Check for updates

EurJOC
European Journal of Organic Chemistry

A Journal of ChemPubSoc Europe

Accepted Article

Title: A Direct Synthesis of 2-(ω-Carboxyalkyl)isoflavones from ortho-Hydroxylated Deoxybenzoins

Authors: Galyna P. Mrug, Bogdan A. Demydchyk, Svitlana P. Bondarenko, Vitaliy M. Sviripa, Przemyslaw Wyrebek, James L. Mohler, Michael V. Fiandalo, Chunming Liu, Mykhaylo Frasinyuk, and David S. Watt

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201801171

Link to VoR: http://dx.doi.org/10.1002/ejoc.201801171

Supported by ACES Asian Chemical Editorial Society

WILEY-VCH

10.1002/ejoc.201801171

COMMUNICATION

WILEY-VCH

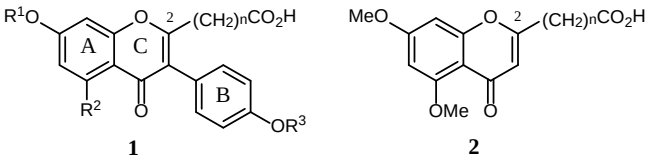
A Direct Synthesis of 2-(ω-Carboxyalkyl)isoflavones from *ortho*-Hydroxylated Deoxybenzoins

Galyna P. Mrug,[a] Bogdan A. Demydchyk,[a] Svitlana P. Bondarenko,[b] Vitaliy M. Sviripa,[c],[d] Przemyslaw Wyrebek,[c], [f] James L. Mohler,[e] Michael V. Fiandalo,[e] Chunming Liu,[f], [g] Mykhaylo S. Frasinyuk,[a],[c],[f]* and David S. Watt [c], [f], [g]*

Abstract: As part of a program focused on the development of new antineoplastic agents based on scaffolds found in natural products, we explored the isoflavone family as potential enzyme inhibitors. We required biotin-modified isoflavones to identify potential biological targets, and we selected the C-2 position in isoflavones as an attachment site for an alkyl group bearing a terminal carboxylic acid to which we could attach a biotin derivative. The base-catalyzed condensation of 2,4-dihydroxy-substituted deoxybenzoins with cyclic anhydrides mediated by a combination of triethylamine and 1,8-diazabicyclo[5.4.0]undec-7-ene led to an efficient synthesis of the desired 2-(ω-carboxyalkyl)isoflavones with functional groups at C-5, 6 and 7 and with various substituents in the C-3 phenyl group.

Introduction

Isoflavones and chromones possess a dazzling spectrum of biological activities in which they alter the catalytic function of numerous enzymatic reactions. As part of our interest in developing natural product-based, antineoplastic agents that target specific enzymes, we required methodology to synthesize isoflavones **1** related to naturally occurring chromones[1] **2** (n=2 or 3) bearing ω-(carboxy)alkyl groups at the C-2 position **(Fig. 1**). We planned to modify these ω-(carboxy)alkyl derivatives with an appropriate biotinylated linker to facilitate enzyme target identification in pull-down assays. In screening studies, we identified the C-2 position as a potential site for modification based on modest changes in cancer cell proliferation seen in chromones bearing either a hydrogen or a methyl group at C-2. In summary, we required a convenient synthetic procedure that would furnish isoflavones **1** with ω-(carboxy)alkyl groups at the C-2 position.



1 **2**

Figure 1. Isoflavone **1** and chromone **2** structures with C-2 ω-(carboxy)alkyl groups.

Isoflavones and chromones with similar modifications at the C-2 position previously found application as haptens for the attachment to carrier proteins and the subsequent development of immunoassay techniques for the epidemiological screening of plant phytoestrogens. [2] In addition to their utility in screening programs, several ω-(carboxy)alkyl chromones occur in nature. Oxalicumone C[3] appears in the marine-derived fungus *Penicillium oxalicum* and bears a C-2 ω-(carbomethoxy)ethyl group in a chromone skeleton. Related chromones **2** also appear in *Penicillium citreonigrum.* [1] Other recent reports also identified isoflavones bearing ω-(carboxy)alkyl groups that possessed promising antiproliferative[4] and anticoccidian activities. [5] These findings, in addition to our own needs, warranted the development of an efficient protocol for the synthesis of isoflavone **1** possessing an ω-(carboxy)alkyl group at the C-2 position in which the number of methylene subunits in the alkyl linker (*i.e.*, the value of n) could be varied over a substantial range.

