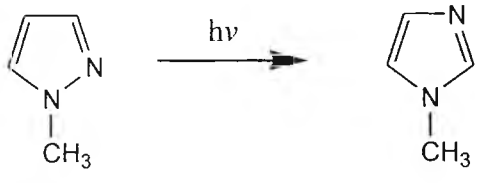
CHAPTER I

INTRODUCTION

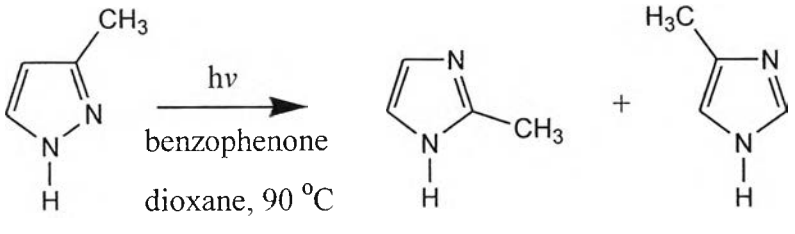
1.1 Photoisomerization of pyrazole

A phototransposition reaction is a photochemical isomerization, which permutes or scrambles the order of ring atoms in aromatic compounds. Schimid and co-workers reported that 1-methylpyrazole **[1]** undergoes photoisomerization to 1-methylimidazole **[2]**.[1]

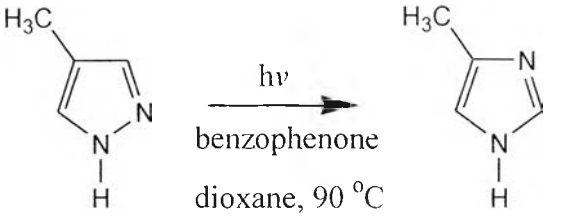


[1] **[2]**

The same workers also reported that 3-methylpyrazole **[3]** underwent photosensitized transposition to 2-methylimidazole **[4]** and 4-methylimidazole **[5]** and 4-methylpyrazole **[6]** underwent photosensitized conversion to 4-methylimidazole **[5]**.[1]

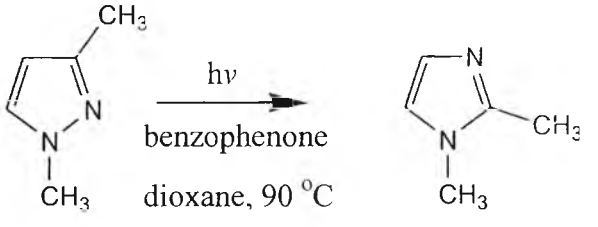


[3] **[4]** **[5]**

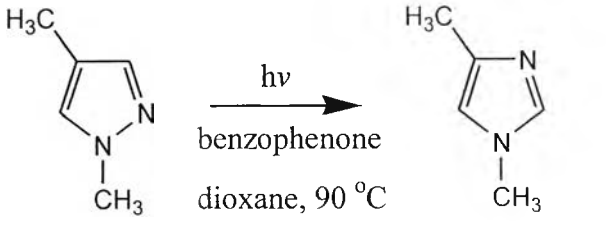


[6] **[5]**

They also reported that 1,3-dimethylpyrazole **[7]** underwent photosensitized conversion to 1,2-dimethylimidazole **[8]** and 1,4-dimethylpyrazole **[9]** underwent phototransposition to 1,4-dimethylimidazole **[10]**.

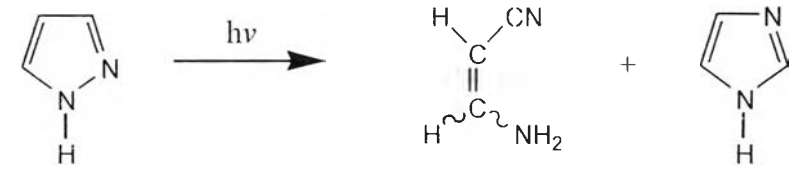


[7] **[8]**

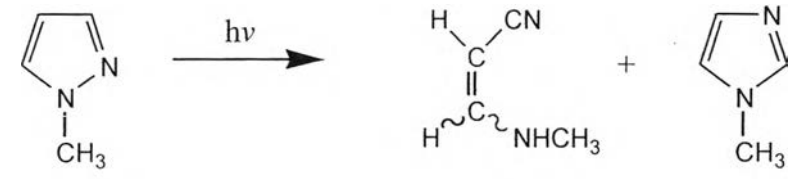


[9] **[10]**

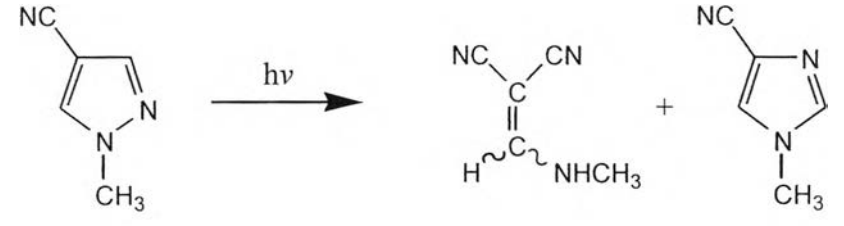
Wakamatsu, Barltrop, and Day reported that pyrazoles with hydrogen in position 3 underwent ring opening in addition to ring transposition.[2] Thus pyrazole **[11]**, 1-methylpyrazole **[1]**, and 1-methyl-4-cyanopyrazole **[15]** undergo photocleavage to 3-aminoacrylonitrile **[12]**, 3-methylaminoacrylonitrile **[14]** and 2-cyano-3-methylaminoacrylonitrile **[16]**, respectively, along with the corresponding imidazoles **[13]**, **[2]**, and **[17]**.



