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One-pot synthesis of azanucleosides from proline derivatives

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Abstract

Common cyclic amino acids, derived from proline and hydroxyproline, can be readily transformed into azanucleosides. The mildness of the reaction conditions, and the good yields obtained, make this procedure an interesting alternative to the conventional processes.

Keywords: Azanucleosides; Nucleoside analogues; Radical reactions; Decarboxylation; Iminium ions

The synthesis of nucleoside analogues has proven very valuable to discover new antiviral, antibiotic, antifungal, and antitumoral drugs. Both the base and the carbohydrate chain have been modified: in the case of the azanucleosides, the sugar ring oxygen has been replaced by a nitrogen function (Fig. 1).[1,2]

The heterocyclic ring can be attached to a nitrogen base (N-azanucleosides) or to an aromatic ring (C-azanucleosides). An example of the former is *N*-acetyl azathymidine (**1**) (Fig. 1), which was incorporated to oligonucleotides to decrease their degradation by 3′-exonucleases.[3] On the other hand, immucillin-H (**2**) is a C-azanucleoside,[4] which is being studied to control T-cell proliferative disorders. An intermediate example is the adenosine analogue **3** that once incorporated to DNA (product **4**), strongly inhibits MutY, a glycosylase which repairs damaged DNA.[5]

In the present work, we will focus on the synthesis of N-azanucleosides **5** (Scheme 1) from readily available amino acids **6**, using a combination of tandem and sequential processes to achieve a one-pot transformation, avoiding intermediate purifications. Such method would save time and materials and would give access to many derivatives for structure–activity studies.

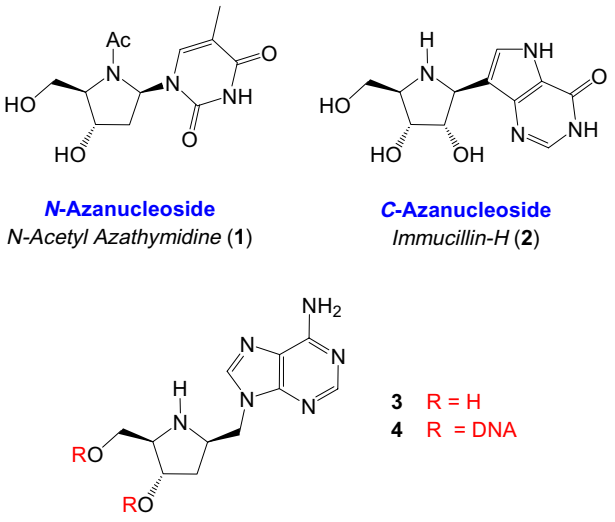

Fig. 1. Azanucleoside families.

In previous articles,[6] we have reported that on treatment with (diacetoxy)iodobenzene (DIB) and iodine and visible light irradiation, amino acids (such as 4-acetoxyproline substrate **7**, Scheme 2) undergo a radical decarboxylation process. The resulting C-radical **8** probably reacts with iodine giving an unstable α-iodopyrrolidine **9**. Extrusion of iodide generates an acyliminium ion **10**, which can be trapped by acetate ions from the reagent, affording the

