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**TOPIC      SYNTHESIS AND REACTIONS OF PHENANTHRIDINE-  
ANNELATED HETEROCYCLIC COMPOUNDS**

- Chapter 1.    Review: Phenanthridine-annelated heterocyclic compounds
- Chapter 2.    Synthesis and characterization of 1,3-bis(alkoxycarbonyl)-1,3-azaphospholo[1,5-*f*]phenanthridines
- Chapter 3.    Diels-Alder reaction of 1,3-bis(methoxycarbonyl)-1,3-azaphospholo[1,5-*f*]phenanthridines
- Chapter 4.    Synthesis and characterization of pyrrolo[2,1-*f*]phenanthridines via 1,3-dipolar cycloaddition using water as solvent
- Chapter 5.    Regioselectivity in 1,3-dipolar cycloaddition of N-phenanthridinium phenacylide: Theoretical and experimental investigation.

**Chapter 1. Review: Phenanthridine-annelated heterocyclic compounds**

In this chapter, phenanthridine-annelated compounds have been reviewed. It includes their synthesis, structural studies, reactions and applications.

After reviewing these compounds, following gaps could be identified:

- No report could be found about the synthesis and reactions of azaphospholo-annelated phenanthridines.
- No attempt has been made so far for using water as the solvent for preparing annelated-phenanthridines.
- The regioselectivity observed in 1,3-dipolar cycloadditions of phenanthridinium ylides has not been investigated theoretically.

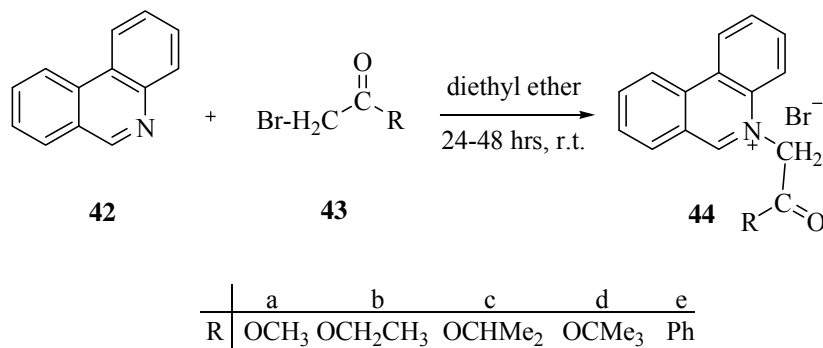
## Chapter-2. Synthesis and characterization of 1,3-bis(alkoxycarbonyl)-1,3-azaphospholo[1,5-*f*]phenanthridines.

In this chapter, synthesis and characterization of a new class of azaphospholo-annelated phenanthridines has been described.

### 2.2 RESULTS AND DISCUSSION

#### 2.2.1 Synthesis and characterization of 5-(alkoxycarbonylmethyl/phenacyl)-phenanthridinium bromides:

*N*-(Alkoxycarbonylmethyl/phenacyl)phenanthridinium bromides were obtained from the reaction of phenanthridine and alkyl bromoacetate or phenacyl bromide (Scheme 2.5).



Scheme 2.15. Synthesis of Phenanthridinium bromide salts.

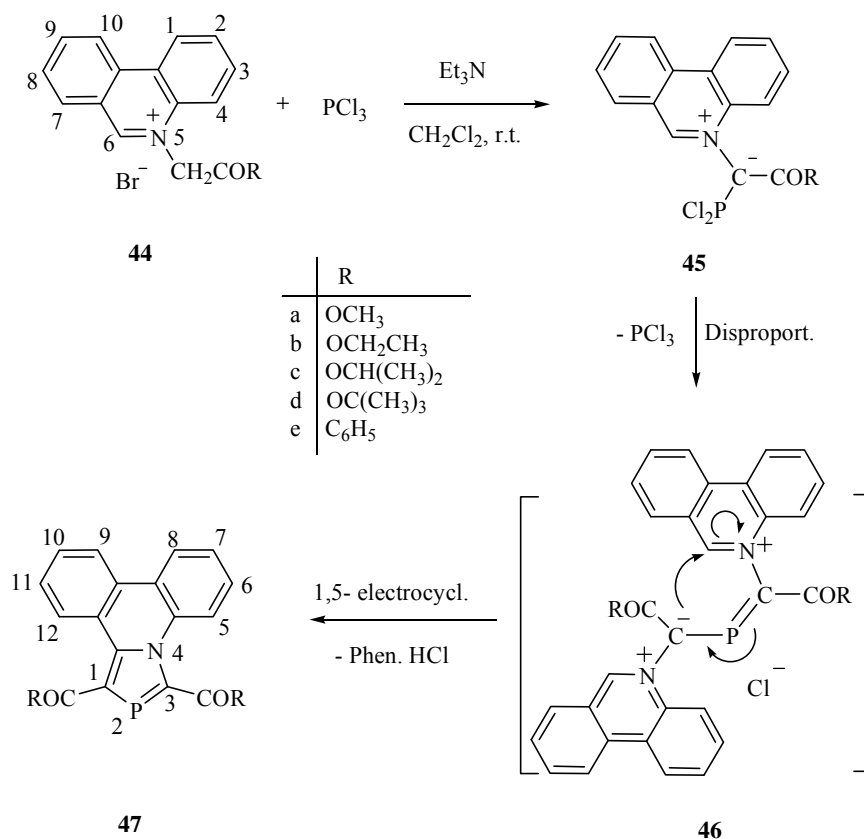
All the salts so obtained were characterized on the basis of <sup>1</sup>H NMR studies.

