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Synthesis of new amino-1,5-benzodiazepine and benzotriazole derivatives from dimedone

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Abstract: High-yielding syntheses of two unpublished series of amino-1,5-benzodiazepines derivatives **3** and 1,2,3-benzotriazoles **4** bearing a dimedone moiety are respectively reported. Derivatives **3** were obtained by intramolecular cyclisation using cyanogenbromide of enaminone **2**. On the other hand, when enaminones **2** were treated with sodium nitrite under acidic conditions, cyclisation led to benzotriazole **4**.

Keywords: Dimedone; benzotriazoles; benzodiazepines, cyanobromide; enaminones.

1. Introduction

The benzodiazepine nucleus is a pharmacophoric scaffold and represent a class of heterocycles with a wide range of biological applications.[1] Many of them are widely used as anticonvulsant, antianxiety, sedative, antidepressive, hypnotic and neuroleptic agents.[2-5] Some heterocycles containing benzodiazepines moiety were reported to possess anti inflammatory[6], antiviral[7], anti-HIV-1[8], antimicrobial[9] and antitumor[10] activities. Other than their biological importance, benzodiazepines are valuable syntons for the preparation of fused ring compounds, such as triazolo[11], thiazolo[12], imidazo[13] and pyrimido-benzodiazepines.[14] It has been noticed that introduction of an additional ring to the benzodiazepine core tends to exert profound influence in conferring novel biological activities in these molecules.[11-15] Although many methods for synthesizing benzodiazepine ring systems have been reported, they continue to receive a great deal attention.[9,16-18]

Another class of heterocycles used as scaffolds in medicinal chemistry is devoted to benzotriazole derivatives. They exhibit useful pharmacological properties and clinical applications.[19-22]

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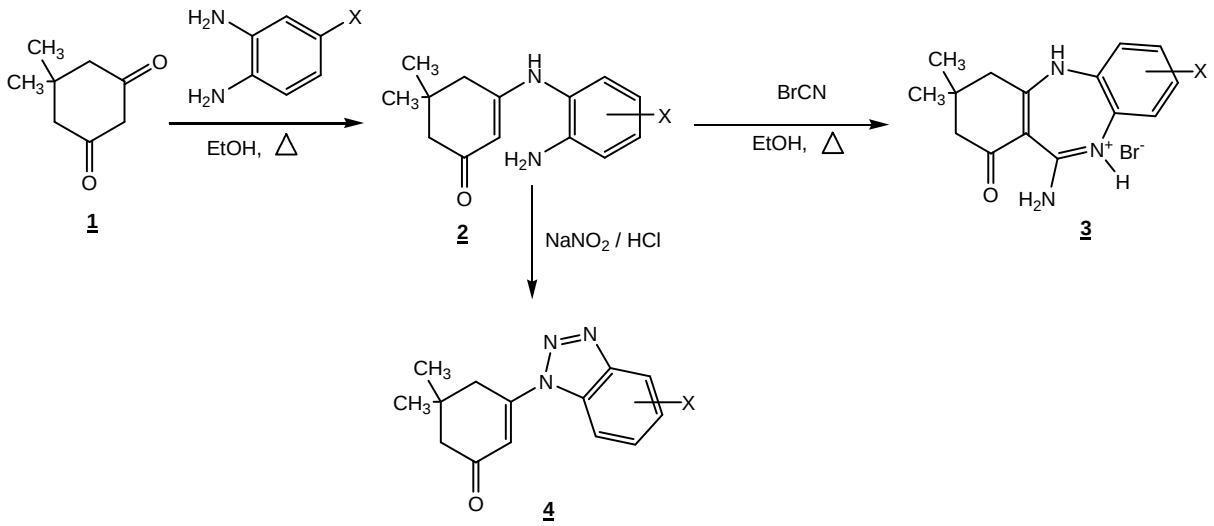
In addition to these considerable biological applications, benzotriazoles are important intermediates, protecting groups and final products in organic synthesis.[23]

