Synthesis of 4-thiazolidinones derived from bicyclic Δ²-1,2,4-oxadiazolines with potential biological activity

Charles Christophe D. B. Mendes¹² (PG), Marlene S. de Araújo Neta¹ (PG), Ronmilson A. Marques¹ (PG), Natanael da S. Bezerra Júnior¹ (PG), Viviane de A. Gouveia⁴ (PO), Renan C. de A. Prado² (IC), Jamerson F. de Oliveira³ (PG), Williams L. Silva³ (PG), Anekéia L. da Silva (PQ)³, Maria do Carmo A. de Lima³ (PQ), Antônio Rodolfo de Faria¹ (PO), charles.mendes@ufpe.br

¹Departamento de Ciências Farmacêuticas – LASOF – Laboratório de Síntese Orgânica Aplicada a Fármacos, Centro de Ciências da Saúde, Universidade Federal de Pernambuco - Cidade Universitária, Recife – PE, CEP 50470-521
²Faculdade Pernambucana de Saúde – Av. Jean Emilie Favre, 422, Imbibeira, Recife – PE, CEP 51200-060
³Departamento de Antibioticos – LQIT – Laboratório de Química e Inovação Terapêutica, Centro de Ciências da Saúde, Universidade Federal de Pernambuco - Cidade Universitária, Recife – PE, CEP 50470-521
⁴Centro Acadêmico de Vitória de Santo Antão - Universidade Federal de Pernambuco, Rua Alto do Reservatório, S/n - Bela Vista, Vitória de Santo Antão - PE, CEP 55608-680

Keywords: Δ²-1,2,4-oxadiazolines, 1,3-dipolar cycloaddition, 4-thiazolidinones, thiosemicarbazones

Abstract

4-thiazolidinones have been obtained by cyclization of thiosemicarbazones derived from a Δ²-1,2,4-oxadiazoline aldehyde.

Introduction

Oxadiazolines have been related as responsible for antinociceptive activity¹. Our research group has recently synthesized oxadiazolinc compounds that presented similar activity². On the other hand, 4-thiazolidinones have been assayed as angiotensin II inhibitors³. In order to obtain molecules containing both pharmacophores, it has been devised a method that aimed the synthesis of the oxadiazolinc aldehyde in C3, thus a condensation with thiosemicarbazides to obtain thiosemicarbazones, and thereafter, cyclization to 4-thiazolidinones.

Results & Discussion

For the purpose of obtaining the oxadiazolinc aldehyde 3 (Scheme 1), a 1,3-dipolar cycloaddition (stage b) has been carried out in order to generate an ester 2 in C3, on the oxadiazolinc ring, from Δ-pyrroline 1 and ethyl chloro-oxime acetate.

(a) THF, reflux; (b) carboethoxyformonitrile oxide, THF; (c) NaBH₄; (d) Swern’s oxidation

Scheme 1. Synthesis of the oxadiazolinc aldehyde

Thence, the aldehyde 3 was submitted to condensation reactions (stage f) with thiosemicarbazides 6, formerly prepared (stage e), by reaction of isothiocyanates 5 and hydrazine 4.

(Scheme 2). Subsequently, the thiosemicarbazones 7 underwent reactions with ethyl chloroacetate (stage g), buffered with sodium acetate, to bring forth 4-thiazolidinones 8 in moderate yields.

(e) EtOH, reflux, 4-8h; (f) EtOH, r.t, 1h.; (g) EtOH, ethyl chloroacetate, reflux, 8-24h.

Scheme 2. Synthesis of the 4-thiazolidinones

Conclusions

Besides hydrazones³ and semicarbazones⁴ derived from bicyclic Δ²-1,2,4-oxadiazolines, published in previous works, it was also possible to obtain thiosemicarbazones and 4-thiazolidinones in reasonable yields (45 – 65%).

Acknowledgements

CNPq (Universal), CAPES and CA-DQF-UFPE.

²Mendes, C. C. D. B.; De Almeida, G. C.; De Faria, A. R., 2010. 33ª Reunião Anual da Sociedade Brasileira de Química