Tetrahedron xxx (2015) 1–12

Contents lists available at ScienceDirect

Tetrahedron

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

A new method for the preparation of 5-acylidene and 5-imino substituted rhodanine derivatives and their antioxidant and antimicrobial activities

Şevket Hakan Üngören [a,*], Sevil Albayrak [b], Ahmet Günay [a], Lutfiye Yurtseven [b], Nurgül Yurttaş [a]

[a] Department of Chemistry, Faculty of Arts and Sciences, Bozok University, Yozgat, Turkey
[b] Department of Biology, Faculty of Sciences, Erciyes University, Kayseri, Turkey

ARTICLE INFO

Article history:
Received 8 February 2015
Received in revised form 8 April 2015
Accepted 20 April 2015
Available online xxx

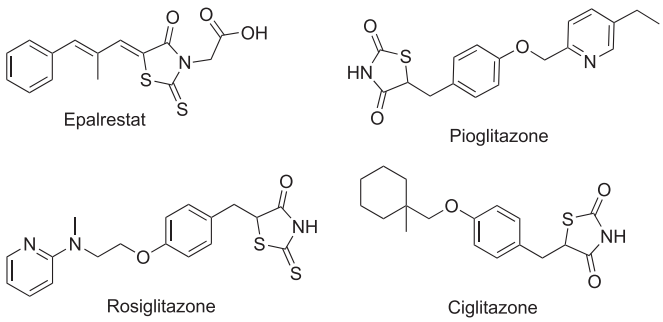
Keywords:
Rhodanines
Wittig reaction
Chalcones
Perimidines
Antioxidant activity
Antimicrobial activity

ABSTRACT

Versatile syntheses of 5-imino or 5-acylidene substituted 1,3-thiazolidin-4-one derivatives are reported from α-dioxothiazole systems and phosphoranes via Wittig reactions. Antimicrobial and antioxidant activity of the compounds were evaluated. 5-Carbonylmethylene substituted 2-thioxo-1,3-thiazolidines have better antioxidant properties than the 5-arylimino substituted ones. The % inhibition value of the compound **3** (90.8%) was near to that of standard BHT (93.6%) at the same concentration. Compounds **5** and **15**, which have the alkyliden-amide group at the C-5 position of the 1,3-thiazolidine ring showed the highest antimicrobial activities among the synthesized compounds.

1. Introduction

2-Thioxo-1,3-thiazolidin-4-one, commonly named as rhodanine,[1] is privileged scaffold[2] that shows multiple biological activities[3] by means of selective affinity towards various enzymes such as aldose reductase,[4] β-lactamase,[5] HCV NS3 protease,[6] histidine decarboxylase,[7] *N*-acetyltransferase[8] and histone acetyltransferase.[9] The 1,3-thioazolidin-4-one skeleton is also a pharmacophore for treatment of type 2 diabetes and is found in the structure of some drugs like Epalrestat, Pioglitazone, Rosiglitazone, Ciglitazone.[3]



Moreover, there is an important application of 5-acylidene substituted rhodanines as dye sensitizer,[10] and also 5-arylimino substituted derivatives of rhodanine framework are very interesting structures as optical materials.[11] Thus, rhodanine structures have become useful for the development of not only bioactive, but also optoelectronic materials.

A short time ago, the synthesis of some 5-imino substituted rhodanines was revealed from the reaction of the corresponding thiazolidines and aryl nitroso compounds.[11] On the other hand, only two methods are known about the preparation of 5-acylidene rhodanines. The first one is well known and it based on the Knoevenagel reaction of 2-thioxo/oxo/imino substituted rhodanine derivatives with aldehydes.[1,12] The second method is the cyclization of thioureas or dithiocarbamic acids with dialkylacetylene dicarboxylates (DAADs).[13] The second method is not used commonly because of the limited availability of DAADs.

Considering the importance of thiazolidine compounds, we can report that a new generalized protocol about the preparation of 5-

* Corresponding author. Tel.: +90 354 242 1021; fax: +90 354 242 1022; e-mail address: hungoren@erciyes.edu.tr (Ş.H. Üngören).

http://dx.doi.org/10.1016/j.tet.2015.04.069
0040-4020/

acylidene and 5-arylimino substituted rhodanine derivatives is able to provide rich sources of valuable chemical materials.

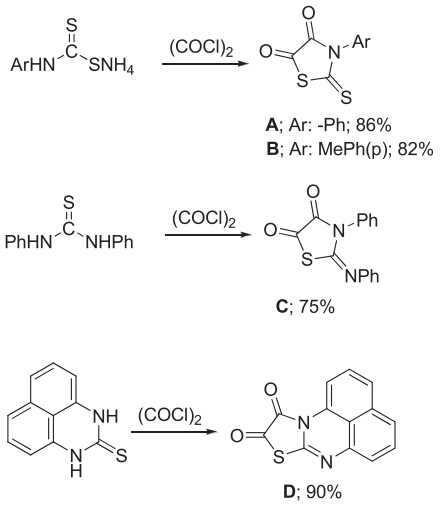
In this study, we propose a new useful method for synthesis of 5-acylidene and 5-imino rhodanine series by rection of 1,3-thiazolidine-4,5-diones (α-dioxothiazole derivatives) with Wittig reagents. The chemical behavior of the Wittig reagents towards α-dioxothiazole derivatives has not been investigated previously, however, the Wittig reactions of similar structures such as α-dioxoimidazole, α-dioxofurane were reported earlier.[14]

In addition to our synthesis study, we have investigated antibacterial and antioxidant properties of the newly synthesized rhodanine analogues.

