Green Chemistry: Comparison of Ionic Liquid *vs* Conventional Solvent for Indole Alkylation

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ABSTRACT

A comparison of the effectiveness of two synthetic methods was done for a green chemistry method using an ionic liquid-based solvent relative to a conventional method using organic solvents for the *N*-alkylation of indole. The green method used potassium hydroxide in the ionic liquid, 1-butyl-3-methylimidazolium tetrafluoroborate, followed by addition of the alkyl halide. The conventional method used sodium hydride in dimethylformamide. Possible advantages of the green method would be the use of a non-volatile solvent, the possibility of recycling the solvent, and the use of a less reactive base. However, its reaction yield was lower than for the conventional method, the reagent expense was higher, and recycling and reuse of the ionic solvent require considerable amounts of conventional solvent to clean it up sufficiently for reuse. On a laboratory scale, the ionic liquid method yielded neither a "green" nor an efficiency advantage. It is possible that with optimization on an industrial scale involving solvent reclamation that the green method could realize its promise.

KEYWORDS

Green Chemistry; Sustainable Chemistry; Ionic Liquids; *N*-alkylation; Indole; Solvent Recycling; Organic Chemistry; 1-Butyl-3-methylimidazolium Tetrafluoroborate; Synthesis

INTRODUCTION

The promise of green chemistry is to develop processes that offer improved effectiveness and environmental impact in terms of reducing hazardous waste, reducing workplace hazards, using sustainable materials, or reducing energy requirements. One development in the field of green chemistry involves utilizing ionic liquids in place of conventional solvents.[1] Ionic liquids are salts with low melting points, where one or both of the ions are large and the cation has a low degree of symmetry that results in a reduced lattice energy for the crystalline form of the salt. These liquids exhibit very low vapor pressures and thermal stabilities, and can often be recovered and reused as solvents. Ionic liquids allow for a triphasic system with aqueous and hydrocarbon phases, adding further to their utility as solvents.

These potential advantages of ionic liquids were explored as an alternative solvent in the N-alkylation of indole as part of a larger combinatorial chemistry effort. The low vapor pressure of ionic liquids allows for use in combinatorial setups that are open to the atmosphere. The conventional method treats indole with sodium hydride (NaH) in dimethylformamide (DMF).[2]

In the conventional reaction, NaH is used as a strong base to create the indole *N*-anion. NaH is commercially available as a 60% dispersion in mineral oil. The mineral oil is removed by trituration of the NaH with hexane. Besides the handling issues in combinatorial synthesis, NaH readily reacts with moisture in the air or in solvents, therefore requiring closed reaction systems and anhydrous solvents. Upon reaction with indole, flammable hydrogen gas is produced. Workup involves quenching in water, extracting with ether, and eluting on a short silica column. No solvents are recycled in the process. Prior experience in our lab with the conventional method[2] shows that the crude product obtained is usually about 90% by weight product with the remainder being primarily solvents as determined by gas chromatography-mass spectrometry (GC-MS) and nuclear magnetic resonance spectroscopy (NMR). This material is sufficiently pure to use for subsequent acylation reactions.

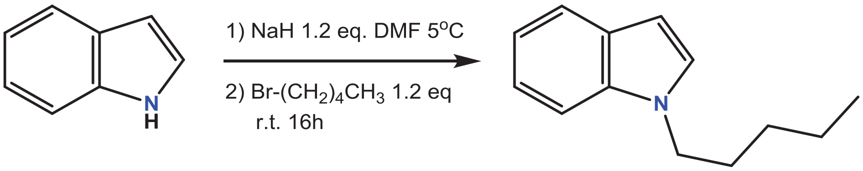
In contrast, the green method in the ionic liquid, 1-butyl-3-methylimidazolium tetrafluoroborate ($[BMIM]^+[BF_4]^-$), uses potassium hydroxide (KOH) as the base in place of NaH.[3] Although KOH is hygroscopic, in a dry atmosphere it is easily handled without special apparatus. This feature, along with the low vapor pressure of the ionic liquid, allows for the use of apparatus that is not as rigorously dry and shut off from the atmosphere. Also, there is no generation of hydrogen and the solvent is not flammable, so fire risk is eliminated.

An additional advantage to the ionic liquid is the opportunity for repurification[4] and reuse, which offers the possibility of producing less hazardous solvent waste. This recoverability is also important from a cost standpoint since the ionic liquid is significantly more expensive than the organic solvent of the conventional method. Therefore, the purpose of this study is to examine the utility of this alternative green method for the production of N-alkylindole intermediates in a combinatorial synthetic scheme involving subsequent acylation of the intermediates.

METHODS AND PROCEDURES

All reagents and solvents were purchased from Sigma-Aldrich, the solvents were HPLC grade, and all were used without further purification.

