Tetrahedron Letters 53 (2012) 6968–6971

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# Practical separation of alcohol–ester mixtures using Deep-Eutectic-Solvents

Zaira Maugeri [a], Walter Leitner [a,b], Pablo Domínguez de María [a,*]

[a] Institut für Technische und Makromolekulare Chemie (ITMC), RWTH Aachen University, Worringerweg 1, 52074 Aachen, Germany
[b] Max-Planck-Institut für Kohlenforschung, 45470 Mülheim an der Ruhr, Germany

ARTICLE INFO

Article history:
Received 2 August 2012
Revised 4 October 2012
Accepted 9 October 2012
Available online 16 October 2012

Keywords:
Deep-Eutectic-Solvents
Separations
Alcohols
Esters
Kinetic resolutions

ABSTRACT

Deep-Eutectic-Solvents (DES) were assessed for the separation of alcohol–ester mixtures, for example those typically obtained from catalytic kinetic resolutions of racemic alcohols. DES can efficiently dissolve molecules containing hydrogen-bond-donors (alcohols), whereas esters remain as second phase. By using this concept, tedious separation chromatographic steps may be easily overcome with bio-based non-hazardous solvents.

During the course of chemical reactions the desired synthetic targets are often generated in mixtures containing different by-products, non-reacted components, etc. As a consequence, a work-up to purify the desired product until *on-spec* levels is always required. This may represent a challenge for many synthetic reactions, and typically involve tedious and time-consuming separation procedures (e.g. chromatographic separations) that may even hamper the industrial use of a certain reaction/process. An example may be the (catalytic) kinetic resolution of racemic alcohols (via enantioselective acylation) to afford optically active compounds. Once an efficient process is set-up (e.g. using enzymes), the separation of both enantiomers—reacted and unreacted—needs to be accomplished. That separation in many cases is challenging, for example involving time-consuming chromatographic steps. Several alternatives have been reported, for example using polymer-supported substrates,[1–6] fluorous-phase solvents,[7–9] ionic liquids, and mixtures of them with $scCO_2$,[10–13] membrane approaches,[14–16] in situ further derivatization of products,[17] or the use of anhydrides as acyl donors.[18,19] Albeit these approaches are successful, there is still the need for generalizable and easy-to-handle strategies for such purposes.

In this Letter a simple and efficient novel approach for the separation of alcohols and esters (e.g. mixtures typically obtained from enzymatically-resolved racemates) is reported. The strategy is based on the use of Deep-Eutectic-Solvents (DES) as separating agents. DES are a new type of ionic solvents that are straightforwardly formed by gently mixing a quaternary ammonium salt (e.g. cheap and non-toxic choline chloride) together with a hydrogen-bond-donor (e.g. cheap and non-toxic urea, glycerol, sugars, carboxylic acids, etc.), with increasing use in organic synthesis, electrochemistry, bio- and organocatalysis, and in material science.[20–26] The mixture of these two components in appropriate molar proportion generates a sink in the melting point, affording liquid mixtures at room temperature. DES are able to dissolve hydrogen-bond-donor molecules (e.g. alcohols), whereas other non-hydrogen-bond-donor molecules (e.g. esters, ketones, etc.) remain as a second phase in contact with DES. Based on this property, herein it is shown that such difficult-to-separate mixtures of alcohol–esters (e.g. those coming from kinetic resolutions of racemates), can be in fact separated in an efficient, clean, and rapid way (Scheme 1).

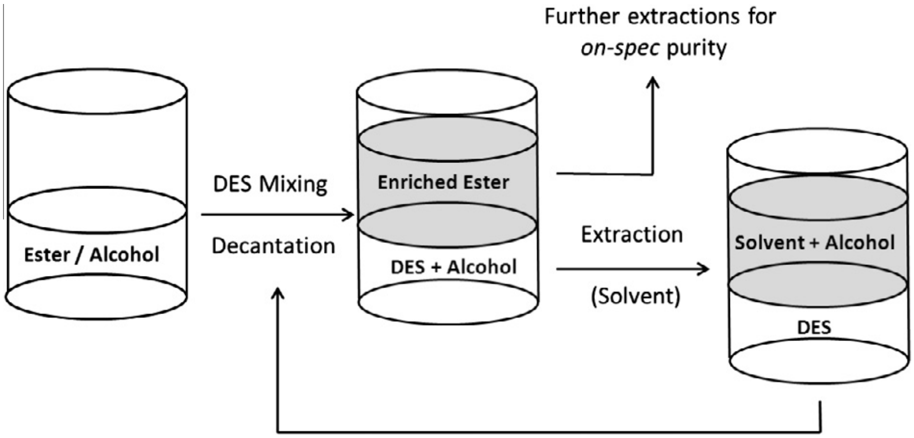
Thus, an ester–alcohol mixture (e.g. as those coming from enzyme-catalyzed kinetic resolution of alcohols) is mixed with DES, and the sample decanted. The upper phase will mainly contain ester (not soluble in DES), whereas the alcohol will dissolve in DES. The upper phase may be subjected to further extractions until *on-spec* purities are reached. Subsequently, the DES-phase can be extracted (e.g. with an organic solvent or with supercritical fluids), to obtain the alcohol and the remnant ester. Despite the potential of DES for such extractive approaches, so far only the biodiesel purification (by removing glycerol),[27–29] or the DES-based extraction of natural products have been reported.[30,31] Very recently the separation of phenol from oils based on DES was reported as well.[32]

