product was obtained as a dark blue solid (4.6 mg, 45%): mp 290–291 °C. ¹H NMR (500 MHz, CDCl₃) δ: 8.09–8.05 (m, 4H), 7.98–7.95 (m, 4H), 7.57–7.52 (m, 4H), 7.50–7.41 (m, 6H), 7.39–7.34 (m, 2H), 7.21 (s, 2H) ppm. ¹⁵N NMR (60.8 MHz, CDCl₃) δ: −86.2 ppm. HRMS (ES) calcd for C₃₂H₂₄¹⁴N₂¹⁵N [M + H]⁺ 451.1941, found 451.1924.

N-(3,5-Diphenyl-2H-pyrrol-2-ylidene)-3,5-diphenyl-1H-pyrrol-2-amine, 2-{1,6-¹⁵N₂}. Compound 8-{1-¹⁵N₁} (5.0 mg, 0.0227 mmol) and **9**-{2-¹⁵N₁} (5.6 mg, 0.0227 mmol) were dissolved in a mixture of AcOH (0.1 mL) and EtOH (0.6 mL), and the solution was heated under reflux for 24 h. The solution was cooled to rt, and the precipitate was collected by filtration, washed with cold EtOH, and dried. The product was obtained as a dark blue solid (7.1 mg, 69%): mp 290–291 °C. ¹H NMR (600 MHz, CDCl₃) δ: 8.08–8.05 (m, 4H), 7.98–7.94 (m, 4H), 7.56–7.52 (m, 4H), 7.50–7.45 (m, 2H), 7.45–7.41 (m, 4H), 7.38–7.34 (m, 2H), 7.22–7.20 (m, 2H) ppm. ¹⁵N NMR (60.8 MHz, CDCl₃) δ: −86.2, −176.2 ppm. ¹⁵N NMR (60.8 MHz, CDCl₃) δ: −86.2, −176.2 ppm. HRMS (ES) calcd for C₃₂H₂₄¹⁴N¹⁵N₂ [M + H]⁺ 452.1911, found 452.1917.

N-(3,5-Diphenyl-2H-pyrrol-2-ylidene)-3,5-diphenyl-1H-pyrrol-2-amine, 2-{1,11-¹⁵N₂}. Compound 8-{1-¹⁵N₁} (5.0 mg, 0.0227 mmol) and **9**-{1-¹⁵N₁} (5.6 mg, 0.0227 mmol) were dissolved in a mixture AcOH (0.1 mL) and EtOH (0.6 mL), and the solution was heated under reflux for 24 h. The solution was cooled to rt, and the precipitate was collected by filtration, washed with cold EtOH, and dried. The product was obtained as a dark blue solid (5.3 mg, 52%): mp 287–288 °C. ¹H NMR (600 MHz, CDCl₃) δ: 8.08–8.05 (m, 4H), 7.98–7.95 (m, 4H), 7.56–7.53 (m, 4H), 7.49–7.49 (m, 2H), 7.45–7.41 (m, 4H), 7.38–7.35 (m, 2H), 7.21 (s, 2H) ppm. ¹⁵N NMR (60.8 MHz, CDCl₃) δ: −175.7 ppm. HRMS (ES) calcd for C₃₂H₂₄¹⁴N¹⁵N₂ [M + H]⁺ 452.1911, found 452.1906.

N-(3,5-Diphenyl-1H-pyrrol-2-yl)acetamide, 11. In a round-bottom flask under inert atmosphere, compound **9** (0.15 g, 0.6 mmol) and activated Zn powder (0.90 g, 1.2 mmol) were suspended in ethanol 10% HOAc (20 mL). The reaction mixture was stirred for 2 h. The resulting suspension was cannulated into acetic anhydride (30 mL), and the solution was stirred for 4 h at rt. The solution was slowly poured into a saturated solution of NaHCO₃ (100 mL) and extracted with ethyl acetate (3 × 100 mL). The organic layers were washed with water (2 × 100 mL) and brine (100 mL) and dried over sodium sulfate. The crude material was purified by chromatography on silica gel using DCM:cyclohexane 9:1, respectively, yielding the purified product as a colorless solid. (0.110 g, 70%): mp: 168–169 °C; ¹H NMR (400 MHz, CDCl₃) δ: 10.76 (bs, 1H), 7.77 (bs, 1H), 7.51–7.49 (d, *J* = 8.0 Hz, 2H), 7.46–7.34 (m, 6H), 7.29–7.26 (m, 1H), 7.20–7.17 (t, *J* = 8.0 Hz, 1H), 6.53–6.52 (d, *J* = 4.0 Hz, 1H), 2.20 (s, 3H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ: 167.9, 135.0, 132.1, 129.7, 128.8, 127.3, 126.3, 126.0, 125.9, 123.3, 110.2, 104.2, 23.9 ppm. IR (KBr disk) cm^{−1}: 3242.73, 3046.03, 1650.31, 1614. ESI-MS: *m/z* [M + H]⁺ = 277.1. HRMS Calcd for C₁₈H₁₇N₂O [M + H]⁺ 277.1341, found 277.1347.

