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Efficient and Low-Impact Acetalization Reactions in Deep Eutectic Solvents

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Abstract: The synthesis of acetals in acidic natural deep eutectic solvents (NADES), in which the solvent itself participates in the catalytic promotion of the reaction, is reported herein. The reaction is performed under feasible conditions, open air, without the need of external additives, catalysts or water-removing techniques, and it is wide in scope. The products are easily recovered, and the reaction medium is fully recycled and reused without weakening of its catalytic activity after 10 times. Remarkably, the entire process has been realized on gram scale.

Introduction

Among organic compounds acetals are basilar and widely represented functional groups. Besides being the key functional group in carbohydrates, they are well represented in many other natural compounds, flavouring additives and aroma enhancers in cosmetic and food products,[1] and anti-freezing additives in biodiesel fuels.[2] Their use as protecting groups in organic synthesis represents a still extensively employed methodology to temporarily suppress the reactivity of carbonyls and to design feasible synthetic strategies.[3]

Traditionally, acetals are generated starting from aldehydes or ketones and alcohols in the presence of typical strong acid catalysts (trifluoroacetic acid, *p*-toluenesulfonic acid, dry HCl or H_2SO_4 among others) which are often used in stoichiometric amount and are corrosive.[4] In addition, acidic conditions are often incompatible with many functional groups of the substrate such as alkenes, alkynes, silyl protected alcohols and *N*-Boc-protected amines.[5] However, acetals often suffer of high hydrolytic instability because of the reversibility of the acetalization reaction, making essential the azeotropic removal of water to avoid backshift of the equilibrium. As a matter of fact, the high temperatures required for the azeotropic distillation process are frequently too harsh for sensitive functionalities. These main drawbacks have been addressed in the last two decades by several greener approaches. $Fe(HSO_4)_3$,[6] InF_3,[7] $In(OTf)_3$,[8] $Bi(OTf)_3$,[9] as well as metal free conditions in the presence of catalytic organic acids as ammonium,[10] phosphonium,[11] tropylium salts,[12] Schreiner's thiourea[13] and arylazo sulfones[14] under photocatalytic conditions have been proposed. Heterogenous catalysis also accounts for successful acetalization conversions at room temperature.[15] Very mild conditions with 0.1 mol% acid and no need of water removal have also been proposed.[16] Both Ionic Liquids (ILs) based on benzimidazolium[17] and Lewis acid-based ILs[18] have been reported as recyclable catalysts to promote acetalizations. Among more recent approaches which rely on the use of unconventional solvents, Azzena et al. developed acetalization processes of aliphatic and aromatic carbonyls with diols employing ammonium salts as acidic catalysts, either under homogeneous[19] or heterogeneous catalysis.[20] Lastly, Deep Eutectic Solvents were used to convert monosaccharides and methyl glycosides in mono- and di-*O*-isopropylidene derivatives,[21] and alcohols in THP (tetrahydropyranyl) derivatives, respectively.[22] However, despite the many reports found in the literature, most of them suffer from several drawbacks such as poor chemoselectivity and atom-economy, need of drying agents, high reaction temperatures, stoichiometric amounts of acids and limited scope of substrates thus limiting the application of acetalization in chemical synthesis. Moreover, the preparation of acetals is commonly achieved in solvents such as acetonitrile, THF, benzene, toluene and DMF leading to complex product recovery and isolation procedures. Therefore, the need for greener, safer and more environmentally friendly technologies is highly desirable.

In this context, we became recently interested in the use of DESs either as solvents[23] or non-innocent solvents in organic synthesis.[22,24] DES are generally defined as mixtures composed by an HDB (Hydrogen Bond Donor) and an HBA (Hydrogen Bond Acceptor). The supramolecular structure of these mixtures, characterized by an extensive hydrogen bonding pattern,[25] impacts on the reactivity of common reagents and often provides an unexpected reactivity to traditional synthetic transformations.[23a,b] When the components are small natural molecules (i.e. organic acids, amino acids) they are referred to as natural deep eutectic solvents (NADES).