[11] **[12]** **[13]**



[1] **[14]** **[2]**

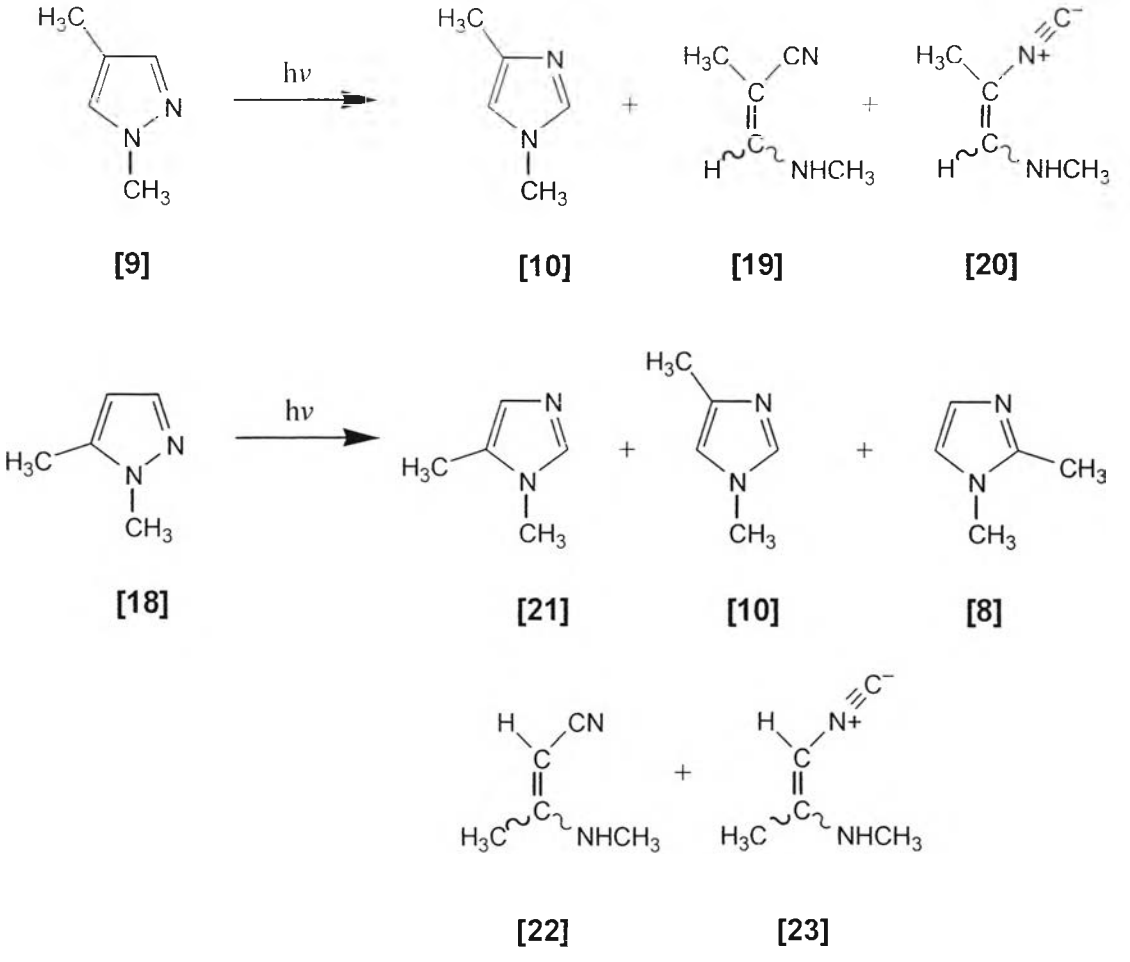


[15] **[16]** **[17]**

Furthermore, in 1991 Pavlik and Kurzweil also reported that 1-methylpyrazole **[1]** undergoes not only photoisomerization to 1-methylimidazole **[2]**, but also photocleavage to 3-(*N*-methylamino)propenenitrile **[14].**[3]

Although upon prolonged irradiation **[14]** is also converted to **[2]**, the efficiency of the conversion of **[1]** to **[14]** and to **[2]** is low and cannot be accounted for a significant fraction observed upon short-duration irradiation.

In addition, Pavlik and Kebede reported that 1,4-dimethylpyrazole **[9]** and 1,5-dimethylpyrazole **[18]** underwent photocleavage not only to 3-(*N*-methylamino)-2-methylpropenenitrile **[19]** or 3-(*N*-methylamino)-3-methylpropenenitrile **[22]** but to 2-(*N*-methylamino)-1-methylisocyanide **[20]** or 2-(*N*-methylamino)-2-methylpropenenitrile **[23]** as well, respectively.[4]

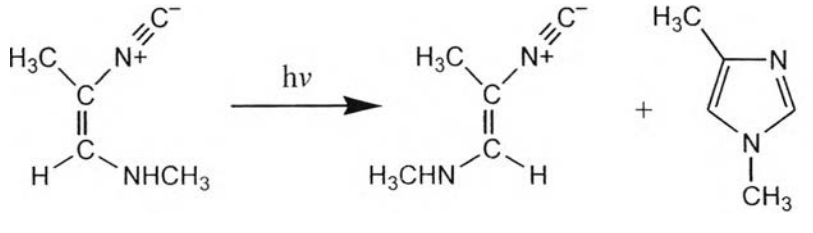


[9] **[10]** **[19]** **[20]**

[18] **[21]** **[10]** **[8]**

[22] **[23]**

The formation and subsequent consumption of enaminoisocyanide **[20]** or **[23]** suggested that the isocyanides might be an intermediate in the phototransposition. Moreover, the direct irradiation of enaminoisocyanide **[(Z)-20]** resulted in the consumption of 42% of **[(Z)-20]** and the formation of **[(E)-20]** and imidazole **[10]** in yields of 36% and 33%, respectively.

