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

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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 Letter 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.

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, this latter being 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 neuroprotective 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 uncatalyzed Knoevenagel condensation of

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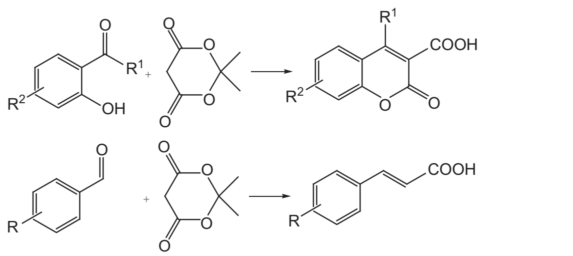


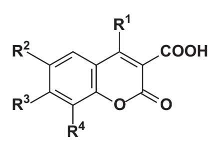
Figure 1. Knoevenagel condensation routes to coumarin-3-carboxylic (R^1 = H, CH_3) and cinnamic acids.

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) (Fig. 1).

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

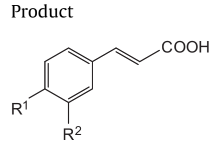
Table 1
Juices or waste waters promoted synthesis of coumarin-3-carboxylic acids

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 = 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.

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

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 = 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.

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