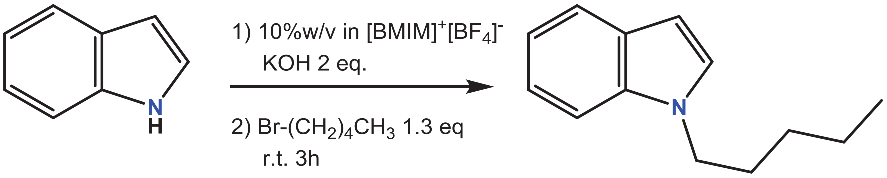
Conventional N-alkylation of Indole



Scheme 1.

Commercially available 1H-indole (11.8 g, 101 mmol) in 90 mL anhydrous N,N-dimethylformamide (DMF) was added to a solution of sodium hydride (NaH) (4.90 g, 122.4 mmol, 60% dispersion in mineral oil, which was removed by triple trituration with hexane) in 70 mL DMF, at 5ºC. The mixture was allowed to warm to ambient temperature and was stirred for 30 min. The mixture was cooled to 5ºC and 1-bromo-*n*-pentane (14.9 mL, 120 mmol) in 50 mL DMF was added drop-wise to the solution. After addition was complete, the mixture was allowed to warm to ambient temperature. After 16 h, the mixture was cooled to 5ºC and quenched with water, then extracted with 4 × 200 mL diethyl ether (Et_2O), dried over anhydrous sodium sulfate (Na_2SO_4), and filtered. The combined organic fractions were concentrated *in vacuo*. Silica gel chromatography (30 mm high × 85 mm diam; 250 mL *n*-hexane followed by 2 × 250-mL portions of dichloromethane (DCM)) yielded 17.7 g of a yellow oil that by NMR consisted of 16.1 g 1-*n*-pentyl-1H-indole (85.2% yield) with 4.8% DMF, 1.9% water, 0.7% DCM, and 1.3% ether.

Green-Chemistry N-alkylation of Indole Using Ionic Liquid



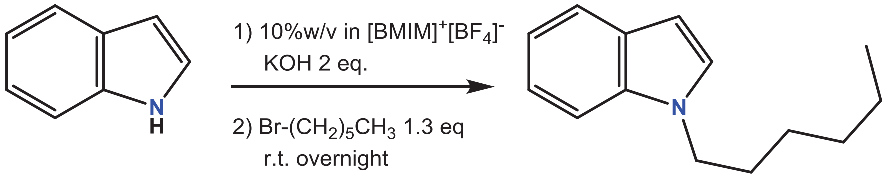
Scheme 2.

1H-indole (4.98 g, 42.5 mmol) at 10% w/v $[BMIM]^+[BF_4]^-$ was stirred with crushed potassium hydroxide (KOH) pellets (2.00 equiv., 4.83 g, 86.2 mmol) and 1-bromo-*n*-pentane (1.30 equiv., 6.85 mL, 55.2 mmol) at room temperature. After 3 h, the mixture was filtered through glass wool to remove undissolved KOH and potassium bromide (KBr), and the filtrate was extracted with 3 × 50 mL Et_2O. The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Silica gel chromatography (30 mm high × 20 mm diam.; 40 mL hexane followed by 11 × 30-mL portions of DCM) was used to separate the reaction products, yielding 1-*n*-pentyl-1H-indole (4.68 g, 58.5% yield) as a colorless oil that contained 7.4% 1-bromo-*n*-pentane and 0.4% water as indicated by NMR.

Purification of the Ionic Liquid

M.J. Earle, et al. reported that after diethyl ether extraction of the reaction products, the ionic liquid only required filtration to be suitable for reuse—as determined by NMR—and that there were only small mechanical losses from process to process.[3] Despite this literature precedent, we were concerned about the possibility of batch-to batch-contamination. Therefore, the extra step of ionic liquid $[BMIM]^+[BF_4]^-$ purification before reuse was employed using the method of L.L. Lazarus, et al.[4] The ionic liquid was diluted with 120 mL DCM and eluted on a column of 1 cm Celite topped with 1 cm silica gel and then with 3 cm Norit. An additional 50 mL DCM was used to completely elute the material. After evaporation *in vacuo*, 67% of the ionic liquid used in the prior reaction was recovered.

Green-Chemistry N-alkylation Using Recycled Ionic Liquid, Compared with Using Fresh Ionic Liquid



Scheme 3.

1H-indole (3.58 g, 30.6 mmol) at 10% w/v recycled $[BMIM]^+[BF_4]^-$ was stirred with crushed KOH pellets (2.0 equiv., 3.43 g, 61.2 mmol) and 1-bromo-*n*-hexane (1.3 equiv., 7.36 mL, 59.4 mmol) at room temperature. After stirring overnight, the mixture was filtered through glass wool to remove undissolved KOH and KBr, and the filtrate was extracted with 3 × 50 mL Et_2O. The combined organic fractions were dried over Na_2SO_4 and concentrated *in vacuo*. Silica gel chromatography (30 mm high × 20 mm diam; 40 mL hexane followed by 11 × 30-mL portions of DCM) gave 7.52 g of a yellow oil that, by NMR and GC-MS analysis, consisted of 2.98 g 1-*n*-hexyl-1H-indole (48.4% yield), 0.228 g residual 1-*n*-pentyl-1H-indole carried over from the previous reaction, and unreacted 1-bromohexane as the remainder.

