



HAL
open science

Efficient Piancatelli rearrangement on a large scale using the Zippertex technology under subcritical water conditions

Guillaume Arcile, Jamal Ouazzani, Jean-François Betzer

► To cite this version:

Guillaume Arcile, Jamal Ouazzani, Jean-François Betzer. Efficient Piancatelli rearrangement on a large scale using the Zippertex technology under subcritical water conditions. *Reaction Chemistry & Engineering*, 2022, 7 (7), pp.1640-1649. 10.1039/D2RE00098A . hal-03767361

HAL Id: hal-03767361

<https://hal.science/hal-03767361>

Submitted on 1 Sep 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Efficient Piantatelli rearrangement on large scale using Zippertex technology under subcritical water conditions

Guillaume Arcile, Jamal Ouazzani* and Jean-François Betzer*

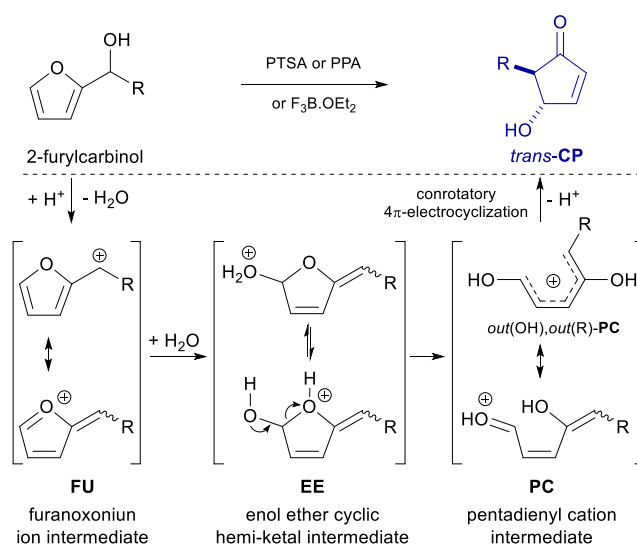
Piantatelli rearrangement of furyl carbinols is a relevant reaction to produce cyclopentenone derivatives. However, on large scale, Piantatelli rearrangement suffers several serious drawbacks such as long reaction period, high dilution conditions, moderate yields and the formation of dark brown polymeric materials. We described here the first use of Zippertex, an innovative technology reaching the subcritical water conditions (100-150 °C and 100 bars). In these conditions, this rearrangement proceeds smoothly to provide clean crude reaction mixtures without the formation of side-products and dark brown polymeric materials. Thus, a series of simple furyl carbinols directly obtained from bio-sourced furfural, and more challenging non-symmetrical furan-2,5-dicarbinol substrates, also obtained from bio-sourced raw material (HMF), were efficiently transformed into cyclopentenone derivatives in good yields. This technology could be applied successfully on challenging substrates substituted by an aliphatic group and also performed on 500 mmol scale.

Introduction

The use of renewable biomass resources for the production of fuels, chemicals, and materials offers a valuable alternative of fossil-based industry.¹ Among the biomass raw materials, lignocellulosic biomass, a cheaper and more abundant material, is one of the most promising feedstock. This sustainable lignocellulose is composed of cellulose (50%), hemicellulose (30%), and lignin (20%).² In the field of lignocellulosic biomass transformation, the production of furfural (FFR), furfuryl alcohol (FA) and hydroxymethylfurfural (HMF) are versatile sustainable substitutes of petrochemical building blocks. Hydrolysis of hemicellulose-derived pentose lead to xylose derivatives, deliver FFR after dehydration and FA under reductive conditions.^{3,4} On the other hand, a hydrolysis/isomerization/elimination sequence of cellulose lead to HMF.^{5,6} FFR and HMF compounds are in the "Top 10" bio-based building blocks listed by the US Department of Energy.⁷ In recent years, HMF production from lignocellulosic biomass showed a keen interest. Taking advantage of the primary hydroxyl, aldehyde and furan functionalities, numerous synthetic transformations have been described, supporting the versatility of HMF as a building block platform.⁸⁻¹¹

Among the synthetic transformations of these furanic starting materials that lead to high added-value chemicals, Piantatelli rearrangement^{12,13} produces cyclopentenones **CP** (Scheme 1). The proposed mechanism starts with the formation of a furanoxonium ion intermediate **FU** driven by a protonation-dehydration sequence of 2-furylcarbinol. The nucleophilic attack of a water molecule then generates an enol ether cyclic hemi-ketal intermediate **EE** which undergoes ring opening to reveal the pentadienyl cation intermediate **PC**. The **PC** intermediate adopts a conformation in which the both terminal substituents (OH and R) are located *outwards* with respect to

the delocalized charged system. This **PC** intermediate next undergoes a 4 π -conrotatory electrocyclic ring closure to provide the *trans*-4-hydroxy-5-substituted-cyclopent-2-enone **CP**.¹⁴

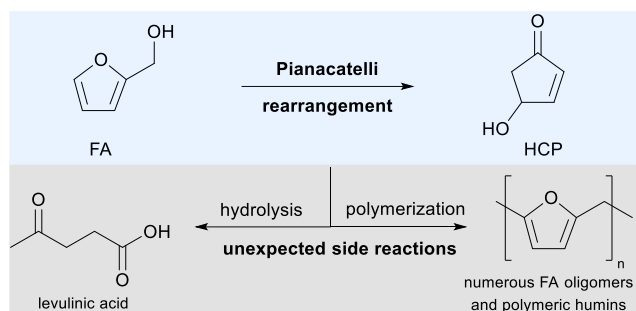


Scheme 1 Rearrangement of furfuryl alcohol in cyclopentenone described by Piantatelli in 1976. PTSA: *para*-toluenesulfonic acid. PPA: polyphosphoric acid.

This rearrangement, described for the first time in 1976, had been scarcely exploited since it requires harsh conditions with the use of stoichiometric amounts of strong Brønsted acid or Lewis acid.^{15,16} In 2007, Batey *et al.* have laid the foundations for the renewal of the Piantatelli rearrangement, highlighting an analogous reaction between furfural and aliphatic or aromatic amines, catalyzed by lanthanides or transition metal in mild conditions.¹⁷ Since this communication, this rearrangement has been the focus of increasing attention from the scientific community. A large number of chemical reactions is based on this transformation over this decade, including *oxa*-, *aza*-, *carba*-Piantatelli rearrangement, intramolecular reactions, asymmetric versions and mechanistic studies.¹⁸⁻²³ Nevertheless, the development of this transformation still faces numerous difficulties, such as the (i) harsh experimental conditions, (ii) high dilute reaction conditions (<0.005M), (iii) long reaction period and (iv) formation of cyclopentenones in

^a Institut de Chimie des Substances Naturelles (ICSN), CNRS UPR 2301
Université Paris-Saclay
1 avenue de la Terrasse, 91198 Gif-sur-Yvette Cedex, France
E-mail : jamal.ouazzani@cnrs.fr
jean-francois.betzer@cnrs.fr
<https://icsn.cnrs.fr/>

moderate yields due to multiple side-reactions. In fact, besides Piancatelli rearrangement process, the furanic starting material might be involved in other reaction process such as hydrolysis into levulinic acid,^{24,25} formation of dimeric compounds,²⁶⁻²⁹ formation of brown black soluble oligomers^{30,31} and production of solid black humins matter as insoluble tarry carbonaceous materials, which were difficult to remove from the desired HCP (Scheme 2).^{8,31-35}



Scheme 2 Rearrangement of furfuryl alcohol (FA) in 4-hydroxy-2-cyclopentenone (HCP) and unwanted side-reactions.

