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# Theoretical study on structural and mechanistic aspects of synthesis of a 3-aminopyrazole derivative

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## ABSTRACT

The structure of 5-hydroxy-3,5-dimethyl-1-*S*-methylisothiocarbamoyl-2-pyrazolinium iodide (HDMCPI), a cyclic intermediate for a 3-aminopyrazole derivative, was determined by means of X-ray analysis and spectroscopic techniques. In a treatment of HDMCPI in alkaline aqueous solution, 4-acetyl-3(5)-amino-5(3)-methylpyrazole (AAMP) was unexpectedly yielded. The reaction of HDMCPI was monitored by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy. It was shown that keto-imine tautomer appears as the only tautomeric form. Density functional theory explained the spontaneous formation of keto-imine tautomer, whose existence is the main condition for generating a carbanion in alkaline medium. The carbanion further undergoes cyclization and elimination of MeSH, thus yielding AAMP. In the reaction of acetylacetone with thiosemicarbazide instead of *S*-methylisothiosemicarbazide, there were no traces of AAMP. This result can be attributed to the absence of keto-imine form in the tautomeric equilibrium, which would provide the formation of a carbanion for a nucleophilic attack and further cyclization.

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## 1. Introduction

The chemistry of 3-aminopyrazole has remained largely underdeveloped until the discovery of its derivatives as antitumor agents with their great therapeutic potential against various proliferative disorders in the role of chemical inhibitors of cyclin-dependent kinases (CDKs), a family of enzymes involved in controlling normal cell proliferation.<sup>1–4</sup> The frequent deregulation of cell cycle progression in cancer has intensified search for kinase inhibitors with high affinity and specificity over the past several years.<sup>5–7</sup> PHA-739358, a small molecule of 3-aminopyrazole derivative with strong activity against Aurora kinases and cross-reactivities with some receptor tyrosine kinases, exhibits significant antitumor activity in a wide range of cancers and shows a favorable pharmacokinetic and safety profile.<sup>8</sup> Recently, a series of 3-aminopyrazole based Aurora kinase inhibitors with a pyrimidine scaffold led to a class of very potent inhibitors of cellular proliferation in treatment of chronic myelogenous leukemia or Philadelphia chromosome-positive acute lymphoblastic leukemia.<sup>9</sup> Very recently, a selective 3-aminopyrazole MK2 kinase inhibitors were discovered and profiled to show potent inhibition MK2 activity and reasonable cellular activity.<sup>10</sup>

Although the synthesis of 4-acetyl-3(5)-amino-5(3)-methylpyrazole (AAMP) has been reported about two decades ago,<sup>11</sup> the recent discoveries in the field of 3-aminopyrazole derivatives and their pharmacological and medicinal importance prompted us to shed much more light on the mechanism of formation of AAMP, starting from relatively simple precursors. In the present study we have focused our attention on theoretical and mechanistical aspects of the synthesis of this 3-aminopyrazole derivative, as a high versatile precursor for preparation of a number of potential kinase inhibitors bearing in mind the great possibilities of transformation of acetyl group linked to 3-aminopyrazole scaffold.

## 2. Results and discussion

### 2.1. The crystal structure of 5-hydroxy-3,5-dimethyl-1-*S*-methylisothiocarbamoyl-2-pyrazolinium iodide (HDMCPI)

The crystal data, details of structure determination and refinement of HDMCPI are given in the [Supplementary data](#). The iodide anion is hydrogen bonded to the organic moiety by the O5–H5...I1 and N7–H7A...I1 interactions (Fig. 1a, Table 1). The packing coefficient is 65.7%, there is no residual solvent accessible void. The basic building unit of the crystal is a dimer organized by the symmetry centre (Fig. 1b, Table 1). H7B is a bifurcated hydrogen

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