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Facile synthesis of functionalized 6-cyano-2-oxa-7-azabicyclo[4.1.0]hept-3-en-1-yl acetates : a catalyst free approach to access the pyran fused 2-acetoxy-NH-aziridines

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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Prasun Mukherjee, Asish R. Das*

Novel 6-cyano-2-oxa-7-azabicyclo[4.1.0]hept-3-en-1-yl acetate scaffold was synthesized directly from 2-amino-3-cyano-4-*H* pyrans as well as 2-amino-3-cyano-spiropyrans using iodobenzene diacetate (PIDA) as oxidant at room temperature in absence of any catalyst. Essentially the enamine fragment of the reactants have reacted with PIDA, that makes this reaction new avenue to synthesize pyran fused 2-acetoxy-NH-aziridine. These remarkably stable pyran fused 2-acetoxy-NH-aziridines can be used in SAR studies in pharmaceutical and medicinal chemistry. Ready availability of the starting materials, operational simplicity, absence of metal catalyst, mild reaction condition, simple workup procedure are the other significant features of this reaction.

Introduction

Aziridines, inherently strained aza-heterocycles, are fundamental precursors to access diverse type of heterocycles due to their strong affinity towards numerous ring opening reactions.[1] Despite their high reactivity due to ring strain, aziridine structural motif can be found in many natural products and synthetic compounds with widespread biological activity.[2] For instance mitomycins, ficellomycins, azinomycins, FR and FK compounds (Figure 1) which contain fused aziridine fragment as their key structural motif, are well known for their potent antitumor and antibiotic activities.[3] In addition, aziridines are also frequently used as chiral auxiliaries and ligands.[4] Regardless of their occurrence as biologically relevant compounds, fused aziridine heterocycles are important in synthetic viewpoint as they can be transformed into numerous other key heterocycles.[5] In addition many fused aziridine heterocycles exhibit photochromic properties.[6]

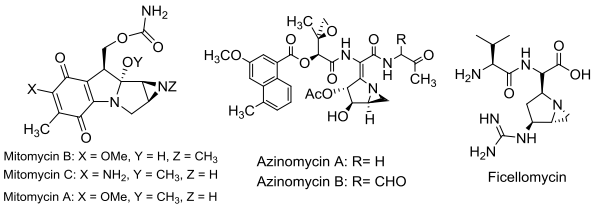
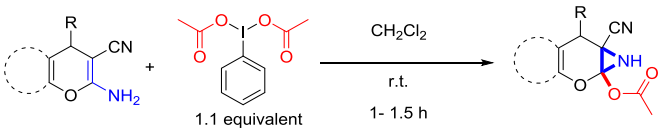


Figure 1. some bioactive natural products possessing aziridine ring as the crucial structural motif

Consequently several methods have been developed over the past decades in order to synthesize aziridines and its fused analogues.[7] The main synthetic routes of those rely on transfer of suitable nitrogen sources to olefins, transfer of suitable carbon sources to imines, reduction of azirines and intramolecular cyclization of amine derivatives. Notably direct synthesis of NH-aziridines is preferred as N-protected aziridines require additional deprotection steps in order to access the NH-form. However, there are hardly any methods to synthesize pyran-fused NH-aziridines, [8] although the resultant scaffold will not only be surplus of biological activity due to the fusion of pyran ring with aziridine but also possess great synthetic utility.

