Accepted Manuscript

A green chemical synthesis of coumarin-3-carboxylic and cinnamic acids using crop-derived products and waste waters as solvents

Serena Fiorito, Vito Alessandro Taddeo, Salvatore Genovese, Francesco Epifano

PII: S0040-4039(16)31181-9
DOI: http://dx.doi.org/10.1016/j.tetlet.2016.09.023
Reference: TETL 48093

To appear in: *Tetrahedron Letters*

Received Date: 30 July 2016
Revised Date: 6 September 2016
Accepted Date: 7 September 2016

Please cite this article as: Fiorito, S., Taddeo, V.A., Genovese, S., Epifano, F., A green chemical synthesis of coumarin-3-carboxylic and cinnamic acids using crop-derived products and waste waters as solvents, *Tetrahedron Letters* (2016), doi: http://dx.doi.org/10.1016/j.tetlet.2016.09.023

A green chemical synthesis of coumarin-3-carboxylic and cinnamic acids using crop-derived products and waste waters as solvents

Serena Fiorito, Vito Alessandro Taddeo, Salvatore Genovese*, Francesco Epifano

[1]*Department of Pharmacy, University "G. d'Annunzio" of Chieti-Pescara, Via dei Vestini 31, 66100 Chieti Scalo (CH), Italy, Email: s.genovese@unich.it, Phone: +3908713554654, Fax: +3908713554912*

Abstract

Crop-derived products, like juices obtained from edible fruits and vegetables, and waste waters deriving from agricultural and industrial processing have been recently exploited to efficiently promote several "classic" and innovative synthetic organic reactions. Such a green chemical approach prevented the use of toxic, polluting, and hazardous materials and in the mean time allowed to increase the commercial values of crop products and industrial byproducts. Coumarin-3-carboxylic and cinnamic acids represent classes of naturally occurring and semi-synthetic compounds with interesting and promising pharmacological activities. In this paper a new and improved methodology for the Knoevenagel condensation yielding the title compounds using juices from edible fruits and vegetables (lemon, grapefruit, carrot, pomegranate, kiwi, vinegar, tomato), liqueurs (limoncello) and waste waters (buttermilk and residues of olive processing) as solvents is described. Coumarin-3-carboxylic and cinnamic acids have been synthesized in excellent yields by ultrasound irradiation from differently substituted 2-hydroxybenzaldehydes, 2-hydroxyacetophenones, and benzaldehydes, and Meldrum's acid as starting substrates. The findings described herein enforce the concept of the usefulness of products and byproducts derived from agriculture and food industry to accomplish green chemical processes.

Keywords: Cinnamic acids; Coumarin-3-carboxylic acids; Crop products; Knoevenagel condensation; Waste water

