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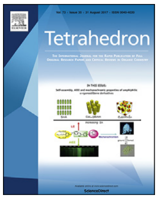

Nitrene insertion into an adjacent *o*-methoxy group followed by nucleophilic addition to the heterocumulene intermediate: Experimental and computational studies

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ABSTRACT

The chemistry of aryl azides and aryl nitrenes is rich and varied in nature with different products being obtained with minor changes in reaction conditions. Thermolysis of azido- dimethylsuccinylosuccinate has been carried out to study the behaviour of this new azide during thermolysis. The products obtained have been studied by various spectroscopic and DFT calculations. These results reveal formation of compound-**II** and compound-**III** from the nitrene intermediate (**1**) generated during the thermolysis process. DFT results rationalized the formation of thermodynamically stable compound-**II** and compound-**III** from the stable intermediates **2** and **4** formed during the thermolysis process. Further, DFT results suggest that the reaction between **4** and **2** is thermodynamically more favourable compared to the further thermal degradation of the intermediate **4** to pyridylcarbene (**4b**) and carbene intermediate (**5**), which corroborates that such products were not formed during thermolysis.

1. Introduction

Aryl azides have been studied extensively and their rich chemistry has a long history.[1] Azides are now considered as “green” reagents, as most of their reactions involve only a benign loss of nitrogen.[2] On the other hand, in the ‘Click’ reaction all the three nitrogen atoms are retained.[3] Aryl azides are reactive and many short-lived intermediates are commonly generated by both photochemical and thermal decomposition of aryl azides. Aryl nitrenes are known to lead to a myriad of possible intermediates yielding products which are often accompanied by tarry resinous materials, posing a major challenge in obtaining pure products. The initially formed singlet nitrene usually rearranges to the more stable triplet nitrene, via other intermediates like the benzazirine and heterocumulene intermediates, whose formation could be regiospecific in some cases. The presence of nucleophiles assists in the formation of 1H- and 3H-azepines. Substituents are known to play a most “mysterious” role[4] and even “a slippery potential energy surface”[5] has been proposed for these reactions. It is known that only nitrile and methoxy carbonyl functionalities do not provide any rate acceleration to intramolecular cyclization and thus o-azido benzoate “reacts in other ways”.[6] Alternatively, ring extrusion may yield the corresponding pyridylcarbenes.[7] Even the formation of cyano-substituted cyclopentadienes is known in these reactions (Scheme 1).

The formation of diazadecaflourofulvalene during the thermolysis of pentaflouro phenyl azide presumably proceeds via the singlet nitrene.[8] The triplet pathway, on the other hand, leads to the formation of the corresponding amine and azo compounds. This

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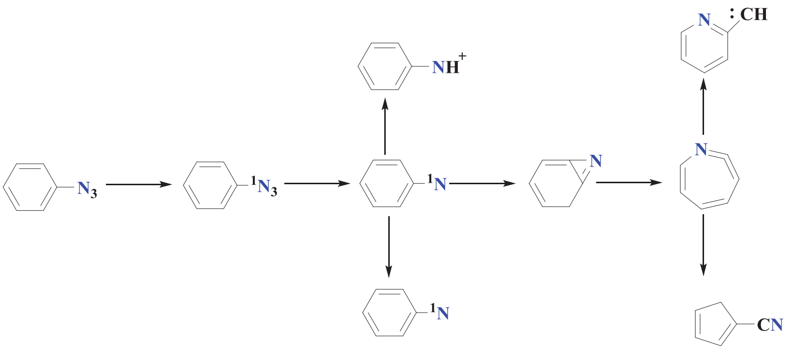

Scheme 1. Schematic representation of the intermediates formed during the photolysis and thermolysis of an aryl azide.

has led to the understanding that the two ortho flanking fluorine atoms, in this case, raises the singlet-triplet gap by 8 kcal/mole.[9]

Nitrenes which are relatively ‘long lived’ show enhanced intermolecular reaction rates and could lead to more efficient photo affinity labelling agents.[10] Such reagents are now commercially available. Nitrenes from perflourophenylazide have found application in materials science, nanotechnology and photovoltaics.[11] We have used such azides for photo-microlithography,[12] photovoltaics.[13] Aryl azides are used for synthesis of new hetero bifunctional crosslinkers.[14] The latter are useful for chemical cross linking-mass spectrometry-bioinformatics as a tool for studying protein-protein interactions and origin of diseases (e. g. cataractogenesis).[15]