Recently synthesis of azirines from enamine derivatives using hypervalent iodine reagents was reported in literature.[9] 2-amino-4-*H*-pyrans and 2-amino-spiropyrans are privileged compounds, well known for their widespread biological activity.[10] Interestingly, they possess an inbuilt enamine structural feature which can be utilized in construction of aziridine molecular scaffold and the consequence will be the formation of a pyran fused aziridine motif. Continuing our efforts on the development of new and efficient methodologies to synthesize bioactive compounds, [11] herein we wish to report an operationally very simple and robust synthesis of novel pyran-fused 2-acetoxy-NH-aziridines by



Scheme 1. PIDA promoted synthesis of 6-cyano-2-oxa-7-azabicyclo[4.1.0]hept-3-en-1-yl acetates

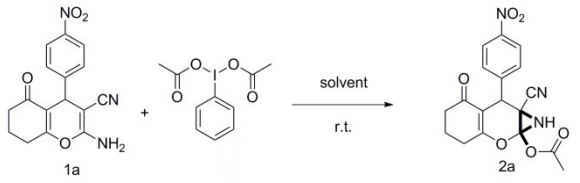
Department of Chemistry, University of Calcutta, Kolkata-700009, India
*Corresponding author: Tel.: +913323501014, +919433120265; fax: +913323519754;
E-mail address: ardchem@caluniv.ac.in, ardas66@rediffmail.com (A R Das)
Electronic Supplementary Information (ESI) available: Spectral data; copies of ^{1}H and ^{13}C NMR spectra for all compounds. See DOI: 10.1039/x0xx00000x

reacting the enamine fragment of 2-amino-3-cyano-4-*H*-pyrans and 2-amino-3-cyano-spiropyrans with iodobenzenediacetate (PIDA) at room temperature in short reaction time (scheme 1) without the involvement of any catalyst. To the best of our knowledge this is the first report for one step synthesis of pyran-fused 2-acetoxy-NH-aziridines from 2-amino-3-cyano-4-*H*-pyrans and 2-amino-3-cyano-spiropyrans. This protocol is essentially metal free and uses PIDA as the sole oxidant which is readily available and less toxic.

Result and discussion

To begin with, a wide variety of functionalized 4-*H*-pyrans and spiropyrans were easily synthesized using known procedures.[12] Taking 2-amino-4-(4-nitrophenyl)-5-oxo-5,6,7,8- tetrahydro-4*H*-chromene-3-carbonitrile (1a) as the model substrate we have then investigated the feasibility of the proposed transformation by treating 1.00 mmol of it with PIDA (1 mmol) in 3 ml of dichloromethane (DCM) at room temperature. The complete consumption of the starting material 1a, monitored by TLC, took only 1 h. Immediate column chromatography of the reaction mixture gave an off white compound in 80% yield (Table 1, entry 1). The ^{1}H NMR spectrum of the compound showed the presence of signals resembling to methyl H's of acetate group at δ 2.257 ppm and a singlet at δ 2.450 ppm

Table 1. Optimization of reaction conditions for the synthesis of 6-cyano-2-oxa-7-azabicyclo[4.1.0]hept-3-en-1-yl acetate[a]



Entry	PIDA (mmol)	Solvent	*T* (°C)	Time (h)	yield(%)[b]
1	1.0	DCM	r.t.	1	80
2	**1.1**	**DCM**	**r.t.**	**1**	**92**
3	1.2	DCM	r.t.	1	90
4	1.5	DCM	r.t.	1	72
5	1.1	DCE	r.t.	2	70
6	1.1	Toluene	r.t.	2.5	68
7	1.1	Dioxane	r.t.	4	60
8	1.1	THF	r.t.	4	64
9	1.1	Acetonitrile	r.t.	2	55
10	1.1	DCM	0	10	72

[a] 1mmol of 1a was taken in 3 ml of solvent in all the cases; [b] yield of the isolated product.

with the disappearance of the signal for the amino group of the starting material. In our delight, the structure of this compound was finally identified and confirmed by X-ray crystallographic analysis as a 6-cyano-2-oxa-7-azabicyclo[4.1.0]hept-3-en-1-yl acetate derivative (Figure 2a). The X-ray analysis also enables us to understand the relative stereochemistry of the compound 2a and permit us to assign the configuration of the C4 centre of compound 2a as R. It can be seen from the ortep diagram of compound 2a that the *p*-nitrophenyl group and the aziridine ring bear a *syn* relationship with each other.

