# New Methods of Preparing Cyclopentenone Ketals: The Photosolvolysis of 3-Alkoxypyridinium Tetrafluoroborates

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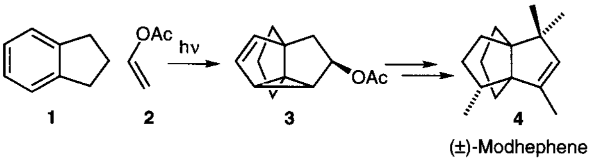
**Abstract:** A new base catalysed method of ketal formation is reported, such that substituted cyclopentenone ketals are prepared from 3-alkoxypyridinium tetrafluoroborate salts.

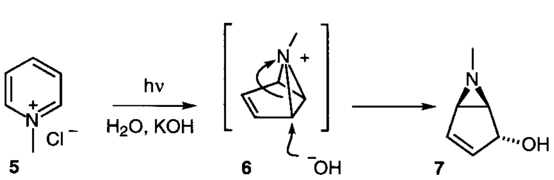
**Key words:** cyclopentenones, photochemistry, pyridinium salts, tetrafluoroborates, ketalisation

The photochemical properties of aromatic compounds are a source of amazement to many organic chemists. In particular the *meta*photocyclo addition[1] has often been described as the reaction that leads to the greatest increase in molecular complexity. This light induced reaction between an aromatic ring and an olefin was concurrently discovered in 1966 by Wilzbach and Kaplan[2] and also by Bryce-Smith, Gilbert and Orger.[3] The *meta*photocycloaddition has been very elegantly utilised by Wender for the synthesis of a number of key natural products, such as (±)-α-cedrene[4] and (±)-modhephene (**4**)[5] (Scheme 1).



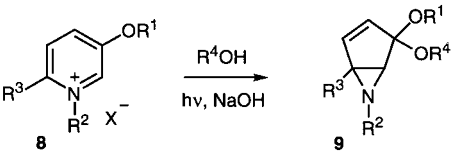
**Scheme 1**

As yet there have been no reports of heteroaromatic compounds being involved with similar reaction sequences, although Wilzbach, Kaplan and Pavlik[6] reported an unusual photohydration reaction of pyridinium ions in 1972. These workers described how the irradiation of an alkaline solution of *N*-methylpyridinium chloride **5** led to the formation of a bicyclic aziridinyl alcohol **7**. It was proposed that the reaction proceeded *via* an *aza*benzvalene **6** cation that was subsequently captured by water from the least hindered face.



**Scheme 2**

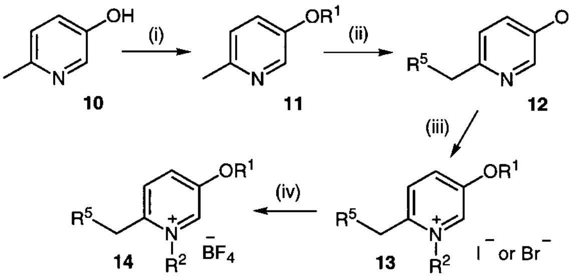
A renaissance of interest in this reaction has led to some important discoveries by Mariano[7] and Burger.[8,9] Mariano reported the results of photosolvolysis of various pyridinium salts and subsequent solvolytic aziridine ring opening of the products.[7] Burger then reported how this reaction could be used for β-lactam synthesis[8] and, more recently, has shown how polyhydroxylated aminocyclopentanes[9] can be made. We were intrigued to know what effect an electron donating group at the 3 position on the pyridine ring would have on the photosolvolysis of pyridinium salts. We reasoned that the incipient cation would be very stable and should be readily captured by the solvent to form a geminal bisalkoxy species. To test our hypothesis various 3-alkoxypyridinium salts **8** were irradiated in different solvents using a 400 W medium pressure mercury vapour lamp with a pyrex filter. Analysis of the different products showed that a series of cyclopentenone ketal derivatives **9** had been made (Scheme 3).