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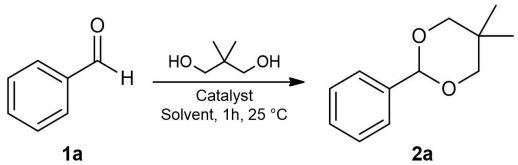
NADESs, being much more than a sustainable alternative to traditional solvents, can have an active role in promoting organic reactions, by improving the reaction rate, the yield and allow for milder conditions.[26] As an extension of our work with unconventional solvents, in this paper we investigated the feasibility of the use of acidic NADESs as non-innocent solvents to perform the acetalization reaction, with a special focus on the scalability and recyclability of the process.

Results and Discussion

Reaction development

Bearing in mind the crucial role played by the medium NADES in promoting the acetalization reaction, we started our investigation by the evaluation of the reaction conditions on benzaldehyde **1a** and neopentyl glycol as model reagents (Table 1). A first set of ChCl/carboxylic acid based NADESs was tested (Table 1, entries 1–5) with 1.2 equiv of neopentyl glycol at room temperature, (1 mmol of **1a** for 400 mg of NADES) and 1 h reaction time. Very good yields were obtained using NADESs containing malonic (entry 1), oxalic (entry 2), L-(−)-malic (entry 3) and L-(+)-lactic acid (entry 5), acceptable yields with glutaric acid (entry 4), very low yields are instead obtained with glycerol and urea-based NADES (entries 6 and 7). Assuming that in general the acidity of the NADES is governed by the acidity of the HBD (Hydrogen Bond Donor) component, we then tried to rationalize these results, taking into consideration the pK_a of the acidic component of the NADES. NADESs containing L-(−)-malic acid (pK_a = 3.40) and L-(+)-lactic acid (3.86), were as effective as those containing oxalic (1.23)[27] and malonic (2.83) acid,[28] whereas with glutaric acid (4.34) (see entry 4, Table 1) there is a drop in the yield to 50%, while glycerol (14.4)[29] and urea (26.9)[30] were ineffective in promoting the reaction. Taken together, these data show that there is a coherence between the performance of the acetalization reaction and the pK_a of the acidic component of the NADES. However, the acidic properties of NADES mixtures can differ from those of their components alone, and moreover they can be significantly affected by the temperature. An increase of temperature leads to an enhancement of the acidity of the medium.[31] In our study, except for compounds **2j**, **2l**, **2m**, **2x** and **2ar** of the scope (see below) all the reactions efficiently worked at room temperature. We then decided to proceed our study with ChCl/malonic acid 1:1 mol/mol and optimize the equivalents of diol used. With 1.0 equiv of diol the yield decreases to 72% (entry 8), while using 2.0 equiv there is no significant gain in the yield (entry 9). Based on these results we decided to proceed in our investigation using 1.2 equiv of diol as the best compromise between yield and amount of reagent used. We then tried to elucidate the role of the acidic component of the NADES. To this purpose, we performed the acetalization reaction in various organic solvents by addition of the NADES single components either in stoichiometric or in catalytic amount with respect to the substrate. The results obtained show that 0.2 equivalents (entry 11) are rather ineffective in promoting the reaction, while the use of 1.6 equiv (entries 10, 12–14) affords good yields in all cases, even though not as high as those obtained in DES, thus confirming an active role of the DES as non-innocent solvent. Finally, we performed the reaction in acetonitrile with 1.6 equiv of ChCl (entry 15) or alternatively in the absence of catalyst (entry 16). In both cases we recovered the starting material thus proving that the acidic component is essential in promoting the reaction and no other mechanisms or alternative pathways come into play in this case.