With this promising result in hand, optimization of the reaction condition was then initiated for the synthesis of 6-cyano-2-oxa-7-azabicyclo[4.1.0]hept-3-en-1-yl acetate by changing various reaction parameters (Table 1). Use of 1.1 mmol of PIDA increased the product yield to 92% (Table 1, entry 2). Further increase in yield was not obtained when 1.2 mmol PIDA was used (Table 1, entry 3). Additional increase in the amount of PIDA resulted in the low yield of the product (Table 1, entry 4). When the reaction was performed in other solvents, e.g., dichloroethane (DCE), toluene, dioxane, tetrahydrofuran (THF), acetonitrile, the reaction time as well as yield of the product was found to be greatly affected and in all cases a decrease in the product yield was observed (Table 1, entry 5-9). Further investigation showed that decreasing the temperature to 0 °C reduced the rate of the reaction and very less amount of product was obtained after a prolonged time (Table 1, entry 10).

Having identified the optimized reaction conditions (Table 1, entry 2), we then investigated the prospect and restriction of this methodology as exemplified in Table 2. A wide range of diversified 4-*H*-pyrans (1 mmol) were reacted with 1.1 mmol of iodobenzene diacetate in 3 ml of DCM at room temperature to synthesize functionalized 6-cyano-2-oxa-7-azabicyclo[4.1.0]hept-3-en-1-yl acetate. Various 4-*H*-pyrans, synthesized from different aromatic aldehydes having strong electron donating as well as withdrawing functional groups, hetero aromatic aldehydes and aliphatic aldehyde as well were subjected to this reaction. This method has found to possess well tolerance towards different substituents in the 4-position of the pyran

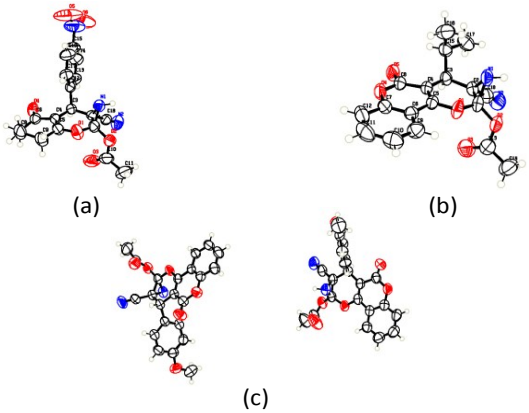
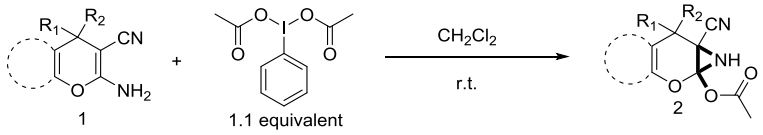