Previously reported methods for the synthesis of isoflavones **1** with C-2 ω-(carboxy)alkyl groups typically required multistep procedures. For example, these procedures involved the acylation of *ortho*-hydroxybenzoins with oxalyl chloride and related bis(acyl) chlorides. The acylation, for example, of *ortho*-hydroxy group of O-protected deoxybenzoins followed by a Baker-Venkataraman rearrangement[6] led to formation of isoflavones. Subsequent deprotection afforded the target genistein-related acids **1** (R^1= R^3 = H, R^2 = OH).[6] Further

[a] G. P. Mrug, B. A. Demydchyk, M.S. Frasinyuk*
Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Science of Ukraine
Kyiv 02094, Ukraine
E-mail: mylhaylo.frasinyuk@ukr.net
[b] S. P. Bondarenko
National University of Food Technologies
Kyiv 01601, Ukraine
[c] V. M. Sviripa, P. Wyrebek, M.S. Frasinyuk, D. S. Watt*
Center for Pharmaceutical Research and Innovation
College of Pharmacy, University of Kentucky
Lexington, KY 40536-0509, USA
E-mail: dwatt@uky.edu
[d] V. M. Sviripa
Department of Pharmaceutical Sciences
College of Pharmacy, University of Kentucky
Lexington, KY 40536-0509, USA
[e] J.L. Mohler, M. V. Fiandalo
Department of Urology
Roswell Park Cancer Institute
Buffalo, NY 14263
[f] P. Wyrebek, M.S. Frasinyuk, C. Liu, D. S. Watt
Department of Molecular and Cellular Biochemistry
College of Medicine, University of Kentucky
Lexington, KY 40536-0509, USA
[g] C. Liu, D. S. Watt
Lucille Parker Markey Cancer Center,
University of Kentucky
Lexington, KY 40536-0509, USA

Supporting information for this article is given via a link at the end of the document.

Accepted Manuscript

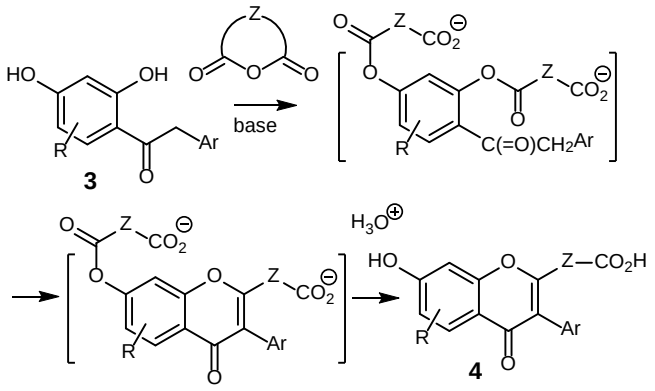
This article is protected by copyright. All rights reserved.

improvements in this procedure included ring-closure reactions using acylation of 2-hydroxydeoxybenzoins with aliphatic ω-alkoxycarbonyl acid chlorides (*i.e.*, $RO_2C(CH_2)_nCOCl$) in the presence of tetra-n-butylammonium bromide[7] or lithium bis(trimethylsilyl)amide[2a] followed by saponification. Finally, the alkylation of an isoflavone bearing a C-2 bromomethyl group with ethyl cyanoacetate led to a dimeric bis-isoflavonoid bearing a carboxylic acid in the bridging propyl group between the two isoflavone subunits. [8]

Results and Discussion

Many naturally occurring isoflavones with alleged health benefits contain hydroxy, methoxy or methylenedioxy groups. Unlike prior efforts that required the selective protection/deprotection of phenolic groups other than the participating *ortho*-hydroxyl group, we describe an efficient synthesis of isoflavones containing C-2 ω-(carboxy)alkyl groups from hydroxylated deoxybenzoins **3** and other readily available materials and without resorting to the use of any protection or activation steps.

