Video Article

Highly Stereoselective Synthesis of 1,6-Ketoesters Mediated by Ionic Liquids: A Three-component Reaction Enabling Rapid Access to a New Class of Low Molecular Weight Gelators

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Abstract

In organic chemistry ionic liquids (ILs) have emerged as safe and recyclable reaction solvents. In the presence of a base ILs can be deprotonated to form catalytically active N-Heterocyclic Carbenes (NHCs). Here we have used ILs as precatalysts in the addition of α,β-unsaturated aldehydes to chalcones to form 1,6-ketoesters, incorporating an *anti*-diphenyl moiety in a highly stereoselective fashion. The reaction has a broad substrate scope and several functional groups and heteroaromatics can be integrated into the ketoester backbone in generally good yields with maintained stereoselectivity. The reaction protocol is robust and scalable. The starting materials are inexpensive and the products can be obtained after simple filtration, avoiding solvent-demanding chromatography. Furthermore, the IL can be recycled up to 5 times without any loss of reactivity. Moreover, the 1,6-ketoester end product is a potent gelator in several hydrocarbon based solvents. The method enables rapid access to and evaluation of a new class of low molecular weight gelators (LMWGs) from recyclable and inexpensive starting materials.

Video Link

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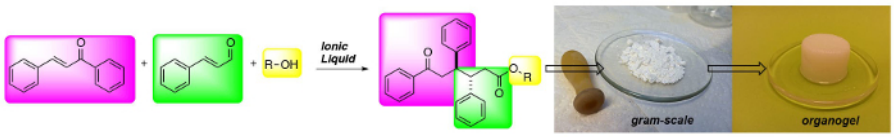
Introduction



(Above) Three-component synthesis of 1,6-ketoesters: a new class of low molecular weight gelators.

Ionic liquids (ILs) have high stability, low volatility, non-flammability and have therefore rendered attention as safe reaction media and ideal solvents for recycling.[1-3] Dialkyl imidazoliums are a certain type of ionic liquids that, in the presence of a base, can be deprotonated to render an N-heterocyclic carbene (NHC).[4] In the field of organocatalysis, NHCs, operating under distinct reaction paths, have found widespread usage in a broad range of generic reactions.[5-11]

Despite this, the connection between ILs and C-C bond forming NHC–catalysis is relatively unexplored. Nevertheless, NHCs derived from ILs have been reported to catalyze C-C bond forming reactions such as the benzoin condensation and the Stetter reaction.[12-22] For example, Davis *et al.* have shown that ILs derived from N-alkyl thiazoliums serve as precatalysts in the formation of benzoin from benzaldehyde.[12]

More recently, Chen and co-workers expanded this concept using an imidazolium based IL, 1-ethyl-3-methyl imidazolium acetate (EMIMAc), to perform the benzoin condensation on 5-hydroxymethylfurfural (HMF) to generate 5,5'-di(hydroxymethyl)furoin (DHMF).[23] Given that ILs are commercially available and offer an inexpensive way of generating NHCs, we were interested in investigating what other types of reactions ILs could perform. To this end, we found that dialkyl imidazoliums could efficiently be used as precatalysts in the formal conjugate addition of unsaturated aldehydes to chalcones (**Figure 1**) giving 1,6-ketoesters. The most efficient IL, EMIMAc, promotes a highly stereoselective reaction between cinnamaldehyde and chalcone. The reaction occurs with high preference for the *anti*-diastereomer and the 1,6-ketoesters can be isolated in yields up to 92%.[24,25,26]

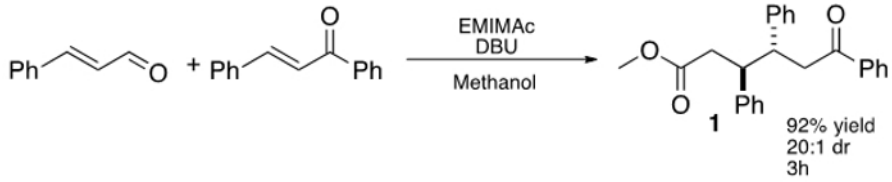


Figure 1: IL-mediated three-component, stereoselective addition of cinnamaldehyde to chalcone.

