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Fructose-derived ionic liquids: recyclable homogeneous supports

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Abstract—A new homogeneous support has been developed that is based on a fructose-derived ionic liquid. It has been applied to the preparation of a series of supported Diels–Alder adducts. The cleavage of these adducts from the ionic liquid has resulted in some interesting observations regarding the base stability of imidazolium cations. Using a transesterification cleavage, the ionic support can be recovered and recycled.

In the context of a project directed at the synthesis of room temperature ionic liquids (RTILs) from biorenewable sources, we have reported the preparation of a new family of RTILs based on fructose.[1] While these new materials can be used as solvents in conventional organic reactions,[2] their protic nature and the presence of a hydroxyl group indicated that there could be some new applications of these materials beyond those typically encountered with 'non-functionalized' RTILs.[3] In this communication, we report our preliminary studies utilizing the hydroxymethylene group as a tether for supported organic synthesis.

Supported synthesis is a widely employed technique that has greatly facilitated the synthesis of many compounds and is the critical element behind the explosion in combinatorial synthesis.[4] Traditionally, supported synthesis has employed a heterogeneous material such as cross-linked polystyrene to support one of the reactants. The primary advantage of such a choice is that the supported material, being heterogeneous, can be readily separated by simple filtration from the reaction medium and by-products. At the same time, this heterogeneity limits the types of reactions and reaction conditions that can be employed. Further, using simple polystyrene supports, which are typically functionalized to <10%, the maximum loading is <2 mmol/g.

These limitations have led more recently to the development of a variety of 'soluble' supports (e.g. the polyethyleneglycol (PEG) supports popularized by Janda).[5] Since the supports are homogeneous in a variety of conventional organic solvents, reactions can be performed under conventional solution-phase conditions. At the same time, by changing the polarity of the solvent (most frequently by the addition of methanol), the support and supported molecule will precipitate, resulting in facile separation by filtration.

While this is a major step forward, there are still limitations to the current soluble supports. First, using simple PEG supports, the maximum loading that can be achieved is even lower than that of polystyrene supports (<1 mmol/g).[6] Second, the highly oxygenated nature of the PEG supports can interfere in certain types of reactions or even be degraded under certain reaction conditions.

With this in mind, our recently reported fructose-derived ionic liquid **1** appeared to hold several advantages. First, the molecular weight of the ionic liquid is relatively low and each molecule can be used as a support, meaning that reasonably high effective loadings of ionic support **1** (>2 mmol/g) could be achieved. Second, it is well established that the solubility properties of ionic liquids in general can be tuned based upon the anion and alkyl chain length in the cation.[7] As a result, supports could be developed that would be immiscible in either polar solvents or non-polar solvents and this immiscibility used to separate reaction by-products from the supported products.[8]

This tunable miscibility was also observed with the fructose-derived ionic liquids. Thus, ionic liquid support **1** was found to be immiscible with very low polarity solvents (hexane and cyclohexane) and with

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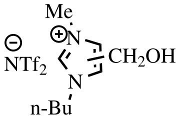
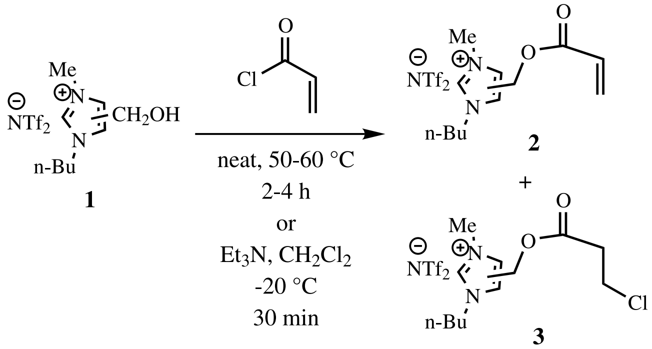
polar solvents (water and methanol). On the other hand, the same ionic liquid with a dicyanimide anion was completely miscible with polar solvents such as water and methanol, but immiscible with lower polarity solvents such as hexane, toluene, and diethyl ether. These complimentary behaviors could be of considerable use in future applications of these ionic liquid supports. For the present research, efforts focussed on the use of the triflimide support **1**.


