A Simple Heterocyclic Fusion Reaction and its Application for Expeditious Syntheses of Rutaecarpine and its Analogs

Guozheng Huang, Dominika Roos, Patricia Stadtmüller, Michael Decker

PII: S0040-4039(14)00757-6
DOI: http://dx.doi.org/10.1016/j.tetlet.2014.04.120
Reference: TETL 44582

To appear in: *Tetrahedron Letters*

Received Date: 7 March 2014
Revised Date: 28 April 2014
Accepted Date: 30 April 2014

Please cite this article as: Huang, G., Roos, D., Stadtmüller, P., Decker, M., A Simple Heterocyclic Fusion Reaction and its Application for Expeditious Syntheses of Rutaecarpine and its Analogs, *Tetrahedron Letters* (2014), doi: http://dx.doi.org/10.1016/j.tetlet.2014.04.120

Tetrahedron Letters

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

A Simple Heterocyclic Fusion Reaction and its Application for Expeditious Syntheses of Rutaecarpine and its Analogs

Guozheng Huang, Dominika Roos, Patricia Stadtmüller and Michael Decker*

Pharmazeutische und Medizinische Chemie, Institut für Pharmazie und Lebensmittelchemie, Julius-Maximilians-Universität, Am Hubland, D-97074 Würzburg, Germany

ARTICLE INFO

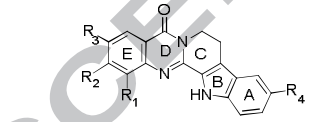
Article history:
Received
Revised
Accepted
Available online

Keywords:
Rutaecarpine
Total synthesis
Isatoic anhydride
Dehydrogenation

ABSTRACT

Abstract—In the search for new inhibitors of cholinesterases, a simple heterocyclic fusion reaction of isatoic anhydride **8** and 3,4-dihydroisoquinoline **22** was discovered which involves a spontaneous dehydrogenation upon heating. Applying the reaction, the bioactive natural alkaloid rutaecarpine and several substituted derivatives out of tryptamines and anthranilic acids or isatoic anhydrides, respectively, can be synthesized without tedious chromatographic purification. This provides simple and fast access to larger amounts of compounds with this privileged structure in medicinal chemistry.

Quinazolinones are among the so-called privileged molecules for drug discovery. Natural and synthetic quinazolinones have been described to possess diverse biological activities including anticancer, antiinflammatory, antimalarial, antiviral, antioxidant, CNS depressant and several other activities.[1]



1a $R_1 = R_2 = R_3 = R_4 = H$ (rutaecarpine)
1b $R_1 = R_2 = R_3 = H$, $R_4 = OCH_3$ (hortiacine)
1c $R_1 = H$, $R_2 = R_3 = OCH_2O$, $R_4 = H$ (euxylophoricine C)
1d $R_1 = H$, $R_2 = R_3 = R_4 = OCH_3$ (euxylophoricine D)
1e $R_1 = OH$, $R_2 = R_3 = R_4 = H$ (1-hydroxyrutaecaprine)
1f $R_1 = H$, $R_2 = OCH_3$, $R_3 = R_4 = H$ (2-methoxyrutaecaprine)
1g $R_1 = R_2 = OH$, $R_3 = R_4 = H$ (1,2-dihydroxyrutaecaprine)
1h $R_1 = OCH_3$, $R_2 = R_3 = R_4 = H$ (1-methoxyrutaecaprine)
1i $R_1 = R_2 = H$, $R_3 = OH$, $R_4 = H$ (3-hydroxyrutaecaprine)
1j $R_1 = H$, $R_2 = R_3 = OCH_3$, $R_4 = H$ (euxylophoricine A)

Figure **1**. Structures of rutaecarpine and its naturally occurring derivatives

Rutaecarpine (**1a**, Figure **1**) is a natural quinazolino carboline-type alkaloid first isolated in 1915 from *Evodia rutaecarpa*[2] which is used in Traditional Chinese Medicine as a herbal remedy for the treatment of inflammation-related disorders.[3,4] Later, it was also separated from other plant families such as *Horita, Zanthoxylum, Euxylophorea,* and several others. A couple of natural derivatives of rutaecarpine (**1b**-**1j**) bearing hydroxy and methoxy groups at ring A or E also have also been isolated from various plants.[1a, 3, 5]

Accumulating research has proven useful biological properties of rutaecarpine **1a** and its natural and synthetic analogs, such as anti-platelet aggregation,[6] vasorelaxing,[7] antiobesity,[8] cytotoxity,[9] and cyclooxygenase-2 inhibitory activitiy.[10]

Its multiple biological activities intrigued many efforts on the syntheses of **1a** and its analogs, which are – despite the simplicity of the pentacyclic structure - in most cases far from being effortless.[11] Briefly, these syntheses can be divided into four distinct types: (1) using derivatives of

* Corresponding author: Michael Decker, Tel.: 0049-931-31-89676,
E-Mail: michael.decker@uni-wuerzburg.de