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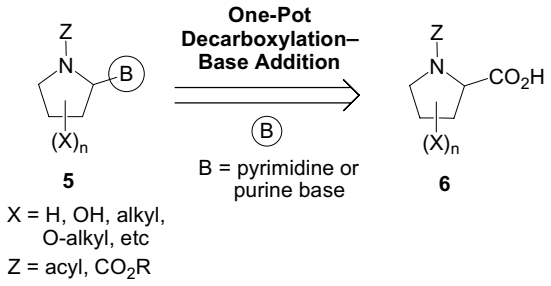
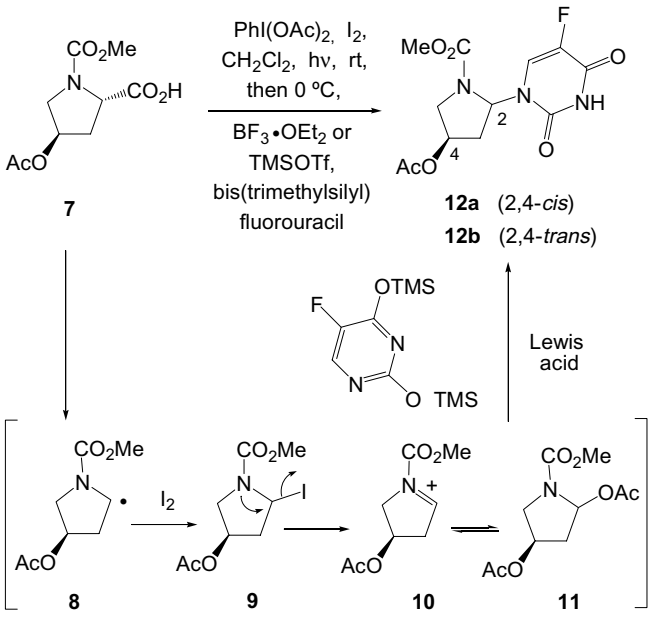


Scheme 1. Azanucleosides from proline derivatives.

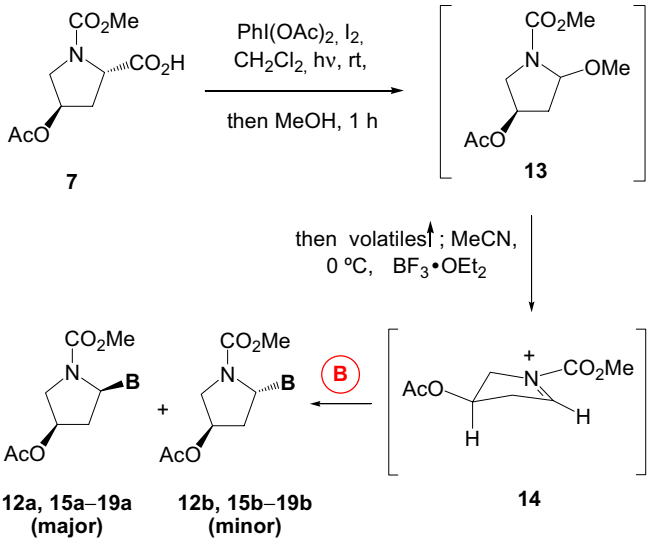


Scheme 2. Synthesis of azanucleosides such as **12a**,**b**.

unstable *N*,*O*-acetal **11**.[7] In the presence of a Lewis acid, this acetal regenerates the acyliminium ion. We reasoned that intermediate **10** could be trapped by silylated nitrogen bases, affording N-azanucleosides (such as products **12a**,**b**).

In a first approach, substrate **7** in CH_2Cl_2 was treated with DIB and iodine, and the scission was carried out for 3 h; then bis(trimethylsilyl)-5-fluorouracil[8] and $BF_3{\cdot}OEt_2$ were added. The reaction gave products **12a**,**b**, although in moderate yields (40–50%, **12a**:**12b**, 5:3).

To improve the yields, different conditions were tried. A two-step procedure was studied first (Scheme 3). Thus, addition of methanol after the scission step generated α-methoxypyrrolidine **13**.[9] This product is more stable than the α-acetoxypyrrolidines, and could be isolated in 86% yield.[6c] Then product **13** was redissolved (CH_2Cl_2 or MeCN) and treated with the nitrogen base and a Lewis acid ($BF_3{\cdot}OEt_2$ or TMSOTf) at different temperatures. MeCN gave better results than CH_2Cl_2, $BF_3{\cdot}OEt_2$ proved to be superior to TMSOTf, and the best temperature for the addition was 0 °C. Thus, treating **13** with $BF_3{\cdot}OEt_2$ and bis(trimethylsilyl)-5-fluorouracil in MeCN at 0 °C,



Scheme 3. Optimized reaction conditions (see Table 1).

afforded azanucleosides **12a**,**b** (5:3) in 92% yield (79% for the two steps).

