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Synthesis of Novel Heterocyclic Compounds Containing 1,5-Benzodiazepine

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The purpose of this work is the development of a synthetic pathway that allows access to heterocyclic compounds containing the 1,5-benzodiazepines. The dehydroacetic acid has been widely studied as a starting material for the synthesis of natural products that exhibit interesting pharmacological properties. In the present work, we describe an easy and cost effective access way to new products 1,5-benzodiazepines involving a pyranic residue. All synthesized products were subjected to IR, ^{1}H NMR and mass spectra studies.

Keywords: Dehydroacetic acid, 1,5-Benzodiazepine.

INTRODUCTION

Benzodiazepines, from the pharmacological standpoint, are very interesting molecules. Numerous studies have demonstrated anxiolytic effect on the human nervous system. They are used in the therapeutic field[1] and have important biological activities, particularly the 1,4- and 1,5-benzodiazepines[2]. Benzodiazepines are also used as anticonvulsant agents[3], anti-inflammatory and analgesic[4], antidepressive of the central nervous system[5] and antibacterial[6]. For instance, Valium (diazepam) is marketed as a sedative and noveril (dibenzepin) as an antidepressive. The strategy of using benzodiazepines essentially depends on the knowledge of their pharmacokinetics that can take advantage of their "qualities" but also to avoid some of their "side effects". In addition, benzodiazepines are the most powerful anticonvulsant substances known so far: they are able of antagonize, common amongst animal, convulsions induced by a wide variety of chemical substances *e.g.*, isoniazid, picrotoxin, strychnine, pentetrazole. On the other hand, they are less effective in protecting seizures due to electric shock[7].

Synthesis of 1,5-benzodiazepines structures were made from different lactones, such as tetronic acid, 4-hydroxy coumarin, demidone and dehydroacetic acid[8]. It therefore seemed interesting to carry on further research by investigating the reactivity of the dehydroacetic acid and its derivatives which are susceptible to serve as starting material for the synthesis of other heterocyclic compounds such as benzodiazepines whose basic cores are known for their pharmacological effects. Moreover, 1,5-benzodiazepine type compounds are particularly active on the central nervous system[9] and anticonvulsants[10], antiinflammatory, analgesics[11] and antibacterial[12].

The present work is focused on the use of dehydroacetic acid and its derivatives in heterocyclic synthesis. We report in this paper the synthesis of new molecules susceptible to present valuable pharmacological properties namely 1.5-benzodiazepine.

The synthesis approach we adopted involves, in one hand, the opening of pyranic ring by binucleophiles reagents such as 2-amino-3-benzyloxypyridine and on the other hand, the action of hydrazine hydrate on pyridopyrimidine. Finally we obtain pyrano-1,5-benzodiazepine (**10**) by the condensation reaction of *o*-phenylenediamines substituted on the cynamoyles from the dehydroacetic acid.

EXPERIMENTAL

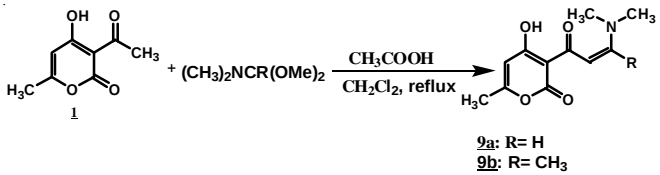
^{1}H NMR spectra were performed on spectrometer Bruker AC 200 MHz and 300 MHz. Chemical shifts are given in ppm relative to TMS (internal reference). The ^{13}C NMR spectra were made in J modulated on a spectrometer Bruker AC 200 and 300 MHz. Infrared spectra were recorded on a Perkin Elmer 225 network spectrophotometer, compounds being in solid suspension in Nujol. The results are given in cm^{-1}. Mass spectra were performed on a Nermag R10-10C spectrometer with the ionization mode by electronic impact to 70 EV and/or by chemical ionization by NH_3. Melting points were taken on using a Köfler bench.

Synthesis of cynamoyles (9): 1.68 g (10^{-2}) Dehydroacetic acid, 1.19 g (10^{-2}) of N,N-dimethylformamide-dimethylacetal (DMF-DMA) in 40 mL of dichloromethane in the presence of a catalytic amount of acetic acid is heated under reflux for 24 h. After evaporation of the solvent, the oil obtained precipitates in ethanol to afford compound **9a** with a yield of 75 % and m.p. = 170-172 °C.