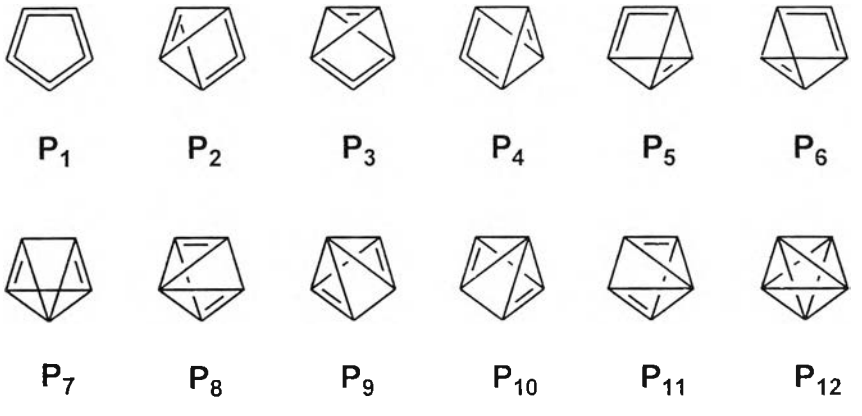


[(Z)-20] **[(E)-20]** **[10]**

1.2 Permutation pattern analysis in *N*-methylpyrazoles

The permutation pattern provides a map of the transposition by determining where each ring atom in the product originated in the reactant and thus provides a precise definition of all bond-forming and bond-breaking processes for each phototransposition pathway.[5]

For five-membered heterocycles containing two heteroatoms, there are 12 different ways of transposing the five atoms resulting in the 12 permutation patterns, as shown in Scheme 1. In this symbolism, the outer pentagon represents the original connections between the atoms of the ring and the internal pattern shows the order in which the ring atoms are connected in the transposed product.



Scheme 1 Permutation pattern for five-membered cyclic compounds

These permutation patterns are represented by the letter P and a subscript number to distinguish between them.

A reaction mechanism can be linked to a permutation pattern as long as it accounts for all bond formation and breaking necessary to realize product formation. However, more than one mechanism may account for some of the permutation patterns. Besides being positional labels, it has to be borne in mind that substituents may influence the course of the phototransposition.

1.3 Mechanistic interpretation of P_4, P_6 and P_7

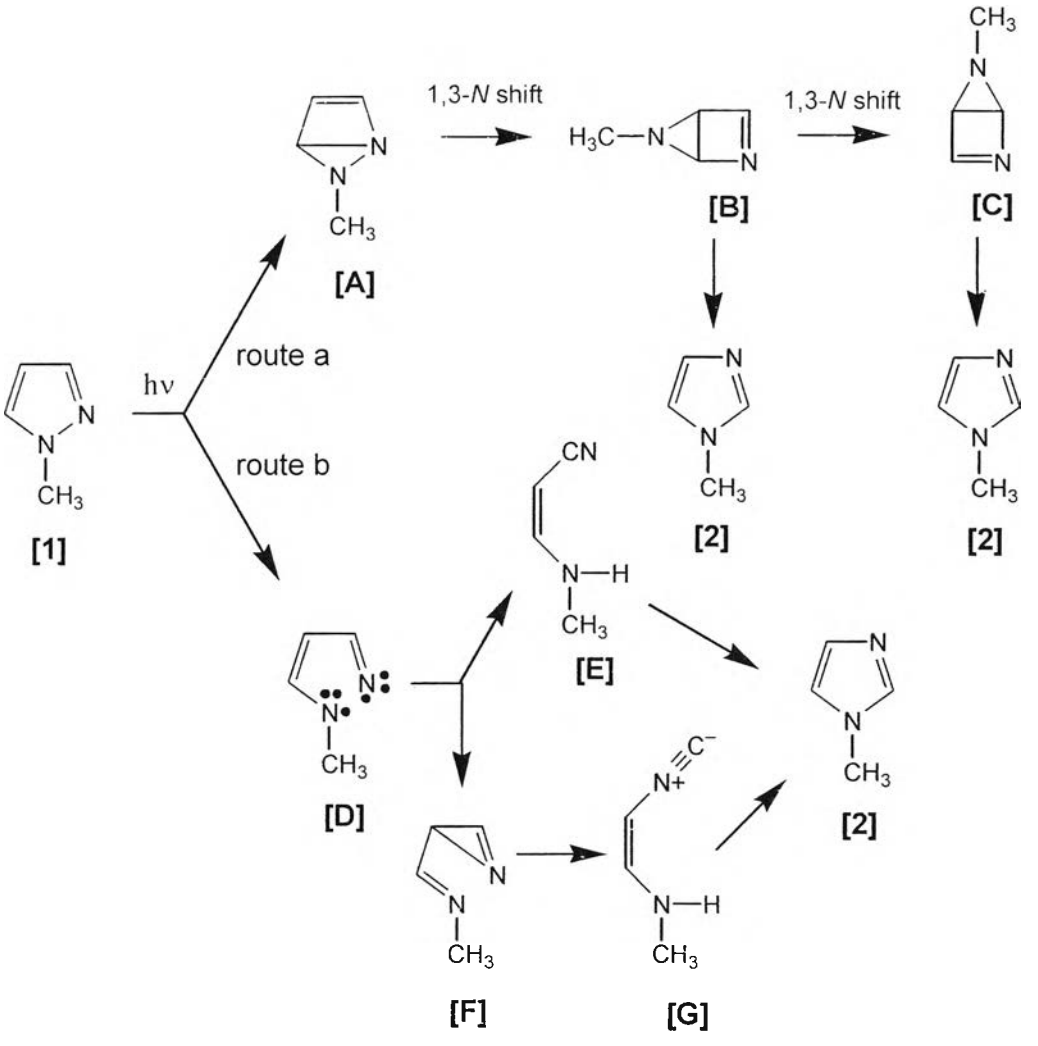
The photochemical reaction of 1-methylpyrazole upon direct irradiation has been found to give rise to fairly uncomplicated products. Imidazoles are the major photoreaction products. Even though five-membered ring compounds can undergo phototransposition by many permutation patterns, the P_4, P_6 and P_7 permutation patterns are the only ones that have actually been observed in *N*-methylpyrazole phototransposition chemistry.[5]

