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The Knoevenagel reaction: analysis and recycling of the ionic liquid medium

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Abstract—A study involving the scope of substrate in the Knoevenagel reaction in an IL medium has been conducted. Reactivity trends favor formation of the condensation product using electron deficient aryl aldehydes. Use of electron rich aldehydes and ketones lead to lower levels of conversion and no measurable amounts of condensation products, respectively. A recycling study confirmed that the reaction medium could be used multiple times affording, with each run, the desired condensation product **1a** in excess of 90% conversion. Post-run analyses of the IL documented that the IL medium was unaltered upon reuse.

1. Introduction

Alternative technologies which circumvent the need to use VOCs (volatile organic compounds) exist.[1,2] One such technology involves the use of ionic liquids.[2,3] Ionic liquid (IL) technology when used in place of classical organic solvents offers a new and environmentally benign approach toward organic synthesis.[4] IL technology has been successfully applied in several classical organic processes.[5] The implementation of task specific ionic liquids (TSILs) further enhances the versatility of classical ionic liquids where both reagent and medium are coupled.[6] The union of reagent with medium is a viable alternative approach toward modern synthetic chemistry especially when considering the growing environmental demands being placed on chemical processes.[7,8]

Previous reports from these laboratories have documented the application and reuse of IL technology in classical organic processes. One study focused on the use of Brønsted acid TSILs.[9,10] An earlier communication reported on the viability of base-promoted reactions in ILs.[11] The reactions surveyed in the latter communication focused on condensation processes, specifically, the Knoevenagel reaction and Robinson annulation and for the first time the use and reuse of IL technology in these two well established base-promoted transformations were documented. The Knoevenagel reaction was of particular interest because of its application in industry. The preparation of several anti-fouling agents, herbicides, and insecticides not only rely on this condensation process but use as their choice of activated methylene, malononitrile.[12] Furthermore, these processes are dependent upon the use of solvents in the conversion of carbonyl derivative to ylidenemalononitrile derivative. The two most commonly used solvents, ethanol and toluene, are part of the TRI hazardous air pollutants inventory and thus do contribute to what is released into the environment.[13]

Research activities focusing on the development and use of inert and recyclable ILs and TSILs are extremely active. Our interests only compliment the research efforts of others which, in part, addresses the need to develop innovative technologies to conduct synthetic transformations void of VOCs.[14] Not surprisingly, as new technologies and applications emerge, limitations become evident. Accordingly, we wish to follow-up on some of our initial findings and report on (1) scope of substrate with respect to the aldehyde in Knoevenagel reactions supported by an IL medium and (2) the structural integrity of the IL medium having performed ten iterations of condensation reactions using the same IL medium.

Keywords: Alternative technologies; Ionic liquid technologies; Reuse; Knoevenagel reaction; Condensation reaction; Organic synthesis; Scope of substrate; Pollution prevention; Clean technology.

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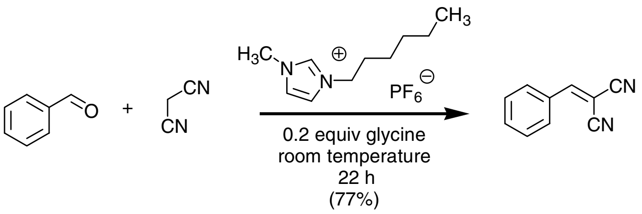
2. Results

The Knoevenagel reaction has been extensively studied since its initial report in 1894.[15] There has been a tremendous amount of research focusing on all aspects of this condensation process. Our initial report on the Knoevenagel reaction established proof of principle (Scheme 1).[11] Reaction of benzaldehyde with malononitrile resulted in 77% isolated yield of the desired product using as reaction medium 1-hexyl-3-methyl imidazolium hexafluorophosphate ([hmim][PF_6]) and glycine as promoter. We were successful in recycling this process with the same IL medium which resulted in 39% isolated yield of the desired condensation product.