The formation of these numerous by-products is even more difficult to control on a large scale.^{36,37} On large scale, following the procedure reported by Nanni *et al.*, furfuryl alcohol (FA) can be converted into the desired 4-hydroxy-2-cyclopentenone (HCP). This transformation requires a deionized and degassed water solution of phosphate buffer using dihydrogen orthophosphate and phosphoric acid (pH 4.1)³⁸ and has been implemented for the synthesis of prostaglandin derivatives,³⁹⁻⁴¹ 2-cyclopenten-1,4-diol derivatives,⁴²⁻⁴⁵ to prepare building blocks for the synthesis of more complex compounds⁴⁶⁻⁵⁰ and for resolution studies of racemic HCP.⁵¹⁻⁵³ However, these thermal conditions required long reaction period (2 days), high dilution and delivered the desired HCP in modest yields (30-40%) due to the formation of numerous side-products and dark brown polymeric material. A slight improvement in terms of chemical yields (50-60%) was obtained using a catalytic amount of hydroquinone.^{41,54-56}

To overcome these limitations, various alternative methods are proposed to improve the transformation of furfuryl alcohol into cyclopentenone derivatives. The use of microwave irradiation for this rearrangement performed on FA,⁵⁷⁻⁵⁹ or substituted furfuryl carbinols,⁶⁰ considerably reduces the reaction time (10 min) and led to a significant improvement of HCP yields (20-75%). However, for a large-scale production this alternative method does not apply or require to perform many times this reaction in numerous microwave vials before to combine them.⁶¹

On large-scale synthesis, the use of microreactor in a continuous flow setup⁶² is more suitable and produced the HCP in better yields (65-85%). However, for an effective transformation, the use of this technology requires to adjust the pH to 4 with addition of acetic acid.^{60,63-66} In addition, through a second inlet, addition of a water-miscible organic cosolvent, toluene^{60,63-66} or *N*-methylpyrrolidinone,³⁶ is necessary to decrease the solvent polarity for limiting side reactions and to dissolve the dark brown polymeric material, thus preventing blockage of the steel tube.

The same rearrangement of FA was also carried out in a semi-continuous reaction system to deliver the HCP compound in 77% yield.^{67,68} The reaction was performed under argon and in presence of small amount of base catalysts to prevent the formation of hydrolysis products such as levulinic acid and to reduce the polymerization of FA. In a similar manner, this transformation was also performed in autoclave reactor using FeZn-double-metal cyanides as catalyst.⁶⁹ Under a nitrogen atmosphere and in a water/organic bi-phasic solvent medium, the HCP was isolated in 88% yield on 10 mmol scale.

With the aim to perform extraction of natural bio-resources (plant parts, dry marine invertebrates, and microbial biomass), we have developed a pilot scale prototype Zippertex (in 4 L and 10 L capacity), with an innovative technology for the static high-pressure high-temperature extraction of natural compounds (Figure 1).⁷⁰⁻⁷⁴ Operating from -10 °C to 150 °C, and ambient to 100 bars pressure, all manipulations are managed by one operator in compliance with international safety regulation of heated and pressurized device.

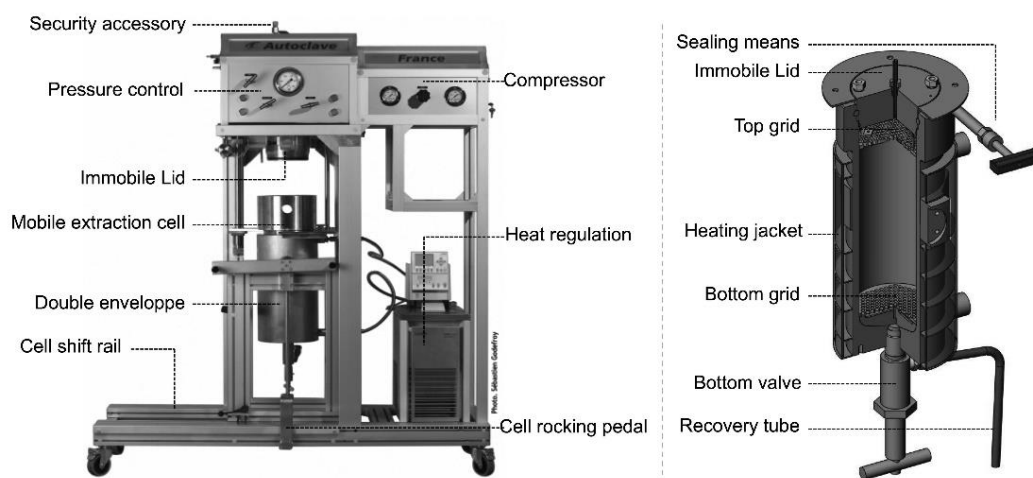
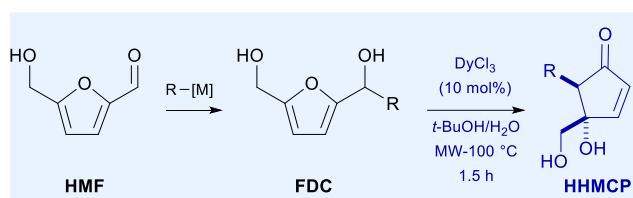


Fig. 1 Zippertex apparatus developed for high-pressure static extraction.

The pressure is ensured by a first step to 40 Bars thanks to a nitrogen bottle, followed by the compressor to reach higher pressure. An appropriate circulating liquid in the Zippertex double envelope regulates the temperature. Beyond the sole “temperature effect,” the subcritical water will cause major changes in physical and chemical properties of water that decisively influences its properties as solvent, opening a new area for the organic chemistry operating at these conditions.⁷⁵⁻⁷⁷

The Zippertex technology, with its specific operating process combining temperature and pressure activations, has been only used for extraction of different bio-resources. Here we propose to take advantage of this subcritical water behaviour for efficient and relevant chemical transformation. Recently, we have described Piancatelli rearrangement of non-symmetrical furan-2,5-dicarbinals (FDC) for the synthesis of 5-substituted-4-hydroxy-4-hydroxymethyl-cyclopentenones (HHMCP).⁷⁸ The starting material FDC was obtained directly in one step from HMF. The Piancatelli rearrangement proceeds in a regioselective manner, on the more substituted carbinol moiety (Scheme 3).



