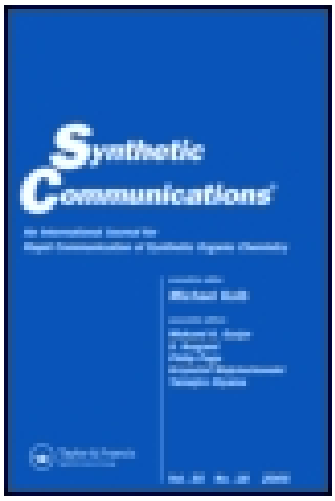

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Arylidene Pyruvic Acids Motif in the Synthesis of New 2H,5H-Chromeno[4′,3′:4,5]thiopyrano[2,3-d]thiazoles via Tandem hetero-Diels-Alder-Hemiacetal Reaction

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Arylidene pyruvic acids motif in the synthesis of new 2*H*,5*H*-chromeno[4′,3′:4,5]thiopyrano[2,3-*d*]thiazoles via tandem *hetero*-Diels–Alder-hemiacetal reaction

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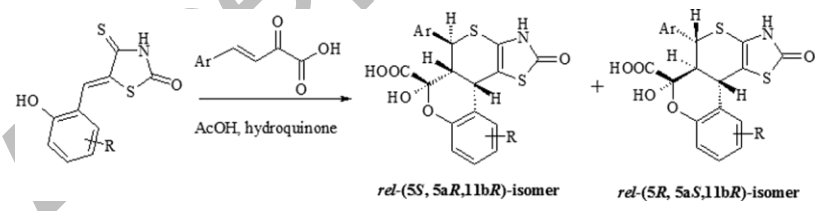
Abstract

We have developed a tandem *hetero*-Diels–Alder-hemiacetal reaction using arylidene pyruvic acids with 5-(*ortho*-hydroxybenzylidene)-substituted 4-thioxo-2-thiazolidinones, leading to 6-hydroxy-2-oxo-5-phenyl-3,5a,6,11b-tetrahydro-2*H*,5*H*-chromeno[4',3':4,5]thiopyrano[2,3-*d*][1,3]thiazole-6-carboxylic acids. The stereochemistry of cycloaddition was confirmed by NMR spectra and a single crystal X-ray diffraction analysis.



KEYWORDS: 5-ylidene-4-thioxo-2-thiazolidinones, thiopyrano[2,3-*d*][1,3]thiazoles, *hetero*-Diels-Alder reaction, tandem reactions

INTRODUCTION

The construction of multiple carbon-carbon bonds in a single chemical step represents a particularly efficient approach to the synthesis of complex molecular structures. In support of this view, the *hetero*-Diels-Alder reaction had particularly evolved as an efficient route to wide range of polycyclic compounds.[1-7] The thiopyrano[2,3-*d*]thiazoles constructed on this principle formed a central skeleton of many compounds which are known for their anticancer, antimicrobial, antiinflammatory, and antitrypanosomal activity.[8-16] A particular interest in the synthesis of these heterocyclic systems includes the study of *hetero*-Diels–Alder reactions and related tandem processes. Earlier we reported the diastereoselective tandem acylation-*hetero*-Diels-Alder reaction of 5-arylidene-4-thioxo-2-thiazolidinones (5-arylideneisorhodanines) with *ortho*-phenolic group at arylidene moiety and α,β-unsaturated carboxylic acids derivatives providing 2*H*,5*H*-chromeno[4',3':4,5]thiopyrano[2,3-*d*]thiazoles formation.[15,17] As a consequence, we decided to investigate the reaction between 5-(*ortho*-hydroxybenzylidene)-substituted isorhodanines and arylidene pyruvic acids (APAs) as dienophiles. The classical regio- and diastereoselective *hetero*-Diels–Alder reaction between 5-arylideneisorhodanines (without *ortho*-phenolic group at arylidene moiety) and APAs providing novel *rel*-(5*R*,6*S*,7*S*)-2-oxo-5,7-diaryl-3,5,6,7-tetrahydro-*2H*-thiopyrano[2,3-*d*]thiazol-6-yl-oxo-acetic acids has been already reported in our research before. Furthermore, previously synthesized compounds could be employed as templates for search of biologically active compounds.[18] Hence, the aim of the presented Letter was the synthesis of new 2*H*,5*H*-chromeno[4',3':4,5]thiopyrano[2,3-*d*]thiazoles via a novel *hetero*-Diels-Alder-hemiacetal reaction.