1. Introduction

In recent times, organic synthetic methodologies are mostly devoted to the development of greener and more eco-friendly protocols involving the use of alternative solvents to replace toxic, hazardous, polluting, and expensive solvents and catalysts. These latter are in the majority of cases represented by heavy metals, that are notoriously very difficult to be recycled and eliminated. Currently several organic reactions have been performed in water, being this latter readily available, inexpensive, and safe.[1] In parallel the applications of fruit and vegetable juices, and waste waters deriving from agricultural and industrial processing recently attracted the attention of several research groups.[2-4] Juices from fruits and vegetables and waste waters in fact can efficiently behave as biocatalysts and solvents, do have environmentally beneficial characters, are non hazardous, non toxic, non polluting, easy available, and generally cheap. Notable examples of organic reactions accomplished using such materials as promoters include the Knoevenagel condensation,[5] the Biginelli reaction,[6] the synthesis of Schiff bases[7]and triazoles,[8] preparation of amides,[9] reduction of carbonyls, hydrolysis of esters and amides,[10] and several other processes, most of which have been recently extensively reviewed.[11] Coumarin-3-carboxylic acids (synonym 3-carboxycoumarins) represent a wide group of heterocyclic compounds with an extensive array of applications. Recent literature reports suggest that coumarin-3-carboxylic acids exert valuable effects as anti-cancer,[12] anti-diabetic,[13] and neuroprotectve agents.[14] They have been also employed as key intermediates for the synthesis of several pharmacologically active compounds like β-lactams,[15] isoureas,[16] and tetrahydropyridones.[17] 3-Carboxycoumarin esters and amides have been shown to have anti-cancer properties consisting in the inhibition of tumor cell growth and invasion *in vitro* and *in vivo*.[18] Finally 3-carboxycoumarins have been frequently employed as fluorescent probes[19] and triplet oxygen sensitizers.[20] An extensive review about the synthetic methodologies to provide coumarin-3-carboxylic acids has been recently reported.[21, 22] Cinnamic acids, like coumaric, ferulic, and caffeic ones, are secondary metabolites ubiquitous in the plant kingdom. Naturally occurring and semisynthetic derivatives exert beneficial effects for human health acting as anti-microbial,[23] anti-cancer,[24] neuroprotective,[25] anti-obesity,[26] anti-oxidant,[27] and anti-inflammatory agents.[28] In the context of a green chemical approach, only two methods for the synthesis of 3-carboxycoumarins and /or cinnamic acids have been described so far. Maggi and coworkers in 2001 described the uncatalysed Knoevenagel condensation of salicylaldehydes and Meldrum's acid[29]. In 2013 Bandgar and Chavan reported the development of this process using the same substrates and an aqueous extract of *Acacia concinna* pods.[30] These two processes however have some drawbacks such as high temperatures, yields strictly depending on the structures of starting materials, and difficulties in availability of the vegetable material. Thus the synthesis of coumarin-3-carboxylic and cinnamic acids can be still considered a challenge to perform further research and development of greener synthetic methods. As a continuation of our investigations devoted to draw and set up easy to handle protocols for the synthesis of starting products and/or compounds of biological interest employing means from the natural kingdom, we wish to report herein that coumarin-3-carboxylic and cinnamic acids can be effectively obtained by ultrasound-assisted Knoevenagel condensation of Meldrum's acid and 2-hydroxybenzaldehydes or 2-hydroxyacetophenones and benzaldehydes respectively using natural juices (lemon, grapefruit, carrot, pomegranate, kiwi, vinegar, tomato), the liqueur "limoncello", or waste waters deriving from agricultural and industrial practices (processing of olives, milk, and cheese) (Figure 1).

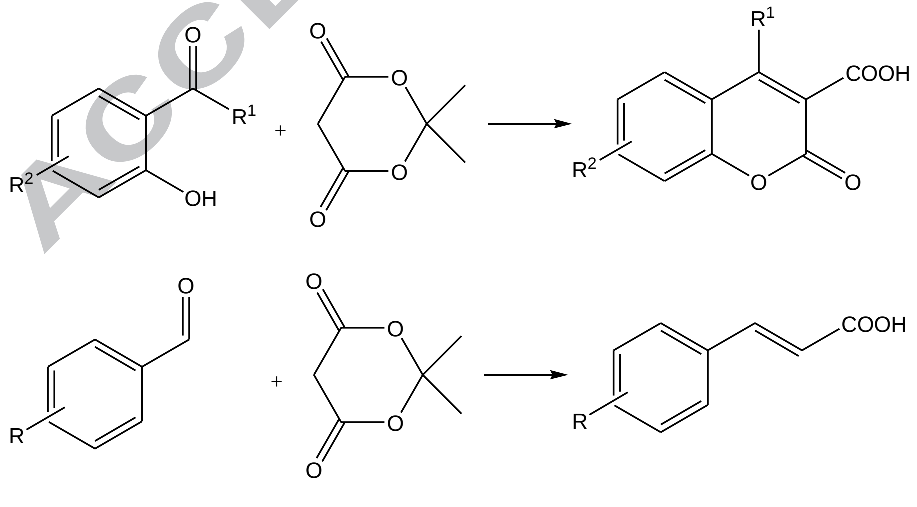
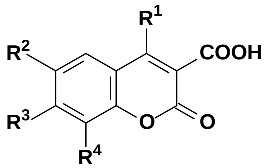


Figure 1. Knoevenagel condensation routes to coumarin-3-carboxylic (R^1 = H, CH_3) and cinnamic acids