Scheme 3 Preparation of furan-2,5-dicarbinals (FDC) from HMF and their Piancatelli rearrangements for the formation 5-substituted-4-hydroxy-4-hydroxymethyl-cyclopentenones (HHMCP).

We have highlighted that combination of two activation modes, that means microwave irradiation and the use of Lewis acid is essential for an efficient transformation. The microwave irradiation allows an efficient conversion of FDC starting material while the use of Lewis acid catalyst ensure the good stereocontrol of the relative configuration of the two contiguous newly generated stereocenters. The formed HHMCP exhibited significant cytotoxic activities against several human tumor cell lines.⁷⁸ In order to provide the amounts needed for pharmacokinetic studies, determination of ADME parameters and *in vivo assays* for a full biological assessment for a future development of these HHMCP compounds, a multigram-scale synthesis is needed. In this study, we propose to use for the first time of the Zippertex technology for a relevant chemical transformation on large scale, which means Piancatelli rearrangement to produce substituted HHMCP. This Piancatelli rearrangement involves polar intermediates and transition states (Scheme 1a) whose formation should be promoted in subcritical water conditions. Specific behaviour of Zippertex apparatus was examined on different furfuryl alcohols.

Results and discussion

Piancatelli rearrangement of furfuryl alcohol (FA)

We began our investigations by reacting the simple substrate furfuryl alcohol (FA) which can be converted into the desired 4-hydroxy-2-cyclopentenone (HCP) by Piancatelli rearrangement. We have performed the reaction on 50 mmol scale of FA in pure water (500 mL) on Zippertex apparatus under static pressure (100 bars) at 100 °C for 2 hours. In these conditions, the HCP was isolated in a low 6% yield as a result of a very low conversion rate (Table 1, entry 1). Indeed, ¹H NMR analysis of crude reaction mixture revealed a large amount of intact starting material, without the formation of side-products. We have achieved the same reaction for 4.5 hours, and even if the HCP was isolated in better yield, a lot of starting material was recovered (entry 2).

Table 1. Piancatelli rearrangement of furfuryl alcohol (FA) on Zippertex^a

Entry	Temp. (°C)	Time (h)	HCP Yield ^b
1	100	2	6%
2	100	4.5	13%
3	150	4.5	65%

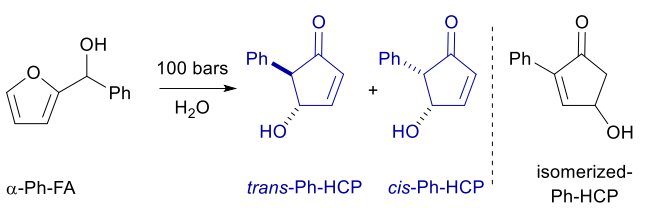
^a Reaction performed on 50 mmol scale. ^b Isolated Yield.

The conversion rate was notably improved by increasing the temperature to 150 °C. In these conditions, we were pleased to observe a complete conversion of FA, a very clean reaction process (see the crude ¹H NMR mixture in SI page S6)⁷⁹ and an efficient formation of HCP, which was isolated in 65% yield after purification (entry 3).

Piancatelli rearrangement of α -phenylfurfuryl alcohol (α -Ph-FA)

We continued the Zippertex technology study for Piancatelli rearrangement by investigating the reactivity of α -substituted furfuryl alcohol. Under the previous optimized conditions, that means 100 bars and 150 °C, the reaction with the α -phenylfurfuryl alcohol (Ph-FA) as substrate lead to a mixture of the desired HCP and the isomerized-HCP in 43% and 27% yields, respectively (Table 2, entry 1). This undesired isomerized product comes from the HCP through a second rearrangement step, which implies a formal intramolecular shift of the hydroxyl group to provide the thermodynamically more stable isomer.^{37,80,81}

With the aim to minimize formation of the isomerized-HCP product, we have decided to perform Piancatelli rearrangement at lower temperature, which means 100 °C. In this case, the formation of isomerized-HCP was significantly reduced to 4% (entry 2).

Table 2. Piancatelli rearrangement of α -phenylfurfuryl alcohol (α -Ph-FA) on Zippertex


Entry	Temp. (°C)	Time (h)	HCP Yield ^c	<i>trans/cis</i> ratio ^d	isomerized-HMCP Yield ^c
1 ^a	150	2	43%	90:10	27%
2 ^b	100	2	70%	90:10	4%
3 ^b	100	3	89%	90:10	9%

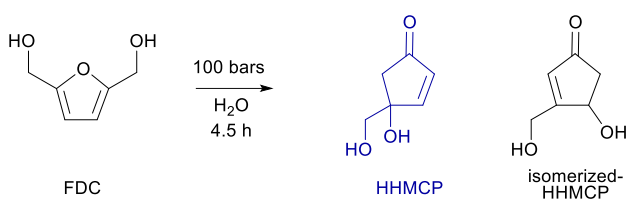
^a Reaction performed on 30 mmol scale. ^b Reaction performed on 15 mmol scale. ^c Isolated Yield. ^d The diastereoisomeric ratio *trans/cis* was determined by ¹H NMR on the crude mixture.

However, as starting material was also recovered, we have achieved the reaction in the same conditions (100 bars and 100 °C) for three hours (entry 3). We were pleased to observe a clean and complete reaction to provide the desired HCP in an excellent 89% yield, accompanied by small amount of isomerized-HCP.⁷⁹ For all attempts performed on α -phenylfurfuryl alcohol (Ph-FA) and irrespective of experimental conditions, the HCP were obtained as a *trans/cis* mixture in 90:10 ratio.

Piancatelli rearrangement of furan-2,5-dicarbinol (FDC)

Despite numerous studies on Piancatelli rearrangement and the effectiveness of this process, direct transformations of HMF derivatives and more generally C-5 substituted substrates have been scarcely explored. For C-5 substituted 2-furylcarbinols, this rearrangement was only described with substrates containing a methyl,^{37,80,82-84} a phenyl⁸⁵ or an ethoxymethyl group.⁸⁶ Thus, in order to expand the synthetic potential of Piancatelli rearrangement, it would be appropriate to perform this reaction on 2-furylcarbinol with a C-5 substituted and functionalized group to afford an efficient access to 2-cyclopentenone derivatives with a C4-quaternary stereogenic center bearing a functionalized side chain.

For this purpose, we have considered furan-2,5-dicarbinol (FDC) as substrate, for which the Piancatelli rearrangement should provide a 4-hydroxycyclopentenone substituted in C-4 position by a functionalized hydroxymethyl side chain. This substrate was previously studied for the preparation of cyclopentanones derivatives under reductive conditions.⁸⁷⁻⁸⁹ In the previous optimized conditions, in water at 100 °C and 100 bars, we have observed a clean reaction but also a very low conversion rate (Table 3, entry 1). After purification, the desired 4-hydroxy-4-(hydroxymethyl)cyclopent-2-en-1-one (HHMCP) was obtained in only 4% yield while the starting material was recovered in 82% yield. In contrast, when the same experiment was performed at 150 °C, the reaction was complete to provide the desired HHMCP in 46% yield after purification with a small amount of isomerized-HHMCP.⁷⁹

Table 3. Piancatelli rearrangement of furan-2,5-dicarbinol (FDC) on Zippertex^a


Entry	Temp. (°C)	HHMCP Yield ^b	isomerized-HHMCP Yield ^b
1	100	4%	-
2	150	46%	5%

^a Reaction performed on 50 mmol scale. ^b Isolated Yield.

