

Mechanistic investigation and DFT calculation of the new reaction between S-methylisothiosemicarbazide and methyl acetoacetate

**Violeta Marković, Svetlana Marković,
Ana Janićijević, Marko V. Rodić,
Vukadin M. Leovac, Nina Todorović,
Snežana Trifunović, et al.**

Structural Chemistry

Computational and Experimental
Studies of Chemical and Biological
Systems

ISSN 1040-0400

Volume 24

Number 6

Struct Chem (2013) 24:2127–2136

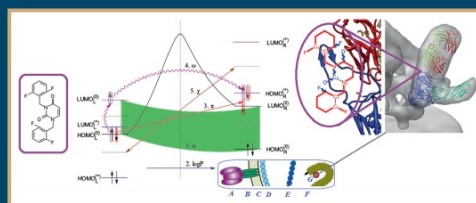
DOI 10.1007/s11224-013-0223-3

VOLUME 24, NUMBER 6

December 2013
24(6) 1785–2222 (2013)
ISSN 1040-0400

STRUCTURAL CHEMISTRY

Computational and Experimental Studies of Chemical and Biological Systems



Special Collection of Contributions Honoring Maria Victoria Roux
Guest Editors: Joel F. Liebman · James S. Chickos · Rafael Notario

 Springer

 Springer

Your article is protected by copyright and all rights are held exclusively by Springer Science +Business Media New York. This e-offprint is for personal use only and shall not be self-archived in electronic repositories. If you wish to self-archive your article, please use the accepted manuscript version for posting on your own website. You may further deposit the accepted manuscript version in any repository, provided it is only made publicly available 12 months after official publication or later and provided acknowledgement is given to the original source of publication and a link is inserted to the published article on Springer's website. The link must be accompanied by the following text: "The final publication is available at link.springer.com".

Mechanistic investigation and DFT calculation of the new reaction between *S*-methylisothiosemicarbazide and methyl acetoacetate

Violeta Marković · Svetlana Marković · Ana Jančićević · Marko V. Rodić · Vukadin M. Leovac · Nina Todorović · Snežana Trifunović · Milan D. Joksović

Received: 6 December 2012 / Accepted: 28 January 2013 / Published online: 8 February 2013
© Springer Science+Business Media New York 2013

Abstract A study on the synthesis and mechanistical aspects of formation of 3-methyl-5-oxo-3-pyrazolin-1-carboxamide (MOPC) starting from *S*-methylisothiosemicarbazide hydrogen iodide and methyl acetoacetate was performed. In the alkaline aqueous solution, the intermediate methyl acetoacetate *S*-methylisothiosemicarbazone undergoes substitution of CH_3S^- anion by hydroxide anion, cyclization, carbanion formation, and elimination of methanol, thus yielding corresponding Na-enolate salt of pyrazol-5-one derivative. The structure of the compound obtained after protonation of the formed enolate salt was determined by means of spectroscopic techniques and single-crystal X-ray diffraction analysis. The mechanism of conversion of methyl acetoacetate *S*-methylisothiosemicarbazone into MOPC was investigated by means of the

B3LYP functional, and it was found that the reaction is thermodynamically controlled.

Keywords Pyrazolone · Reaction mechanism · DFT · Thermodynamic and kinetic control

Introduction

Pyrazolones represent an important class of heterocyclic compounds with a wide range of applications in both chemistry and biology due to their favorable pharmacological properties. These characteristics caused an increasing interest of medicinal chemists for this research area in the last decades. For example, antipyrine (2,3-dimethyl-1-phenylpyrazol-5-one) and its analogs aminopyrine, dipyrone and propyphenazone are known for a long time as antipyretic, analgesic, and anti-inflammatory substances [1, 2]. A new pyrazol-5-one compound, edaravone (3-methyl-1-phenyl-2-pyrazoline-5-one, Radicut[®], Mitsubishi Tanabe Pharma Corporation) has been presented as a strong free radical scavenger and a promising drug for the treatment of brain ischemia [3]. A number of other pyrazolone compounds have been synthesized and found to exhibit diverse biologic and pharmacological properties [4–7].

The synthesis of carboxamide derivatives of pyrazolones starting from β -keto esters and semicarbazide hydrochloride is the known way of preparation of this class of compounds [8]. The study by microwave irradiation was carried out to investigate the possibility of performing this reaction without use of any solvent and in much shorter reaction time [9].

The reaction mechanism of the known synthesis of 3-methyl-5-oxo-3-pyrazolin-1-carboxamide (MOPC, **1**) occurs by initial regioselective attack of the least hindered and more nucleophilic nitrogen atom of the semicarbazide hydrazine

Electronic supplementary material The online version of this article (doi:10.1007/s11224-013-0223-3) contains supplementary material, which is available to authorized users.

V. Marković · S. Marković · A. Jančićević · M. D. Joksović (✉)

Department of Chemistry, Faculty of Science, University of Kragujevac, R. Domanovica 12, 34000 Kragujevac, Serbia
e-mail: mjoksovic@kg.ac.rs

M. V. Rodić · V. M. Leovac
Department of Chemistry Biochemistry and Environmental Protection, Faculty of Science, University of Novi Sad, Trg D. Obradovića 3, 21000 Novi Sad, Serbia

N. Todorović
Institute for Chemistry, Technology and Metallurgy, Njegoševa 12, 11000 Belgrade, Serbia

S. Trifunović
Faculty of Chemistry, University of Belgrade, Studentski trg 16, P.O. Box 158, 11000 Belgrade, Serbia

