Photochemical transformations of pyridinium salts: mechanistic studies and applications in synthesis

Teresa Damiano,* Daniel Morton* and Adam Nelson

Received 24th April 2007
First published as an Advance Article on the web 29th June 2007
DOI: 10.1039/b706244n

The discovery, understanding and synthetic exploitation of the photochemical transformation of pyridinium salts are described. The investigations surrounding the remarkable transformation of pyridinium salts into a host of structurally complex motifs have helped extend the comprehension of aromatic and heteroaromatic photochemistry. The synthetic community has, in recent years, recognised the potential inherent in these compounds and has since exploited the irradiation of variously substituted pyridinium salts as key steps in the preparation of advanced intermediates in numerous synthetic programmes.

1. Introduction

Photochemical reactions can transform structurally simple molecules into compounds with complex skeletons, often with high stereo- and regiocontrol.1 Recently, during a detailed study of a range of photochemical transformations,2 methods have been developed that enable photochemical reactions to be routinely performed on a large scale, making these processes more accessible to the synthetic organic chemistry community. The irradiation of pyridinium salts provides the facile, stereocontrolled synthesis of a range of molecular architectures such as bicyclic aziridines, fused heterocycles and various functionalised aminocyclopentenes.3

School of Chemistry, University of Leeds, Leeds, UK LS2 9JT

Teresa obtained her PhD from the University of Geneva (Switzerland), where she worked on the application of the phototransformation of pyridinium salts to synthesis of aminocyclopentitols. She then moved as a Marie Curie Fellow to the HTMC department of Sanofi-Aventis (France). In 2005 she joined the group of Prof. Nelson as a post-doctoral fellow. Her work focussed on the synthesis of GSK-3beta inhibitor libraries and in the elucidation of the role of protein kinases in the self-renewal of marine stem cells (in collaboration with Prof. Melanie Welham, University of Bath).

Daniel Morton was born in Louth, UK (1979). He received his MChem in 2001 from the University of East Anglia (UK), where he remained and under the joint supervision of Dr Robert Stockman and Professor Robert Field obtained his PhD in 2005 for work on the reaction of sulfur ylides with tert-butylsulfinimines for the synthesis of chiral aziridines. He is currently employed at Leeds University under the supervision of Adam Nelson as a postdoctoral fellow involved in studies toward the Diversity-Oriented Synthesis of natural product-like molecules.

Adam Nelson is Professor of Chemical Biology at the University of Leeds, with research interests in synthetic organic chemistry and chemical biology. He obtained a BA in Natural Sciences from Churchill College, University of Cambridge in 1993, and his PhD (under the supervision of Dr Stuart Warren) in Synthetic Organic Chemistry, also from Cambridge, in 1996. He undertook postdoctoral research with Prof. E. J. Thomas at the University of Manchester before joining the academic staff at the University of Leeds in 1998.
This review covers several aspects of the photochemical reactions of pyridinium salts: their mechanism, their scope and limitations in synthetic chemistry and their exploitation in the synthesis of a variety of biologically active molecules.

1.1. Phototransformations of aromatic compounds

Aromatic compounds have been found to undergo a remarkable range of photochemical reactions. The diversity of scaffolds and transformations accessible through irradiation of aromatic substrates has inspired chemists for over forty years. Key landmarks in the study of the photochemistry of benzene (Scheme 1) include the characterisation of Dewar benzene 2 (in 1962), benzvalene (or tricyclo[2.1.1.0^2,6]hex-2-ene) 1 (in 1964) and fulvene 3 (in 1967). These and many other investigations have contributed to build a detailed mechanistic and theoretical understanding of equilibria under photochemical conditions. It was from this intense period of investigation that the initial exploration of pyridine and pyridinium salt photochemistry emerged, a logical extension of the fundamental studies into the photochemistry of benzene. In 1970, Wilzbach and Rausch reported their findings on the photoirradiation of pyridine, in which Dewar pyridine was identified and described for the first time. In 1972, Wilzbach, Kaplan and Pavlik expanded upon these studies, describing the photoirradiation of a range of N-methyl pyridinium chlorides. Photosolvolyis of pyridinium salts (such as 4) in basic aqueous solution gave the exo-6-methylazabicyclo[3.1.0]hex-3-en-2-ols (such as 5) with high stereoselectivity (Scheme 2). In more recent years the bicyclic aziridine product 5 has become recognised as a key synthetic intermediate in the preparation of molecules with more complex skeletons.

![Scheme 1](image1)

Scheme 1 Photoisomerisation of benzene.

![Scheme 2](image2)

Scheme 2 Photochemical transformation of N-methylpyridinium chloride under basic conditions.

2. Mechanistic and theoretical studies on the photochemistry of pyridinium salts

2.1 Initial contributions of Kaplan, Pavlik and Wilzbach

In 1972, Kaplan, Pavlik and Wilzbach described the irradiation of several substituted N-methylpyridinium chlorides 6 (Scheme 3). Irradiation of the pyridinium salts 6 at 254 nm in aqueous base furnished the bicyclic aziridines 10–12. The methylether analogues of the aziridines were obtained when the reaction was performed in methanol. Moreover, it was found that irradiation of the more substituted pyridinium derivatives, i.e. the 3,5-lutidinium salts, furnished analogous products in comparable yields. A key observation was the transposition of the substituents around the ring (as in 10, 11 and 12), which was thought to originate from the involvement of a key intermediate: the azabenzvalene cation 8 (see Scheme 3). The relative configuration of the bicyclic aziridine products 10–12 stems from exo addition of the incoming nucleophile, anti to the aziridine ring of the bicyclic cations 7 and 9.

