Synthesis of (Carbo)nucleoside Analogues via [3+2] Annulation of Aminocyclopropanes**

Sophie Racine, Florian de Nanteuil, Eloisa Serrano and Jérôme Waser *

Abstract: (Carbo)nucleoside derivatives constitute an important class of pharmaceuticals, yet there are only few convergent methods to access new analogues. In this communication, we report the first synthesis of thymine, uracil and 5-fluorouracil substituted diester donor-acceptor cyclopropanes and their use in the indium- and tin-catalyzed [3+2] annulations with aldehydes, ketones and enol ethers. The obtained diester products could be easily decarboxylated and reduced to the corresponding alcohols. The method gives access to a broad range of new (carbo)nucleoside analogues in only four-five steps and will be highly useful for the synthesis of libraries of bioactive compounds.

The natural nucleosides constitute the building blocks of DNA and RNA. The interaction of enzymes and other biomolecules with nucleosides is essential for the regulation of genetic expression and cell replication. Therefore, the nucleoside scaffold constitutes a privileged structure in medicinal chemistry (Figure 1).[1] In addition to bioactive natural products, such as the antiviral and antibiotic aristeromycin (1), more than 45 FDA approved drugs are nucleoside analogues. Besides only slightly modified analogues, such as cytarabine (2) and telibudine (3), more elaborated compounds derived from thymine have been successful, such as the carbonucleoside stavudine (4), the anti-HIV front drug azidothymidine (5) or the fluorinated floxuridine (6). Nevertheless, resistances are emerging in viral infections, and less toxic anti-cancer agents would be highly desirable, asking for the development of new bioactive nucleoside analogues.

The synthesis of nucleoside analogues has been the focus of intensive effort since several decades.[13] Nevertheless, most methods are based on a linear approach involving first the synthesis of a ribose analogue followed by introduction of the nucleobase, either via formation of the C-N bond using a substitution reaction from an acetate I (Vorbrüggen reaction)[26] or a condensation reaction from an aminoglycoside II[26] (Scheme 1, A). This approach is efficient if the targeted analogue is similar to a natural ribose derivative, but can involve a long multi-step sequence if a more elaborate scaffold is desired.[3] This is particularly true for carbonucleoside analogues, for which elegant synthetic approaches involving ring-closing metathesis,[ha] Pauson-Khand[hb] or desymmetrization starting from cyclopentadiene and proceeding via diols,[hc-e] Vince’s lactam[hd-g] or nitroso cycloaddition reactions[3b] have been developed.

Figure 1. Natural and synthetic bioactive nucleoside analogues.

Our group has introduced the use of imide-substituted diester cyclopropanes in [3+2] annulation reactions.[4] With this new class of donor-acceptor cyclopropanes,[5] access to intermediates of type II became possible (Scheme 2, B). Nevertheless, the efficiency of the annulation process was mitigated by the necessary removal of the phthalimide group followed by DNA-base construction, which would add several steps to the synthetic sequence. Furthermore, the deprotection of the phthalimide group could not be achieved on the tetrahydrofurylamines.

If a DNA-base could be used as amino substituent on the cyclopropane, a more efficient synthesis would become possible (Scheme 1, C). Herein, we would like to report the successful

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implementation of this strategy, including: (1) the first efficient three-step synthesis of thymine/uracil donor-acceptor cyclopropanes, (2) their successful [3+2] cycloaddition with enol ethers, aldehydes and ketones and (3) their further derivatization to access hydroxylated analogues.

\[ \text{Scheme 1: Traditional approach (A), our previous work (B) and new strategy (C) to access (carbo)nucleoside analogues. Phth = Phthalimido, Pg = protecting group, LA = Lewis Acid.} \]

In our work with phthalimide-substituted cyclopropanes, modulating the electronic density on the nitrogen was essential for a successful annulation reaction. Based on the fact that thymine and phthalimide have similar pKa values (8.3 and 9.9 respectively), we started our investigations with thymine-substituted cyclopropanes (Scheme 2, A). Cyclopropane 7a was easily accessed by selective mono benzylation of thymine (10), followed by Pd-catalyzed vinylation under slightly modified conditions and cyclopropanation using Du Bois’ Rhodium-espino complex. As N3-selective tert-butylenzylbenzyl was not possible, a longer sequence involving temporary Boc protection of the N1 nitrogen was necessary in the case of cyclopropane 7b.

