Journal of Molecular Structure 1056–1057 (2014) 70–78

Contents lists available at ScienceDirect

Journal of Molecular Structure

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

Synthesis, spectral, crystal and theoretical studies of some novel 4-heterocyclic substituted pyrazolones

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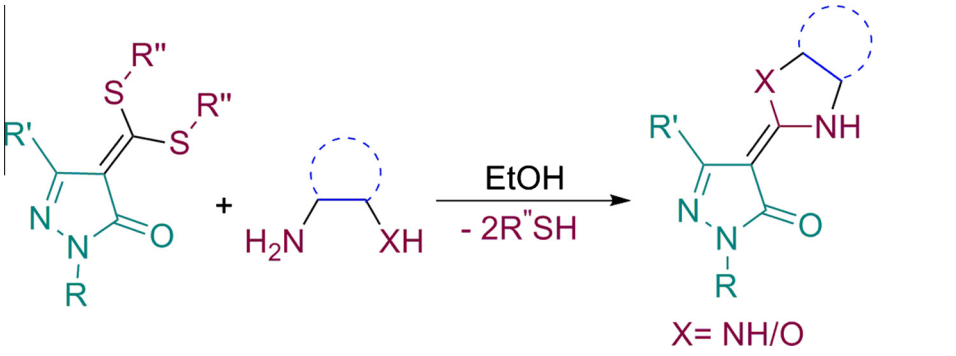
HIGHLIGHTS

- Pyrazolone ketene dithioacetals were synthesised by mild/PTC/strong bases.
- Regioselective products were obtained from dithioacetals reacting with 1,2-binuclephiles.
- Biologically potent imidazole/oxazole fused pyrazolones were synthesized.
- Compounds **3a-i** were characterized by IR, NMR and X-ray diffraction techniques.
- Theoretical data of **3e** by B3LYP/6-31G** method gives best fit with X-ray data.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 21 July 2013
Received in revised form 8 October 2013
Accepted 8 October 2013
Available online 15 October 2013

Keywords:
Pyrazolone
Oxoketene dithioacetals
Conjugate addition–elimination
1,3-Azoles
1,3-Oxazoles
Density Functional Theory

ABSTRACT

Reactions of pyrazolone ketene dithioacetals with various binucleophiles afforded 4-heterocyclic substituted pyrazolone compounds as ketene *N,N*-, *N,O*-acetals in the absence of any acid/base catalyst in good yields. The products **3a–i** formed by the direct displacement of dithioacetals exhibited high regioselectivity towards binucleophiles. All the synthesized compounds were characterized by IR, ^{1}H, ^{13}C, 2D NMR and X-ray diffraction techniques. Optimized geometry of compound **3e** has been computed by Density Functional Theory (DFT) method in B3LYP 6-31G** level basis set. The title compounds **3d–f** were crystallized in monoclinic space group Pc, $P2_1/n$, $P2_1/c$ with cell parameters: $a = 7.6647(3)$, $b = 26.7020(8)$, $c = 12.8364(5)$ Å, $\beta = 102.842(4)°$, $V = 2561.42(16)$ Å^3, $Z = 9$ (for **3d**), $a = 13.448(5)$, $b = 7.539(5)$, $c = 14.832(5)$ Å, $\beta = 94.747(5)°$, $V = 1498.6(12)$ Å^3, $Z = 4$ (for **3e**) and $a = 13.6468(17)$, $b = 15.905(2)$, $c = 7.9029(9)$ Å, $\beta = 100.774(9)°$, $V = 1685.1(4)$ Å^3, $Z = 4$ (for **3f**) respectively. The spectral and crystal studies revealed that the compounds **3a–i** exist in amine-one tautomeric form in solid state and the optimized structure **T5** of the compound **3e** exhibit good agreement with X-ray diffraction data.

1. Introduction

Pyrazolone is a five membered lactum ring compound containing two nitrogens which is an active ingredient of many drugs, especially in the class of nonsteroidal anti-inflammatory agents used in the treatment of arthritis and other musculoskeletal and joint disorders. The term of pyrazolone is sometimes used to refer anti-inflammatory agents [1,2]. The structures of a few drugs with pyrazolone as one of the component [3] are shown in (Fig. 1). NH-substituted 3-pyrazolin-5-ones are important targets as a consequence of their prevalence in numerous pharmaceuticals, agrochemicals, dyes and pigments as well as chelating and extracting agents [4,5]. Moreover pyrazolones with a heterocycle

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http://dx.doi.org/10.1016/j.molstruc.2013.10.018

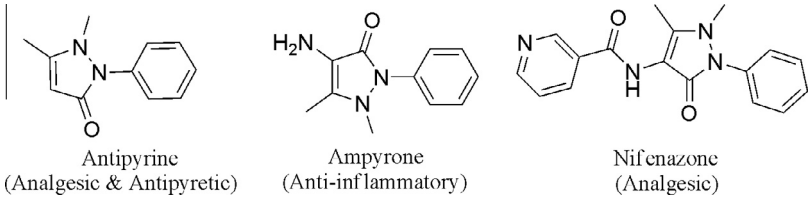

Fig. 1. Structures of a few drugs with pyrazolone moiety.

