Low-melting sugar–urea–salt mixtures as solvents for Diels–Alder reactions†

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Sweet solutions are obtained upon heating mixtures of simple carbohydrates, urea and inorganic salts to moderate temperatures, to give new chiral media for organic reactions.

The reduction of the use of organic solvents is one goal in current efforts towards more environmentally benign chemical processes. Organic solvents are typically used in large excess compared to the reactants and have the tendency to escape into the environment by evaporation or leakage. Therefore the scope of reaction media for chemical transformations in solution has been extended in the past years to ionic liquids,[1] water[2] and scCO$_2$.[3] In principle, water is the ideal solvent being non-toxic, cheap and available, but its use is limited because most organic compounds do not dissolve in pure water and many reactive substrates or reagents decompose in water.[4] scCO$_2$ is an interesting environmentally friendly, non-toxic alternative to organic solvents with additional benefits as a reaction medium, such as its ready availability, ease of removal, disposal or recycling. However, its use requires more sophisticated equipment than standard lab apparatus. Ionic liquids have received a lot of attention as green solvents for their properties: no measurable vapour pressure, stability in a wide temperature range and recyclability. However, in most cases their preparation uses non-renewable resources[5] and toxicity issues remain to be addressed. We report here the use of low-melting mixtures of sugars or sugar alcohols, urea and inorganic salts as solvents for Diels–Alder reactions. The reaction medium consists only of non-toxic compounds from readily available resources and has, like ionic liquids, small vapour pressure.

An initial screening identified stable and low-melting mixtures of bulk carbohydrates, urea and inorganic salts. Table 1 summarizes the most suitable melts in terms of stability and melting temperature (see ESI for additional data†). To evaluate the thermal stability of the melts all mixtures were analysed by differential scanning calorimetry (DSC), through three heating–cooling cycles, which showed no thermal decay. In addition, the mixtures were heated for 4 h to 95 °C without any evident decomposition.

The fructose–urea mixture gives a clear viscose melt at 65 °C, while for sorbitol the addition of NH$_4$Cl was necessary to achieve such low melting temperature (see Fig. 1). Other carbohydrate, urea and salt mixtures with melting temperatures around 75 °C were identified and surprisingly even a citric acid–urea mixture

Table 1 Stable melts of carbohydrates, urea and inorganic salts

| Melting points[a]	Carbohydrate	Urea	Salt
65 °C	Fructose (60%)[b]	Urea (40%)	—
67 °C	Sorbitol (70%)	Urea (20%)	NH$_4$Cl (10%)
73 °C	Maltose (50%)	DMU[c] (40%)	NH$_4$Cl (10%)
75 °C	Glucose (50%)	Urea (40%)	CaCl$_2$ (10%)
75 °C	Mannose (30%)	DMU[c] (70%)	—
77 °C	Sorbitol (40%)	DMU (60%)	—
77 °C	α-Cyclodextrin (30%)	DMU[c] (70%)	—
65 °C	Citric acid (40%)	DMU[c] (60%)	—

[a] Melting points are at normal pressure in air. [b] w/w percent of the compounds in the mixture. [c] DMU = *N,N*-dimethylurea

gave a stable melt at 65 °C. Our survey is not comprehensive and we presently cannot derive simple indicators to predict stability and melting temperature of such mixtures, but the examples show that the concept is rather general.

The water content of a solvent is an important parameter, which was determined to be exemplary for the mixture of sorbitol (70), urea (20) and NH$_4$Cl (10) by Karl Fischer titration. Using vacuum-dried raw materials for preparation of the mixture, a typical water content of 0.07% was found; using raw materials as received, the water content is approx. 1.3% (see ESI†). A vapour pressure of 1.2×10^{-1} mbar at 70 °C was determined for a melt of this composition. The thermal stability of some mixtures was investigated by differential scanning calorimetry (see ESI for data†). The melts are stable in subsequent heating–cooling cycles to 120 °C. For the mixture sorbitol (70), urea (20), NH$_4$Cl (10) a decomposition temperature of 220 °C was determined. The thermal behaviour is identical for mixtures prepared from dried or as-received raw material.

Fig. 1 Sorbitol (left) and a mixture of sorbitol/urea/NH$_4$Cl (70:20:10) (right) at 80 °C.
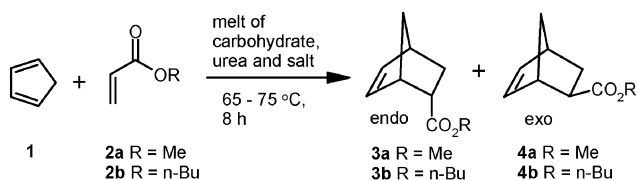
Scheme 1 Diels–Alder reactions performed in carbohydrate melts.

