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Synthesis of 4-pyrano-1, 5-benzodiazepines catalysed by bismuth (III) derivatives

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ABSTRACT

Condensation reactions on dehydroacetic acid (DHA) generate a rich variety of heterocyclic systems. In particular, they proved to be very useful for the preparation of benzodiazepine derivatives. In the present study, the experimental conditions of these reactions were investigated with the aim of developing a new heterocyclization method using bismuth derivatives.

Keywords: Pyrano-benzodizepine, bismuth (III), dehydroacetic acid

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INTRODUCTION

Condensation reactions on dehydroacetic acid (DHA) generate a rich variety of heterocyclic systems [1]. In particular, they proved to be very useful for the preparation of benzodiazepine derivatives, which are known for their neuroleptic activity [2-5] and interesting pharmacological properties [6-10]. We showed in a previous work [11] that DHA reacts with substituted ortho-phenylenediamine and leads to the imine intermediate. The catalytic cyclization of the latter compound in basic medium in the presence of aromatic and masked (dimethylformamide-dimethylamine, DMA-DMF) aldehydes allowed pyrano-1,5-benzodiazepines to be isolated. Recently, the imine derivatives obtained by condensation of DHA with primary monoamines were reacted with tosyl isocyanide (TosMIC) in the presence of bismuth triflate as catalyst, and gave imidazole derivatives [12].

In the present study, the experimental conditions of these reactions were investigated with the aim of developing a new heterocyclization method using bismuth derivatives. The choice of these compounds is justified by their Lewis acid character. They have recently attracted a new burst of interest in organic synthesis [13]. In particular, bismuth (III) salts are efficient catalysts for a number of reactions such as Friedel-Crafts [14], imine allylation [15] and acylation reactions [16]. They also efficiently catalyze Mannich reactions [17], the intermolecular variant of the Pictet-Spengler reaction [18]. Additionally, Bismuth compounds are nontoxic and easy to handle.

Experimental section

Melting points were taken on a Thomas Hoover apparatus and are uncorrected. Nuclear magnetic resonance spectra were obtained with a Bruker AC 250 at 300 MHz (^{1}H) or 60 MHz (^{13}C). The impact ionization mass spectra were recorded on a Nermag R10-10C at 70 eV. Infrared spectra were recorded in KBr pellets containing compounds in 5% weight, with a Perkin Elmer Paragon 1000 PC spectrometer, the precision of which is 2 cm^{-1} in the 4000-400 cm^{-1} range.

General procedure for synthesis

In 40 mL methanol, a cetimine derivative **1** (**a** to **d**) (10^{-2} mol) was reacted with N,N-dimethylformamide diméthylacétal (1.19 g,10^{-2} mol), in the presence of bismuth triflate (65.6 mg, 10^{-4}mol) or bismuth chloride (0.315 g, 10^{-3}mol). The mixture was refluxed for 48 h under magnetic stirring. Then, it was allowed to cool down and filtered, yielding the corresponding compound **2** (**a** to **d**) as a dark purple powder.

3-(1*H*-1,5-Benzodiazepin-4-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (2a):

Mp = 240-242°C. IR (KBr, υ(cm^{-1})): 3400 (OH), 3290 (NH), 1690 (C=O/C=N), 1620 (=CH). ^{1}H NMR (d$_6$-DMSO, 300M Hz): 2.04 (s, 3H, CH_3), 5.65 (s, 1H, CH=C), 6.10 (dd,1H, J = 9.7, 1.98, N-CH_a=CH),

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6.25 (dd,1H, J = 9.7, 7.2, N-CH_b=CH), 6.35-6.65(m, 4H, arom), 8.65 (d, 1H, J = 7.2, NH), 13.96 (s, 1H, OH). ^{13}C NMR (d_6-DMSO, 300 MHz)**:** 20.4 ($\underline{C}H_3$C=CH), 93.5 ($\underline{C}$H=C-Me), 93.6 (CH_a=$\underline{C}H_b$), 95.2 (HO-C=$\underline{C}$-), 113.5, 123.9, 124.1, 126.6, 127.9, 138.7 ($\underline{C}$arom), 153.7 ($\underline{C}H_a$=CH_b), 162.5 ($\underline{C}$=N-), 162.8 ($\underline{C}$=O), 171.7 (CH=$\underline{C}$-Me), 184.7 (HO-$\underline{C}$=C-). MS. m/z (%) : 268 ([$M^{\cdot}$]$^+$, 10), 253 (25), 224 (51), 143 (60), 119 (37).

