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Substituted pyrrole synthesis from nitrodienes

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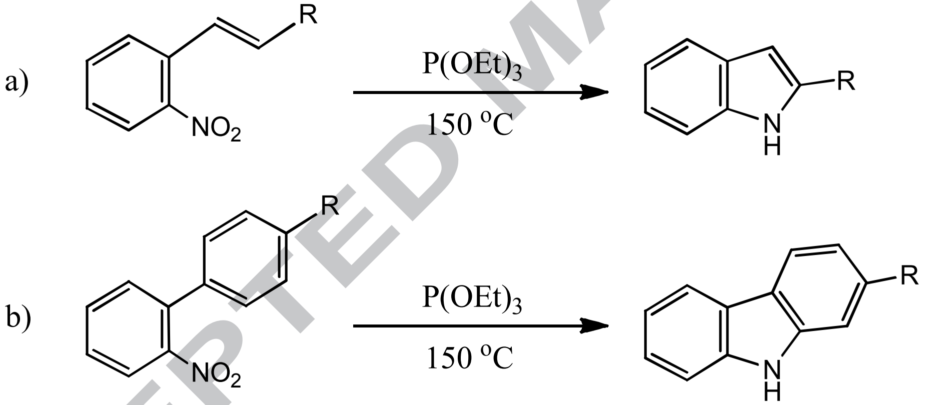
Abstract: Though the Cadogan-Sundberg approach has been employed to synthesize a variety of indole and carbazole derivatives from nitroarenes, surprisingly, very little is reported for making pyrroles using the same approach from non-arene nitrodienes. Herein, we report a general method to synthesize substituted pyrroles, in one step with modest yields, from nitrodienes using triphenylphosphine in the presence of an Mo catalyst, bis(acetylaceto)dioxomolybdenum (VI). To shed light on the mechanism of this reaction, we performed DFT calculations using uB3LYP/6-31+G(d) basis set and observed that the reaction favors a path through a nitrene intermediate.

Key words: Cadogan-Sundberg, nitrodienes, Mo catalyst, nitrene intermediate, DFT calculations

Introduction

The importance of pyrrole, a simple heterocycle, in medicinal and pharmaceutical chemistry is well documented.[1] The pyrrole skeleton is found in many natural products such as chlorophyll, hemoglobin, and indigo. Some of its substituted derivatives have biological activities and a trisubstituted derivative is a biosynthetic precursor to many natural products such as heme.[2] Pyrrole is also found in some marine natural products such as nakamuric acid[3] and chiral marinopyrroles which show activity against *Staphylococcus aureus* strains.[4] It is noteworthy that some of the derivatives of pyrrole are intermediates to many heterocyclic compounds such as chiral indolizidines.[5]