Work from our laboratory has shown that thermolysis of ‘azido-*meta*-hemipinate’, in the absence of any added nucleophile leads to concomitant ring expansion and ring extrusion.[16] This has been described as “a most unusual reaction involving a series of involved rearrangement reactions”.[17] The life span of one such transient was later measured by ultra- fast spectroscopy (II) to be 700 ps.[18] Formation of three different products, presumably via a ‘long-lived’ singlet nitrene and concomitant nitrene and carbene insertion in the same reaction has been demonstrated.[19] The thermolysis of ‘azido-*m*-meconine’ leads to the formation of a benzoxazole via an intramolecular nitrene insertion into the adjacent methoxy substituent.[20] In our quest to understand the role of substituents in altering the reaction pathway, involving the formation of nitrenes, we carried out the thermolysis of ‘Azido- dimethyl succinylosuccinate’. This azide is the *para*- analogue of the “azido-*meta*-hemipinate” studied by us previously. The aim of the study was to analyze the effect of the position of the substituents on the formation of the nitrene intermediate and to study changes in the products, if any.

In the present work, Dimethyl succinylosuccinate,[21] the starting material (Scheme 2) was subjected to aromatization, followed by methylation, nitration, reduction and diazotization- displacement which yielded Dimethyl-3-Azido-2,5-dimethoxy-terephthalate (‘Azido-dimethyl succinylosuccinate’). Thermolysis of this aryl azide, **I**, led to the isolation of compound-**II** and compound-**III** (Scheme 3), which have been isolated with much difficulty from a complicated mixture containing much polymeric tarry material.

The absence of any broad signal in ^{1}H- NMR spectrum of the two compounds, clearly ruled out the possibility of any amine formation and any products from the triplet pathway. The two compounds isolated are proposed to be ‘dimeric’ and ‘trimeric’ products of the starting nitrene intermediate. Compound-**II** and compound–**III** have been characterized spectroscopically and their structures are discussed here.

2. Results and discussion

Compound-**II** and compound-**III** were isolated from the reaction mixture and analyzed spectroscopically, especially using 2D- NMR and Mass Spectrometry. HRMS for compound-**II** was observed to be, $M + H^+ = 535.1465$. Its ^{1}H NMR (400 MHz) spectrum showed seven methoxy signals between δ 3.5 to δ 3.9. It also showed the presence of five protons at δ 4.99(s), δ 5.9 (d, $J = 3.6$ Hz), δ 6.13 (s), δ 6.6 (d, $J = 3.6$ Hz), δ 7.09 (s). No broad signal due to NH was observed. Its ^{13}C NMR spectrum showed the presence of seven different methoxycarbonyl groups and methoxy signals. The DEPT-135 spectrum showed a downward peak at 86.76 ppm which correlated (HSQC) with the two doublets of the CH_2 protons at δ 5.9 and δ 6.6. The HSQC spectrum helped in assigning the olefinic and aromatic CH bearing carbons along with the new carbons generated. Further, the HMBC spectrum helped in assigning the methoxy and methoxy carbonyl groups on the basis of their correlation with the carbonyl and other quaternary carbons. The compound in its ^{1}H NMR spectrum (see the Supplementary Material) showed the presence of seven methoxy/methoxycarbonyl signals from δ 3.49 to δ 3.88. Along with this, five different olefinic/aromatic signals were seen at δ 4.99, 5.9 (d), 6.13, 6.6 (d), 7.09. The coupling constant of the two protons at δ 5.9 and δ 6.6 was 3.6 Hz.

The ^{13}C NMR (see the Supplementary Material) showed eight peaks in the region of 50.7–56.5 ppm, out of which we expect seven signals to be that of methoxy/methoxycarbonyl group. A ‘new’ peak at 87 ppm was seen together with olefinic and aromatic CH bearing carbons at 101 and 108 ppm, respectively.

DEPT-135 spectrum (see the Supplementary Material) showed that the signal at 86.66 ppm belongs to a methylene (CH_2) group. It also points towards the CH bearing olefinic and aromatic carbons at 101.02 and 107.2 respectively. Eight different signals are seen in the methoxy/methoxycarbonyl region which may involve the presence of a new carbon centre as well.

The HSQC spectrum (see the Supplementary Material) showed correlations between the seven methoxy signals seen in ^{1}H & ^{13}C NMR spectra. It also showed correlations between δ 4.9 and 54.3 ppm which indicated that this is a ‘new’ carbon centre generated. The doublets at δ 5.9 and δ 6.6 correlated with the downward peak in DEPT-135 i.e. 86.66 ppm which confirmed that these two protons have a same carbon centre i.e. a CH_2group. The olefinic proton at δ 6.1 showed correlation with 101.02 ppm and the aromatic proton at δ 7.09 with 107.2 ppm, which confirmed that these two are CH bearing carbons in the compound.

The HMBC spectrum (see the Supplementary Material) showed correlations between methoxy and methoxycarbonyl groups with the neighbouring carbons (max. 4 bond distance). It helped in pointing out the methoxycarbonyl groups based on its correlations