Tetrahedron 68 (2012) 2374–2382

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis, X-ray characterization and computational Studies of *N*-imidazolyl and *N*-pyrazolyl pyrimidine derivatives

Marta Torres [a], Pablo Cañellas [a], Carolina Estarellas [a], Angel García-Raso [a,*], Juan J. Fiol [a], Francisca M. Albertí [a], Antonio Frontera [a,*], Elies Molins [b], Ignasi Mata [b], Pere M. Deyà [a]

[a] *Departament de Química, Universitat de les Illes Balears, Crta. Valldemossa km 7.5, E-07122 Palma de Mallorca, Baleares, Spain*
[b] *Institut de Ciència dels Materials (CSIC), Campus de la Universitat Autònoma, E-0183 Cerdanyola del Vallés, Barcelona, Spain*

ARTICLE INFO

Article history:
Received 22 November 2011
Received in revised form 3 January 2012
Accepted 11 January 2012
Available online 24 January 2012

Keywords:
Pyrimidines
Imidazole and benzimidazole
Ab initio calculations
X-ray crystal structures
Anion–π interactions

ABSTRACT

In this manuscript we report the synthesis and X-ray characterization of neutral 2-(1*H*-imidazol-1-yl)-pyrimidine (**1**), 2-(1*H*-pyrazol-1-yl)-pyrimidine (**2**) and 1-(2-pyrimidinyl)-1*H*-benzimidazole (**3**). We have also obtained crystals of the corresponding hydrochlorides of compounds **1** and **3**. Finally, the outer sphere complex of protonated 2-(1*H*-imidazol-1-yl)-pyrimidine with $[CoCl_4]^{2-}$ as counterion is described. In several charged structures interesting anion–π interactions determine the crystal packing. Moreover, in neutral systems some stacking interactions are governed by double lone pair–π interactions. High level ab initio calculations (RI-MP2/def2-TZVP) have been used to evaluate the noncovalent interactions observed in the solid state and the interplay between them.

1. Introduction

For many years there has been great interest in the chemistry of pyrazoles, imidazoles, pyrimidines and related *N*-containing heterocyclic derivatives.[1,2] Such systems play a significant role in many biological processes, due to their coordinating ability to metal ions.[3] The chemistry of transition metals associated with polydentate ligands with sp^2 hybridised nitrogen atoms has been developed and very interesting inorganic architectures have been generated using this approach.[4] In particular, ligands designed for this purpose consist of triazine or pyrimidine moieties attached to one or more pyrazol-1-yl substituents.[5] These architectures are usually governed by a variety of noncovalent interactions.[6] These forces include hydrogen-bonding,[7] π–π stacking,[8] cation–π[9] and C–H/π[8b,10] contacts, which are very common and well accepted among the supramolecular chemists. For around ten years, a new type of supramolecular interaction, namely anion–π interaction,[11] has been increasingly reported in the literature, notwithstanding the preliminary improbability of considering repulsive interactions among the aromatic clouds and electron rich molecules.[12] The design of highly selective anion receptors and channels represent important advances in this nascent field of supramolecular chemistry. Matile et al.[13] have also published remarkable synthetic ion channels based on anion–π interactions. In addition, its important role in enzymatic processes has been recently described.[14] The closely related lone pair (lp)–π interactions have been recently reviewed by Gamez et al.,[15] designating the lone pair–π contacts as a new supramolecular bond and rigorous analysis of the Cambridge Structure Database revealed that such contacts are not unusual in organic compounds, but have been overlooked in the past. Egli et al. have studied the importance of lone pair–π interactions in biomacromolecules (Z-DNA and RNA).[16] Indeed, lone pair–π interactions have been found to be of great importance for the stabilization of biological macromolecules, as well as for the binding of inhibitors in the binding pocket of biochemical receptors.[17]