2. Results and Discussion

Preliminary tests of the Knoevenagel condensation have been accomplished using salicylaldehyde and Meldrum's acid as substrates, both suspended in the aqueous medium represented by lemon, grapefruit, carrot, pomegranate, kiwi, vinegar, and tomato juices, limoncello (an hydroalcoholic solution deriving from overnight maceration of lemon zest), or olive and buttermilk waste waters. The processes were carried out for 24 h under magnetic stirring at room temperature. Employing these experimental conditions, monitoring the reaction by thin layer chromatography (TLC) allowed to assess that no or poor (< 10 %) conversions of the starting materials into the desired coumarin-3-carboxylic acid was achieved in any of the listed media. Increasing temperature up to 60 °C, resulted in a rapid darkening of the solution and in many instances large decomposition of the starting products, even when shorter reaction times were applied. Ultrasounds have been frequently recently employed to promote green chemical processes. We then decided to screen the efficiency of ultrasound irradiation for the synthesis of coumarin-3-carboxylic acids using the same stoichiometric ratios and volumes of solvent as above. The complete conversion of the substrates into the desired products has been observed in every case after 5 min. irradiation. Pure coumarin-3-carboxylic acid (entry 1, Table 1) has been isolated as a white solid after filtration in very good yields (93 – 99 %) without the need of further purification. A blank experiment accomplished employing pure water as the solvent under ultrasound irradiation for the same time resulted in a poor conversion (yield < 20 %) of salicylaldehyde into 3-carboxycoumarin. Having optimized the Knoevenagel condensation conditions, the same experimental protocol was applied to differently substituted 2-hydroxybenzaldehydes and 2-hydroxyacetophenones and the corresponding 3-carboxycoumarins have been synthesized in excellent yields as summarized in Table 1. Independently from their individual structure, 2-hydroxybenzaldehydes and 2-hydroxyacetophenones provided the desired compounds in yields ranging from 94% to 99%.

Table 1. Juices or waste waters promoted synthesis of coumarin-3-carboxylic acids

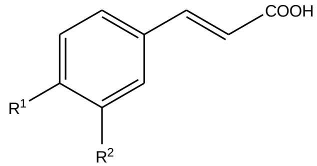
Entry	Carbonyl compound	Product	Yield (%)[a]									
			**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**L**
1	Salicylaldehyde	$R^1 = R^2 = R^3 = R^4 = H$	99	96	97	96	95	95	95	92	94	99
2	4-(Diethylamino)salicylaldehyde	$R^1 = R^2 = R^4 = H$, $R^3 = N(Et)_2$	99	99	92	93	94	96	96	97	91	96
3	4-Nitrosalicylaldehyde	$R^1 = R^2 = R^4 = H$, $R^3 = NO_2$	98	97	97	98	99	98	99	98	96	97
4	5-Bromosalicylaldehyde	$R^1 = R^3 = R^4 = H$, $R^2 = Br$	99	97	99	99	98	95	97	99	98	98
5	2,4-Dihydroxybenzaldehyde	$R^1 = R^2 = R^4 = H$, $R^3 = OH$	97	97	95	98	98	98	99	95	98	99
6	2-Hydroxy-5-nitroacetophenone	$R^1 = Me$, $R^2 = NO_2$, $R^3 = R^4 = H$	96	99	97	99	95	99	98	99	97	98
7	5-Chloro-2-hydroxyacetophenone	$R^1 = Me$, $R^2 = Cl$, $R^3 = R^4 = H$	98	97	99	99	96	98	99	96	97	98
8	2-Hydroxy-4-methoxyacetophenone	$R^1 = Me$, $R^3 = OMe$, $R^2 = R^4 = H$	96	95	98	98	98	99	98	99	96	98
9	2,5-Dihydroxyacetophenone	$R^1 = Me$, $R^2 = OH$, $R^3 = R^4 = H$	94	94	98	97	99	97	98	99	97	96
10	2,3,5-Trihydroxyacetophenone	$R^1 = Me$, $R^2 = R^4 = OH$, $R^3 = H$	95	96	99	96	99	99	96	99	98	95
11	2-Hydroxyacetophenone	$R^1 = Me$, $R^2 = R^3 = R^4 = H$	94	98	98	94	97	98	99	99	97	95

[a]Yields of pure isolated products. Structural characterization by IR, GC-MS, ^1H NMR, and ^{13}C NMR Purity degree > 97.8 % assessed by HPLC.

