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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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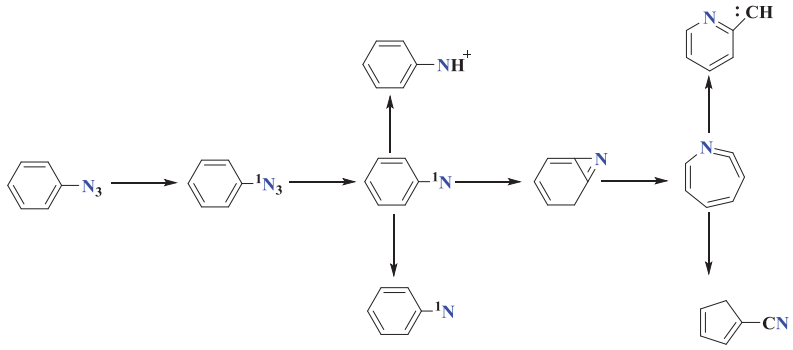


Scheme 1. Schematic representation of the intermediates formed during the photolysis and thermolysis of an aryl azide.

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

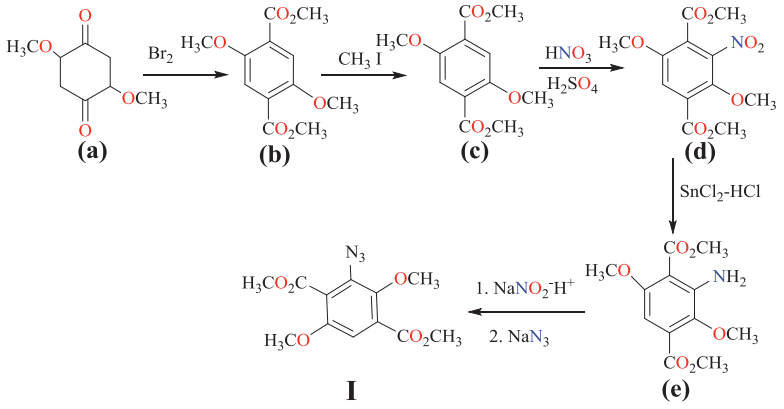
Compound-**II** and compound-**III** were isolated from the reaction mixture and analyzed spectroscopically, especially using 2D- NMR and Mass Spectrometry. HRMS for compound-**II** was observed to be, $M + H^+ = 535.1465$. Its ^{1}H NMR (400 MHz) spectrum showed seven methoxy signals between δ 3.5 to 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.

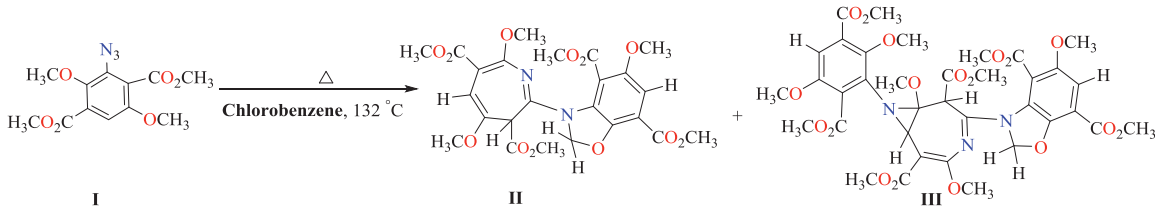
DEPT-135 spectrum (see the Supplementary Material) showed that the signal at 86.66 ppm belongs to a methylene (CH_2) group. It also points towards the CH bearing olefinic and aromatic carbons at 101.02 and 107.2 respectively. Eight different signals are seen in the methoxy/methoxycarbonyl region which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



Scheme 2. Synthesis of dimethyl-3-azido-2,5-dimethoxybenzene-1,4-dicarboxylate.



Scheme 3. Formation of the new compound-**II** and compound-**III** from the thermolysis of "azido-dimethyl succinylosuccinate", **I**.

with the four different carbonyl signals from 164.15 to 166.35 ppm. Together with this, a correlation between the aromatic proton at δ 7.09 and 117 ppm was also seen. HRMS analysis (see the Supplementary Material) confirmed that the compound is 'dimeric' in nature with m/z = 535.1465 $[M+H]^+$ and m/z = 557.1316 $[M+Na]^+$. Hence, the molecular weight of the compound is 534 Da. The structure of the new compound, as evident from its NMR and HRMS studies revealed that azido dimethyl succinylosuccinate behaves similar to "azido-*meta*-hemipinate". In this case as well, a 'dimeric' compound would have been expected to show a total of eight methoxy signals instead of seven observed. The absence of any broad signal (NH) excluded nitrene insertion which was further confirmed by the absence of formation of the corresponding azo compound or the amine via the triplet nitrene pathway. A 'missing' signal in the methoxy/methoxycarbonyl region is evident. Generation of a 'new' carbon at 86.66 ppm, which is actually a CH_2 was confirmed by DEPT-135 analysis and in HSQC a correlation between this and the doublet protons at δ 5.9 and δ 6.6 clearly indicating that these were geminal protons with coupling constant, J = 3.6 Hz.

Based on the detailed NMR and HRMS studies, the structure for compound-**II** is proposed (Scheme 2). NMR assignment for compound-**II** is shown in Table 1 and Table 2. Fig. 1 represents the atoms numbered for NMR assignment.

The first clue for the possible insertion product was obtained by the presence of 5 different signals in olefinic/aromatic region with

Table 2
HSQCand HMBC correlations for compound-**II**.