Protocol

1. Gram-scale Synthesis of Methyl 6-oxo-3,4,6-triphenylhexanoate

1. Dry 1-ethyl-3-methyl imidazolium acetate (EMIMAc) in a round bottom flask on a rotary evaporator at 10 mBar, 40 °C for 1 hr.
2. Add 2.1 g of dry EMIMAc and 1.0 g of 1,3-diphenyl-2-propen-1-one to a 100 ml round bottom flask equipped with a magnetic stirrer.
3. Add 2.019 ml of methanol and 2.3 g of cinnamaldehyde to the flask.
4. At room temperature (22 °C) dissolve the mixture in 60 ml of dichloromethane by stirring for 1 min.
5. Subsequently add 0.37 ml of 1.8-diazabicyclo[5.4.0]undec-7-ene (DBU) to the stirring mixture (step 1.4) and cap the round bottom flask.
6. Stir with a magnetic stir bar at a speed of 500 rpm at room temperature (22 °C).
7. Check completion of the reaction with ^{1}H NMR.[24] Look for disappearance of double bond of the chalcone in the 7.8 ppm area.
8. When the reaction has reached completion remove the volatiles on a rotary evaporator at 10 mBar, 20 °C for 15 min.
9. Add 50 ml methanol to the residue to dissolve the EMIMAc by stirring with a magnetic stir bar.
10. Remove the solids from the walls of the flask by stirring violently with a magnetic stir bar at a speed of 750 rpm for 30 min. If necessary, use a spatula to remove remaining solids from the walls.
11. Filter the mixture on a frit (pore size 3).
12. Wash with additional 20 ml of methanol. If recycling of the EMIMAc is desired evaporate the methanolic filtrate. (step 2.1).
13. Still on the frit, gently divide the filter cake (from step 1.11) into smaller pieces with a spatula and transfer the solids via a powder funnel to a pre-weighed round bottom flask and dry the solids under vacuum.
14. Weigh the flask and calculate the yield.
15. Analyze the product by ^{1}H NMR (step 1.7). Compare with reported spectra.[24]

2. Recycling of EMIMAc

1. Remove the volatiles from the methanolic mixture (from step 1.12) under reduced pressure of 10 mBar, at 40 °C for 30 min.
2. Analyze the resulting oil by ^{1}H NMR and ^{13}C NMR to check that EMIMAc is present.[24]
3. Use the recycled EMIMAc starting from step 1.2.

3. Gelation

1. Preparation of a Stock Solution
    1. Add 200 mg of Methyl 6-oxo-3,4,6-triphenylhexanoate (the product from step 1.15) and a magnetic stir bar to a vial. Add 2.0 ml dichloromethane to dissolve the ketoester. Stir until everything has dissolved.

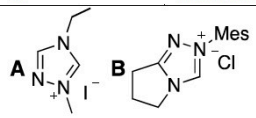
2. Gelation
    1. Add 50 ml of heptane to a 500 ml beaker. Add 1.5 ml of the stock solution to the heptane. Stir swiftly to ensure adequate mixing and let stand without stirring at ambient temperature until gelation occurs.

Representative Results

As exemplified above, EMIMAc serve as a precatalyst in the formal conjugate addition of α,β-unsaturated aldehyde to chalcones. Other commercially available imidazolium based ILs such as 1-ethyl-3-methylimidazolium chloride (EMIMCl) and 1-butyl-3-methylimidazolium chloride (BMIMCl) were also investigated, however, these reactions proceeded in lower yields indicating that the acetate anion may be important for reactivity (**Table 1**, entry 1-3).[27,28*]

* The role of the anion in this reaction is at the moment unclear. For studies on the role of the anion in NHC-catalysis see, references 27 and 28.