Different mechanisms have been proposed for different permutation patterns. The ring contraction-ring expansion mechanism *via* an azirine intermediate results in the P_4 product, while the single N-walk (1,3-sigmatropic nitrogen shift) mechanism and the double N-walk mechanism result in the formation of P_6 and P_7 products, respectively.

The photoisomerization of 1-methylpyrazole has been suggested to take place mainly *via* two mechanisms:

1) Ring contraction ring expansion

2) Electrocyclic ring closure resulting in the formation of a bicyclic intermediate that can undergo 1,3-sigmatropic nitrogen shift once (single nitrogen walk) or twice (double nitrogen walk) as in Scheme 2.



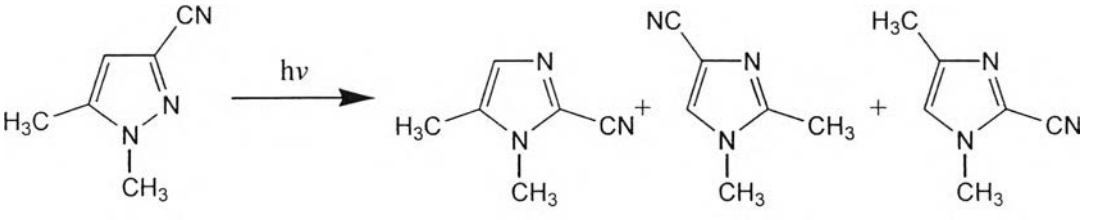
Scheme 2 Mechanism for photoisomerization of 1-methylpyrazole

The first mechanism (route a) involves an intermediate 1,5-diazabicyclo [2.1.0]pentene **[A]** that is formed by electrocyclic ring closure. The intermediate **[A]** is suggested to undergo a 1,3-*N* shift (single nitrogen walk) with the formation of a 2,5-diazabicyclo[2.1.0]pentene **[B]**, which upon rearomatizing will give imidazole **[2]**. Furthermore, **[B]** can again undergo a second 1,3-N shift (double nitrogen walk) to another 2,5-diazabicyclo[2.1.0]pentene **[C]** that can be rearomatized to form imidazole **[2]**.

The initial step of the second mechanism (route b) involves N-N ring cleavage with the formation of a biradical **[D]**. The biradical **[D]** can undergo ring closure reaction with the formation of an azirine **[F],** which further undergoes a ring expansion pass through enaminoisocyanide **[G]** resulting in the formation of

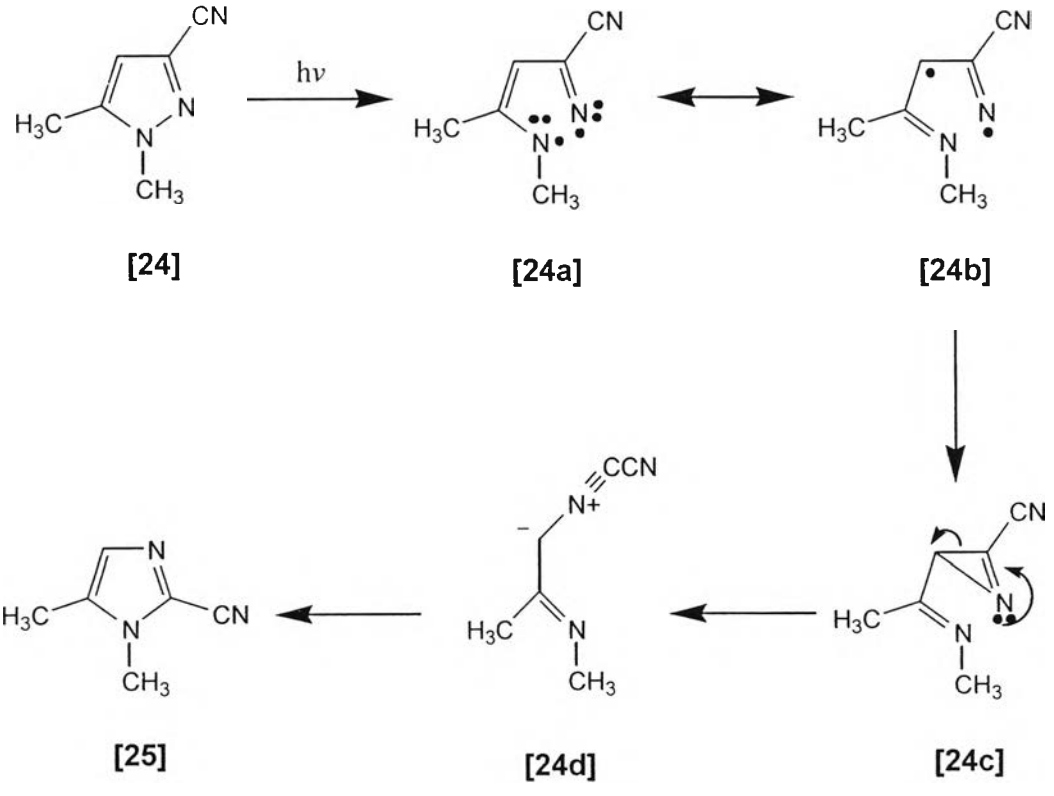
product **[2]**. On the other hand, **[D]** can undergo [1,4]-H shift with the formation of 3-(*N*-methylamino)propenenitrile **[E]** that can undergo ring closure giving the final product **[2]**.