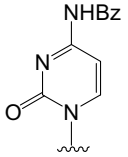
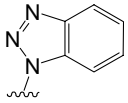
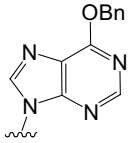
Having optimized the two-step procedure, a one-pot variation was developed. Thus, the scission of substrate **7** was carried out for 3 h, and then methanol was added.[10] The *N*,*O*-acetal **13** was not isolated, but the solvent and excess methanol were removed under vacuum and the crude residue was redissolved in dry MeCN and treated with bis(trimethylsilyl)-5-fluorouracil and $BF_3{\cdot}OEt_2$ at 0 °C. Under these conditions, products **12a**,**b** were isolated in good yield (78%, **12a**,**b** 5:3). This one-pot procedure was later applied to the other nucleophiles (see Table 1).

As shown in Scheme 3 and Table 1, the addition of the silylated nitrogen bases to the acyliminium ion **14** gave separable mixtures of the 2,4-*cis* and 2,4-*trans*-azanucleosides. Interestingly, the cis diastereomers **12a** and **15a**–**19a** predominated over trans isomers **12b** and **15b**–**19b**. We have previously obtained similar results by using carbon nucleophiles.[6c,11]

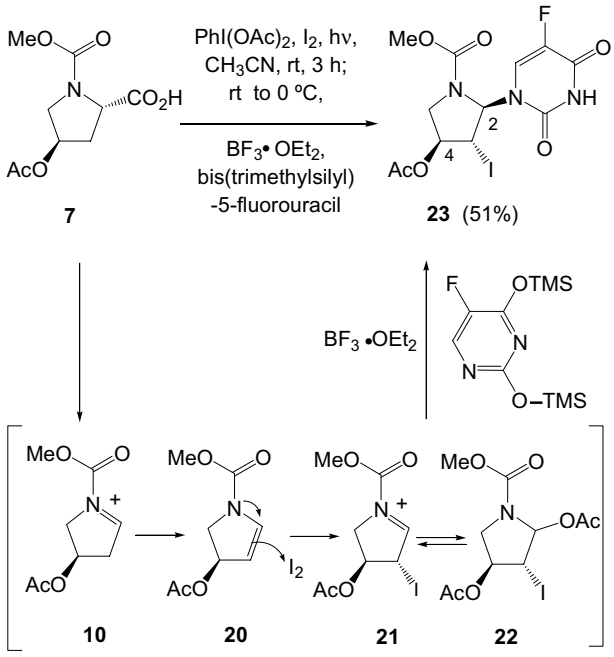
The scope of this procedure can be further expanded by modification of the reaction conditions. When excess iodine was added, and MeCN was used as the solvent both in the scission and the base addition steps, a one-pot scission–β-iodination–base addition process took place (Scheme 4). The increased solvent polarity favored the isomerization of the acyliminium intermediate **10** to the encarbamate **20**,[12] which reacted with iodine generating a second acyliminium ion **21**, precursor of acetate **22**. The addition of boron trifluoride regenerated intermediate **21**, which was trapped by the base (bis(trimethylsilyl)-5-fluorouracil), affording the iodinated 2,3-*trans*-3,4-*trans* azanucleoside **23** (51%). Since the whole process involves at least six reaction steps, each of them must take place in excellent yield to account for the final results.

This methodology allows to introduce an iodo group in a previously non-functionalized position. The manipulation of the halo function can generate a variety of azanucleo-

Table 1
Azanucleosides **12a**,**b**, and **15a/b**–**19a/b** produced via Scheme 3

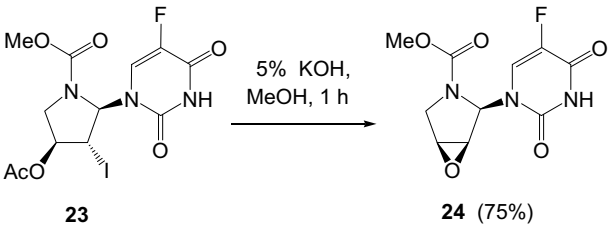
Entry	Base	B	Products[a] (%)
1	Bis(TMS)-5-fluorouracil	X = F	**12a** (49), **12b** (29)
2	Bis(TMS) thymine	X = Me	**15a** (48), **15b** (39)
3	Bis(TMS) uracil	X = H	**16a** (59), **16b** (30)
4	Bis(TMS) cytosine		**17a** (54), **17b** (27)
5	TMS-benzo triazole		**18a** (43), **18b** (33)
6	TMS-benzyl oxypurine		**19a** (34), **19b** (31)

[a] Yields for products purified by chromatography on silica gel.



