



Eco-friendly one pot synthesis of caffeic acid phenethyl ester (CAPE) via an in-situ formed deep eutectic solvent



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ABSTRACT

In this paper, a new strategy towards the synthesis of caffeic acid phenethyl ester (CAPE) is introduced. The reaction is carried out in a deep eutectic solvent made of caffeic acid and choline chloride. Caffeic acid is used as part of the solvent and as reactant. Phenethyl alcohol is soluble in this mixture in every molar ratio, and as a consequence no additional solvent is necessary. Reaction conditions were optimised with respect to the molar ratio of phenethyl alcohol and caffeic acid, and by varying the amount and nature of the acid catalyst as well as the reaction time. The obtained CAPE ester could easily be separated from the reaction mixture by simply adding water to destroy the deep eutectic by solubilisation of choline chloride in the aqueous phase.

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1. Introduction

Caffeic acid phenethyl ester (CAPE) has become an interesting molecule since it shows favorable pharmacological and biological properties, such as antimicrobial effects, anti-inflammatory or anticancer and immune modulatory activities (Demestre et al., 2009; Natarajan et al., 1996; Orban et al., 2000; Huang et al., 1996; 1988). Further, CAPE is an active flavonoid which plays an important role in the antioxidant activity of propolis (Russo et al., 2002; Shahidi et al., 1992; Chen et al., 1996; Lee et al., 2000; Jung et al., 2008; Murtaza et al., 2014). However, the isolation of CAPE from honeybee propolis is time-consuming and suffers from remaining impurities (Marcucci, 1995). Moreover, there are some disadvantages concerning the synthesis of CAPE, since hazardous and deleterious chemical reagents are used (Chen et al., 1996; Lee et al., 2000; Hashimoto et al., 1988; Touaibia and Guay, 2011; Nakamura et al., 2014; Burke et al., 1995), for example dicyclohexyl carbodiimide as condensing agent or iso-butyl chloroformate as protecting agent or benzene or dioxane as a solvent together with SOCl_2 . To overcome these drawbacks, new synthetic approaches are investigated. For example, Ha et al. prepared CAPE via an enzyme-catalysed reaction, which was performed in an ionic liquid (IL) (Ha et al., 2012; 2013). ILs are salts which show melting points below 100 °C and are proposed for a wide range of applications. In

organic synthesis they can be employed as reaction media as an alternative to classic organic solvents (Welton, 1999). Unfortunately, the used IL: [Emim][Tf2N] cannot be considered as a green solvent, although this was precisely the goal of the mentioned synthesis by Ha et al.

It is well-known that a lot of ILs are (eco)toxic and harmful to the environment (Ranke, 2007; Pham et al., 2010). Further, their synthesis and purification is often expensive and time-consuming (Deetlefs and Seddon, 2010; Clark and Tavener, 2007). A promising alternative to ILs are deep eutectic solvents (DESS). In general, a eutectic system is a mixture of chemical compounds or elements which exhibits a single chemical composition, at which it solidifies at a lower temperature than any other composition. The depression of the freezing point is related to the strength of interaction between the components (Smith and Hashemi, 2003; Abbott et al., 2003). The term *deep* eutectic solvent derives from the large depression of the melting point, which can be up to 200 °C (Abbott et al., 2003). Besides the easy preparation, low costs, non-volatility and non-inflammability, they are expected to have a better biodegradability than ionic liquids, as many DESSs are derived from natural molecules (Abbott et al., 2004; Maugeri and Dominguez de Maria, 2012).

DESSs and low melting mixtures (LMMs) are mainly composed of non-toxic, natural-based and environmentally benign substances (Smith et al., 2014). For instance, CHCl_3 , which is often used in DESSs and LMMs, is biocompatible and known as former vitamin B4. It has some important key functions in the human body, e.g. as

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a precursor of phospholipids and acetylcholine (Blusztajn, 1998). ChCl is a cheap animal feed and also food additive, and as will be shown, at the end of the reaction discussed here, it can be easily separated from the desired product. Note that since ChCl is environmentally benign (and even edible), it fulfills an important criterion of sustainability (IUCN/UNEP/WWF, 1991).

Further, urea, another important molecule in the development of DESs and LMMs, is not toxic to the human body. It is produced during the mammalian metabolism and even salvaged due to the metabolized activity of the colonic microflora. It is further used in the body and can be easily excreted in the urine (Jackson, 1994). Also eco-friendly and biodegradable organic compounds like several carboxylic acids (e.g. oxalic acid, malonic acid, succinic acid, etc.), amino acids or sugars (glucose, sorbitol, fructose, etc.) can be part of a DESs or LMMs (Abbott et al., 2004; Maugeri and Dominguez de Maria, 2012; Imperato et al., 2005; Franciso et al., 2012; Dai et al., 2013; Kerton and Marriott, 2013; Fischer and Kunz, 2014). DESs have been proposed for many applications, e.g. for the extraction of glycerol from biodiesel (Abbott et al., 2007), metal extraction (Abbott et al., 2005), electrochemistry (Nkuku and Le-Suer, 2007), nanoscience (Liao et al., 2008), biochemistry (Choi et al., 2011), as well as in biocatalysis (Gorke et al., 2008) and organic synthesis (Ruß and König, 2012).