The proposed involvement of the azabenzvalene cationic intermediate highlights a key difference between the photochemistry of pyridine derivatives and pyridinium salts: the formation of the azabenzvalene is a consequence of a \(\pi \rightarrow \pi^*\) excitation, whereas the irradiation of pyridine, resulting in a \(\pi \rightarrow \pi^*\) excitation, leads to the bicyclic valence isomer, Dewar pyridine. Thus, the phototransformation of pyridinium salts is more reminiscent of the photochemistry of benzene, where hydration of benzvalene 1 leads to bicyclo[3.1.0]hex-3-en-2-exo-ol 14 (Scheme 4). The mechanism of the photochemical transformation of benzene (\(\rightarrow 1 \rightarrow 13 \rightarrow 14\)) was proposed by Wilzbach, Kaplan and Rischter, and later ratified by others.

![Scheme 3](image3)

Scheme 3 Photosolvation of 1,4-dimethylpyridinium chloride.

![Scheme 4](image4)

Scheme 4 Photohydration of benzene.

2.2. Theoretical and mechanistic studies of Burger and co-workers

Extensive theoretical studies of the mechanisms of the photochemical reactions of benzene and pyridine have been carried out,
however the photochemical reactions of pyridinium salts have only recently received significant attention. In 2001, prompted by the renaissance of the synthetic photochemistry of pyridinium salts, Burger and Lüthi et al. reported their insights into the events originating from $\pi \rightarrow \pi^*$ excitation.18

Completely optimised geometries for the equilibrium, intermediate and transition state structures of species arising from pyridinium and methyl pyridinium ions were determined using a combination of restricted Hartree–Fock (RHF) and density functional theory DFT (B3LYP) calculations (Fig. 1). Both the endo- and exo-methyl bicyclic ions (endo- and exo-15) were minima on the potential energy surface: the RHF calculations predicted that both endo- and exo-15 would have $C_3$ symmetry, while B3LYP predicted some distortion of the exo-form towards the azabenzvalene structure. The azabenzvalene structure 16 was predicted to be $C_3$-symmetric. These three structures (exo-15, endo-15 and exo-16) were found to be the only optimisable structures following the initial photoexcitation event. The presence of the nitrogen atom, unsurprisingly, caused the electronic structures of the species 15 and 16 to differ significantly from the analogous species derived from benzene (see Scheme 3 and 4). The exo-bicyclic cation 15 was stabilised through overlap of the nitrogen lone-pair with the $\pi$-system. The $C_3$-symmetric nature of the azabenzvalene structure 16 demanded that it would equilibrate with the bicyclic cation exo-15 through statistical cleavage of its enantiotopic allylic C–N bonds, of course, in the case of a substituted azabenzvalene, unselective ring-opening would lead to transposition of the nitrogen atom around the cyclopentene ring (for an example of this transposition see Scheme 3).

Having established a detailed picture of the species involved, Burger and Lüthi then turned their focus to the investigation of the reaction mechanism. The study supported a mechanism which was broadly analogous to that of benzene (see Scheme 4); the initial $\pi \rightarrow \pi^*$ excitation resulted in rearrangement to the exo-bicyclic ion 15 via a 2,6-bridging mechanism (Fig. 2). For both the pyridinium and methylpyridinium-derived species, there was a strong preference for the exo-invertomers exo-18 and exo-23. In both cases, the transition state for pyramidalisation of the aziridine nitrogen (19 and 24) was around 17 kcal mol$^{-1}$ above the exo inverter, a result which was in excellent agreement with the barriers found for other $N$-alkyl aziridines.19

The conversion of the exo-bicyclic cations 18 and 23 into the corresponding azabenzvalene species was found to proceed via a low-lying transition state (exo-18 $\rightarrow$ 20 $\rightarrow$ 21 and exo-23 $\rightarrow$ 25 $\rightarrow$ 26). These low-lying transition states are reached through twisting of the cyclopentyl ring to allow attack of the aziridine nitrogen lone pair onto one of the ends of the allylic cation. The facile equilibration between exo-18 and the corresponding azabenzvalene species 21 (Fig. 2) was also observed in more substituted systems.

A series of deuterium labelling experiments have provided further insight into the rearrangement process (Scheme 5).20,21,22 3,4,5-Trideuterio-$N$-(3-hydroxypropyl)pyridinium chloride was used as the substrate for these studies, as the resulting photoproduct was not prone to Grob fragmentation. The major product 31, obtained in 80% yield, was clearly the result of rapid trapping of the initially formed allylic cation 28. The remaining material was presumed to be formed by rearrangement of 28 to the azabenzvalene ion 29 and, hence, 30, with subsequent trapping with water. Presuming no secondary isotope effects, it was suggested the observed unequal mixture of 32 and 33 was due to some of 32 being formed through direct trapping of the azabenzvalene ion intermediate.

---

**Scheme 5** Deuterium labelling studies of pyridinium salt phototransformations.
The effect of substitution on the rearrangement process was also probed (Scheme 6). A 4-methyl substituent—as in 1,4-dimethylpyridinium chloride 6—did not have a significant effect on the product distribution of the photosolvolyis reaction. The major product 10 (80%) was formed through direct trapping of the initially formed allylic cation, and the mass balance (→ 11 and 12) stemmed from rearrangement, followed by trapping. However, with a 3-methyl substituent (34), there was no evidence for rearrangement: the equimolar mixture of the products, 11 and 12, arose from unselective trapping of the initially formed allylic cation. Conversely, with a 2-methyl substituent (35), an equimolar mixture of products, 11 and 12, was formed, this time the products stemmed solely from rearrangement, followed by trapping.

To try and gain an understanding of the effect of methyl substituents on the regioselectivity of the hydration reaction, Burger and Lüthi conducted further theoretical studies (see Fig. 3). With a 4-methyl substituent on the pyridinium ring, the energy profile was rather similar to that for an unsubstituted pyridinium salt (starting at 40). However, the additional methyl group meant that the allylic C–N bonds in the azabenzvalene 38 were no longer enantiotopic: ring-opening to give 36 was favoured over ring-opening to give 40 due to stabilisation of the developing allylic cation 37 by the methyl group. In contrast, with a 3-methyl group, the initially formed bicyclic cation exo-36 was highly stabilised by the additional methyl group, and was trapped to give both 11 and 12. With a 2-methyl group in the starting...
Scheme 6  Product distribution and yields for the photohydration of the picoline derivatives 6, 34 and 35.