Synthesis of pyrano-1,5-benzodiazepines (10): To an ethanolic solution of 30 mL containing 2.23 g (0.01 mol) of compound **9a**, we add 1.08 g (0.01 mol) of *o*-phenylenediamine in the presence of a catalytic amount of triethylamine. The reaction mixture was heated under reflux with magnetic stirring for 6 h. Benzodiazepine (**10a**) precipitates by cooling in the form of a very dark purple solid with a yield of 48 % and m.p. = 238-241 °C.

RESULTS AND DISCUSSION

As a first step, the condensation of N,N-dimethylformamide-dimethylacetal (DMF-DMA) on dehydroacetic acid (**1**) under reflux in dichloromethane in the presence of a catalytic amount of acetic acid, leads to the isolation of the cynamoyles **9a** (**Scheme-I**).



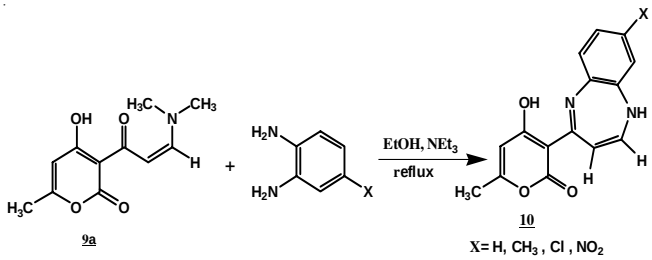
Scheme-I: Formation of cynamoyles (**9**) by condensation N,N-dimethylformamide dimethylacetal (DMF-DMA) on dehydroacetic acid (**1**)

Characteristics of 9a: ^{1}H NMR ($CDCl_3$, 200 MHz): 2.11 (s, 3H, CH_3), 2.99 (s, 3H, CH_3), 3.17 (s, 3H, CH_3), 5.72 (s, 1H, CH=C), 6.59 (d, 1H, *J* = 8.20, CH=CHa), 7,99 (d, 1H, *J* = 8,20, CH_b=CH), 14,28 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 200 MHz): 184(C2), 104(C3), 164(C4), 92(C5), 162(C6), 186(C8), 20(C11), 105(C12), 156(C13), 38(C15), 46(C17). S.M (IE, 70 ev): M = 223.

Characteristics of 9b: This derivative is obtained under the same operating conditions as the derivative **9a** with a yield of 81 % and m.p. = 193-195 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): 2.11(s, 3H, CH_3), 2.98 (s, 3H, CH_3), 3,15 (s, 3H, CH_3), 3.95 (s, 3H, CH_3), 5.75 (s, 1H, CH=C), 8,11 (s, 1H, CH_b=CH_3), 14,30 (s, 1H, OH). S.M (IE, 70 ev): M = 237

^{1}H NMR spectrum of compound **9** shows the disappearance of the signal due to the protons of -CH_3 of the acetyl grouping and the appearance of dimethylamino system. The aromatic protons signals appear at about 6.59 and 7.99 ppm. When compound **9** is heated under reflux with *o*-phenylenediamine in equimolar amounts in ethanol solution in the presence of triethylamine for 6 h, it affords compound **10** (**Scheme-II**).

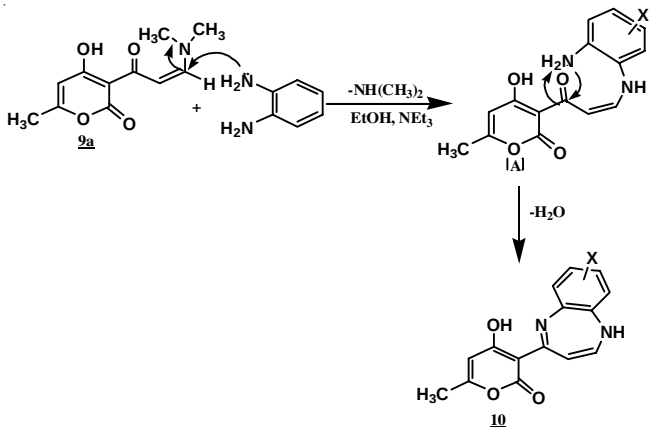
^{1}H NMR spectrum at 300 MHz of derivatives **10** shows the expected signals for the considered structure. It is noted that the absence of the signals due to the protons of dimethylamino group, the appearance of a broad peak due to NH proton in position 1 and the presence of the signals due to protons of an aromatic system AB at 6.05 and 6.25 ppm.