2. Results and discussion

2.1. Synthesis

First, 3-aryl-2-thioxo-1,3-thiazolidine-4,5-diones (**A**, **B**) were prepared from corresponding ammonium dithiocarbamates with oxalyl chloride at reflux condition in benzene.[15] 2-Arylimino substituted 1,3-thiazolidinedione analogues (**C**, **D**) were synthesized with similar pathway as second-type of starting materials in MeCN (as shown Scheme 1).[16,13a]



Scheme 1. Preparations of 1,3-thiazolidine-4,5-dione structures as substrates (**A**–**D**).

Subsequently, heating a benzene solution of compounds **A**–**D** with various methylenephosphoranes leads to the regioselectively formation of 1,3-thiazolidine-5-ylidene derivatives at good yields as shown Table 1. Also, iminophosphoranes are reacted on the S–*C*=*O* group, but not N–*C*=*O* group of the substrates, similarly. The alkylidene substituted products were isolated in *Z*-form.

In the ^{13}C NMR spectra of **A**–**D**, S–*C*=O signals of α-dioxotihiazole derivatives were observed in the range of 178–190 ppm. In the ^{13}C NMR spectrum of the Wittig reaction products, these signals were disappeared and new signals, which belong to substituted group of the products were appeared. For example, 16 resonances were seen in the ^{13}C NMR spectra of **29**, and signals of a methyl group and two carbonyl group (acetyl and amide) were observed at 30.7, 196.7, 153.0 ppm, respectively. The other carbon signals are convenient for the proposed structure.

Validation studies for the proposed method were performed by using reported spectroscopic data of compounds **27**[17] and **20**.[13a,d] These compounds can be prepared from the reaction of dimethylacetylene dicarboxylate with corresponding thiourea derivatives in methanol. According to published ^{1}H NMR data of the compound **20**, which is formed in *Z*-geometry, and also supported with X-ray analyses,[13d] the olefinic proton signal is observed at δ 7.00 ppm. In this study, the same compound (**20**) showed a signal at δ 7.01 ppm in $CDCl_3$ due to the olefinic proton in *Z*-form. Thus, we have clearly proved the structures of the synthesized compounds in *Z*-geometry.

Before performing biological studies of the novel rhodanine derivatives, two chalcone analogues of 5-acylidene rhodanines were synthesized from **13** with aldehydes for structural diversity of 5-acylidene rhodanines. Therefore, structure–activity relationship of antibacterial and antioxidant properties of the new rhodanine derivatives would be better understood.

The condensation reactions occurred in presence of BF_3 as catalyst, in moderate yields, (Table 2). The chalcone derivatives (**33**, **34**) were purified by column chromatography, and their spectroscopic data were correspond with proposed structures.

2.2. In vitro antioxidant activity

The inhibitory effects of some of the synthesized compounds (**1**–**20**, **33**, **34**) on DPPH radical are presented as % inhibition in Table 3. Statistical differences among the DPPH scavenger activities of the compounds were important ($p<0.05$). DPPH radical scavenging activity of the synthesized compounds was detected to be good to moderate as compared to the standard BHA. % Inhibition value of the compound **3** (90.8%) was near to that of standard BHT (93.6%) at the same concentration. It appears that compounds **3**, **13**, **14**, **4**, **1**, **11** and **17** were found to be a significant scavenger of the DPPH radical (90.8%, 82.1%, 81.2%, 71.2%, 71.2%, 55.9% and 54.4%, respectively) when compared to BHT. The other compounds except for **20** were showed moderate inhibitory effect and inhibition rates in the range of 42.2–11.6%. Compound **20** was exhibited the weakest inhibitory effect with 6.1%.

The study reveals that the sulfur atom attached on C-2 atom of 1,3-thiazolidine skeleton increases the antioxidant potential of the rhodanine derivatives, compared to effect of nitrogen atom attached on the same point. 5-Carbonylmethylen substituted 1,3-thiazolidines have much more antioxidant properties from the 5-arylimino substituted ones, generally. Moreover, in the event that there are methyl, methylene and methine groups attached to carbonyl group of 1,3-thiazolidine analogues, the protons of these groups provide additional antioxidant activity by transferring the protons to oxidizing agent.

2.3. Antimicrobial activity

The antimicrobial activity of compounds **1**–**34** against fourteen microorganisms determined by agar diffusion method was investigated. The results revealed that most of the synthesized rhodanine compounds (**2**–**7**, **13**–**18**) showed significant antibacterial activities (Table 4). Among the tested rhodanine compounds, **4**, **5**, **14** and **15** had the strongest antibacterial activity.

As clearly seen in Table 4, among the Gram (−) bacteria tested, the most sensitive bacteria were *Aeromonas hydrophila*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* while the most resistant bacteria were *Escherichia coli, Salmonella typhimurium, Proteus mirabilis* and *Yersinia enterocolitica*. Amongst the tested five Gram (+) bacteria the most sensitive bacteria were *Bacillus cereus, Bacillus subtilis, Listeria monocytogenes* and *Staphylococcus aureus* while none of the tested compounds had inhibitory activity against *Mycobacterium smegmatis*. **2** exhibited inhibitory activity against only *S. aureus* (7.0 mm) while **7** showed inhibitory activity against *B. cereus* (9.0 mm). All other compounds did not show antibacterial activity against the bacteria tested. Only **5**, **15** and **18** had an inhibitory effect on *Candida albicans* with inhibition zones of 11.0, 12.5 and 7.5, respectively. Compound **18** did not exhibit any activity

Please cite this article in press as: Üngören, Ş. H.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.04.069