#### 2.2.2 Synthesis and characterization of 1,3-azaphospholo[1,5-*f*]phenanthridines:

5-(Alkoxycarbonylmethyl)/phenacylphenanthridinium bromides (44a-e) on reacting with PCl<sub>3</sub> (0.5 equiv.) in the presence of Et<sub>3</sub>N (3equiv.) in

dichloromethane at room temperature afforded 1,3-bis(alkoxycarbonyl)/r benzoyl-1,3-azaphospholo[1,5-*f*]phenanthridines (**47a-e**) in quantitative yields.

The mechanism of the formation of **47** involves initial generation of N-phenanthridinium dichlorophosphinomethylide (**45**), which undergoes disproportionation to afford a highly unstable intermediate, namely bis(phenanthridiniumylidyl)phosphenium chloride (**46**). The latter, however, could not be detected. The intermediate undergoes immediate intramolecular 1,5-electrocyclization followed by elimination of one equivalent of phenanthridinium hydrochloride to furnish 1,3-azaphospholo [1,5-*f*]phenanthridine. (Scheme 2.16).



**Scheme 2.16.** Synthesis of 1,3-azaphospholo [1,5-*f*]phenanthridines via 1,5-electrocyclization.

Formation of the annelated azaphospholes **47(a-e)** is confirmed by the appearance of  $^{31}\text{P}$ -NMR signal at  $\delta$ 170-176 ppm (Table 2.3), the range characteristic for the  $\sigma^2,\lambda^3$ -phosphorous atom in an azaphosphole ring.

All compounds are new and were characterized on the basis of  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR studies.

### 2.2.3 Spectral Characterization

The most deshielded signal in the  $^1\text{H}$  NMR spectra of **47** is a doublet of H-5 at  $\delta \sim 8.7$  showing three bond coupling of  $\sim 8.4$  Hz with H-6, H-8. Next to the H-5, H-12 gives a doublet at  $\sim 8.4$  showing three bond coupling of  $\sim 8.4$  Hz. Other protons appeared in aromatic region.

The characteristic feature in the  $^{13}\text{C}$  NMR spectra of **47a-d** (Table 2.5) is the appearance of doublets for C-1 and C-3 atoms showing  $^1J_{\text{P,C}}$  coupling constant of 16-41 Hz. C-3 carbon atom, on constituting a formal double bond with the phosphorous atom, shows larger coupling than C-1. The two most deshielded, less intense signals correspond to the two carbonyl groups and most upfield signals correspond to the aliphatic carbon atoms of the alkyl groups. C-5 carbon atom shows most upfield signal in comparison to the other closely placed aromatic carbon atoms

## 2.3 EXPERIMENTAL DETAILS

Reaction procedure and experimental techniques used during the synthesis of 1,3-azaphospholo[1,5-*f*]phenanthridines and their purification are given in this section.

## 2.4 CONCLUSION

Synthesis of a new class of annelated azaphospholes, namely 1,3-azaphospholo[1,5-*f*]phenanthridines has been accomplished from the reaction of 5-(alkoxycarbonylmethyl/phenacyl)phenanthridinium bromides with phosphorus trichloride in the presence of triethylamine at room temperature. The reaction involves intramolecular 1,5-electrocyclization of the initially generated bis(phenanthridiniumylidyl)phosphenium chloride accompanied by 1,2-elimination to afford the title compounds in good yields. All the compounds so obtained are new and have been characterized on the basis of  $^{31}\text{P}$ ,  $^1\text{H}$  and  $^{13}\text{C}$  NMR studies.