In the 1920's, the first reports appeared involving the cyclization of 2'-hydroxydeoxybenzoins with carboxylic acid anhydrides in presence of base,[9] now known as Kostanetski-Robinson reaction and the related Baker-Venkataraman rearrangement. In recent years, this method found wide application in the preparation of 2-alkyl, [10] 2-fluoroalkyl, [10b, 11] 2-arylisoflavones, [12] and their C-2 unsubstituted counterparts when using mixed carboxylic acid-formic anhydrides. [13] However, there is no precedent for using this pathway for the synthesis of isoflavones bearing functional groups at position C-2 of the chromone subunit.

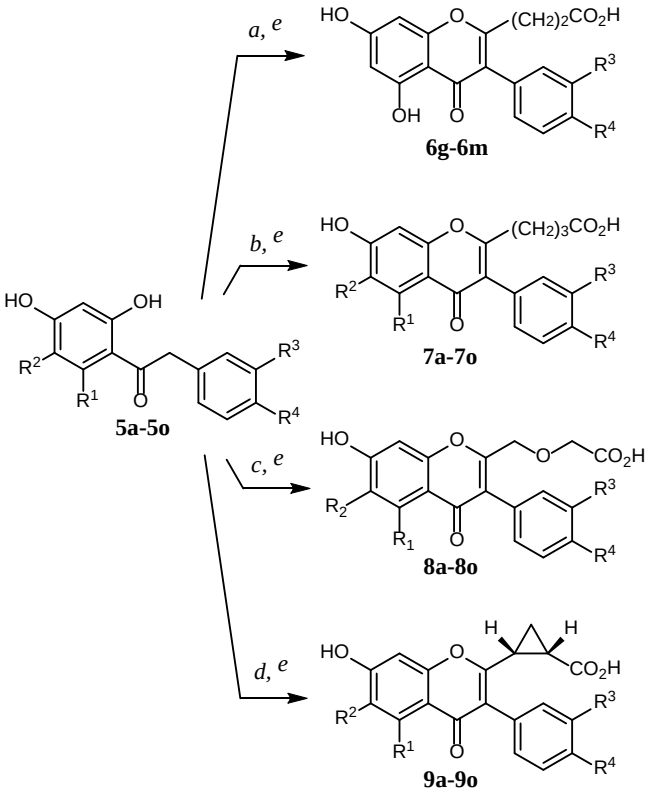


Scheme 1. Synthesis of ω-(carboxy)alkyl isoflavones **4** from *ortho*-hydroxylated deoxybenzoins **3.**

Acylation of polyhydroxylated deoxybenzoins **3** with cyclic dicarboxylic anhydrides in presence of an organic base (*e.g.*, triethylamine; pK_b 10.7) led to polyacylation of the free phenolic groups and cyclization (Scheme 1). After quenching the reaction with aqueous acid, we obtained principally unreacted **3** and only traces of the desired isoflavone **4**.

However, the addition of a more basic reagent than triethylamine, namely 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (pK_a 12), promoted the desired acylation and condensation and led, after acidification, to the efficient synthesis of isoflavone **4**.

Applying these conditions to condensations using glutaric anhydride, diglycolic anhydride, or 1,2-*cis*-cyclopropane dicarboxylic anhydride and using 2,4-dihydroxyacetophenones **5a-5f**[14] or 2,4,6-trihydroxyacetophenones **5g-5m**[6, 15] led to the desired isoflavones **6**, **7**, **8** and **9**, respectively, in 22-96% yields (Scheme 2). The use of succinic anhydride under similar conditions gave dark-colored mixtures and was limited to condensations with 2,4,6-trihydroxyacetophenones **5g–5m**.



