Journal of Molecular Structure 1160 (2018) 333–341

Contents lists available at ScienceDirect

Journal of Molecular Structure

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

Experimental and theoretical investigations on acid catalysed stereoselective synthesis of new indazolyl-thiazole derivatives

Poonam Gautam, Deepika Gautam, R.P. Chaudhary*

Department of Chemistry, Sant Longowal Institute of Engineering & Technology, Longowal, Sangrur, Punjab, 148106, India

ARTICLE INFO

Article history:
Received 13 August 2017
Received in revised form
18 December 2017
Accepted 1 February 2018
Available online 3 February 2018

Keywords:
1-Arylidene-2-tetralone
Indazol-2-carbothioamide
Indazolyl-thiazol-4(5*H*)- one
X-ray diffraction
DFT
Antimicrobial activities

ABSTRACT

1-Arylidene-2-tetralone (2), obtained from condensation of 2-tetralone and aromatic aldehydes in acetic acid and HCl, on condensation with thiosemicarbazide in acidic and alkaline medium afforded tetrahydro-2*H*-benzo[*e*]indazole-2-carbothioamide as *trans* (3) and *cis* (4) diastereoisomers of 1-*H* and 9b-*H* respectively. The synthesis of new indazolyl-thiazol-4(5*H*)-ones (5) from *trans* isomer (3) and α-halo acids is reported. A DFT study along with single crystal X-ray diffraction data of a representative compound (5a) is presented. The chemistry of the reaction of indazole-2-carbothioamides with methyl iodide, DMAD and acetic anhydride is described. Eight newly synthesised compounds were screened for their antibacterial and antifungal activities. Some of the compounds have shown promising antimicrobial activities.

1. Introduction

Indazoles, benzoannulated analogues of pyrazole, have attracted great attention in the past decades due to their wide range of pharmaceutical applications [1]. Fused tricyclic systems containing pyrazole moiety have shown enhanced inhibitory activity against a variety of protein kinases [2–4] and been found useful in the treatment of several cell proliferative disorders such as cancer, inflammatory and autoimmune diseases. The benzo[g]indazole moiety has been found to be an integral part of many bio molecules and has generated enormous interest in the new drug discovery. For example as shown in Fig. 1, A, it has been reported to constitute effective ligand moiety for cannabinoid receptors [5], B for human dopamine D4 receptor with improved selectivity over ion channels [6], and C has been reported to be potent inhibitors of IKK-2 [7] with improved inhibition of IL-8 production in stimulated synovial fibroblasts. Many indazole derivatives have long been well known for their biological activities such as anti-depressant [8], anti-inflammatory [9], analgesic, antipyretic [10], dopamine antagonistic [11], anti-tumour [12], antiemetic [13], and anti-HIV activities [14]. Similarly thiazolidin-4-one framework is associated with a variety of pharmacological activities such as antimicrobial [15–18], anti-inflammatory [19], cytotoxic [20], antiviral [21], antitubercular [22], and anticancer [23] activities. The well established approach of combination of pharmcaphores on the same scaffold to obtain synergically more potent compounds motivated us to incorporate indazole moiety and thiazolidin-4-one ring in the same molecule. In continuation to our work on synthesis of new thiazolidin-4-one derivatives [24–27] herein we report the stereoselective synthesis of some new indazolyl-thiazolidin-4-ones.

2. Result and discussion

The condensation of 2-tetralone **1** with aromatic aldehydes in presence of acetic acid and conc. HCl at 0–5 °C afforded 1-arylidene-2-tetralone **2** as reported in our earlier communication in case of 1-benzylidene-2-tetralone [28]. The synthesis of 1-arylidene-2-tetralone **2** is also reported in the literature [29,30] from 2-tetralone and aldehydes in presence of ethanol, acetic acid, piperidine and molecular sieves under stirring conditions at room temperature. The structure of arylidene derivatives has been confirmed by means of spectral data. ^{1}H NMR spectra of **2b** and **2c** displayed benzylic proton (=CH) between δ 7.49–7.60 ppm, which is consistent with the assigned structure. Arylidene derivatives **2** on cyclocondensation with thiosemicarbazide in ethanol and HCl can lead to the formation of 1-*H*, 9b-*H trans* **3** and/or 1-*H*, 9b-*H cis* **4**