Piancatelli rearrangement of α -phenylfuran-2,5-dicarbinol (α -Ph-FDC)

We continued the Zippertex technology study for substrates combining substitution on carbinol moiety and a functionalized hydroxymethyl side chain on the furan moiety, that means α -phenylfuran-2,5-dicarbinol (α -Ph-FDC). These substrates cumulates three difficulties. Firstly, the low reactivity for Piancatelli rearrangement due to the C-5 substitution with hydroxymethyl side chain on the furan ring. Secondly, as these non-symmetrical furan-2,5-dicarbinols possess two different carbinol moieties, the Piancatelli rearrangement can occur on each carbinol function. Finally, the efficient control of the relative configuration of two newly contiguous stereogenic centres, one of which is quaternary, is more challenging for these substrates. During the electrocyclic process, the aryl substituent will adopt an *outward* orientation in the pentadienyl cation **PC** intermediates (Scheme 1a). The key issue of relative stereocontrol will depend on the relative preference of the two other terminal substituents (OH and CH₂OH) for *inward* or *outward* orientation.¹⁴

We initially performed the Piancatelli rearrangement on α -Ph-FDC in the same conditions optimized for α -Ph-FA, that means in pure water at 100 °C and 100 bars. In these conditions (Table 4, entry 1) the desired Ph-HHMCP was formed and could be isolated in modest yield (32%). For this attempt, the crude ¹H NMR spectrum was complex but any trace of starting material α -Ph-FDC was observed. Performing the reaction at 150 °C, a decrease of the diastereoselectivity has been noted and the formation of isomerized-Ph-HHMCP was observed without any improvement of the yield of Ph-HHMCP even if a cleaner crude ¹H NMR spectrum was obtained (entry 2).

For this substrate with an aromatic moiety, we have decided to add a protic solvent with lipophilic properties to increase the solubility of substrate and/or product. For this purpose, and in analogy with our previous work,⁷⁸ we have added a small amount of *tert*-butanol, a green and safe solvent.⁹⁰ Performing the reaction at 100 °C, 100 bars and in a mixture of water/*tert*-butanol (5:1) as solvent, α -Ph-FDC has been efficiently converted into Ph-HHMCP in good yield (67%) without formation of the isomerized product (entry 3).⁷⁹ The desired substituted cyclopentenone was isolated as a mixture of *trans*- and *cis*-Ph-HHMCP in a 90:10 diastereoisomeric ratio.

Table 4. Piancatelli rearrangement of α -phenylfuran-2,5-dicarbinol (α -Ph-FDC) on Zippertex^a

Entry	Temp. (°C)	Solvent	Cat. ^d	Ph-HHMCP Yield ^e	<i>trans</i> / <i>cis</i> ratio ^f	isomerized Ph-HHMCP Yield ^e
1 ^a	100	H ₂ O	-	32%	90:10	-
2 ^b	150	H ₂ O	-	33%	35:65	3%
3 ^a	100	H₂O/<i>t</i>-BuOH^c	-	67%	90:10	-
4 ^a	100	H ₂ O/ <i>t</i> -BuOH ^c	DyCl ₃	50%	85:15	-

^a Reaction performed on 12 mmol scale. ^b Reaction performed on 24 mmol scale. ^c Reaction performed in a mixture of water/*tert*-butanol (5:1). ^d Catalyst loading: 10 mol%. ^e Isolated Yield. ^f The diastereoisomeric ratio *trans*/*cis* was determined by ¹H NMR on the crude mixture.

We have previously observed that the use of a Lewis acid as catalyst is able to increase the diastereoselectivity of the

Piancatelli rearrangement.⁷⁸ We have performed the reaction with 10 mol% of DyCl₃, the best catalyst identified for this rearrangement, but any improvement was observed for the diastereocontrol (entry 4).

Since the beginning of this study, it should be noted that Piancatelli rearrangement proceeded smoothly and led to a very clean crude mixture. For instance, the reaction performed on α -Ph-FDC on Zippertex apparatus produce a colourless crude mixture suggesting a low formation of humins matter (Figure 2a). Similarly, the same observation was made on the NMR tube of crude product (Figure 2b, left), which appears as a pale yellow solution. The analysis of ¹H NMR spectrum on the crude mixture (Figure 2c) revealed (i) a complete conversion of starting material α -Ph-FDC, (ii) a clean conversion into Ph-HHMCP, (iii) a good *trans*/*cis* diastereoisomeric ratio (90:10) and (iv) a very low formation of side-products.

From a remarkable point of view, the ¹H NMR spectrum of crude product (Figure 2c) is almost identical to the ¹H NMR spectrum of the purified product (Figure 2d).⁷⁹ After purification on chromatography, the Ph-HHMCP was obtained as a clean colourless sample (Figure 2b, right).

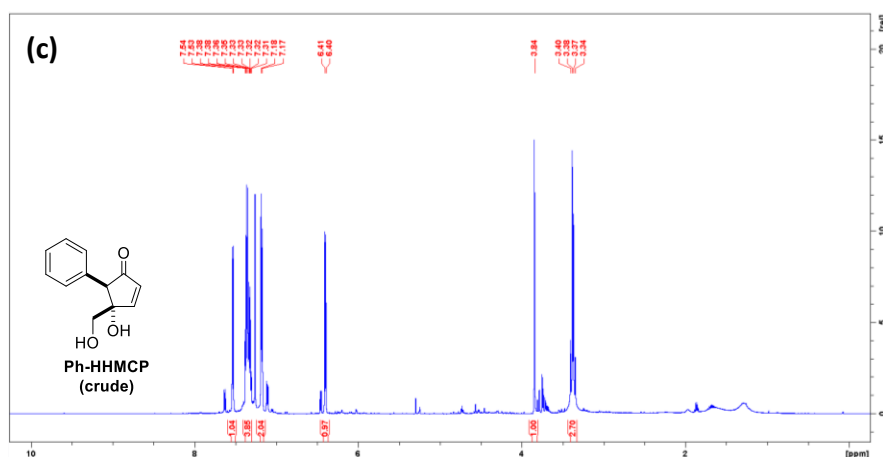
(a)



(b)



(c)



(d)