HSQC	HMBC
δ 3.49–51.7	δ 3.67–138.9
δ 3.50–53.7	δ 3.50–156.47
δ 3.52–50.9	δ 3.80–152.0
δ 3.64–50.5	δ 3.87–164.15
δ 3.67–56.4	δ 3.52–164.2
δ 3.80–56.5	δ 3.64–167.8
δ 3.88–52.03	δ 3.49–166.35
δ 4.9–54.3	δ 7.09–117
δ 5.9 and 6.6–86.66	
δ 6.1–101.02	
δ 7.09–107.2	

Table 1
^{1}H NMR, ^{13}C NMR and DEPT-135 data for compound-**II** with the assignments of the corresponding protons and carbon atoms.

^{1}H NMR	Assignment	^{13}C NMR (ppm)	Assignment	DEPT-135	^{13}C NMR (ppm)	Assignment	DEPT-135
δ3.49 (s)	H6′	51.7	C 6′	Up	117	C 12	QC
δ3.50 (s)	H 5′	53.7	C 5′	Up	138.9	C 2	QC
δ3.52 (s)	H 3′	50.9	C 3′	Up	152.0	C 14	QC
δ3.64 (s)	H 12′	50.5	C 12′	Up	156.47	C 5	QC
δ3.67 (s)	H 2′	56.4	C 2′	Up	164.15	Carbonyl carbon	QC
δ3.80 (s)	H 14′	56.5	C 14′	Up	164.2	Carbonyl carbon	QC
δ3.88 (s)	H 15′	52.03	C 15′	Up	167.8	Carbonyl carbon	QC
δ4.9 (s)	H6	54.3	C 6	Up	166.35	Carbonyl carbon	QC
δ5.9 (d)	H 9	87	C 9	Down			
δ6.1 (s)	H 4	101	C 4	Up			
δ6.6 (d)	H 9′	107.2	C 13	Up			
δ7.09 (s)	H 13						

QC = quaternary carbon.

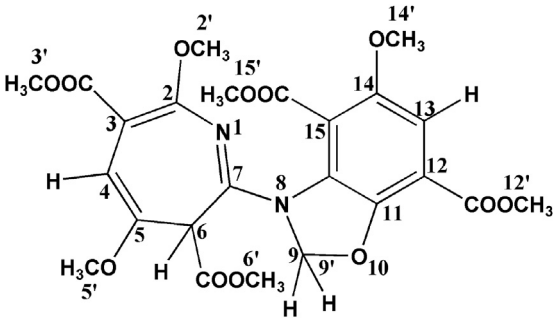


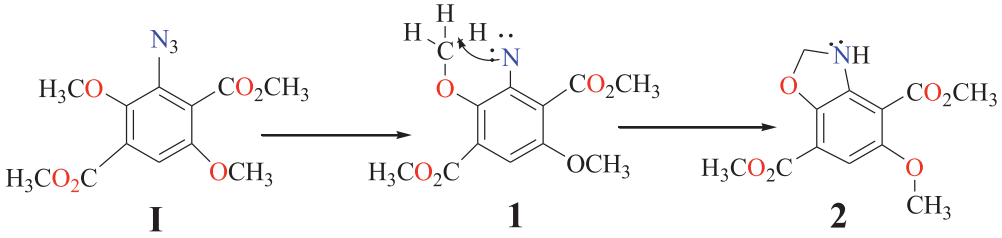
Fig. 1. Structure of the compound-**II** for NMR assignments.

two splitting each other (J = 3.6 Hz) in ^{1}H NMR spectrum and its correlation with 86.66 ppm signal in ^{13}C NMR which is a CH_2 signal in DEPT-135. The HSQC spectrum showed a correlation between the olefinic type proton at δ 4.9 with 54.3 ppm indicating the formation of a new carbon centre in the azepine ring possibly formed via the ring expansion followed by the intermolecular nucleophilic addition. The HMBC spectrum confirmed that the 'loss' of a signal in methoxy/methoxycarbonyl region is that of a methoxy group as the four correlations were seen with carbonyl groups.

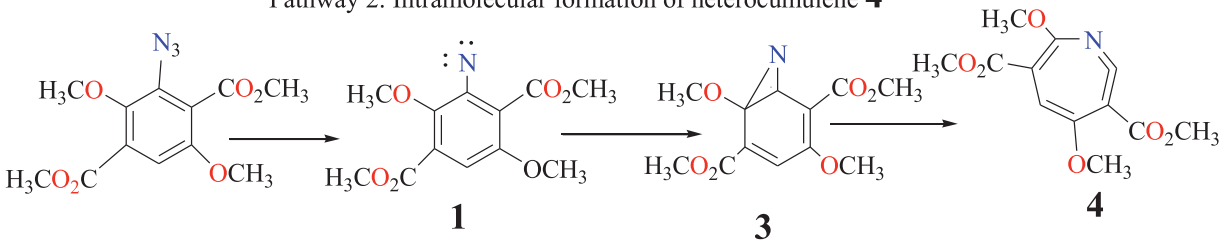
Herein, we propose the formation of the nitrene intermediate (**1**) during the thermolysis which as in the earlier two cases, remain in the singlet state long enough to undergo the intermolecular reaction and does not flip to the triplet state. The mechanism is similar to the regiospecific conversion of the nitrene to the benzazirine (**3**) and heterocumulene or cyclic ketenimine (**4**) intermediates, as proposed by us in an earlier case (Scheme 4).[16] The nitrene generated further undergoes an insertion into the neighbouring methoxy group resulting in the formation of a nucleophilic amine i.e. an analogous benzoxazolidine (**2**) which undergoes an intermolecular reaction to the heterocumulene intermediate, thereby yielding compound-**II** (Scheme 4).

