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# Functionalization of C=C Double Bonds of Pyrimidino-pyranoside Platform Groups

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***Authors' contributions***

*This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.*

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## ABSTRACT

In the search for peptidomimetic structures capable of mimicking endogenous peptides, we have studied the reactivity of C=C double bonds of pyrimidino-pyranoside platform groups. The exploitation of this reactivity by ozonolysis and reductive amination reactions allowed us to develop a fast and efficient route for the introduction of amine function capable of mimicking bioactive peptides.

*Keywords: Pyrimidino-pyranoside; peptidomimetics; ozonolysis; reductive amination.*

## 1. INTRODUCTION

Chemists have been interested in the problem of converting endogenous peptide ligands into polyfunctional heterocycles with improved bioavailability and metabolic stability in the hope of paving the way for potential drug discovery [1-2].

Saccharide derivatives [3] have developed as novel platforms for the construction of peptidomimetics. Their cyclic, rigid structures,

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chiralities and the presence of multiple hydroxyl functions are key elements for the creation of specific molecules capable of mimicking bioactive peptides [4-6].

The functionalization of the latter SMe-pyrimidino-pyranoside platform was explored by first studying the reactivity of the heterocycle part by Suzuki and Stille type pallado-catalyzed coupling reactions [7]. This allowed a fast and efficient anchoring of different carbon residues, some of which carry functions that can mimic amino acid side chains.

The exploration of the reactivity of compounds 1 and 2 resulting from coupling reactions of the SMe-pyrimidino-pyranoside platform was fruitful and allowed the development of its functionalization.

## 2. FUNCTIONALIZATION OF COMPOUNDS 1 AND 2 FROM PALLADIUM COUPLINGS

The palladic couplings having yielded interesting products with a C=C double bond [7].

In order to exploit the two products from the palladic couplings which present a C=C double bond, we considered performing an oxidative cleavage reaction by ozonolysis. The resulting carbonyl compound is also engaged in a reductive amination reaction.

### 2.1 Ozonolysis Reaction

An ozonolysis reaction [8] performed on the coupling products compounds 1 and 2 led to the corresponding aldehyde in excellent yields of 75% and 93% respectively.

### 2.2 Reductive Amination Reaction

In order to verify the possibility of introducing an amine function, we performed a reductive amination on the aldehyde 3. The reductive amination reaction [9,10] with benzylamine in the presence of $Ti(OiPr)_4$ followed by a reduction of the imine intermediate by the addition of $NaBH_4$ leads to the product 4 obtained with a good yield of 69%.

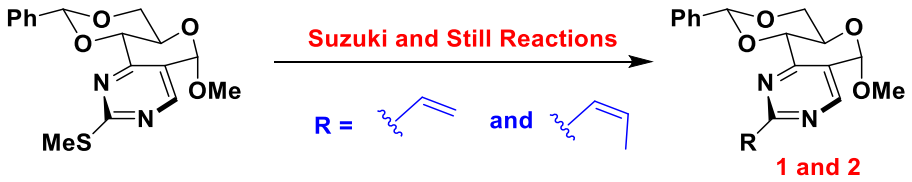



**Schéma 1.**

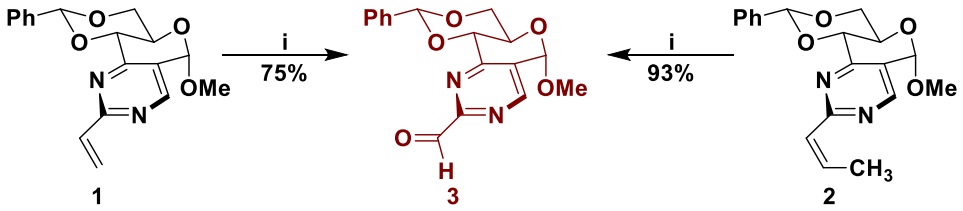



**Schéma 2. i) $O_3$, $CH_2Cl_2$, -78°C and $Me_2S$**

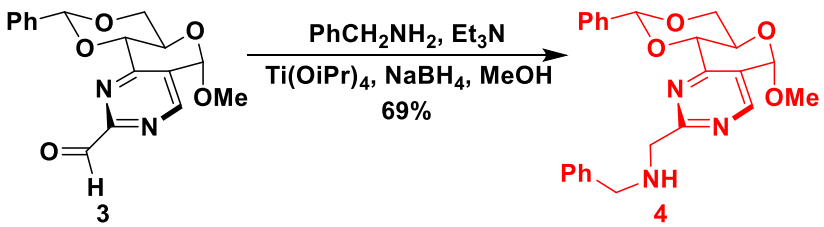
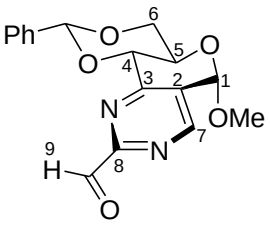



**Schéma 3.**

## 3. EXPERIMENTAL PART

**Composé 3:** *(2R,4aR,6S,10bS)-4,4a,6,10b-Tétrahydro-6-méthoxy-2-phényl-9-formyl-1,3-dioxino[4',5':5,6]pyrano[4,3-d]pyrimidine.*

Under an inert argon atmosphere, 50 mg of compound 1 (or 2) is dissolved in 5 ml of dichloromethane. The solution is brought to -78°C then ozone is bubbled into the reaction medium. The reaction followed by TLC is completed after 2 hours of stirring at -78°C, 1 ml of dimethylsulfide is added and the medium is allowed to return to room temperature. After dry evaporation, the reaction crude is purified by silica gel chromatography (Hexane/EtOAc, 1:1) and the aldehyde 3 is thus obtained in 93% (or 75%) yield.