Mariano and co-workers almost succeeded in reviving the interest in the photochemistry of pyridinium salts\(^\text{20}\). Irradiation of a methanolic solution of the \(N\)-allylpyridinium perchlorate 41, followed by neutralisation and distillation, yielded the trans,trans-aminocyclopentene 44 in 86% yield (Scheme 7). The authors proposed that attack of methanol on the bicyclic allylic cation 42 was followed by methanolysis of the resulting protonated aziridine 43 to give the trisubstituted cyclopentene 44.

Scheme 7  Photosolvation of \(N\)-allylpyridinium perchlorates in methanol.

In 1996, Mariano extended his approach to the synthesis of more highly substituted aminocyclopentene derivatives and dramatically revitalised interest in the synthetic photochemistry of pyridinium salts\(^\text{21}\). Photoreaction of the pyridinium salts 45a–c gave mixtures of the bicyclic aziridine 46 and 4-aminocyclopentene 47 products (Scheme 8). Remarkably, with the pyridinium perchlorates 45b and 45c, participation of the tethered nucleophile was not observed. Indeed, even with less nucleophilic solvents, cyclisation was not observed, presumably because the resulting products would be highly strained. A pertinent observation from these studies was that the efficiency of the phototransformation

Fig. 3  Adaptation of Burger and Lüthi’s representation of the schematic relative energies for reaction of dimethylpyridinium salts (kcal mol\(^{-1}\)).

material, the presence of an additional methyl group on the aziridine bridgehead destabilised the initially formed bicyclic cation. Rapid rearrangement to the stabilised bicyclic cation 36—via the azabenzvalene cation 38—was therefore expected. Indeed with 1,2-dialkylated pyridinium salts, rearrangement of the initially formed allylic cation, prior to nucleophilic addition, is generally observed. These general principles may also be used to rationalise the reactivity of 1,3,5-substituted lutidinium salts\(^\text{18}\).

3. Phototransformation of substituted pyridinium salts

3.1. Photosolvation under acidic conditions

The synthetic potential of this remarkable transformation had remained largely unexplored for over ten years. In 1982 however,
was strongly dependent upon the polarity of the solvent employed, with more polar solvents affording higher yields. The ratio of the products depended on the work-up procedure: neutralisation prior to concentration allowed the partial survival of the bicyclic aziridine 46, with the deprotonated bicyclic aziridine 46 not being so susceptible to methanolysis. On the other hand concentration prior to treatment with base gave the resultant methanolysis products, the aminocyclopentenes 47, exclusively.

3.2. Photosolvation under basic conditions

The photochemical reaction of the 4-(3-hydroxybutyl)pyridinium perchlorate 48 provided new mechanistic insights. Participation of the tethered alcohol did not occur and the tricyclic product was not obtained (Scheme 9). Further, the bicyclic aziridine 51 was formed in high yield and regioselectivity, and the transposition of substituents around the ring was not observed. The authors suggested that the high levels of regioselectivity observed for this transformation were due to the rapid capture of the bicyclic cation 49, preventing the involvement of the azabenzvalene cation 50.

To extend their exploration of the scope of photohydration of pyridinium salts, Mariano and co-workers examined the reaction in both methanolic and aqueous potassium hydroxide solution (Scheme 10). The respective hydroxyl- (52) and methoxy-substituted (46) bicyclic aziridines were formed in good yield.

3.3. Photosolvation of C-substituted hydroxyalkylpyridinium salts

Burger and co-workers explored the photohydration of the 2-, 3- and 4-hydroxymethylpyridinium halides (53–55) in basic media. The photoreactions were typically done on a 0.07 to 0.1 mmol scale, over a period of 45 to 65 h. Photocontraction of the meta-substituted derivatives 53 afforded equimolar mixtures of two bridged aziridines, 57 and 58 (Scheme 11), in poor to reasonable (10–49%) yield. The relative configuration of the products 57 and 58 (R = Et) was confirmed by X-ray crystallography (Fig. 4). In accord with the observations of Mariano, participation of hydroxyl-substituted N-substituents (R = (CH2)3OH and CH2CH(OH)CH2OH) was not observed. Irradiation of the ortho-substituted pyridinium salt 54 under the same conditions, provided, in comparable yield (43%), the same equimolar mixture of the 1,2-diol 57 and 1,4-diol 58. The outcome of these reactions is consistent with attack of the nucleophile onto the exo face of the allylic cation 56.

3.4. Photosolvation of 3-alkoxypyridinium salts

Penkett and Simpson studied the effect of an electron donating substituent at the 3-position of the pyridinium ring. Irradiation of 5-methoxy-1,2-dimethylpyridinium tetrafluoroborate 64 in methanolic sodium hydroxide gave the intermediate 65 (Scheme 12).†

The presence of the electron donating methoxy substituent directed the regioselective formation of the ketal product, 66

† For safety reasons, and ease of preparation, the reactions of the pyridinium tetrafluoroborate salts were studied.
Scheme 11  Photohydration of 2-, 3- and 4-hydroxymethylated pyridinium halides.

(Scheme 12). The ketal 66 was formed under basic conditions, and hence was not susceptible to equilibration. To demonstrate that the regiochemistry was kinetically controlled, a series of mixed ketals were prepared (Scheme 13). It was possible to prepare both diastereomers through judicious choice of substrates and conditions (compare entries 11 and 13, Table 1). Initially, the configuration of the product, assigned through NOE studies, was believed to be consistent with attack of the alcohol nucleophile on the endo face of the cationic intermediate. However, later work, in which the X-ray crystal structure of an adduct was obtained, suggested that the configuration of the product may have been misassigned, and that exo attack was favoured.