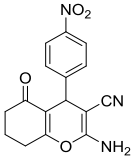
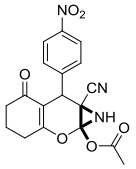
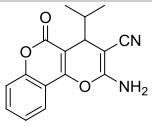
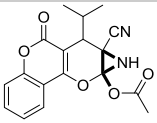
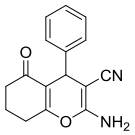
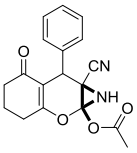
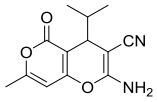
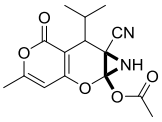
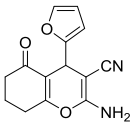
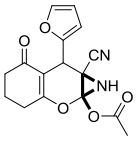
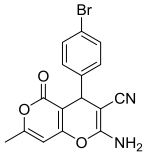
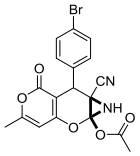
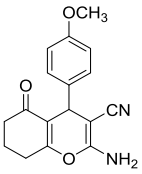
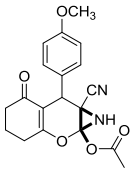
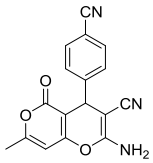
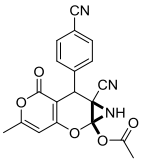
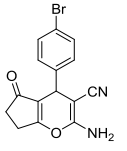
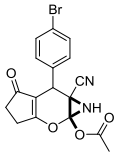
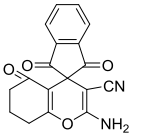
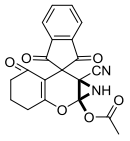
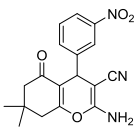
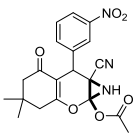
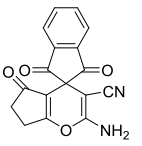
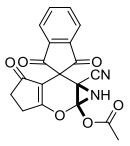
Figure 2. Ortep diagram of single crystal of compounds 2a, 2h and 2j. (a) ORTEP diagram of single crystal of compound 2a (CCDC 1404567), (b) ORTEP diagram of single

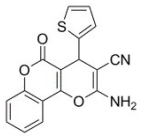
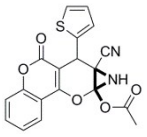
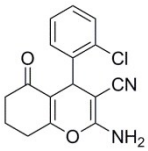
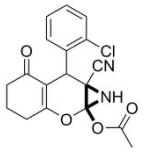
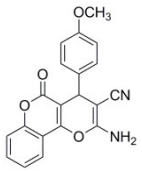
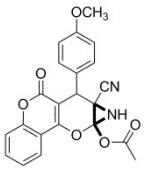
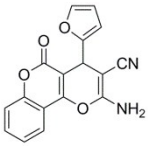
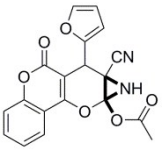
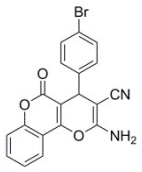
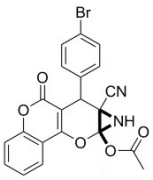
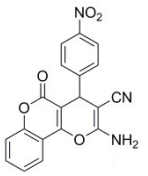
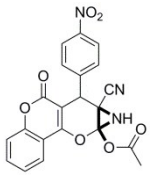
crystal of compound 2j (CCDC 1404581), (c) ORTEP diagram of single crystal of compound 2h (CCDC 1404569).

ring. However a small decrease in the product yield was observed when thiophene ring was present as the substituent (Table 2, 2g). When the nitrile group of the reactants was replaced by $-CO_2Et$ group, complete conversion of the starting material observed at the same condition but we failed to isolate and identify any compounds due to the presence of multiple intimate components in the reaction mixture. Different active methylene compounds, e.g., cyclohexane-1,3-dione, dimedone, cyclopentane-1,3-dione, 4-hydroxycoumarin, 4-hydroxy-6-methyl-2-pyrone, were employed to derive various substituted 4-*H*-pyrans. The reaction proceeded well reliably, affording good to excellent product yield in all the cases (Table 2, 2a-2p). Notably the coumarin and pyrone moiety have found to possess well tolerance towards PIDA. To further explore substrate scope, spiropyrans were subjected to this reaction under the same optimized conditions. The reaction was found to be equally efficient affording excellent yields (Table 2, 2n & 2o).