**Scheme 3**

The pyridinium salts were made according to standard literature procedures, starting from either 3-hydroxypyridine or 3-hydroxy-6-methylpyridine **10**. The hydroxyl group was initially protected as an ether **11** using an alkyl halide.[10] In order to introduce larger alkyl groups at the 6 position of the pyridine ring, the 6-methylpyridine derivative was metallated using LDA and quenched with an appropriate alkyl halide.[11] The pyridine species were quaternised by heating in neat alkyl bromide or iodide inside a sealed tube and, after filtration, the pyridinium halides **13** were converted to the tetrafluoroborate salts **14** using silver carbonate and fluoroboric acid. Chloride[6,8,9] and perchlorate[7] salts have previously been used for photosolvolysis reactions, although we opted to use tetrafluoroborate salts; they were easy to make from the halide salt (which tended to undergo photoinduced charge transfer reactions) and were less likely to detonate than perchlorate salts.

A series of different pyridinium salts were synthesised and subsequently irradiated in a solution of sodium hy-



(i) $R^1I$ or $R^1Br$, DMSO, KOH; (ii) LDA, $R^5I$ or $R^5Br$; (iii) $R^2I$ or $R^2Br$, Δ, sealed tube; (iv) $Ag_2CO_3$, $HBF_4$, acetone, MeOH

**Scheme 4**

droxide in either methanol or *n*-propanol. In one example (entry 5), the reaction was performed using the perchlorate salt as well as the tetrafluoroborate salt to compare the efficacy of the two counterions. The results are displayed in the Table.

The points to note from these results are:

1) In entry 5, the perchlorate salt yielded slightly more product than the tetrafluoroborate salt, although from a safety point of view it is preferable to use the latter.

2) The yield of cyclopentene product increases up to a certain point as the size of the group ($R^3$) at the 6 position of the pyridinium ring increases from hydrogen to *n*-propyl.

3) The same also appears to be true of the *N*-alkyl group ($R^2$) and the *O*-alkyl group ($R^1$).

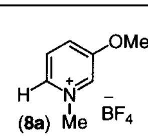
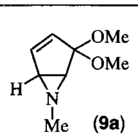
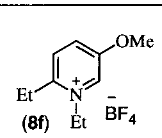
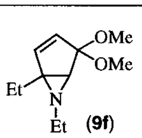
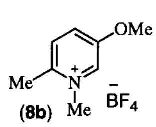
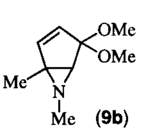
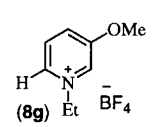
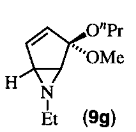
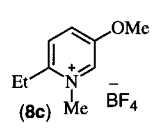
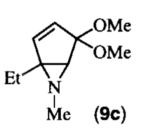
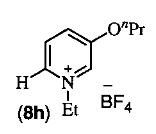
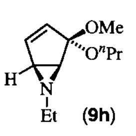
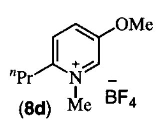
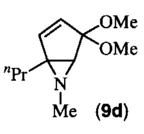
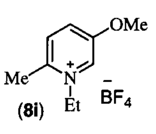
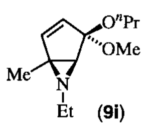
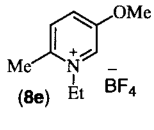
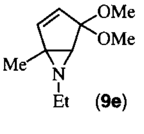
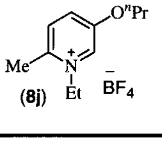
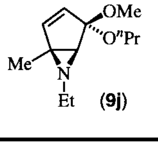
4) The alkoxypyridinium salts react in solvents other than methanol, although lower yields of product were recorded if the reaction was performed in *n*-propanol.[7]

5) The basic conditions under which the reactions take place do not allow the ketal moiety to equilibrate with the solvent. This allows the formation of mixed ketals.