Table 1. Acetalization reaction of benzaldehyde **1a** under different reaction conditions.[a]



1a **2a**

entry	Solvent	Diol (equiv)[b]	**2a** (yield [%])[c]
1	ChCl/malonic acid 1:1	1.2	89
2	ChCl/oxalic acid 1:1	1.2	81
3	ChCl/L-(−)-malic acid 1:1	1.2	86
4	ChCl/glutaric acid 1:1	1.2	50
5	ChCl/L-(+)-lactic acid 1:1	1.2	78
6	ChCl/glycerol 1:2	1.2	8
7	ChCl/urea 1:2	1.2	0
8	ChCl/malonic acid 1:1	1.0	72
9	ChCl/malonic acid 1:1	2.0	87
10	Toluene[d]	1.2	73
11	Toluene[e]	1.2	28
12	CPME[d]	1.2	74
13	DCM[d]	1.2	84
14	MeCN[d]	1.2	83
15	MeCN[f]	1.2	0
16	MeCN	1.2	0

[a] Reaction conditions: **1a** (1.0 mmol), NADES (mol mol^{-1} ratio, 400 mg) *or* solvent (0.500 mL), 1 h, 25 °C, under vigorous stirring. [b] Neopentyl glycol. [c] Determined by quantitative GC-FID analyses using calibration curves of **2a** (see Supporting Information for details). [d] 1.6 equiv of malonic acid were added as promoter. [e] 0.2 equiv of malonic acid were added as promoter. [f] 1.6 equiv of ChCl were added.

Reaction kinetic

We also investigated the kinetic of the reaction at two different temperatures, 25 °C and 0 °C respectively (see Supporting Information). The obtained results indicate that the process is very fast, and high conversions are reached within less than 5 min at room temperature. The highest conversion is reached in 10 min and remains unchanged even after 3 h. This supports the hypothesis that the NADES itself retains the water formed during the acetalization reaction thus preventing the backshift of the equilibrium to the starting reagents. Indeed, most DES have already been demonstrated to show hygroscopic behaviour. Water can be absorbed both at the surface and in the bulk.[32] At 0 °C the reaction is as expected slower, and the highest conversion is reached in 30 min.

Gram scale reaction and NADES recycling

We then investigated the recyclability of the active solvent system. To this purpose, the reactions were performed on a 25 mmol scale starting from 2.65 g of benzaldehyde **1a**, 3.12 g (30 mmol, 1.2 equiv) of neopentyl glycol and 10 g of ChCl/malonic acid 1:1 mol/mol. The mixture was stirred at RT for 1 h and 20 mL of water were then added to dilute the NADES. Product **2a** precipitates as white crystals and was easily recovered via vacuum filtration. NADES was then regenerated after removal of water by *in vacuo* distillation. After every cycle we carefully checked the structure of the NADES by ^{1}H NMR and evaluated the content of residual water by Karl-Fischer titration (see Supporting Information). We performed experiments with recycled NADES at various content of residual water (from 0.4 to 17.1% w/w, see Table S6) and did not observe a significant variation in yield of the product within this range of water content. The NADES was then reused again for the reaction together with the water recovered by distillation and used for the dilution (Figure 1, top). Ten reaction cycles were successfully performed without any decrease in the yield, which remains always above 88% (Figure 1, bottom) with a total of 45.7 g of product obtained with the same recycled NADES.

Key *Green Chemistry* metrics like E-factor and process mass intensity (PMI) were also evaluated for the gram-scale acetalization reaction of **1a** in ChCl/malonic acid (1:1 mol/mol). From the results shown in Figure 2 a comparison between the single run reaction and the ten-cycle process from NADES recycling highlights clear advantages in terms of sustainability.

Reaction scope and chemoselectivity

We then explored the scope of the reaction on various substrates, as reported in Scheme 1. Different diols have been used with benzaldehyde **1a** giving acetals **2a–2d** in good yields, with 1,3-propanediol achieving the highest yield (**2c**, 96%). Unfortunately, under these conditions ethylene glycol acetals cannot be obtained. The scope on the carbonyl substrate was then explored starting with electron poor benzaldehydes (Scheme 1, box EWG) with yields ranging from 62 to 96%. The reaction proceeds with excellent chemoselectivity as ketones (**2m**), amides (**2n**), esters (**2o**), carboxylic acids (**2p**), acyl chlorides (**2q**), nitriles (**2r**). Good yields have been also obtained with electron donating substituted benzaldehydes (Scheme 1, box EDG). The scope of the reaction was extended to polyaromatic substrates (**2aa–ac**), to heteroaryls like furyl (**2ad**) and thienyl (**2ae**), and to ferrocenyl carboxaldehyde (**2af**, Scheme 1, box Hetero and Polycyclic Arenes). Alkyl (**2ag**, **2ai**, **2aj**), cycloalkyl (**2ah**), alkenyl aldehydes (**2ak–2am**) gave very high yields without any isomerization or hydration/electrophilic addition side products. Ketones show a very limited reactivity in the acetalization reaction under these conditions (**2ap** and **2aq**, Scheme 1). The methodology can be also extended to the formation of thioacetals **2as** and **2at**. Remarkably, this procedure can be also applied to the synthesis of open-chain acetals.[33] In this case the replacement of diol with 1.5 equivalents of trimethylorthoformate or triethylorthoformate afforded the dimethyl **2au** and diethyl **2av** acetals of benzaldehyde in good yields at room temperature.