All reactions reported here and in our initial communication were clean as judged by GC and NMR analysis of the crude reaction mixture. That is, although incomplete reactions were observed, analysis of the crude reaction mixtures revealed no by-products other than the desired product and unreacted starting material. Albeit low in yield especially when considering the recycling experiment, the unoptimized reaction conditions using equimolar quantities of aldehyde and activated methylene would serve as our benchmark from which studies focusing on scope of substrate with respect to the aldehyde would begin. For each system examined, toluene was used to extract the products from the reaction medium.[16]

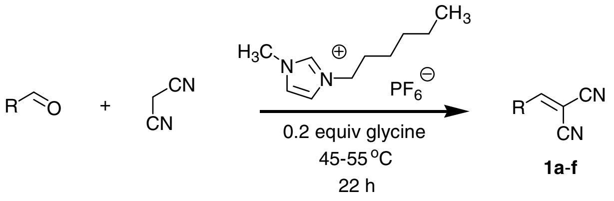
Since a host of carbonyl derivatives which ranged from electron deficient aryl aldehydes to comparatively less reactive electron rich carbonyl systems were examined and we observed a notable difference in overall conversion during the recycling experiment,[11] a decision was made to offset systems of lesser reactivity with warmer reaction conditions. The reactions were run not at room temperature but a warmer setting of 50 °C (±5 °C). Our focus was on the scope of the substrate using IL technologies, reuse of the IL medium and examination of the IL medium, but not conversion. Except for this single modification, all other reaction conditions were kept the same. A total of eight carbonyl derivatives were surveyed. The data from the study are presented below.

Table 1 reveals some interesting trends. Overall, aryl aldehydes (entries 1–4) were superior to aliphatic and conjugated aryl aldehydes (entries 5 and 6). Electron rich anisaldehyde (entry 4) yielded the desired product in good yield but not as high when compared to the more reactive systems benzaldehyde (entry 3) and electron deficient aryl aldehydes (entries 1 and 2). Use of ketones did not yield any of the desired condensation products (entries 7 and 8). Several attempts with varying reaction conditions with these carbonyl derivatives were made which resulted in either very low yields or levels of nondetection as determined by GC analysis. Isolation of the starting carbonyl derivatives in >95% recovery confirmed poor efficiency of methylene transfer under these reaction conditions.[17]

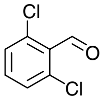
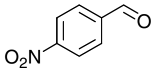
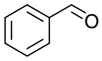
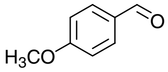
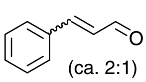
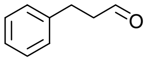
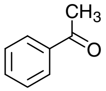
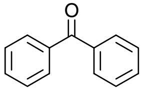


Scheme 1.

Table 1. Condensation reactions of aldehydes with malononitrile in an IL medium



1a-f

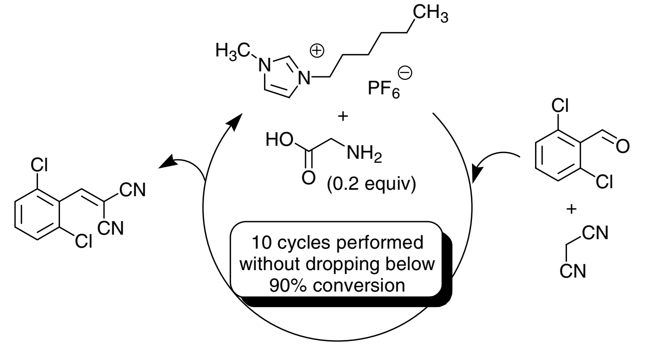
Entry	Carbonyl derivative	**1** (%)[a]
1, **a**		86
2, **b**		74
3, **c**		77
4, **d**		62
5, **e**		52
6, **f**		32
7		—[b]
8		—[b]

[a] Yields reported are unoptimized.

[b] Desired condensation product not observed, recovery of carbonyl derivative >95%.