* Corresponding author.
E-mail address: rpchaudhary65@gmail.com (R.P. Chaudhary).

https://doi.org/10.1016/j.molstruc.2018.02.003
0022-2860/

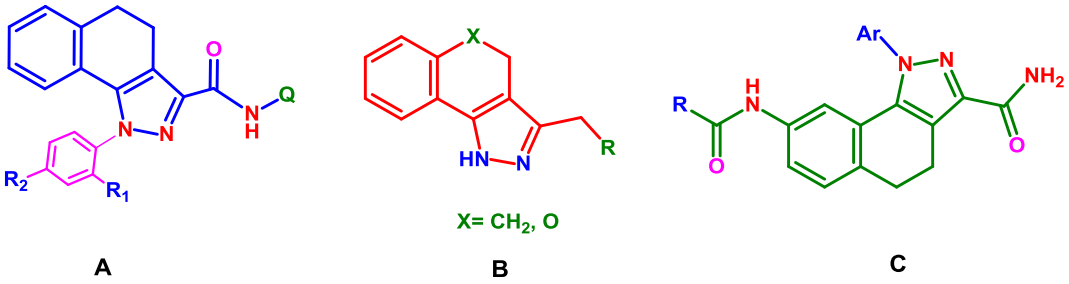
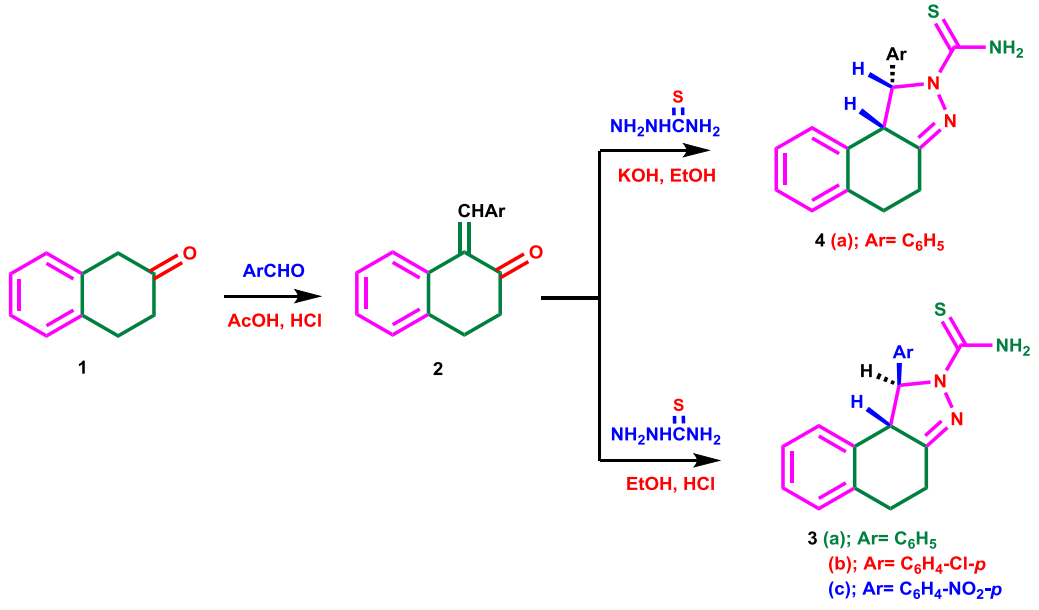


Fig. 1. Indazole frame work as inhibitors.