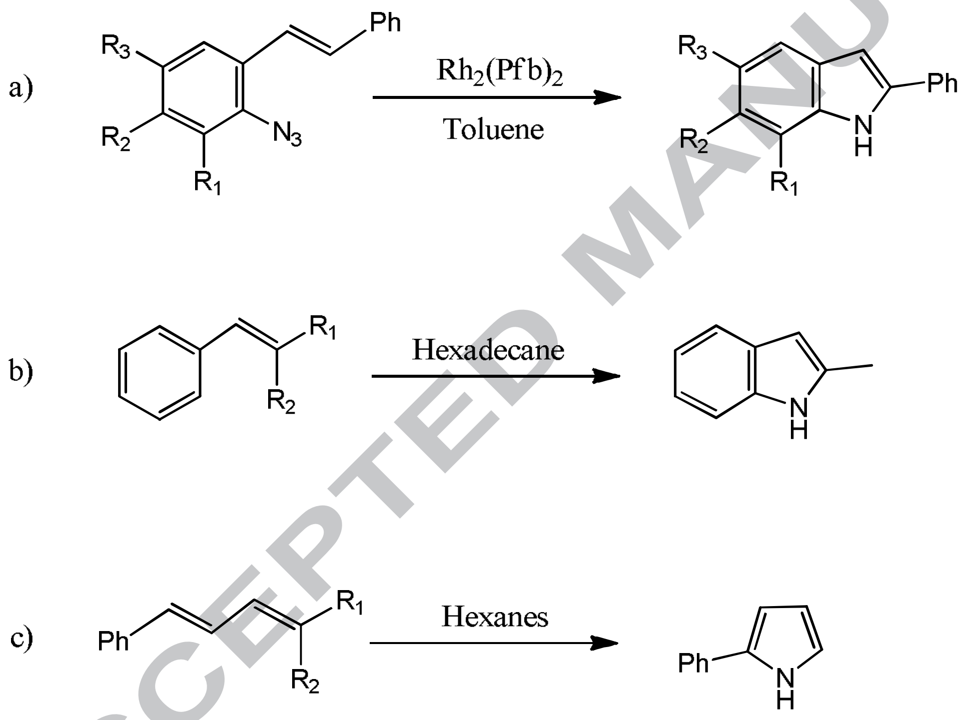
The Cadogan-Sundberg synthesis of indoles and carbazoles involves deoxygenation/cyclization of *o*-nitrostyrenes or *o*-nitrobiphenyls with a trialkyl phosphite.[6] For example, *o*-nitrostyrene is converted to indole (Scheme 1a),[6a] and *o*-nitrobiphenyl is converted to carbazole (Scheme 1b),[6c] using a reducing agent which produces a nitrene and/or a nitroso intermediate. A recent study on the mechanism of the Cadogan-Sundberg synthesis of indole from a nitroarene illustrates the presence of a nitroso intermediate through a labeling experiment.[6d] In a typical experiment, one dissolves the nitro compound in triethylphosphite and refluxes the mixture until the starting material is consumed, usually within 2-24 hrs. This method of indole synthesis is similar to that of the Leimgruber-Batcho approach except there is no need to prepare a dinitrostyrene before reduction, thus avoiding an extra step.[7] Reductive cyclization of *o*-nitrostyrenes to indoles has also been observed with many different reducing agents.[8]



Scheme 1. Synthesis of indoles and carbazoles using the Cadogan-Sundberg reaction

Another approach for making indoles and carbazoles involves reduction of nitroarenes with carbon monoxide in the presence of a metal catalyst (e.g. $Pd(OAc)_2$).[9] Of the two likely mechanisms of this reaction, one involving a nitroso derivative and the other a nitrene, the nitrene mechanism appears to be favored.[10]

Thermal decomposition of an organic azide has also been employed to synthesize indoles (from *o*- or β-azidostyrenes, as in Scheme 2a or Scheme 2b), carbazoles, and in particular, pyrroles from azido-dienes (Scheme 2c).[11] As noted, many pyrroles have been made from the appropriate azides, but the corresponding reactions of structurally similar nitro compounds have not been shown to produce simple pyrroles from nitrobutadienes, even though they are readily made! One must note that organic azides are potential explosives,[12] nitrodienes are safer to use.