a $R^1 = R^2 = R^3 = H$, R^4= OH;
b $R^1 = R^2 = R^3 = H$, R^4= OMe;
c $R^1 = R^2 = R^3 = H$, R^4= F;
d $R^1 = R^2 = R^3 = H$, R^4= OCF_3;
e $R^1 = R^2 = H$, $R_3 = R^4$ = OMe;
f $R^1 = R^2 = H$, $R^3R^4 = OCH_2O$;
g R^1 = OH, $R^2 = R^3 = H$, R^4 =OH;
h R^1 = OH, $R^2 = R^3 = H$, R^4 =OMe;
i R^1 = OH, $R^2 = R^3 = H$, R^4 = F;
j R^1 = OH, $R^2 = R^3 = H$, R^4 = Cl;
k R^1 = OH, $R^2 = R^3 = H$, R^4 = OCF_3
l R^1 = OH, $R^2 = H$, $R^3 = R^4$ = OMe;
m R^1= OH, $R^2 = H$, $R^3R^4 = OCH_2O$;
n $R^1 = R^3 = H$, $R^2 = R^4$ = OMe,
o $R^1 = H$, $R^2 = R^3 = R^4$ = OMe

Scheme 2. Synthesis of isoflavones bearing ω-(carboxy)alkyl group. Reagents and conditions: *a,* succinic anhydride, Et_3N, DBU, dioxane, 100°C, 6-8 h; *b,* glutaric anhydride, Et_3N, DBU, dioxane, 100°C, 6-8 h; *c,* diglicolic anhydride, Et_3N, DBU, dioxane, 100°C, 6-8 h; *d,* 1,2-cyclpropanedicarboxylic acid anhydride, Et_3N, DBU, dioxane, 100°C, 6-8 h; *e,* H_2SO_4, H_2O, 80°C, 10-20 min.

The efficient formation of isoflavones **6-9** under these conditions was dependent on the presence of electron-donating substituents in the deoxybenzoin substrates **5**. Despite this limitation, the procedure reported here provided access to not

Accepted Manuscript

This article is protected by copyright. All rights reserved.

only C-2 ω-(carboxy)alkyl analogs of unnatural isoflavones but also analogs of natural products. For example, the use of 2,4-dihydroxy-5,5'-dimethoxydeoxybenzoin **5n**[16] and 2,4-dihydroxy-4',5,5'-trmethoxydeoxybenzoin **5o**[17] furnished derivatives of naturally occurring isoflavones afromosin (7-hydroxy-4',6-dimethoxyisoflavone) and cladrastin (7-hydroxy-3',4',6-trimethoxyisoflavone). We also extended this approach to the synthesis of analogs of irilone (*i.e.*, 7-(4-hydroxyphenyl)-8*H*-[1,3]dioxolo[*4,5-g*]chromen-8-one). To acquire these analogs, we first synthesized the appropriate deoxybenzoins **5p-5r** with benzo[*d*][1,3]dioxole rings using a standard Hoesch procedure catalyzed by zinc chloride.

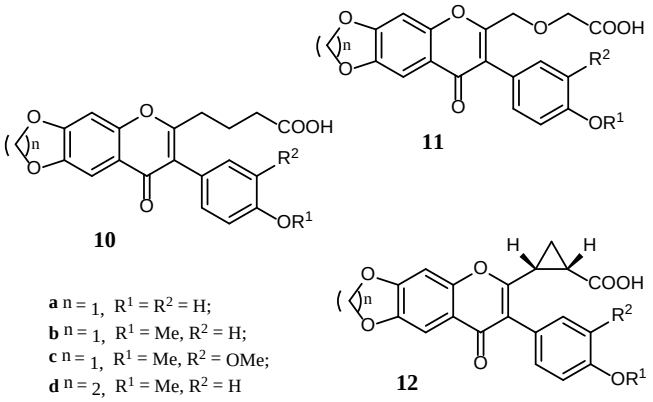


Figure 2. Structure of synthesized irilone analogs **10-12** with C-2 ω-(carboxy)alkyl groups.

We also synthesized the corresponding ring-expanded 2,3-dihydrobenzo[*b*][1,4]dioxins using a condensation of 2,3-dihydrobenzo[*b*][1,4]dioxin-6-ol with 4-methoxyphenylacetic acid in boron trifluoride etherate[18] to afford the appropriate deoxybenzoin **5s**. Condensation of these deoxybenzoins **5p-5s** with cyclic anhydrides led to the formation of the desired irilone analogs **10**, **11** and **12** bearing C-2 ω-(carboxy)alkyl groups (**Fig. 2**).

