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2D-NMR, X-ray crystallography and theoretical studies of the reaction mechanism for the synthesis of 1,5-benzodiazepines from dehydroacetic acid derivatives and *o*-phenylenediamines

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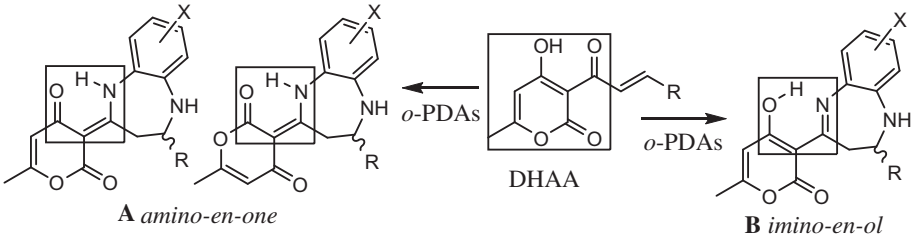
HIGHLIGHTS

- 1,5-Benzodiazepines from *o*-phenylenediamines and dehydroacetic acid is discussed.
- Difficulties of characterizing the prototropy of 1,5-benzodiazepines were discussed.
- The presence of the (*E*)-amino-en-one tautomer of 1,5-benzodiazepines **A** was confirmed.
- Theoretical calculations, NMR data and especially single-crystal X-ray diffraction were used.

GRAPHICAL ABSTRACT



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ABSTRACT

The synthesis of 1,5-benzodiazepines by the reaction of *o*-phenylenediamines (*o*-PDAs) with dehydroacetic acid DHAA [3-acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one] or conjugate analogues is largely reported in the literature, but still with uncontrolled stereochemistry. In this work, a comprehensive mechanistic study on the formation of some synthesized 1,5-benzodiazepine models following different organic routes is established based on liquid-state 2D NMR, single-crystal X-ray diffraction and theoretical calculations allowing the classification of two prototropic forms **A** (enaminopyran-2,4-dione) and **B** (imino-4-hydroxypyran-2-one). Evidences are presented to show that most of the reported 1,5-benzodiazepine structures arising from DHAA and derivatives preferentially adopt the (*E*)-enaminopyran-2,4-diones **A**.

1. Introduction

Benzodiazepines are a class of outstanding organic compounds mainly due to their application as psychoactive drugs, which are used in the treatment of anxiety, insomnia, psychomotor agitation, convulsions, spasms, or in the context of alcohol withdrawal syndrome. Benzodiazepines act on neurotransmitters in neurons of

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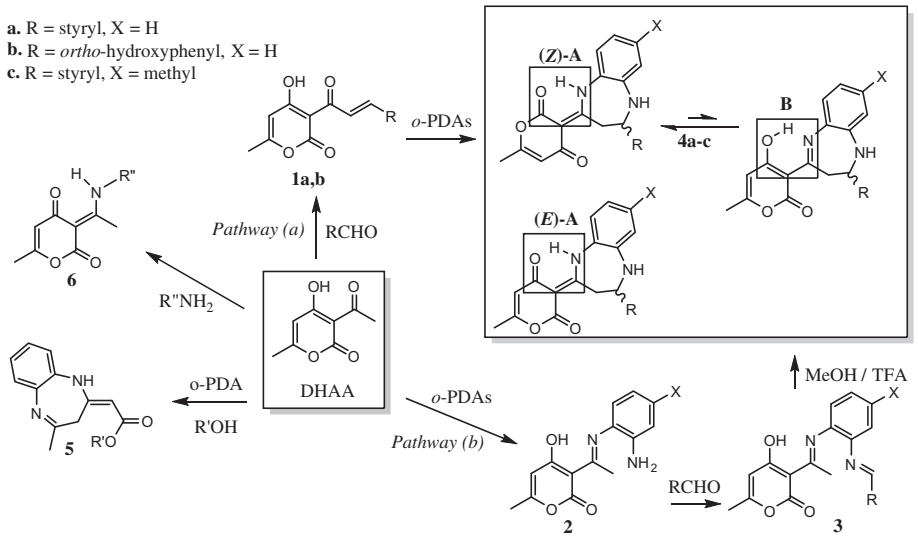
the central nervous system by increasing their inhibitory activity. They are also used to induce a state of sedation or for their hypnotic, anxiolytic, antiepileptic, muscle relaxant and amnesic activities. Because of such biological importance, the synthesis of benzodiazepine has received much attention in the field of medicinal chemistry [1]. In this context, our interest is especially focused on 1,5-benzodiazepines obtained from the reaction of *o*-phenylenediamines (*o*-PDAs) with 3-acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one (DHAA) or conjugate derivatives, such as 3-[(2*E*)-3-(4-aryl/styryl)prop-2-enoyl]-4-hydroxy-6-methyl-2*H*-pyran-2-ones **1a,b** which have been thoroughly studied. Among these benzodiazepines various forms can be sorted from the recent literature descriptions [2–11]. Accordingly, we distinguish the two tautomeric forms, including enaminopyran-2,4-dione **A** and imino-4-hydroxypyran-2-one **B**, which can be synthetically accessible through different reaction pathways (a and b) (Scheme 1) by coupling DHAA or conjugate analogues **1a,b** with *o*-PDAs, for instance, in the presence of catalytic amounts of acetic acid [2–5]. Form **B** was reported to result from the reaction of *o*-PDA with DHAA to form the imino intermediate **2** followed by the addition of aromatic aldehydes, giving rise **3** and finally to the diazepine cyclisation that was carried out under conventional heating conditions in the presence of catalytic amounts of trifluoroacetic acid (TFA) (Scheme 1, pathway b) [6]. Investigations such as those conducted by Prakash et al. [2] have also reported the synthesis of benzodiazepines **B**, underlining the same physicochemical characteristics as those described by Fodili et al. [6], and undoubtedly confirming that the 4-hydroxy-6-methyl-2-pyrone scaffold is conserved in the resulting benzodiazepine scaffolds, further supported by the work performed by Chergui et al. [7]. Other synthetic attempts have, however, shown that the reaction of DHAA with *o*-PDA in refluxing alcohols (R′OH) may cause a pyrone ring opening through the amino attack at position 6 of DHAA, and diazepine ring closure at position 4 affording esters of 2-{(*Z*)-4-methyl-1*H*-benzo[*b*][1,4]diazepin-2(3*H*)-ylidene}acetic acid **5**, which were classified as another interesting form of 1,5-benzodiazepines but received far less attention [8] (Scheme 1). Claramunt et al. [3] have recently reported the synthesis of benzodiazepines **A** by adopting exactly the same procedures that allowed the access to benzodiazepines **B** [2], these findings reveal the difficulties faced in differentiating between benzodiazepines of form **A** or **B** in solution using NMR. To date, Kaoua et al. [9] discussed the possibility to obtain 1,5-benzodiazepines **B** from the reaction of *o*-PDA with DHAA using heteropolyacids as catalysts.