In the course of our research and as part of our program involving the synthesis of new heterocyclic compounds having potential biological interest, we have already reported the synthesis of many pyranobenzodiazepines[24-31], pyranobenzodiazepin-2-thione and benzotriazoles derivatives[32] using enaminolactones as starting material. Recently, reactions of 5-amino-3-methyl-1H-pyrazole with dimedone and aldehydes was reported to give regioselectivelly tricyclic linear 3,7,7-trimethyl-4,7,8,9-tetrahydro-2H-pyrazolo[3,4-b]quinolin-5(6H)-ones.[33]

In pursuance of our interests for investigating the reactivity of enaminones towards electrophile reagents we now extend the scope of these reactions to an other active compound the 5,5-dimethylcyclohexan-1,3-dione(dimedone). They appear in a natural tricyclic heterocycle Benzylhiocrellidone isolated from sponge *Crella spinulata*[34-35] and is an effective synton in the synthesis of several polyheterocyclic compounds.[36-38] As expected, we get access to 1,5-benzodiazepines **3** and Benzotriazoles **4** fused and linked respectively to a dimedone moiety (Scheme 1).

2. Results and discussion

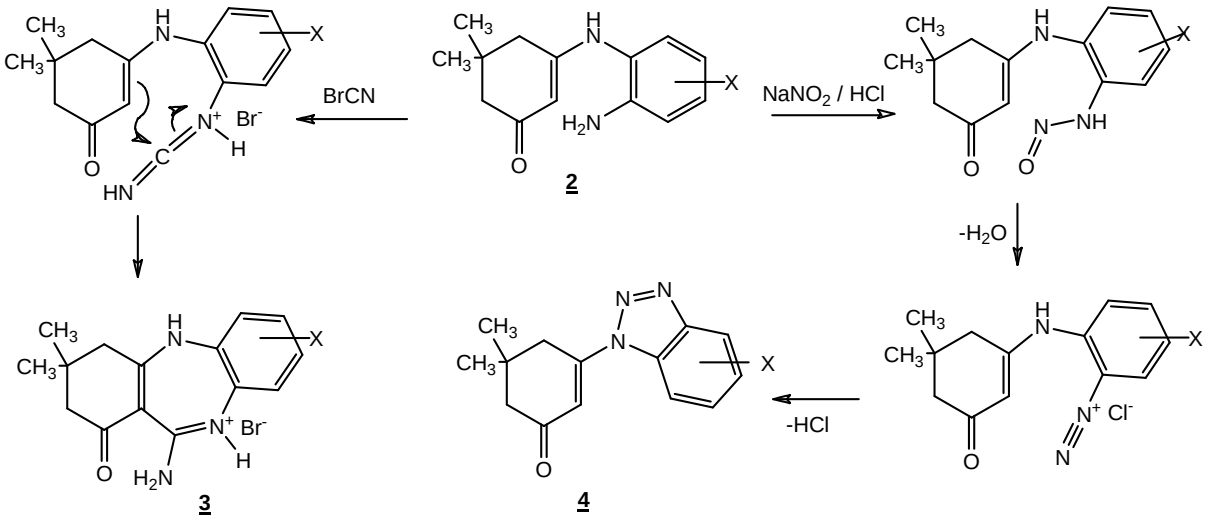
We have previously demonstrated that the enaminolactones intermediates allowed versatile access to different heterocycles[24-30], depending on the nature of electrophile used. In this work intermediate **2**, obtained by reaction of dimedone with substituted o-phenylenediamines under similar conditions to already described procedure[24], was used as starting point for the synthesis of benzodiazepines **3** and benzotriazoles **4** according to our synthetic pathways which are outlined in the scheme 1.



Scheme 1: Intramolecular cyclisations of enaminones **2**

Treatment of **2** with 1 equivalent of cyanobromide proceeds smoothly in refuxing, yielding by filtration product **3** in high purity.

As shown in scheme 2, the formation of seven membered ring **3** was due to the nucleophilic attack on the iminium ion by the adjacent electron-rich double bond of the dimedone moiety.