Entry	Solvent	Precatalyst	Base	Time (hr)	Yield (%)[b]
1	dichloromethane	EMIMAc	DBU	3	92
2	dichloromethane	EMIMCl	DBU	3	72
3	dichloromethane	BMIMCl	DBU	3	62
4	dichloromethane	A	DBU	16	33[c]
5	dichloromethane	A	DBU	16	52[d]
6	dichloromethane	B	DBU	2	46[c,e]
7	methanol	EMIMAc	DBU	21	32
8	acetonitrile	EMIMAc	DBU	3	60
9	dichloromethane	EMIMAc	-	2	0
10	dichloromethane	EMIMAc	Et_3N	24	4
11	dichloromethane	EMIMAc	Cs_2CO_3	1.5	72
12	dichloromethane	EMIMAc	DBU	16	9[f]



a) Reactions performed at room temperature, solvent, base (0.5 equiv.), precatalyst (2.5 equiv.), chalcone (1 equiv., 0.08M), cinnamaldehyde (3 equiv.), methanol (10 equiv.). b) Isolated yield of 1 c) 0.1 equiv. of precatalyst. d) 2.23 equiv. of A e) chalcone consumed after 2h. f) EMIMAc (0.25 equiv.).

Table 1: Optimization of reaction conditions for the synthesis of 1.

Other commonly used NHC precatalysts such as **A** and **B** were less efficient than EMIMAc and gave ketoester **1** in 33% and 46% yields, respectively (**Table 1**, entry 4 and 6). In addition, to achieve an efficient reaction the use of a co-solvent is necessary, where the co-solvent provides a homogeneous phase reaction by both dissolving the IL and end product. As a co-solvent, dichloromethane provided the best result with regard to reaction yield. Efforts to find a more benign solvent were made; methanol and acetonitrile are also possible to use as co-solvents but at the expense of lower yields (**Table 1**, entry 7 and 8). The choice of base is also important, without added base no reaction can be observed (**Table 1**, entry 9). DBU was found to be the optimal base (**Table 1**, entry 1) but carbonate bases were also viable giving full conversion within 1.5 hr but with a higher degree of byproduct formation (**Table 1**, entry 11, 72% yield). Milder bases such as triethylamine only gave trace amounts of product (**Table 1**, entry 10). Furthermore, the individual components of the IL mediated three-component reaction can be varied to introduce several functional groups to the ketoester backbone. Chalcones bearing electron donating groups and halogen substituents are well tolerated and proceed in high dr and good yields (**Figure 2**, entries 2-10). For example, ketoester **6** bearing a bromo-substituent on the aromatic ring, a convenient scaffold for cross-coupling chemistry, can be isolated in 75% yield. The α,β-unsaturated aldehyde can also be altered allowing the introduction of a chloro-, methyl- and methoxy-group on the ketoester backbone without affecting the selectivity or yield (**Figure 2**, entries 11-13). Moreover, different primary alcohols such as ethanol and benzyl alcohol can also be introduced (**Figure 2**, entries 14 and 15).

