From Pyrylium to Pyridinium Salts: Understanding Physicochemical Features

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Abstract

It is known that physical properties of pyridinium salts can be modulated by their chemical characteristics. Owing to their broad range of applications in biology, biotechnology and chemical research, the design and synthesis of a series of 2,4,6-tri-arylpyridinium salts with modified structural backbone have been carried out. The main strands of work have included modifications on pyrylium cation and nature of amines used as precursors. For pyrylium moiety electronic and steric changes in *ortho* and *para* positions were performed. The steric influence of the neighbouring groups into the amine reactivity and the changes of the nucleophile strength of this function have also been investigated. Thus, we have analyzed all these aspects to understand the chemical reactivity and seeking further applications.

Keywords

Pyridinium salts; Pyrylium salts; Amines; Carbohydrates

Introduction

Pyridinium salts are widely applied as synthetic building blocks to obtain substituted pyridine, dihydropyridine or piperidine. This synthetic strategy has been described for different applications such as total synthesis of Geissoschizine,[1] cannabisativine, Lepadin B, among others. Pyridinium salts have been also used to achieve asymmetric and regioselective synthesis by additions of Grignard reagents.[2] Furthermore, pyridinium salts have been applied as acylating agents, phase transfer catalyst or ionic liquid and dyes as a result of its intrinsic fluorescence. More recently, bispyridinium moieties have been employed in a tandem cyclization for the synthesis of indolizine derivatives.[3]

Different methods are available for the synthesis of pyridinium salts depending on the symmetry around of cation. One of them involves the use of pyrylium salts as

precursor. These salts are cationic organic molecules with trivalent oxygen in a six member aromatic rings.[4] These compounds have been exploited to design sensors for anions, amines, amino acids and chameleon labels for quantifying proteins.[5] The factors that govern the reactivity of these cations have been previously reported.[6]

In this communication, we have focused on the design and synthesis of different 2,4,6-tri-arylpyridinium salts. Mechanistic considerations, acid and base catalyst or steric hindrance are some general requirements that have been explored.

Experimental Methods

All chemicals were purchased and used without further purification. Evaporations were conducted under reduced pressure. TLC was performed on silica gel plates (DC-Alufolien F254, E. Merck); The synthesis of pyrylium tetrafluorobate from chalcone was previously carried out[7] and detection of compounds was accomplished with UV light (254 nm) and by charring with H_2SO_4 and characterization with NMR spectroscopy and Mass spectrometry.

For the synthesis of pyridinium salts reaction between different pyrylium salts and amines were carried out by using acetic acid as catalyst. All compounds were isolated after few minutes and purified by crystallization.

E.g.: *N*-prop-1-yne-2,4,6-tri-phenylpyridinium tetrafluoroborate (**6**)

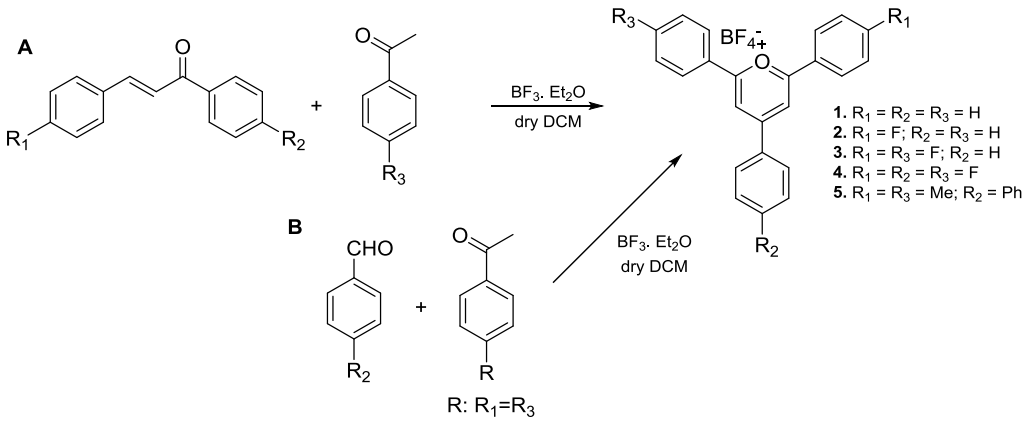
To a solution of propargylamine (3.2 equiv.) in CH_2Cl_2 dry (2 mL) and glacial acetic acid, compound **1** (1 equiv., two portions at 10 min. intervals) was added. The mixture was stirred at room temperature. After 1 h, the complete transformation of the starting product was observed. Solvent was evaporated to dryness to give compound **6** (71% yield) after crystallization from Et_2O. This compound can be also purified by column chromatography (EtOAc/hexane gradient 3:1→1:1→AcOEt→MeOH). ^{1}H-RMN (300 MHz, Acetone-d_6, δ ppm, *J* Hz) δ 8.50 (s, 2H, H-3 and H-5), 8.23 [m, 2H, 4-(2´-,6´)-H], 7.92 [m, 4H, 2,6-(2´-,6´)-H], 7.74-7.67 (m, 9H, aromatics proton), 5.18 (d, 2H, *J* = 2.6, N-CH_2), 3.24 (t, 1H, *J* = 2.5,-C*H*)

Results and discussion

Control of chemical and physical properties of pyridinium salts is a critical goal in the design of this kind of compounds for different applications.

Nucleophilic attack of an amine necessarily occurs at the electrophilic position, C-2, of pyrylium cation. Then, the new intermediate formed can be cycled again by action of an acid. It known that the ring-closure by secondary amines is not possible. For this reason, reactions of three primary amines were studied.