diastereoisomeric pyrazoline derivatives (Scheme 1). The selectivity that leads to formation of **3** or **4** results from the 1, 2-addition of thiosemicarbazide to carbonyl group and subsequent N–H intramolecular cycloaddition to double bond of thiosemicarbazone intermediate by an accepted mechanism. Under the reaction conditions (ethanol/HCl) only single product (TLC) is obtained. The single product has been assigned structure **3** or **4** on the basis of ^{1}H NMR and mass data. Appearance of two doublets for 1-*H* and 9b-*H* protons in NMR spectrum suggests the formation of **3** or **4**. The mass spectrum of the product exhibits peak at 308.2 [M+H^{+}, 100%] which support structure **3** or **4**. The stereochemical assignment of 1-*H* and 9b-*H* remain to be solved. It may be 1-*H*, 9b-*H cis* or 1-*H*, 9b-*H trans* diastereoisomer. This problem could be solved by comparing the NMR spectra of both the diastereoisomers. The reaction of 1-benzylidene-2-tetralone **2a** with thiosemicarbazide was then carried out in presence of alc. KOH. As a result of happening of many side reactions in alkaline medium, gummy reaction product is obtained. Recrystallization from ethanol and then purification by column chromatography result in low yield of the product **4a**. Comparison of ^{1}H and ^{13}C NMR spectra of **3a** and **4a** solved the stereochemical assignments of C-1 and C-9b. The protons 1-*H* and 9b-*H* appeared as doublets at δ 5.86 ppm and δ 4.32 ppm respectively in ^{1}H NMR spectrum of **3a** with spin-spin coupling constant values $^{3}J_{\text{H-1,9b}} = 5.92$ Hz and 5.84 Hz respectively. The protons 9b-*H* and *H*-1 appeared as doublets at δ 5.5 ppm and δ 5.9 ppm in **4a** with spin-spin coupling constant values $^{3}J_{\text{H-1,9b}} = 4.82$ Hz and 4.96 Hz respectively. The difference is too small for a firm differentiation between *cis* and *trans* configurations. ^{13}C NMR field effect arising in the *cis* isomer firmly identifies the C-1,9b configurations. C-9b chemical shifts for the *trans* and *cis* isomers **3a** and **4a** are 59.0 ppm and 56.0 ppm respectively. The significant upfield shift for C-9b in **4a** suggested its *cis* configuration. Also, the downfield signal of 9b-*H* (δ 5.5 ppm) in **4a** as compared with 9b-*H* (δ 4.32 ppm) in **3a** indicates it is *anti* to pendant aryl group. The comparison of chemical shifts of significant protons and carbons along with coupling constants is reported in (Table 1). The X-ray crystal structure of compound **5a**, obtained from condensation of **3a** with chloroacetic acid, reported in this study, further confirmed the stereochemistry and *trans* orientation of 1-*H* and 9b-*H* protons.

1,4,5,9b-tetrahydro-2*H*-benzo[*e*]indazole-2-carbothioamides **3a-b** on cyclocondensation with α-halo acids in anhydrous sodium acetate furnish thiazolidin-4-one derivatives **5a-d** (Scheme 2). The structure of compound **5** is established by means of spectral data. The appearance of a strong peak at 1698 cm^{-1} due to carbonyl group (C=O) in IR spectrum and double doublet of SCH_2 protons of thiazolidinone ring at δ 3.78 ppm ($J = 1.7$ and 17.1 Hz) in ^{1}H NMR spectrum of **5a** proved the formation of five member thiazolidin-4-one ring. The exhibition of molecular ion peak at *m*/*z* 348.2 [M+H^{+}, 100%] in mass of **5a** confirm its structure. The structure of compound **5a** was confirmed from single crystal X-ray diffraction studies. The crystal for X-ray was obtained from hexane-ethyl acetate (2:1) mixture by slow evaporation method. ORTEP diagram of



Scheme 1. Synthetic route to synthesis of (*1S,9bR*)- (*1R,9bR*) diastereoisomers of tetrahydro-2*H*-benzo[*e*]indazole-2-carbothioamide.