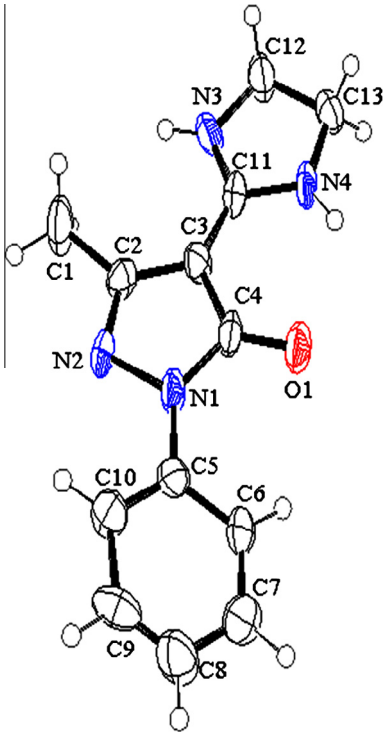

Fig. 2. Crystal structure of the compound **3d**.

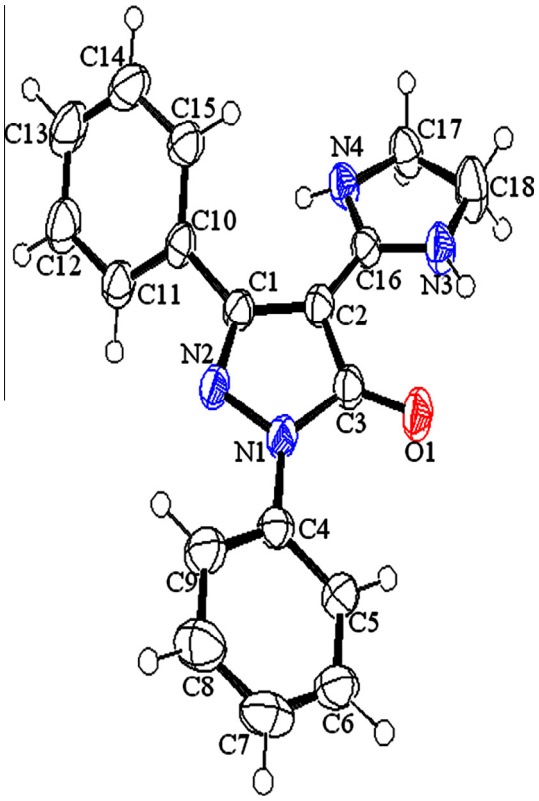

Fig. 3. Crystal structure of the compound **3e**.

substituent either at C-4 or C-3 are behave as kinase inhibitors [6,7]. Particularly, they are found to inhibit a class of enzymes that function in the catalysis of phosphoryl transfer reactions. Therefore, heterocycle substituted pyrazolones can be effective against targets in central nervous system disorders (Alzheimer disease), inflammatory disorders (psoriasis), bone diseases (osteoporosis), cardiac diseases (atherosclerosis, restenosis and thrombosis), metabolic disorders (diabetes) and infectious diseases such as viral and fungal infections. A few heterocycle substituted pyrazolones that are inhibitors of protein kinases such as vascular endothelial growth factor receptor (VEGFR) kinase, trkA tyrosine kinase (trkA), mixed lineage kinase (MLK) or fibroplast growth factor receptor kinase.

Pyrazolones are readily synthesized by condensation between β-ketoester and hydrazine hydrate. The physical and chemical properties of pyrazolones are modulated by their tautomeric property. In the case of 3-phenyl-5-pyrazolones, the nucleophilic character and the basicity of the nitrogen atoms change from tautomer to tautomer [8]. The hydrogen on C-4 can be readily deprotonated, generating a carbon nucleophile. Ketene dithioacetals have become an important synthon in organic chemistry and it can be readily prepared by reaction between a carbon nucleophile and carbon disulphide. The sulphur atom exercises the stabilizing effect on neighboring positive as well as negative species. This makes the double bond in ketene dithioacetals responsive towards both nucleophilic as well as electrophilic attack; an extremely useful feature for organic synthetic purposes. The synthesis of ketene dithioacetals and their applications in manipulation of the functionality or in the synthesis of heterocyclic system has been extensively investigated and reviewed [9–17].

In our present investigation various new heterocycle substituted pyrazolones have been synthesized with the reported [18–21] synthons and with 1,2-binucleophiles. Especially, dithioacetals in 3-methyl-1H-phenylpyrazolone derivative, we improved the synthesis of ketene dithioacetals in the absence of strong bases. Moreover the reported reactions were carried out only with 3-methyl-1H-phenylpyrazol-5-one. However the reaction of 4-(bis(methylthio)methylene)-3-methyl-1H-pyrazol-5-one/4-(bis(methylthio)methylene)-1,3-diphenyl-1H-pyrazol-5(4H)-one with aliphatic 1,2-binucleophile are not reported. Similar reactions with 3-methyl-1H and 3-phenyl-1H-phenylpyrazolone isomers are not also known. Hence in the present work it was proposed to synthesize heterocyclic substituted pyrazolones using ketene dithioacetals and to investigate their preferred tautomeric existence by the crystal structure.