The phototransposition of 3-cyano-1,5-dimethylpyrazole **[24]** gives three primary products, 2-cyano-1,5-dimethylimidazole **[25]**, 4-cyano-1,2-dimethylimidazole **[26]** and 2-cyano-1,4-dimethylimidazole **[27]**.[3]



[24] **[25]** **[26]** **[27]**

The phototransposition of **[24]** can be shown to yield **[25]** by P_4 permutation.

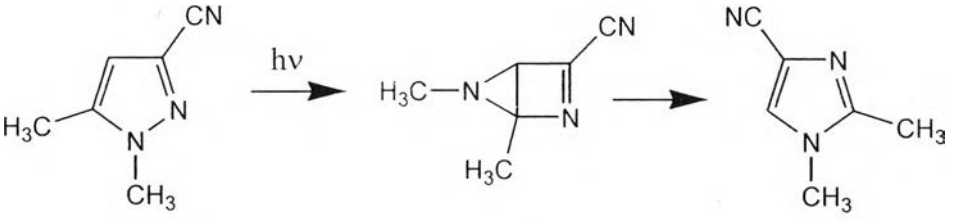


[24] **[24a]** **[24b]**

[25] **[24d]** **[24c]**

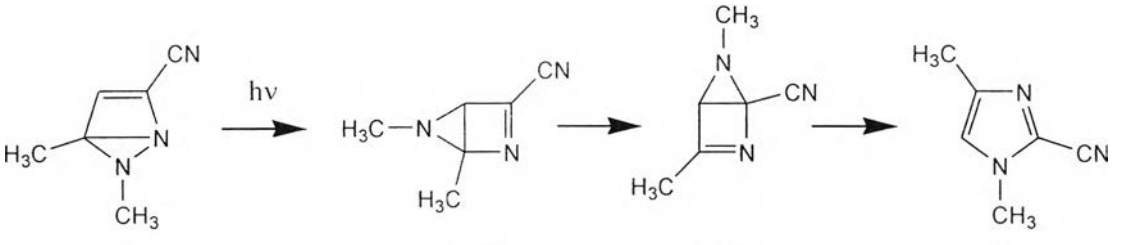
P_4 - Ring contraction-ring expansion

The phototransposition of **[24]** can be shown to yield **[26]** by P_6 mechanism and **[27]** by P_7 mechanism.



[24] **[24e]** **[26]**

P_6 – Single-N-walk

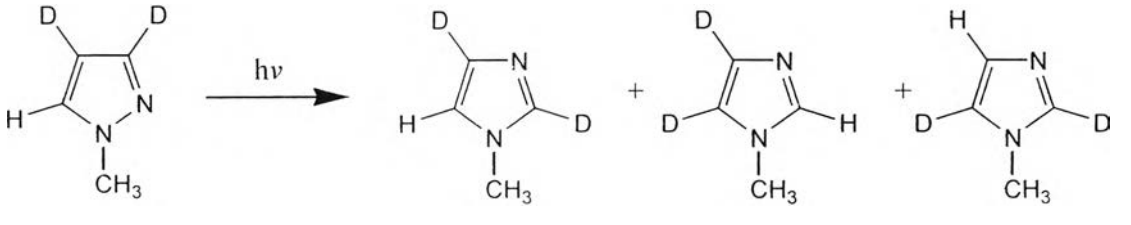


[24] **[24e]** **[24f]** **[27]**

P_7 – Double-N-walk

1.4 Related amounts of P_4 and P_6/P_7 in *N*-methylpyrazoles.

The course of phototransposition reactions is influenced by the nature and the position of substitutents in the ring. In order to study the transposition process with minimum substituent perturbation, Pavlik and Kurzweil synthesized and studied the phototransposition chemistry of 3,4-dideuterio-1-methylpyrazole **[1-3,4d$_2$]**.[3]



[1-3,4d$_2$] P_4 (4.8) P_6 (6.5) P_7 (1.0)

