Synthesis Of New Polyanionic Acyclonucleosids By Knoevenegel, Addition Of Michael And Trans-Esterification Reactions In The Presence Of Natural Phosphate As Catalyst

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Abstract: An efficient Knoevenegel reaction, addition of Michael, trans-esterification for the synthesis of new polyanionic acyclonucleosids using natural phosphate as catalyst

Index Terms: Polyanionic acyclonucleosids Knoevenegel reaction, addition of Michael, trans-esterification; Natural phosphate (NP).

INTRODUCTION

The pandemic of the AIDS and the characterization of her agent etiologic, the VIH, motivated the research of potentially active agents against this virus. A certain number of compounds revealed, in vitro, of powerful and selective anti-VIH activities, bound to an interference with one stages of the cycle of replication of this retrovirus. The inverse transcriptase (IT) seems to be the best chemotherapeutic intervention target, not only because of her role in the replication of the virus, but also of the possibilities that it offers concerning selectivity of the drugs. One of the stages key of the cycle of replication of the VIH is the adsorption of the virus the cells hosts. This adsorption results from a specific interaction between the glycoproteine viral gp120 and the cell host receiving CD4. As a rule, only the cells containing the receiving CD4 can be infected by the VIH. The interaction gp120-CD4 can be considered like target potential in the struggle against the AIDS. Among the classes of substances preventing this interaction, one finds the polyanionic compounds represented by the acidic aurintricarboxylic (ATA)[1], the suramine [2], the gycyrrhizine [3] and the bruise of evan. [4] The acidic functions of the ATA are essential for her activity. Indeed, the Aurin, her structural analog not possessing the three functions acidic carboxylic is inactif. [4]

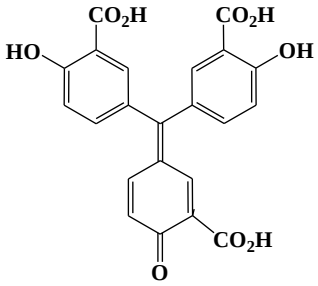

Figure1 : Acidic aurintricarboxylic (ATA)

On the basis of these bibliographic data, we considered preparing new acyclonucleosides containing several functions acidic carboxylic. This polyanionic compounds could interact therefore with the receiving CD4 and could block the stage of the adsorption of the VIH to the cells hosts.The acyclonucleosides can be gotten according to three different strategies (i) total synthesis (ii). From a nucleoside preformed by rupture of one or several links of the cycle osidique.(iii) By condensation of a heterocycle appropriately protected with a chain alkyle or alkoxyle. This last is the more used,it is about a reaction of N-alkylation of the nucleobasebases. The C-N link of the acyclonucleoside is formed after condensation of the nucleobase, activated or no, and of an acyclic chain appropriately substituted according to a mechanismof substitution nucleophile.These condensations present two major inconveniences to know a lack of regioselectivity and enantioselectivity. Regioselectivity: When the basis possesses several sites possible of alkylation, one often gets a mixture of position isomers : (i)N-1 and N-3 alkylation in the case of the pyrimidine nucleobase,(ii)N-7 and N-9 alkylation in the case of the purine nucleobase. However, the two gotten isomers are generally separable by chromatographie on column of silica frost or by fractional crystallization

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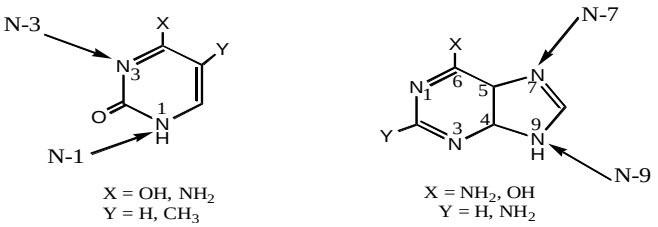
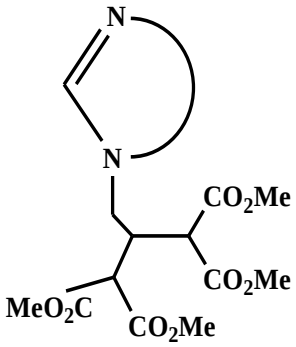
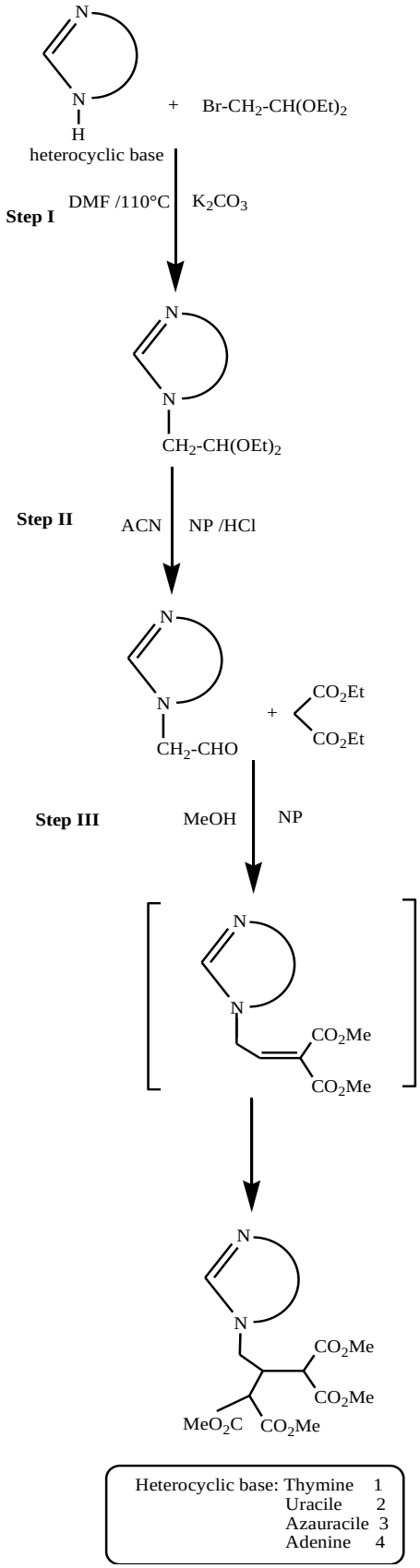


