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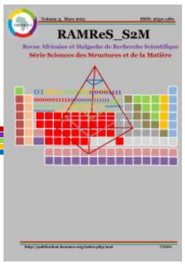

Reactivity of chiral functionalized pyrazoles: Alcohol protection

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***Abstract*:**

Having an original route to chiral pyrazoles derived possessing aldehyde and alcohol functions, we wished to investigate the functionalization potentialities of these new compounds. Protection reactions of the free alcohol function were performed on the compound and the acylation was successful and constitutes a good route for the functionalization of chiral pyrazoles.

***Keywords*:** Pyrazole; Protection; Alkylation and acylation reactions.

1. Introduction

Chemists have been interested in the problem of converting endogenous peptide ligands into small synthetic molecules with improved bioavailability and metabolic stability in the hope of paving the way for potential drug discovery. The concept of peptidomimetics, non-peptidic mimetics of biologically active peptides, consists in replacing the peptidic structure by a function distributor, most often a polyfunctional heterocycle capable of orienting in space the elements necessary for the biological activity [1, 2].

The general objective of this work is to contribute to the synthesis of new bis-heterocyclic platforms based on carbohydrates and nitrogenous heterocycles and to the study of their functionalization in order to access peptidomimetics. Starting from an α,β-unsaturated keto-sugar, it is possible to rapidly access platforms with pyrazole-like heterocycles [3-6]. The study of the reactivity of the pyrazolo-pyranoside platform led us to a new route to a series of highly functionalized chiral pyrazoles [7].

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2. Experimental

Four compounds were targeted in this work, named Compounds 1 to 4. Their characteristics are shown in table 1.

Compound 1: *Méthyl 4-formyl-5-[(2R,4S,5R)-5-hydroxy-2-phényl-1,3-dioxan-4-yl]-1H-Pyrazole-1-acétate*

Pyrazole (0.5 mmol) was treated with PTSA (20 mol %) in THF (15 mL) at room temperature. The progress of the reaction was monitored by TLC and after completion, the reaction mixture was diluted with $NaHCO_3$ saturated aqueous solution and extracted with dichloromethane. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuum and purified by column chromatography on silica gel. Compound 1 is isolated in 71% yield.

^{1}H NMR (DMSO-d6, 250 MHz) : δ_H (ppm) 3.55 (s, 3H, COO*Me*), 3,76 (app t, 1H, H_6, $J_{6-5} = J_{6-6'}$ = 10 Hz), 3.85-3.95 (m, 1H, H_5), 4.29 (dd, 1H, $H_{6'}$, $J_{6-6'}$ = 10 Hz, $J_{6'-5}$ = 4.5 Hz), 5.28 (s, 2H, $2H_8$), 5.38 (d, 1H, H_4, J_{4-5} = 10 Hz), 5.69 (d, 1H, OH, J_{OH-5} = 5.8 Hz), 5.76 (s, 1H, *H* benzylidene), 7.40-7.50 (m, 5H, *H* aromatic), 8.02 (s, 1H, H_7), 10.06 (s, 1H, H_1).

^{13}C NMR (DMSO-d6, 62.9 MHz) : δ_C (ppm) 52.1 (C_8), 52.4 (COO*Me*), 64.6 (C_5), 71.1 (C_6), 75.6 (C_4), 100.9 (C benzylidene), 122.3 (C_2), 126.1 (C aromatic), 128.2 (C aromatic), 129.0 (C aromatic), 137.2 (C_7), 138.9 (Cq aromatic), 144.6 (C_3), 167.8 (CO ester), 185.1 (C_1).

Compound 2: *Methyl 2-((4S,5aR,8R)-4-(benzyloxy)-8-phenyl-4,5a,6,9a-tetrahydro-1H-[1,3]dioxino[4',5':5,6]pyrano[4,3-c]pyrazol-1-yl)acetate*

0.5 g of compound 1 (1 eq, 1.1 mmol) dissolved in 10 mL of THF was added at 0 °C, NaH (60%, 1.3 eq). After 5 minutes stirring at 0 °C, Benzyl bromide (1.3 eq) was added drop by drop. The reaction followed by TLC, is complete after 4 hours. The mixture was extracted three times with diethyl ether, and then washed with water. The organic phase is dried over $MgSO_4$ and concentrated in vacuum. The crude is purified by chromatography on silica gel. Compound 2 is isolated in 63 % yield.