The scope and limitations of the photochemistry of 3-alkoxypyridinium salts in aqueous solution were explored in more detail. Under these conditions, β-hydroxycyclopentenone derivatives 69 were obtained (Scheme 14). Hydrolysis of the cation would yield a hemi-ketal 67 and, hence, an enone 68; conjugate addition of a second molecule of hydroxide would yield the observed product 69. The configuration of the products 69 has been tentatively assigned using NOE experiments, and was consistent with addition of nucleophile to the endo face of the bicyclic enone 68. The size of the group at the 2-position of the pyridinium ring had a direct influence on the yield of the reaction: with R2 = H, very poor yields were observed (6%, Table 1, entry 1 and <5%, Table 2, entry 1), which improved with larger R2 groups (Table 1, R2 = Me, 41% (entry 3); R2 = Et, 77% (entry 4); R2 = Pr, 70% (entry 5); Table 2, R2 = Me, 38% (entry 2), R2 = Et, 40% (entry 3), R2 = Pr, 44% (entry 4)). Thus through careful choice of solvent and conditions, Penkett developed methods for the synthesis of two different scaffolds.
Table 1 Scope and limitations of the photosolvation of 3-alkoxy pyridinium salts in alcoholic sodium hydroxide solution

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R¹ OH</th>
<th>R²</th>
<th>R³</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64a</td>
<td>MeOH</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>66a</td>
</tr>
<tr>
<td>2</td>
<td>64b</td>
<td>MeOH</td>
<td>Me</td>
<td>H</td>
<td>Et</td>
<td>66b</td>
</tr>
<tr>
<td>3</td>
<td>64c</td>
<td>MeOH</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>66c</td>
</tr>
<tr>
<td>4</td>
<td>64d</td>
<td>MeOH</td>
<td>Et</td>
<td>Me</td>
<td>Me</td>
<td>66d</td>
</tr>
<tr>
<td>5</td>
<td>64e</td>
<td>MeOH</td>
<td>Me</td>
<td>Pr</td>
<td>Me</td>
<td>66e</td>
</tr>
<tr>
<td>6</td>
<td>64f</td>
<td>MeOH</td>
<td>Me</td>
<td>Et</td>
<td>Et</td>
<td>66f</td>
</tr>
<tr>
<td>7</td>
<td>64g</td>
<td>MeOH</td>
<td>Me</td>
<td>Et</td>
<td>Et</td>
<td>66g</td>
</tr>
<tr>
<td>8</td>
<td>64h</td>
<td>MeOH</td>
<td>Me</td>
<td>Me</td>
<td>allyl-</td>
<td>66h</td>
</tr>
<tr>
<td>9</td>
<td>64i</td>
<td>MeOH</td>
<td>Me</td>
<td>Me</td>
<td>Bn-</td>
<td>66i</td>
</tr>
<tr>
<td>10</td>
<td>64j</td>
<td>MeOH</td>
<td>Pr</td>
<td>H</td>
<td>Et</td>
<td>66j</td>
</tr>
<tr>
<td>11</td>
<td>64k</td>
<td>MeOH</td>
<td>Pr</td>
<td>Me</td>
<td>Et</td>
<td>66k</td>
</tr>
<tr>
<td>12</td>
<td>64b</td>
<td>PrOH</td>
<td>Me</td>
<td>H</td>
<td>Et</td>
<td>66b</td>
</tr>
<tr>
<td>13</td>
<td>64f</td>
<td>PrOH</td>
<td>Me</td>
<td>Et</td>
<td>Et</td>
<td>66f</td>
</tr>
</tbody>
</table>

* See text for a discussion of the configuration of the products.

Scheme 12 Photoirradiation of 3-alkoxypyridinium tetrafluoroborates in basic methanol.

Scheme 13 Photosolvation of 3-alkoxypyridinium salts in alcohol.

Reaction in basic alcoholic media afforded cyclopentenone ketals (such as 66), whilst in water, β-hydroxycyclopentanones (such as 69) were obtained.

Table 2 Scope and limitations of the photosolvation of 3-alkoxy pyridinium salts in aqueous sodium hydroxide solution

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64a</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>69a</td>
<td>&lt;5</td>
</tr>
<tr>
<td>2</td>
<td>64c</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>69c</td>
<td>38</td>
</tr>
<tr>
<td>3</td>
<td>64d</td>
<td>Me</td>
<td>Et</td>
<td>Me</td>
<td>69d</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>64e</td>
<td>Me</td>
<td>Pr</td>
<td>Me</td>
<td>69e</td>
<td>44</td>
</tr>
<tr>
<td>5</td>
<td>64f</td>
<td>Me</td>
<td>Me</td>
<td>Et</td>
<td>69f</td>
<td>34</td>
</tr>
<tr>
<td>6</td>
<td>64g</td>
<td>Me</td>
<td>Et</td>
<td>Et</td>
<td>69g</td>
<td>35</td>
</tr>
<tr>
<td>7</td>
<td>64k</td>
<td>Pr</td>
<td>Me</td>
<td>Et</td>
<td>69k</td>
<td>42</td>
</tr>
</tbody>
</table>

3.5. Phototransformation of polycyclic fused pyridinium salts

Irradiation of the berberinephenolbetaine analogues 72a-c in methanol afforded the corresponding aziridines 73 in high yield (70–85%) (Scheme 15). These results were remarkable as previous studies had shown that irradiation of the 3-oxido-1-phenylpyridinium betaine 70 gave the corresponding aziridine 71 in only 6% yield. Interestingly this phototransformation was shown to be reversible. Irradiation of a methanolic solution of betaine 72 with a 100 W mercury lamp fitted with a Pyrex filter afforded the aziridine 73, while on the other hand irradiation of a methanolic solution of aziridine 73 with a 400 W mercury lamp furnished the aziridine 72 in 55% yield. Though there is a clear change in the conjugation of this system upon phototransformation, the authors reported no observations regarding possible photochromic properties of the system.