We have recently reported that protonated adenines and pyrimidines are well suited for establishing strong anion–π interactions with a variety of anions, including BF_4^-, NO_3^-, Cl^-, $ZnCl_4^{2-}$, etc.[18] In this manuscript we report the synthesis of 2-(1*H*-imidazol-1-yl)-pyrimidine (imipyr, **1**), 2-(1*H*-pyrazol-1-yl)-pyrimidine (pyrapyr, **2**) and 1-(2-pyrimidinyl)-1*H*-benzimidazole (bimipyr, **3**). Their molecular structures in the solid state have been elucidated by X-ray diffraction analysis. Furthermore, we also report the synthesis and X-ray characterization of the corresponding hydrochlorides of **1** and **3** (compounds **4** and **5**, respectively). Moreover, a multicomponent assembly has been characterized by X-ray crystallography (compound **6**), which consist in a co-crystal of **2** and the nitrate salt of protonated pyrimidin-2-one (see Fig. 1).

---

* Corresponding authors. Fax: +34 971 173426; e-mail addresses: angel.garcia-raso@uib.es (A. García-Raso), toni.frontera@uib.es (A. Frontera).

doi:10.1016/j.tet.2012.01.023

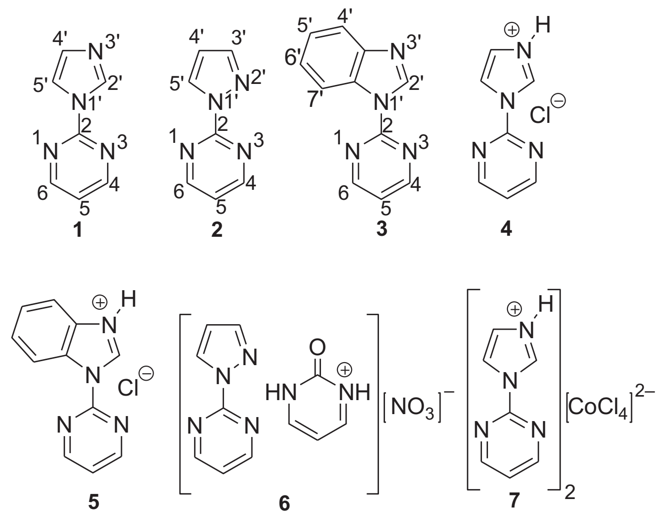


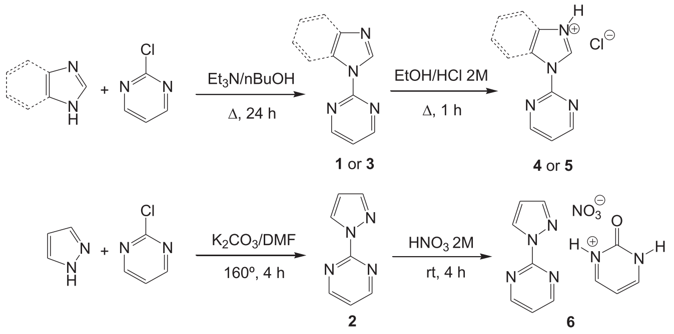
Fig. 1. Compounds **1**–**7** reported in this manuscript and the numbering scheme.

Finally, an outer sphere complex of protonated **1** with $CoCl_4^{2-}$ is also reported (compound **7**). Latter complex and the hydrochloride salt of **1** exhibit interesting anion–π interactions in the solid state, which are important in the crystal packing. The neutral complexes **1**–**3** present different stacking modes that have been analyzed. The different noncovalent interactions observed in the solid state have been studied using high level ab initio calculations. The anion–π binding properties of the protonated 2-(1*H*-imidazol-1-yl)-pyrimidine via hydrogen-bonding and anion–π interactions have been studied using the Molecular Interaction Potential with polarization (MIPp)[19] calculations. The MIPp is a convenient tool for predicting binding properties. It has been successfully used for rationalizing molecular interactions, such as hydrogen bonding and ion–π interactions and for predicting molecular reactivity.[20]

