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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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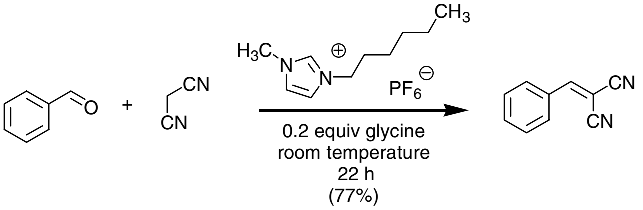
2. Results

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.

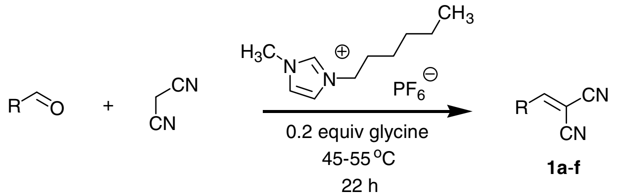
All reactions reported here and in our initial communication were clean as judged by GC and NMR analysis of the crude reaction mixture. That is, although incomplete reactions were observed, analysis of the crude reaction mixtures revealed no by-products other than the desired product and unreacted starting 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]

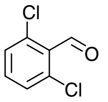
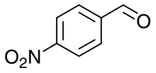
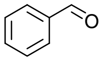
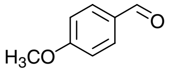
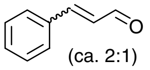
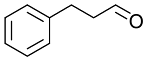
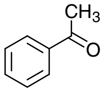
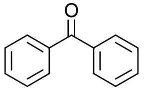
Since a host of carbonyl derivatives which ranged from electron deficient aryl aldehydes to comparatively less reactive electron rich carbonyl systems were examined and we observed a notable difference in overall conversion during the recycling experiment,[11] a decision was made to offset systems of 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.



Scheme 1.

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



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%.

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]

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