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One-step ring condensation of hydrazine derivatives and cyclic anhydrides

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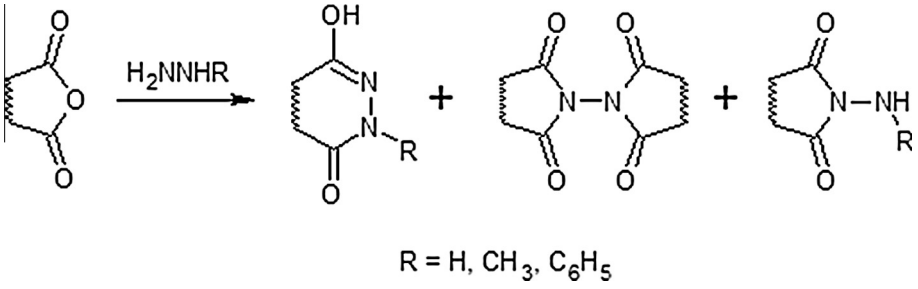
HIGHLIGHTS

- Ring-condensation.
- Pyridazinone.
- Over-accommodation effects.
- Molecular and crystal structure.

GRAPHICAL ABSTRACT



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ABSTRACT

Hydroxypyridazinone and pyrroledione rings condensation in the reactions of hydrazine hydrate with citraconic, 2,3-dimethylmaleic, succinic and cis-cyclohexanedicarboxylic anhydrides have been conducted in the HCl aqueous solution. The pyridazine-ring condensation yields products unexpected for these conditions. They have been identified by $^{1}H/^{13}C$ NMR and X-ray diffraction. The course of the reaction toward the five- and six-membered ring condensation strongly depends on methyl and other substituents in the anhydrides and in hydrazine. The obtained products indicate that the ring condensation is controlled by the molecular strains and steric hindrances between the substituents in anhydrides and pyridazinone products. The condensation of cyclic anhydrides with hydrazines has been reduced to one-step reaction and its yield significantly increased.

Introduction

Pyridazine derivatives exhibit numerous biological activities desired for pharmaceutical applications. The pyridazine ring is a fragment of many biologically active compounds of broad activity, for example analgesic, anti-inflammatory, anticonvulsant, antitumor, antiviral, antibacterial, antifungal [1–5]. Likewise, the growing interest in hydroxypyridazinone originates from its biological properties. This molecule can act either as purine or pyrimidine analog, forming base pairs with uracil and thymine, or with adenine. This feature of hydroxypyridazinone has been used as a growth inhibitor in agriculture [6].

Pyridazine can by synthesized in the reactions of hydrazine with cyclic anhydrides. These reactions were described in the literature several decades ago, however they afford only low yields of pyridazine products [7–13]. Therefore we have undertaken this systematic study aimed at understanding the mechanism of pyridazine ring condensation and at optimizing the conditions for this reaction. In particular, the effect of substituents has been investigated in the reactions of citraconic, 2,3-dimethylmaleic, succinic and cis-cyclohexanedicarboxylic anhydrides with hydrazine hydrate and its methyl and phenyl derivatives. Three products are obtained in the condensation facilitated to one-step reaction

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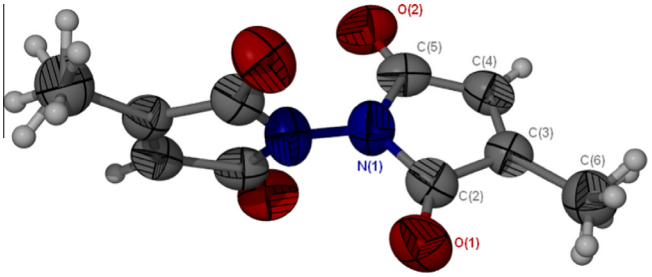


Fig. 1. The molecular structure of compound **2a**, as present in the crystal structure. The thermal ellipsoids are drawn at the 50% probability level. The methyl H-atoms were refined each in two disordered sites. Torsion angle C2-N1-N1′-C2′ is 89.7(2)° and C5-N1-N1'-C5′ 70.1(3)°.

illustrated in Scheme 1, their yield depending on the substituents in substrates.

Results and discussion

The reaction of citraconic anhydride (**1**) with hydrazine dihydrochloride in aqueous solution was first described in 1954 by Mizzoni and Spoerri [8a]. The obtained product was identified as 4-methyl-3,6-pyridazinediol. In 1966 Hedaya et al. confirmed that citraconic hydrazide is the only product of this reaction conducted in glacial acetic acid [9]. Instead of conducting the reaction of hydrazine dihydrochloride in glacial acetic acid we used hydrazine hydrate in 10% HCl. This reaction produced a mixture of 6-hydroxy-5-methylpyridazin-3-one (**2**), as the main product, and 3,3′-dimethyl-1,1′-bipyrrole-2,2′,5,5′-tetraone (**2a**), as a byproduct (Fig. 1). Compound **2** was obtained as precipitate, and compound **2a** was found in the filtrate. In the ^{1}H NMR spectrum of compound **2** two broad peaks originating from 'acidic' protons at nitrogen or oxygen appear at 10.82 ppm and 11.79 ppm. The ^{1}H NMR spectrum of compound **2a** contains the signal of two methyl groups at 2.18 ppm, and the signal of the hydrogen atoms at pyrrole carbon atoms at 6.55 ppm. The low magnitude of the coupling constant (J = 1.4 Hz) testifies to a long-range coupling between the C-methyl group and hydrogen atom at C-4(4′).

