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Synthesis, structure and antimicrobial evaluation of new 3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazol-2-yl-thiazol-4(5*H*)-ones

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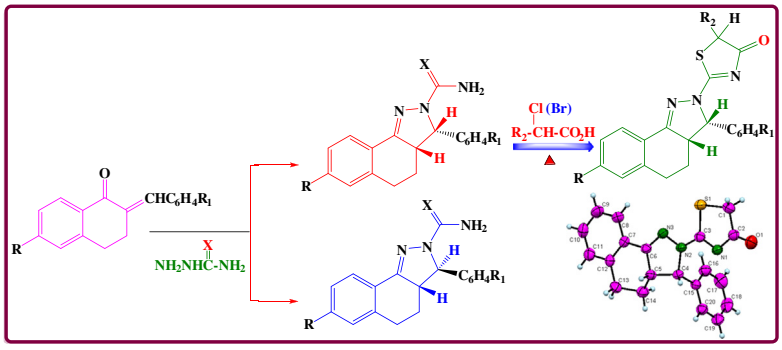
HIGHLIGHTS

- Synthesis of eight new indazolyl-thiazol-4(5*H*)-ones have been accomplished.
- Stereo chemical assignments were made on the basis of spectroscopic experiments.
- X-ray diffraction of one indazolyl-thiazol-4(5*H*)-one derivative has been reported.
- Results of DFT studies on diastereoisomers are correlated with experimental values.
- Newly synthesised compounds exhibit promising antimicrobial activities.

GRAPHICAL ABSTRACT



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ABSTRACT

The reaction of semicarbazide or thiosemicarbazide with 2-arylidene-1-tetralones under alkaline condition affords 3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole-2-carbo(thio)amides as a mixture of *cis* and *trans* diastereoisomers of 3-H and 3a-H. The synthesis of new indazolyl-thiazol-4(5*H*)-ones from the condensation of *cis* isomer and α-halo acids is reported. A DFT study along with X-ray single crystal data of a representative compound is presented. All the eight newly synthesised indazolyl-thiazol-4(5*H*)-ones were screened for their antibacterial and antifungal activities and some compounds have shown promising activities.

Introduction

Pyrazoles, in general, and their benzocondensed analogues, tetrahydroindazoles, in particular have been proved to be an effective pharmacophore in medicinal chemistry and constitutes the key sub unit in many biologically active compounds with a broad range of pharmacological activities including anti-inflammatory [1], anti-depressant [2], anticancer [3], antituberculosis [4], and antimicrobial activities [5]. Tetrahydroindazole derivatives have been shown to possess antiproliferative activity against leukaemia cells [6] and lonidamine, an indazole-3-carboxylic acid derivative is a new nonconventional anticancer drug that inhibits the energy metabolism of neoplastic cells and increases the cell membrane permeability [7]. Owing to the immense importance and varied bioactivities exhibited by tetrahydroindazole derivatives, efforts have been made to fuse or couple tetrahydroindazole nucleus with other bioactive scaffolds, possibly for synergic increase in their activity profile [8].

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Also it is well documented that thiazol-4(5*H*)-one nucleus display a variety of pronounced pharmacological activities such as anticonvulsant [9], antimicrobial [10], anti-inflammatory [11], anti cancer [12], anti-HIV [13], and antitumor [14]. Considering the importance of tetrahydroindazole and thiazol-4(5*H*)-one nucleus it was thought worthwhile to design and synthesise some new thiazol-4(5*H*)-one derivatives bearing tetrahydroindazole moiety and screen them for potential biological activities. In continuation to our work on synthesis [15–17] and antimicrobial studies [18,19] of new thiazol-4(5*H*)-ones, we report here the synthesis, X-ray diffraction, DFT and antimicrobial studies of new thiazol-4(5*H*)-ones bearing tetrahydroindazole moiety.