R_1	R_2	R_3
H	H	F
H	H	OMe
H	H	Me
H	H	CF_3
H	Me	H
H	OMe	H

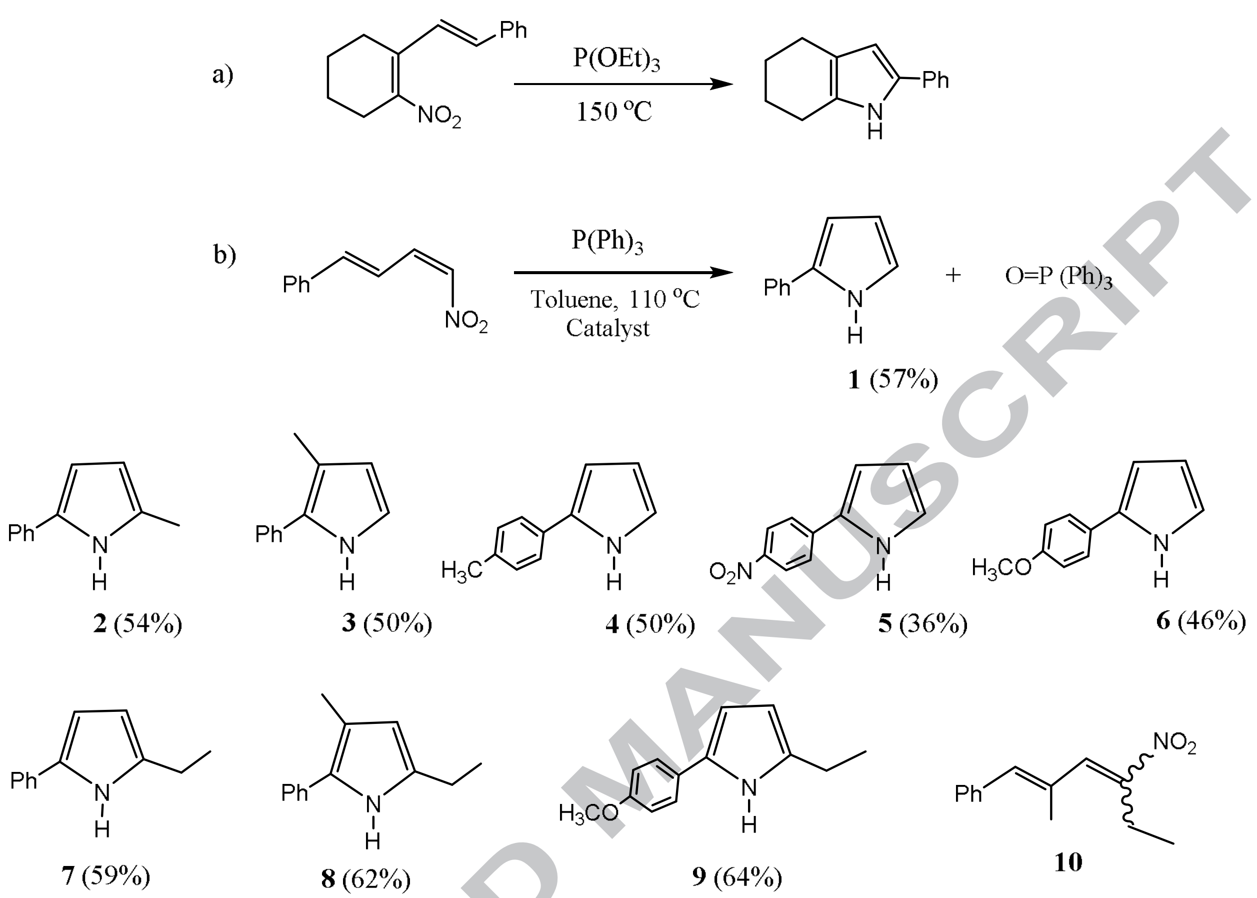
R_1	R_2
CH_3	N_3
N_3	CH_3

R_1	R_2
H	N_3
N_3	H

Scheme 2. Synthesis of indoles and pyrrole from azido-dienes

Results and Discussion

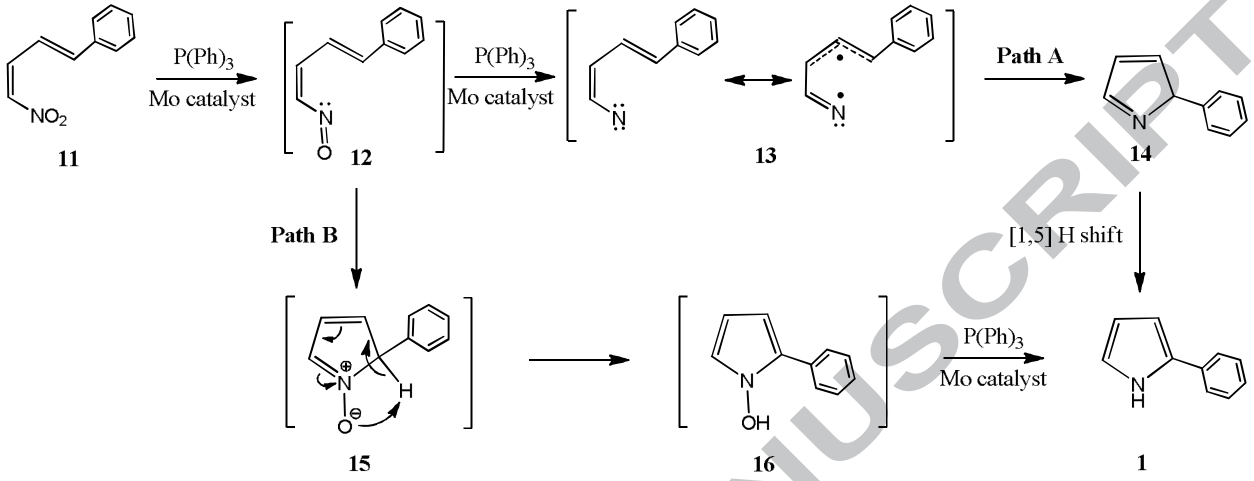
Although the Cadogan-Sundberg approach has been extensively used to synthesize indoles and carbazoles, to date, there is only one example found in the literature which uses this approach to convert a simple non-arene nitrodiene to a pyrrole derivative (Scheme 3a).[13] Therefore, we sought a general method to synthesize a series of pyrrole derivatives that would add to the lacking literature. With the traditionally used triethylphosphite as the reducing agent, our yield was unacceptably low (10-12%) for making the pyrrole derivatives from the corresponding nitrodienes. However, with triphenylphosphine in the presence of an Mo catalyst, bis-(acetylacetonato)dioxo-molybdenum (VI),[14] we were able to synthesize a number of known pyrrole derivatives from the corresponding nitrodienes. The nitrodiene precursors leading to compounds **1-9** were synthesized using the aldol condensation of an aldehyde with nitromethane, nitroethane, and nitropropane.[15] The nitrodiene **10** (mixture of E and Z), leading to pyrrole **8**, was the only unknown diene synthesized (29%) using the above procedure. The yields for the cyclization reactions for compounds **1**,[16] **2**,[17] **3**,[18] **4**,[19] **5**,[20] **6**,[21] **7**,[22] **8**,[23] and **9**[24] are listed in Scheme 3. To observe if the substituents on the aromatic ring have an effect on the yield of the reaction, we examined the effect of electron donating (CH_3, OCH_3) versus the electron withdrawing (NO_2) groups in the *p*-position. The yield of the cyclization reaction remained primarily unaffected. The low yield in **5**, however, is not surprising since the catalyst can also reduce the *p*-nitro group. It is noteworthy that the yields for the 2-ethyl substituted pyrroles (**7-9**) were actually higher compared to the 2-methyl substituted (**2** and **3**) or the unsubstituted derivatives at position 2 (**1**, **4**, **5**, and **6**).



Scheme 3. Cyclization reactions of nitrodienes

The use of dichlorodioxomolybdenum (VI) catalyst for the oxidation of thiols to disulfides with dimethylsulfoxide has been reported.[25] Based on this report, the authors extended their methodology to include synthesis of indoles and carbazole using the same catalyst.[14] They proposed that the mechanism of the cyclization of nitroaromatic compounds to the corresponding indoles and carbazoles involves a rapid oxidation of triphenylphosphine to triphenylphosphine oxide and reduction of Mo (VI) to Mo (IV). Subsequently, the Mo (IV) species reacts with the remaining Mo (VI) to form a dinuclear Mo (V) complex.[26] They further postulate that either the mononuclear Mo (IV) or the dinuclear Mo (V) can convert the nitroaromatic compound to the corresponding nitroso and then to the nitrene intermediate which then undergoes C-H insertion to afford indoles or carbazoles. Similarly, we suggest that our nitrodiene **11** undergoes reduction first to the corresponding nitroso-diene intermediate **12** (Scheme 4). Repeat of this step will convert **12** to the nitrene-diene intermediate **13**. C-H insertion in **13** produces **14** followed by 1,5-H shift to **1** (Path A). Alternatively, intermediate **12** can cyclize to give **15** (Path B).