Table 2. Substrate scope of the reaction[a]



entry	reactant	product	time (h)	yield (%)	entry	reactant	product	time (h)	yield (%)
1	 1a	 2a	1	92	10	 1j	 2j	1.5	85
2	 1b	 2b	1	89	11	 1k	 2k	1.5	84
3	 1c	 2c	1	84	12	 1l	 2l	1.5	86
4	 1d	 2d	1	90	13	 1m	 2m	1.5	88
5	 1e	 2e	1	90	14	 1n	 2n	1.5	88
6	 1f	 2f	1	89	15	 1o	 2o	1.5	86

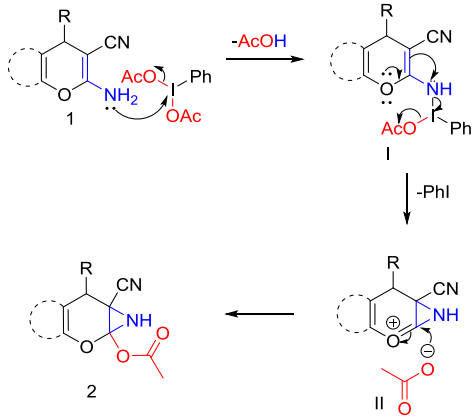
7	 1g	 2g	1.5	76	16	 1p	 2p	1	94
8	 1h	 2h	1.5	90	17	 1q	 2q	1.5	86
9	 1j	 2i	1.5	88	18	 1r	 2r	1.5	90

[a] Reaction conditions: 1a (1 mmol), PIDA (1.1 mmol), DCM (3 ml), r.t.

It is noteworthy to mention here that the product 6-cyano-2-oxa-7-azabicyclo[4.1.0]hept-3-en-1-yl acetate was stable enough and unaffected by silica gel (mesh size 100-200) during column chromatography. The structure of the products was well characterized by spectral (^{1}H, ^{13}C NMR, IR, HRMS) analysis. The structural motif was fully confirmed by X-ray crystallographic analysis of compound 2a, 2h and 2j (Figure 2). The configuration of C4 centre of 2h and 2j was found to be S and R respectively.

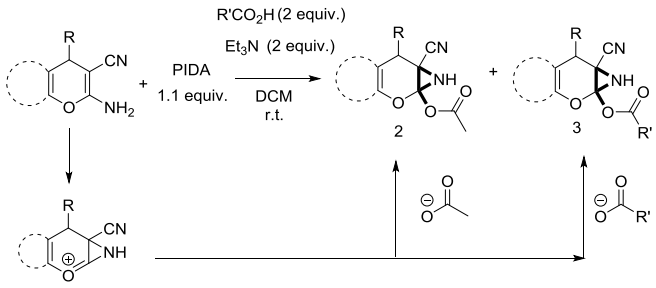
A plausible mechanism[13] for this reaction is depicted in scheme 2. Initial reaction between the amino group of the starting material (**1**) and PIDA results in the formation of N-iodo intermediate **I**. The electron donating resonance effect of oxygen atom of the pyran ring then assists the attack of the double bond to the electrophilic nitrogen center and consequently intermediate **I** converted to **II** by releasing iodobenzene and an acetate anion. In the next step nucleophilic attack of that acetate anion at the C-2 position of the pyran ring results in the formation of the desired product 6-cyano-2-oxa-7-azabicyclo[4.1.0]hept-3-en-1-yl acetate (**2**). The attachment of both –CN and pyran oxygen to the enamine double bond of the molecular scaffold is probably the key reason for the specific formation of 2-acetoxy-NH-aziridines. During the azirine synthesis, as reported by Zhao et al.[9(a, b)], the reaction essentially stops after azirine ring formation, but in this case electron releasing ability of the pyran oxygen atom strongly disfavours the formation of azirine ring and eventually the reaction takes the course of formation of 2-acetoxy-NH-aziridines. The role of strong electron withdrawing –CN group is to preserve the enamine form in the starting materials.[9(b)]

In support of the proposed reaction mechanism we have attempted to trap the intermediate **II** by carrying out control experiments. The reaction was performed in presence of other carboxylate anion by employing 1:1 mixture of triethyl amine (2 equiv.) and a carboxylic acid (2 equiv.) in the reaction mixture (Scheme 3). The outcome of this experiment is shown in Table 3. All reactions were carried out in optimized reaction