Results and discussion

Chemistry

2-Arylidene-1-tetralones **2a–d** were obtained by condensation of 1-tetralones **1** and substituted aromatic aldehydes in the presence of 5% NaOH in aqueous medium [20]. 2-Arylidene-1-tetralones **2a–d** on condensation with nucleophilic reagents (phenyl hydrazine, semicarbazide and thiosemicarbazide) forms isomeric products. The isomeric composition of products was reported to be influenced by nucleophilic reagents as well as reaction conditions. Lorand et al. [21] have reported that condensation of **2** with thiosemicarbazide afforded only *cis* isomer and its formation is independent of solvent and catalyst used in the reaction. In another communications by the same author [22,23] it has been reported that the condensation of semicarbazide and thiosemicarbazide with 2-arylidene-1-tetralones **2** in acidic medium furnished a mixture of 3-H, 3a-H *cis* and *trans* diastereoisomers in the former case and only one cis diastereoisomer in the latter case. In contrast, Jagtap et al. [24] have reported the formation of mixture of *cis* and *trans* diastereoisomers during the condensation of 2-arylidene-1-tetralones **2** with semicarbazide or thiosemicarbazide in acidic medium. Herein, we found that condensation of 2-arylidene-1-tetralones **2a–d** with semicarbazide or thiosemicarbazide in presence of alc. KOH afforded a readily separable mixture (HPLC) of *cis* and *trans* diastereoisomers (3-H, 3a-H) **3** (*i.e. 3S, 3aS-rel* isomer) and **4** (i.e. *3R, 3aS-rel* isomer) in 42% (X = O) and 58% (X = O) yields. In case of carbothioamides (X = S), *cis* isomer **3** is the major product (90–95%, HPLC) and isomer **4** is only a minor product (5–10%). A mixture of **3a** and **4a** was separated by column chromatography (4:1 pet. ether: ethyl acetate) and the relative configuration of the isomers was established by 2D-COSY, ^{1}H NMR and ^{13}C NMR experiments. The reaction of 2-arylidene-1-tetralones **2** with semicarbazide or thiosemicarbazide proceeds via hydrazone formation resulting from 1,2-addition of semicarbazide or thiosemicarbazide to the carbonyl group and subsequent N—H intramolecular cycloaddition to the double bond of **2**′ as depicted in Scheme 1. In ^{1}H NMR spectrum, the proton H-3 in **3a** and **4a** appeared as a doublet at δ 5.50 and δ 4.79 ppm respectively, with spin–spin H-3 and H-3a vicinal coupling constant values ($^{3}J_{H\text{-}3,3a}$) of 10.9 Hz and 11.1 Hz. The difference in J values is too small to distinguish between *cis* and *trans* isomers. The difference in chemical shifts of H-3 in diastereoisomeric pair **3a** and **4a** is due to the diamagnetic anisotropy of C—(3a)—C-4 bonds and to the orientation of the pendent phenyl group. Firm decision on the configuration of the isomers is made on the basis of ^{13}C NMR spectroscopy. The C-3a chemical shifts for the *cis* and *trans* isomers **3a** and **4a** are 48.1 and 55.1 ppm respectively. The significant up field shift for C-3a in **3a** proved its *cis* configuration unambiguously. Finally, the structure of *cis* diastereoisomer **3b** (X = S) is proved by single crystal X-ray diffraction studies reported in our earlier accepted communication to Journal of Heterocyclic Chemistry. The ortep diagram obtained from X-ray structure of **3b** is shown in Fig. 1. CCDC 935909 contains the supplementary crystallographic data of **3b** and these data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Compounds **3b–e,** with X = S**,** on condensation with chloroacetic acid and α-bromopropionic acid in presence of anhydrous sodium acetate afford substituted 3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazol-2-yl)thiazol-4(5*H*)-ones (**5a–h**, Scheme 2). Appearance of carbonyl peak at 1697 cm^{-1} in the IR spectrum of **5a** indicates the cyclisation has indeed taken place. In ^{1}H NMR spectrum of **5a**, appearance of singlet of two protons at δ 3.88 is assigned to SCH_2 group of thiazolidinone ring. ^{13}C NMR of **5a** displays carbonyl group at δ 186.5 and C-3a at δ 49.2. The appearance of peak at *m*/*z* 348 $(M+H)^+$ (54%) in mass spectrum supports the cyclised structure **5a**. Similarly, ^{1}H NMR spectrum of **5b** displays a doublet at δ 1.5 of CH_3 group and a quartet of one proton at δ 4.15 due to $SC(H)CH_3$ group confirm the formation of thiazolidinone ring. ^{13}C NMR spectrum of **5b** exhibits C═O and C-3a at δ 189.3 and δ 48.8 respectively. The mass spectrum of **5b**, displays base peak at *m*/*z* 362 $(M+H)^+$ (100%) in support of its cyclised structure. The structure of other derivatives **(5c–h)** has been established in a similar fashion by analytical and spectral data. The analytical data of all the synthesised compounds is in accordance with the assigned structures and is in good agreement with calculated values (within range of ±0.4%).

The X-ray crystal structure of compound **5a**, which is reported for the first time in this study, further confirmed the stereochemistry and *cis* orientation of H-3 and H-3a protons (Fig. 2). The crystallographic data and refinement parameters of **5a** are reported in Table 1. CCDC 986834 contains the supplementary crystallographic data and these data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Computational studies

The molecular geometry optimisation and ^{1}H and ^{13}C NMR spectra calculations were performed with the Jaguar software package version 6.5112 by using DFT methods with B3LYP (Becke three parameter Lee–Yang–Parr) exchange correlation functional, which combines the hybrid exchange functional of Becke [25] with the gradient-correlation functional of Lee et al. [26]. The 6-31G** basis set was used for calculations in the gas phase of *cis* diastereoisomer **5a** and its *trans* isomer **6a.**

A DFT calculation was carried out to predict the geometry of the molecules. The initial coordinates for DFT calculation were obtained from X-ray data. The experimental and optimised bond parameters (bond lengths and bond angles) obtained from X-ray crystallographic study and by geometry optimisation at B3LYP/6-31G** level of theory respectively for structure **5a** is in close agreement and is reported in Table 2. It may be noted here that slight differences in bond parameters can be attributed to the fact that the experimental results are derived from the solid phase whereas the theoretical calculations cater to the gaseous phase. However, the general agreements are good and therefore, the theoretical calculations amply corroborate the solid-state structures. The optimised configurations of **5a** and **6a** with atom numbering schemes are shown in Figs. 3 and 4 respectively.

Shielding tensors of structure **5a** and its *trans* isomer **6a** were evaluated by using B3LYP functional with basis set given above. In order to express the chemical shifts in ppm, the geometry of tetramethylsilane (TMS) and chloroform molecules had been optimised and then their ^{1}H and ^{13}C NMR spectra were calculated by the same method using same basis set as in case of the calculations on structures **5a** and its *trans* isomer **6a**. The shielding of TMS is 32.3379 for ^{1}H NMR and 202.8593 for ^{13}C NMR. The calculated isotropic shielding constants σ_i were then transformed to chemical