A = lemon juice, B = grapefruit juice, C = carrot juice, D = pomegranate juice, E = kiwi juice, F = vinegar, G = tomato juice, H = limoncello, I = olive mil waste water, L = buttermilk

Ultrasound irradiation has been subsequently applied to the synthesis of cinnamic acids using benzaldehydes and Meldrum's acid. The only difference in performing such experiments was the reaction time that has to be increased to 15 min. to observe the complete conversion of the starting material into the desired adducts (Table 2).

Table 2. Juices or waste waters promoted synthesis of cinnamic acids



Entry	Aldehyde	Product	Yield (%)[a]									
			A	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**L**
1	Benzaldehyde	$R^1 = R^2 = H$	98	91	96	92	98	92	96	98	95	94
2	Vanillin	$R^1 = OH$ $R^2 = OCH_3$	95	92	94	91	94	93	97	98	93	98
3	p-OH-Benzaldehyde	$R^1 = OH$ $R^2 = H$	97	97	94	95	96	95	92	97	98	96
4	p-F-Benzaldehyde	$R^1 = F$, $R^2 = H$	92	95	94	95	97	97	93	98	97	99
5	p-Cl-Benzaldehyde	$R^1 = Cl$, $R^2 = H$	93	95	98	95	96	95	98	99	99	95
6	p-Br-Benzaldehyde	$R^1 = Br$, $R^2 = H$	95	95	99	98	99	91	99	97	98	97
7	p-I-Benzaldehyde	$R^1 = I$, $R^2 = H$	97	94	94	99	95	94	92	95	99	97
8	3,4-Dihydroxybenzaldehyde	$R^1 = R^2 = OH$	98	99	96	99	97	98	91	98	96	97
9	p-NO_2-Benzaldehyde	$R^1 = NO_2$, $R^2 = H$	98	98	96	99	97	99	95	94	99	94
10	p-NH_2-Benzaldehyde	$R^1 = NH_2$, $R^2 = H$	99	95	97	93	98	94	97	98	99	97
11	4-(3',3'-dimethylallyloxy)-3-methoxybenzaldehyde	R^1 = 3,3-dimethylallyloxy $R^2 = OCH_3$	95	99	97	92	99	96	97	97	96	99

[a]Yields of pure isolated products. Structural characterization by IR, GC-MS, ^1H NMR, and ^{13}C NMR. Purity degree > 98.4 % assessed by HPLC.

A = lemon juice, B = grapefruit juice, C = carrot juice, D = pomegranate juice, E = kiwi juice, F = vinegar, G = tomato juice, H = limoncello, I = olive mil waste water, L = buttermilk

Pure cinnamic acids have been isolated as solids after filtration in very good yields also in this latter case (91 – 99 %). Juices and waste waters were recovered after filtration from all reaction media and re-used to accomplish other condensation processes without significant loss of efficiency in terms of yields of carboxylic acids. Thus the reaction leading to coumarin-3-carboxylic acid (entry 1, Table 3) has been carried out six additional times with lemon juice, olive mil waste water, and buttermilk providing the final product in 92 % - 99 % yields. Similarly the step leading to ferulic acid (entry 2, Table 3) has been repeated six additional times using the same media listed above providing the desired adduct in 95 % - 98 % yields.

Table 3. Examples of recyclability of juices and waste waters as promoters of Knoevenagel condensation.