Conclusions

In summary, using a 1:(n+1):(n+2):0.1 ratio of deoxybenzoin:cyclic anhydride:tertiary amine:DBU where n is the number of phenolic hydroxyl group in starting deoxybenzoin furnished a procedure that did not require activation, protection and deprotection steps and led to an array of ω-(carboxy)alkyl-substituted isoflavones. Application of this technology to the construction of D-(+)-biotin derivatives of these ω-(carboxy)alkyl-substituted isoflavones for studies focused on biological targets will be reported in due course.

Experimental Section

Supplementary data for compounds and copies of NMR spectra are given in supporting information.

General procedures for the synthesis of deoxybenzoins 5a-5e and 5n-5o. A solution of 0.11 mol resorcinol or 4-methoxyresorcinol, 0.1 mol of the appropriate arylacetonitrile in 50 mL of boron trifluoride etherate was saturated with anhydrous HCl gas over a 6h period at room temperature. The mixture was carefully poured into 500 mL of water at 80^{0}C. The resulting mixture was heated to reflux for 2h, and cooled to room temperature. The resulting solid was collected by fitltration and recrystallized from MeOH/H_2O.

General procedures for the synthesis of deoxybenzoines 5f-5m and 5p-5r. A vigorously stirred solution of 0.11 mol of resorcinol, either phloroglucinol, or sesamol, and 0.1 mol of the appropriate arylacetonitrile in 100 mL of anhydrous ether was saturated with HCl gas for 1h at 0 ^{0}C. A suspension of 0.1 mol (in case of compounds **5f**, **5p-5r**) or 0.001 mol (in case compounds **5g-5m**) of freshly fused zinc chloride in 100 mL of anhydrous ether was added, and the mixture was saturated with anhydrous HCl gas for an additional 6-8h at room temperature. The ethereal layer was decanted, and the residue washed with 100 mL of ether. To the residue was added 300 mL of 0.1M H_2SO_4 solution, and the mixture was heated at reflux for 2h. The mixture was cooled, and the resulting solid was collected by filtration and recrystallized from methanol or water-methanol mixtures.

1-(7-Hydroxy-2,3-dihydro-1,4-benzodioxin-6-yl)-2-(4-methoxyphenyl)ethanone (5s). A mixture of 3.80 g (25 mmol) of 2,3-dihydrobenzo[*b*][1,4]dioxin-6-ol, 4.15 g (25 mmol) of 4-methoxyphenylacetic acid in 50 mL of $BF_3{\cdot}Et_2O$ under an argon atmosphere was heated at 90^{0}C for 6 h. The mixture was cooled and poured into 200 mL of a ice-cooled 10% NaOAc solution. The resulting solid was collected by filtration, and after drying, the solid was purified by column chromatography on silica gel using 100:1 CH_2Cl_2-MeOH as eluent.

General procedure for the synthesis of isoflavones with C-2 ω-(carboxy)alkyl groups. To a solution of 2 mmol of deoxybenzoin **5** in 5 mL of 1,4-dioxane was added 6 mmol (or 8 mmol in case of 2,4,6-trihydroxydeoxybenzoins) of a dicarboxylic acid anhydride and 1.12 mL (8 mmol) (or 1.4 mL, 10 mmol in case of 2,4,6-trihydroxydeoxybenzoins) of Et_3N. The mixture was heated to reflux for 0.5 h, and 0.3 mL of DBU (2 mmol) in 1,4-dioxane was added. The mixture was refluxed for an additional 6-16h. After cooling, the mixture was diluted with 30 mL of aqueous 1N H_2SO_4 solution, heated at 80^{o}C for 2h, cooled and diluted with 50 mL of water. The resulting solid was collected by filtration and recrystallized from acetonitrile. Some isoflavones required additional purification by column chromatography on silica gel using a mixture of 100:1 CH_2Cl_2-MeOH as eluent.