The 'trimeric' compound-**III** was also isolated from this reaction and was subjected to spectroscopic studies. Its mass spectrum showed the molecular ion peak [M + H+$^+$] at m/z = 802, confirming its 'trimeric' nature and indicating that the m/z value for the molecular ion to be m/z 801. Its HRMS showed a peak at m/z 825.136 (M^++K (39)−CH_3) again confirming the 'trimeric' nature of compound-**III**. MS/MS of the m/z 825.138 peak, showed a peak at m/z 781.1678, formed by the loss of $-CO_2CH_3$ [M^++K (39)−CO_2CH_3], (see Supplementary Material) from the molecular ion, which itself is not observed. In the ^{1}H NMR spectrum, signals in the aromatic region were observed at δ 7.036 and δ 7.188. Five different signals were seen in the region from δ 4.943 to 6.1 regions, reminiscent of nitrene insertion into the adjacent *ortho*-methoxy group, discussed in our earlier paper.[19] In addition, a signal due to a CH_2 group was also observed in this region. The DEPT-135 spectrum showed a signal at 53.85 due to the new CH_2, generated from the *ortho*-methoxy group after the nitrene insertion. Compound-**III** showed signals in the methoxy region (δ3.447 to 3.996). In the HSQC spectrum, the signal at 48.86 correlated with the signal in the ^{1}H NMR spectrum at δ 4.945. Similarly, the signal at 57.30 ppm correlated with the CH signal in ^{1}H NMR spectrum at δ 5.555. The new CH_2 generated at 88 ppm after nitrene insertion, shows one hydrogen at δ 5.505 and other at δ 5.555. In the HMBC spectrum, no correlation was observed between any of the aliphatic hydrogen

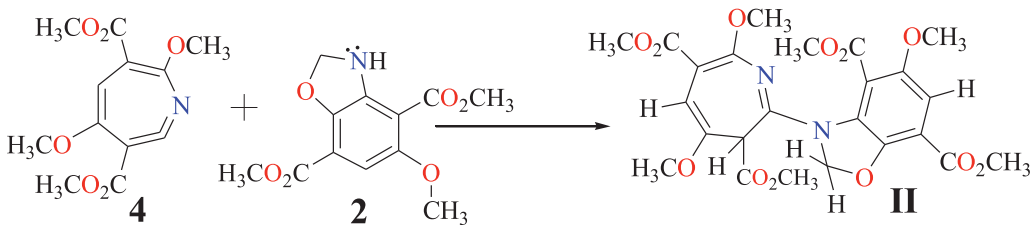
Pathway 1: Intramolecular nitrene insertion into the adjacent methoxy group leading to the secondary amine **2**



Pathway 2: Intramolecular formation of heterocumulene **4**



Pathway 3: Formation of Compund-**II** via nucleophilic addition.



Scheme 4. Proposed mechanism for the formation of compound-**II** via intramolecular nucleophilic addition of the secondary amine **2** on heterocumulene **4**.

with a methoxy or methoxycarbonyl group. Apart from the above discussion, complete assignments for compound III were not undertaken. This would require a very detailed NMR study because inversion of the lone pair on the nitrogen of the aziridine ring coupled with tautomeric possibilities in the central seven membered ring will have to be taken into consideration. Thus the aryl nitrene intermediate further attacks compound-**II** leading to the formation of the three membered fused aziridine structure-**III** (Scheme 5). Computational studies using Gaussian 09 software were then undertaken to confirm these conclusions.

We have examined the formation of compound-**II** and compound-**III** from azido-dimethyl succinylosuccinate during the thermolysis using DFT calculations (Scheme 3) with the B3LYP/6-31 + G(d,p) level of theory in chlorobenzene solvent. The nitrene intermediate (1) can also form other intermediate during the thermolysis process (Scheme 4). This Scheme 4 shows the formation of benzoxazolidine analogue and seven membered cyclic-ketenimine intermediates from **1**. However, there are other possibilities, where cyclic-ketenimine can further undergo to carbene 5 or else to pyridylcarbene **4b** (Scheme 1 and Fig. 2).

The potential energy surface generated for the formation of these intermediates is given in Fig. 2 using B3LYP/6-31+(d,p) level of theory in chlorobenzene solvent. The nitrene intermediate (**1**) can easily be converted to the benzoxazolidine (**2**) intermediate via a concerted proton transfer from the methoxy group to nitrene nitrogen and then the N–C bond formation.[20] The free energy barrier, calculated using Equation (1), for the formation of benzoxazolidine (**2**) is 6.5 kcal/mol (TS1), and the intermediate **2** is remarkably stable by 65.2 kcal/mol (Fig. 2). The nitrene **1** can also form ketenimine **4** via benzazirine (**3**) intermediate. The free energy barrier for the formation of benzazirine (**3**) intermediate is 12.0 kcal/mol, which subsequently leads to seven membered cyclic-ketenimine via small energy barrier 2.3 kcal/mol (TS3, Fig. 2). The ketenimine intermediate is energetically stable by 11.7 kcal/mol compared to the nitrene (**1**).