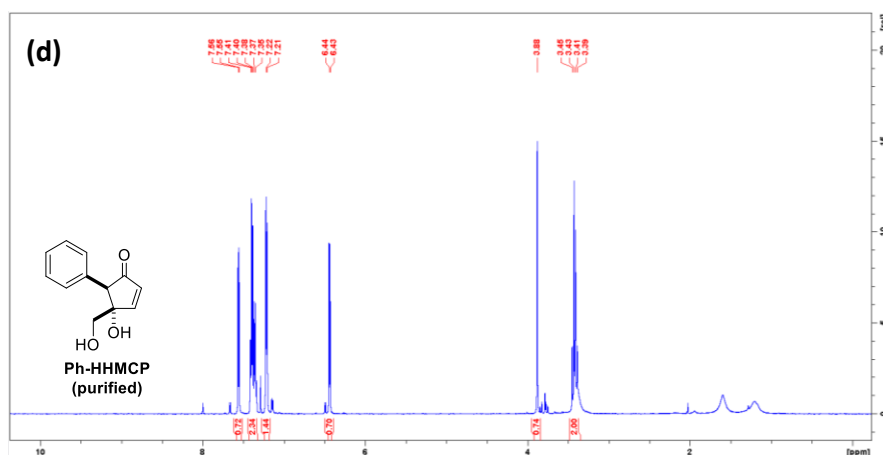


Fig. 2 Piancatelli rearrangement for the formation of Ph-HHMCP performed on Zippertex apparatus. (a) Zippertex reactor after reaction (24 mmol scale). (b) NMR tubes (in CDCl₃) of crude (left) and purified (right) Ph-HHMCP. (c) ¹H NMR (in CDCl₃) of crude mixture of Ph-HHMCP. (d) ¹H NMR (in CDCl₃) of purified Ph-HHMCP.

In order to better understand the relation between diastereoselectivities and experimental conditions, we carried out a series of control experiments on a sample of a mixture *trans/cis* 90:10 Ph-HHMCP, which was produced on large scale on Zippertex (Table 4, entry 3).

The first control experiment was conducted under the optimized conditions, by reacting once again the sample for two hours in a mixture of water/*tert*-butanol (5:1) at 100 °C and 100 bars. By ¹H NMR analysis of the crude mixture, we have observed a clean process and a small decrease of diastereoisomeric ratio, which is now measured at *trans/cis* 80:20 ratio (Figure 3a).

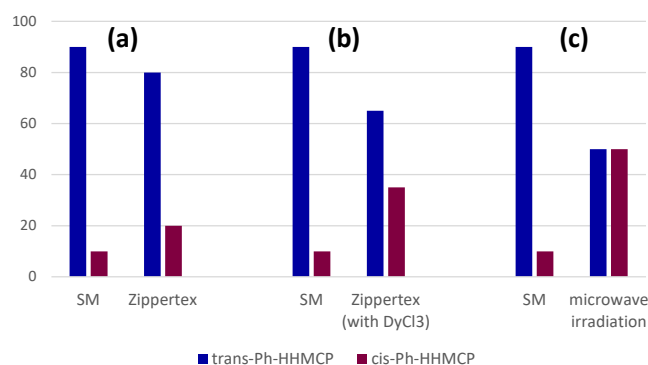
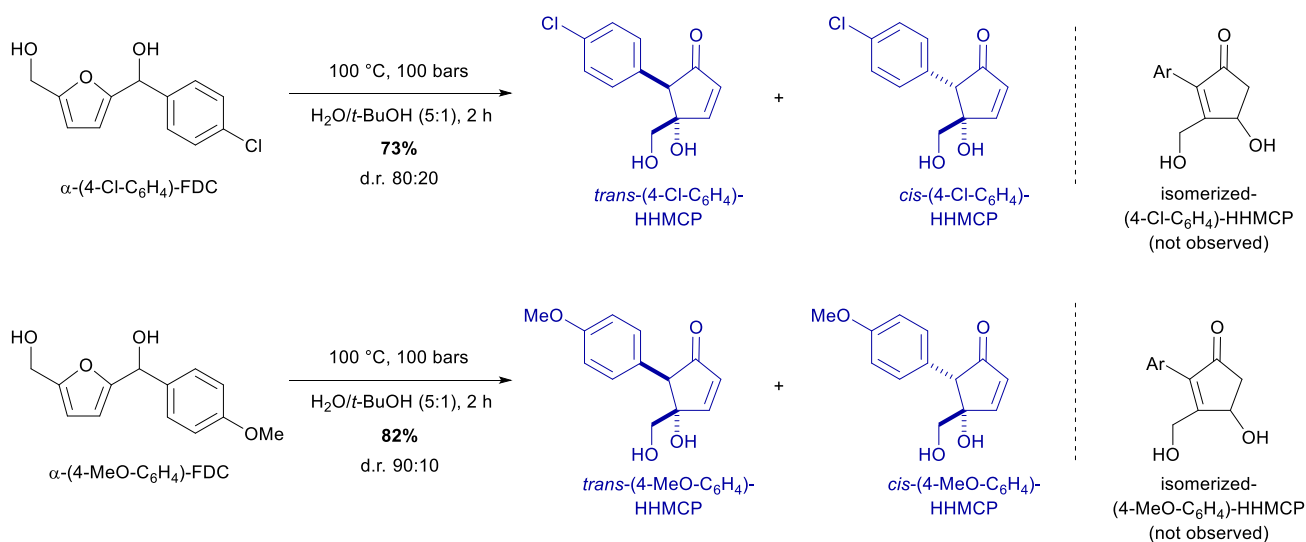


Fig. 3 Control experiments for the evolution of diastereoisomeric ratio of *trans*- and *cis*-Ph-HHMCP starting from a mixture of *trans/cis* 90:10 of Ph-HHMCP as starting material (SM). (a) Result after reaction on Zippertex (2 h, 100 °C and 100 bars). (b) Result after reaction on Zippertex in presence of a catalytic amount of Lewis acid (2 h, 100 °C, 100 bars and DyCl₃ 10 mol%). (c) Result after reaction under MicroWave irradiation (3 min., MW-180 °C).

The same control experiment performed in presence of DyCl₃ (10 mol%) lead to a strongest erosion of diastereoisomeric ratio (65:35) (Figure 3b).

For comparison, the same control experiment was realized under microwave irradiation. In these thermal conditions, a complete epimerisation was observed and an equimolar amount of *trans*- and *cis*-Ph-HHMCP was obtained (Figure 3c). This result is consistent with our previous study on Piancatelli rearrangement of non-symmetrical furan-2,5-dicarbonyls, where the use of microwave activation lead to a poor 60:40 diastereoisomeric ratio.⁷⁸

Under the optimized reaction conditions on Zippertex apparatus (100 °C, 100 bars, 2 h), both FDC substrates substituted by an electron-withdrawing and an electron-donating groups on the aromatic moiety were investigated. The FDC substrates were obtained in one-step by addition of Grignard reagents on HMF. We were pleased to find that these two functionalized substrates, α -(4-Cl-C₆H₄)-FDC and α -(4-MeO-C₆H₄)-FDC, reacted efficiently under our optimized conditions and provide the Piancatelli products in good yields (Scheme 4). The (4-Cl-C₆H₄)-HHMCP was isolated in a lower 80:20 diastereoisomeric ratio and in a good 73% yield. The (4-MeO-C₆H₄)-HHMCP was isolated in a very satisfying 82% yield and 90:10 diastereoisomeric ratio. For these both reactions, the rearrangement proceeded smoothly and neither isomerized (aryl)-HHMCP was observed.⁷⁹



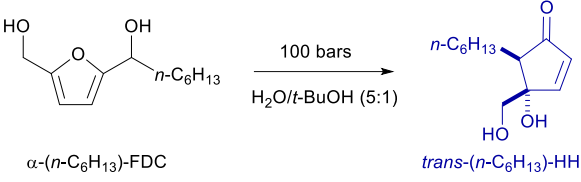
Scheme 4 Piancatelli rearrangement of α -(aryl substituted with electron-withdrawing or electron-donating group)-FDC on Zippertex. Reaction performed on 12 mmol scale. Isolated Yield. Diastereoisomeric ratio *trans/cis* was determined by ¹H NMR on the crude mixture.

