Bioorganic & Medicinal Chemistry Letters 23 (2013) 548–551

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Facile regioselective synthesis of novel bioactive thiazolyl-pyrazoline derivatives via a three-component reaction and their antimicrobial activity

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ARTICLE INFO

Article history:
Received 19 September 2012
Revised 5 November 2012
Accepted 7 November 2012
Available online 22 November 2012

Keywords:
Thiazolyl-pyrazoline
Chalcone
Thiosemicarbazide
Three-component
Antibacterial activity

ABSTRACT

A series of novel 2-(3,5-diphenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-4-phenylthiazoles have been prepared by a three-component cyclo-condensation of various chalcones, thiosemicarbazide and phenacyl bromide. The easy work-up of the products, rapid reaction, and mild conditions are notable features of this protocol. The reaction was efficiently catalyzed in one-pot by a few drops of HCl in EtOH under reflux conditions providing the title compounds in moderate to high yields. The antibacterial activity of the selected products was examined. Some products exhibit promising activities.

Chalcones are well known as intermediates for the synthesis of various heterocyclic compounds, many of which have remarkable biological activities and play a principal role in medicinal chemistry. The presence of the α,β-unsaturated carbonyl system in chalcones makes them biologically attractive.[1–3]

The tetralone moiety plays an important role in diverse biological activities and is a feature of some of the most interesting and important classes of compounds. Many tetralones are pharmacologically active, functioning as antidepressants, anti-parkinson, antifungals, antibacterials, COX-2 inhibitors, and anticonvulsants.[4–9] Two tetralone-containing compounds, sertraline and tametraline, have been used clinically as antidepression agents.[10,11] Finally, thiazolyl-pyrazoline derivatives were reported to exhibit significant antimicrobial, antiviral and antihypertensive activities.[12–16]

Our goal in this work was to incorporate these three independently biologically active moieties into one molecule to generate compounds with synergistic in vitro antimicrobial activities.

Structural evaluations, properties, and synthetic routes to the thiazolyl-pyrazoline skeleton have been reported in only limited sources.[17–21] A literature survey shows that thiazolyl-pyrazoline derivatives containing a tetralone-derived moiety have not been reported to date. Because of our interest in the design and synthesis of chemically and biologically medicinal heterocycles[22–26] we decided to explore the synthesis of these novel thiazolyl-pyrazoline derivatives.

Herein, we report an efficient method for the regioselective synthesis of new thiazolyl-pyrazoline derivatives (**6a–i**) via a three-component reaction (Scheme 1). Due to the incorporation of different pharmacophores into their structures these compounds could display superior antibacterial properties.

Condensation of chalcones with thiosemicarbazide can lead to two different pyrazolines **5** or **5′** as shown in Scheme 2. The selectivity that leads to the formation of intermediate **3** results from 1,2-addition of thiosemicarbazide to the carbonyl group of chalcone (**2**) and subsequent N–H intramolecular cycloaddition to the double bond of (**3**). This occurs more readily than formation of intermediate (**3′**) resulting from 1,4-addition to provide (**4′**). As a result and in accordance with the currently accepted mechanism[27] the formation of (**6**), instead of the regioisomer (**6′**), is favored via hydrazone formation (**3**). Under these reaction conditions, the product structure is determined via steps **4** → **5** rather than via **4′** → **5′** where a regioselective enamine-imine tautomerism may take place[28] to form the more stable 2-pyrazoline (**5**).

Pyrazoline formation is followed by the Hantzsch thiazole synthesis. Initially, nucleophilic substitution of Br in phenacylbromide by the S-atom of thioamide **5** generates the isothiourea, which subsequently undergoes cyclocondensation and H_2O elimination give the thiazole ring of **6** (Scheme 2).