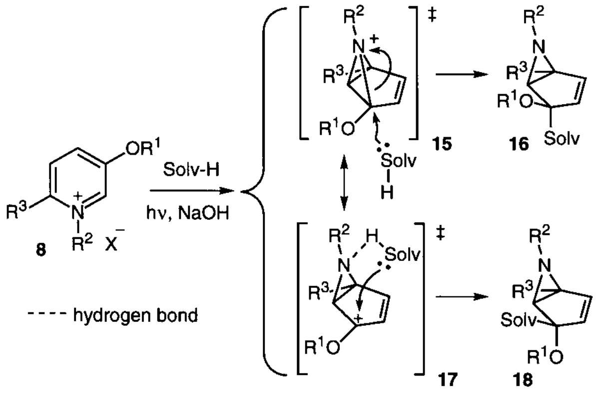
6) The reaction shows stereoselective incorporation of the solvent, as observed by comparing the spectroscopic data of the two mixed ketals **9i** and **9j**. The relative stereochemistry of the products has been assigned from NOE difference data, the most obvious differences being shown for compound **9h**.[12]

This last point appears to conflict with the results published in earlier papers,[6–9] where one might expect the solvent (SolvH) to attack from the opposite side to the newly formed aziridine. We attribute this unexpected observation to different stereoelectronic effects controlling the direction of attack. The electron donating alkoxy group will tend to stabilise adjacent carbocations, making the positively charged intermediate more carbocation like **17** and less *aza*benzvalene like **15**. This allows a hydrogen bonding interaction between the solvent and the aziridinyl nitrogen, which will direct the solvent to attack the carbocation **17** from the same face as the aziridine and so favour the formation of **18** (Scheme 5).

**Table**

| Entry | Substrate | Solvent | Product | Yield | Entry | Substrate | Solvent | Product | Yield |
|---|---|---|---|---|---|---|---|---|---|
| 1 |  (8a) | MeOH |  (9a) | 6 % | 6 |  (8f) | MeOH |  (9f) | 92 % |
| 2 |  (8b) | MeOH |  (9b) | 41 % | 7 |  (8g) | ${}^nPrOH$ |  (9g) | 0 % |
| 3 |  (8c) | MeOH |  (9c) | 77 % | 8 |  (8h) | MeOH |  (9h) | 50 % |
| 4 |  (8d) | MeOH |  (9d) | 70 % | 9 |  (8i) | ${}^nPrOH$ |  (9i) | 42 % |
| 5* |  (8e) | MeOH |  (9e) | 65 % | 10 |  (8j) | MeOH |  (9j) | 81 % |

* Entry 5 was repeated using the perchlorate salt of **8e** and resulted in a 79 % yield of **9e**



Scheme 5

### Irradiation of 1-ethyl-3-methoxy-6-methylpyridinium tetrafluoroborate (8e)

A $N_2$-purged solution of 1-ethyl-3-methoxy-6-methylpyridinium tetrafluoroborate (**8e**) (400 mg, 1.67 mmol) and sodium hydroxide (308 mg, 7.7 mmol) in methanol (350 ml) was irradiated for 3 hours in a quartz immersion well with a pyrex filter using a 400 W medium pressure mercury vapour lamp. The photolysate was concentrated *in vacuo* and the residue was triturated with dichloromethane. The resulting orange solution was concentrated *in vacuo* and subjected to column chromatography (silica gel, dichloromethane:ethanol:ammonia 200/8/1) to yield 1-methyl-4,4-dimethoxy-6-ethyl-*aza*bicyclo[3.1.0]hex-2-ene (**9e**) (197 mg, 1.08 mmol, 65 %) as a yellow oil.

$^1$H-NMR (300 MHz, $CDCl_3$) δ: 1.20 (3H, t, *J* 7), 1.46 (3H, s), 2.00 (1H, d, *J* 1.3), 2.42 (2H, m), 3.31 (3H, s), 3.40 (3H, s), 5.70 (1H, dd, *J* 1.8, 5.8), 6.07 (1H, d, *J* 5.8). $^{13}$C-NMR (75 MHz, $CDCl_3$ with DEPT 135) δ: 9.94 (CH or $CH_3$), 14.98 (CH or $CH_3$), 46.92 ($CH_2$), 48.59 (CH or $CH_3$), 49.07 (C), 49.32 (CH or $CH_3$), 51.11 (CH or $CH_3$), 110.49 (C), 131.28 (CH or $CH_3$), 141.56 (CH or $CH_3$). IR: (thin film) 3054, 2963, 2937, 2873, 2831, 1610 cm$^{-1}$. EI MS *m/z* (rel. intensity): 166 (11), 152 (100, $[M\text{-}OCH_3]^+$), 137 (10), 124 (37).

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## References and Notes

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(12) NOE difference results for compound (**9h**);