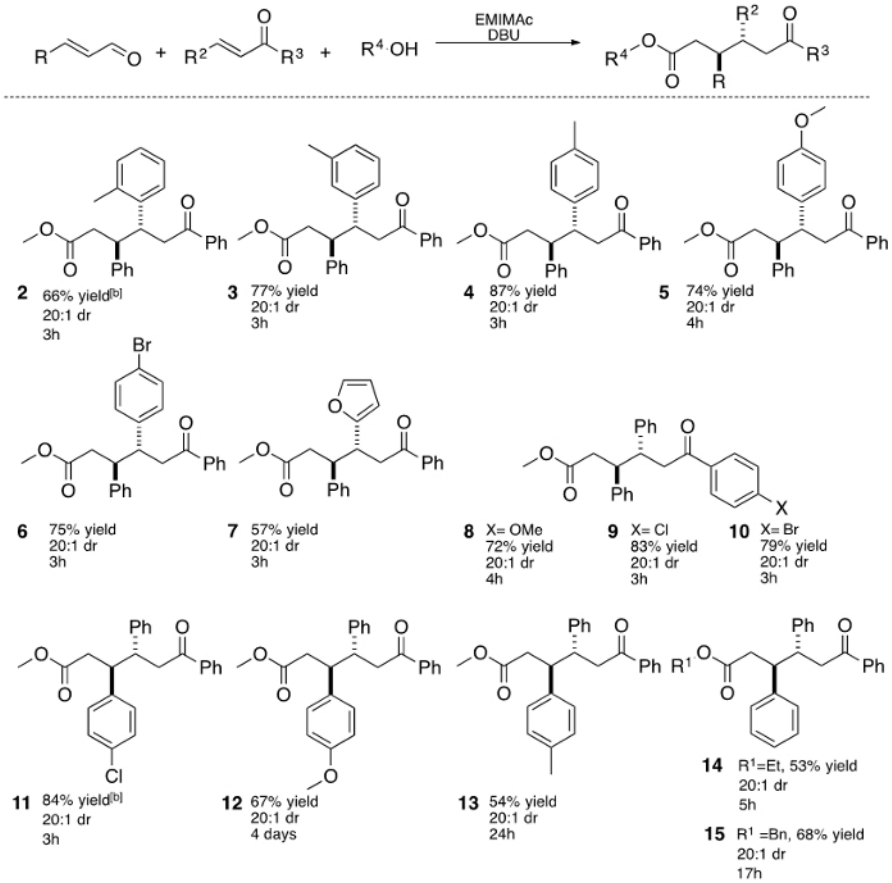


Figure 2: Reaction scope of the formal conjugate addition of α,β-unsaturated aldehydes to chalcones. (**a**) Reactions performed at RT, dichloromethane, DBU (0.5 equiv.), IL (2.5 equiv.), aldehyde (3 equiv.), chalcone (1 equiv. 0.08 M), alcohol (10 equiv.). (**b**) Yields refer to isolated yields after purification. Modified from reference [24].

Notably the reactions are extremely stereoselective and only the *anti*-diastereoisomer is obtained. The *anti*-oriented vicinal diphenylethylene was determined by X-ray analysis on compound **3** (**Figure 3**).

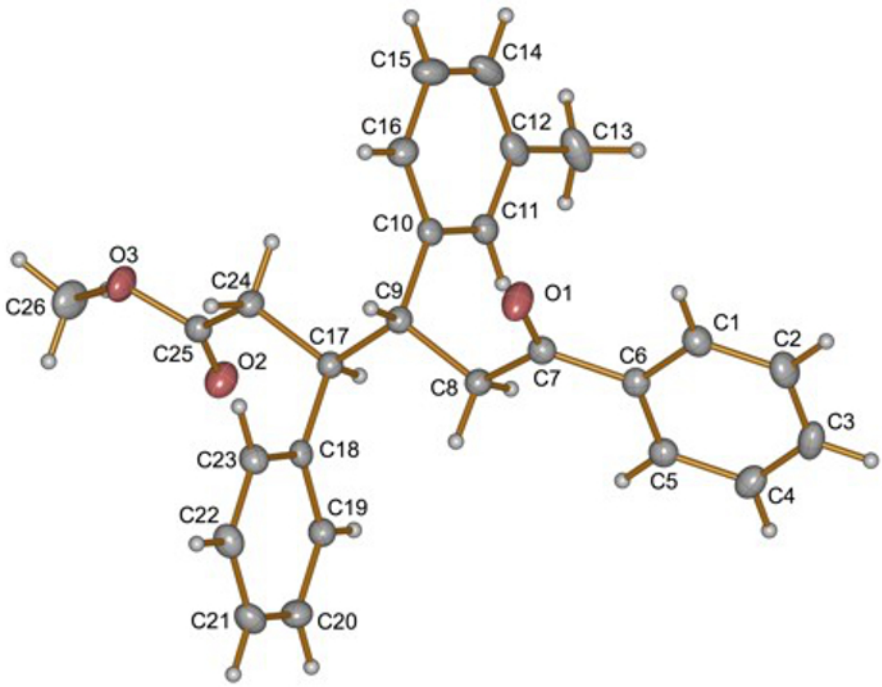


Figure 3: ORTEP drawing of ketoester 3. Re-print with permission from reference [24].

As shown the pure ketoester **1** can be obtained after a simple workup and washing protocol. The IL can then be recycled after evaporation of the methanolic solution. The IL has been recycled up to five times with no decrease in reaction yield.[24]

Moreover, the 1,6-ketoesters are also potent gelators in hydrocarbon solvents such as hexane and heptane (**Figure 4**).[29] The gelation is concentration dependent and ketoester 1 gelates already at a concentration of 2 mg/ml within 10 min. At higher concentrations the gelation occurs within a min. The gelation is reversible and addition of dichloromethane or heating will re-dissolve the ketoester.

Figure 4: Gelation in heptane. (**a** and **b**) organogel of gelator 1 in heptane (**5 mg/ml**). (**c**) Gel removed from the beaker.