The **A** and **B** forms of 1,5-benzodiazepines constitute a pair of functional tautomers due to the possible 1,5-prototropic shift between *amino-en-one* and *imino-en-ol*, respectively. To the best of our knowledge, no report to date has revealed their coexistence. It should also be mentioned that form **A** can display (*E*/*Z*)-amino-en-one isomerism with an intramolecular hydrogen (C═O···H—N—) bond. In form **B** the intramolecular hydrogen bond (—OH···N═C—) can impose the *s-cis* conformation depicted in Scheme 1. Despite the presence of an asymmetric carbon (C-4) on the diazepine ring, no enantioselective preparation of these benzodiazepines is yet reported.

In this work our focus is oriented to the **A** and **B** prototropic forms of 1,5-benzodiazepine reviewing their ^{1}H NMR data analysis reported in the literature. To this end, we have retaken their preparations under the reported experimental conditions [2,3,6] in order to establish a comparative study to allow the setup of adequate operating conditions. The target benzodiazepines **4a–c** were synthesized by the reaction of *o*-PDA or *p*-Me-*o*-PDA with DHAA derivatives **1a,b** (Scheme 1) to study and confirm their structures in solution based on 2D NMR analysis. While in the solid state, single-crystal X-ray diffraction studies allowed the confirmation of the structure **A** of the designed 1,5-benzodiazepine. We further update the mechanistic explanations for the formation of 1,5-benzodiazepine on the basis of theoretical chemistry calculations of their total energy and electronic density distribution of the starting materials. This includes studies applied on some proposed reaction intermediates involved in the **A**/**B** tautomerization and rearrangement steps.

2. Experimental

Melting points were determined on a Stuart scientific SPM3 apparatus fitted with a microscope and are uncorrected. NMR spectra were recorded on a Bruker Avance 300 spectrometer (operating at 300.13 for ^{1}H and 75.47 MHz for ^{13}C), in $CDCl_3$ as solvent. Chemical shifts (δ) are reported in ppm and coupling constants (J) in Hz. The signals are described as s (singlet), d (doublet), dd (doublet of doublet), ddd (double doublet of doublet) and m (multiple). The internal standard was TMS. Unequivocal ^{13}C assignments were made with the aid of 2D HSQC and HMBC (delays for one bond and long-range $J_{C/H}$ couplings were optimized for 145 and 7 Hz, respectively) experiments. NOESY spectra aided in the ^{1}H resonances assignments and in the spatial arrangements of the structures (mixing time 800 ms). Electron impact mass spectra were obtained



Scheme 1. Different organic pathways for the synthesis of 1,5-benzodiazepines from DHAA and *o*-phenylenediamines.