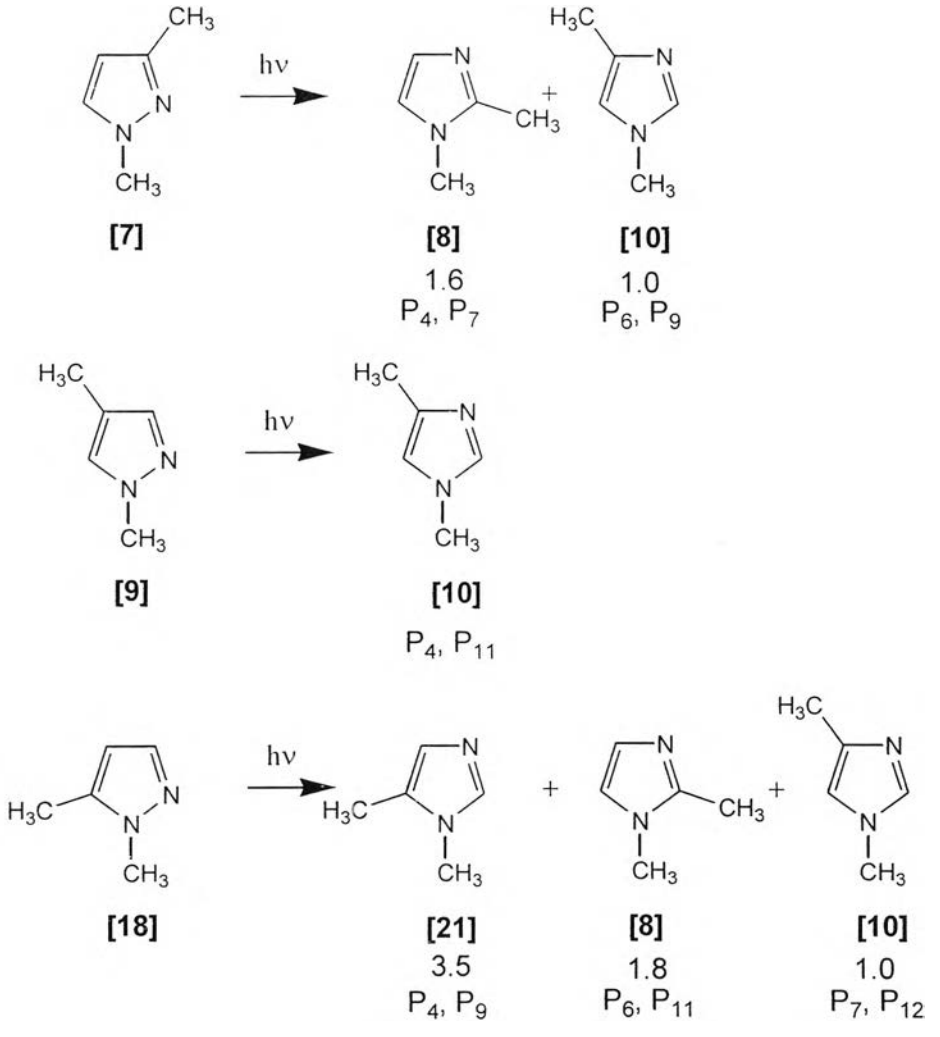
^{1}H-NMR analysis of the isolated dideuterated 1-methylimidazole in DMSO-d_6 revealed signals of almost equal area at δ 7.08 and δ 7.54 due to protons at C-5 and C-2 of the 1-methylimidazole ring, and a signal of much smaller area at δ 6.86 due to the C-4 ring proton.

These results clearly show that the C-5 proton of **[1-3,4d$_2$]** has transposed with approximately equal frequency to ring position 5 and 2 of the 1-methylimidazole product-signaling almost equal operation of the P_4 and P_6 pathways whereas to a less extent the C-5 proton has transposed to ring position 4, revealing that a smaller amount of 1-methylimidazole arises via the P_7 pathway. More quantitatively, these results show that phototransposition occurs via P_4, P_6, and P_7 pathways in a ratio 4.8 : 6.5 : 1.0.