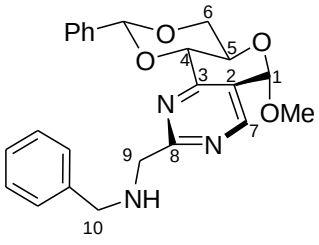

**3**

$C_{17}H_{16}N_2O_5$
MM = 328,1 g/mol,
yellow powder
$R_f$ = 0.2 ($SiO_2$, Hexane/EtOAc, 1:1)

**$^1$H NMR ($CDCl_3$, 250 MHz):** σ 3.64 (s, 3H, O*Me*), 4.00 (app t, 1H, $H_6$, $J_{6\text{-}5} = J_{6\text{-}6'}$ = 10 Hz), 4.23 (app td, 1H, $H_5$, $J_{5\text{-}6} = J_{5\text{-}4}$= 10 Hz, $J_{5\text{-}6'}$ = 4.4 Hz), 4.49 (dd, 1H, $H_{6'}$, $J_{6\text{-}6'}$ = 10 Hz, $J_{6\text{-}6'}$ = 4.4 Hz), 4.81 (d, 1H, $H_4$, $J_{4\text{-}5}$ = 10 Hz), 5.66 (s, 1H, $H_1$), 5.82 (s, 1H, *H* benzylidene), 7.30-7.45 (m, 3H, *H* aromatic), 7.55-7.62 (m, 2H, *H* aromatic), 8.90 (s,1H, $H_7$), 10.14 (s, 1H, *H* aldehyde). **$^{13}$C NMR ($CDCl_3$, 62.9 MHz):** σ 56.8 (O*Me*), 63.2 ($C_5$), 69.3 ($C_6$), 75.8 ($C_4$), 96.1 ($C_1$), 103.1 (C benzylidene), 122.0 ($C_2$), 128.6 (2C aromatic), 129.7 (2C aromatic), 129.9 (C aromatic), 136.8 (Cq aromatic), 157.9 ($C_7$), 159.1 ($C_3$), 162.6 ($C_8$), 190.7 (CO). **HRMS (ESI$^+$)** : 329.112 (calculated for $C_{17}H_{17}N_2O_5$ : 329.1132).

**Composé 4 :** *(2R,4aR,6S,10bS)-4,4a,6,10b-Tétrahydro-6-méthoxy-2-phényl-9-[(benzylamino)méthyl]-1,3-dioxino[4',5':5,6]pyrano[4,3-d]pyrimidine*

50 mg of aldehyde 3 (0.15 mmol) and 1.2 eq of benzylamine are solubilized in 5 mL of methanol under argon atmosphere. 1.2 eq. Et3N and three drops of $Ti(OiPr)_4$ are added. The mixture is stirred at room temperature for 24 h, then the medium is cooled to 0°C and 1 eq of NaBH4 is added. After 30 min of stirring, the reaction is hydrolyzed with water. The methanol is evaporated and the mixture is extracted with dichloromethane, the organic phase is dried over magnesium sulfate and concentrated under vacuum. A purification by chromatography on silica gel allows the isolation of compound 4 with a yield of 69% (45 mg).




**4**

$C_{24}H_{25}N_3O_4$
MM = 419.2 g/mol,
foam
$[\alpha]_D$ = +5.3°(c = 1.01, $CHCl_3$)
$R_f$ = 0.15 (EtOAc, 100%)
IR : 2927, 1588
Pf = 68°C

**$^1$H NMR ($CDCl_3$, 250 MHz):** σ 3.61 (s, 3H, *OMe*), 3.86 (s, 2H, $H_9$), 3.97 (app t, 1H, $H_6$, $J_{6\text{-}5} = J_{6\text{-}6'}$ = 10 Hz), 4.12 (s, 2H, $H_{10}$), 4.20 (app td 1H, $H_5$, $J_{5\text{-}4} = J_{5\text{-}6}$ = 10 Hz, $J_{6'\text{-}5}$ = 4.7 Hz), 4.46 (dd, 1H, $H_{6'}$, $J_{6\text{-}6'}$ = 10 Hz, $J_{6'\text{-}5}$ = 4.7 Hz), 4.70 (d, 1H, $H_4$, $J_{4\text{-}5}$ = 10 Hz), 5.58 (s, 1H, $H_1$), 5.78 (s, 1H, *H* benzylidene), 7.20-7.45 (m, 9H, *NH*, *8H* aromatic), 7.50-7.60 (m, 2H, *H* aromatic), 8.62 (s,1H, $H_7$). **$^{13}$C NMR ($CDCl_3$, 62.9 MHz):** σ 53.4 ($C_{10}$), 54.5 ($C_9$), 56.5 (*OMe*), 63.2 ($C_5$), 69.4 ($C_6$), 76.0 ($C_4$), 96.5 ($C_1$), 102.9 (C benzylidene), 125.4 ($C_2$), 126.8 (2C aromatique), 127.4 (2C aromatic), 128.5 (2C aromatic), 128.6, (2C aromatic), 128.8 (2C aromatic), 129.5 (C aromatic), 137.0 (Cq aromatic), 139.3 (Cq aromatic), 156.7 ($C_7$), 161.1 ($C_3$), 168.9 ($C_8$). **HRMS (ESI$^+$)** : 420.1909 (calculated for $C_{24}H_{26}N_3O_4$ : 420.1918)

## 4. CONCLUSION

Carried out on the products resulting from the coupling and which have a double bond C=C, this ozonolysis-reductive amination strategy seems very promising since it allows to functionalize efficiently the pyrimidine part with different amines. The encouraging result obtained by reaction with benzylamine seems quite applicable with other amines.

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## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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