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Synthesis of Tertiary Alcohols via an Ionic Liquid Catalyst

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Abstract

The core of furans has been found to be present in many pharmaceuticals, such as polyether antibiotics, as well as flavors and fragrances, optoelectronics, and many natural products with therapeutic potential. A similar class of compounds called the 2-pyrones has been reported to be vital in natural products with antimicrobial, antifungal, and anti-HIV effects. Despite their usefulness, current synthetic approaches are limited. One method used to synthesize furans is the intramolecular cyclization of ynols via a 5-endo cyclocondensation mechanism. Cyclocondensation reactions offer the advantage of occurring in one step and thus prevent the isomerization and resulting regioselectivity problems associated with multi-step reactions. In order to complete these cyclocondensation reactions we have used a new environmentally safer ionic liquid catalyst in the Grignard reaction to prepare several ynols and additional tertiary alcohols.

Keywords: catalyst, ionic liquids, alcohols, ynols, Grignard reagent, pharmaceuticals

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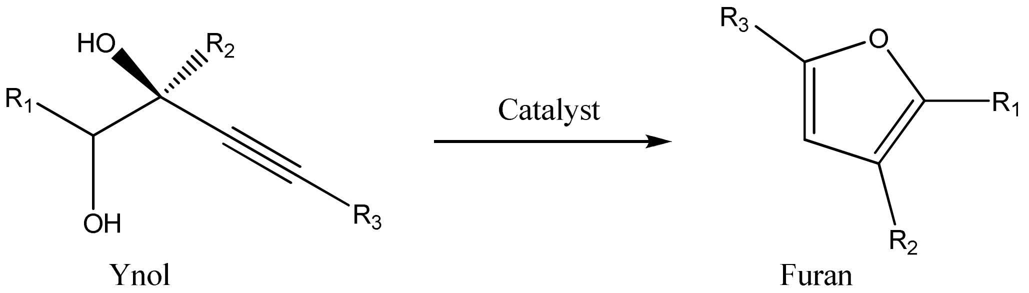
Introduction

Ynols are organic compounds containing a triple bond and an alcohol in the same molecule. They can undergo intramolecular cyclocondensation to produce furans [1], shown in Figure 1.

Because they are important synthetic intermediates used as building blocks for a variety of larger molecules, they have been the subject of a great deal of research. These compounds are important synthetic targets due to their numerous applications which range from uses as antibiotics [2] and medications for Alzheimer's and Parkinson's diseases [3] to "molecular wires" and electrooptic materials in photonic devices for telecommunications and optical information processing [4-7]. Ynols are also important intermediates used as precursors for compounds having anticonvulsant activity [8] and the 2-pyrones, with antimicrobial, antifungal, and anti-HIV effects [9-11].

Figure 1. Intramolecular Cyclocondensation Reaction of an Ynol to Produce a Furan

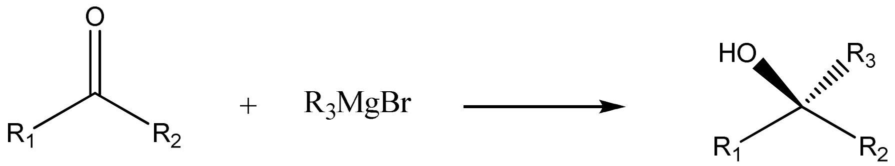


Methods to synthesize ynols need to be improved because syntheses using these ynols often lead to a mixture of products due to a lack of control of regioselectivity [12]. In order to control regioselectivity, various transition metal catalysts have been developed for use in many coupling reactions. Examples of these reactions include the Heck [13], Stille and Suzuki [14], Sonogashira [15], Ullmann [16], Diels-Alder [17], Trost-Tsuji [18], aldol [19], and transition-metal-catalyzed cross-coupling reactions [20]. However, the environmental and financial costs for reactions dependent on metals are huge. Room-temperature ionic liquids (RTILs) are a class of solvents that are finding increasing applications because they are reusable, environmentally safe, and versatile solvents for a variety of organic reactions [21]. One reason for their usefulness is their ability to create an internal pressure that promotes the association of the reactants within a solvent cavity during the activation process that accelerates a reaction, thus decreasing the entropy of reaction in the transition state, which is especially useful for controlling regioselectivity via cyclocondensation and coupling reactions. Our investigations involve the application of the ionic liquid 1-butyl-2-isopropyl-3-methylimidazolium triflimide to the Grignard reaction to produce tertiary alcohols, including ynols.