We continued our investigation by exploring a more challenging Piancatelli rearrangement with less reactive substrate that means FDC substituted by an aliphatic alkyl chain. As mentioned above, the α -(*n*-C₆H₁₃)-FDC was obtained in one step by addition of *n*-hexylmagnesium bromide onto HMF.

As anticipated, the α -(*n*-C₆H₁₃)-FDC was less reactive and under our optimized conditions (100 °C, 100 bars, 2 h), the reaction led to a very low amount of product together with recovered starting material (Table 5, entries 1-2). In contrast, working at 150 °C, the starting material α -(*n*-C₆H₁₃)-FDC was completely

consumed and the desired (*n*-C₆H₁₃)-HHMCP was isolated in 23% yield. For this substrate, although the conversion rate was complete, the chemical yield was lower than FDC substituted by an aryl group. For this α -(*n*-C₆H₁₃)-FDC substrate, we can explain this reduced yield by the formation of polymeric and humins matter as a brown reaction mixture was produced. However, we were pleased to observed an excellent diastereoselectivity as only the *trans*-(*n*-C₆H₁₃)-HHMCP was observed in ¹H NMR spectra.⁷⁹

Table 5. Piancatelli rearrangement of α -(*n*-C₆H₁₃)-FDC on Zippertex^a

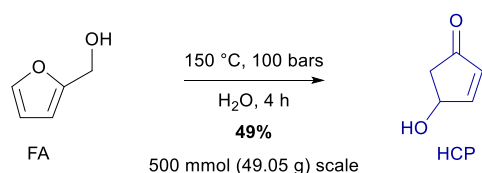


Entry	Temp. (°C)	time (h)	<i>trans</i> -(<i>n</i> -C ₆ H ₁₃)-HHMCP Yield
1	100	2	< 5% ^b
2	100	8	< 5% ^b
3	150	4.5	23% ^c

^a Reaction performed on 12 mmol scale. ^b ¹H NMR yield. ^c Isolated Yield.

It was also important to mention that despite higher temperature, the isomerized-(*n*-C₆H₁₃)-HHMCP was not formed. For comparison, Piancatelli rearrangement on similar substrate with a hexyl chain on the carbinol moiety led to a 1:2 cyclopentenone and the isomeric one.⁹¹ Another side reaction for this alkyl-substituted substrate, the dehydration on the carbinol moiety which can be the main reaction, was not observed in our conditions.⁸⁴

To conclude this study and demonstrate the efficiency of the Zippertex technology to produce cyclopentenone compounds from 2-furylcarbinols, we have performed Piancatelli rearrangement on large scale. The previous studied reactions were performed on 12-50 mmol scale. To demonstrate the feasibility for scaling up, we have realized this rearrangement on 500 mmol scale. Treatment of 49 g of furfuryl alcohol in pure water at 150 °C and 100 bars led to HCP in a 49% isolated yield. The Zippertex technology does not require working at high dilution. The production of HCP was realized at 0.17 M concentration, requiring only 3 L of water for 49 g of substrate.



Scheme 5 Rearrangement of furfuryl alcohol (FA) in 4-hydroxy-2-cyclopentenone (HCP) on large scale on Zippertex. Isolated Yield.

Conclusions

Besides extraction, we have demonstrated for the first time the Zippertex technology for valuable and challenging chemical

transformations and applied for an efficient access to highly substituted and functionalized cyclopentenone derivatives. These cyclopentenones were obtained by Piancatelli rearrangement performed on large scale (up to 500 mmol scale) and starting from renewably-sourced raw materials such as furfuryl alcohol and hydroxymethylfurfural derivatives.

Zippertex is a robust technology with easy handling, limited solvent use, and power only for temperature regulation by external recycling. Zippertex was engaged in pure water without any additive. At these condition furfuryl alcohol, α -phenylfurfuryl alcohol and furan-2,5-dicarbino were transformed into cyclopentenone derivatives in 65%, 89% and 46% yields, respectively. The more challenging non-symmetrical furan-2,5-dicarbino substrates requires the use of small amount *tert*-butanol and affords 5-substituted-4-hydroxymethyl-4-hydroxycyclopentenones in a regio- and diastereoselective manner in good yields (67-82%). Furthermore, the presence of an aliphatic group on the carbinol moiety was also tolerated even if the process is less efficient (23% yield).

Very clean crude reaction mixtures were obtained and directly followed without any work-up by water evaporation and a rapid chromatography. This first attempt for the replacement of microwave irradiation by Zippertex offers the proof of concept for the scale-up reaction, opening a new area for organic synthesis applications operating under these reported conditions.

Author Contributions

JO and JFB conceived and designed the experiments. GA performed the experiments. JFB and GA carried out acquisition, interpretation and produced the figures. JFB wrote the manuscript. JO and GA revised the manuscript. JO for provision of Zippertex technology. All authors have given approval to the final version of the manuscript.

Conflicts of interest

The authors are no conflicts to declare.

Acknowledgements

The authors acknowledge the support of the “Centre National de la Recherche Scientifique” (CNRS) and “Institut de Chimie des Substances Naturelles” (ICSN).

Notes and references

- 1 D. C. Elliott, *Energy Fuels*, 2007, **21**, 1792-1815.
- 2 C. Liu, H. Wang, A. M. Karim, J. Sun and Y. Wang, *Chem. Soc. Rev.*, 2014, **43**, 7594-7623.
- 3 X. Li, P. Jia and T. Wang, *ACS Catal.*, 2016, **6**, 7621-7640.
- 4 S. Chen, R. Wojcieszak, F. Dumeignil, E. Marceau and S. Royer, *Chem. Rev.*, 2018, **118**, 11023-11117.
- 5 F. Menegazzo, E. Ghedini and M. Signoretto, *Molecules*, 2018, **23**, 2201.