To validate the principle, the kinetic resolution of (*R*,*S*)-1-phenylethanol catalyzed by immobilized *Candida antarctica* lipase B (CAL-B) under solvent-free conditions (vinyl acetate–alcohol,

---

* Corresponding author. Tel.: +49 241 8020468; fax: +49 241 8022177.
*E-mail address:* dominguez@itmc.rwth-aachen.de (P. Domínguez de María).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.10.044



**Scheme 1.** Concept for the DES-based extraction.

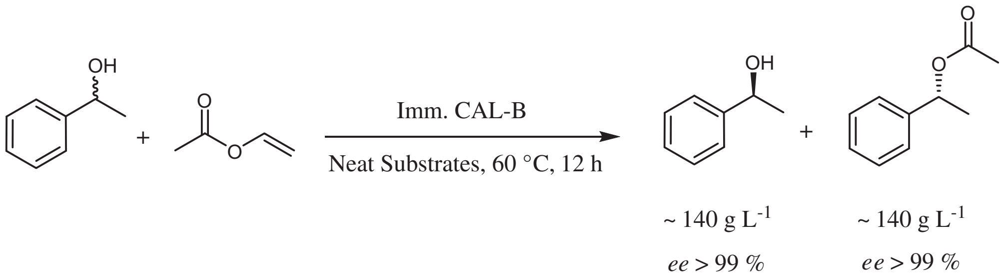
3:1 equiv) was conducted. Full conversions for a kinetic resolution (50%) were enantiospecifically obtained (~140 g $L^{-1}$ in 12 h for each enantiomer) (Scheme 2).

Once the reaction was performed and excess of vinyl acetate removed by distillation, the product mixture (alcohol–ester) was subjected to DES separation. To validate our idea, an inexpensive and easy-to-form DES based on choline chloride and glycerol (1:2 equiv/equiv)[21] was used as extractive agent. Equimolar amounts of 1-phenylethanol and correspondent acetate (Scheme 1) were mixed with DES (Sample:DES 1:5 v/v) and centrifuged. The upper phase was extracted and analyzed ($^1$H NMR). After several extraction cycles ester was isolated in the upper phase with high purity (>99%) and with high efficiency for these non-optimized extraction conditions (~70% recovery, Fig. 1A). Likewise, another assessment was performed in the same extractive conditions for butyl esters, leading to analogous performances, in this case with even higher efficiencies (82% of ester of the mixture recovered, Fig. 1B). To reach a high purity in ester (>99%), four extractive steps were needed. However, each extractive and separation step can be conducted in a matter of minutes (mixing and centrifugation are immediate), and therefore the efficiency and practicality of the method can be assured. Therefore, by applying this novel concept, the need of further chromatographic steps to purify product mixtures would not be necessary at all—or might be significantly simplified—for many synthetic applications (not only related to kinetic resolution of racemates). The broad versatility of DES and their ease of handling may make this proof-of-concept highly valuable and versatile.

To explore the concept in a wider extent, other alcohol–ester mixtures, as well as alcohol–ketone and amine–ketone mixtures, were assessed under the same extractive conditions (Table 1). In all cases purities of 85–99% were achieved in the upper phases, albeit with less efficiencies for aliphatic alcohols and amines with ketones. Given the broad versatility to form DES (at low cost and under environmentally-friendly conditions), it appears feasible that some other tailored DES might provide outstanding separations for these mixtures as well.

Once the upper phase was removed (ester), the extraction of the remnant mixture from the DES was assessed. To this end, an equimolar solution of 1-phenyl-ethanol/1-phenyl-ethyl-acetate was mixed with DES (Choline Chloride: Glycerol, 1:2 equiv/equiv) in the same proportion as before (Sample:DES 1:5, v/v), stirred, and decanted. The upper phase was removed, with a composition of ~70% acetate, and 30% alcohol (1st extraction, see also Fig. 1A). The DES mixture, containing mainly 1-phenyl-ethanol with a part of 1-phenyl-ethyl-acetate was then extracted using either ethyl-acetate or ethyl-acetate–water mixtures (Table 2). The remnant alcohol–acetate could be efficiently extracted from the DES mixture. Other alternatives like distillation (when possible), or solvents (e.g. supercritical fluids) or mixtures thereof might also be considered as extractive agents for further optimized and integrated procedures.

In summary, this Letter has explored the possibility of using DES as extractive agents for work-up procedures. As an example, mixtures of alcohols and esters (e.g. derived from enzyme-catalyzed kinetic resolutions) can be efficiently separated in a straightforward and environmentally-benign manner, along with several extractive cycles, reaching efficiencies of 70–90% in ester, with purities of >99%. Furthermore, the remnant can be extracted from DES by means of another solvent, thus allowing the recovery of the chemicals and DES recycling. The non-toxic nature and low-cost of DES components represent a highly promising alternative for many practical applications with challenging separation steps. Furthermore, the broad versatility in producing DES may obviously be envisaged as a future tool for tailored extractive solvents in (industrial) synthetic procedures.



**Scheme 2.** CAL-B-catalyzed kinetic resolution of (*R*,*S*)-1-phenylethanol under 'solvent-free', neat substrates. Reaction conditions: 2.4 mmol of (*R*,*S*)-1-phenylethanol; 7.5 mmol of vinyl acetate; enzyme loading 30 mg $mL^{-1}$, temperature 60 °C; 12 h.