Scheme 14 Photohydration of 3-alkoxypyridinium salts in water.

Scheme 15 Irradiation of a series of berberinephenolbetaines.
3.6. Phototransformation of bicyclic fused pyridinium salts

Mariano et al. studied the photochemical reactions of fused pyridinium salts \(74\).\(^{27}\) Initial investigations examined the irradiation of the fused pyridinium perchlorate \(74\) under basic aqueous conditions. Irradiation of \(74\) furnished a complex mixture of photolysis products, from which the tricyclic allylic alcohol \(75\) and the dihydropyridone \(76\), presumably originating from elimination of \(75\), could be isolated (Scheme 16). In contrast, irradiation of \(74\) under aqueous acidic conditions, followed by treatment with acetic anhydride in pyridine, led to the formation of the spirocyclic diester \(81\) and the fused hydroazepine \(80\) (Scheme 17). Presumably, addition of water to the \textit{exo} face of the cation \(77\) occurred preferentially at the less hindered \(C-5\) position, giving a 7 : 1 mixture of the tricycles \(78\) and \(79\); \(S_N^2\) (\(78 \rightarrow 80\)) or \(S_N^2\) (\(79 \rightarrow 81\)) ring opening, and peracetylation, would then give the observed products. Irradiation of the cyclopenta-fused pyridinium salt \(82\) in methanolic potassium hydroxide gave the tricyclic allylic alcohol \(84\) as the major product (Scheme 18).\(^{27}\) \(S_N^2\) ring-opening of \(84\), followed by peracetylation, furnished the \textit{meso} diester \(85\) in high yield. To understand the selectivity of the process, a series of DFT calculations were undertaken. The authors proposed that the unusual regioselectivity in the nucleophilic attack on the cation \(83\) stemmed from the strained conformation of the tricyclic aziridine \(83\) which is peculiar to the cyclopenta-fused ring system.

3.7. Photocyclisation of aryl-substituted pyridinium salts

Lyle et al. examined the reaction of a series of 1-(2-chlorobenzyl)pyridinium chlorides \(86–88\) (Scheme 19).\(^{28}\) Irradiation of the pyridinium chlorides \(86–88\) afforded the cyclisation products \(89–91\), in low to modest yield (20–47%). It was found that, even with greater substitution, alkaloid-like skeletons could be prepared with good regiocontrol. Furthermore photocyclisation was shown to be favoured \textit{ortho}\- to the methyl substituent on the pyridinium ring. Cyclisation of \(87\) afforded exclusively \(90\) and

\[
\begin{align*}
\text{Scheme 16} & \quad \text{Photoirradiation of the cyclohexa-fused pyridinium salt under basic conditions.} \\
\text{Scheme 17} & \quad \text{Photoirradiation of the cyclohexa-fused pyridinium salt under acidic conditions.} \\
\text{Scheme 18} & \quad \text{Photoirradiation of penta-fused pyridinium salts under basic conditions.}
\end{align*}
\]
transformation of 88 furnished a mixture of 91a and 91b in a 2 : 1 ratio.

3.8. Asymmetric photosolvation of pyridinium salts

Burger and co-workers\(^{29}\) employed a chiral auxiliary approach to control the absolute configuration of the products of photochemical reactions (Scheme 20). Photoirradiation of the (+)-α-glucopyranosyl-N-pyridinium chloride 92 under basic conditions gave the diastereomeric bridged aziridines 93 and 94 in a 1 : 1 ratio. Peracetylation, and separation by recrystallisation, gave the enantiomerically pure bicyclic aziridine (+)-α-95 whose relative and absolute configuration was determined by X-ray crystallography. The product 95 was subsequently used in a formal total synthesis of (+)-mannostatin A (see Section 6.2).

Scheme 20  Photohydration of the enantiomerically pure pyridinium salt 92.

4. Single electron transfer (SET) photochemistry of pyridinium salts

Mariano has investigated the single electron transfer (SET) photochemistry of pyridinium salts bearing an appropriately positioned electron-rich alkene donor.\(^{31}\) Irradiation of N-prenylpyridinium perchlorate 96 in methanol, followed by hydrogenation, neutralisation and distillation, gave the perhydroindolizidine 97 in good yield (Scheme 21). The hexahydroindolizidine 98 was produced exclusively when the hydrogenation step was omitted. The proposed mechanism of the photoreaction of the pyridinium salt 96 is summarised in Scheme 22. Excited-state electron transfer would yield a diradical cationic intermediate 99; subsequent nucleophilic addition to 99, and cyclisation of the resulting 1,5-diradical 100, would yield the 1,2-dihydropyridine 101.

The remarkable photochemical reduction of the dihydropyridine 101 (→ 98) merits further comment. Mariano proposed that the dihydropyridine 101 may be in dynamic equilibrium with the iminium ion 102 (Scheme 23).\(^{31}\) Single electron transfer from 101 to 102 would yield the α-amino radical 104 and the radical cation 103. Abstraction of a hydrogen atom from methanol by 104 would give the observed indolizidine 98. This mechanism was supported by deuterium labelling studies.

Mariano then focused on the effect of substitution on the electron-transfer process.\(^{31}\) While it was found that 3-alkoxy substituents could be tolerated, and yielded the expected perhydroindolizidines, incorporation of alkenyl side chain at other positions led to unexpected reactions and complex mixtures of products.