4-Hydroxy-6-methyl-3-(8-methyl-1*H*-1,5-benzodiazepin-4-yl)-2*H*- pyran-2-one (2b):

Mp = 244-246°C. IR (KBr, υ(cm^{-1})) : 3380 (OH), 3300 (NH), 1685 (C=O/C=N), 1610 (=CH). ^{1}H NMR (d_6-DMSO**,** 300 MHz**):** 2.10 (s, 3H, CH_3), 2.32 (s, 3H, p-CH_3), 5.72 (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), 6.42-6.72 (m, 3H, arom), 8.71(d, 1H, J = 7.15, NH), 14.30 (s, 1H, OH). ^{13}C NMR (d6-DMSO, 300 MHz)**:** 20.4 ($\underline{C}H_3$C=CH), 26.8 ($\underline{C}H_3$-Arom), 93.1 ($\underline{C}$H=C-Me), 93.1 (CH_a=$\underline{C}H_b$), 94.9 (HO-C=$\underline{C}$-), 112.7, 122.87, 124.1, 125.4, 126.9, 137.6 ($\underline{C}$arom), 153.1 ($\underline{C}H_a$=CH_b), 162.1 ($\underline{C}$=N-), 162.5($\underline{C}$=O), 171.6 (CH=$\underline{C}$-Me), 184.7 (HO-$\underline{C}$=C-). MS. m/z (%) : 282 ([$M^{\cdot}$]$^+$, 14), 267 (33), 238 (45), 143 (56), 133 (27).

3-(8-Chloro-1*H*-1,5-benzodiazepin-4-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (2c):

Mp = 250-252°C. IR (KBr, υ(cm^{-1})) : 3385 (OH), 3310 (NH), 1695 (C=O/C=N), 1625 (=CH). ^{1}H NMR **(**d_6-DMSO, 300 MHz**):** 2.12 (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), 8.68 (d, 1H, J = 7.22, NH), 14.30(s, 1H, OH). ^{13}C NMR (d_6-DMSO, 300 MHz)**:** 20.2 ($\underline{C}H_3$C=CH), 93.4 ($\underline{C}$H=C-Me), 93.1 (CH_a=$\underline{C}H_b$), 94.9 (HO-C=$\underline{C}$-), 119.3, 123.5, 125.4, 126.9, 166.9, 138.2 ($\underline{C}$arom), 152.1 ($\underline{C}H_a$=CH_b), 162.8 ($\underline{C}$=N-), 162.3 ($\underline{C}$=O), 172.1 (CH=$\underline{C}$-Me), 184.6 (HO-$\underline{C}$=C-). M.S. m/z (%): 302 ([$M^{\cdot}$]$^+$, 19), 287 (22), 267 (15), 214(39), 143 (44), 119 (23).

4-Hydroxy-6-methyl-3-(8-nitro-1*H*-1,5-benzodiazepin-4-yl)-2*H*-pyran-2-one (2d):