The synthesis of pyrilium salt **1** was performed by two strategies: (**A**) synthesis from commercial available chalcone or (**B**) directly by reaction between benzaldehyde and acetophenone. In both cases, the Lewis acid $BF_3.Et_2O$ was used to mediate dehydration and cyclization steps of 1,5 dicarbonyl compound formed *in situ*. (Scheme 1)



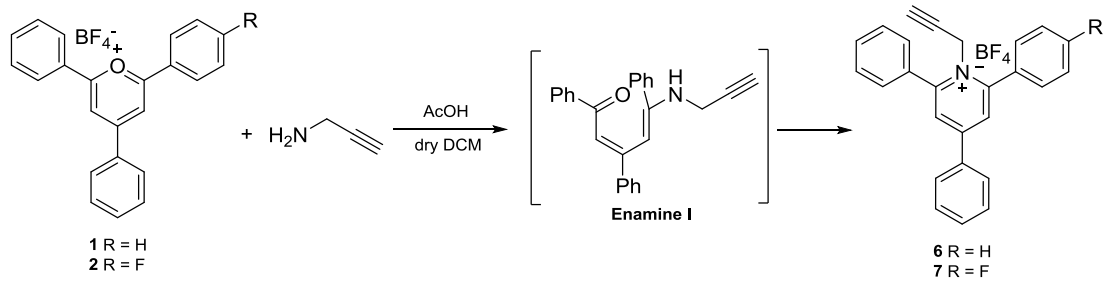
Scheme 1. Synthesis of pyrylium salts from (**A**) chalcone and (**B**) directly from aldehydes and ketones

Following the later approach, symmetric compounds **2-5** were synthesized with intrinsic fluorescence in acceptable yields. For this kind of structures singlets for H-3 and H-5 at 9 ppm approximately that confirm the presence of pyrylium cation were observed in ^{1}H NMR.

Reaction of compound **1** with propargyl amine gave a new compound, **6**, in excellent yield. It is interesting to note that in the course of this preparation, the solution turned on red colored due to the formation of the characteristic mixture of 5-aminoketones (enamine **I** named "*divinylogous amide*") before the cyclization step was observed.[8] The same conditions were applied for obtaining desired pyridinium salt **7** from compound **2** (Scheme 2). ^{1}H NMR spectrum shows the propargylic proton at δ 3.25 ppm with *J* 2.6 Hz and a doublet at 5.19 ppm for methylene protons.

The next reaction studied to obtain carbohydrate-based pyridinium salts between 1,3,4,6-tetra-O-acetyl-*β*-D-glucosamine (**8**) and pyrylium cation **1** not provided the desired pyridinium salts successfully. A number of conditions were tried to improve the

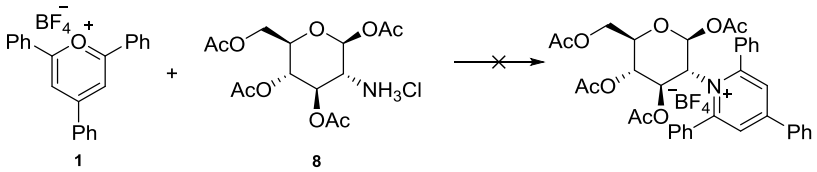
reaction, such as acid concentration, base to deprotonate the enamine I, scavenger for water, among others. (Table 1)



Scheme 2. Synthesis of pyridinium salts **6** and **7**. It is shown the intermediate "divinylogous amide" **I**

The attempts to enhance the nucleophilic properties of the amino groups by treatment with bases as K_2CO_3, NaOH or DIPEA proved to be useless. Specifically dramatic is the use of NaOH which hydrolyzed the pyrylium salts to form 1,5-di-ketones and removed acetyl groups on carbohydrate moiety. Other conditions as an increase of temperature (r.t. to 70 ºC) and reaction times were not satisfactory. This fact can be due to steric hindrance between the aromatic system with acetyl groups on anomeric and C-3 position. Previous works of our research group have demonstrated that aromatic rings at C-2 and C-6 are slightly rotated out of the plane of pyrylium cation.

Table 1. Reaction conditions used to obtain carbohydrate-based pyridinium salts



Conditions	Solvent	Base	Acid	Other Conditions
A	CH_2Cl_2	K_2CO_3[a]	AcOH	-
B	MeOH	Et_3N	AcOH	Ac_2O, 70 ºC
C	CH_2Cl_2	NaOH[a], Et_3N	AcOH	EtOH, Ac_2O
D	EtOH	NaOH	-	-
E	CH_2Cl_2	NaOH[a], Et_3N	AcOH	-

[a]NaOH 2*M* was initially applied to enhance the nucleophilicity of the aminocarbohydrate.

Finally, by means of ^{13}C NMR studies we have concluded on the basis of the observed chemical shifts that in basic aqueous medium the formation of the di-ketone is the predominant process. However, when this reaction was carried out on chitosan (copolymer of glucosamine and *N*-acetylglucosamine) the pyridinium salts **9** and **10**

from **1** and **5**, respectively were effectively obtained. Degrees of *N*-substitution (DS) of 1 to 6% were determined by ^{1}H NMR.

Conclusions

Synthesis of pyrylium salts (**1**-**5**) was easily carried out. From these compounds the synthesis of pyridinium salts was explored. In this context, propargylamine derivatives synthesized provide supported alkynes for different synthetic applications. However, after many attempts synthesis of glucosamine-based pyridinium salts has not reached. Contrary to expectations, formation of pyridinium cation on polymer of *β*(1-4) linked glucosamine has successfully accomplished. This derivative may provide a good potential candidate for gene therapy.

Acknowledgements

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