Entry	Aldehyde	Product	Yield (%)					
			Lemon juice					
1	Salicylaldehyde	Coumarin-3-carboxylic acid	95	95	94	95	99	98
			Olive mil waste water					
			96	92	99	93	93	92
			Buttermilk					
			98	99	92	92	94	92
			Lemon juice					
2	Vanillin	Ferulic acid	95	95	95	96	95	97
			Olive mil waste water					
			98	96	96	96	97	95
			Buttermilk					
			98	98	97	97	98	99

It can be hypothesized that the strong capacity of fruits and vegetable juices and waste waters to promote the Knoevenagel condensation can be ascribed to the presence of organic acids (citric, tartaric, malic, oxalic, succinic, lactic, pyruvic, and several others) in all the used aqueous media. Such acids in turn may act as effective catalysts of the coupling reactions. pH measurements for juices and waste waters in fact revealed values in the range 4.2 – 5.1. Thus from a mechanistic point of view, these acids may be able to protonate the oxygen atom of the carbonyl function of benzaldehydes or acetophenones enhancing its reactivity towards the nucleophilic attack by Meldrum's acid in a way similar to that already depicted in the literature.[31]

3. Conclusions

In this manuscript we have demonstrated that non toxic, safe, non polluting, cheap, easy to obtain and handle juices and waste waters deriving from agricultural practices and industrial processes are efficient and high yielding promoters for the Knoevenagel condensation of 2-hydroxybenzaldehydes, 2-hydroxyacetophenones, and benzaldehydes with Meldrum's acid leading to 3-carboxycoumarins and cinnamic acids respectively. The main advantages of our process are the simple work-up, mild reaction conditions, short times, and excellent yields. Thus the reaction reported herein can be regarded as a valid and additional example to the already described methodologies that employ crop-derived products and byproducts as solvent and/or catalysts to promote organic reactions. The efficient use described herein of water residues of industrial processing of olives, milk, and cheese in particular represents also an example of useful waste management and recycling. Further investigation into the potentialities, applications, and general scopes of the above listed and other media of natural origin are now in progress in our laboratories and will be reported in due course.

Acknowledgements

Financial support to this research from University “G. d’Annunzio” of Chieti-Pescara (Fondi FAR 2015) is gratefully acknowledged.

References

1. Li, C.J.; Chen, L. *Chem. Soc. Rev.* **2006**, *35*, 68-82.

2. Pal, R.; Khannobis, S.; Sarkar, T. *Chem. J.* **2013**, *3*, 7-12.

3. Pramanik, T.; Pathan, A.H. *Res. J. Pharm. Biol. Chem. Sci.* **2014**, *5*, 444-449.

4. Bakht, M. A. *Bull. Env. Pharmacol. Life Sci.* **2015**, *4*, 94-100.

5. Deshmukh, M.B.; Patil, S.S.; Jadhav, S.D.; Pawar, P.B. *Synth. Commun.* **2012**, *42*, 1177-1183.

6. Patil, S.; Jadhav, S.; Deshmukh, M.B. *Arch. Appl. Sci. Res.* **2011**, *3*, 203-208.

7. Sachdeva, H.; Saroj, R.; Khaturia, S.; Dwivedi, D.; Chauhan, O.P. *Open J. Chem.* **2014**, *2014*, article ID 848543.

8. Sachdeva, H.; Saroj, R.; Khaturia, S.; Dwivedi, D. *Org. Chem. Int.* **2013**, *2013*, article ID 659107.

9. Mote, K.; Pore, S.; Rashinkar, G.; Kambale, S.; Kumbhar, A.; Salunkhe, R. *Arch. Appl. Sci. Res.* **2010**, *2*, 74-86.

10. Fonseca, A.M.; Monte, F.J.; Oliveira, M.C.F.; Mattos, M.C.M.; Cordell, G.A.; Braz-Filho, R.; Lemos, T.L.G. *J. Mol. Catal. B.: Enzyme* **2009**, *57*, 78-83.

11. Pal, R. *Open J. Org. Chem.* **2013**, *1*, 47-56.

12. Gurrapu, S.; Jonnalagadda, S.K.; Alam, M.A.; Ronayne, C.T.; Nelson, G.L.; Solano, L.N.; Lueth E.A.; Drewes, L.R.; Mereddy, V.R. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 3282-3286.

13. Ali, M.Y.; Jannat, S.; Jung, H.A.; Choi, R.J.; Roy, A.; Choi, J.S. *Asian Pac. J. Trop. Med.* **2016**, *9*, 103-204.