3,5-Diphenyl-1H-pyrrol-2-amine, 10. Compound **9** (100 mg, 0.40 mmol) was dissolved in methanol (11 mL), and 10% Pd on activated charcoal (21 mg, 0.02 mmol) was added. The suspension was frozen using liquid nitrogen, and the apparatus was evacuated then filled with H₂ (1 atm). The mixture was allowed to reach rt and stirred for 2 h. The suspension was filtered over a plug of Celite, and the filter cake was washed with methanol, carefully avoiding air to enter in contact with the mixture. The solvent was removed under vacuo (below 25 °C), yielding a light blue powder (89 mg, 94%): mp 144–

145 °C (decomp). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ : 10.44 (s, 1H, NH), 7.50–7.44 (m, 4H), 7.32–7.26 (m, 4H), 7.02 (t, J = 7.3 Hz, 2H), 6.62 (d, J = 3.0 Hz, 1H), 4.63 (s, 2H, NH_2) ppm. ^{13}C NMR (125 MHz, $\text{DMSO}-d_6$) δ : 137.3, 136.8, 133.0, 128.6, 128.3, 124.8, 123.8, 123.0, 122.6, 121.7, 104.6, 104.3 ppm. HRMS (ES) calcd for $\text{C}_{16}\text{H}_{13}\text{N}_2$ [$\text{M} - \text{H}$] $^-$ 233.1079, found 233.1073.

3,5-Diphenyl-1H-pyrrol-2-amine, 10-{ $1\text{-}^{15}\text{N}_1$ }. Compound 9-{ $1\text{-}^{15}\text{N}_1$ } (100 mg, 0.40 mmol) was dissolved in methanol (11 mL), and 10% Pd on activated charcoal (21 mg, 0.02 mmol) was added. The suspension was frozen using liquid nitrogen, and the apparatus was evacuated then filled with H_2 (1 atm). The mixture was allowed to reach rt and stirred for 2 h. The suspension was filtered over a plug of Celite, and the filter cake was washed with methanol, carefully avoiding air to enter in contact with the mixture. The solvent was removed under vacuo (below 25 °C), yielding a light blue powder (91 mg, 96%): mp 143–145 °C (decomp). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ : 10.44 (dd, J = 94.3, 3.1 Hz, 1H, ^{15}NH coupling), 7.50–7.45 (m, 4H), 7.32–7.26 (m, 4H), 7.05–7.00 (m, 2H), 6.64–6.61 (m, 1H), 4.63 (s, 2H, NH_2) ppm. ^{13}C NMR (125 MHz, $\text{DMSO}-d_6$) δ : 137.3 (d, J = 16.7 Hz), 136.8 (d, J = 1.7 Hz), 133.0 (d, J = 2.2 Hz), 128.6, 128.3, 124.8, 123.8, 123.0, 122.6 (d, J = 13.7 Hz), 121.7 (d, J = 1.0 Hz), 104.6 (d, J = 5.1 Hz), 104.3 (d, J = 3.6 Hz) ppm. ^{15}N NMR (60.8 MHz, $\text{DMSO}-d_6$) δ : –240.0 ppm. HRMS (ES) calcd for $\text{C}_{16}\text{H}_{13}\text{N}_2$ [$\text{M} - \text{H}$] $^-$ 234.1049, found 234.1047.

3,5-Diphenyl-1H-pyrrol-2-amine, 10-{ $2\text{-}^{15}\text{N}_1$ }. Compound 9-{ $2\text{-}^{15}\text{N}_1$ } (140 mg, 0.56 mmol) was dissolved in methanol (16 mL), and 10% Pd on activated charcoal (30 mg, 0.028 mmol) was added. The suspension was frozen using liquid nitrogen, and the apparatus was evacuated then filled with H_2 (1 atm). The mixture was allowed to reach rt and stirred for 2 h. The suspension was filtered over a plug of Celite, and the filter cake was washed with methanol, carefully avoiding air to enter in contact with the mixture. The solvent was removed under vacuo (below 25 °C), yielding a light blue powder (91 mg, 96%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ : 10.44 (s, 1H, NH), 7.51–7.45 (m, 4H), 7.31–7.26 (m, 4H), 7.02 (t, J = 7.3 Hz, 2H), 6.62 (d, J = 3.0 Hz, 1H), 4.63 (d, J = 77.4 Hz, 2H, $^{15}\text{NH}_2$ coupling) ppm. ^{13}C NMR (125 MHz, $\text{DMSO}-d_6$) δ : 137.3 (d, J = 12.2 Hz), 136.8, 133.0, 128.6, 128.3, 124.8, 123.8, 123.0, 122.6 (d, J = 0.9 Hz), 121.7, 104.6 (d, J = 2.1 Hz), 104.3 ppm. ^{15}N NMR (60.8 MHz, $\text{DMSO}-d_6$) δ : –337.1 ppm. HRMS (ES) calcd for $\text{C}_{16}\text{H}_{13}\text{N}_2$ [$\text{M} - \text{H}$] $^-$ 234.1049, found 234.1045.