Results and Discussion

One method to synthesize ynols uses a Grignard reagent to nucleophilically attack the carbonyl of an appropriately substituted ketone in order to produce a tertiary alcohol, as shown in Figure 2.

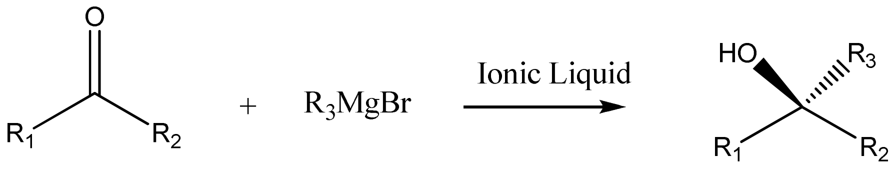
Figure 2. A General Grignard Reaction Between a Ketone and a Grignard Reagent



The polarized carbon-metal bond of a Grignard reagent (R_3MgBr in Figure 2) allows it to behave as a nucleophile and attack the electrophilic carbon of a carbonyl group, making it a very useful reaction to form carbon to carbon bonds. Typically the formation of a Grignard reagent, which is an organomagnesium halide, occurs in a heterogeneous reaction between magnesium metal and an alkyl, alkenyl, or aryl halide in either diethyl ether or tetrahydrofuran solvents. Diethyl ether and tetrahydrofuran are the best solvents to use because they are aprotic solvents, whereas a protic solvent, such as water or an alcohol, reacts with the very basic Grignard reagent, R-MgX to produce an undesired hydrocarbon by-product. Therefore, Grignard reagents are usually prepared by reaction of an alkyl halide with magnesium using a nitrogen atmosphere to prevent reaction with the oxygen and water that can produce an undesired alkane product.

In order to overcome these difficulties and increase the yields, investigations for improved reaction conditions have been actively pursued. Ionic liquids are a class of highly polar solvents composed of ions that are liquids at low temperature and their lack of volatility and nonflammability makes them an attractive alternative for the typical Grignard reaction conditions [22]. Wilhelm, Jurcik, and Handy [23] reported that the use of 2-arylated-imidazolium salts and 2-alkylated-imidazolium salts were useful for the Grignard reaction, and Chan reported the successful use of ethyl magnesium iodide in the ionic liquid, *N*-butylpyridinium tetrafluoroborate ([bpy][BF_4]) [24]. These ionic liquids can also be easily recovered and recycled which allows them to help protect the environment and human health. Their lack of volatility and nonflammability makes them an attractive alternative for the useful but potentially dangerous and sometimes problematic Grignard reaction, which typically requires a highly flammable and volatile solvent such as diethyl ether or tetrahydrofuran. The general reaction procedure in shown in Figure 3.

Figure 3. General Synthetic Route for the Preparation of Tertiary Alcohols

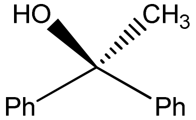
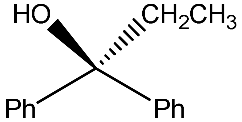
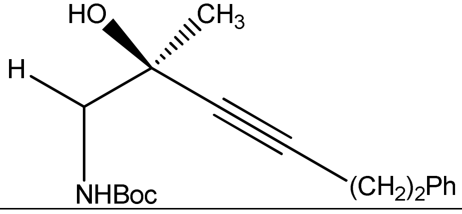
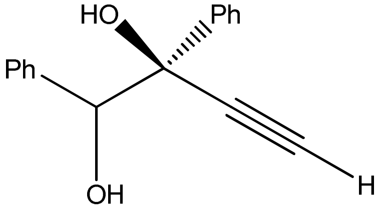


Ionic liquids are sometimes called “designer solvents” because of their high polarity which allows them to solubilize both organic and inorganic compounds. The extent of this polarity is important due to its potential enhancement of reaction rates and improved selectivity compared to conventional more toxic solvents. Furthermore, many of the properties of ionic liquids, such as hydrophilicity, hydrophobicity, Lewis acidity, viscosity and density can be designed by changing the cations and/or the counteranions.