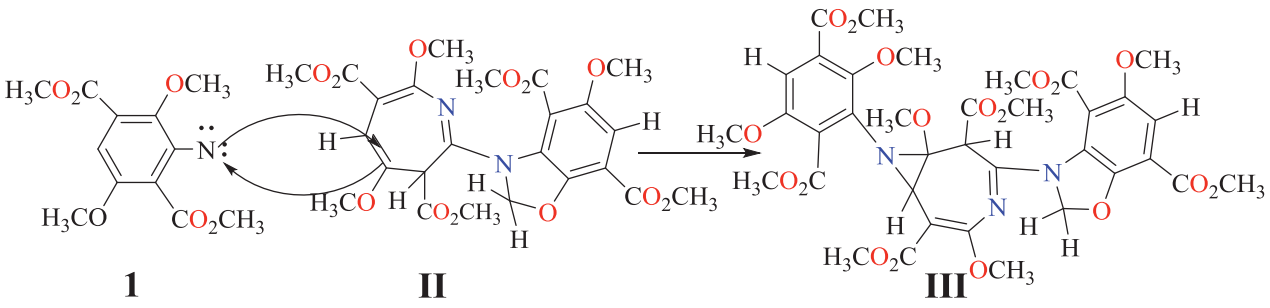
The ketenimine intermediate (**4**) is relatively less stable compared to the benzoxazolidine intermediate (**2**) and hence would be more reactive in nature. The intermediates **2** and **4** can react with each other and can lead to compound-**II**. The potential energy surface calculated for the formation of compound-**II** suggests that this is a 2 step process. In the first step, the nitrogen lone-pair of **2** attacks the carbon centre of ketenimine to form the intermediate **6**. The calculated activation barrier is ~18.0 kcal/mol. The intermediate 6 further undergoes proton transfer process, which leads to the formation of compound-**II** (Fig. 3). This result suggests that the formation of compound-**II** is thermodynamically feasible. This compound-**II** can also react with the nitrene intermediate generated from aryl azide **I,** which leads to the formation of compound-**III** (Figs. 3 and 4). The formation of **III** is a single step process and is thermodynamically stable. The activation free energy barrier for the formation of the compound–**III** is 38.9 kcal/mol compared to the reactants **II** and **I**. The experimental observations show that the compounds-**II** and –**III** formed is thermodynamically feasible upon thermolysis of aryl azide (**I**).

Thermolysis of the azido-dimethyl succinylosuccinate **I** can lead to the formation of product **II** and **III** through concomitant bond breaking and making process along with ring expansion and ring extrusion during the thermolysis process. However, there is a possibility that pyridylcarbene (**4b**) and carbene (**5**) intermediates can also form from the cyclic-ketenimine intermediate (**4**). The carbene intermediate is ~16.0 kcal/mol less stable than **4**, whereas the pyridylcarbene intermediate is 9.0 kcal/mol unstable (Figs. 2 and 4). These results indicate that the formation of the carbene intermediates would be less likely in this case as the stable intermediate **4** formed from **1** can immediately react with the **2**. The experimental results reveal that only compounds-**II** and compound-**III** form under this condition and no products were obtained containing the carbene intermediates.

3. Conclusions

Thermolysis of azido dimethyl succinylosuccinate was carried out to study the behaviour of this new azide during thermolysis to compare the products obtained in our earlier work on the thermolysis of 'azido-*m*-hemipinate'. The products obtained have been studied by various spectroscopic & computational methods techniques and based on these their structures proposed. Compound-**II** obtained in this study, is 'dimeric' in nature with an evidence for the insertion of the nitrene intermediate into neighbouring *o*-methoxy group resulting into the formation of a nucleophilic oxazole ring which further adds intermolecularly to the 7-membered heterocumulene intermediate to give compound-**II**. Compound-**III** is 'trimeric' in nature and is presumably formed via the addition of nitrene**1**to the double bond in compound-**II**, resulting in the formation of the fused aziridine ring in compound-**III**.

The DFT calculations with B3LYP/6-31 + G(d,p) level of theory in chlorobenzene solvent have been carried out to examine the thermal degradation of the **I**. Nitrene intermediate (**1**), obtained during the thermolysis, further decomposes to the stable benzoxazolidine intermediate (**2**) and cyclic-ketenimine intermediate (**4**). The computational calculations show that **4** and **2** intermolecularly react to form the compound-**II**. Compound-**II** can further react with nitrene intermediate (**1**) to form the compound-**III** via a nitrene addition to an alkene bond of compound-**II**. The DFT calculations suggest that the compound-**II** and compound-**III** are thermodynamically stable by 9.0 kcal/mol and 17.2 kcal/mol, respectively. The cyclic ketenimine intermediate could further thermally degrade to pyridylcarbene (**4b**) and carbene intermediate (**5**). However, the carbene intermediate is unstable by ~16.0 kcal/mol compared to **4**, whereas, the pyridylcarbene intermediate, on the potential energy



Scheme 5. Formation of compound-**III** by attack of the aryl nitrene intermediate on the double bond of compound-**II**.

