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Synthesis of novel *O*-alkylbenzochromeno-1,5-benzodiazepinones. Study of the N–H····N and C=O····HN hydrogen bonding interactions with 2-aminopyridines

Synthèse de nouvelles O*-alkylbenzochroméno-1,5-benzodiazépinones. Étude des liaisons hydrogène intermoléculaires avec les 2-aminopyridines*

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ABSTRACT

A series of novel 6-(*O*-alky)lbenzochromeno-1,5-benzodiazepin-2-ones **4a–c** was prepared through the condensation between the [1]benzopyrano[4,3-*c*][1,5]benzodiazepin-7(*8H*)one **1** and a series of alkylalcohols. Scaffold **4** exhibited interesting hydrogen-bonding interaction with 2-aminopyridine derivatives. The so obtained self-assembled systems **5** were fully characterized by 1D/2D-NMR techniques and mass spectrometry. The hydrogen-bonding interaction was supported by IR and Raman spectroscopy and by ^{1}H NMR titration experiments, and was confirmed by an X-ray crystal structure analysis.

RÉSUMÉ

De nouvelles 6-(*O*-alky)lbenzochroméno-1,5-benzodiazépin-2-ones **4a–c** ont été isolées via la condensation de la [1]benzopyrano[4,3-*c*][1,5]benzodiazépin-7(8*H*)one **1** avec une série d'alcools. Les hétérocycles **4** ont montré une capacité particulière à développer de fortes liaisons hydrogène intermoléculaires avec les 2-aminopyridines en donnant naissance à des édifices stables **5**. Les systèmes auto-assemblés **5** ont été caractérisés par spectrométrie de masse et par RMN 1D/2D. D'autre part, l'établissement des liaisons hydrogène a été appuyé par spectroscopie IR et Raman ainsi que par des expériences de titration en RMN ^{1}H, et confirmé par radiocristallographie aux rayons X.

1. Introduction

Compounds possessing the 1,5-benzodiazepine core are well recognized for their broad spectrum of pronounced biological and pharmacological activities [1,2]. Thus, interest in their chemistry continues unabated. Moreover, new insights have recently been found into the development of more efficient and versatile methods for the synthesis of these 1,5-benzodiazepinic scaffolds [3,4]. In a previous work, our research team has explored the condensation between the [1]benzopyrano[4,3-*c*][1,5]benzodiazpin-7(8*H*)one **1** and a series of *N,N*-binucleophiles to give the aforementioned heterocoumarins as a result of a multiple-step sequence involving successive ring-opening and recyclization processes [5,6].

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As a continuation of our ongoing efforts directed towards the synthesis of novel polyheterocycles containing the 1,5-benzodiazepine moiety, especially promising bioactive compounds [7–10], we were prompted to study the behavior of **1** towards 2-aminopyridine derivatives as 1,3-dinitrogenated nucleophile and we report herein our results, which are of particular interest.