We chose to synthesize the 2-alkylated-imidazolium salt developed by Handy [23b] for several reasons. The alkylation at the 2 position is important because otherwise this 2-position would have an acidic proton which would react with the basic Grignard reaction much as a protic solvent would, and simply produce an undesired hydrocarbon by-product. This 2-alkylated-imidazolium salt is also base-stable and has been applied to the addition of Grignard reagents to ketones to produce tertiary alcohols at room temperature. The imidazolium cation facilitates the formation of a separate phase and when the anion is the triflimide anion, the hydrophobicity of this imidazolium ionic liquid is dramatically increased. We did find that by using this 1-butyl-2-isopropyl-3-methylimidazolium triflimide ionic liquid, the formation of 2 separate layers was visible after approximately 45 minutes of reaction. This formation of the aqueous layer separate from the product-containing organic layer greatly facilitates product isolation and also increases the yield, while simultaneous allows less of the Grignard reagent being required. Also, less of the flammable diethyl ether and tetrahydrofuran solvents are necessary.

As can be seen by entries 1 and 2 in Table 1, good yields of the tertiary alcohols prepared from the sterically hindered benzophenone even after reuse of the ionic liquid catalyst, shown as yield after second ionic liquid use in Table 1. In order to recycle the ionic liquid after the tertiary alcohol product had been removed, an additional 5 mL of methylene chloride was added, and extraction was completed two additional times, each time combining the organic layers. The organic layers were dried over sodium sulfate, solvent was removed, and then the ionic liquid was dried under vacuum for 22 hours. However, after the third usage, the catalytic activity was significantly diminished and yields of the tertiary alcohols were no longer useful. Yields of the less sterically hindered ynols, entries 3 and 4 in Table 1, were higher, especially for the diol entry 4. Presumably the known ability of oxygen coordination to the magnesium atom of the Grignard reagent helped to facilitate the complexation to the starting material, thus enhancing the already favorable cavitational effect exerted by the ionic liquid.

Table 1. Percentage Yields of Alcohol Products After First and Second Ionic Liquid Uses

Entry	**Name**	**Structure**	**Yield After First IL Usage**	**Yield After Second IL Usage**
1	**1,1-diphenyl-1-ethanol**		81%	81%
2	**1,1-diphenyl-1-propanol**		80%	79%
3	***N*-Boc-1-amino-2-methyl-6-phenyl-3-hexyn-2-ol**		83%	82%
4	**1,2-Diphenyl-3-butyne-1,2-diol**		86%	85%

Materials and Methods

Materials

All reagents and solvents were pure analytical grade materials purchased from commercial sources and used without further purification unless stated otherwise. The NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a 300 MHz instrument with TMS as internal standard. FTIR spectra were recorded as neat samples on sodium chloride plates. TLC was completed using 0.2 mm thick silica gel plates. Visualization was accomplished by using UV light or staining using iodine vapors or potassium permanganate in solution.

Preparation of the Ionic Liquid, 1-butyl-2-isopropyl-3-methylimidazolium triflimide:
The procedure developed by Handy [23b] was followed: 2-isopropylimidazole (90.8 mmol) was added to a 250 mL round bottom flask and toluene (90 mL) was added. A magnetic stir bar was added and stirring was initiated. Butyl bromide (109 mmol) was added dropwise, followed by tetrabutylammonium bromide (9.0 mmol). Slowly, a solution of sodium hydroxide (1M, 110 mmol, 110 mL) was poured into the flask. A water cooled reflux condenser was attached and the solution was heated to reflux for 22 hours, then allowed to cool to room temperature. The organic layer was poured into a separatory funnel, washed with brine, dried using sodium sulfate, filtered, and the solvent was removed to produce the residue, which was added to the top of a column slurry-packed with silica gel. Then a gradient of 20% diethyl ether in 80% hexanes to 100% diethyl ether was used to elute. After evaporation of the solvent, the product was dissolved into methylene chloride (100 mL), and methyl iodide (98.1 mmol) was added. The solution was heated at reflux for 19 hours and then allowed to cool to room temperature. Lithium bis(trifluoromethanesulfonyl)imide (40 mmol) was added and the mixture stirred at room temperature for 21 hours. The lithium iodide precipitate was removed via filtration, the solution was added to a separatory funnel, washed with brine, water, dried using sodium sulfate, and then the solvent was evaporated to produce the product in 89% yield.