Scheme 2. A plausible mechanism of the PIDA promoted synthesis of 6-cyano-2-oxa-7-azabicyclo[4.1.0]hept-3-en-1-yl acetate

condition in presence of aliphatic as well as aromatic carboxylic acids. When cyclohexanecarboxylic acid, phenylacetic acid and diphenylacetic acid were employed products 3a-c, r were obtained as the minor product in low but reasonable yields along with product 2 (Table 3, entry 1-4). However when the reaction was carried out in presence of



Scheme3. Control experiments in support of the proposed mechanism

aromatic acids, 3 was not obtained and the yield of 2 was also affected. The structural motif of compound 3a-c, r were well characterized through spectral analysis (^{1}H, ^{13}C NMR, IR, HRMS) and fully confirmed by X-ray crystallographic analysis of a single crystal of compound 3b (Fig. 3). The S configuration of the C4 centre of 3b was established from X-ray crystallographic analysis. These experimental observations evidently suggest the formation of the intermediate II during the reaction. However employing

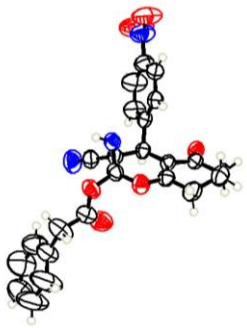
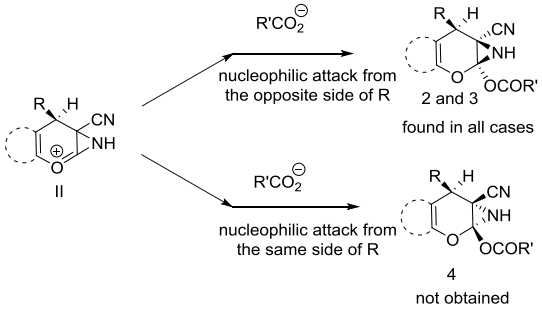


Figure 3. Ortep diagram of single crystal of compounds 3b (CCDC 1434523)

aromatic acids, the reaction did not ends up with the formation of product 3 is not very clear and further exploration is under process.

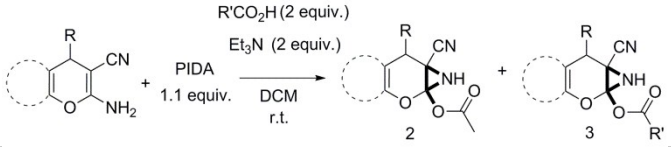
From the X-ray crystallographic analysis of 2a, 2h, 2j and 3b it was established that all the compounds, synthesized using this protocol, possess a *syn* relationship between aziridine ring and the aliphatic or aromatic substituents of the C4 centre. This information further clarified the sterochemical course of the attack of acetate or a carboxylate to the intermediate **II**

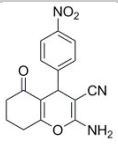
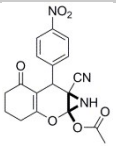
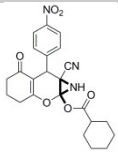
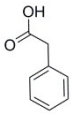
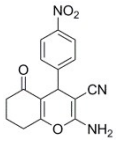
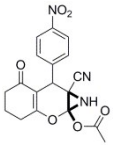
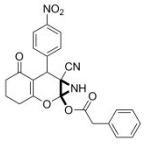
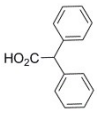
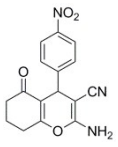
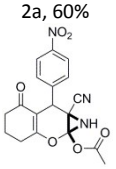
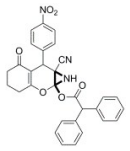
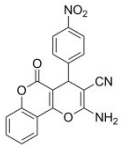
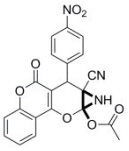
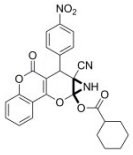
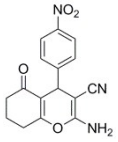
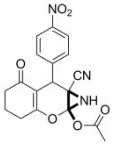
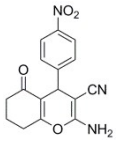
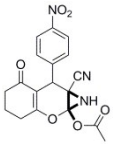
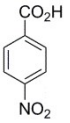
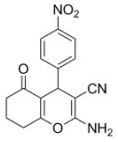
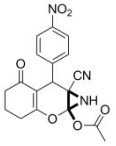