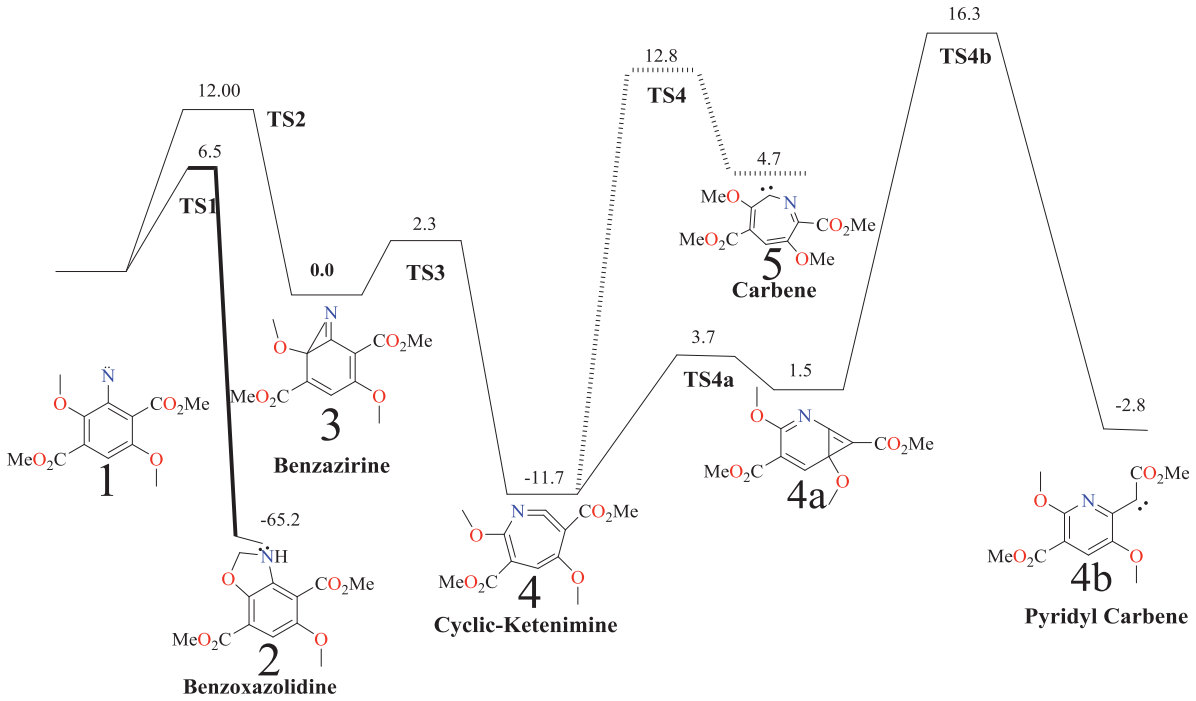


Fig. 2. Potential energy surface of the various intermediates obtained during thermolysis of the azido-dimethyl succinylosuccinate calculated at B3LYP/6-31 + G(d,p).

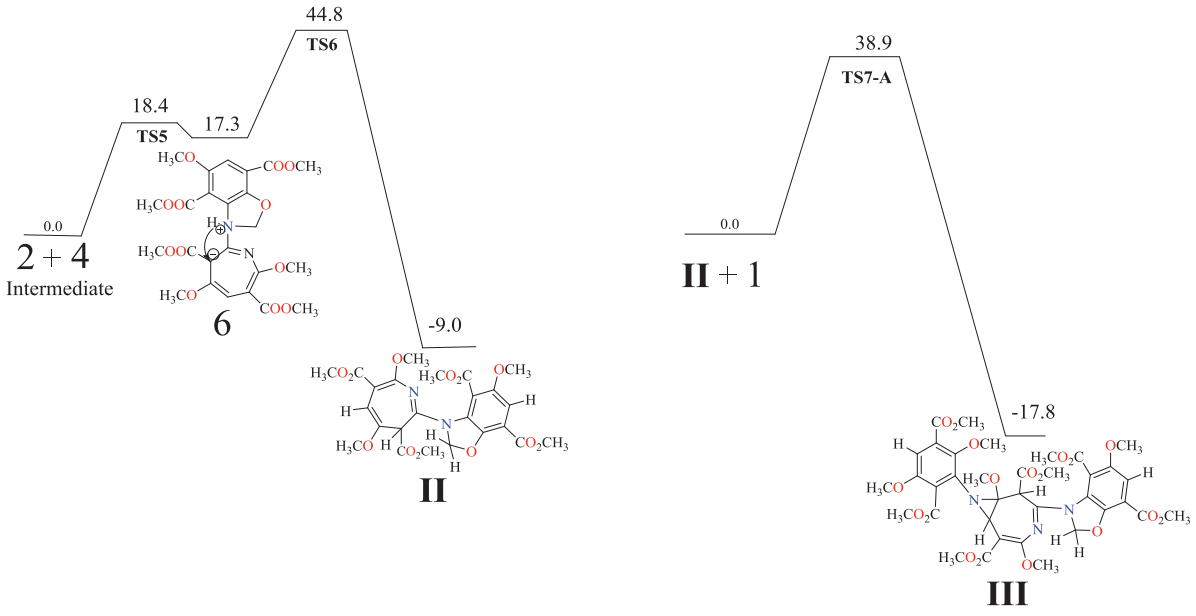


Fig. 3. Potential energy surface for the formation of the compound-**II** and compound-**III** from azido-dimethyl succinylosuccinate calculated at B3LYP/6-31 + G(d,p).

surface, is unstable by 9.0 kcal/mol. DFT calculations reveal that the formation of the compound-**II** and compound–**III** are thermodynamically favourable which corroborate the experimental formation of the compound-**II** and compound-**III**.

