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Proceeding Paper

Synthesis of New Aza-Heterocyclic Based on 2-Pyridone †

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Abstract: In this work, we present new methods of synthesis of different molecules including a 2-pyridone nucleus. First, we prepared a series of 1*H*-free 2-pyridones and *N*-alkyl 2-pyridones from ethyl cyanoacetate, aromatic aldehydes, various acetophenone derivatives and ammonium acetate or diamino-alkane. These molecules have served as building blocks that, in conjunction with acyl chloride derivatives, glycoside derivatives, etc. have resulted in various heterocyclic hybrid structures carrying a 2-pyridone ring. Moreover, based on the cyano group reactivity of the 2-pyridone ring, we synthesized 5-pyridone 1*H*-tetrazole in a single step by a cycloaddition reaction [3 + 2] between 3-cyano-2-pyridone nitriles and sodium azide in the presence of metal-free L-proline.

Keywords: aza-heterocyclic; 2-pyridone; acyl chloride derivatives; glycosides; 5-1*H*-tetrazole

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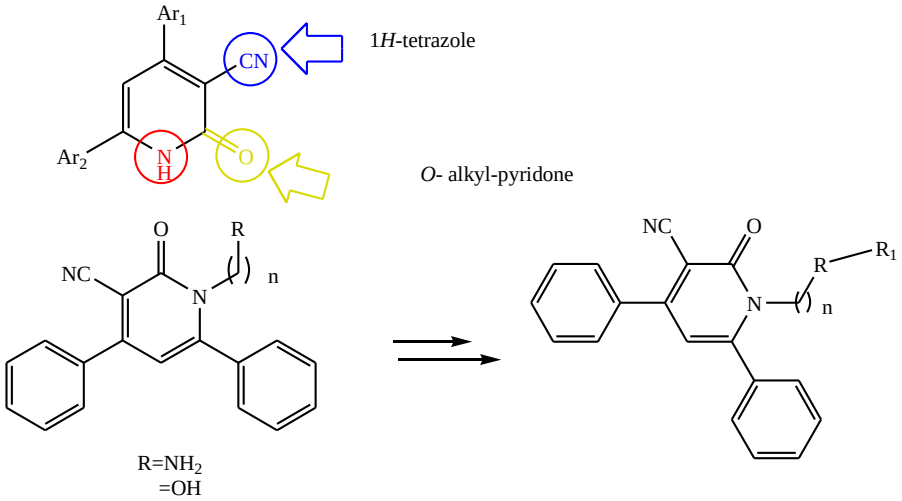
1. Introduction

2-Pyridone derivative synthesis is an important research area. Various applications of 2-pyridone and its derivatives have attracted considerable attention over the recent decades [1], including the development of biologically active products [2], dyes, and fluorescents products [3,4].

The 2-pyridones have at least three active sites based on the presence of the non-substituted "NH", "C=O", and "CN" groups. The regio-selectivity of *N*- versus *O*-alkylation is still debated, it depends on various factors, including the catalyst type, the structure of alkyl halides, the substituents on the 2-pyridone ring, solvents, and temperature. However, developing new approaches for the selective synthesis of substituted *N*-alkyl 2-pyridones still needs to be explored and remains an interesting research topic [5–7].

In our research on the development of compounds based on 2-pyridone, we are interested in the two structural nuclei: 1*H*-free pyridones and 2-pyridones N-alkyl synthesized in advance [1] to access different aza-heterocyclic (Scheme 1).