Results from the scope of the substrate study were next used as a basis for exploring the inherent stability of the IL medium while performing recycling experiments. Our aim was to recycle the IL medium, and using indicators such as mass balance and percent conversion in conjunction with NMR spectroscopy, examine the IL medium after each run in an effort to learn more about the application of this technology in modern synthetic transformations. For this study, reaction of malononitrile with 2,6-dichlorobenzaldehyde in the presence of catalytic quantities of glycine was selected (Scheme 2).[18]

Analysis of the crude reaction mixture for each run in the recycling study revealed no less than 90% conversion of aldehyde to dinitrile. Mass balance and NMR



Scheme 2.

analyses of the crude reaction mixtures confirmed the high level of conversion. Perhaps more interesting were the post-run analyses. The IL medium, [hmim][PF_6], remained intact throughout the entire 10-cycling study and thus, for the first time, an analysis of the IL medium itself upon recycling the medium multiple times is reported. While we cannot confirm changes in situ, we can definitively state that the NMR spectra of the IL medium prior to and post reaction were identical. The ^{1}H NMR spectrum presented in Figure 1 was taken after having completed 10-cycles of the Knoevenagel reaction using 2,6-dichlorobenzaldehyde and malononitrile in the presence of catalytic quantities of glycine.

Analysis of the reaction mixture prior to completion of reaction was found to be informative when considering the presence (or absence) of isolable reaction intermediates. The ^{1}H NMR spectrum revealed the presence of [hmim][PF_6], 2,6-dichlorobenzaldehyde, malononitrile, and small quantities of the condensation product. This observation further supports our position that under these reaction conditions, the reaction medium remains intact. Throughout this study, aside from the retention of the catalyst glycine and trace amounts of malononitrile, the condensation product **1a** and trace amounts of 2,6-dichlorobenzaldehyde were successfully extracted from the IL medium leaving it intact and ready for reuse.

3. Discussion

Based upon control reactions, glycine serves as promoter for these reactions. We have no evidence that glycine is extracted from the IL when washed with