4. Experimental section

All the starting chemicals for the synthesis were commercially purchased. Reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60F254, 200 μm thick aluminium sheets and the spots were visualized either under UV or by iodine vapour. The crude reaction mixture was purified using column chromatography silica gel (100–200 mesh, 8: 2, petroleum ether/ethyl acetate) and preparative thin layer chromatography (TLC). The compounds purified were analyzed by High Pressure Liquid Chromatography, Nuclear Magnetic Resonance Spectroscopy (FT- NMR, 400 MHz) in $CDCl_3$ at 298 K and High Resolution Mass Spectrometry (HRMS) in positive ionization mode (+TOF MS). The UV- Vis spectra (UV- 1800) and FT-IR were recorded. The synthesis of **I** was carried out starting with dimethylsuccinylosuccinate (Scheme 2). High Pressure Liquid Chromatogram (HPLC) traces for the thermolysis products of Dimethyl-3-Azido-2,5-dimethoxy-

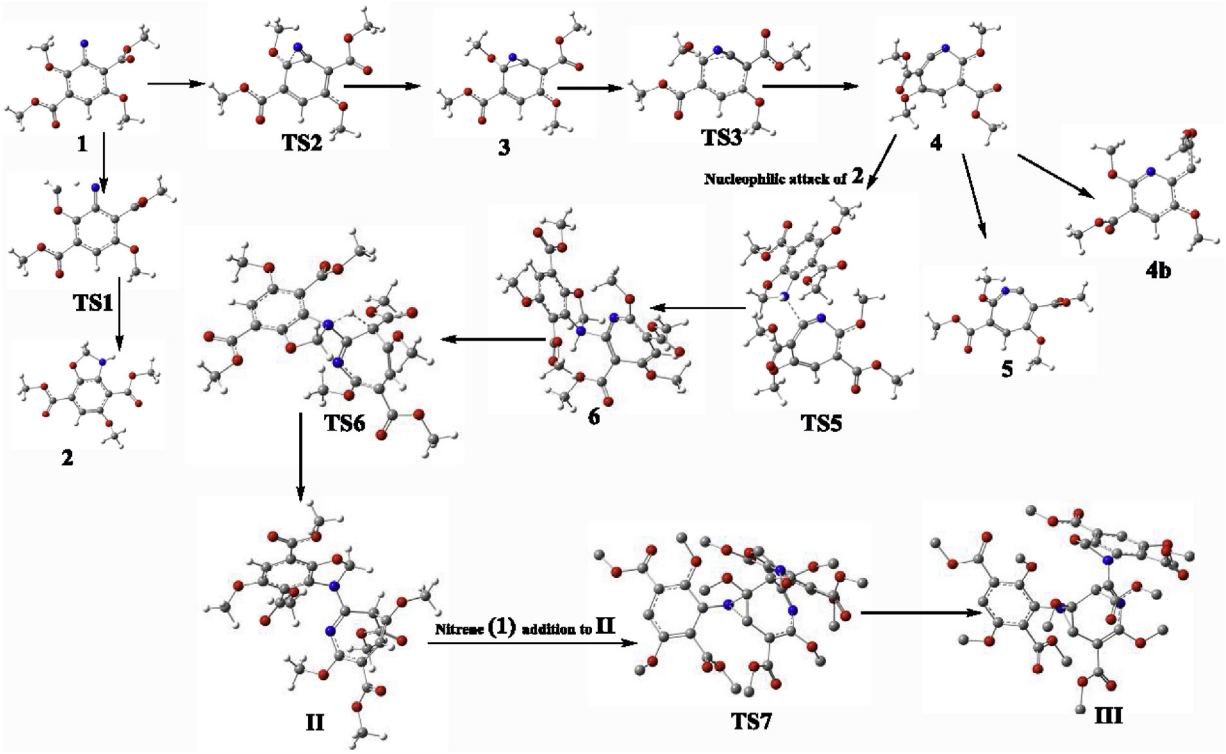


Fig. 4. SMD-B3LYP/6-31+(d,p) in chlorobenzene calculated geometries of various intermediates, compound-**II** and compound-**III**. We have removed hydrogen from TS7 and compound-**III** for clarity.

terephthalate demonstrate the purity of compound II and III (Fig. S13). Compound II and III eluting at 2.50 min and 3.59 min, respectively, with a reverse phase (RP)-C18 column [HPLC Column used Kinetex 2.6μ XB-C18 100A] 150 × 2, 10 mm], using 7: 3 Acetonitrile-water gradient at 30 °C, using a UV detector at 207 nm, with a flow rate of 200 μl/min.

*4.1. 2,5-Dioxo-1, 4-cyclohexane dicarboxylate (**a**) was prepared as previously published method.*[21a]

Found: δ_H (400 MHz, $CDCl_3$) 12.1 (2H, s, −OH), 3.78 (6H, s, -OMe), 3.17 (4H, s, $-CH_2$); δ_C (100 MHz, $CDCl_3$), 171.6, 168.5, 93.1, 51.8, 28.5.

4.2. 2,5-Dihydroxyter ephthalic aciddimethylester(b)was prepared as previously described[21b]

Yield 7.4 g, M. pt.: 177-178 °C (lit.: 177-179 °C). Found: δ_H(400 MHz, $CDCl_3$)3.85 (s, 6H), 7-25 (s, 2H), 9.8 (s, 2H); δ_C (100 MHz,$CDCl_3$,)52.5, I 17.6, 119.9, 150.5, 167.3.

*4.3. 2,5-Dimethoxyter ephthalic acid dimethylester (**c**)*

To a solution of 2, 5-dihydroxy terephthalic acid dimethyl ester (4.5 g, 19.8 mmo1) in dry acetone (100 ml), anhydrous potassium carbonate (13 g, 97 mmol) and methyl iodide (0.2 mol) were added and the mixture was refluxed for 8 h. The reaction mixture was then cooled and washed with water to dissolve excess potassium carbonate and extracted with dichloromethane. The organic layer was dried and solvent was removed in vacuum. The crude solid was recrystallized with hexane: ethyl acetate (2: 8). Yield 5 g (96%); M. pt.: 140 °C (lit.: 141–142 °C).