Aromatization of **15** will produce the pyrrole-1-ol **16** which gets further reduced to **1**. We performed calculations to shed light on the mechanisms for the cyclization reactions *via* both the nitroso **12** and nitrene **13** intermediates, *vide infra*.



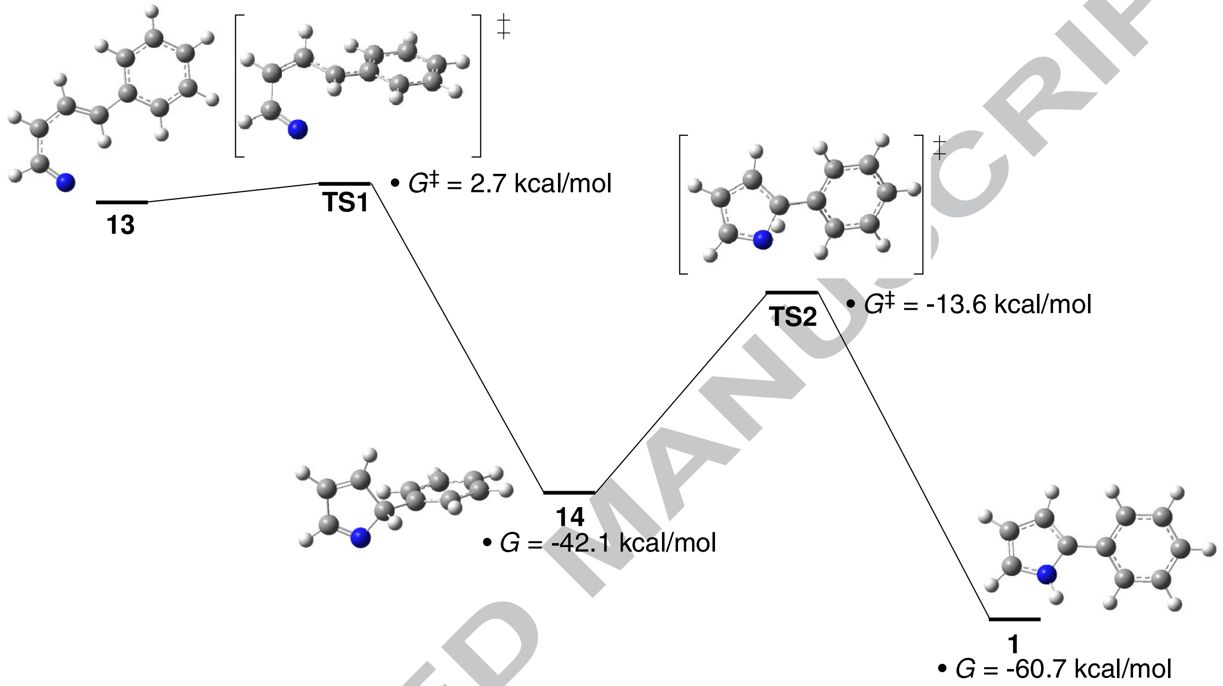
Scheme 4. Possible reaction paths for the cyclization of nitrodiene to pyrrole

Computational Methods. Gaussian 09 package[27] was employed to perform all the calculations. The calculations for optimizing the geometries were performed at the uB3LYP[28] functional and 6-31+G(d)[29] level of theory using broken symmetry wave function using the command Guess=(mix,always), and extra quadratic convergence for self-consistent field method (scf=xqc). The uB3LYP/6-31+G(d) level of theory has been used to study nitrenes and nitroso species alike.[30] The wavefunction of singlet nitrene was found to be unstable, and stability optimization calculation was performed (stable=opt). The energies from the stabilized wavefunction were obtained and used to calculate the energetics of the nitrene pathway (Path A, Scheme 4). The natures of all minima and first-order saddle points were verified by harmonic vibrational analyses. All first-order saddle points were confirmed *via* intrinsic reaction coordinates calculations.[31]

Computational Results. The energetics of Path A and Path B (Scheme 4) were computed at the uB3LYP/6-31+G(d) level of theory to determine which pathway is more favorable for the formation of pyrrole. The results are summarized in Figure 1. In Path A, the first step is the ring closure between N and the benzylic carbon to form **14**. The energy barrier ($\Delta G^{\ddagger}$) was calculated to be 2.7 kcal/mol, and the ΔG for the ring closure was calculated to be -42.1 kcal/mol. The [1,5]H-shift from **14** to **1** has a $\Delta G^{\ddagger}$ = -13.6 kcal/mol with respect to the **13**, or 28.5 kcal/mol from **14**, and the overall ΔG = -60.7 kcal/mol.