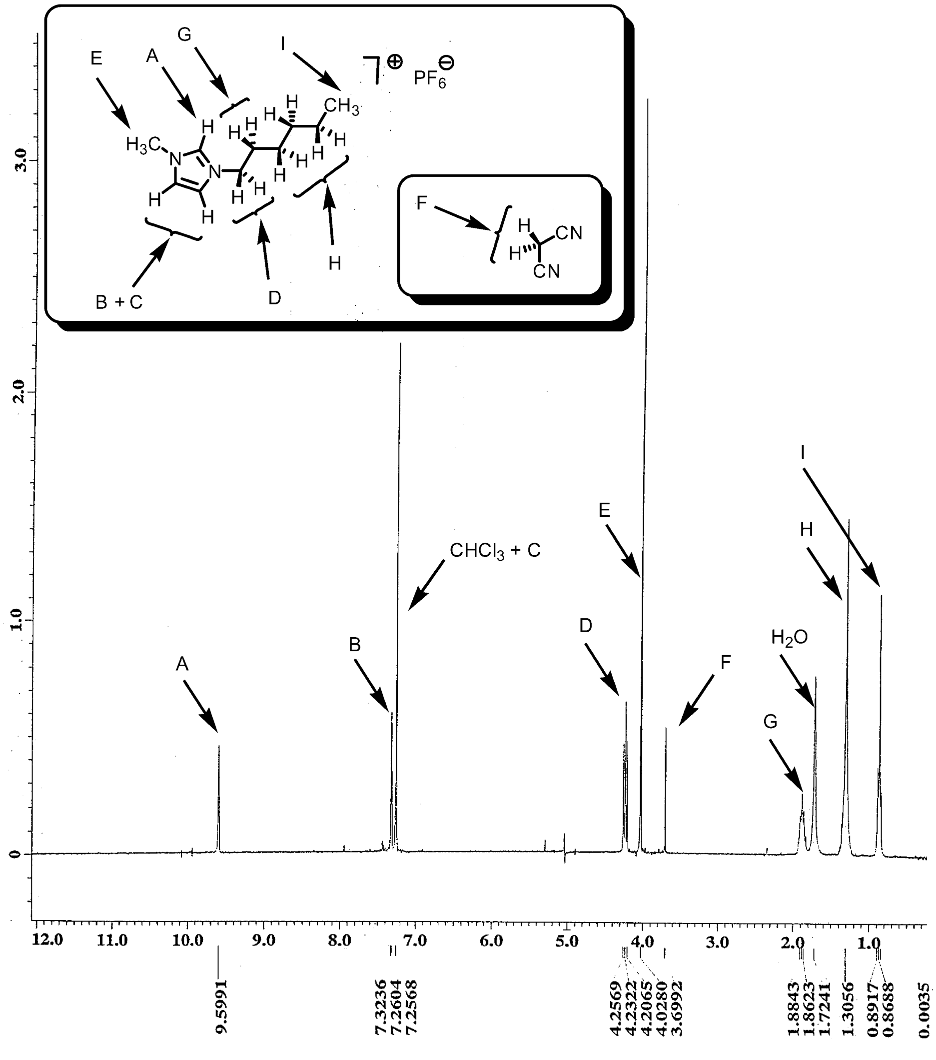


Figure 1. ^{1}H NMR spectrum of [hmim][PF_6] after 10 cycles.

toluene. We do believe that glycine was part of the IL medium throughout the recycling study. Glycine is soluble in water and slightly soluble in alcohols and ether and thus the absence of glycine in the NMR spectra. Removing glycine from the IL could be accomplished by washing the IL with water.[19]

Imidazolium cations should not be considered spectator ions.[20,21] The intermolecular properties of these salts have been an active area of research. One area of research has focused on the unique hydrogen bond donor properties at C-2.[22] Welton and co-workers have reported on the role of the hydrogen bond at C-2 in a Diels–Alder reaction.[23] Rationale for *endo*-selectivity was because of favorable participation of the hydrogen at C-2 of the imidazolium cation with the carbonyl oxygen of the dienophile. While we cannot confirm participation of the imidazolium cation with the carbonyl oxygen in our study, control studies support that these reactions are facilitated by the presence of a general catalyst. The addition of the methylene compound to the carbonyl derivative is probably assisted by a number of possible coordination events. Coordination of the carbonyl oxygen with a proton source creates a more electrophilic carbon. It is not unreasonable to assume that the source of the proton donor may come from either the ammonium salt of glycine or the hydrogen at C-2 of the imidazolium salt. However, if competition of hydrogen bonding with the carbonyl oxygen exists, participation would favor the ammonium salt of glycine and not the C-2 hydrogen of the imidazolium cation. Because glycine is a stronger acid and amino acids have been shown to be effective catalysts in the condensation reaction of carbonyl derivatives and active methylene compounds, we do believe that glycine is acting as the acid promoter in these condensation reactions.[12,24] Studies which include an examination of the role of the catalyst and the scope of the substrate of activated methylene compounds using optimized reaction conditions are currently being investigated and will be reported in due course.

4. Conclusions

A study involving the scope of the substrate in the Knoevenagel reaction supported in an IL medium has been conducted. Reactivity trends favor formation of the condensation product using electron deficient aryl aldehydes. A recycling study confirmed that the reaction medium could be used multiple times affording, with each run, the desired condensation product in excess of 90% conversion. Post-run analyses documented for the first time that the IL medium was unaltered upon reuse. Our continued research in this area will explore (1) the function of the promoter, (2) the role of the IL medium and (3) the scope of the substrate with activated methylene donors.

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was allowed to stir at 50 °C (±5 °C) for a period ranging from approximately 18–24 h at which time the reaction mixture was extracted with toluene (3 × 2.0 mL). Temperatures did gradually fluctuate, ±5 °C, and were recorded externally. Analysis of the crude reaction mixture revealed that aside from glycine, >95% (wt) of the organic residues introduced to the [hmim][PF_6] were removed after performing three 2.0 mL washes with toluene (^{1}H NMR of IL and mass balance of materials extracted). The organic extracts were then combined and concentrated in vacuo. The resulting viscous oil was immediately purified via silica gel chromatography [hexane/EtOAc, 1/1, 10 × 30 mm SiO_2, 3 mL fractions] to afford the title compound. Spectral data obtained on each system were in agreement with previous reports.

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