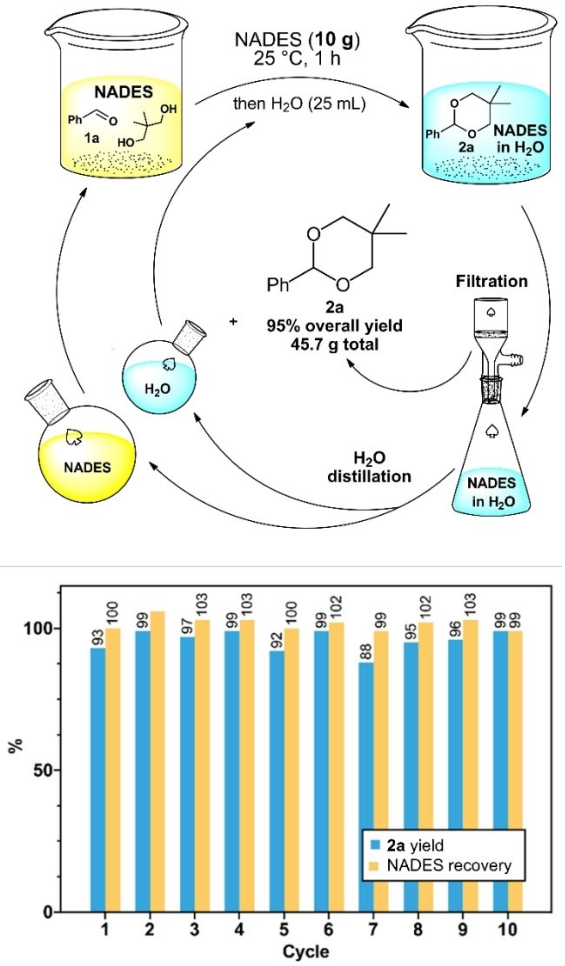


Figure 1. Gram-scale reaction and recycling procedure (top), and recyclability of the ChCl/malonic acid (1:1 mol mol^{-1}) deep eutectic mixture (bottom). Yields refer to isolated products.