With aminocyclopropanes 7a and 7b in hand, we first examined the iron-catalyzed [3+2] annulation reaction with benzaldehyde (14) (Scheme 2, B). The reaction was successful for both substrates 7a and 7b. Nevertheless, we were never able to remove either of the protecting groups on the nitrogen of thymine. We decided consequently to turn to the easily removable tert-butoxycarbonyl (Boc) protecting group.

Due to the incompatibility of the Boc group with the vinylation conditions, a method to access selectively N1-vinyl thymine prior to introduction of the Boc group was required. All the reported methods to access this substrate proceeded with low yield and reproducibility in our hands. Nevertheless, we discovered that N1-selective Pd-catalyzed vinylation was possible in 45% yield from thymine itself in presence of trimethylsilyl triflate (TMSOTf) as additive (Scheme 3, A). Boc-protecting and cyclopropanation then proceeded in good yields, giving access to 7c in only three steps.

\[ \text{Scheme 2: Synthesis of aminocyclopropanes 7a and 7b (A) and first attempts of [3+2] annulation (B). Reaction conditions: a) BaCl, pyridine, CH\text{[3+2]}CN, 69%, b) 4 mol% NaB\text{[3+2]}Cl\text{CN}, vinylacetate, 80 °C, 65%, c) 0.2 mol% Rh\text{[3+2]} (esp), diazidimethylmalonate, CH\text{[3+2]}CN, d) Boc\text{[3+2]}O, DMAP, CH\text{[3+2]}CN, e) BuBnBr, NaH, DMF, 0 °C, quant. f) K\text{[3+2]}CO\text{[3+2]}, MeOH, 81%, g) 4 mol% NaB\text{[3+2]}Cl\text{CN}, vinylacetate, 80 °C, 23%, h) 5 mol% Fe\text{[3+2]}Cl\text{CN}, CH\text{[3+2]}Cl.} \]

First attempts towards the annulation of 7c with benzaldehyde (14) using an iron catalyst gave the desired product only in low yield (~27%). This was due to loss of the Boc protecting group during both reaction and purification. Changing to In(OTf)3 as catalyst and direct Boc deprotection of the crude product by heating in ethanol at 70 °C afforded the desired NH-free product 8c in 87% yield (Scheme 3, B). Aminocyclopropane 7c could also be used in other [3+2] annulation processes involving either ketones or silyl enol ethers to give tetrahydrofurfuryl amine 8d and cyclopentyl amine 9a in 94% and 84% yield respectively. In this case, the lower reactivity of 7c compared with phthalimide-substituted...
cyclopropanes required the use of a higher temperature (-20 instead of -78 °C) in the tin-catalyzed process.

We then turned to the investigation of the scope of the [3+2] annulation (Figure 2).[1] The reaction was successful in the case of aromatic (products 8c and 8e), aliphatic (products 8f) and vinylic aldehydes product 8g). Excellent diastereoselectivity (> 20:1) was observed, except for product 8g (5:1). The same was also true for ketones (products 8d and 8h–k), although the diastereoselectivity was lower for vinylic ketones (product 8k). With enol ethers, more substituted derivatives, such as tetrasubstituted cyclopentane 9c, could also be accessed. The [3+2] annulation product was obtained in 55% yield with a dienol ether as partner (product 9d). Finally, modification of the thymine substituent was also examined. Both cyclopropanes derived from uracil and 5-fluoro-uracil could also be used in the annulation reaction with aldehydes, ketones and enol ethers (products 18–21).[14]