The most suitable mixtures were then used as solvent for a Diels–Alder reaction. The reaction of cyclopentadiene with methyl (**2a**) and *n*-butyl acrylate (**2b**) (Scheme 1) proceeded cleanly and with high conversions in 8 h. Table 2 summarizes the results (for more data see ESI†). Work up and product isolation requires simply addition of water to the reaction mixture while still hot. The reaction medium dissolves, leaving an aqueous phase and the organic product for isolation.[6] Alternatively, products with a low boiling point can be removed from the reaction mixture by applying high vacuum, which allows a simple reuse of the melt for several reaction runs.

The observed *endo–exo* selectivity of the Diels–Alder reactions of **2a** and **2b** with cyclopentadiene in the melted mixtures range from 2.5:1 to 5:1, with the highest selectivity in the sorbitol melt. These ratios are comparable to selectivities reported for other green solvents, such as scCO$_2$ (**2a** at 50 °C, 3:1),[7] water (85 °C; **2a**, 3:1; **2b**, 2.5:1),[8] 1-butyl-3-methylimidazolium trifluoromethanesulfonate (20 °C, ethyl acrylate, 6:1),[9] 1-butyl-3-methylimidazolium tetrafluoroborate (−15 °C, ethyl acrylate, 5:1) or 1-butyl-3-methylimidazolium hexafluorophosphate (20 °C, ethyl acrylate, 8:1). As well known for reactions in organic solvents, Lewis acids catalyze Diels–Alder reactions and can improve rate and selectivity in alternative reaction media too.[7,10] Therefore the reactions in carbohydrate–urea melts were repeated with the addition of 1 equiv. of LiClO$_4$ or 10 mol% of Ce(OTf)$_3$, but selectivity ratios

did not change significantly (see ESI for data†). Interestingly the addition of 10 mol% of Sc(OTf)$_3$ to the sorbitol/DMU/NH$_4$Cl (70:20:10) melt improved the *endo–exo* selectivity to 6:1 for **2a** and 10:1 for **2b**. The effect of this Lewis acid is comparable to selectivity improvements observed for Diels–Alder reactions in toluene [50 °C, 10 mol% Sc(OTf)$_3$: **2a**, 4:1; **2b**, 10:1], but smaller than in scCO$_2$ [50 °C, 10 mol% Sc(OTf)$_3$: **2a**, 10:1; **2b**, 24:1]. All of the reaction media used in this study are chiral solvents and therefore the possibility of a stereoinduction was investigated. However, the analysis of the products by chiral GC did not reveal any significant stereoinduction, as for many other attempts using chiral solvents.[11,12]

In summary, we have reported the use of low-melting mixtures of bulk natural products, such as simple carbohydrates, sugar alcohols or citric acid, with urea and inorganic salts as reaction media for Diels–Alder reactions. In comparison to conventional organic solvents a fast conversion[13] with good *endo–exo* selectivities was observed. The addition of Sc(OTf)$_3$ improved the *endo–exo* selectivity ratios similarly as observed for the reaction in toluene, but less than in scCO$_2$. Although chiral, no significant stereoinduction of the medium on the course of the reaction was detected. The non-toxic reaction media, made only from bulk, readily available compounds, qualify as green solvents. Their application as reaction media for other organic transformations and as a substitute to ionic liquids may be envisaged.

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Table 2 Diels–Alder reactions in carbohydrate–urea–salt melts

Composition of melt	Reaction temp. (°C)	Dienophile	Yield^a (%)	*Endo/exo* ratio^b
Fructose/DMU^c	71	**2a**	quant.	2.9:1
(70:30)		**2b**	95	3.0:1
Maltose/DMU/NH$_4$Cl	83	**2a**	79	3.3:1
(50:40:10)		**2b**	80	3.9:1
Lactose/DMU/NH$_4$Cl	88	**2a**	83	3.6:1
(60:30:10)		**2b**	72	2.1:1
Mannitol/DMU/NH$_4$Cl	89	**2a**	74	2.7:1
(50:40:10)		**2b**	92	3.5:1
Glucose/urea/CaCl$_2$	75	**2a**	76	3.2:1
(50:40:10)		**2b**	93	2.6:1
Sorbitol/DMU/NH$_4$Cl	67	**2a**	quant.	5.0:1 (6.0:1)^e
(70:20:10)		**2b**	83	3.7:1 (10:1)^e
Citric acid/DMU	65	**2a**	quant.^{d}	3.6:1
(40:60)		**2b**	quant.^{d}	2.6:1
α-Cyclodextrin/DMU	77	**2a**	quant.^{d}	3.5:1
(30:70)		**2b**	quant.^{d}	3.6:1

^{a} Isolated yields after extraction. ^{b} Determined by gas chromatography (GC). ^{c} DMU = *N,N*-dimethylurea. ^{d} Quantitative conversion as monitored by GC. ^{e} Selectivity ratio with addition of 10 mol% of Sc(OTf)$_3$.

Notes and references

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4 Another drawback is the high heat capacity, which makes removal of the solvent from reaction mixtures or products very energy consumptive.

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6 For small scale reactions extraction with an organic solvent, such as pentane or toluene, is necessary to avoid loss of material.

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