^{1}H NMR (DMSO-d6, 250 MHz) : δ_H (ppm) 3.55 (s, 3H, COO*Me)*, 3,85 (app td, 1H, H_5, $J_{5-6} = J_{5-4}$ = 9.5 Hz, $J_{5-6'}$ = 4.5 Hz), 4.03 (app t, 1H, H_6, $J_{6-5} = J_{6'-6}$ = 9.5 Hz), 4.31 (dd, 1H, $H_{6'}$, $J_{6'-6}$ = 9.5 Hz, $J_{5-6'}$ = 4.5 Hz), 4.94 (d, 1H, H_4, J_{4-5} = 9.5 Hz), 4.98 (d, 1H, H_8, J_{gem} = 17.7 Hz), 5.12 (d, 1H, $H_{8'}$, J_{gem} = 17.7 Hz), 5.28 (s, 2H, CH_2Bn), 5.59 (s, 1H, H_1), 5.84 (s, 1H, *H* benzylidene), 7.25-7.50 (m, 10H, *H* aromatic), 7.46 (s, 1H, H_7).

^{13}C NMR (DMSO-d6, 62.9 MHz) : δ_C (ppm) 52.6 (COO*Me*), 52.9 (C_8), 55.7 (CH_2Bn), 64.6 (C_5), 69.0 (C_6), 74.0 (C_4), 96.2 (C_1), 101.4 (C benzylidene), 117.5 (C_2), 126.8 (3C aromatic), 129.0 (3C aromatique), 129.8 (2C aromatic), 136.8 (C_7), 137.5 (2Cq aromatic), 138.1 (C_3), 169.1 (CO).

Compound 3: *Methyl (4S,5aR,8R,9aS)-4,5a,6,9a-tetrahydro-4-((tert-butyldimethyl) silyloxy)-8-phenyl-1H-[1,3]Dioxino[4',5':5,6]-pyrano[4,3-c]-pyrazole-1-acetate*

0.4 g of compound 1 (1 eq, 1.1 mmol) is solubilized in 10 mL of anhydrous dichloromethane, 0.36 mL of collidine (2.5 eq., 2.7 mmol) and 0.63 mL of tertbutyldimethylsilyl trifluoromethanesulfonate TBDMSOf (2.5 eq., 2.7 mmol) are added. The reaction is followed by TLC for 2 hours under constant of stirring at room temperature. The reaction is stopped and a few drops of a saturated NaHCO$_3$ solution are added. The mixture is then washed with a saturated NaCl solution and a saturated NH$_4$Cl solution. The organic phase is dried with MgSO$_4$ and concentrated under vacuum. The product is purified by chromatography on silica gel. Compound 3 is isolated in 77% yield.

^{1}**H NMR (DMSO-d6, 250 MHz)** : δ_H (ppm) 0.21 (s, 3H, Si$(CH_3)_2$), 0.22 (s, 3H, Si$(CH_3)_2$), 0.95 (s, 9H, SiC$(CH_3)_3$), 3.58 (s, 3H, COO*Me*), 3.96 (app td, 1H, H$_5$, $J_{5\text{-}6} = J_{5\text{-}4} = 9.5$ Hz, $J_{5\text{-}6'} = 4.1$ Hz), 4.07 (app t, 1H, H$_6$, $J_{6\text{-}6'} = J_{6\text{-}5} = 9.5$ Hz), 4.24 (dd, 1H, H$_{6'}$, $J_{6\text{-}6'} = 9.5$ Hz, $J_{6'\text{-}5} = 4.1$ Hz), 4.96 (d, 1H, H$_4$, $J_{4\text{-}5} = 9.5$ Hz), 5.01 (1d, 1H, 1H$_8$, $J_{8\text{-}8'} = 17.8$ Hz), 5.16 (1d, 1H, 1H$_{8'}$, $J_{8\text{-}8'} = 17.8$ Hz), 5.88 (s, 1H, H$_1$), 6.06 (s, 1H, *H* benzylidene), 7.43-7.45 (m, 6H, *5H* aromatic, H$_7$).

^{13}**C NMR (DMSO-d6, 62.9 MHz)** : δ_C (ppm) -5.2 (C Si$(CH_3)_2$), -4.4 (C Si$(CH_3)_2$), 17.6 (C Si*C*(CH$_3$)$_3$), 25.6 (C SiC$(CH_3)_3$), 51.6 (C$_8$), 52.0 (COO*Me*), 63.9 (C$_5$), 68.2 (C$_6$), 73.1 (C$_4$), 89.0 (C$_1$), 100.5 (C benzylidene), 118.9 (C$_2$), 125.9 (2C aromatic), 128.0 (2C aromatic), 128.9 (C aromatic), 135.4 (C$_7$), 135.9 (Cq aromatic), 137.2 (C$_3$), 168.3 (CO).