For most nucleoside drugs enzymatic phosphorylation of a hydroxy group is an important step in the mode of action.[11] Modification of the obtained products to include hydroxy group(s) would be consequently highly rewarding in the quest of new bioactive compounds. To reach this goal, saponification followed by decarboxylation of diester 8c gave access to a single isomer of the corresponding carboxylic acid,[15] which could be reduced to primary alcohol 22 in 71% overall yield (Scheme 4, A). The same sequence was also successful for styrene derivative 8g, giving the corresponding alcohol 24 in 59% yield. Products 8d and 8h could also be converted into the desired alcohols 23 and 25 in 62 and 64% yield respectively. In the case of the carbonucleoside analogues, dibenzyl ester cyclopentylamine 26 could be converted into the corresponding diacid by hydrogenation.[16] Heating the neat crude diacid to 80 °C led then to decarboxylation and silyl ether elimination to give acid 27 (Scheme 4, B). Pd-catalyzed hydrogenation followed by acid reduction gave the corresponding unstable saturated alcohol, which was isolated as silyl ether 28.

From Aldehydes

Thy

MeO₂C

MeO₂C

Ph

8c 87%

MeO₂C

MeO₂C

Ph

8e 79%

MeO₂C

MeO₂C

Pr

8f 75%

MeO₂C

MeO₂C

Pr

8g 96% 5:1 dr

From Ketones

Thy

MeO₂C

MeO₂C

Ph

8d 94%

MeO₂C

MeO₂C

Ph

8h 93%

MeO₂C

MeO₂C

Ph

8i 85%

MeO₂C

MeO₂C

Ph

8j 97%

From Enol Ethers

Thy

MeO₂C

OTIPS

9a 84%

MeO₂C

OTIPS

9b 80%

MeO₂C

MeO₂C

OTIPS

9c 79%

MeO₂C

MeO₂C

OTIPS

9d 79%

Thy

MeO₂C

OTIPS

9c 79%


A) Thy

MeO₂C

R₁

MeO₂C

R₂

R₁

R₂

8c, 8d, 8g, 8h

B) Thy

BnO₂C

OTIPS

26

Ph

BnO₂C

OTIPS

27

Ph

d, e

Pr₂SiCl

28

Scheme 4. Modification of the tetrahydrofuran (A) and cyclopentane (B) products. Reaction conditions: a) KOH, MeOH. b) BH₃·SMe₂, THF, 10% Pd/C, 1 atm H₂, EtOH, 57 °C, then neat, 80 °C, d) 5% Pd/C, 1 atm H₂, EtOH, 85%. e) Pr₂SiCl, DME, imidazole, 55% over two steps.

In conclusion, we have reported the first synthesis of nucleobase-substituted diester cyclopropanes and their use in cyclodaddition with aldehydes, ketones and enol ethers. This new transformation gave access in a few steps to important nucleoside analogues, which were easily modified to give hydroxylated derivatives. Future work will focus on the synthesis of a broader range of analogues to build up a chemical library for biological testing and extending the scope of the reaction to the purine class of nucleobases.

Keywords: Annulation • Cyclopropanes • Catalysis • Nucleosides • Stereoselective Synthesis


References


[13] The stereochemistry of compounds 8e, 8i, and 9a has been determined by X-ray crystallography. The data is available at the Cambridge Crystallographic Data Centre with the numbers CCDC 995573, CCDC 994755 and CCDC 994948 respectively. The stereochemistry of the other compounds has been assigned by analogy or NMR experiments. See Supporting Information for further details.

[14] The uracil and 5-fluoro-uracil substituted cyclopropanes were obtained using a similar synthetic sequence. In the case of the 5-fluoro uracil derivatives, it was necessary to use a more stable benzoyl protecting group. See Supporting Information for further details.

[15] The diastereoselectivity in the decarboxylation step was usually high (>5:1, >20:1 for 8c). The products are obtained under kinetic control, but the rationalization of the high selectivity will require further investigations.

[16] Cyclopentylamine 26 was obtained in 94% yield from the [3+2] annulation of the corresponding dibenzylester-substituted cyclopropane with enol ether 17.
Synthetic Method

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