Acknowledgements

CL and DSW were supported by CA172379 from the NIH. DSW was also supported by the Office of the Dean of the College of Medicine, by the Center for Pharmaceutical Research and Innovation in the College of Pharmacy, and by NIH Grant Number P30 GM110787 from the National Institute of General Medical Sciences to L. Hersh, PI. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH or the NIGMS. DSW was also supported by a subcontract under CA205108 to J. Mohler, PI and by the Office of the Assistant Secretary of Defense for Health Affairs, through the Prostate Cancer Research Program under Award No. W81XWH-16-1-0635. Opinions, interpretations,

Accepted Manuscript

This article is protected by copyright. All rights reserved.

conclusions and recommendations are those of the author and are not necessarily endorsed by the Department of Defense.

Disclosure

CL and DSW have partial ownership of a new-start company, Epionc, Inc., that seeks to develop these compounds as commercial agents. CL and DSW disclosed this information and complied with requirements to mitigate any potential conflicts of interest in accord with University of Kentucky policy.

Keywords: Baker-Venkataraman rearrangement • cyclic anhydride • isoflavone • natural compound • ring-closure reaction

[1] W.-H. Yuan, Z.-W. Wei, P. Dai, H. Wu, Y.-X. Zhao, M.-M. Zhang, N. Jiang, W.-F. Zheng, *Chem. Biodiv.* **2014**, *11*, 1078-1087.

[2] a) C. Le Houérou, C. Bennetau-Pelissero, V. Lamothe, F. Le Menn, P. Babin, B. Bennetau, *Tetrahedron* **2000**, *56*, 295-301; b) P. Boltovets, S. Shinkaruk, C. Bennetau-Pelissero, B. Bennetau, B. Snopok, *Talanta* **2011**, *84*, 867-873.

[3] Y.-L. Sun, J. Bao, K.-S. Liu, X.-Y. Zhang, F. He, Y.-F. Wang, X.-H. Nong, S.-H. Qi, *Planta Med.* **2013**, *79*, 1474-1479.

[4] a) G.-H. Yan, X.-F. Li, B.-C. Ge, X.-D. Shi, Y.-F. Chen, X.-M. Yang, J.-P. Xu, S.-W. Liu, P.-L. Zhao, Z.-Z. Zhou, C.-Q. Zhou, W.-H. Chen, *Eur. J. Med. Chem.* **2015**, *90*, 251-257; b) F. Kohen, B. Gayer, T. Kulik, V. Frydman, N. Nevo, S. Katzburg, R. Limor, O. Sharon, N. Stern, D. Somjen, *J. Med. Chem.* **2007**, *50*, 6405-6410.

[5] G. Gargala, A. Baishanbo, L. Favennec, A. François, J. J. Ballet, J.-F. Rossignol, *Antimicrob. Agents Chemother.* **2005**, *49*, 4628-4634.

[6] A. Pelter, R. S. Ward, J. L. Whalley, *Synthesis* **1998**, 1793-1802.

[7] N. Al-Maharik, I. Mutikainen, K. Wahala, *Synthesis* **2000**, 411-416.

[8] N. I. Al-Maharik, S. A. A. Kaltia, I. Mutikainen, K. Wähälä, *J. Org. Chem.* **2000**, *65*, 2305-2308.

[9] a) W. Baker, R. Robinson, *J. Chem. Soc., Trans.* **1925**, *127*, 1981-1986; b) W. Baker, *J. Chem. Soc., Trans.* **1925**, *127*, 2349-2358; c) U. S. Cheema, K. Venkataraman, *J. Chem. Soc.* **1932**, 918-925; d) W. Baker, *J. Chem. Soc.* **1933**, 1381-1389.

[10] a) B. W. Dymock, X. Barril, P. A. Brough, J. E. Cansfield, A. Massey, E. McDonald, R. E. Hubbard, A. Surgenor, S. D. Roughley, P. Webb, P. Workman, L. Wright, M. J. Drysdale, *J. Med. Chem.* **2005**, *48*, 4212-4215; b) A. Matin, N. Gavande, M. S. Kim, N. X. Yang, N. K. Salam, J. R. Hanrahan, R. H. Roubin, D. E. Hibbs, *J. Med. Chem.* **2009**, *52*, 6835 - 6850; c) A. Lévai, A. M. S. Silva, J. A. S. Cavaleiro, J. Elguero, I. Alkorta, J. Jeko, *Aust. J. Chem.* **2007**, *60*, 905-914; d) K.-M. J. Cheung, T. P. Matthews, K. James, M. G. Rowlands, K. J. Boxall, S. Y. Sharp, A. Maloney, S. M. Roe, C. Prodromou, L. H. Pearl, G. W. Aherne, E. McDonald, P. Workman, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3338-3343.