Found: δ_H(400 MHz, $CDCl_3$)7.40 (2H, Ar), 3.92 (6H, -OMe), 3.89 (6H, -OMe); δ_C(100 MHz, $CDCl_3$)166, 152, 123, 115, 57, 52.

*4.4. Dimethyl-3-nitro-2,5-dimethoxybenzene-1,4-dicarboxylate (**d**)*

The above diester (2.2 g) was taken in a boiling tube equipped with a small needle; it was cooled to 0 °C, and 12 ml of nitrating mixture (1:1 H_2SO_4: HNO_3) kept at the same temperature was added drop wise over 10 min. The solution was further stirred at same temperature for 20 min. The reaction mixture was poured onto ice and a yellow solid was obtained. The solid was filtered at pump and recrystallized from aq. methanol. Yield: 2 g, M. pt.: 90 °C.

Found: λ_{max} (KBr) 3433 (br), 2957, 1736, 1723, 1616, 1536, 1433, 1255, 1233, 1141, 1036, 777 cm^{-1}; δ_H(400 MHz, $CDCl_3$)7.56 (1H, s, Ar), 3.98 (3H, -OMe), 3.93 (3H, -OMe), 3.92 (3H, -OMe), 3.89 (3H, -OMe); δ_C (100 MHz, $CDCl_3$)164, 162, 152, 145, 128, 120, 116, 64, 57, 53.5, 53.1.

*4.5. Dimethyl-3-amino-2,5-dimethoxybenzene-1,4-dicarboxylate (**e**)*

To a stirred mixture of stannous chloridedihydrate (2 g) and conc. Hydrochloric acid (10 ml) was added the nitro- diester (2 g, 10.8 mmol). The reaction mixture was stirred for 5–6 h and was monitored using TLC. After the completion of the reaction, a small amount of water was added, carefully neutralized with mild sodium hydroxide and was immediately extracted with ethyl acetate. The organic layer was dried over sodium sulphate and the solvent removed. The product solidified as a yellowish brown fluorescent solid on drying in a desiccator. Yield: 500 mg; M. pt.: 82 °C.

Found: δ_H(400 MHz, $CDCl_3$)7.07 (1H, s, Ar), 5.64 (2H, br, $-NH_2$) 3.88 (3H, -OMe), 3.79 (6H, -OMe), 3.73 (3H, -OMe); δ_C (400 MHz, $CDCl_3$)167, 146, 142, 140, 139, 107, 103, 59.8, 59.3, 55.4, 50.5.

4.6. Dimethyl-3-azido-2,5-dimethoxybenzene-1,4-dicarboxylate (*I*)

A solution of amino-diester (100 mg, 0.5 mmol) in HCl (5 M, 10 ml, 1:1 HCl:H_2O) was cooled to 0 °C and diazotized by the slow addition of a solution of sodium nitrite (70 mg, 1 mmol) in water (5 ml). The resulting diazonium chloride was stirred for 10 min at 0 °C. A solution of sodium azide (60 mg, 1 mmol) and sodium acetate (3.36 g, 40 mmo1) in water (9 ml) was slowly added to the diazonium chloride. The reaction mixture was stirred for 2 h at 0 °C and then it was filtered at pump. Yield 72 mg; m.p. 67 °C.

Found: λ_{max}max (KBr) 3447 (br), 2949, 2845, 2122, 1732, 1605, 1574, 1486, 1451, 1413, 1341, 1275, 1231, 1140, 1044, 1005, 857, 752 cm^{-1}; δ_H (400 MHz, $CDCl_3$)7.12 (1H, s, Ar), 3.95 (3H, -OMe), 3.93 (3H, -OMe), 3.88 (3H, -OMe), 3.83 (3H, -OMe); δ_H(100 MHz, $CDCl_3$) 165.2, 152.2, 148, 132.7, 126.2120.6, 109.4, 63.5, 56.4, 52.9, 52.7; FAB-MS: 318 (M^+ + Na).

4.7. Thermolysis of *I*

"Azido-dimethyl succinylosuccinate", **I** (400 mg) was dissolved in chlorobenzene (15 ml). N_2 was flushed through the reaction mixture and was then heated at 132 °C for 4 h in the dark with a guard tube maintained at the top of the condenser to avoid any moisture. The reaction was monitored using TLC. At the end of 4 h, reaction mixture was cooled, and excess of chlorobenzene was distilled off using a rotary evaporator (in the dark). The crude reaction mixture was then subjected to neutral silica gel column chromatography (petroleum ether: ethyl acetate). The compound eluted was further recrystallized from petroleum ether- benzene (8:2).