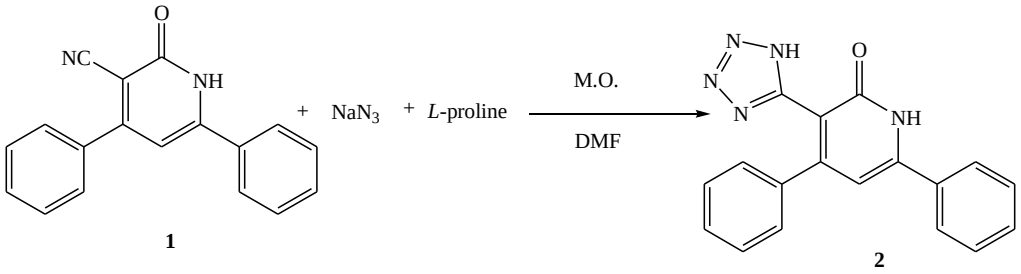


Scheme 1. Aza-heterocyclics preparation strategies based on 2-pyridone.

2. Results and Discussion

2.1. Reactivities of 3-cyano-pyridin-2(1H)-one Derivatives

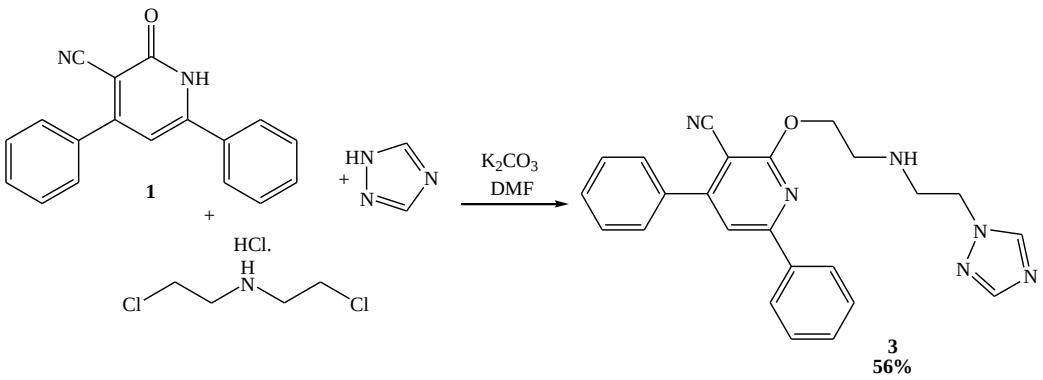
The [2 + 3] cycloaddition reaction was implemented between the nitrile group of the 3-cyano-2-pyridone 1 derivative and sodium azide in the presence of 30 mole % of L-proline to produce 1*H*-tetrazole 2-pyridones 2 (Scheme 2) which was isolated with a good yield. In the absence of the catalyst, no reaction took place.



Scheme 2. Synthesis of (1H-tetrazol-5-yl)pyridin-2(1H)-one **2**.

The hybrid compound 3 was prepared from a reaction between the derivatives 3-cyano-pyridin-2(1*H*)-one 1 and 1,2,4-1*H*-triazole through the bis(2-chloro-ethyl)amine hydrochloride binder in the presence of K_2CO_3/DMF (Scheme 3). Product 3 was obtained with a good yield.