[11] a) M. S. Frasinyuk, S. P. Bondarenko, N. V. Gorbulenko, A. V. Turov, V. P. Khilya, *J. Heterocycl. Chem.* **2014**, *51*, 768-774; b) S. P. Bondarenko, A. V. Levenets, M. S. Frasinyuk, V. P. Khilya, *Chem. Nat. Compd.* **2003**, *39*, 271-275; c) M. S. Frasinyuk, S. P. Bondarenko, V. P. Khilya, *Chem. Nat. Compd.* **2006**, *42*, 142-147; d) X. Sun, J. Qiu, J. Wasley, WO2011099978, **2011.**

[12] A. Lévai, T. Patonay, A. Székely, E. B. Vass, W. Adam, J. Jekö, *J. Heterocycl. Chem.* **2000**, *37*, 1065-1069.

[13] a) D. F. Liu, C. C. Cheng, *J. Heterocycl. Chem.* **1991**, *28*, 1641-1642; b) B. Burdet, A. Ruettimann, WO2004009576, **2004**; c) V. G. Pivovarenko, V. P. Khilya, *Chem. Heterocycl. Compd.* **1992**, *28*, 497-502.

[14] a) L.-T. Ng, H.-H. Ko, T.-M. Lu, *Bioorg. Med. Chem.* **2009**, *17*, 4360-4366; b) P. Valenti, F. Belluti, A. Rampa, A. Bisi, *Synth. Commun.* **1999**, *29*, 3895-3899; c) P. F. Schuda, W. A. Price, *J. Org. Chem.* **1987**, *52*, 1972-1979.

[15] a) M. S. Frasinyuk, G. P. Mrug, O. D. Fedoryak, S. P. Bondarenko, *Chem. Nat. Compd.* **2012**, *48*, 570-573; b) J. M. Hastings, M. K. Hadden, B. S. J. Blagg, *J. Org. Chem.* **2008**, *73*, 369-373.

[16] H. Goto, Y. Terao, S. Akai, *Chem. Pharm. Bull.* **2009**, *57*, 346-360.

[17] M. Shamma, L. D. Stiver, *Tetrahedron* **1969**, *25*, 3887-3893.

[18] K. Wahala, T. A. Hase, *J. Chem. Soc., Perkin Trans. 1* **1991**, 3005-3008.

Accepted Manuscript

This article is protected by copyright. All rights reserved.

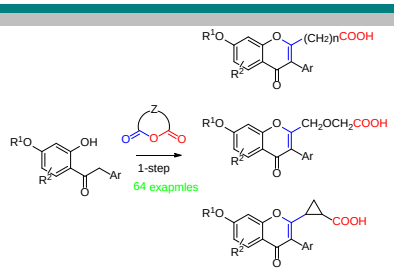
10.1002/ejoc.201801171

WILEY-VCH

Entry for the Table of Contents

COMMUNICATION

The base-catalyzed chromone ring-closure reaction was developed for one-step synthesis of various 2-(ω-carboxyalkyl)isoflavones bearing electron-donating and electron-withdrawing groups.



Biological Scaffolds

Galyna P. Mrug, Bogdan A. Demydchyk, Svitlana P. Bondarenko, Vitaliy M. Sviripa, Przemyslaw Wyrebek, James L. Mohler, Michael V. Fiandalo, Chunming Liu, Mykhaylo S. Frasinyuk, and David S. Watt**

Page No. – Page No.

A Direct Synthesis of 2-(ω-Carboxyalkyl)isoflavones from *ortho*-Hydroxylated Deoxybenzoins

Accepted Manuscript

This article is protected by copyright. All rights reserved.