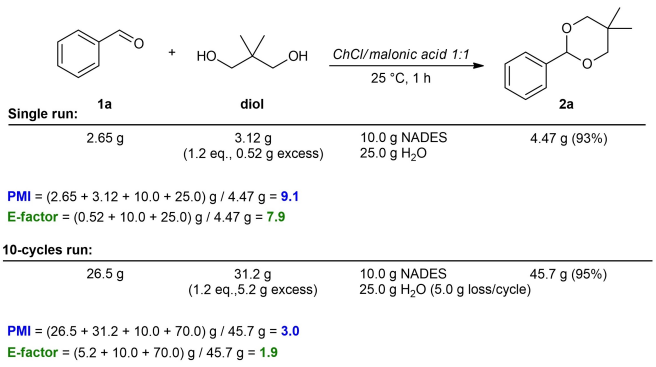
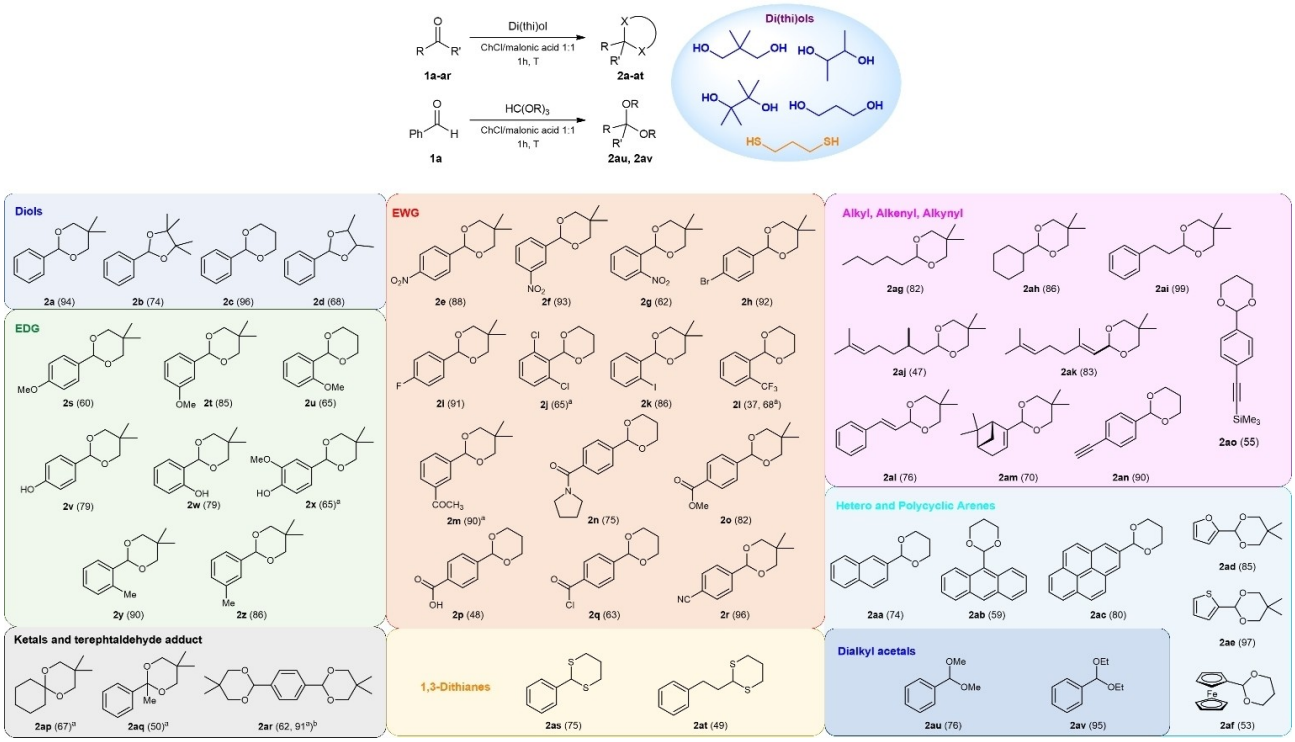


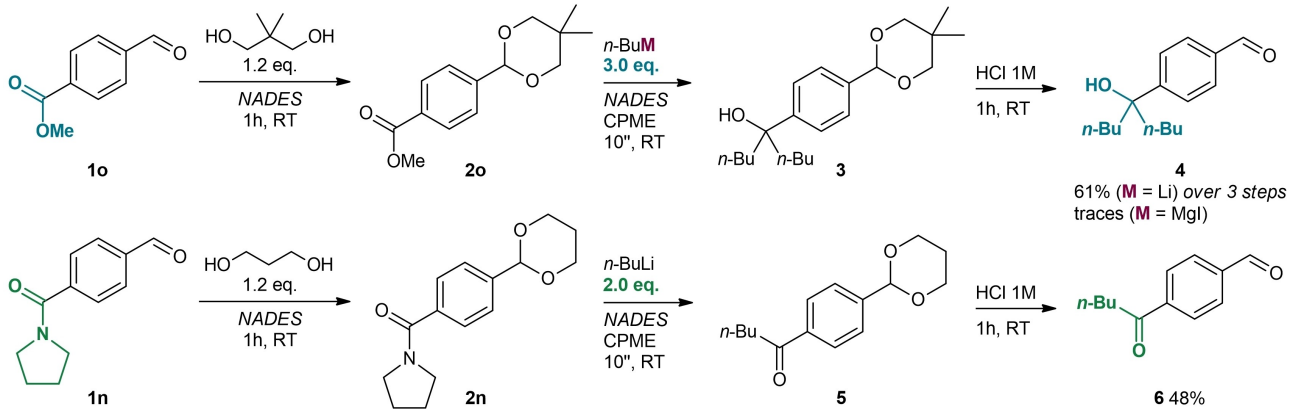
Figure 2. E-factor and process mass intensity (PMI) for the gram-scale acetalization reaction of **1a** in ChCl/malonic acid (1:1 mol mol^{-1}).