4.8. Dimethyl-3-(4,7-dimethoxy-3,6-bis-methoxycarbonyl-3H-azepin-2-yl)-5-methoxy-2,3-dihydrobenzoxazole-4,7-dicarboxylate, compound-*II*

Compound-**II** was eluted using petroleum ether/EtOAc = 70:30. The compound obtained was subjected to preparative TLC (Petroleum ether/EtOAc = 60:40) followed by recrystallization with petroleum ether/benzene: 90:10. % Yield = 6% (based on the percentage of the azide converted). Found: R_f (30% EtOAc/Pet. Ether) 0.4.M. pt = 148-150 °C; δ_H(400 MHz,Aceton-d_6,) 3.50 (s, 3H), 3.51 (s, 3H), 3.53 (s, 3H), 3.64 (s, 3H), 3.67 (s, 3H), 3.80 (s, 3H), 3.88 (s, 3H), 4.99 (s, 1H), 5.9 (d, J = 3.6 Hz, 1H), 6.13 (s, 1H), 6.6 (d, J = 3.6 Hz, 1H), 7.09 (s, 1H); δ_C (100 MHz,Aceton-d_6,) 50.4, 50.9, 51.7, 52.1, 53.7, 54.3, 56.5, 86.8, 100.9, 103,107.5, 117, 138.9, 152, 156.5, 164.1, 167.8, 166.4; DEPT-135: δ = 86.76 (downward peak); HSQC: δ = 4.9 correlating 54.3, δ = 5.9 and δ = 6.6 correlating 86.6, δ = 6.13 correlating 101.3, δ = 7.09 correlating 107.3; HMBC: δ = 5.6 and δ = 6.6 correlating 103, δ = 7.09 correlating 117; HRMS: [Positive ion HR-ESI mass spectrum]: found 535.1465 and 557.1316 (base peak) $[M+H]^+$and $[M+Na]^+$, respectively; C_{24} H_{26} O_{12} N_2 H+ requires 535.4777 and C_{24} H_{26} O_{12} N_2 Na^+ requires 557.4595.

4.9. Dimethyl 3-((3E,5Z)-2,6-di)methoxycarbonyl)-8-(2,5-di(methoxycarbonyl)-3,6-dimethoxyphenyl)-1,5-dimethoxy-4,8-diaza-bicyclo[5.1.0]octa-3,5-dien-3-yl)-2,3-dihydro-5-methoxybenzo[d]oxazole-4,7-dicarboxylate (compound-*III*)

Compound-**III** was eluted using petroleum ether/EtOAc = 50:50. The compound obtained was further subjected to preparative TLC (Petroleum ether/EtOAc = 60:40) followed by recrystallization with petroleum ether/benzene: 90:10. %; M.pt. 113 °C; Yield = 5% (based on the percentage of the azide converted). Found: R_f (30% EtOAc/Pet. Ether) 0.5; δ_H(400MHzCDCl$_3$) 3.47 (s, 3H), 3.52 (s, 3H), 3.55 (s, 3H), 3.66 (s, 3H), 3.77 (s, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 3.91 (s, 3H), 3.92 (s, 3H), 3.95 (s, 3H), 3.96 (s, 3H), 4.94 (s, 1H), 5.34 (d, J = 2.8 Hz, 1H), 5.50 (d, J = 2.8 Hz, 1H), 5.55 (d, J = 1.6 Hz, 1H), 6.1 (d, J = 2.0 Hz, 1H),7.03 (s, 1H), 7.18 (s, 1H); δC-NMR (100 MHz,$CDCl_3$)14.2, 19.1, 22.6, 23.1, 26.7, 29.3, 30.1, 30.5, 31.9, 33.2, 33.7, 51.7, 52.7, 56.7, 57.2, 65.5, 77.2, 101.2, 117, 138.9, 152, 156.5, 164.1, 167.8, 166.4; DEPT-135: δ = 57.2 (downward peak); HSQC: δ = 4.9 correlating 48.8, δ = 5.5 correlating with 57.3,δ = 5.50 and δ = 5.55 correlating 8.8, δ = 6.13 correlating 101.3, δ = 7.09 correlating 107.3; HMBC: δ = 7.03 and δ = 7.18 correlating 77.2, δ = 6.9 correlating 111 and 163; HRMS (MALDI-MS) found 825.138; C_{36} H_{39} O_{18} N_3 K + $-CH_3$ requires 825.7743. MS/MS of the m/z 825.138 peak, showed a peak at m/z 781.1678, formed by the loss of $-CO_2CH_3$ [M^++K (39)$-CO_2CH_3$], from the molecular ion, which itself is not observed.

4.10. Computational methods

We have optimised all the geometries in chlorobenzene solvent at B3LYP[22,23] DFT functional with 6-31 + G(d,p)[24,25] Pople basis set. The solvent phase calculations have been performed with Self Consistent Reaction Field (SCRF) method[26] using SMD solvation model with B3LYP/6-31 + G(d,p) level of theory in the chlorobenzene solvent (ε = 5.69).[27] The SMD solvation model is known to be a universal solvation model, where "universal" denotes its applicability to any charged or uncharged solute in any solvent or liquid medium for which a few key descriptors are known. We have carried out harmonic frequency calculations at the same level of theory to confirm minima of optimised geometries with no imaginary frequencies. The B3LYP DFT functional is one of the best DFT functional to study the carbene and nitrene chemistry and reports reveal the superiority of the B3LYP functional over other DFT functional methods.[28,29] Transition state geometries have been located on the potential energy surface with B3LYP/6-31 + G(d,p) in chlorobenzene solvent and a transition state is confirmed with one imaginary frequency. Further, we have carried out IRC reaction path calculation to connect the TS geometries with the initial and final complex.[30] The reported free energy differences have been calculated with respect to the initial molecule as follow:

$$\Delta G = G_X - G_N \quad (1)$$

where, G_X is free energy of intermediate, transition state or final complex and G_N is the free energy of initial molecules and ΔG is the difference in the free energies. All quantum chemical calculations were performed using the G09 package.[31]

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2017.07.024.

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