Scheme 2: Postulated mechanism for the formation of compounds **3** and **4**

Table 1: Physico-chemical data of derivatives **3a-c** and **4a-c**

Compounds	X	Yields [%]	Time (h)	mp (ºC)
3a	H	45	4	274-276
3b	CH_3	49	4	280-282
3c	Cl	30	6	292-294
4a	H	86	1	180-182
4b	CH_3	77	1	190-192
4c	Cl	65	1	200-202

Similarly the reaction of binucleophilic enaminone intermediates **2** with sodium nitrite under acidic conditions according to a described procedure,[36-38] allowed in all cases a single product **4** bearing a dimedone moiety in good yield (table-1). The probable mechanism in this case seems to be the diazotization of the primary amine of **2**, thus the formed diazo salt undergo cyclization, by nucleophilic attack of the secondary amino group leading to a triazole nucleus. The formation of benzotriazepine that would result from an intramolecular cyclization through the double bond of dimedone moiety as reported in the case of formation of benzodiazepines **3** was not observed. The purity and structures of the newly synthesized compounds were established by elemental analysis, IR, ^1H, ^{13}C NMR DEPT, and mass spectroscopic analysis.

Compounds **3a-c** exhibit in particular a ^1H NMR spectrum with a broadened singlet around 9.6-9.8 ppm characterizing the presence of NH^+. In addition the complete lack of the ethylenic proton at the C-2 of the dimedone ring in the ^1H NMR is accompanied by absorption for the quaternary

carbon of junction C-11a and C-11 of amidine bond at~ 96 ppm and~ 174 ppm respectively. The ^{1}H NMR spectra of **4a-c** not only showed the absence of both signals of NH at 8.06-8.13 ppm and NH_2 at 4.75-5.19 ppm, but also indicate the presence of C(2)-H signal at 6.55-6.58 ppm. Moreover ^{13}C NMR spectrum contains a signal around 112.8-114.8 ppm assigned to the tertiary ethylenic carbon C-2 in the dimedone unit thus substantiate the formation of all suggested compounds.

3. Conclusion

In conclusion, enaminones **2** resulting from the commercially available dimedone and o-phenylenediamines derivatives constitute an interesting and efficient precursor for the synthesis of new 1.5-benzodiazepines and benzotriazoles systems which are condensed and linked respectively to a dimedone moiety. These products are expected to possess biological activities.

4. Experimental

Melting points were determined using a Stuart Scientific SMP1 melting point apparatus and were uncorrected. The IR spectra were recorded in KBr pellets on a Perkin-Elmer FTIR Paragon 1000 spectrometer. The ^{1}H NMR spectra (400 MHz) and ^{13}C NMR (100.6 MHz) were run in DMSO- d6 on a Bruker Avance II spectrometer. Chemical shifts are given in ppm relative to TMS as internal standard. The positive-mode electrospray ionisation (ESI) mass spectra were recorded on a Perkin-Elmer SCIEX API 300 spectrometer. The elemental analysis data were performed on a Thermo Electron Flash EA 1112. Chemicals were purchased from Aldrich and Acros Organics and used without further purification.

General procedure for the preparation of compounds 2:

To a magnetically stirred solution of **1** (20 mmol, 1 eq) in 100 ml of absolute ethanol was added 4- substituted -1,2-phenylenediamine compounds (20 mmol, 1eq), and the mixture was allowed to react at room temperature for 12 h (as monitored by TLC). The reaction mixture was concentrated by rotatory evaporation to a volume of 20 ml and then stored in a refrigerator for 3 h. The precipitate obtained was filtered, washed several times with diethyl ether and recrystallized from ethanol to afford compounds **2**.Yields: 59-65 %.

General procedure for the preparation of compounds 3:

Cyanobromide 3M soln. EtOH (2.3 mmol, 1.15 eq) was added dropwise to a magnetically stirred solution of **2** (2 mmol, 1 eq) in ethanol 15 ml over a period of 30 min at room temperature. The mixture was then heated under reflux for 4-6 h. The precipitate formed was collected by filtration. Recrystallization from the proper solvent furnished the desired products **3a-c** as yellow solid.