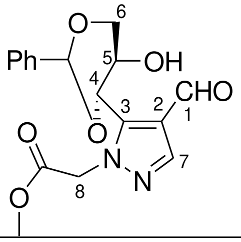
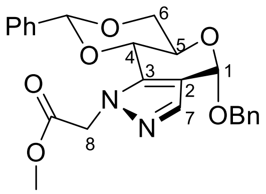
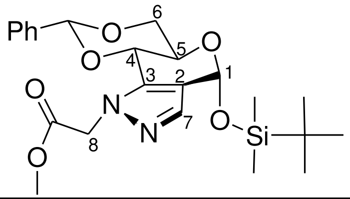
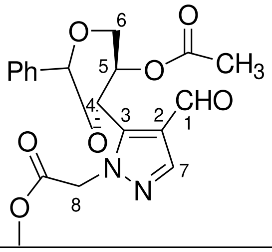
Compound 4: *Methyl 4-formyl-5-[(2R,4S,5R)-5-acetoxy-2-phenyl-1,3-dioxan-4-yl]-1H-Pyrazole-1-acetate*

0.16 g of compound 1 (1 eq, 0.46 mmol) is solubilized in 5 mL of anhydrous dichloromethane at -40 °C under argon atmosphere. At this temperature, DMAP (10 mol%), pyridine (1 eq., 0.46 mmol) and acetyl chloride (6 eq., 27.6 mmol) are added. The reaction is followed by TLC for 3 hours under constant of stirring at -40 °C. After dilution with dichlorométhane, 2mL of NaHCO$_3$ is added and washed with water. The organic phase is dried with MgSO$_4$ and concentrated under vacuum. After purification by silica gel chromatography, compound 4 is obtained in 72% yield (0.13 g).

^{1}**H NMR (DMSO-d6, 250 MHz)** : δ_H (ppm) 1.88 (s, 3H, CH_3), 3.47 (s, 3H, *COOMe*), 3.92 (app t, 1H, H$_6$, $J_{6\text{-}6'} = J_{6\text{-}5} = 10$ Hz), 4.39 (dd, 1H, H$_6$, $J_{6\text{-}6'} = 10$ Hz, $J_{6'\text{-}5} = 5$ Hz), 5.11 (app td, 1H, H$_5$, $J_{5\text{-}6'} = 5$ Hz, $J_{5\text{-}6} = J_{5\text{-}4} = 10$ Hz), 5.23 (d, 1H, H$_8$, $J_{8\text{-}8'} = 17.7$ Hz), 5.35 (d, 1H, H$_{8'}$, $J_{8\text{-}8'} = 17.7$ Hz), 5.79 (d, 1H, H$_4$, $J_{4\text{-}5} = 10$ Hz), 5.84 (s, 1H, *H* benzylidene), 7.35-7.55 (m, 5H, *H* aromatic), 8.03 (s, 1H, H$_7$), 10.01 (s, 1H, H$_1$).

^{13}**C NMR (DMSO-d6, 62.9 MHz)** : δ_c (ppm) 20.2 (CH_3(CO)), 52.1 (C$_8$), 52.5 (COO*Me*), 65.2 (C$_5$), 67.5 (C$_6$), 71.9 (C$_4$), 101.2 (C benzylidene), 122.1 (C$_2$), 128.2 (C aromatic), 128.5 (2C aromatic), 129.2 (2C aromatic), 136.7 (Cq aromatic), 140.2 (C_7), 141.9 (C_3),167.3 (CO ester), 167.7 (CO ester), 187.7 (C_1).

Table 1
Characteristics of Compounds 1 to 4.

Compound number	Molecular Formula	Characteristics
1		$C_{17}H_{18}N_2O_6$ MW : 346.12 g/mol Appearence : foam $[\alpha]_D$ = +39.0° (c = 1.05, $CHCl_3$) Rf = 0.28 (Hexane/EtOAc, 1/1) IR : 3435 ; 1757 ; 1678 cm^{-1} Fp : 54 °C
2		$C_{24}H_{24}N_2O_6$ MW : 436.16 g/mol Appearence : powder $[\alpha]_D$ = -31.3° (c = 1.08, $CHCl_3$) Rf = 0.58 (Hexane/EtOAc, 1/1) IR : 2985 ; 1765 cm^{-1} Fp : 144 °C
3		$C_{23}H_{32}N_2O_6Si$ MW : 460.2 g/mol Appearence : oil $[\alpha]_D$ = -35.9° (c = 1.03 , $CHCl_3$) Rf = 0.75 (Hexane/EtOAc, 1/1) IR : 1758 cm^{-1}
4		$C_{19}H_{20}N_2O_7$ MW : 388.13 g/mol Appearence : oil $[\alpha]_D$ = +20.6° (c = 1.02 , $CHCl_3$) Rf = 0.33 (Hexane/EtOAc, 1/1) IR : 1750; 1685 cm^{-1}

3. Results and discussion

In the previous study on deprotection of benzylidene in acidic medium [5, 6], we observed that the pyrazolo-pyranoside platform subjected to acidic hydrolysis conditions in THF causes hydrolysis of the anomeric acetal, opening of the pyranose ring and formation of an aldehyde.