- 6 F. Delbecq and C. Len, *Molecules*, 2018, **23**, 1973.
- 7 J. J. Bozell and G. R. Petersen, *Green Chem.*, 2010, **12**, 539-554.
- 8 A. A. Rosatella, S. P. Simeonov, R. F. M. Frade and C. A. M. Afonso, *Green Chem.*, 2011, **13**, 754-793.
- 9 R.-J. van Putten, J. C. van der Waal, E. de Jong, C. B. Rasrendra, H. J. Heeres and J. G. de Vries, *Chem. Rev.*, 2013, **113**, 1499-1597.
- 10 X. Kong, Y. Zhu, Z. Fang, J. A. Kozinski, I. S. Butler, L. Xu, H. Song and X. Wei, *Green Chem.*, 2018, **20**, 3657-3682.
- 11 W. Fan, C. Verrier, Y. Queneau and F. Popowycz, *Curr. Org. Synth.*, 2019, **16**, 583-614.
- 12 G. Piancatelli, A. Scettri and S. Barbadoro, *Tetrahedron Lett.*, 1976, **17**, 3555-3558.
- 13 G. Piancatelli and A. Scettri, *Tetrahedron*, 1977, **33**, 69-72.
- 14 O. Nieto Faza, C. Silva López, R. Álvarez and Á. R. de Lera, *Chem. Eur. J.*, 2004, **10**, 4324-4333.
- 15 G. Piancatelli, *Heterocycles*, 1982, **19**, 1735-1744.
- 16 G. Piancatelli, M. D'Auria and F. D'Onofrio, *Synthesis*, 1994, 867-889.
- 17 S.-W. Li and R. A. Batey, *Chem. Comm.*, 2007, 3759-3761.
- 18 C. Piutti and F. Quartieri, *Molecules*, 2013, **18**, 12290-12312.
- 19 L. I. Palmer and J. Read de Alaniz, *Synlett*, 2014, **25**, 08-11.
- 20 C. Verrier, S. Moebis-Sanchez, Y. Queneau and F. Popowycz, *Org. Biomol. Chem.*, 2018, **16**, 676-687.
- 21 R. F. A. Gomes, J. A. S. Coelho and C. A. M. Afonso, *Chem. Eur. J.*, 2018, **24**, 9170-9186.
- 22 L. Marin, G. Force, V. Gandon, E. Schulz and D. Leboeuf, *Eur. J. Org. Chem.*, 2020, 5323-5328.
- 23 S. Zhong, L. Xu and Y. Cai, *Synthesis*, 2022, **54**, 589-599.
- 24 M. Sajid, U. Farooq, G. Bary, M. M. Azim and X. Zhao, *Green Chem.*, 2021, **23**, 9198-9238.
- 25 Y. Tian, F. Zhang, J. Wang, L. Cao and Q. Han, *Bioresour. Technol.*, 2021, **342**, 125977.
- 26 H. Wang, Y. Wang, T. Deng, C. Chen, Y. Zhu and X. Hou, *Catal. Commun.*, 2015, **59**, 127-130.
- 27 K. I. Galkin, E. A. Krivodaeva, L. V. Romashov, S. S. Zalesskiy, V. V. Kachala, J. V. Burykina and V. P. Ananikov, *Angew. Chem. Int. Ed.*, 2016, **55**, 8338-8342.
- 28 A. Pérez, H. A. Rojas, O. Portilla, G. Sathicq, C. A. M. Afonso, G. P. Romanelli and J. J. Martínez, *ChemCatChem*, 2017, **9**, 3322-3329.
- 29 R. F. A. Gomes, Y. N. Mitrev, S. P. Simeonov and C. A. M. Afonso, *ChemSusChem*, 2018, **11**, 1612-1616.
- 30 S. Bertarione, F. Bonino, F. Cesano, A. Damin, D. Scarano and A. Zecchina, *J. Phys. Chem. B*, 2008, **112**, 2580-2589.
- 31 M. K. Stones, E. M. J. Banz Chung, I. T. da Cunha, R. J. Sullivan, P. Soltanipanah, M. Magee, G. J. Umphrey, C. M. Moore, A. D. Sutton and M. Schlaf, *ACS Catal.*, 2020, **10**, 2667-2683.
- 32 S. J. Dee and A. T. Bell, *ChemSusChem*, 2011, **4**, 1166-1173.
- 33 X. Li, K. Peng, X. Liu, Q. Xia and Y. Wang, *ChemCatChem*, 2017, **9**, 2739-2746.
- 34 A. Sangregorio, N. Guigo, E. d. Jong and N. Sbirrazzuoli, *Polymers*, 2019, **11**, 1804.
- 35 R. M. Abdilla-Santes, S. Agarwal, X. Xi, H. Heeres, P. J. Deuss and H. J. Heeres, *J. Anal. Appl. Pyrolysis*, 2020, **152**, 104963.
- 36 T. Kumaraguru, P. Babita, G. Sheelu, K. Lavanya and N. W. Fadnavis, *Org. Process. Res. Dev.*, 2013, **17**, 1526-1530.
- 37 D. Fisher, L. I. Palmer, J. E. Cook, J. E. Davis and J. Read de Alaniz, *Tetrahedron*, 2014, **70**, 4105-4110.
- 38 M. Nanni, H. Tamachi and S. Moriyama, *Jpn Kokai Tokkyo Koho*, 1982, 57062236.
- 39 G. Krüger, C. Harde and F. Bohlmann, *Tetrahedron Lett.*, 1985, **26**, 6027-6030.
- 40 H. L. Holland, F. M. Brown, P. C. Chenchaiyah and J. A. Rao, *Can. J. Chem.*, 1990, **68**, 282-293.
- 41 W. Zhong, J. R. Springstead, R. Al-Mubarak, S. Lee, R. Li, B. Emert, J. A. Berliner and M. E. Jung, *J. Med. Chem.*, 2013, **56**, 8521-8532.
- 42 T. T. Curran, D. A. Hay, C. P. Koegel and J. C. Evans, *Tetrahedron*, 1997, **53**, 1983-2004.
- 43 T. J. N. Watson, T. T. Curran, D. A. Hay, R. S. Shah, D. L. Wenstrup and M. E. Webster, *Org. Process. Res. Dev.*, 1998, **2**, 357-365.
- 44 N. Hamon, M. Kaci, J.-P. Uttaro, C. Périgaud and C. Mathé, *Eur. J. Med. Chem.*, 2018, **150**, 642-654.
- 45 N. M. Maguire, A. Ford, J. Balzarini and A. R. Maguire, *J. Org. Chem.*, 2018, **83**, 10510-10517.
- 46 N. Becker and E. M. Carreira, *Org. Lett.*, 2007, **9**, 3857-3858.
- 47 R. L. Beingsner, J. A. Farand and L. Barriault, *J. Org. Chem.*, 2010, **75**, 6337-6346.
- 48 L. Song, H. Yao, L. Zhu and R. Tong, *Org. Lett.*, 2013, **15**, 6-9.
- 49 J. Yu, X. Yang, Y. Sun and Z. Yin, *Angew. Chem. Int. Ed.*, 2018, **57**, 11598-11602.
- 50 Y. Liu, Z. Mao, A. Pradal, P.-Q. Huang, J. Oble and G. Poli, *Org. Lett.*, 2018, **20**, 4057-4061.
- 51 S. R. Ghorpade, K. B. Bastawade, D. V. Gokhale, P. D. Shinde, V. A. Mahajan, U. R. Kalkote and T. Ravindranathan, *Tetrahedron Asym.*, 1999, **10**, 4115-4122.
- 52 B. S. Morgan, D. Hoenner, P. Evans and S. M. Roberts, *Tetrahedron Asym.*, 2004, **15**, 2807-2809.
- 53 A. O'Byrne, C. Murray, D. Keegan, C. Palacio, P. Evans and B. S. Morgan, *Org. Biomol. Chem.*, 2010, **8**, 539-545.
- 54 S. K. Basra, M. G. B. Drew, J. Mann and P. D. Kane, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3592-3598.
- 55 N. Nazef, R. D. M. Davies and M. F. Greaney, *Org. Lett.*, 2012, **14**, 3720-3723.
- 56 K. Ren, M. Zhao, B. Hu, B. Lu, X. Xie, V. Ratovelomanana-Vidal and Z. Zhang, *J. Org. Chem.*, 2015, **80**, 12572-12579.
- 57 A. Saitman and E. A. Theodorakis, *Org. Lett.*, 2013, **15**, 2410-2413.
- 58 S. Specklin, A. Dikova, A. Blanc, J.-M. Weibel and P. Pale, *Tetrahedron Lett.*, 2014, **55**, 6987-6991.
- 59 G. Le Goff, E. Adelin, G. Arcile and J. Ouazzani, *Tetrahedron Lett.*, 2017, **58**, 2337-2339.
- 60 K. Ulbrich, P. Kreitmeier and O. Reiser, *Synlett*, 2010, 2037-2040.
- 61 N. J. Truax, S. Ayinde, K. Van, J. O. Liu and D. Romo, *Org. Lett.*, 2019, **21**, 7394-7399.
- 62 M. Guidi, P. H. Seeberger and K. Gilmore, *Chem. Soc. Rev.*, 2020, **49**, 8910-8932.
- 63 M. Nettekoven, B. Püllmann, R. E. Martin and D. Wechsler, *Tetrahedron Lett.*, 2012, **53**, 1363-1366.
- 64 K. Ulbrich, P. Kreitmeier, T. Vilaivan and O. Reiser, *J. Org. Chem.*, 2013, **78**, 4202-4206.
- 65 N. Arisetti and O. Reiser, *Org. Lett.*, 2015, **17**, 94-97.
- 66 D. Dobler and O. Reiser, *J. Org. Chem.*, 2016, **81**, 10357-10365.
- 67 G. Li, N. Li, M. Zheng, S. Li, A. Wang, Y. Cong, X. Wang and T. Zhang, *Green Chem.*, 2016, **18**, 3607-3613.
- 68 G. Li, B. Hou, A. Wang, X. Xin, Y. Cong, X. Wang, N. Li and T. Zhang, *Angew. Chem. Int. Ed.*, 2019, **58**, 12154-12158.
- 69 X. Li, Q. Deng, L. Yu, R. Gao, Z. Tong, C. Lu, J. Wang, Z. Zeng, J.-J. Zou and S. Deng, *Green Chem.*, 2020, **22**, 2549-2557.
- 70 M. Bourjot, C. Apel, M.-T. Martin, P. Grellier, V. H. Nguyen, F. Guéritte and M. Litaudon, *Planta Med.*, 2010, **76**, 1600-1604.
- 71 G. Marti, V. Eparvier, M. Litaudon, P. Grellier and F. Guéritte, *Molecules*, 2010, **15**, 7106-7114.
- 72 A. Leverrier, M. E. T. H. Dau, P. Retailleau, K. Awang, F. Guéritte and M. Litaudon, *Org. Lett.*, 2010, **12**, 3638-3641.