Scheme 1. Scope of the acetalization reaction in NADES (ChCl/malonic acid 1 : 1 mol mol^{-1}, 400 mg per 1.0 mmol of substrate). [a] Reaction performed at 50 °C. [b] 2.4 equiv of diol were used. Yields (in brackets) refer to isolated products.

Cascade process

We then explored the feasibility of this methodology in cascade processes (Scheme 2). *Para*-formyl methyl benzoate **1o** which possesses both an aldehyde and an ester as functional groups was chosen as substrate to realize the synthesis of final compound **4** (Scheme2, top). The addition of an organolithium reagent to the ester to obtain **4** implies the protection of the more electrophilic aldehyde. We then applied our protocol starting from 0.5 mmol of *p*-formyl methyl benzoate **1o** to form acetal **2o**, which was not isolated and directly used in the following step. In this case, CPME (cyclopentyl methyl ether) is then added as co-solvent[23a,c,e] to form a heterogeneous mixture and thus facilitating the vigorous stirring, then 3.0 equiv of *n*-BuLi were rapidly spread over the heterogeneous mixture under air. The reaction was quenched after 10 seconds with water to finalize the formation of the tertiary alcohol **3**. Final product **4** was then obtained by simple acidic work-up with diluted HCl in 61 % yield over three steps. It has already been demonstrated that organolithium reagents can be used in protic medium,[23a,c,d,e] however it is noteworthy to emphasize that in this case the reaction successfully proceeds even in an acidic



Scheme 2. One-pot cascade processes (NADES: ChCl/malonic acid 1 : 1 mol/mol).

medium, implying that the kinetic of addition to the electrophile is faster than the protonolysis. On the other hand, the use of the corresponding Grignard reagent (*n*-BuMgI) to perform the same cascade transformation was unsuccessful. Indeed, previous studies reported the complete protonation of Grignard reagents in competition with nucleophilic additions in protic environments.[34]

To further highlight the utility and the robustness of our methodology, we designed a cascade process for an efficient preparation of 4-pentanoylbenzaldehyde **6**. One pot acetalization of aldehyde **1n**, followed by an in situ nucleophilic acyl substitution reaction promoted by *n*-BuLi (2.0 equiv) on *N*-acylpyrrolidine **2n** intermediate, afforded **6** in 48% overall yield (Scheme 2, bottom).[23b,c] Taken together, these cascade, one-pot protection/nucleophilic addition sequences contribute to enlarge the portfolio of organolithium-mediated transformations in protic eutectic mixtures under aerobic conditions.[22, 23a,c,d,e]

Conclusion

Deep eutectic solvents nowadays find a large number of applications in organic synthesis. We have demonstrated that the NADES, in which one of the components is an organic acid, not only acts as a green and renewable solvent but plays an active role as promoter of the acetalization reaction. The procedure is easily performed at room temperature, open air and in short reaction times. There is no need of water-removal techniques to shift the reaction equilibrium towards the products as the NADES itself retains the water byproduct. The scope of the reaction is wide and applicable to almost every aldehyde, with high functional group tolerance including acid labile moieties. Reactivity versus ketones is instead limited thus opening the way to chemoselective transformations. A very simple procedure allows the recyclability of the solvents without decrease in the yield. Remarkably, after 10 reuses the yield of both the product and the solvent recovery remain close to quantitative.

