Reaction of benzoylpyruvate with a mixture of aromatic aldehydes and 5-amino-1,3,4-thiadizole-2-thiol

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Abstract
Reactions of benzoylpyruvate with a mixture of aromatic aldehydes and 5-amino-1,3,4-thiadizole-2-thiol in a 1:1:1 molar ratio, afforded 5-(aryl-4-benzoyl-3-hydroxy-2-oxo-2,5-dihydro-1H-pyrrol-1-yl)-1,3,4-thiadizole-2-thiols (3a-c). The structure of the resulted products was confirmed by determination of the melting point and spectrophotometric techniques such as IR and 1H-NMR spectroscopy.

Keywords: Benzoylpyruvate; Aromatic aldehydes; 5-amino-1,3,4-thiadizole-2-thiol; Multi-component reactions (MCRs);

Introduction
N-Substituted 4-acyl-5-aryl-3-hydroxy-3-pyrrolin-2-ones have been synthesized via reactions of acylpyruvic acid esters with a mixture of aromatic aldehyde and amine [1-6].
The reaction of acylpyruvate esters with a mixture of aromatic aldehyde and aliphatic diamine, such as, 1,2-diaminoethane in equimolar amounts formed 1-(2-aminoethyl)-4-acyl-5-aryl-3-hydroxy-3-pyrrolin-2-ones [7,8]. While the three-component condensation between an acylpyruvate ester, aromatic aldehyde and 0.5 equiv of aliphatic diamine performed, both amino groups involved, and leads to formation of 1,2-bis(4-acyl-5-aryl-3-hydroxy-2-oxo-3-pyrroline-1-yl)ethanes [9,10].

1,4,5-Trisubstituted 3-hydroxy-3-pyrrolin-2-ones represent interesting derivatives of pyrroles from point of view of the syntheses of many further derivatives and biologically active compounds. In recent years, much effort has been done via V. L. Gain on the synthesis and biological evaluation of 1,4,5-trisubstituted tetrahydropyrrrol-2,3-diones due to their possible applications. It is known that N-substituted 4-acyl-5-aryl-3-hydroxy-3-pyrrolin-2-ones possess various types of pharmacological activity such as antimicrobial [3-5,11-13], antiinflammatory [6,14,15], analgesic [6,15,16], antiviral [15,17], antiamnestic [14,18], nootropic [8], antiaggregant [19], and neurotropic [20,21]. 1-Substituted 4-arylm-3-hydroxy-5-phenyl-1H-pyrrol-2(5H)-one has promising properties as inhibitors of the interaction between annexin A2 and S100A10 and may help to elucidate the cellular function of this protein interaction [22]. In continuation of the search for biologically active compounds among 4,5-substituted 1-aminoaryl-3-hydroxy-3-pyrrolin-2-ones, it seems interesting to study the reaction of acylpyruvates with a mixture of aromatic aldehyde and diaminoaromatic and to investigate the pharmacological activity of the products.

Herein, we wish to report a simple reaction between benzoylpyruvate with a mixture of aromatic aldehydes and 5-amino-1,3,4-thiadizole-2-thiol in 1:1:1 molar ratios, leading to 5-(5-aryl-4-benzoyl-3-hydroxy-2-oxo-2,5-dihydro-1H-pyrrol-1-yl)-1,3,4-thiadizole-2-thiols (3a-c).

**Results and discussion**

1. **Synthesis of 5-(5-aryl-4-benzoyl-3-hydroxy-2-oxo-2,5-dihydro-1H-pyrrol-1-yl)-1,3,4-thiadizole-2-thiols (3a-c)**

   It seems reasonable to examine how the reactant ratio affects the direction of the above three-component reaction. For this purpose, benzoylpyruvate was used into reaction with a mixture of equimolar amounts of an aromatic aldehyde and 5-amino-1,3,4-thiadizole-2-thiol. The reactions were carried out in acetic acid and the products were the corresponding 5-(5-aryl-4-benzoyl-3-hydroxy-2-oxo-2,5-dihydro-1H-pyrrol-1-yl)-1,3,4-thiadizole-2-thiols (3a-c) (Scheme 1).
Scheme 1. Three-component condensations of benzoylpyruvate with a mixture of aromatic aldehydes and 5-amino-1,3,4-thiadizole-2-thiol.

Structures 3a-c was assigned on the basis of their IR and $^1$H NMR spectra. The IR spectra of compounds 3a-c have shown three characteristic absorption bands at 3304-3321, 1689-1686 and 1626-1622 cm$^{-1}$ attributable to enol OH, amide C=O and ketone C=O, functions, respectively. In the $^1$H NMR spectra of 3a-c we have observed a singlet at $\delta$ 6.38-6.40 ppm for proton in position 5 of the pyrrole, a set of multiplet signals integrated for 9 protons at $\delta$ 7.12-8.05 ppm for aromatic protons. Compounds 3a-c give rise to brown-red color with an alcoholic solution of iron (III) chloride and pyridine, indicating that they exist in the enol form.

Presumably, the reaction mechanism includes formation of Schiff base from aromatic aldehyde and 5-amino-1,3,4-thiadizole-2-thiol, followed by reaction with benzoylpyruvate to give 4-amino-3-benzoyl-2-oxobutanoic acid ester which then undergoes intramolecular ring closure to the final product (Scheme 2). The yield depends on the substituent in the aryl fragment: electron-acceptor substituents favor the condensation.
Conclusion

In the present work, it has been shown that benzoylpyruvate reacted with a mixture of aromatic aldehydes and 5-amino-1,3,4-thiadizole-2-thiol in 1:1:1 molar ratios, to form cyclocondensation products that were heterocyclic compounds of 5-(5-aryl-4-benzoyl-3-hydroxy-2-oxo-2,5-dihydro-1H-pyrrol-1-yl)-1,3,4-thiadizole-2-thiols (3a-c).