Mp = 262°C. IR (KBr, υ(cm^{-1})): 3380 (OH), 3290 (NH), 1685 (C=O/C=N), 1615 (=CH). ^{1}H RMN (d_6-DMSO**,** 300 MHz): 2.13 (s, 3H, CH_3), 5.70 (s, 1H, CH=C), 6.07 (dd, 1H, J = 9.68, 1.97, N-CH=CH_a), 6.25 (dd, 1H, J = 9.68, 7.28 Hz, N-CH_b=CH), 6.74-6.92 (m, 3H, arom), 8.70 (d, 1H, J = 7.28, NH), 14.28 (s, 1H, OH). ^{13}C RMN (d_6-DMSO, 300 MHz)**:** 20.1 ($\underline{C}H_3$C=CH), 93.4 ($\underline{C}$H=C-Me), 92.8 (CH_a=$\underline{C}H_b$), 95.2 (HO-C=$\underline{C}$-), 117.4, 118.4, 121.2, 137.3, 138.7, 143.5 ($\underline{C}$arom), 152.1 ($\underline{C}H_a$=CH_b), 162.8 ($\underline{C}$=N-), 162.3 ($\underline{C}$=O), 172.1 (CH=$\underline{C}$-Me), 184.6 (HO-$\underline{C}$=C-). M.S. m/z (%) : 311 ([$M^{\cdot}$]$^+$, 26), 296 (17), 281 (9), 267(34), 143 (39), 119 (14).

RESULTS AND DISCUSSION

Firstly, cetimine derivatives **1** were synthesized from substituted ortho-phenylenediamine [11]. These cetimine compounds were reacted with DMF-DMA in the presence of bismuth acid and lead to benzodiazepine derivatives in only one step (Scheme1).

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Scheme 1

Spectroscopic methods (^{1}H NMR, ^{13}C NMR and mass spectrometry) allowed the tautomeric form **2** to be evidenced. In fact, ^{1}H NMR spectra showed a broad peak at around 8.7 ppm, attributable to the NH proton in the 1-position, and two doublets of doublet at around 6.10-6.25 ppm, corresponding to aromatic (N-CH=CH) protons. In ^{13}C NMR, the spectra displayed signals situated at 93.6 ppm and 153.7 ppm that can be assigned to the carbon atoms in the 2- and 3-positions, respectively. It is noteworthy that the tautomeric form **2** is similar to that previously obtained by basic catalysis with triethylamine [11].

The catalytic activity of two Lewis acids, specifically $BiCl_3$ and $Bi(OTf)_3$, was compared in the same experimental conditions (Table 1). Pyranobenzodiazepines **2** were systematically prepared in better yields in the presence of 1% $Bi(OTf)_3$ than with 10% $BiCl_3$. This can be explained by the strong acidic nature of the Bi^{3+} cation, due to the extensive delocalization of the negative charge of the triflate anions, stabilized by mesomeric effect. No clear tendency was found between the obtained yields and the nature of the substituent electronic effect (Table 1).

Table 1: Comparison of the catalytic activity of two Lewis acids

Compounds	X	Yield %	
		Catalyst **10% $BiCl_3$**	Catalyst **1% $Bi(OTf)_3$**
2a	H	40	68
2b	*p*-CH_3	53	70
2c	*p*-Cl	48	75
2d	*p*-NO_2	35	48

The formation of pyrano-1,5-benzodiazepines **2** can be schematized as below (Scheme 2). In a first time, owing to acidic catalysis, an interaction takes place between the amino group borne by the phenyl ring of **1** and the carbonyl group of the masked aldehyde, resulting in elimination of a methanol molecule. Then, a diimine intermediate is formed by elimination of a second methanol molecule. This diimine intermediate is in equilibrium with its tautomeric enamino-imine form. The latter undergoes cyclization under acidic catalysis and leads to a