11-amino-3,3-dimethyl-2,3,4,5-tetrahydro-1H-dibenzo[b,e][1,5]diazepin-1-one hydrobromide (3a). Yield: 45%. IR (KBr): 3443-3250 (NH,NH_2); 1652 (C=O), 1580 (C=N) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) (/ppm): 1.01 (s, 6H, $2CH_3$), 2.34 (s, 2H, NC-CH_2), 2.73 (s, 2H, OC-CH_2), 6.89-7.22 (m, 4H, Ar), 8.55 (s, br, 1H, NH), 9.72 (s, br, 1H, NH), 10.65 (s, 1H, NH_2), 10.73 (s, 1H, NH_2). ^{13}C NMR (100.6 MHz, DMSO-d_6) (/ppm): 27.08, 29.21, 45.99, 50.65, 96.04, 121.31, 122.57, 126.06, 128.11, 130.62, 131.02, 164.41, 174.28, 195.93. MS (ESI) m/z 256.5 [$(M\text{-}HBr)^{+}$, 16%]. Anal. Calcd. For. $C_{15}H_{17}N_3O$, HBr: C, 53.58%; H, 5.40%; N,12.50%. Found: C, 53.37 %; H, 5.20%; N. 12.29%.

11-amino-3,3,7-trimethyl-2,3,4,5-tetrahydro-1H-dibenzo[b,e][1,5]diazepin-1-onehydrobromide (3b). Yield: 49%. IR (KBr): 3431-3237 (NH,NH_2), 1667 (C=O), 1596 (C=N) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) (/ppm): 1.01 (s, 6H, $2CH_3$), 2.23 (s, 3H, Ar-CH_3), 2.34 (s, 2H, NC-CH_2), 2.71 (s, 2H, OC-CH_2), 6.70-7.05 (m, 3H, Ar), 8.53 (s, br, 1H, NH), 9.67 (s, br, 1H, NH), 10.61 (s, 1H, NH_2), 10.81 (s, 1H, NH_2). ^{13}C NMR (100.6 MHz, DMSO-d_6) (/ppm): 20.13, 27.06, 29.19, 46.00, 50.64, 95.48, 121.45, 122.53, 126.45, 128.22, 130.47, 138.04, 164.41, 173.65, 195.85. MS (ESI) m/z 270.5 [$(M\text{-}HBr)^+$, 22%]. Anal. Calcd. For. $C_{16}H_{19}N_3O$, HBr: C, 54.87 %; H, 5.76 %; N, 12.00 %. Found: C, 54.74 %; H, 5.74 %; N, 11.87 %.

11-amino-7-chloro-3,3-dimethyl-2,3,4,5-tetrahydro-1H-dibenzo[b,e][1,5]diazepin-1-one hydrobromide (3c). Yield: 30%. IR (KBr): 3460-3255 (NH,NH_2), 1660 (C=O), 1590 (C=N) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) (/ppm): 1.02 (s, 6H, $2CH_3$), 2.35 (s, 2H, NC-CH_2), 2.73 (s, 2H, OC-CH_2), 6.90-7.22 (m, 3H, Ar), 8.60 (s, br, 1H, NH), 9.81 (s, br, 1H, NH), 10.75 (s, 1H, NH_2), 10.92 (s, 1H, NH_2). ^{13}C NMR (100.6 MHz, DMSO-d_6) (/ppm): 27.04, 29.20, 46.15, 50.69, 95.72, 121.01, 121.8, 122.50, 126.00, 129.8, 130.44, 164.92, 173.85, 195.78. MS (ESI) m/z 290.5 [$(M\text{-}HBr)^+$, 10%]. Anal. Calcd. for. $C_{15}H_{16}N_3OCl$, HBr: C, 48.60 %; H, 4.62 %; N, 11.34 %. Found: C, 48.32 %; H, 4.42 %; N, 11.09 %.