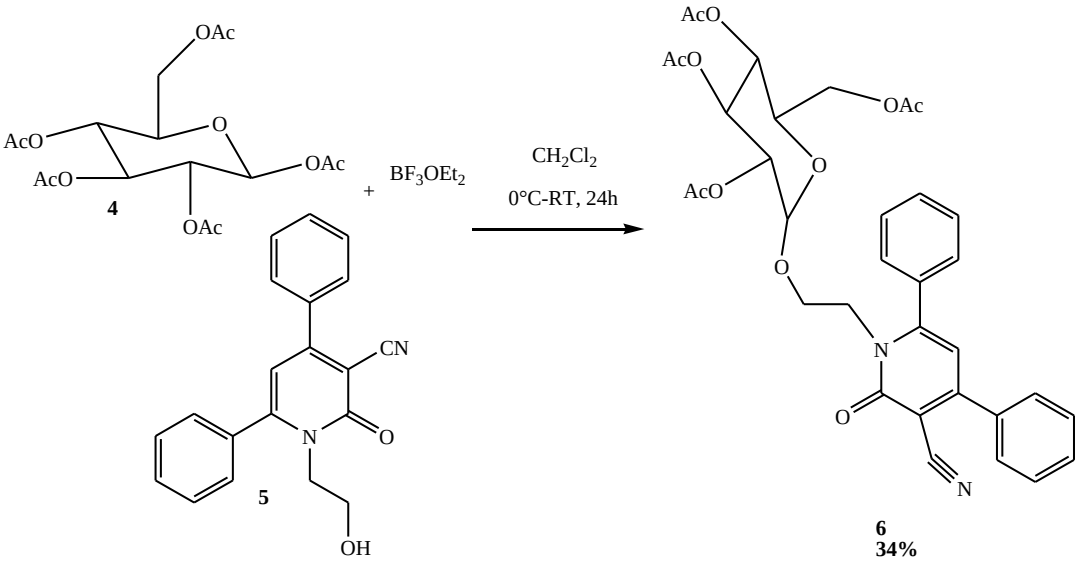
As expected, we observed a concomitant 2-alkoxy-pyridine to *N*-alkyl-pyridone, for the hybrid 3 isolated as an O/N bound dimer, *O*-alkyl-pyridone is the only product retained.



Scheme 3. Synthesis of the hybrid **3**.

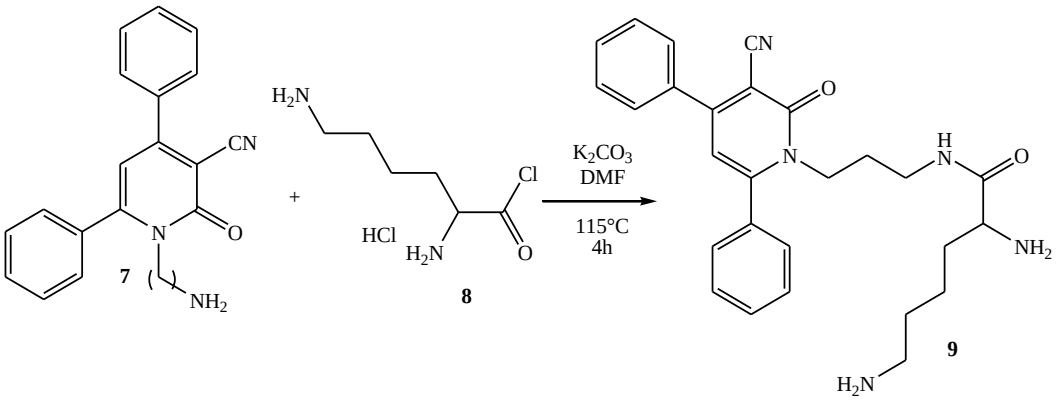
2.2. Reactivities of N-alkyl-pyridin-2-one Derivatives

The synthesis of compound 6, an *O*-glycoside derivative based on *N*-alkyl-pyridin-2-one, is done by a very convenient reaction, that is to say without the regeneration of the hydroxyl group of the anomeric carbon beforehand as intermediate. Thus, glucose pentaacetate 4 reacted with 1.2 equivalent of compound 5 in the presence of $BF_3.Et_2O$ (1.5 equivalent) in dichloromethane. Compound 6 was generated as a β-anomer solid with no detectable formation of α-anomer (Scheme 4).



Scheme 4. Synthesis of the O-glycosyde derivative **6**.

The preparation of hybrid 9 took place by reaction between 3-cyano-2-pyridine *N*-alkyl 7 and acetylated lysine 8 in the presence of K_2CO_3 (1 equivalent) in *N*, *N*-dimethylformamide (Scheme 5).



Scheme 5. Peptide hybrid synthesis **9**.