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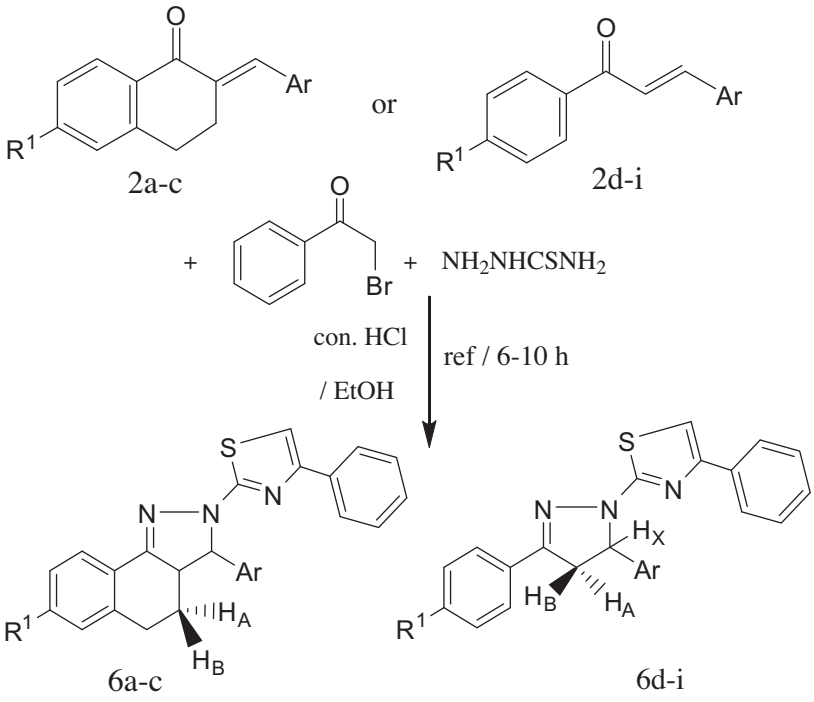
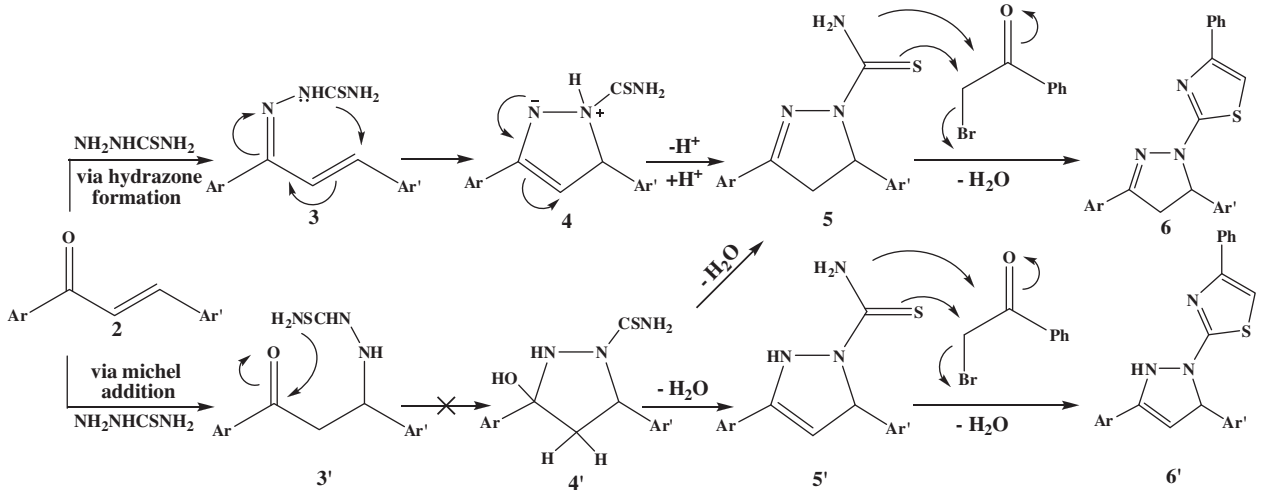
http://dx.doi.org/10.1016/j.bmcl.2012.11.024



Scheme 1. Synthesis of thiazolyl-pyrazolines (**6a–i**).



Scheme 2. Mechanism for addition of thiosemicarbazide to chalcone 2.

All of compounds described in Table 1 were characterized by spectroscopic methods (IR, ^{1}H NMR, ^{13}C NMR) and elemental analysis.[29]

The IR spectra of thiazolyl-pyrazoline derivatives **6a–i** reveal the presence of thiocarboxamide amino stretching vibration bands at υ 3482–3123 cm^{-1}, absorption bands in the 1509–1610 cm^{-1} region corresponding to endocyclic C=N stretching bands, and peaks in the regions 1355–1365 cm^{-1} and 1055–1096 cm^{-1} which indicate the presence of C–S and C–N groups.

The ^{1}H NMR spectra of thiazolyl-pyrazolines **6a–i** showed a sharp singlet at δ 7–8 ppm due to the thiazole ring proton. The vicinal protons of the adjacent carbon atom in the pyrazole ring of compounds **6a–c** appear in the region of 3.91–4.2 and 5.91–6.05 ppm. The reaction for compounds **6a–c** generates one diastromer as pair of enantiomer. The ^{1}H NMR spectrum of thiazolyl-pyrazoline **6a–c** showed only one precipitate indicating that chemoselectively one diastromer is formed and recovered. In addition MM2 structural minimize energy using Chem3D Ultra 8 (Cambridge soft) indicate a *trans* bond of H_c and H_d structure as a most stable isomer for **6a–c** (Scheme 3). However, *cis* isomer possesses more steric bulk hindrance effects compare to the *trans* isomer.

The geminal methylene protons of the pyrazoline rings (H_A and H_B in **6d–i**) appear in the region of 3.11–3.2 ppm (J_{AB} = 17.44 Hz, J_{AX} = 3.08 Hz, H_A) and 3.83–3.9 ppm (J_{AB} = 17.45 Hz, J_{BX} = 11.13 Hz, H_B) as doublet of doublets. The CH (H_X) protons appeared as doublet of doublets in the region 5.99–6.11 ppm (J_{AX} = 3.08 Hz, J_{BX} = 11.12 Hz, H_X) due to vicinal coupling with the two nonequivalent geminal protons of the adjacent carbon atom. Protons bound to the aromatic ring were observed within the expected chemical shift region and exhibited the expected integral values.

The in vitro antibacterial activities of compounds **6a–i** were evaluated against gram-positive and gram-negative bacteria using