Scheme-II: Formation of 1,5-benzodiazepines by the action of *o*-phenylenediamine on cynamoyles (**9**); (10a: X = H, 10b: X = CH_3, 10C: X = Cl, 10d: X = NO_2)

^{13}C NMR spectrum shows the cyclization of cynamoyles (**9**) in pyrano-1,5-benzodiazepines (**10**) by the disappearance of the signals due to the carbons of the dime-thylamino group and the presence of two peaks at about 129 and 130 ppm corresponding to carbons in position 2,5.

The obtained result from the reaction of cynamoyles (**9**) with the *o*-phenylenediamine allows proposing a mechanism explaining the formation of **10** (**Scheme-III**).



Scheme-III: Formation of product **10** by initial attack of an amino group of the *o*-phenylenediamine of the carbon in position 13

The formation of pyrano-1,5-benzodiazepines (**10**) can be explained by an initial attack of an amino group of *o*-phenylenediamine on carbon at position 13 leading to the intermediate [A], after the elimination of dimethylamine molecule. The cyclization of [A] involves the attack of the second nitrogen of the amino group on the carbonyl in position 8 followed by the elimination of a water molecule to lead to compounds of benzodiazepine **10** structure.

Characteristics of 10a: ^{1}H NMR ($CDCl_3$, 200 MHz): 2.15 (s, 3H, CH_3), 5.80 (s, 1H, CH=C), 6.05 (dd, 1H, *J* = 9.7, 1.98, N-CH=CH_a), 6.25 (dd, 1H, *J* = 9.7, 7.2, N-CH_b=CH), 6.75-6.85 (m, 4H, arom), 8,7 (d, 1H, *J* = 7.2, NH), 14,30 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 200 MHz): 185(C2), 107(C3), 165(C4), 94(C5), 152(C6), 174(C8), 139(C10), 140(C11), 129(C13), 130(C14), 123(C15), 128(C16), 127(C17), 124(C18). S.M (IE, 70 ev): M = 268.

Characteristics of 10b: Under the same operating conditions as **10a**, we get compound **10b** with a yield of 55 %, m.p. = 244-246 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) : 2.17 (s, 3H, CH_3), 2.35 (s, 3H, p-CH_3), 5.78 (s, 1H, CH=C), 6.08 (dd, 1H, *J* = 9.5, 2.0, N-CH=CH_a), 6.28 (dd, 1H, *J* = 9.5, 7.15, N-CH_b=CH), 6.73-6.87 (m, 3H, arom), 8,9 (d, 1H, *J* = 7.15, NH), 14,28 (s, 1H, OH). S.M (IE, 70 ev): M = 268.

Characteristics of 10c: Under the same operating conditions as **10a**, we get compound **10c** with a yield of 51 %, m.p. = 250-252 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) : 2.14 (s, 3H, CH_3), 5.75 (s, 1H, CH=C), 6.10 (dd, 1H, *J* = 9.6, 2.10, N-CH=CH_a), 6.28 (dd, 1H, *J* = 9.6, 7.22, N-CH_b=CH), 6.71-6.89 (m, 3H, arom), 8,5 (d, 1H, *J* = 7.22, NH), 14,35 (s, 1H, OH). S.M (IE, 70 ev): M = 302.

Characteristics of 10d: Under the same operating conditions as **10a**, we get compound **10d** with a yield of 45 %, m.p > = 260 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) : 2.15 (s, 3H, CH_3), 5.70 (s, 1H, CH=C), 6.07 (dd, 1H, *J* = 9.68, 1.97, N-CH=CHa), 6.25 (dd, 1H, *J* = 9.68, 7.28, N-CH_b=CH), 6.74-6.92 (m, 3H, arom), 8,53 (d, 1H, *J* = 7.28, NH), 14,33 (s, 1H, OH). S.M (IE, 70 ev): M = 313.

Conclusion

The obtained results confirm the interest of dehydroacetic acid for the synthesis of heterocyclic compound derived from the 1,5-benzodiazepine.

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