1.5 Substituent effects

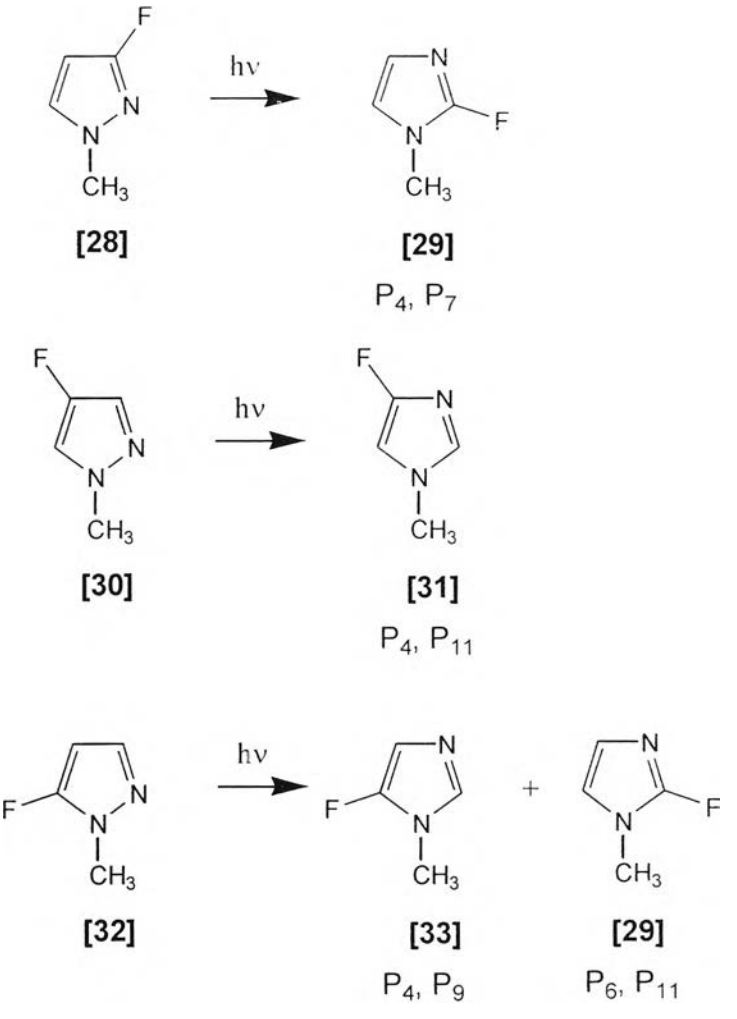
1.5.1 Methyl substitution

Pavlik and Kurzweil[3] studied the effect of ring methyl substitution on the photochemistry of pyrazoles. They observed that 1,3-dimethylpyrazole **[7]** phototransposed to 1,2-dimethylimidazole **[8]** and 1,4-dimethylimidazole **[10]** in the ratio of 1.6 to 1.0, and 1,4-dimethylpyrazole **[9]** phototransposed to 1,4-dimethylimidazole **[10]** and that 1,5-dimethylpyrazole **[18]** phototransposed to 1,5-dimethylimidazole **[21]**, 1,2-dimethylimidazole **[8]** and 1,4-dimethylimidazole **[10]** in the ratio of 3.5 : 1.8 : 1.0. Thus the methyl substitution in pyrazole enhances the P_4 pathway relative to the P_6 and the P_7 pathways.



1.5.2 Fluorine substitution

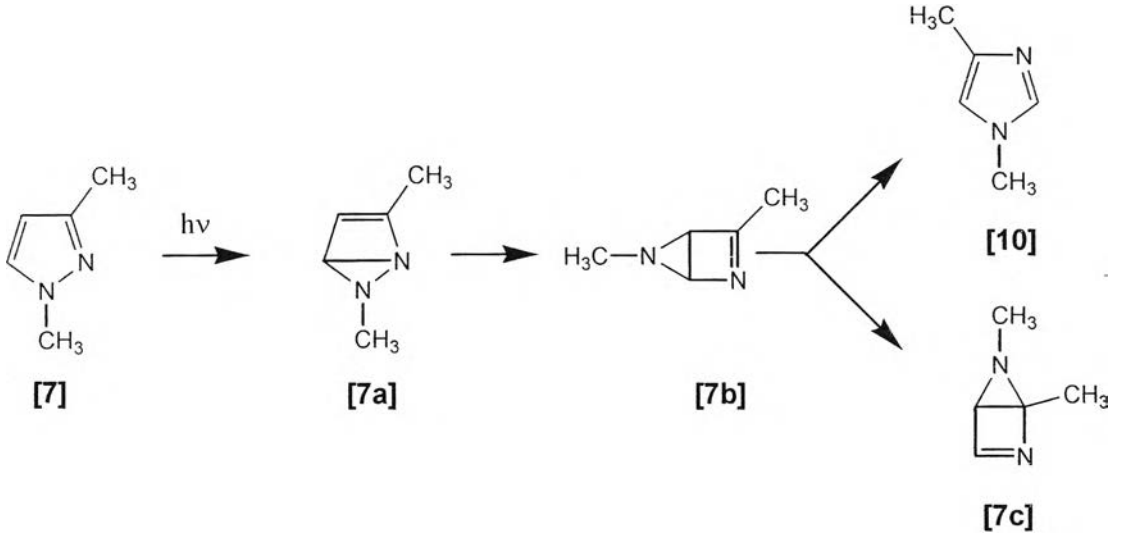
The effect of fluorine on the phototransposition of *N*-methylpyrazole has also been studied.[3] 3-Fluoro-1-methylpyrazole **[28]** and 4-fluoro-1-methylpyrazole **[29]** were observed to phototranspose to 2-fluoro-1-methylimidazole **[30]** and 4-fluoro-1-imidazole **[31]**, respectively. Photolysis of 5-fluoro-1-methylpyrazole **[32]** yielded 5-trifluoro-1-methylimidazole **[33]** and 2-fluoro-1-methylimidazole **[29]** in the ratio of 9.7 : 1.0.



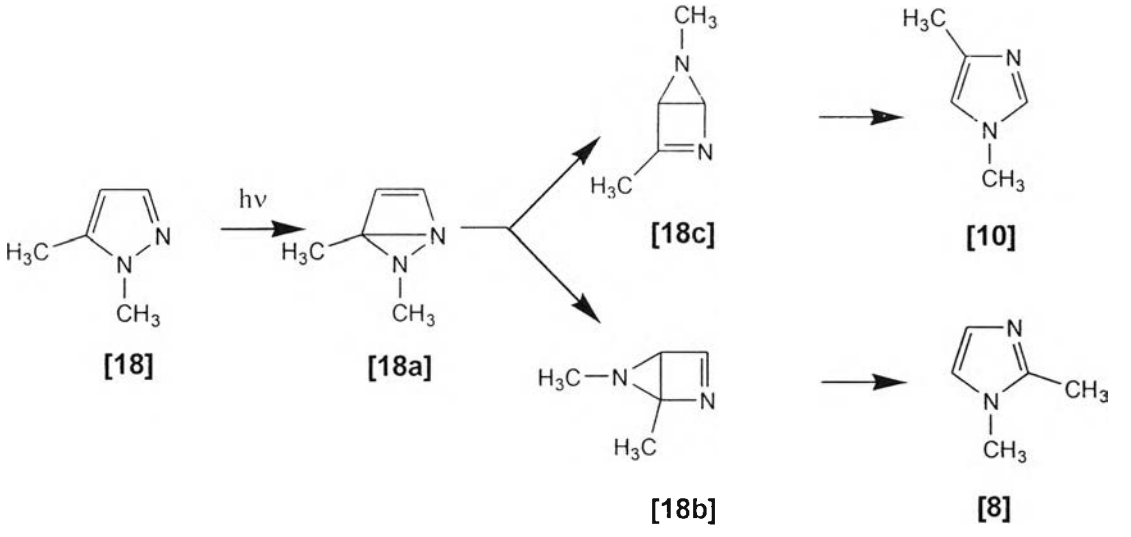
The methyl and fluorine ring substitution enhances the P_4 process relative to the P_6 and P_7 walk pathways. Thus, although 1,5-dimethylpyrazole **[18]** transposes to P_4, P_6 and P_7 products, the total P_6 and P_7 walk pathways constitute only 40% of the total transposition process.