Experimental

Melting points were measured in open capillaries and are reported uncorrected. Infrared spectra were measured from KBr disk using a FT-IR Perkin Elmer GX spectrometer and frequencies are reported in cm\(^{-1}\). \(^1\)H-NMR and \(^13\)C-NMR spectra were recorded on a Bruker Ultra Shield\textsuperscript{TM}-500MHz instrument using TMS as an internal standard. Chemical shifts are reported in ppm. Column chromatography was performed on silica gel L 100/250. Thin-layer chromatography was performed on "Silufol-UV 254" plates.

1. Material

Ethyl 2,4-dioxo-4-phenylbutanoate was prepared from diethyl oxalate and the acetophenone by known methods [23]. 5-amino-1,3,4-thiadizole-2-thiol (1) was obtained by careful addition of thiosemicarbazide to carbon disulfide in absolute ethanol with stirring at 60°C [24].

2. Synthesis of 5-(5-aryl-4-benzoyl-3-hydroxy-2-oxo-2,5-dihydro-1H-pyrrol-1-yl)-1,3,4-thiadizole-2-thiols (3a-c). General Procedure

To a solution of 1.0 mmol 5-amino-1,3,4-thiadizole-2-thiol (1) and 1.0 mmol of the aromatic aldehyde in 10 ml of glacial acetic acid was added with boiling a solution of 1.0...
mmol 2,4-dioxo-4-phenylbutanoate in 10 ml of glacial acetic acid and the mixture was refluxed for 3 hours. Then the solvent was evaporated and the residue washed with warm 2-propanol to give 3a-c, respectively [6].

5-(4-benzoyl-5-(4-chlorophenyl)-3-hydroxy-2-oxo-2,5-dihydro-1H-pyrrol-1-yl)-1,3,4-thiadizole-2-thiol (3a)
Orange powder; (Yield 61%); m.p. 203-205 °C (decom.). IR (KBr): $\tilde{\nu} = 3304$ (OH), 1684 (C=O, amide), 1626 (C=O, ketone) cm$^{-1}$. $^1$H NMR (DMSO-$d_6$): $\delta = 6.39$ (1H, s, C$^5$H), 7.12 (2H, d, $^3J_{HH}$=8.3 Hz, 2CH$_{meta}$ of Ph-Cl), 7.21 (2H, d, $^3J_{HH}$=8.3 Hz, 2CH$_{ortho}$ of Ph-Cl), 7.38 (2H, t, $^3J_{HH}$=7.6 Hz, 2CH$_{meta}$ of Ph-CO), 7.54 (1H, t, $^3J_{HH}$=7.6 Hz, CH$_{para}$ of Ph-CO), 7.65 (2H, d, $^3J_{HH}$=7.6 Hz, 2CH$_{ortho}$ of Ph-CO) ppm, OH and SH protons are missing in spectrum.

5-(4-benzoyl-5-(4-bromophenyl)-3-hydroxy-2-oxo-2,5-dihydro-1H-pyrrol-1-yl)-1,3,4-thiadizole-2-thiol (3b)
Orange powder; (Yield 59%); m.p. 220-222 °C (decom.). IR (KBr): $\tilde{\nu} = 3321$ (OH), 1686 (C=O, amide), 1622 (C=O, ketone) cm$^{-1}$. $^1$H NMR (DMSO-$d_6$): $\delta = 6.38$ (1H, s, C$^5$H), 7.12 (2H, d, $^3J_{HH}$=8.5 Hz, 2CH$_{meta}$ of Ph-Br), 7.26 (2H, d, $^3J_{HH}$=8.5 Hz, 2CH$_{ortho}$ of Ph-Br), 7.42 (2H, t, $^3J_{HH}$=7.7 Hz, 2CH$_{meta}$ of Ph-CO), 7.58 (1H, t, $^3J_{HH}$=7.7 Hz, CH$_{para}$ of Ph-CO), 7.67 (2H, d, $^3J_{HH}$=7.7 Hz, 2CH$_{ortho}$ of Ph-CO) ppm, OH and SH protons are missing in spectrum.

5-(4-benzoyl-3-hydroxy-5-(3-nitrophenyl)-2-oxo-2,5-dihydro-1H-pyrrol-1-yl)-1,3,4-thiadizole-2-thiol (3c)
Orange powder; (Yield 65%); m.p. 228-230 °C (decom.). IR (KBr): $\tilde{\nu} = 3315$ (OH), 1689 (C=O, amide), 1625 (C=O, ketone), 1518, 1354 (NO$_2$) cm$^{-1}$. $^1$H NMR (DMSO-$d_6$): $\delta = 6.40$ (1H, s, C$^5$H), 7.35 (2H, t, $^3J_{HH}$=7.6 Hz, 2CH$_{meta}$ of Ph-CO), 7.42 (1H, t, $^3J_{HH}$=7.3 Hz, CH$_{meta}$ of Ph-NO$_2$), 7.49 (1H, t, $^3J_{HH}$=7.6 Hz, CH$_{para}$ of Ph-CO), 7.51 (1H, d, $^3J_{HH}$=7.3 Hz, CH$_{ortho}$ of Ph-NO$_2$), 7.65 (2H, d, $^3J_{HH}$=7.6 Hz, 2CH$_{ortho}$ of Ph-CO), 8.05 (1H, d, $^3J_{HH}$=7.3 Hz, CH$_{para}$ of Ph-NO$_2$), 8.07 (1H, s, CH$_{ortho}$ of Ph-NO$_2$) ppm, OH and SH protons are missing in spectrum.
References