Discussion

Based on the *anti*-configuration determined by X-ray analysis of ketoester 3 and on the mechanistic investigation proposed by Bode and co-workers[30] the following reaction path is suggested (**Figure 5**). Deprotonation of the IL generates NHC species; the NHC reacts with the unsaturated aldehyde to form the Breslow intermediate I. The Breslow intermediate and the chalcone react in a cross-benzoin reaction to form diene II. Intermediate II undergoes an oxy-Cope rearrangement via boat transition state (TS), setting the *anti*-oriented stereogenic centers III. After tautomerization, acyl azolium IV reacts with methanol to deliver the product and regenerating the catalyst.

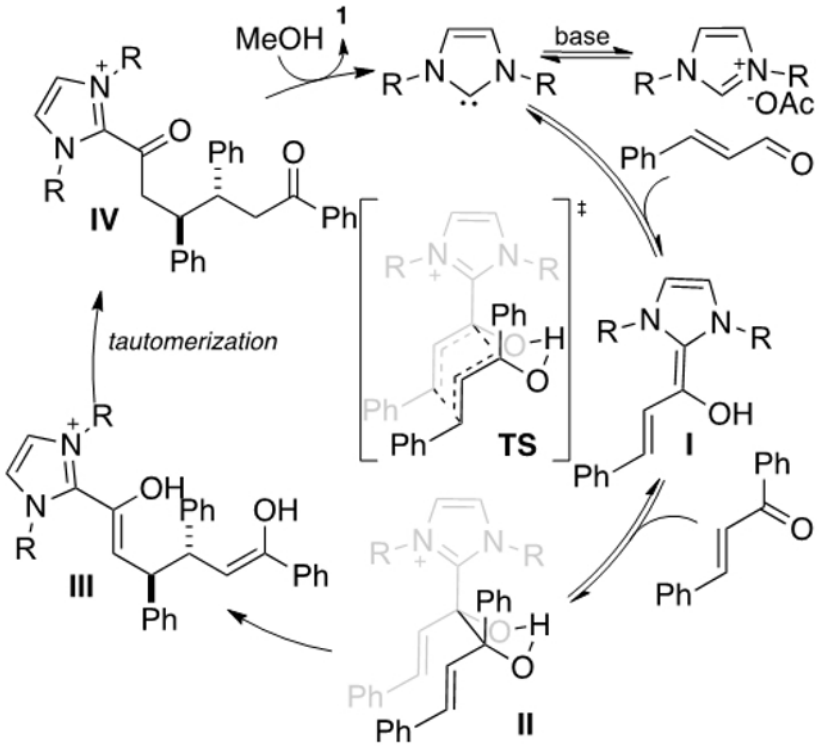


Figure 5: Catalytic cycle of the NHC-catalyzed addition of chalcone to cinnamaldehyde (R = Me, Et). Re-print with permission from reference [24].

Critical step of importance is the addition sequence of the reagents. If DBU is not added as the last reagent the reaction yields tend to become very low. It is also recommended to evaporate the EMIMAc before usage since residual amount of volatile material present in EMIMAc may lead to byproducts. In the washing step (1.12) the large chunks of product must be crushed in order to obtain sufficiently pure material.

Troubleshooting

The gel state is a metastable state and the gels inevitably become grainy over time. However, if the gels are grainy directly after formation a possible reason could be that the gelation is conducted at a to high gelator concentration.

At present, the reactions need to be conducted with excess amounts of EMIMAc, aldehyde and methanol in order to achieve a high conversion. From efficiency perspective this is not optimal but lower loadings of either reagents result in decreased reaction yields.

The synthesis of the 1,6-ketoesters is highly stereoselective, proceeds in good to excellent yields. In addition, an efficient washing protocol renders a pure ketoester end product without the need for solvent-demanding chromatography. Alternative methods to selectively access the highly functionalized 1,6-ketoesters are considerably more laborious.

Given the easy synthesis of 1 via a three-component reaction, the methodology presented offers a fast way to generate molecular diversity. Combined with the potency of 1 as an organogelator, this technique can thus be used for a rapid evaluation of the 1,6-ketoesters as a new class of LMWG. The method allows production of tailored gelators with desirable properties, enabling access to new materials.

Disclosures

The authors have nothing to disclose.

Acknowledgements

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