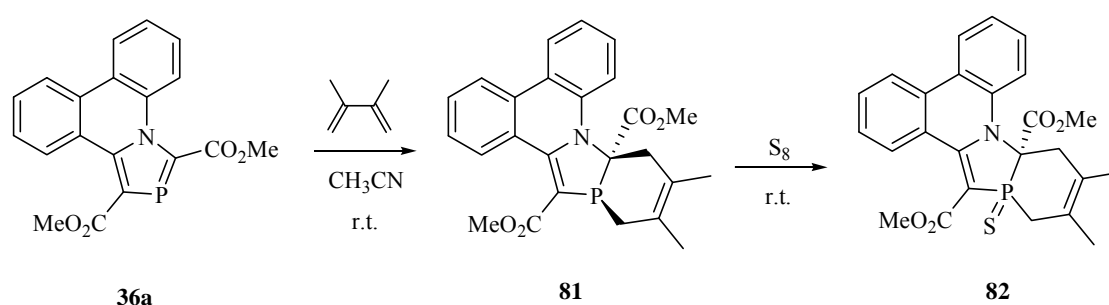
### **Chapter-3. Diels-Alder reaction of 1,3-bis(methoxycarbonyl)-1,3-azaphospholo[1,5-*f*]phenanthridine.**

In this chapter, Diels-Alder reaction across  $>\text{C}=\text{P}$ - functionality of 1,3-Bis(methoxycarbonyl)-1,3-azaphospholo[1,5-*f*]phenanthridine with 2,3-dimethylbutadiene (DMB) is described.

## 3.2 RESULTS AND DISCUSSION

### 3.2.1 DA reaction of 1,3-Bis(methoxycarbonyl)-1,3-azaphospholo[1,5-*f*]phenanthridine DMB

1,3-Bis(methoxycarbonyl)-1,3-azaphospholo[1,5-*f*]phenanthridine (**47a**) on reaction with DMB in presence of sulphur using acetonitrile as solvent at ambient temperature undergoes [2+4] cycloaddition to afford the cycloadduct **82**.<sup>105</sup>



**Scheme 3.18.** The DA reaction of 1,3-Bis(methoxycarbonyl)-1,3-azaphospholo[1,5-*f*]phenanthridine with DMB.

### 3.2.2 Structural elucidation of [2+4] cycloadduct

The cycloadduct of 1,3-bis(methoxycarbonyl)-1,3-azaphospholo[1,5-*f*]phenanthridine with DMB was characterized on the basis of <sup>1</sup>H, <sup>31</sup>P and <sup>13</sup>C NMR spectroscopic data.

In <sup>31</sup>P NMR spectrum, a <sup>31</sup>P NMR signal at  $\delta$  59.5 ppm confirms the three co-ordinated phosphorous atom (in **81**). After the addition of sulphur, the <sup>31</sup>P NMR signal is shifted to  $\delta$  72.5 ppm (in **82**) which confirms four co-ordinated nature of the phosphorous atom.

In  $^1\text{H}$  NMR spectrum, The most deshielded signal in the  $^1\text{H}$  NMR spectrum of **82** is a doublet of H-5 at  $\delta$  8.8 ppm showing three bond coupling of  $\delta$  9.6 Hz with H-6. Next to the H-5, H-12 gives a doublet at  $\delta$  8.7 ppm showing three bond coupling of 8.8 Hz. The diastereotopic behaviour can be seen for methylene protons at C-13 and C-16 in  $^1\text{H}$  NMR spectrum. Ha and Hb of C-16 show three bond coupling with phosphorous ( $^3J_{\text{PH}} = 16.8$  Hz and  $^3J_{\text{PH}} = 22.0$  Hz respectively) while Ha and Hb of C-13 show two bond coupling with phosphorous ( $^2J_{\text{PH}} = 16.8$  Hz for both).

In  $^{13}\text{C}$  NMR spectrum, The carbonyl carbon atoms are found most deshielded and show signals at  $\sim \delta$  166.0 ppm. C-12b particularly gives low intensity singlet at  $\delta$  157.9 ppm. Signals of the aromatic carbon atoms appear in characteristic region.

### 3.3 EXPERIMENTAL DETAILS

Reaction procedure and experimental techniques used during the synthesis and their purification are given in this section.