General Procedure for Synthesis of Tertiary Alcohol Products:
The appropriately substituted ketone (0.50 mmol) was added to a 50 mL round bottom flask containing a magnetic stir bar, followed by the addition of the ionic liquid (3.0 mL), and then the Grignard reagent was added. The reaction was stirred at room temperature for 55 minutes, or until reaction completion as monitored by TLC (Diethyl ether: hexanes, 20:80). Upon reaction completion, the solution was extracted in a separatory funnel, washed with brine, then washed with water, and the isolated organic layers were dried over sodium sulfate, filtered, and evaporated to yield the product.

Spectral Data:

1,1-diphenyl-1-ethanol [25, 26]
^{1}H NMR ($CDCl_3$, 300 MHz); δ (ppm): 7.45-7.21 (10H, m), 2.19 (1H, brs), 1.97 (3H, s). ^{13}C NMR ($CDCl_3$, 50 MHz); δ (ppm): 147.8, 128.1, 125.8, 76.0, 30.8.

1,1-diphenyl-1-propanol [25, 26]
^{1}H NMR ($CDCl_3$, 300 MHz); δ (ppm): 7.47-7.17 (10H, m), 2.31 (2H, q, J=7.2 Hz), 2.07 (1H, brs), 0.89 (3H, t, J=7.2 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz); δ (ppm): 146.8, 128.2, 126.8, 126.2, 78.5, 34.3, 8.2.

N-Boc-1-amino-2-methyl-6-phenyl-3-hexyn-2-ol [27]
^{1}H NMR ($CDCl_3$, 300 MHz); δ (ppm): 7.34-7.17 (5H, m), 4.87 (1H, brs), 3.30 (1H, dd, J=6.9, 13.7 Hz), 3.18 (1H, dd, J=5.7, 13.7 Hz), 2.89 (1H, brs), 2.82 (2H, t, J=7.4 Hz), 2.49 (2H, t, J=7.4

Hz), 1.49 (9H, s), 1.40 (3H, s). ^{13}C NMR ($CDCl_3$, 50 MHz); δ (ppm): 156.8, 140.6, 128.6, 128.2, 126.5, 83.9, 83.1, 79.9, 68.3, 51.5, 34.9, 28.4, 27.3, 20.9.

1,2-Diphenyl-3-butyne-1,2-diol [28]
^{1}H NMR ($CDCl_3$, 300 MHz); δ (ppm): 7.45-7.41 (2H, m), 7.31-7.14 (8H, m), 4.89 (1H, d, J=3.0 Hz), 2.98 (1H, s), 2.76 (1H, d, J=3.5 Hz), 2.74 (1H, s). ^{13}C NMR ($CDCl_3$, 50 MHz); δ (ppm): 139.6, 137.2, 128.3, 128.1, 127.9, 127.5, 126.6, 84.7, 80.9, 76.2, 75.9.

Conclusion

We have used the ionic liquid 1-butyl-2-isopropyl-3-methylimidazolium triflimide ionic liquid as a catalyst and solvent system to prepare tertiary alcohols in high yields, which have not been produced via this environmentally friendly method previously. The yields of alcohol products are comparable with previous, less environmentally safe methods, and this method did not require the use of a flammable ether solvent. Yield of product was also increased by using the hydrophobic anion triflimide by decreasing the possibility of water contamination. As a further cost savings, the ionic liquid could be easily reused without loss of activity.

Acknowledgments

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