5. Studies on the reactivity of the photoisomerisation products

5.1. Nucleophilic aziridine opening with overall retention at the allylic carbon

The bridged aziridines 105 could be opened with overall retention of configuration at the allylic carbon α to the nitrogen. For instance, application of the Sepúlveda-Arques conditions\(^{32}\) to the aziridine 105 led to the formation of the oxazolidinone 106 (Scheme 24). The opening of the aziridine ring by iodide was followed by in situ protection, and participation of the resulting carbamate: the oxazolidinone 106 was obtained in good yield. With an unprotected aziridine, however, substitution did not occur,
instead, only a product derived from a Grob fragmentation was observed.\textsuperscript{34,35}

Treatment of the aziridines 107 with iron nonacarbonyl afforded air-sensitive complexes 108.\textsuperscript{36} Oxidation of the complexes 108 with cerium ammonium nitrate (CAN) led to the formation of the \( \beta \)-lactams 109 in poor to good yield (Scheme 25).

5.2. Nucleophilic aziridine opening with inversion at the allylic carbon

Treatment of the bridged aziridines 110 with oxygen- or sulfur-based nucleophiles resulted in regioselective opening of the aziridine ring with clean inversion of configuration. The cyclopentenes 111, obtained by substitution at the allylic carbon \( \alpha \) to the nitrogen, were obtained in variable yield (Scheme 26 and Table 3). The ring-opened products 111 have been exploited as advanced intermediates in the synthesis of glycosidase inhibitors (Section 6.5).

5.3. \( S_n, 2' \) Opening with organocuprate reagents

Penkett and Simpson\textsuperscript{24} have studied the reaction of bicyclic aziridines 66 with organocuprates. The aminocyclopentenes 112, stemming from \( S_n, 2' \) attack of the nucleophile \textit{anti} to the aziridine, were obtained in modest to good yield (Scheme 27, Table 4).
Penkett and Simpson have reported the oxidative rearrangement of the bicyclic aziridine 66a. Treatment of 66a with mCPBA in a basic medium gave the endo N-oxide 114, which underwent Meisenheimer rearrangement to the oxa-azabicycloheptene 115; further oxidation (→ 116) and elimination afforded the nitrone 117 (Scheme 28).

Burger and co-workers have investigated the stereocontrolled epoxidation of N-protected cyclopentenols (118, 120 and 122), using mCPBA, trifluoroperoacetic acid (derived from urea-hydroperoxide, UHP, and trifluoroacetic anhydride), and DDO (Scheme 29).‡ A high level of stereoselectivity was observed, with epoxidation occurring exclusively syn to the allylic alcohol.

6. Applications in the total synthesis of natural products

A rigorous test of a new synthetic methodology is its application in total synthesis. This section provides a chronological summary of the application of the photochemistry of pyridinium salts in the total synthesis of natural products.

6.1. (±)-Dihydrofumariline-1

In 1985, Hanaoka et al. reported the stereoselective total synthesis of (±)-dihydrofumariline-1 126, with the irradiation of a berberine betaine as the key stereoselective step (Scheme 30). Irradiation of the betaine 124 in methanol afforded the aziridine 125, which was converted into the spirobenzylisoquinoline alkaloid, dihydrofumariline-1, 126, in four further steps. Unlike earlier studies in this area, the reversibility of this reaction was not examined, and furthermore no observations on the potential photochromism of the system were reported.

6.2. (+)-Mannostatin A

In 1998, Mariano and Ling reported the total synthesis of mannostatin A 132, a mannosidase inhibitor (Scheme 31). The aminocyclopentene 128 was obtained by photosolvolysis of pyridinium perchlorate (127) under acidic conditions, followed by peracetylation. Enzymatic desymmetrisation of 128 using electric eel acetylcholinesterase (EEACE) afforded the key intermediate 129 in 80% ee. Palladium-catalysed substitution of 130, with overall retention of configuration, gave the thioether 131. Inversion of the configuration of the allylic alcohol 131 following Wipf’s procedure, and directed dihydroxylation, afforded, after

‡ The relative configuration of the epoxide 119 was initially mis-assigned and later corrected by the authors (ref. 38). Here we report the corrected one.

Table 3  Stereocontrolled opening of the bicyclic aziridine 110 with various nucleophiles

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R¹</th>
<th>R²</th>
<th>NuH; conditions</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>110a</td>
<td>(CH₃)₂OH</td>
<td>H</td>
<td>PhCO₂H; CHCl₃, r.t.</td>
<td>111a</td>
<td>92</td>
<td>33</td>
</tr>
<tr>
<td>2</td>
<td>110b</td>
<td>(CH₃)₂OH</td>
<td>H</td>
<td>PhCH(OAc)CO₂H; CHCl₃, r.t.</td>
<td>111b</td>
<td>87</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>110c</td>
<td>(CH₃)₂OCbz</td>
<td>PhCO</td>
<td>MeSH; BF₃·OEt₂, CH₂Cl₂, -48 °C</td>
<td>111c</td>
<td>82</td>
<td>21</td>
</tr>
<tr>
<td>4</td>
<td>110d</td>
<td>Pr</td>
<td>Me</td>
<td>MeOH; H₂O₂, r.t.</td>
<td>111d</td>
<td>42</td>
<td>21</td>
</tr>
<tr>
<td>5</td>
<td>110d</td>
<td>Pr</td>
<td>Me</td>
<td>H₂O; HClO₄, r.t.</td>
<td>111e</td>
<td>81</td>
<td>21</td>
</tr>
<tr>
<td>6</td>
<td>110d</td>
<td>Pr</td>
<td>Me</td>
<td>AcOH; r.t.</td>
<td>111f</td>
<td>36</td>
<td>21</td>
</tr>
<tr>
<td>7</td>
<td>110d</td>
<td>Pr</td>
<td>Me</td>
<td>AcSH; r.t.</td>
<td>111g</td>
<td>74*</td>
<td>21</td>
</tr>
<tr>
<td>8</td>
<td>110d</td>
<td>Pr</td>
<td>Me</td>
<td>EtO₂CO₂CH₂Cl, r.t.</td>
<td>111h</td>
<td>90*</td>
<td>21</td>
</tr>
<tr>
<td>9</td>
<td>110e</td>
<td>Pr</td>
<td>H</td>
<td>MeOH; H₂O₂, r.t.</td>
<td>111i</td>
<td>67</td>
<td>21</td>
</tr>
<tr>
<td>10</td>
<td>110e</td>
<td>Pr</td>
<td>H</td>
<td>AcOH; r.t.</td>
<td>111k</td>
<td>34</td>
<td>21</td>
</tr>
<tr>
<td>11</td>
<td>110f</td>
<td>CH₂CONH₂</td>
<td>Me</td>
<td>MeOH; H₂O₂, r.t.</td>
<td>111j</td>
<td>93</td>
<td>21</td>
</tr>
<tr>
<td>12</td>
<td>110f</td>
<td>CH₂CONH₂</td>
<td>Me</td>
<td>EtOH; HClO₄, r.t.</td>
<td>111l</td>
<td>79</td>
<td>21</td>
</tr>
<tr>
<td>13</td>
<td>110f</td>
<td>CH₂CONH₂</td>
<td>Me</td>
<td>AcOH; MeCN, reflux</td>
<td>111m</td>
<td>54</td>
<td>21</td>
</tr>
<tr>
<td>14</td>
<td>110f</td>
<td>CH₂CONH₂</td>
<td>Me</td>
<td>EtO₂CO₂CH₂Cl, r.t.</td>
<td>111n</td>
<td>18*</td>
<td>21</td>
</tr>
<tr>
<td>15</td>
<td>110g</td>
<td>(CH₃)₂OH</td>
<td>Me</td>
<td>MeOH</td>
<td>111o</td>
<td>99</td>
<td>21</td>
</tr>
<tr>
<td>16</td>
<td>110h</td>
<td>(CH₃)₂OH</td>
<td>H</td>
<td>MeOH; HClO₄, r.t.</td>
<td>111p</td>
<td>99</td>
<td>21</td>
</tr>
</tbody>
</table>