1

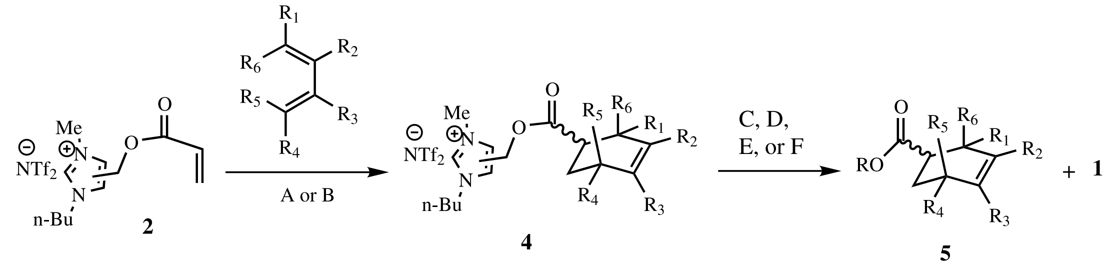
In order to explore the possible application of fructose-derived ionic liquids as a new class of soluble supports, our first focus was on the preparation of some simple acrylate-derived Diels–Alder adducts. The first stage in these studies was therefore to prepare acrylate **2** by the reaction of acryloyl chloride with alcohol **1** (Scheme 1). Immediately, problems were encountered. Attempts using standard pyridine or triethylamine mediated conditions afforded a dark, tarry mixture from which only modest amounts of the desired acrylate could be separated. A report by Aggarwal did shed some light as to the potential problem, since he had noted that the use of imidazolium-based ionic liquids as the solvent for the Baylis-Hillman reaction resulted in extensive deprotonation of the C2-position of the imidazolium ring, thereby greatly complicating the resulting reaction mixture.[9]



Scheme 1. Acylation of ionic support **1**.

In an effort to determine if a similar situation was responsible for our observations, an attempt was made to acylate alcohol **1** in the absence of base. Under neat reaction conditions, acrylate **2** was obtained along with hydrogen chloride addition product **3** in a 3:1 ratio. Since product **3** did not interfere in subsequent reactions, this mixture could be used as is. Further optimization lead to the discovery that acrylate **2** could be cleanly prepared by acylation at low temperature (–20°C) in the presence of triethylamine without the concomitant formation of any of product **3**.[10]

Table 1. Diels–Alder reactions and support cleavage reactions using acrylate **2**



Entry	R$_1$	R$_2$	R$_3$	R$_4$	R$_5$	R$_6$	R	Conditions[a]	Yield (%)[b]	*endo*/*exo*[c]	Recovered **1**
1	H	H	H	H	-CH$_2$-		H	A,C	65	3:1	
2	H	CH$_3$	CH$_3$	H	H	H	H	B,D	66	NA	
3	CH$_3$	H	H	H	H	H	H	B,D	29	6:1[d]	
4	H	CH$_3$	H	H	H	H	H	B,E	74	5:1	
5	H	H	H	H	-(CH$_2$)$_2$-		CH$_3$	B,F	60	all *endo*	
6	H	H	H	H	-CH$_2$-		CH$_3$	A,F	60	3:1	97
7	H	CH$_3$	CH$_3$	H	H	H	CH$_3$	B,F	63	NA	92
8[e]	H	CH$_3$	CH$_3$	H	H	H	CH$_3$	B,F	57	NA	91
9	H	CH$_3$	H	H	H	H	CH$_3$	B,F	46	5:1	90
10	H	H	H	H	-(CH$_2$)$_2$-		CH$_3$	B,F	66	all *endo*	98
11	H	H	H	H	-CH$_2$-		Bn	B,G	91	3:1	90
12	H	H	H	H	-CH$_2$-		Et	B,H	77	3:1	92

[a] A = Toluene, reflux, 4 h; B = neat, hydroquinone, 120°C, 12 h; C = LiOH, EtOH/H$_2$O, 12 h; D = LiOH, MeOH/H$_2$O, 12 h; E = 2.5 N NaOH, reflux, 2 h; F = KCN, MeOH, 12 h; G = KCN, BnOH, 12 h; H = KCN, EtOH, 12 h.

[b] Isolated yield over three steps from ionic support **1**.

[c] Determined by ^{1}H NMR.

[d] *Ortho*/*meta* ratio determined by ^{1}H NMR.

[e] Using ionic support recycled from entry 7.

With the desired acrylate in hand, the Diels–Alder reactions themselves could be investigated (Table 1). In all cases, standard thermal conditions were employed.[11] For cyclopentadiene, a solution of the acrylate and the diene was heated to reflux in toluene until starting material was consumed by TLC. For the other dienes, the reaction was performed neat in the presence of hydroquinone to avoid extensive oligomerization of the diene.[12] In all cases, the Diels–Alder products **4** could be readily isolated by removal of the volatiles in vacuo.

The final step in this short sequence was cleavage of the Diels–Alder adducts from the ionic liquid support. Initial attempts focused on simple basic saponification of the ester linkage (Table 1, entries 1–4). Although this proved to be an efficient method for obtaining the carboxylic acid products in reasonable overall yield, recovery of the ionic liquid support was not as straightforward. The recovered material was a dark brown, viscous liquid that was impure by ^{1}H NMR. Again, we suspected that the basic conditions were deprotonating the C2 position of the imidazolium core and leading to a variety of side reactions. This was supported by the observation that basic transesterification with sodium methoxide in methanol also resulted in a dark brown, viscous liquid.