General procedure for the preparation of compounds 4:

To an ice-cooled (0-5°C) and stirred solution of (2 mmol, 1eq) of the appropriate enaminones **2** in 6 ml of an 1M solution of HCl a solution of sodium nitrite 0.165g (2.4 mmol, 1.2 eq) in10 ml of H_2O was added drop by drop. After 20 min, the ice- bath was removed an the resulting solution was stirred for an additional hour. The precipitate obtained was collected by filtration and washed with H_2O. Recrystallization from ethyl acetate/petroleum ether gave the target compounds 4a-c.

3-(1H-Benzotriazol-1-yl)-5,5-dimethylcyclohex-2-en-1-one (4a). Yield: 86%. IR (KBr): 1669 (C=O), 1629 (C=N) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) (/ppm): 1.17 (s, 6H, $2CH_3$), 2.43 (s, 2H, NC- CH_2), 3.25 (s, 2H, OC- CH_2), 6.59 (s, 1H, NC=CH), 7.54-8.25 (m, 4H, Ar).^{13}C NMR (100.6 MHz, DMSO-d_6) (/ppm): 27.63, 32.80, 40.00, 50.12, 112.80, 114.34, 120.13, 125.50, 129.56, 130.87, 146.16, 152.18, 198.05. MS (ESI) m/z 242.0 [$(M^+\text{-}H)^+$, 100%], 264.0 [$(M^+\text{-}Na)^+$, 65%]. Anal. Calcd. For. $C_{14}H_{15}N_3O$: C, 69.69 %; H, 6.27 %; N, 17.41 %. Found: C, 69.88 %; H, 6.22 %; N, 17.25 %.

5,5-dimethyl-3-(5-methyl-1H-benzotriozol-1-yl)cyclohex-2-en-1-one (4b). Yield: 77%. IR (KBr): 1667 (C=O), 1626 (C=N) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) (/ppm): 1.15(s, 6H, $2CH_3$), 2.41 (s, 2H, NC-CH_2), 2.50 (s, 3H, Ar-CH_3), 3.23 (s, 2H, OC-CH_2), 6.55 (s, 1H, NC=CH), 7.53-7.99 (m, 3H, Ar). ^{13}C NMR (100.6 MHz, DMSO-d_6) (/ppm): 20.68, 27.65, 32.76, 40.06, 50.11, 112.37, 113.82, 119.05, 129.29, 131.38, 135.36, 146.78, 152.21, 198.08. MS (ESI) m/z 256.5 [$(M^+\text{-}H)^+$, 100 %], 278 [$(M^+\text{-}Na)^+$, 47%] Anal. Calcd. for. $C_{15}H_{17}N_3O$: C, 70.56 %; H, 6.71 %; N, 16.46 %. Found: C, 70.74 %; H, 6.55 %; N, 16.28 %.

3- (5-chloro-1H-Benzotriazol-1-yl-5,5-dimethylcyclohex-2-en-1-one (4c). Yield: 65%. IR (KBr): 1670 (C=O), 1630 (C=N) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) (/ppm): 1.16 (s, 6H, $2CH_3$), 2.43 (s, 2H, NC-CH_2), 3.22 (s, 2H, OC- CH_2), 6.58 (s, 1H, NC=CH), 7.71-8.40 (m, 3H, Ar). ^{13}C NMR (100.6 MHz, DMSO-d_6) (/ppm): 27.61, 32.81, 39.92, 50.10, 114.38, 115.01, 119.41, 129.74, 129.81, 129.87, 146.83, 151.82, 198.01. MS (ESI) m/z 276.0 [$(M^+\text{-}H)^+$, 100%]. 298.0 [$(M^+\text{-}Na)^+$, 43%]. Anal. Calcd. For. $C_{14}H_{14}ClN_3O$: C, 60.98 %; H, 5.12 %; N, 15.24 %. Found: C, 60.72 %; H, 4.93 %; N, 14.92 %.

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