RESULTS AND DISCUSSION

Combination of highly reactive sulfur atom at the 4th position and methylidene group in position 5 in 5-arylideneisorhodanines allows them to be used as highly active heterodiene components in *hetero*-Diels-Alder reactions.[19] Thus, the starting 5-(2-hydroxybenzylidene)-4-thioxo-2-thiazolidinones **1a-b** were synthesized via Knoevenagel condensation (ethanol medium in the presence of ethylendiaminediacetate).[18] The APAs were synthesized by the reaction of the corresponding aromatic aldehyde with a pyruvic acid in aqueous methanol solution.[20] The reactions between 5-(2-hydroxybenzylidene)-4-thioxo-2-thiazolidinones **1a-b** and arylidene pyruvic acids **2a-c** followed by the tandem *hetero*-Diels-Alder and hemiacetal formation processes, affording tetracyclic fused 6-hydroxy-2-oxo-5-phenyl-3,5a,6,11b-tetrahydro-2*H*,5*H*-chromeno[4',3':4,5]thiopyrano[2,3-*d*][1,3]thiazole-6-carboxylic acids **3a-d/3a-d** (Scheme 1).

Moreover, the stereochemical features of final products were predicted by the ^{1}H NMR spectra. In particular, we have observed that the use of APAs in the *hetero*-Diels-Alder reaction with 5-(2-hydroxybenzylidene)-4-thioxo-2-thiazolidinones **1a-b** proved to be regio- and moderate stereoselective yielding the mixture of *rel*-(5*S*,5a*R*,11b*R*) and *rel*-(5*R*,5a*S*,11b*R*)-annulated diastereisomers. This reaction leads to a 2:1 diastereomeric ratio of cycloadducts **3a-d** and **3a-d**. Considering this fact, the reaction can occur through *endo* or *exo* transition states, leading in each case to a distinct stereochemical relationship between the protons at the C-5, C-5a, and C-11b positions of the adducts. In this case, the addition is predominantly *exo* was caused by the steric properties of arylidene pyruvic

acids as dienophiles in the *hetero*-Diels-Alder reaction. This statement is based on equatorial-pseudoaxial interactions of protons 5, 5a and 11b and established from the coupling constants value of the *endo*-isomer within the range of 6.0-6.4 Hz and *exo*-isomer within 4.0 Hz. In addition, the structure of adducts **3a**/**3a** was established by X-ray crystallography (Fig. 1).

Thus, the X-ray analysis of **3a**/**3a** showed that two isomers of 6-hydroxy-2-oxo-5-phenyl-3,5a,6,11b-tetrahydro-2*H*,5*H*-chromeno[4',3':4,5]thiopyrano[2,3-*d*][1,3]thiazole-6-carboxylic acid are presented in the crystal with the site occupancy factor of 0.942 (**3a**) and 0.058 (**3a**). In molecule **3a** dihydrothiopyrane and dihydropyrane rings are *cis* while in molecule **3a** *trans*-fused. The torsion angles H7–C7–C16–H16 and H7'–C7'–C16'–H16' amount to 55° and -149°, respectively. Moreover, an inversion of configuration at C6 is observed (Fig. 1).

EXPERIMENTAL

All starting materials were purchased from commercial sourses and used without purification. Melting points are uncorrected and were measured in open capillary tubes on a Buchi B-545 melting-point apparatus. The ^{1}H NMR spectra were recorded on a Varian Gemini 400-MHz instrument and ^{13}C NMR spectra on Varian Mercury-400 100-MHz instrument in dimethylsulfoxide (DMSO-d_6) with tetramethylsilane (TMS) as an internal standard [chemical shift values are reported in parts per million (ppm) units, coupling constants (J) are in hertz]. The elemental analyses (C, H, N) performed on the Perkin-Elmer 2400 CHN analyzer were within ±0.4% of the theoretical values. Mass spectra were obtained on the Varian 1200L instrument.

The starting compounds: 2,4-thiazolidinedione [21], 4-thioxo-2-thiazolidinone[19] were obtained according to methods described previously. 5-Ylidene-4-thioxo-2-thiazolidinones (**1a-1b**) were prepared by treating 4-thioxo-2-thiazolidinone with the corresponding aldehydes and refluxed for 10 min in the ethanol medium in the presence of catalytic amount of EDDA according to published procedures.

General Procedure Of Diels-Alder And Tandem Reactions Affording 3a-D/3a-D.

A mixture of appropriate 5-arylidene-4-thioxo-2-thiazolidinone **1a-b** (5 mmol) and arylidene pyruvic acid **2a-c** (5.5 mmol) was refluxed for 1 h with a catalytic amount of hydroquinone (2-3 mg) in 15 ml of glacial acetic acidand left overnight at room temperature. The precipitated crystals were filtered off, washed with ethanol, and recrystallized from appropriate solvent.