Conversion of 10 into 2 in the Absence of NH_4OAc . A solution of 10 (40 mg, 0.17 mmol) in EtOH (4.3 mL) was heated under reflux for 18 h. The precipitate that was formed during the reaction was collected by filtration, washed with cold EtOH, and dried. Compound 2 (2.9 mg, 8%) was obtained as a dark blue solid. ^1H NMR (400 MHz, CDCl_3) δ : 8.06 (d, J = 7.4 Hz, 4H), 7.96 (d, J = 7.5 Hz, 4H), 7.57–7.51 (m, 4H), 7.50–7.41 (m, 6H), 7.39–7.34 (m, 2H), 7.21 (s, 2H) ppm. ES-MS: m/z [$\text{M} + \text{H}$] $^+$ = 450 (100%), 451 (36%), 452 (6%).

Conversion of 10 into 2 in the Presence of NH_4OAc . A solution of 10 (40 mg, 0.17 mmol) and NH_4OAc (0.46 g, 6.0 mmol) in EtOH (4.3 mL) was heated under reflux for 18 h. The precipitate that was formed during the reaction was collected by filtration, washed with cold EtOH, and dried. Compound 2 (21 mg, 56%) was obtained as a dark blue solid. ^1H NMR (400 MHz, CDCl_3) δ : 8.06 (d, J = 7.4 Hz, 4H), 7.96 (d, J = 7.5 Hz, 4H), 7.57–7.51 (m, 4H), 7.50–7.41 (m, 6H), 7.39–7.34 (m, 2H), 7.21 (s, 2H) ppm. ES-MS: m/z [$\text{M} + \text{H}$] $^+$ = 450 (100%), 451 (36%), 452 (6%).

Conversion of 10-{ $1\text{-}^{15}\text{N}_1$ } into 2-{ $1\text{-}^{15}\text{N}_1$ } in the Absence of NH_4OAc . A solution of 10-{ $1\text{-}^{15}\text{N}_1$ } (40 mg, 0.17 mmol) in EtOH (4.3 mL) was heated under reflux for 18 h. The precipitate that was formed during the reaction was collected by filtration, washed with cold EtOH, and dried. Compound 2-{ $1\text{-}^{15}\text{N}_1$ } (3.4 mg, 9%) was obtained as a dark blue solid. ^1H NMR (600 MHz, CDCl_3) δ : 8.08–8.05 (m, 4H), 7.98–7.95 (m, 4H), 7.56–7.52 (m, 4H), 7.49–7.46 (m, 2H), 7.45–7.41 (m, 4H), 7.38–7.34 (m, 2H), 7.22–7.20 (m, 2H) ppm. ^{15}N NMR (60.8 MHz, CDCl_3) δ : –176.2 ppm. ES-MS: m/z [$\text{M} + \text{H}$] $^+$ = 451.2 (100%), 452.2 (39%), 453.2 (10%).

Conversion of 10-{ $2\text{-}^{15}\text{N}_1$ } into 2-{ $1,6\text{-}^{15}\text{N}_2$ } in the Absence of NH_4OAc . A solution of 10-{ $2\text{-}^{15}\text{N}_1$ } (40 mg, 0.17 mmol) in EtOH (4.3 mL) was heated under reflux for 18 h. The precipitate that was formed during the reaction was collected by filtration, washed with cold EtOH, and dried. Compound 2-{ $1,6\text{-}^{15}\text{N}_2$ } (2.0 mg, 5%) was obtained as a dark blue solid. ^1H NMR (600 MHz, CDCl_3) δ : 8.08–8.05 (m, 4H), 7.98–7.95 (m, 4H), 7.57–7.52 (m, 4H), 7.50–7.46 (m, 2H), 7.45–7.41 (m, 4H), 7.38–7.34 (m, 2H), 7.22–7.20 (m, 2H) ppm. ^{15}N NMR (60.8 MHz, CDCl_3) δ : –86.2, –176.2 ppm. ES-MS: m/z [$\text{M} + \text{H}$] $^+$ = 452.2 (100%), 453.2 (37%), 454.2 (8%).