In an effort to avoid this problem, attention was turned to milder methods for cleaving the Diels–Alder product from the ionic liquid support. After exploring a few sets of conditions, the one that proved to be most effective was a cyanide-mediated transesterification.[13] Using a catalytic amount of potassium cyanide in methanol, the methyl esters **5** were obtained in generally good overall yield (Table 1, entries 5–10).[14,15] More importantly, the ionic liquid support could be recovered in greater than 90% yield. After some experimentation, it was determined that this recovery could be best accomplished by taking up the residual mixture of potassium cyanide and ionic support **1** in 4N sodium hydroxide, followed by extraction with methylene chloride and ethyl acetate. Addition of basic alumina to remove coloration, followed by filtration and removal of the volatile solvents then afforded nearly colorless ionic support **1**. This support was pure and free of solvent and/or Diels–Alder adducts as determined by ^{1}H NMR.

This transesterification method for cleavage from the support has one additional interesting feature—the ability to prepare a number of different esters from the same supported carboxylate. This attribute was briefly examined by treatment of cyclopentadiene Diels–Alder adduct **4** with potassium cyanide and either ethanol or benzyl alcohol (Table 1, entries 11–12). In both cases, the anticipated ester products were obtained in good yield and the ionic support **1** could be recovered in nearly quantitative yield.

Finally, the fact that the ionic support **1** can be recovered so readily means that it can be recycled and used in further applications of supported synthesis. The efficiency of this recycling can be seen in entries 7 and 8 of Table 1 in which it can be seen that >90% of the ionic support was recovered in both the first and second use. Further the isolated yield of the final ester product is very similar between the two runs, indicating that the support remains intact.

In conclusion, we have developed a new type of soluble support—a hydroxylic ionic liquid based on fructose. This support affords higher potential loadings than other simple homogeneous or heterogeneous supports and can be readily recovered and recycled. Product/by-product separation can be performed by either extraction or removal of the volatiles in vacuo. The key present challenge in using this support is the limited base stability of the imidazolium core, since it can be readily deprotonated. Efforts are currently underway to develop new ionic supports that avoid this limitation and will be reported in due course.

Acknowledgements

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10. General procedure for acylation: To 0.2443 g (0.5487 mmol) of ionic support **1** was added 660 μL of dichloromethane followed by 116 μL (0.8339 mmol) of triethylamine. The solution was chilled to −20°C and a solution of 46 μL (0.5487 mmol) of acryloyl chloride in 110 μL of dichloromethane was added dropwise. The reaction was stirred for 30 min and then quenched with 200 μL of 5N sodium hydroxide. The resulting mixture was diluted with 5 mL of dichloromethane and 2 mL of water. The aqueous layer was extracted with dichloromethane (3×5 mL) and the combined organic extracts were dried with magnesium sulfate, filtered, and concentrated to afford 0.2604 g (96% by ^{1}H NMR) of acrylate **2**. The method of quenching this reaction was quite important, since unless all of the amine hydrochloride by-product was neutralized prior to extraction and concentration, significant amounts (up to 20%) of the hydrogen chloride addition product **3** were obtained.
11. All crude Diels–Alder adducts displayed spectral properties consistent with those reported in the literature.
12. General procedure for the Diels–Alder reaction: In a pressure tube with 0.2688 g (0.5339 mmol) of acrylate **2** was added 1.0 mg (0.0053 mmol) of hydroquinone and 0.5 mL (5 mmol) of 2,3-dimethylbutadiene. The mixture was purged with argon, then sealed and heated in an oil bath to 120°C. After 12 h, the tube was cooled to room temperature and the excess diene and any volatile by-products removed by concentration in vacuo. The crude product was the triturated with cyclohexane (2×10 mL) and any residual cyclohexane was removed from the supported product in vacuo to afford the Diels–Alder adduct ready for cleavage from the support.
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14. General procedure for transesterification: the supported Diels–Alder adduct with 2,3-dimethylbutadiene (crude, 0.5339 mmol) was dissolved in 5 mL of methanol. To this solution was added 17 mg (0.2668 mmol) of potassium cyanide and the reaction was stirred 12 h. The methanol was removed in vacuo and the remaining residue was triturated with cyclohexane (3×10 mL). The combined cyclohexane washes were concentrated in vacuo to afford 0.60 g (63% isolated over three steps) of methyl 1,2-dimethylcyclohexene-4-carboxylate.
15. The modest yields of the Diels–Alder adducts over this three step sequence are most likely due to the volatility of the methyl esters, since the yield for the less volatile benzyl ester is much higher.