Experimental Section

General procedure for the acetalization of carbonyl compounds 1: Reactions were performed under air at room temperature unless otherwise specified. In an open screw cap vial, substrate **1** (1.0 mmol, 1.0 equiv), di(thi)ol (1.2 mmol, 1.2 equiv) or trialkylorthoformate (1.5 mmol, 1.5 equiv) and ChCl/malonic acid (1:1 mol/mol, 400 mg) were added. The resulting mixture was stirred for 1 h. The mixture was then diluted with water (10 mL) and extracted with the selected solvent (3×5 mL). The combined organic extracts were washed with sat. aqueous $NaHCO_3$ (1×5 mL), $NaHSO_3$ (1×5 mL) and brine (1×5 mL) then dried over Na_2SO_4 and the solvent removed under reduced pressure. When required, the crude product was purified by flash column chromatography or by recrystallization (see Supporting Information).

General procedure for the gram-scale acetalization of 1a: Reactions were performed under air at room temperature. A 100 mL round bottom flask was charged with benzaldehyde **1a** (2.65 g, 25 mmol, 1.0 equiv), neopentyl glycol (3.12 g, 30 mmol, 1.2 equiv) and ChCl/malonic acid (1:1 mol/mol, 10 g, 0.4 g per mmol of substrate). The mixture was then stirred for 1 h. Deionized water (15 mL) was added, causing the precipitation of the product as white crystals. Product **2a** was recovered via vacuum filtration and washed with water (2×5 mL). Water (25 mL total) was then evaporated and recovered by distillation under reduced pressure to afford the eutectic mixture and both were used for the next reaction cycle (see Supporting Information). Product **2a** was obtained as a white solid (R_f = 0.75 pentane/Et_2O 95/5 v/v), mp 32.5–33.6 °C (pentane). **^{1}H NMR** (600 MHz, DMSO-d_6): δ 7.45–7.40 (m, 2H), 7.39-7.33 (m, 3H), 5.41 (s, 1H), 3.67 (d, *J* = 11.0 Hz, 2H), 3.63 (d, *J* = 10.7 Hz, 2H), 1.19 (s, 3H), 0.75 (s, 3H). **^{13}C{^{1}H} NMR** (150 MHz, DMSO-d_6): δ 138.7, 128.6, 128.0, 126.2, 100.8, 76.5, 29.8, 22.7, 21.4. **EI-MS** *m/z* (%): 192 (M^+, 51), 191 (100), 107 (74), 105 (57), 77 (24), 56 (29).

Cascade process for the synthesis of compound 4: General procedure for cyclic acetals (see Supporting Information) starting from **1o** (0.5 mmol, 1.0 equiv) and 2,2-dimethylpropane-1,3-diol (0.6 mmol, 1.2 equiv). After 1 h, CPME (200 μL) was added and then *n*-BuLi (1.5 mmol, 3.0 equiv, 2.5 M in hexanes) was rapidly spread over the mixture. After 10 seconds water (2 mL) then HCl 1 M (8 mL) and CPME (5 mL) were added and the mixture stirred vigorously for 1 h at room temperature. Then the aqueous phase was further extracted with CPME (2×5 mL). The combined organic phases were washed with sat. $NaHCO_3$ (1×5 mL), dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography (PE/EtOAc 9/1 v/v) gave **4** as a colorless oil (76 mg, 61%, R_f = 0.31 PE/EtOAc 9/1 v/v). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 10.00 (s, 1H), 7.85 (d, *J* = 8.3 Hz, 2H), 7.55 (d, *J* = 8.3 Hz, 2H), 1.89–1.70 (m, 5H), 1.30-1.19 (m, 6H), 0.98–0.90 (m, 2H), 0.82 (t, *J* = 7.2 Hz, 6H). **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$): δ 192.3, 153.9, 134.8, 129.8, 126.2, 43.0, 25.6, 23.1, 14.1. **EI-MS** *m/z* (%): 230 (1), 192 (14), 191 (100), 135 (7), 91 (6), 28 (4).

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: acetalization · acid catalysis · deep eutectic solvents · protecting groups · sustainable chemistry

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