### 3.4 CONCLUSION

Diels-Alder reaction across the  $>\text{C}=\text{P}$ - functionality of the synthesized 1,3-bis(methoxycarbonyl)-1,3-azaphospholo[1,5-*f*]phenanthridine could be accomplished successfully with DMB.

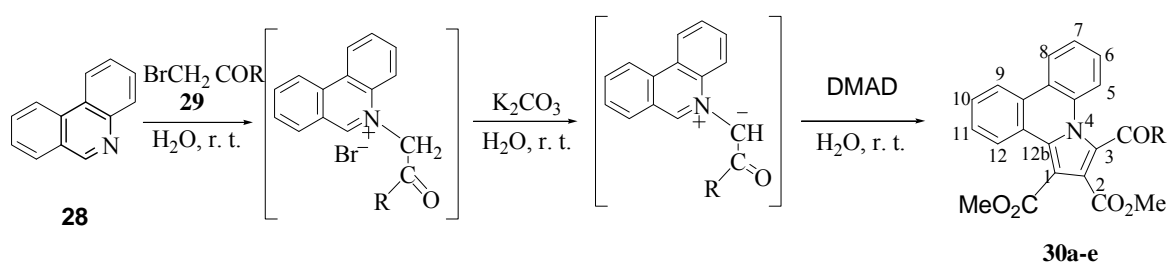
## Chapter-4. Synthesis and characterization of pyrrolo[2,1-*f*]phenanthridines via 1,3-dipolar cycloaddition using water as solvent

In this chapter, 1,3-dipolar cycloaddition of phenanthridinium ylides generated in situ using water as solvent is described.

### 4.2 RESULTS AND DISCUSSION

#### 4.2.1 Synthesis of pyrrolo[2,1-*f*]phenanthridines via 1,3-dipolar cycloaddition

The reaction of phenanthridine (**28**) with  $\alpha$ -bromoketone or *tert*-butyl bromoacetate (**29**) in water produces a clear solution at room temperature after stirring for 3-4 days. This clear solution contains cycloiminium bromide salt in soluble form. Addition of potassium carbonate to this solution generates cycloiminium ylide by deprotonation which undergoes 1,3-dipolar cycloaddition with DMAD to afford dimethyl pyrrolo[2,1-*f*]phenanthridine-1,2-dicarboxylates (**30a-e**) in good yields without using any external oxidizing agent.

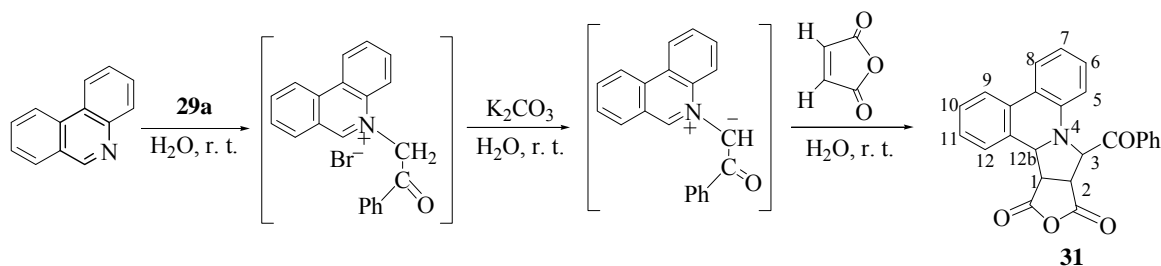


<b>29,30</b>	<b>R</b>
a	Ph
b	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>
c	<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>
d	<i>p</i> -FC <sub>6</sub> H <sub>4</sub>
e	OCMe <sub>3</sub>

**Scheme 4.12.** 1,3-Dipolar cycloaddition of phenanthridinium ylide with DMAD.



In one case, the initially formed ylide, namely phenanthridinium phenacylide was trapped with maleic anhydride to give tetrahydropyrrolo[2,1-*f*]phenanthridine derivative **31**.



**Scheme 4.13.** 1,3-Dipolar cycloaddition of phenanthridinium ylide with maleic anhydride.

#### 4.2.2 Characterization of the products

All the compounds were characterized on the basis of IR,  $^1\text{H}$  NMR, and  $^{13}\text{C}$  NMR spectral studies and elemental analysis.

#### 4.3 EXPERIMENTAL DETAILS

Reaction procedure and experimental techniques used during the synthesis of pyrrolo[2,1-*f*]phenanthridine-1,2-dicarboxylates are given in this section.