* Of the N-acylated derivative. * Of the N-ethoxycarbonyl derivative, Nu = Cl. † 40% of a six-membered azalactone also isolated

Table 4  Formation of aminocyclopenteneketals by organocuprate addition

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R¹</th>
<th>R²</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>66a</td>
<td>Et</td>
<td>Me</td>
<td>112a</td>
<td>40*</td>
</tr>
<tr>
<td>2</td>
<td>66a</td>
<td>Et</td>
<td>Bu</td>
<td>112b</td>
<td>39</td>
</tr>
<tr>
<td>3</td>
<td>66a</td>
<td>Et</td>
<td>Vinyl</td>
<td>112c</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>66b</td>
<td>Allyl</td>
<td>Me</td>
<td>112d</td>
<td>51</td>
</tr>
<tr>
<td>5</td>
<td>66b</td>
<td>Allyl</td>
<td>Bu</td>
<td>112e</td>
<td>62</td>
</tr>
<tr>
<td>6</td>
<td>66b</td>
<td>Allyl</td>
<td>Vinyl</td>
<td>112f</td>
<td>35</td>
</tr>
</tbody>
</table>

* Also isolated 13% of 113.
Scheme 29  Stereoselective epoxidation of the aminocyclopentenols.

![Scheme 29](image)

Scheme 30  Photochemical transformation of berberine betaine in the stereoselective synthesis of dihydrofumariline-1 126.

![Scheme 30](image)

deprotection, the hydrochloride salt of (+)-mannostatin A (132). The hydrochloride salt of the natural product was obtained in 11% overall yield in eleven synthetic steps.

![Scheme 31](image)

Scheme 31  Total synthesis of (+)-mannostatin A by Mariano and co-workers.

The versatility of Mariano’s synthetic strategy for the construction of (+)-mannostatin A was later exemplified by the preparation of a series of stereo- and regioisomeric analogues.44

In Burger’s approach to mannostatin A, a chiral auxiliary was used to induce asymmetry in the photochemical step (see Section 3.8 and Scheme 20). The enantiomerically pure aziridine 95 was opened with thioacetic acid to afford 134 (Scheme 32). It is worth noting that the regio- and stereocontrolled attack of the nucleophile was accompanied by inversion of the anomeric centre.29 Finally, ester hydrolysis, methylation, removal of the chiral auxiliary, and acetylation, gave the advanced intermediate 131, in Mariano’s synthesis of mannostatin A, obtained in 20% overall yield and 96% ee.17
6.3. The aminocyclopentanol core of allosamidine

In 2001 Mariano et al.\textsuperscript{45} completed the synthesis of the aminocyclopentanol core of (−)-allosamizoline,\textsuperscript{46} the aglycone of the chitinase inhibitor allosamidine (Scheme 33).\textsuperscript{47} Inversion of the configuration of the allylic alcohol 129, an intermediate in their total synthesis of mannostatin A, was accomplished using Burgess′ reagent 133; silylation and ester hydrolysis gave the cyclopentenol 135. A [2,3]-Wittig rearrangement\textsuperscript{48} was used to prepare the alcohol 136. Stereoselective epoxidation of the N,O-acetal 137 gave the epoxide 138 in 84% yield. Regioselective opening of the epoxide 138 under basic conditions and deprotection afforded the aminocyclopentanol core of allosamidine, 139, in 17% overall yield.

6.4. Trehazoline

Burger and co-workers have worked on a synthetic approach to trehazolamine analogues (Scheme 34).\textsuperscript{22} Trehazolamine 146 is the cyclopentenol component of the trehalase inhibitor trehazolamine.\textsuperscript{49} Irradiation of meta-hydroxymethylpyridinium bromide 53 afforded the separable bridged aziridines 57 and 58 (Section 3.3). The aziridine 141 was converted into the oxazolidinone 143 with overall retention of configuration of the allylic carbon α to nitrogen; hence, inversion of this stereocenter of 142 was followed by Boc-protection of the resulting amine, and cyclisation (→ 143).\textsuperscript{5} Basic cleavage of the oxazolidinone afforded the allylic alcohol 144 which directed an epoxidation reaction to yield the syn diastereomeric epoxide 145.