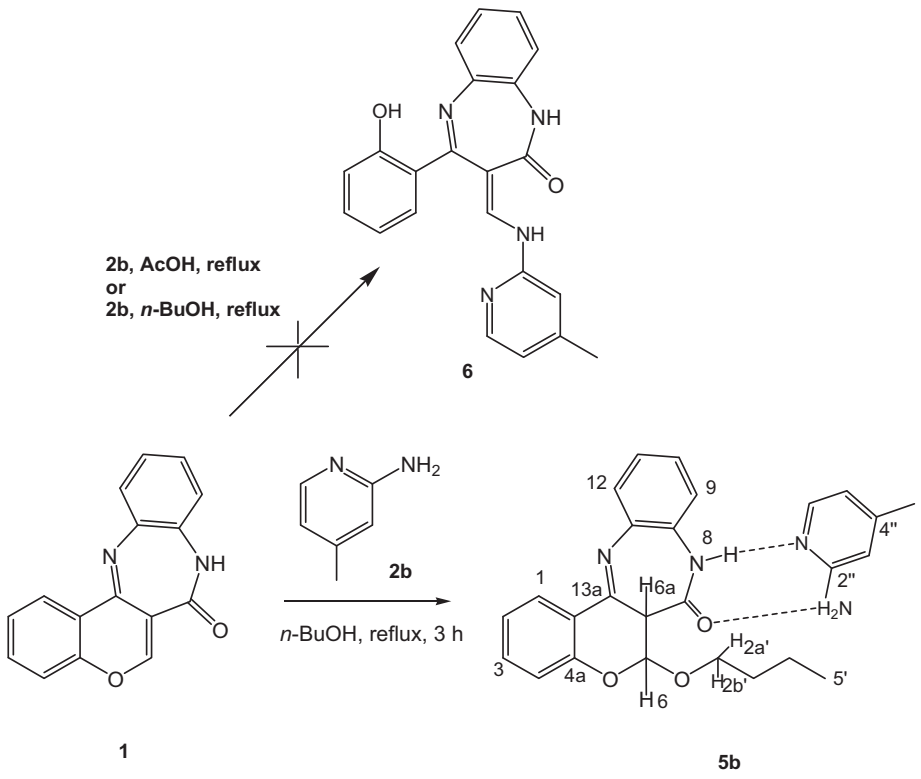
2. Results and discussion

Keeping in mind our previous report on the synthesis of new heterocoumarins [5,6], we firstly carried out the reaction between **1** and 2-aminopyridine under drastic acidic conditions, aiming thereby to achieve the 3(*N*-pyridinylamino)methylene-1,5-benzodiazepinone **6** via a nucleophilic attack of the amino group at the C-2 of the benzopyran ring. The key intermediate **6**, if obtained, would probably undergo a series of rearrangements to afford interesting benzodiazepine derivatives.

Nevertheless, under such vigorous conditions, all attempts led to the formation of complex crudes and directed us to opt for milder conditions using *n*-butanol instead of acetic acid. Thus, when a mixture of benzopyrano-benzodiazepine **1** and 2-aminopyridine **2a** or 2-amino-4-methylpyridine **2b** in *n*-butanol was heated under reflux for 3 h, the attempted 3(*N*-pyridinylamino)-methylene-1,5-benzodiazepinone **6** was not obtained. On the basis of their spectral data, the isolated products were identified as a self-assembled molecular system **5a,b** linked via an intermolecular hydrogen bonding between the 6-(*O*-butyl)benzochromeno-1,5-benzodiazepinone **4a** and the 2-aminopyridine **2** (Scheme 1).

According to this finding, we made a careful review of the literature that revealed a continual growing interest in benzodiazepinic systems for their specificity to recognize and bind through intermolecular hydrogen bonding and π–π stacking to a modulatory site on GABA receptors [11]. In addition, Pavlovsky et al. previously described the arrangement of 3-arylidene-1,2-dihydro-3*H*-1,4-benzodiazepin-2-one in dimers due to the N(1)-H···O(2) hydrogen bonds [12]. On another hand, the 2-aminopyridine also revealed a great tendency to develop intermolecular hydrogen bonding [13,14]. Such self-assembled systems continuously attract the researcher's interest due to their potential to be applied in the field of chemistry, biology and physics [15–17].

Here, one can return to the first spectroscopic evidence that emerged from the mass spectrum (ES + mode) of the self-assembled system **5b** (**4a** + **2b**) chosen as an illustration example which exhibited a molecular ion peak [MH^+] at m/z = 445.3. In fact, this value represents the sum of the molecular weights of diazepine **1**, 2-amino-4-methylpyridine **2b**, and *n*-butanol. On the other hand, the ^{1}H NMR spectrum of **5b** showed a large singlet (4.51 ppm, 1H), which was attributed to the free amino group of the pyridinic ring. This confirmed that the 2-amino-4-methylpyridine **2b** did not participate in the reaction. However, it is worth noting that all the protons of the 2-aminopyridine were easily located in the ^{1}H NMR spectrum. Moreover, the absence of the deshielded phenolic hydrogen singlet



Scheme 1. Synthesis of the self-assembled systems **5b** in one-pot.