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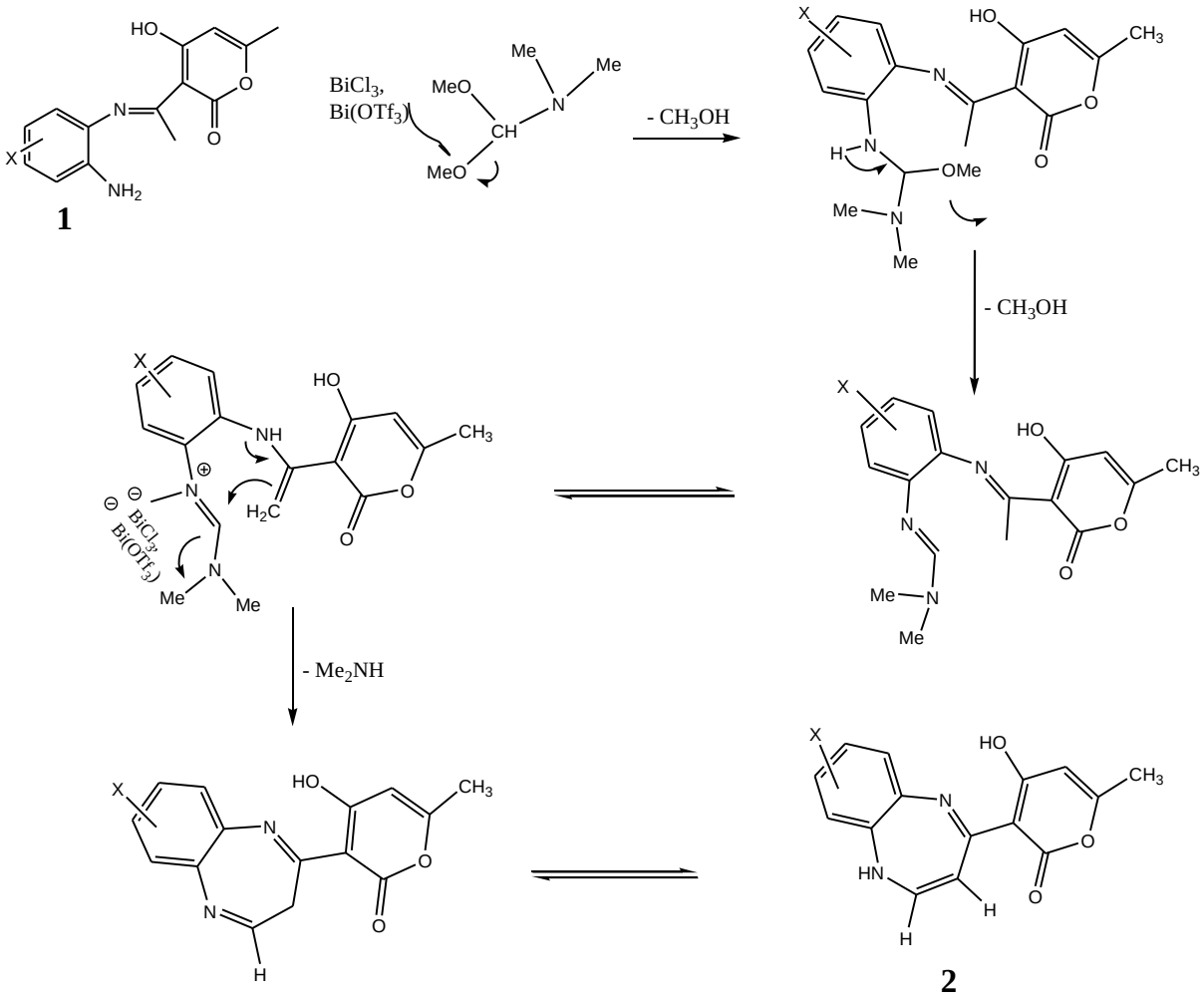
benzodiazepine structure after protonation of the imino group, on the one hand, and mobility of the methyl group due to hyperconjugation, on the other hand. This benzodiazepine derivative is actually present as its tautomeric form **2**, as evidenced by the spectral characteristics.



Scheme 2

CONCLUSION

This work shows the effect of bismuth-based catalysis on heterocyclization of DHA cetimine to give pyrano-1,5-benzodiazepines. Some new molecules (**2b**, **2c** and **2d**) were obtained. It can be noticed that the electronic effects of the various groups borne by the phenyl ring of diamines only have a weak influence on the reaction yield.

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