6-Hydroxy-2,5-dimethylpyridazin-3-one (**3**) was the only product of the reaction of **1** with methyl hydrazine in 10% HCl. In the ^{1}H NMR spectrum of **3** a broad signal of the acidic proton is present in the region of high values of the chemical shifts at 11.22 ppm.

By treating **1** with phenylhydrazine in 10% HCl, two products in the comparable yields were obtained: 6-hydroxy-5-methyl-2-phenylpyridazin-3-one (**4**) and 3-methyl-1-(phenylamino)-1*H*-pyrrole-2,5-dione (**4a**, Fig. 2) have been isolated by column chromatography. Compound **4a** was obtained as the major product when **1** reacted with phenylhydrazine in acetic acid [10,11]. In the ^{1}H NMR spectrum of compound **4** the broad signal of the acidic proton appears at about 11.47 ppm. The ^{1}H NMR signal of imino proton (NH) of compound **4a** appears at 8.70 ppm as a sharp peak (Scheme 2).

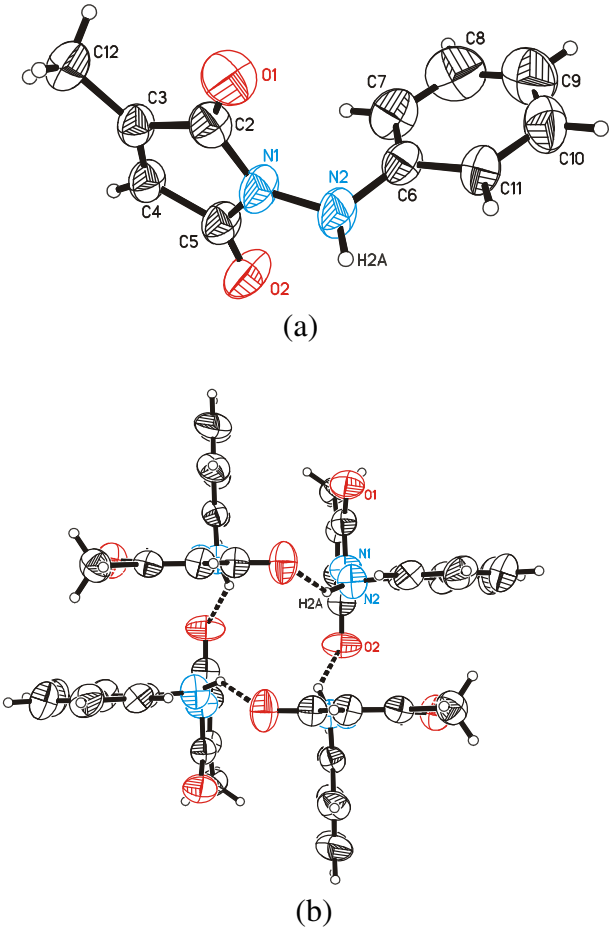
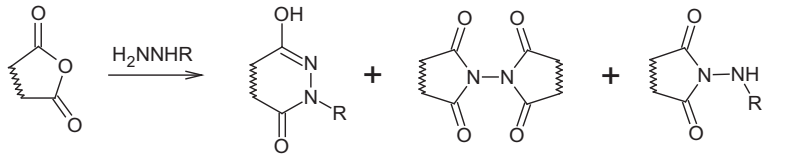


Fig. 2. Molecule **4a** (a); and the NH···O hydrogen-bonded cyclic tetramer (b), as present in the crystal structure. The thermal ellipsoids are drawn at the 50% probability level. The methyl H-atoms were refined each in two disordered sites.

In the reaction of 2,3-dimethylmaleic anhydride (**5**) with hydrazine hydrate in 10% HCl 6-hydroxy-4,5-dimethylpyridazin-3-one (**6**) and 3,3′,4,4′-tetramethyl-1,1′-bipyrrole-2,2′,5,5′-tetraone (**6a**, Fig. 3) precipitated. Compounds **6** and **6a** have been isolated by column chromatography. Derivative **6a** was found also in the filtrate. It was obtained as the only product when **5** reacted with hydrazine hydrate in acetic acid [9]. In the ^{1}H NMR spectrum of compound **6** the signal of two methyl groups was found at 3.36 ppm and the broad signals of hydrogen atoms appear at 10.83 ppm and 11.73 ppm. The ^{1}H NMR spectrum of compound **6a** consists of one signal at 2.05 ppm of four equivalent methyl groups (Scheme 2).

Only one product, 6-hydroxy-2,4,5-trimethylpyridazin-3-one (**7**, Fig. 4) was formed when **5** was treated with methylhydrazine. In the ^{1}H NMR spectrum a broad signal at about 10.98 ppm was



Scheme 1. Substrates and main products of the cyclization reaction between hydrazine and cyclic anhydride derivatives.