Scheme 4. Synthesis of β-iodo-pyrrolidines such as **23**.

sides to study structure–activity relationships. For instance, when compound **23** was treated with 5% methanolic KOH (Scheme 5), the acetate was hydrolyzed, and the epoxy derivative **24** was formed (75%; 38% from amino acid **7**). In a simplified version of this process, the scission–iodination was carried out but iodoazanucleoside **23** was not

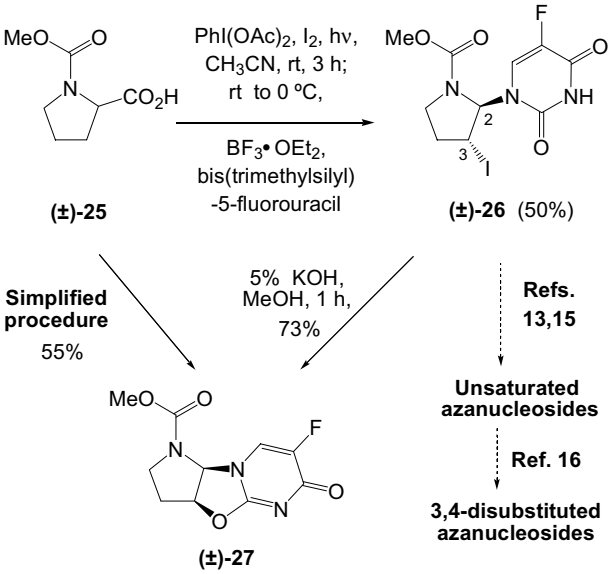


Scheme 5. Conversion of the β-iodo-pyrrolidine **23** into the epoxy derivative **24**.

purified. After the aqueous work-up and solvent evaporation, the residue was treated with 5% methanolic KOH giving epoxide **24** in better global yield (50%). Compound **24** can generate many other azanucleosides by epoxide cleavage with different nucleophiles.[13]

In a related example (Scheme 6), substrate **25** underwent the one-pot scission–β-iodination–base addition process, affording exclusively the 2,3-*trans* β-iodo-azanucleoside **26** (50%). When pure compound **26** was treated with methanolic KOH, an intramolecular S_N2 reaction took place, affording the tricyclic derivative **27** in 73% yield (37% for the two steps). Satisfactorily, the simplified scission–iodination–basic treatment protocol afforded compound **27** in 55% yield. To our knowledge, only one example of related tricyclic azacompounds has been reported,[14] and the biological activity was not studied. We are currently using this protocol to prepare other derivatives and to study their antiviral and antifungal properties.

The iodinated pyrrolidine **26** is also interesting as a possible precursor of unsaturated azanucleosides, which are analogues of antiviral compounds such as stavudine (D4T) or abacavir.[15] The formation of olefinic azanucleosides and their transformation into dihydroxylated or amino hydroxylated azanucleosides[2b,16] currently under study, and will be reported in due time.



Scheme 6. Synthesis of tricyclic compound **27**.

In summary, this work illustrates how readily available substrates can be directly converted into potential drugs by combination of tandem and sequential processes. Thus, proline and hydroxyproline derivatives were transformed into azanucleosides, using a one-pot fragmentation–base addition process. The method is versatile, and allows the introduction of an iodo group in previously non-functionalized positions. The manipulation of the halo substituent can generate new compounds to study structure–activity relationships; thus, the iodinated azanucleosides were transformed into epoxy and fused tricyclic derivatives.

Acknowledgments

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Supplementary data

General procedure for the one-pot fragmentation–base addition reaction, spectroscopic data of compounds **12a**, **12b**, **23**, **24**, **26**, and **27**. Supplementary data associated with this article can be found, in the online version, at doi: 10.1016/j.tetlet.2007.11.113.

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