***rel*-(5*S*,5a*R*,11b*R*)- and *rel*-(5*R*,5a*S*,11b*R*)-6-Hydroxy-2-oxo-5-phenyl-3,5a,6,11b-tetrahydro-2*H*,5*H*-chromeno[4',3':4,5]thiopyrano[2,3-*d*][1,3]thiazole-6-carboxylic acid** (**3a/3a**). Yield 80%, mp 218-220ºC (DMF:AcOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.11 (d, 1H, *J* = 6.0 Hz, 11b-H, **3a**), 4.34 (dd, 1H, *J* = 9.6, 11.5 Hz, 5a-H, **3a**), 4.51 (d, 1H, *J* = 6.0 Hz, 5-H, **3a**), 4.56 (d, 1H, *J* = 11.5 Hz, 5-H, **3a**), 4.78 (d, 1H, *J* = 4.0 Hz, 11b-H, **3a**), 4.85 (dd, 1H, *J* = 4.0, 11.5 Hz, 5a-H, **3a**), 6.87 (t, 1H, *J* = 7.4 Hz, arom.), 7.03 (d, 1H, *J* = 7.4 Hz, arom.),7.11 (t, 1H, *J* = 7.4 Hz, arom.), 7.22-7.30 (m, 5H, arom., OH), 7.39 (d, 2H, *J* = 7.0 Hz, arom.), 11.57 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 31.01, 45.52, 47.91, 96.62, 108.09, 120.01, 121.37, 126.62, 128.22, 128.55, 128.77,

129.23, 131.43, 137.15, 150.44, 160.37, 169.33, 170.37. Anal. Calcd for $C_{20}H_{15}NO_5S_2$: C, 58.10; H, 3.66; N, 3.39. Found: C, 58.12; H, 3.65; N, 3.40. ESI-MS m/z 413 $(M+H)^+$.

SUPPLEMENTAL MATERIAL

Structural characterization, spectral data for synthesized compounds **3b-d/3b-d**, crystal data and refinement details for **3a**/**3a** for this article can be accessed on the publisher's website.

Crystallographic data (CCDC-1401842 for molecules **3a**/**3a**) have been deposited at the Cambridge Crystallographic Database Centre (www.ccde.cam.ac.uk).

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Scheme 1. Synthesis of *rel*-(5*S*, 5a*R*, 11b*R*) and *rel*-(5*R*, 5a*S*, 11b*R*)- 6-hydroxy-2-oxo-5-phenyl-3,5a,6,11b-tetrahydro-2*H*,5*H*-chromeno[4',3':4,5]thiopyrano[2,3-*d*][1,3]thiazole-6-carboxylic acids **3a-d/3a-d**.

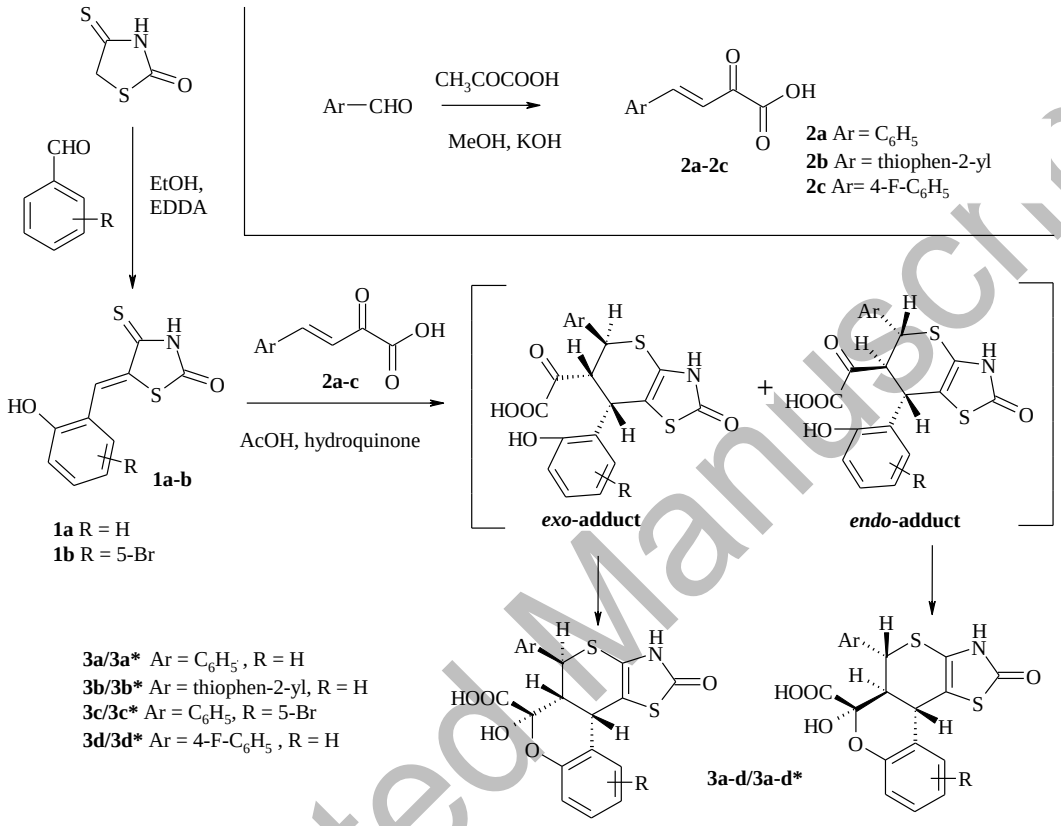

Figure 1. The alternative molecules (**3a**/**3a**) (ORTEP plot) in the same monocrystal (Figure is provided in color online).

molecule **3a**	molecule **3a***