2. Results and discussion

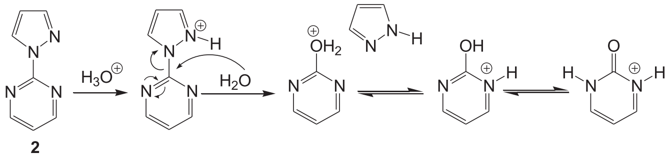
2.1. Synthesis of the compounds

We have synthesized compounds **1**–**6** using our own developed methodology by means of the general procedure shown in Scheme 1. Compounds **1**–**3** are easily prepared, in acceptable yields (40–60%), from 2-chloropyrimidine and the corresponding (benzo) diazole under refluxing conditions in the presence of a base (K_2CO_3 or Et_3N). Dissolution of compound **1** or **3** in EtOH/HCl 2 M yields the corresponding salts, **4** and **5**, respectively.



Scheme 1. Synthetic route to compounds **1**–**6**.

As can be seen in Scheme 1, although the corresponding hydrochloride derivatives of imidazole compounds have been easily obtained by treatment of EtOH/HCl 2 M, intents to prepare the similar pyrazole hydrochloride have been unsuccessful, yielding always different mixtures of compound **2** and products derived from the C–N bond cleavage. In addition, when the reaction time was 24 h/Δ the products detected by ^1H NMR spectroscopy were only pyrazole and protonated pyrimidinone. In a single experience at room temperature, 4 h, using HNO_3 2 M few crystals of the mixture **6** were obtained. A possible explanation of this particular reactivity of compound **2** is shown in Scheme 2, where a nucleophilic attack of a water molecule on C-2 by means of an addition–elimination mechanism yields the protonated pyrimidinone.



Scheme 2. Plausible mechanism of the unexpected formation of protonated pyrimidinone.

Finally, compound **7** was obtained by slow evaporation at 40 °C of a solution of **1** and $CoCl_2$, yielding blue crystals suitable for X-ray analysis.

2.2. Crystal structure description of neutral compounds

Although compounds **1**–**3** were previously synthesized,[21] their X-ray characterization is surprisingly missing in the literature. Actually, X-ray structures of derivatives of **1** and **3** either complexed to transition metals or alone are not found in the CSD. The ORTEP diagrams of compounds **1**–**3** are shown in Fig. 2. Compound **1** crystallizes in the triclinic crystal system and compounds **2** and **3** crystallize in the monoclinic crystal system. The crystallographic data collection and refinement parameters are listed in Table 1.

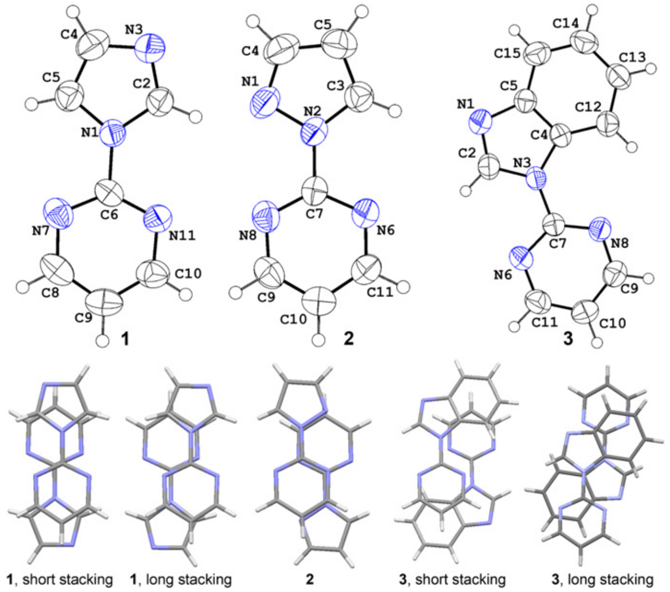


Fig. 2. Top: ORTEP diagrams of **1**–**3**. The thermal ellipsoids are drawn at the 50% probability level. Bottom: stacking modes observed in compounds **1**–**3**.

In solid state, compounds **1**–**3** basically present C–H···N hydrogen bonds and π–π stacking interactions. The geometric parameters of the hydrogen bonds observed in compounds **1**–**3** are summarized in Table 2. Stacking interactions are characterized by an antiparallel orientation of the molecules and a small