- 73 C. Rabhi, G. Arcile, L. Cariel, C. Lenoir, J. Bignon, J. Wdzieczak-Bakala and J. Ouazzani, *J. Med. Food*, 2015, **18**, 1065-1072.
- 74 A. Gallego, I. Metón, I. V. Baanante, J. Ouazzani, E. Adelin, J. Palazon, M. Bonfill and E. Moyano, *Biomed. Pharmacother.*, 2017, **89**, 565-572.
- 75 M. Möller, P. Nilges, F. Harnisch and U. Schröder, *ChemSusChem*, 2011, **4**, 566-579.
- 76 A. G. Carr, R. Mammucari and N. R. Foster, *Chem. Eng. J.*, 2011, **172**, 1-17.
- 77 F. Chemat, M. Abert Vian, H. K. Ravi, B. Khadhraoui, S. Hilali, S. Perino and A.-S. Fabiano Tixier, *Molecules*, 2019, **24**, 3007.
- 78 F. Cacheux, G. Le Goff, J. Ouazzani, J. Bignon, P. Retailleau, A. Marinetti, A. Voituriez and J.-F. Betzer, *Org. Chem. Front.*, 2021, **8**, 2449-2455.
- 79 In the supporting information, for comparison purposes, the crude ¹H NMR mixture and purified product are provided for each studied compound.
- 80 A. Scettri, G. Piancatelli, M. D'Auria and G. David, *Tetrahedron*, 1979, **35**, 135-138.
- 81 K. Michalak and J. Wicha, *Synlett*, 2013, **24**, 1387-1390.
- 82 G. Piancatelli, A. Scettri, G. David and M. D'Auria, *Tetrahedron*, 1978, **34**, 2775-2778.
- 83 F. G. West and G. U. Gunawardena, *J. Org. Chem.*, 1993, **58**, 5043-5044.
- 84 R. Katsuta, K. Aoki, A. Yajima and T. Nukada, *Tetrahedron Lett.*, 2013, **54**, 347-350.
- 85 M. D'Auria, F. D'Onofrio, G. Piancatelli and A. Scettri, *Gazz. Chim. Ital.*, 1986, **116**, 173-175.
- 86 A. Bredihhin, S. Luiga and L. Vares, *Synthesis*, 2016, **48**, 4181-4188.
- 87 J. Ohyama, R. Kanao, A. Esaki and A. Satsuma, *Chem. Comm.*, 2014, **50**, 5633-5636.
- 88 J. Ohyama, R. Kanao, Y. Ohira and A. Satsuma, *Green Chem.*, 2016, **18**, 676-680.
- 89 Y.-J. Xu, J. Shi, W.-P. Wu, R. Zhu, X.-L. Li, J. Deng and Y. Fu, *Appl. Catal., A*, 2017, **543**, 266-273.
- 90 K. Duarte, C. I. L. Justino, A. M. Gomes, T. Rocha-Santos and A. C. Duarte, in *Comprehensive Analytical Chemistry*, eds. T. Rocha-Santos and A. C. Duarte, Elsevier, 2014, vol. 65, pp. 59-78.
- 91 M. D'Auria, *Heterocycles*, 2000, **52**, 185-194.