Recently, Mariano and co-workers\textsuperscript{50} have reported the total synthesis of the peracetylated trehazolamine using a similar approach (Scheme 35).

Photohydration of the meta-substituted pyridinium salt 147 afforded a mixture of the aziridines 148 and 149. After suitable protecting group manipulations, inversion of the configuration of the allylic alcohol 152 was accomplished using Burgess′ reagent 133 and opening of the resulting oxazolidine with sodium dihydrogen phosphate. Opening of the epoxide 154 with aqueous sodium hydrogen carbonate is needed to yield the desired product 155.

\textsuperscript{§} The one-pot Sepúlveda-Arques methodology was not successful with this substrate (see Section 5.1).
Scheme 34 Synthetic approach to the trehazolamine analogue by Burger and co-workers.

Scheme 35 Synthesis of the peracetylated trehazolamine by Mariano and co-workers.

benzoxate, hydrolysis and peracetylation, afforded the known\(^{51}\) peracetylated trehazolamine derivative \(155\) in 9.3% overall yield over 12 steps. In the same paper, the use of Burger’s chiral auxiliary (see Section 3.8) in an asymmetric synthesis of \(150\) was also reported.

6.5. Aminosugars

In 2002, Mariano et al. reported stereodivergent syntheses of both enantiomers of the aldehyde \(158\) from the enantiomerically enriched cyclopentenol \(129\) (Scheme 36).\(^{42}\) Ozonolysis and reduction of the orthogonally-protected aminocyclopentenol \(156\) afforded the tetrox \(157\); desilylation, acetonide formation and Swern oxidation afforded the D-aminosaccharide \(158\). By changing the order of the protection steps, the enantiomeric aminocyclopentenol \(ent-156\) was prepared which could, in principle, be converted into the enantiomeric product \(ent-158\).

Starting from the key intermediate \(129\), the authors also prepared an advanced intermediate, \(163\), in a synthesis of N-acetylneuraminic acid \(164\) (Scheme 37).\(^{52}\) In this instance, the synthetic strategy began by inverting the configuration of the allylic alcohol \(129\) (\(\rightarrow 159\)). Aldehyde \(161\) was homologated using a stabilised ylide reagent (\(\rightarrow 162\)). The Z-isomer of \(162\) underwent \(\text{Hg(II)}\)-mediated cyclisation to give the intermediate \(163\) in 30% overall yield over 12 steps.

6.6. (−)-Swainsonine

In 2004 Mariano et al. prepared (−)-swainsonine, a potent glycosidase inhibitor (Scheme 38).\(^{53}\) Photoirradiation of pyridinium chloride in acidic aqueous medium, was followed by conversion into the functionalised cyclopentene \(165\). Ru-catalysed ring rearrangement metathesis (RRM), and protecting group manipulation, gave the key intermediate \(166\). Dihydroxylation of \(166\) using catalytic \(\text{OsO}_4\), with NMO as co-oxidant, provided a diastereomeric 81 : 19 mixture of diols \(167\). The major diol was converted into (−)-swainsonine with 80% ee.

6.7. (+)-Castanospermine

In 2005, as a further demonstration of the flexibility of their methodology, Mariano and co-workers applied their RRM strategy to the total synthesis of (+)-castanospermine, a glycosidase inhibitor (Scheme 39).\(^{54}\) The key intermediate \(165\), obtained as previously reported from photohydroxylation of the pyridinium
perchlorate and suitable functional group manipulation, underwent smooth RRM to afford tetrahydropyridine 170.

Regio- and stereoselective epoxidation of the endocyclic double bond was achieved with vanadyl acetylacetonate to afford, after benzylaition, the tetraol 171. Oxidative hydroboration of the terminal alkene afforded the desired primary alcohol with concomitant deacetylation of the nitrogen. Mitsunobu cyclisation followed by hydrogenolytic debenzylation afforded (+)-castanospermine 173 in 6.2% yield over 8 steps (starting from 165).

6.8. (−)-Cephalotaxine

In 2006, Mariano and Zhao described the preparation of two late-stage intermediates in the synthesis of (−)-cephalotaxine 177 (Scheme 40). Irradiation of the cyclopenta-fused pyridinium salt 82 (see Section 3.6) gave the spiro-fused diester 85 which was desymmetrised in an enzymatic reaction. The rapid assembly of the complex aza-spiro-skeleton 174 was used to great effect to prepare advanced intermediates in two formal syntheses of (−)-cephalotaxine (Scheme 40).

Mariano synthesised the spirocyclic amido-allylic alcohol 174 from the pyridinium salt 82 in eleven steps and 11% yield, the alcohol 176 had previously been prepared by Mori and Isono in the first nonracemic total synthesis of the natural product. Yoshida et al. and Tietze and Schirok have independently reported approaches towards (−)-cephalotaxine which exploit a Heck reaction of 176 as a key synthetic step.
7. Summary and perspectives

Despite the only sporadic attention paid to the phototransformation of pyridinium salts during the first twenty years since its discovery, the concerted effort now apparent from a number of groups demonstrates that the potential of this powerful transformation has begun to be realised. Strategies have emerged that exploit this remarkable rearrangement, the rapid construction of dense functionality and stereochemistry from simple, planar aromatic substrates has inspired the chemical community. The synthetic utility of variously substituted pyridinium salts has been examined and annealed into techniques that provide facile access to advanced intermediates toward biologically active species and synthetically powerful stereochemically enriched synthons. The interest in this transformation is expanding, and with improving photochemical reaction technologies, doubtless there will be further advancements and applications in the photochemistry of pyridinium salts.
Application of fused 1,2-pyridinium salts to the formal synthesis of (−)-cephalotaxine 177.

References