With their low to vanishing toxicity, their rapid biodegradability, and their biological origin, DES perfectly fulfill several of the 12 principles of green chemistry (Anastas and Warner, 1998): the use of less hazardous chemicals, the use of safer chemicals and solvents, inherently safer chemistry etc. They are also in agreement with most of the 12 principles of green solvents (Gu and Jérôme, 2013), of green engineering (Anastas and Zimmerman, 2003) and even of some principles of green extraction (Chemat et al., 2012; Rombaut et al., 2014).

Of course, there are also Ionic Liquids, in particular those with choline cations that fulfill many of the above mentioned criteria. However, they have to be synthesized first, whereas DES form spontaneously. In any case, the perfect solvent does not exist, and hence the best solvent would be – no solvent. Indeed, there are some efforts to make chemical reactions without any solvent (Marvaniya et al., 2011). In the case of DES, the main disadvantage is that it cannot be easily separated from the product by simple evaporation (distillation). We will come back to this point later on.

Since from what we discussed in the preceding paragraph, it is of evident advantage to perform reactions in non-toxic and biodegradable media, especially for the synthesis of drugs, we present a new synthetic route to CAPE. The synthesis is carried out with no additional solvents and the work-up is performed only with water. The reaction scheme of the esterification of caffeic acid (CA) and phenethyl alcohol (PA), providing CAPE, is shown in Fig. 1.

The formal reaction looks trivial; it is indeed a simple esterification. But the problem is to find an acceptable solvent in which both reactants are soluble. Benzene is an option, but it is not a green solvent (Grodowska and Parczewski, 2010).

The novel feature of the procedure proposed here is that in a first step, a DES is formed consisting of CA and choline chloride (ChCl). This is necessary, since CA is nearly insoluble in PA. By forming a deep eutectic mixture, the solubility properties of CA are changed and the CA-ChCl (molar ratio 1:2) mixture becomes miscible with PA in every ratio measured. As a consequence, CA is not only a reactant, but simultaneously part of the solvent and no further harmful solvent is required.

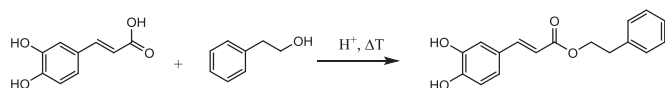


Fig. 1. Acid-catalyzed esterification of caffeic acid with phenethyl alcohol.

Of course, it is well-known and widely explored that a reactant can also be the solvent, e.g. methanol for esterification processes. But in that case, the second reactant is soluble in it. In our case, caffeic acid is insoluble in the alcohol. Our approach would even be possible if both reactants are solid, provided that one of them can be transformed into a DES with a convenient additive.

A double role of a DES was also explored by Gore et al. (2012a, 2012b) who used a DES both as solvent and catalyst, but not as solvent and reactant. A DES with the present composition of ChCl and CA was first mentioned by Maugeri and Dominguez de Maria (2012). As its melting point was determined to be 67 °C, this DES has not received much attention. However, the required temperature for the reaction proposed in the present paper is 80 °C and thus, the high melting temperature of the DES is not a drawback.

Of course, it is not excluded (and even probable) that an environmentally benign Ionic Liquid, for example a choline based one with a convenient non-reactive counterion, could also dissolve both reactants. However, choline chloride as the additive is a cheap and readily available salt that is produced in large quantities, whereas any appropriate IL would have to be synthesized first for this purpose, which would cost further energy and require further resources. Further, as ChCl, any imaginable choline-based IL would also have a negligible vapor pressure and could not be separated from the product by distillation either.

2. Materials and methods

Choline chloride (Alfa Aesar, >98%) and caffeic acid (Sigma Aldrich, 98%) were combined in an inert atmosphere in a molar ratio of 2:1. The vial was sealed and the mixture stirred at 90 °C until a yellowish homogeneous liquid was formed. Subsequently, the temperature was reduced to 80 °C, and phenethyl alcohol was added under vigorous stirring until the mixture was homogeneous. The progress of the reaction was determined by HPLC measurements. The samples (6.5–70 mg) were diluted with MeOH (5 mL), filtered, and subsequently submitted to HPLC separation using gradient elution. Amberlyst 15 (Sigma-Aldrich) was added and the reaction mixture was stirred under exclusion of light to prevent degradation. Amberlyst 15 is a macro-reticular polystyrene based ion exchange resin with acidic sulfonic groups which can be used for several acidic catalyzed reactions (Pal et al., 2012). Its easy removal from the reaction mixture, the uncomplicated use and regeneration afterwards are further advantages (Pal et al., 2012; Petrini et al., 1988). Amberlyst 15 was filtered off and the remaining liquid was poured slowly into hot water. Upon cooling to room temperature, caffeic acid phenethyl ester precipitated and was collected by filtration. The product was washed with water. Caffeic acid phenethyl ester was obtained as a slightly purple to off-white powder (56.4%). Note that the reaction conditions have been optimised with respect to the molar ratio of PA and CA, and by varying the amount and nature of the acid catalyst, as well as the reaction time. Without acid catalyst no CAPE was formed. By using sulphuric acid or p-toluenesulfonic acid the results indicated a decent conversion rate after 12 h, and the rate was dependent on the amount of PA used. The products have been characterized by NMR and HPLC.

Concerning the work up, only the method stated above was used.

2.1. High-performance liquid chromatography (HPLC)

Reversed-phase high performance liquid chromatography (RP-HPLC) was performed on a Waters HPLC system with two Waters 515 HPLC pumps, Waters 717 plus autosampler, Waters

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