The alternative Path B, involving the ring closure of the nitroso intermediate **12** to **15**, requires $\Delta G^{\ddagger}$ = 10.3 kcal/mol, and the ΔG = -9.9 kcal/mol. Intramolecular proton transfer followed by aromatization of **15** to **16** required $\Delta G^{\ddagger}$ = 43.8 kcal/mol with respect to the nitroso intermediate **12** (or 53.7 kcal/mol with respect to **15**), and the overall ΔG = -19.8 kcal/mol.

Path A



Path B

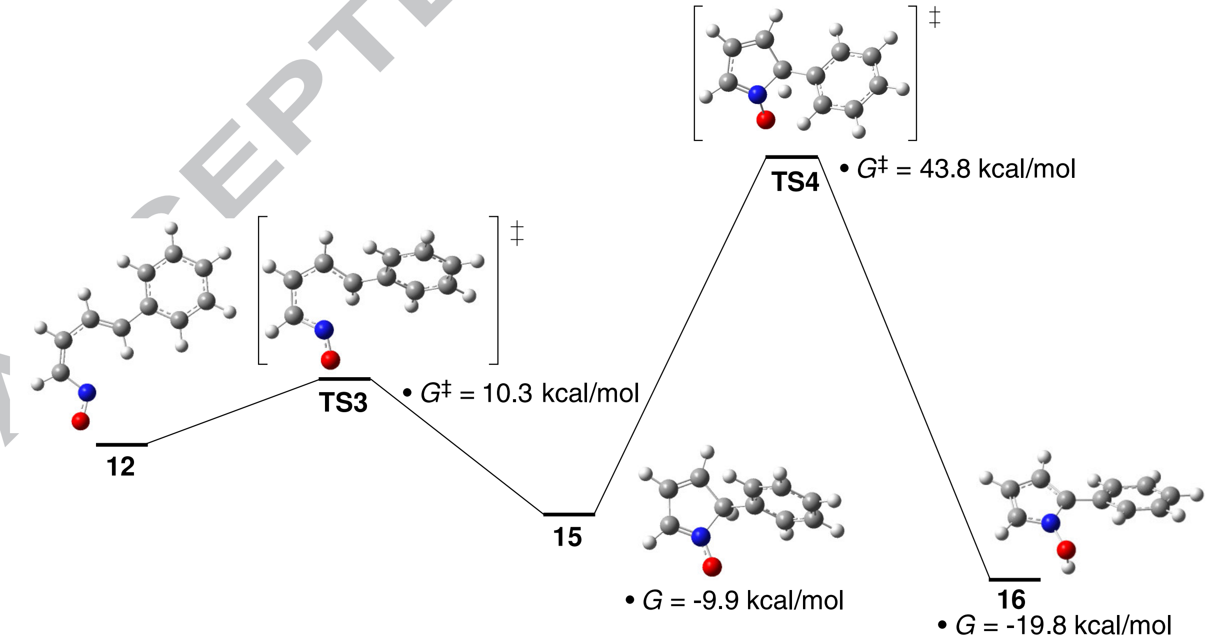


Figure 1. uB3LYP/6-31+G(d) energetics of cyclizations involving intermediates **12** and **13**.

Conclusion

We have shown that the Cadogan-Sundberg approach towards the synthesis of indoles and carbazoles can be applied to synthesize pyrroles. Though the reaction works with both $P(OEt)_3$ and PPh_3 in poor yields (12-14%), the yield improves considerably (50-60%) in the presence of the Mo catalyst. Based on the computational results, the pathway involving the nitrene intermediate is found to be more energetically favored compared to the nitroso intermediate, consistent with the widely accepted nitrene path leading to the indole and carbazole derivatives.