3. Experimental

3.1. Preparation of 4,6-diphenyl-3-(1H-tetrazol-5-yl)pyridin-2(1H)-one (2)

In a 25 mL flask, a mixture of organic nitrile **1** (1 mmol), NaN_3 (1.5 mmol), and L-proline (0.03 g, 30 mol%) in DMF (5 mL) was irradiated under microwave conditions for 20 min. The progress of the reaction was followed by CCM. After cooling to room temperature, 20 mL of water was added, and then (3 × 15 mL) of ethyl acetate. The organic phase was washed with water (2 × 20 mL) and the saturated water in NaCl (20 mL), was dried

on magnesium sulfate, filtered, and evaporated under reduced pressure. The crude obtained was filtered and washed with diethyl ether.

3.2. Preparation of 2-(2-(2-(1H-1,2,4-triazol-1-yl)ethylamino)ethoxy)-4,6-diphenylnicotinonitrile (3)

In a 25 mL flask, compound **1** (1.2 mmol) was dissolved in dry DMF (15 mL), bis(2-chloro-ethyl)amine hydrochloride (1.2 mmol), and K_2CO_3 (2.4 mmol, 2eq) were added and the mixture was stirred for 30 min. The 1,2,4-1H-triazole (1.2 mmol) was added to the mixture and left to shake for 24 h at room temperature. The whole was poured into water (20 mL) and then the phases were separated by extraction with ethyl acetate (3 × 15 mL), the combined organic phases were washed with water (2 × 20 mL) and the saturated water in NaCl (20 mL), was dried on magnesium sulfate, filtered, and evaporated under reduced pressure. The crude obtained was filtered and washed with diethyl ether.

3.3. Preparation of 1-(2-(2,3,4,6 tétra-O-acétyl-D-glucopyranosyle) ethoxy)-2-oxo-4,6-diphenyl -1,2-dihydropyridine-3-carbonitrile (6)

In a 100 mL bicol flask, a solution of **4** (0.01 mol) pentaacetate and molecular sieve (4 Å, 5.2 g) in CH_2Cl_2 (50 mL), was added to compound **5** (0.04 mol). The mixture was cooled to 0 °C and $BF_3.OEt_2$ (0.04 mol) was added drip for 1h30 min. The mixture was stirred for 24 h at room temperature, then filtered through the celt, washed with CH_2Cl_2 (100 mL), and concentrated under a vacuum. The residue was dissolved in CH_2Cl_2 (100 mL), extracted with water (2 × 25 mL), and NaCl saturated water (20 mL), dried on magnesium sulfate, filtered, and evaporated under reduced pressure. The crude obtained was filtered and washed with diethyl ether.

3.4. Preparation of 2,6-diamino-N-(3-(3-cyano-2-oxo-4,6-diphenylpyridin-1(2H)-yl)propyl)hexanamide (9)

In a 25 mL bicol flask, we added 3-cyano-2-pyridine N-alkyl **7** (0.55 mmol), K_2CO_3 (0.55 mmol), and acetylated lysine **8** (0.55 mmol) in N, N-dimethylformamide (5 mL), the mixture was stirred for 4 h at 115 °C. The residue was concentrated under a vacuum, then dissolved in CH_2Cl_2 (50 mL) and extracted with water (2 × 20 mL), and saturated water in NaCl (20 mL), dried on magnesium sulfate, filtered, and evaporated under reduced pressure. The crude obtained was filtered and washed with diethyl ether.

4. Conclusions

In this work, we studied the reactivity of pyridin-2(1*H*)-one and *N*-substituted 2-pyridones derivatives from reactions environmentally friendly by applying the catalyst; inexpensive reagents; the micro-irradiation, which has led to a considerable reduction in reaction time and energy consumption.

Furthermore, the synthesis of hybrids from *N*-alkyl-2-pyridones resulted in the corresponding *N*-alkyl products selectively. In contrast, the synthesis of hybrids from pyridin-2(1*H*)-one derivative resulted in the formation of *O*-alkyl hybrids, but in both cases, we isolated a single product by the alkylation of 2-pyridones.

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Conflicts of Interest: The authors declare no conflicts of interest.

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