Figure 2: Sites of N-alkylation of the purine and pyrimidine nucleobase

Enantioselectivity: When the condensation drives to the formation of an asymmetric carbon, one gets two difficult enantiomers to separate. The regioselectivity and the enantioselectivity are very important in chemotherapy. Indeed, although several isomers of position can be gotten by condensation, one only among them can possess a biologic activity possibly. Several syntheses have been achieved while using the liquid strong catalysis. The inorganic supports are varied very, among which one can mention as an example, the alumine[5], the silice[6], fluorides alkali and most recent of these supports is the natural phosphate (PN) [7]. This last is an efficient catalyst in the organic chemistry, because he has a lot of advantages as: recyclable, more environmental. Several works have been returned in this sense, they showed the interest of the PN in the reactions of Claisen-Schmidt [8,9,10],hétérocyclisation [11], Knoevenagels, reaction[12]. In the previous studies the natural Phosphate (NP) have exhibited an excellent ability to catalyze various reactions [13].In the light of these successes, we envisioned that such a catalyst might be effective for synthesis of new plyanionic acyclonucleosids (**Figure 3)**



Recently, the Natural phosphate and natural phosphate doped with HCl has received considerable attention in organic synthesis because of its low cost, its high tolerance to air and moisture and its ready availability. Here, we report an easy synthesis of new polyanionic acyclonucleosids using natural phosphate as catalyst by Knoevenegel reaction, addition of Michael, trans-esterification (Scheme 1)



RESULTS AND DISCUSSION

Step I

This stage consists has the alkylation of the heterocyclic base by bromoacetaldehyde diethylactal, this survey has been achieved on the uracile. Several tests have been achieved, while modifying either the temperature, either the quantity of K_2CO_3 or the alkylating agent or the equivalent of the uracile. When using To heterocyclic base(0.79 mmoles) K_2CO_3 (0.5 eq , 0.45 mmoles) , DMF (15 ml) . and alkylating agent ($BrCH_2CH(EtO)_2$) (1.5 eq , 1.185 mmoles) at (110-120 ° C) for atime ranging from3 to 4 hours in acetonitrile (8ml),the derivatives acetals correspondents were obtained in good yield.

Step II

This stage consists has the deprotection of the acetals indeed, this survey has been achieved on the uracile. Several tests have been achieved, while modifying either the temperature, either the quantity of NP/HCl or the acetal derivative of the uracile. When using acetonitrile (8ml), NP/ HCl (400mg)and water (2 ml) the aldehydde desired is obtained in good yield 77%. The method has been generalized thereafter to the other (acetals). in any case, the derivatives aldehydes correspondents were obtained in good yield.

Step III

This stage consists has the Preparation of the derivatives esters precurceurs of the polyanionic acyclonucleosides . To this effect we achieved several tests to try to optimize the operative conditions us have remarqued that the best yield are gotten when one uses three equivalents of the ethyl malonate in presence of the natural phosphate as catalyst.After filtration of the NP, the residue evaporated and purified on column of silica frost (eluaent: gradient of the methanol in the dichlorométhane 0-2%).The wanted esters have been gotten with satisfactory yield .

CONCLUSION

The work achieved in our laboratory has for goal: the synthesis of the polyanionic acyclonucleosids, and the valorization of the NP in the organic synthesis. In this work one was interested in the natural phosphate as catalyst. The set of this work allowed us to conclude on the points follow: (i)The NP doped with HCl is an acidic catalyst that can be used in the reaction of déprotection of the acétals (ii)The only NP can be used like catalysts in the organic synthesis (Knoevenegelreaction,addition of Michael, trans-esterification). The NP is an efficient catalyst in the organic chemistry.it is recyclable, toxic, more environmental.

EXPERIMENTAL

Preparation of natural phosphate coated with HCl To 5ml of water, 2,76 ml HCl was added. The mixture is agitated during 5 minutes. To the gotten residual,3g of the natural phosphate was added. The mixture was stirred for 15 min, and evapored to druness.

General Procedure:

StepI:

To heterocyclic base (0.79 mmoles) was added K2CO 3 (0.5 eq, 0.45 mmoles) , DMF (15 ml) . and alkylating agent ($BrCH_2CH(EtO)_2$)(1.5eq,1.185mmoles).The mixtureis refluxed at (110-120 ° C) for a time ranging from 3 to 4 hours. At the end of the reaction, the middle reaction is neutralized by acetic acid. The crude reaction is then filtered and washed with methanol. The filtrate is evaporated. The crude product is purified on silica gel column (eluent: CH2Cl2/ MeOH).

StepII:

A suspension of acetal (0.411 mmol) in acetonitrile (8ml) , 400mg of NP / HCl and water (2 ml) and the mixture was heated (80°C) for 2 h . After filtration, washing by CH 3CN and evaporation of solvent, the aldehyde was isolated with a quantitative performance.

StepIII: **Knoevenegel reaction, addition of Michael, trans-esterification** To aldehyde (0.411mmol)was added methanole (10ml) (1.32mmole) of ethyl malonate , 344mg of NP.The mixture is refluxed for 12h. At the end of the reaction, the resulting suspension was filtered and washed by methanole . The crude product is purified on silica gel column(eluent: CH2Cl2/ MeOH).

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