Typical experimental procedure

In a typical experiment, Mo catalyst (5 mol%, 0.014 mmol), bis(acetylaceto)dioxomolybdenum (VI), was added to a solution of nitrodiene (0.28 mmol) and Ph_3P (0.67 mmol) in toluene (3 mL). The mixture was refluxed (1.5-2.5 hrs) until the starting material was consumed as indicated by TLC. After completion of the reaction, solvent was removed. The residue was chromatographed on silica gel using hexanes first to remove unreacted PPh_3 and later by 1% EtOAc/hexanes to obtain the substituted pyrrole product. All pyrrole compounds gave satisfactory spectroscopic and analytical data as compared to the literature.

Compound 10: ((1E,3E)-2-methyl-4-nitrohexa-1,3-dien-1-yl)benzene and ((1E,3Z)-2-methyl-4-nitrohexa-1,3-dien-1-yl)benzene. To a mixture of commercially available (Aldrich) α-methyl-trans-cinnamaldehyde (3.2063 g, 22 mmol) and nitropropane (30mL) was added ammonium acetate (0.6 g). The solution was heated to 110 °C for 3hr. Evaporation of excess nitropropane followed by purification of the crude on silica gel (2% EtOAc/hexane) gave 1.3793 g (29%) of compound **10** as an oil as a mixture of E and the Z isomers.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ isomer 1: 0.95 (3H, t, J = 7.4 Hz), 2.08 (3H,s), 2.81 (2H, q, = 7.4 Hz), 6.65 (1H, s), 7.13 (2H, d, J = 8.0 Hz), 7.21 (1H, t, J = 7.2 Hz), 7.24 (2H, t, J =7.2 Hz), 7.70 (1H, s) & isomer 2: 1.14 (3H, t, J = 7.4 Hz), 2.08 (3H,s), 2.59 (2H, q, = 7.4 Hz), 6.76 (1H, s), 7.25 (1H, t, J = 7.2 Hz), 7.26 (2H, d, J = 7.2 Hz), 7.32 (2H, t, J =7.2 Hz), 7.61 (1H, s)

^{13}C NMR: ($CDCl_3$, 100 MHz) δ isomer 1: 12.4, 21.2, 23.5, 128.0, 128.49 (2C), 129.2 (2C), 129.7 (q), 133.1, 136.4 (q). 136.5, 153.3 (q) & isomer 2: 13.4, 17.4, 21.1, 128.1, 128.47 (2C), 129.5 (2C), 131.3 (q), 136.2 (q), 138.0, 138.9, 152.1 (q)

ESI-HRMS (m/z) for $C_{13}H_{15}NO_2$ (exact mass 217.1103): [M+H]+ calc. 218.1176, obs. 218.1176.

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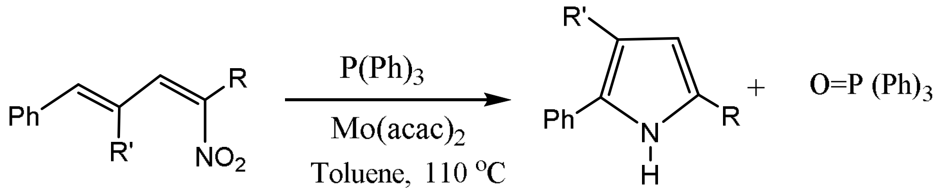
The Professional Staff Congress of the City University of New York is acknowledged for financial support of this work. E. M. G. and K. K. acknowledge support from the donors of the Petroleum Research Fund of the American Chemical Society, Grant No. 54244-UR4. Computational support was provided by the Extreme Science and Engineering Discovery Environment (XSEDE), which is supported by the National Science Foundation Grant No. ACI01053575.

References and notes

- A general method to make pyrroles from nitrodienes, in one step, is reported.
- The yield of cyclization is increased with the use of Mo catalyst.
- DFT calculations supports a reaction path through a nitrene intermediate.



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