14.Ali, M.Y.; Jannat, S.; Jung, H.A.; Jeong, H.O.; Chung, H.Y.; Choi, J.S. *Chem. Biol. Interact.* **2016**, *25*, 93-101.

15. Bonsignore, L.; Cottiglia, F.; Elkhaili, H.; Jehl, F.; Lavagna, S.M.; Loy, G.; Manna, F.; Monteil, H.; Pompei, D.; Secci, D. *Farmaco* **1998**, *53*, 524-527.

16. Bonsignore, L.; De Logu, A.; Lavagna, S.M.; Loy, G.; Secci, D. *Eur. J. Med. Chem.* **1994**, *29*, 479-485.

17. Jonsson, D.; Erlandsson, M.; Unden, A. *Tetrahedron Lett.* **2001**, *42*, 6953-6956.

18. Kempen, I.; Hemmer, M.; Counerotte, S.; Pochet, L.; de Tullio, P.; Foidart, J.M.; Blacher, S.; Noel, A.; Frankenne, F.; Pirotte, B. *Eur. J. Med. Chem.* **2008**, *43*, 2735-2750.

19. Peroni, E.; Caminati, G.; Baglioni, P.; Nuti, F.; Chelli, M.; Papini, A.M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1731-1734.

20. Specht, D.P.; Martic, P.A.; Farid, S. *Tetrahedron* **2002**, *38*, 1203-1206.

21. Abdel-Wahab, B.F.; Mohamed, H.A.; Farhat A.A. *Org. Commun.* **2014**, *7*, 1-14.

22. Vekariya, R. H.; Patel. H.D. *Synth. Commun.* **2014**, *44*, 2756-2788.

23. Guzman, J.D. *Molecules* **2014**, *19*, 19292-19349.

24. Su, P.; Shi, Y.; Wang, J.; Shen, X.; Zhang, J. *Anticancer Agents Med Chem.* **2015**, *15*, 980-986.

25. Gunia-Krzyżak, A; Pańczyk, K; Waszkielewicz, A.M; Marona, H. *ChemMedChem.* **2015**, *10*, 1302-1325.

26. Alam M.A.; Subhan N.; Hossain H.; Hossain M.; Reza H.M.; Rahman M.M.; Ullah M.O. *Nutr. Metab.* **2012**, *13*, 27-33.

27. Sova M. *Mini Rev. Med. Chem.* **2012**, *12*, 749-767.

28. de Cássia da Silveira E.; Sá R.; Andrade L.N.; Dos Reis Barreto de Oliveira R.; de Sousa D.P. *Molecules* **2014**, *19*, 1459-1480.

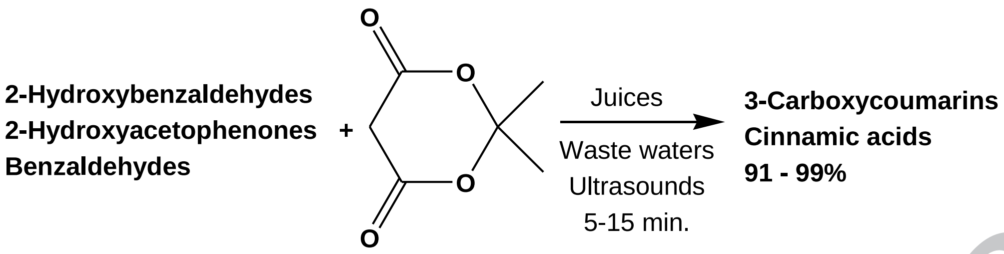
29. Maggi, R.; Bigi, F.; Carloni, S.; Mazzacani, A.; Sartori, G. *Green Chem.* **2001**, *3*, 173-174.

30. Chavan, H.V.; Bandgar, B.P., 2012. *ACS Sustainable Chem. Eng.* **2012**, *1*, 929-936.

31. Poor Heravi, M.R.; Piri, S. *J. Chem.* **2013**, *2013*, article ID 652805.

ACCEPTED MANUSCRIPT

Graphical abstract



Highlights

1) Natural juices or waste waters used for a green Knoevenagel condensation

2) 3-Carboxycoumarins and cinnamic acids have been obtained in very good yields

3) Easy to handle and powerful technology have been applied