#### 4.4 CONCLUSION

Water could be used as the solvent for 1,3-dipolar cycloaddition of phenanthridinium ylides generated in situ with DMAD and maleic anhydride.

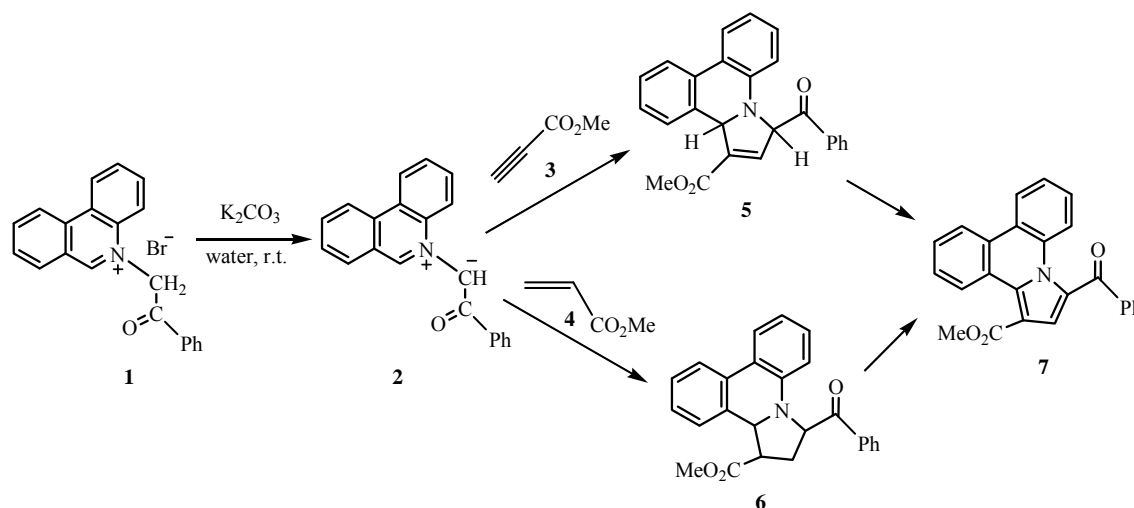
## Chapter-5. Regioselectivity in 1,3-dipolar cycloaddition of N-phenanthridinium phenacylide: Experimental and theoretical results

### 5.1 RESULTS AND DISCUSSION

#### 5.2.1 Experimental results

##### 5.2.1.1 Reaction of phenanthridinium phenacylide with methyl propiolate and methyl acrylate

Phenanthridinium phenacylide (**2**) generated *in situ* from deprotonation of N-phenacylphenanthridinium bromide (**1**) in water on reacting with equimolar amount of methyl propiolate (**3**) or methyl acrylate (**4**) at room temperature afforded the product **7** in quantitative yield (Scheme 5.1). The reaction was complete in 14 hrs.

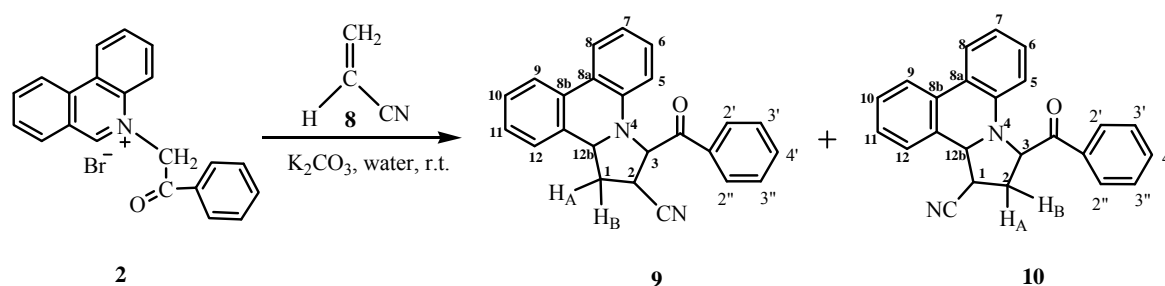


**Scheme 5.1.** 1,3-Dipolar cycloaddition of phenanthridinium phenacylide with methyl propiolate and methyl acrylate.

The product was characterized on the basis of IR,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR studies.

### 5.2.1.2 Reaction of phenanthridinium phenacylide with acrylonitrile

The reaction of phenanthridinium phenacylide generated *in situ* from the deprotonation of N-phenacylphenanthridinium bromide in water with acrylonitrile (**8**) afforded a mixture of two regioisomers **9** and **10** (Scheme 5.5). However, the products could not be separated even after repeated efforts.