Scheme 4. Stereospecific nucleophilic attack of carboxylate

(Scheme 4). The aromatic or aliphatic substituent of the C4 chiral center controls the regioselective nucleophilic attack of the carboxylate. The β-attack of the carboxylate to the intermediate-II at the α-position of positively charged oxygen center i.e. from the same side of R is sterically inhibited and so did not proceed at all to realize the compound 4 However, attack by the carboxylate ion to the intermediate II from the opposite side of R i.e. from the α-face is sterically favourable and eventually took place at ease to the α-position of positively charged oxygen center regioselectively and ultimately afforded compound 2 and 3 in a diastereoselective manner.

Table 3. PIDA promoted synthesis of 6-cyano-2-oxa-7-azabicyclo[4.1.0]hept-3-en-1-yl acetate [a]



entry	RCO_2H	reactant	Product 2 (yield[b] %)	Product 3 (Yield[b] %)	Time (h)
1		 1a	 2a, 50%	 3a, 40%	1
2		 1a	 2a, 60%	 3b, 25%	1
3		 1a	 2a, 55%	 3c, 22%	1
4		 1r	 2r, 52%	 3r, 35%	1.5
5		 1a	 2a, 70%	[c]	1
6		 1a	 2a, 68%	[c]	1
7		 1a	 2a, 74%	[c]	1

[a] Reaction conditions: 1a (1 mmol), PIDA (1.1 mmol), Et_3N (2 mmol), $R'CO_2H$ (2 mmol) and DCM (3 ml); [b] Isolated yield; [c] no formation of 3.

Experimental Section

General procedure for the synthesis of 4-*H*-pyrans.

Triethylamine (1 drop) was added to a solution of aromatic aldehydes (2 mmol), malononitrile (2 mmol), and 1,3-diketones (2 mmol) in EtOH (5 ml) and the reaction mixture

was refluxed for 15 min. The precipitate that formed was filtered off, washed with water (5×10 ml) and EtOH (3×5 ml), and finally recrystallized from EtOH. The crystallized pure compounds were then subjected for the synthesis of 6-cyano-2-oxa-7-azabicyclo[4.1.0]hept-3-en-1-yl acetates.

General procedure for the synthesis of spiropyrans.

Triethylamine (1 drop) was added to a solution of ninhydrin (2 mmol), malononitrile (2 mmol), and 1,3-diketones (2 mmol) in EtOH (5 ml) and the reaction mixture was refluxed for 15 min. The precipitate that formed was filtered off, washed with water (5×10 ml) and EtOH (3×5 ml), and finally recrystallized from EtOH. The crystallized pure compounds were then subjected for the synthesis of 6-cyano-2-oxa-7-azabicyclo[4.1.0]hept-3-en-1-yl acetates.

General procedure for the synthesis of 6-cyano-2-oxa-7-azabicyclo[4.1.0]hept-3-en-1-yl acetate 2.

To a stirring suspension of 2-amino-3-cyano-4-*H*-pyrans (1 mmol) in 3 ml of DCM, 1.1 mmol of PIDA was added and stirring was continued at r.t. After the total consumption of the starting material, indicated by TLC (20-40 % ethyl acetate in petroleum ether), the reaction mixture was directly subjected for column chromatography (15- 30% ethyl acetate in petroleum ether) to afford the pure product. Same procedure was applied in case of 2-amino-3-cyano-spiropyrans. The isolated products were characterized by spectral (^{1}H NMR, ^{13}C NMR, IR, HRMS), and X-ray crystallographic analysis.