Conversion of 10-{ $2\text{-}^{15}\text{N}_1$ } into 2-{ $^{15}\text{N}_{\text{mixture}}$ } in the Presence of NH_4OAc . A solution of 10-{ $2\text{-}^{15}\text{N}_1$ } (40 mg, 0.17 mmol) and NH_4OAc (0.46 g, 6.0 mmol) in EtOH (4.3 mL) was heated under reflux for 18 h. The precipitate that was formed during the reaction was collected by filtration, washed with cold EtOH, and dried. Compound 2-{ $^{15}\text{N}_{\text{mixture}}$ } (21.9 mg, 57%) was obtained as a dark blue solid. ^1H NMR (600 MHz, CDCl_3) δ : 8.08–8.05 (m, 4H), 7.98–7.95 (m, 4H), 7.56–7.52 (m, 4H), 7.49–7.46 (m, 2H), 7.45–7.41 (m, 4H), 7.38–7.34 (m, 2H), 7.21 (s, 2H) ppm. ^{15}N NMR (60.8 MHz, CDCl_3) δ : –86.2, –175.7, –176.2 ppm. ES-MS: m/z [$\text{M} + \text{H}$] $^+$ = 450.2 (12%), 451.2 (50%), 452.2 (100%), 453.2 (43%), 454.2 (14%).

Reaction of 8-{ $1\text{-}^{15}\text{N}_1$ } and 10 To Form 2-{ $1\text{-}^{15}\text{N}_1$ } and 2. A solution of 8-{ $1\text{-}^{15}\text{N}_1$ } (8 mg, 0.036 mmol), 10 (8.5 mg, 0.036 mmol), and NH_4OAc (0.097 g, 1.26 mmol) in EtOH (0.9 mL) was heated under reflux for 24 h. The precipitate that was formed during the reaction was collected by filtration, washed with cold EtOH, and dried. Compound 2-{ $1\text{-}^{15}\text{N}_1$ } and unlabeled 2 (8.0 mg, 49%) were obtained as a dark blue solid. ^1H NMR (600 MHz, CDCl_3) δ : 8.08–8.05 (m, 4H), 7.98–7.95 (m, 4H), 7.56–7.52 (m, 4H), 7.49–7.46 (m, 2H), 7.45–7.41 (m, 4H), 7.38–7.35 (m, 2H), 7.22–7.20 (m, 2H) ppm. ^{15}N NMR (60.8 MHz, CDCl_3) δ : –176.3 ppm. ES-MS: m/z [$\text{M} + \text{H}$] $^+$ = 450.6 (91%), 451.7 (100%), 452.6 (26%), 453.6 (5%).

Reaction of 8-{ $1\text{-}^{15}\text{N}_1$ } and 1 To Form 2-{ $1\text{-}^{15}\text{N}_1$ }. A solution of 8-{ $1\text{-}^{15}\text{N}_1$ } (10 mg, 0.045 mmol), 1 (12 mg, 0.045 mmol), and NH_4OAc (0.12 g, 1.6 mmol) in EtOH (1.1 mL) was heated under reflux for 24 h. The precipitate that was formed during the reaction was collected by filtration, washed with cold EtOH, and dried. Compound 2-{ $1\text{-}^{15}\text{N}_1$ } (6.6 mg, 33%) was obtained as a dark blue solid. ^1H NMR (600 MHz, CDCl_3) δ : 8.08–8.05 (m, 4H), 7.98–7.95 (m, 4H), 7.56–7.52 (m, 4H), 7.49–7.46 (m, 2H), 7.45–7.41 (m, 4H), 7.38–7.34 (m, 2H), 7.22–7.20 (m, 2H) ppm. ^{15}N NMR (60.8 MHz, CDCl_3) δ : –176.2 ppm. ES-MS: m/z [$\text{M} + \text{H}$] $^+$ = 450.4 (5%), 451.5 (100%), 452.5 (34%), 453.5 (7%).

■ ASSOCIATED CONTENT

● Supporting Information

ESI-MS/MS of 2-{ $1\text{-}^{15}\text{N}_1$ }, 2-{ $6\text{-}^{15}\text{N}_1$ }. ^1H , ^{13}C , and ^{15}N NMR and ESI-MS of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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- (23) It is possible that other sites for nitrogen exchange exist at earlier stages of the reaction sequence that converts **1** into **2**.
- (24) Reflux of unlabeled **2** with $^{15}\text{NH}_4\text{OAc}$ in EtOH did not give rise to any ^{15}N label being introduced into the azadipyrromethene.
- (25) The reaction of **8**- $\{1\text{-}^{15}\text{N}_1\}$ alone in $\text{NH}_4\text{OAc}/\text{EtOH}$ did not give rise to product.
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