Regioisomeric alkylation products subjected to acid hydrolysis in the presence of 20 mol% PTSA in THF allows access to pyrazole aldehydes (Figure 1) in good yields [7].

This new study aims to observe the reactivity of the pyrazole aldehydes (Compound 1).

3.1. Protection of the alcohol function by alkylation

We opted in the first instance for a classical method of alkylation of the alcohol by a benzyl group. The product 2 obtained results from a condensation of the alcoholate formed *in situ* on the carbonyl of the aldehyde leading to the cyclization of the sugar and the introduction of the benzyl group in anomeric position (Figure 2).

The corresponding compound 2 was obtained with a good yield of 63%.

The reaction conditions required for silylated ether placement seemed more appropriate for this protection. But we observed here again the closure of the sugar with a yield of 77% and the introduction of the $OSi(CH_3)_2tBu$ group in anomeric position (Figure 3).

3.2. Protection of the alcohol function by acylation

An acetylation reaction with acetyl chloride allowed the protection of the free hydroxyl without causing the cyclization of pyrazole to pyrazolo-pyranoside (Figure 4).

The corresponding compound 4 was obtained with a good yield of 72%.

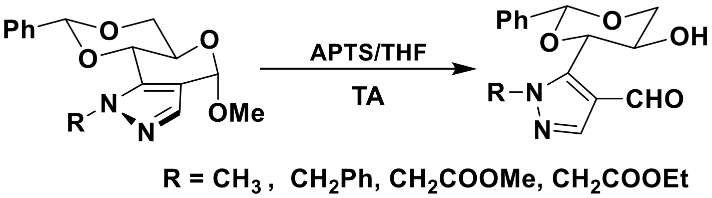
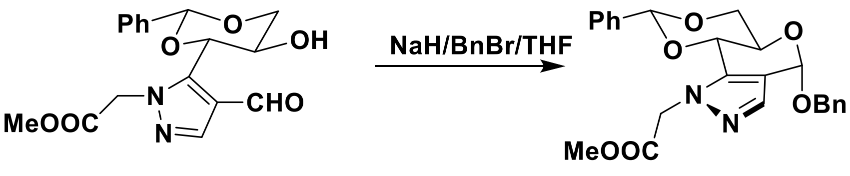


Fig. 1. Anomeric acetal hydrolysis.



1 2

Fig. 2. Introduction of the benzyl group in anomeric position.

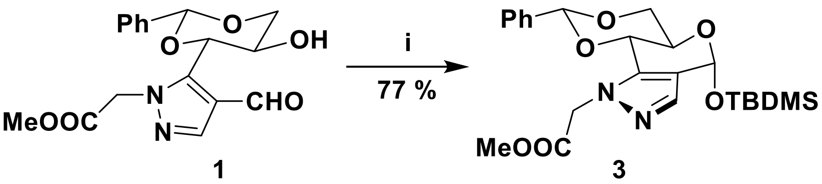


Fig.3. Introduction of the $OSi(CH_3)_2tBu$ group in anomeric position.
i) Collidine/TBDMSOTf/CH_2Cl_2.

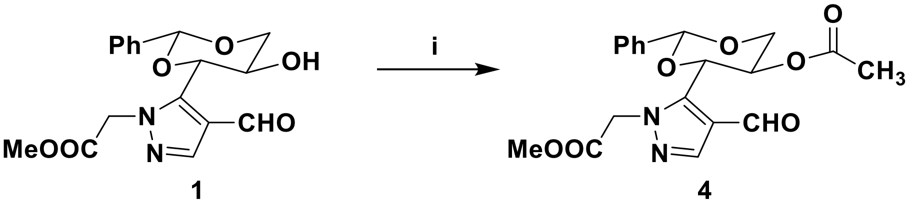


Fig. 4. Acetylation reaction.
i) CH_3COCl/Pyridine/DMAP/CH_2Cl_2/-40 °C.

4. Conclusion

The present work allows us to consider the functionalization of pyrazole aldehydes, in particular by exploiting the reactivity of the aldehyde function and of the diol part which can be obtained by opening the benzylidene. The unexpected reactivity of the anomeric center and the possibilities of functionalization have allowed the development of an original access to highly functionalized chiral pyrazoles, this type of compounds being able to present a marked therapeutic interest.

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