General procedure for the synthesis of 6-cyano-2-oxa-7-azabicyclo[4.1.0]hept-3-en-1-yl carboxylate 3

To a stirring mixture of 2-amino-3-cyano-4*H*-pyrans (1 mmol), triethylamine (2 mmol) and carboxylic acids (2 mmol) in 3 ml of DCM, 1.1 mmol of PIDA was added and stirring was continued at r.t. After the total consumption of the starting material, indicated by TLC (20-40% ethyl acetate in petroleum ether), the reaction mixture was directly subjected for column chromatography (15-30% ethyl acetate in petroleum ether) to afford the pure product. The isolated products were characterized by spectral (^{1}H NMR, ^{13}C NMR, IR, HRMS), and X-ray crystallographic analysis.

Conclusion

In conclusion, 4-*H*-pyrans have been successfully hybridized into novel 6-cyano-2-oxa-7-azabicyclo[4.1.0]hept-3-en-1-yl acetate molecular scaffold. The methodology appeared to be the first example of one step synthesis of pyran fused 2-acetoxy-NH-aziridines from 4-*H*-pyrans and spiropyrans using iodobenzene diacetate as the sole oxidant and involving no other reagent or catalyst. The diastereoselective nature of this reaction makes this protocol highly interesting from synthetic chemistry aspect. The product of this reaction is well fascinating as it is a pyran fused 2-acetoxy-NH-aziridine molecular scaffold possessing high functionalization, and we are sure that this methodology as well as this molecular architecture will grab the attention of the chemists.

Acknowledgement

We gratefully acknowledge the financial support from U.G.C. and University of Calcutta. P. M. thanks U.G.C. New Delhi, India for the grant of his Senior Research Fellowship. Crystallography was performed at the DST-FIST, India-funded Single Crystal Diffractometer Facility at the Department of Chemistry, University of Calcutta.

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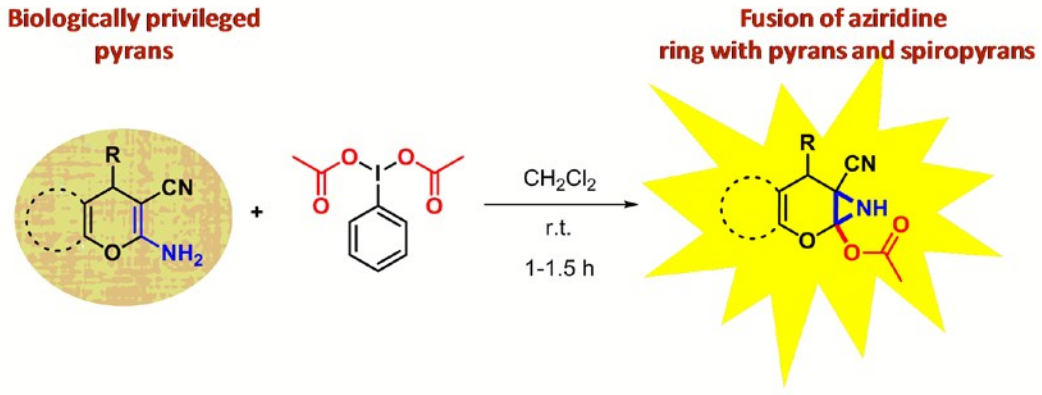
Novel pyran fused 2-acetoxy-NH-aziridine scaffold was constructed by reacting the enamine fragment of 4-*H*-pyrans and spiropyrans using iodobenzene diacetate under catalyst free environment.



Construction of novel pyran fused 2-acetoxy-N-H aziridine scaffold ▪

Metal free aziridine ring formation ▪

Mild reaction condition ▪

18 examples
upto 94% yield