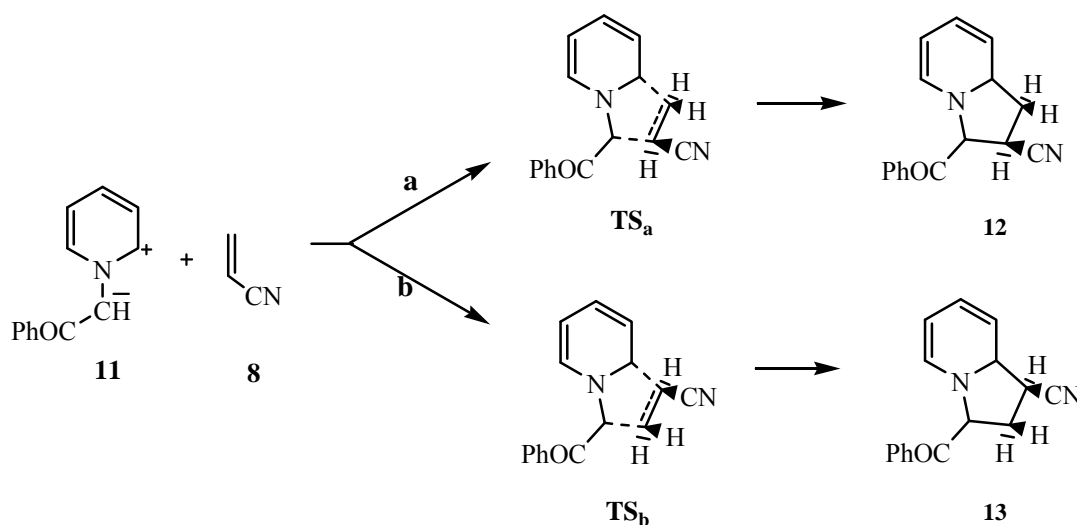
**Scheme 5.5.** Reaction of phenanthridinium phenacylide with acrylonitrile.

The product was characterized on the basis of IR and  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectral studies. After a close examination of the  $^1\text{H}$  NMR spectrum, particularly the region of  $\delta$  2.0-6.5, two important conclusions could be drawn:

- The product is a mixture of two regioisomers, and
- In contrast to the products formed from 1,3-dipolar cycloadditions with methyl propiolate and methyl acrylate, in the present case, the initially formed 1,3-dipolar cycloadducts are not auto-oxidized.

## 5.2.2 THEORETICAL RESULTS

In the case of the reaction of phenathridinium ylide with acrylonitrile a mixture of two regioisomers was obtained. To explain formation of the two products, we theoretically investigated 1,3-dipolar cycloaddition reaction of a model reaction using pyridinium ylide with acrylonitrile at B3LYP/6-31+G\*\* level.



**Scheme 5.6.** Model 1,3-dipolar cycloaddition of pyridinium phenacylide (11) with acrylonitrile (8).

It is found that reaction occurs through a concerted mechanism involving asynchronous transition states. Furthermore, formation of both regioisomers is exothermic. It is interesting to find that formation of the regioisomer **13** is both kinetically as well as thermodynamically preferred path in the gas phase and in the solvent phase i.e. water. However, the difference in the activation energies of paths a and b in aqueous phase (taken implicitly) is 10.06 kcal mol<sup>-1</sup>, according to which only the **13** regioisomer should be formed. Thus, theoretical results although

support preferential formation of regioisomer **13**, it fails to explain the observed regioselectivity which is only 16%.

### 5.3 EXPERIMENTAL DETAILS

Reaction procedure and experimental techniques used for the reaction are described in this section.

### 5.4 COMPUTATIONAL DETAILS

Geometries optimization were performed at the B3LYP/6-31+G\*\* level.

### 5.5 CONCLUSION

1,3-Dipolar cycloadditions of phenanthridinium phenacylide, generated *in situ* from deprotonation of N-phenacylphenanthridinium bromide in water could be accomplished successfully. The reactions with methyl propiolate and methyl acrylate occurred with complete regioselectivity affording a single product in each case. However, reaction with acrylonitrile yielded a mixture of two regioisomers with low (16%) regioselectivity. Theoretical investigation of a model reaction of 1,3-cycloaddition of pyridinium phenacylide with acrylonitrile at the DFT level supports the preferential formation of the regioisomer **13**; however, the observed low regioselectivity cannot be accounted for by DFT calculation.