In the case of 1,3-dimethylpyrazole **[7]**, although the walk mechanism constitutes 45% of the total transposition, this reaction is restricted to the one-step P_6 process. The relative decrease in the walk process is even more pronounced with fluorine substitution. Thus only 10% of the 5-fluoro-1-methylpyrazole **[32]** transposition occurs via the P_6 pathway. Finally, 3-fluoro-1-methylpyrazole **[28]** and both 4-methyl and 4-fluoro-substituted 1-methylpyrazole **[9]** and **[30]** transpose only to P_4 permutation pattern products.

The extent to which the nitrogen walk mechanism operates may be controlled by the position of the methyl group in the intermediate diazabicyclopentene. In all isomers it would be expected that the first nitrogen walk would be favorable since a 2,5-diazabicyclo[2.1.0]pentene should be substantially more stable than the initially formed 1,5-diazabicyclo[2.1.0]pentene.



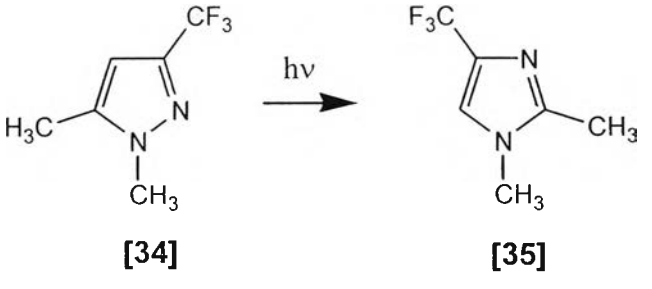
In the case of 1,3-dimethylpyrazole **[7]**, the second nitrogen walk converting **[7b]** to **[7c]** would not be expected to occur since it would result in the conversion of **[7b]**, stabilized by methyl substitution at the polar C-N double bond, to less stable isomer **[7c]** with the methyl substituent at the bridgehead position. Aromatization of **[7b]** to **[10]**, the observed products would be expected to occur faster than the second nitrogen walk to yield **[7c]**. Absence of P_7 product in this reaction is consistent with this reasoning.



In the case of 1,5-dimethylpyrazole **[18]**, in addition to the first nitrogen walk converting **[18a]** to **[18b]**, the second [1,3]-shift would also be favorable since it would lead to **[18c]**, the more stable isomer. Thus in addition to aromatization of **[18b]** to the observed P_6 product **[8]**, aromatization of **[18c]** would provide **[10]**, the observed P_7 product.

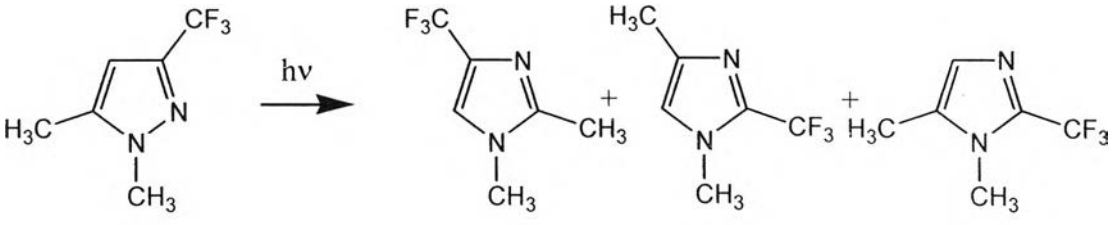
1.5.3 Trifluoromethyl substitution

Baltrop, Day and colleagues have studied the effect of introducing the electron withdrawing trifluoromethyl group onto the pyrazole ring.[6] They observed that 3-trifluoromethyl-1,5-dimethylpyrazole **[34]** phototransposed to only 4-trifluoromethyl-1,2-dimethylimidazole **[35]** via the P_6 pattern, the single N-walk mechanism.



Rangaraj and Pavlik[7] have also studied this reaction and observed that 3-trifluoromethyl-1,5-dimethylpyrazole **[34]** underwent phototransposition to yield 4-

trifluoromethyl-1,2-dimethylimidazole **[35]**, 2-trifluoromethyl-1,4-dimethylimidazole **[36]**, and 2-trifluoromethyl-1,5-dimethylimidazole **[37]** in yields of 48.2%, 1.8%, and 1.8% respectively.



[34] **[35]** **[36]** **[37]**

Since all ring positions in the pyrazole reactant are uniquely labeled, it can be concluded that these products arise via P_6, P_7, and P_4 permutation processes, respectively.

Although methyl and fluorine substitutions are known to enhance phototransposition via the P_4 pathway, these results show that trifluoromethyl substitution favors isomerization via the P_4 permutation process.

1.6 Objectives

It is of interest to study the effect of substituents of different types on the phototransposition chemistry of pyrazole. The trifluoromethyl group is an interesting substituent on *N*-methylpyrazole. It is considered to have strong electronic effect as an electron-withdrawing group. By comparison in electronic effects of trifluoromethyl and fluorine groups, obviously, the trifluoromethyl group has much more electronic effect than the fluorine group. Thus, it is the aim of this new investigation to understand how the strong electron withdrawing substituents affect the phototransposition reaction of pyrazole.

The goal of this thesis is to gain further insight into the substituent effects of trifluoromethyl group on the pyrazole phototransposition reaction.