1H-indole (4.98 g, 42.5 mmol) at 10% w/v fresh $[BMIM]^+[BF_4]^-$ was stirred with crushed KOH pellets (2.0 equiv., 4.77 g, 83.0 mmol) and 1-bromo-*n*-hexane (1.30 equiv., 6.86 mL, 55.3 mmol) at room temperature. After stirring overnight, the mixture was filtered through glass wool to remove undissolved KOH and KBr, and the filtrate was extracted with 3 × 50 mL Et_2O. The combined organic fractions were dried over Na_2SO_4 and concentrated *in vacuo*. Silica gel chromatography (30 mm high × 20 mm diam; 40 mL hexane followed by 11 × 30-mL portions of DCM) gave 9.92 g of a yellow oil that, by NMR and GC-MS analysis, consisted of 2.13 g 1-*n*-hexyl-1H-indole (24.9% yield) and unreacted 1-bromohexane as the remainder.

Gas Chromatography – Mass Spectrometry (GC-MS)

Samples of the 1-hexyl-1H-indole products in 1 mL *n*-hexane were prepared for GC-MS analysis using a Hewlett-Packard 6890 Series GC System with Mass Selective Detector and Auto-Injector. These were run on HP-5 5% phenyl methyl silane columns (30.0 m × 0.250 mm). The flow rate of helium was at 1.1 mL/min. Splitless injections of 2 μL were run at an injection temperature of 250ºC. The temperature gradient was 70ºC for 3 min., then increased to 290ºC at a rate of 10º C/min., and held at 290ºC for 10 min. The total flow rate was 23.5 mL/min.

Nuclear Magnetic Resonance (NMR)

NMR spectra were recorded on a Varian 400MR spectrometer (proton frequency 399.765 MHz) equipped with an AutoX DB broadband probe. Pulse sequences, acquisition, and data processing were accomplished using VnmrJ software (VnmrJ 4.2, Agilent Technologies, Santa Clara, CA). The spectrometer was locked on to D_2O and spectra were acquired at 28°C without spinning. Water suppression suitability studies were carried out using the presaturation (presat), WET (WET1D), and excitation sculpting (water_ES) pulse sequences (VnmrJ 4.2, Agilent Technologies, Santa Clara, CA) with automatic suppression of the tallest peak (water at δ 4.86 ppm), an observation pulse of 90° (10.8 μs), a spectral width of 6410.3 Hz, a relaxation time of 30 s, and an acquisition time of 5.112 s. Eight scans were taken. Quantitation spectra were recorded using the WET pulse sequence (wet 1D) (VnmrJ 4.2, Agilent Technologies, Santa Clara, CA) with automatic suppression of the tallest peak (water at δ 4.86 ppm) with an observation pulse of 90° (10.8 μs), a spectral width of 6410.3 Hz, a relaxation time of 30 s, and an acquisition time of 5.112 s. Waltz decoupling was used during the acquisition time to suppress ^{13}C side-bands. The gain was set to 24 dB and 64 scans. Three replicates were taken for each sample.

RESULTS AND DISCUSSION

Following a conventional synthetic procedure using NaH with DMF, 1-*n*-pentylindole was produced at an 85.2% yield, which is consistent with literature.[2] The purity level was 90% by weight with the impurities consisting of solvents, which produces acceptable results in subsequent acylation reactions. Following the green synthetic procedure using KOH with $[BMIM]^+[BF_4]^-$, 4.31 g of product was produced at a 54.2% yield. This is significantly lower than similar procedures in literature that have reported yields of around 90%.[3] To improve the yield we increased the reaction time from 3 hours to overnight (approx. 16 hours) for the reactions involving 1-*n*-bromohexane; however, subsequent yields were even lower. These lower yields are likely due to factors other than the chain length of the alkyl halide. It seems more likely that either the starting material was insufficiently pure or another contaminant was present that interfered with the reaction. As such, the effect of lengthening the reaction time cannot be determined; however, it is unlikely to be detrimental since the product is stable.

The green method has significantly higher cost due to the price of the ionic liquid. The ionic liquid used for this procedure was 1-butyl-3-methyl-imidazolium tetrafluoroborate ($[BMIM]^+[BF_4]^-$), which cost us $172/100g. The cost of DMF needed for the same scale reaction was approximately $12. There is no cost advantage to reusing the ionic liquid at the scales we are exploring since organic solvents are used in the recycling process. This need for purification and additional solvent use runs counter to the environmental ideal of reduced solvent use, as these wash solvents are not recovered at the lab scale. In an industrial process, recycling of these organic solvents may produce some cost efficiencies that are not realized on a lab scale.

Other factors involved in reusing the ionic liquid are its recovery yield and quality after purification. First, our ionic liquid recovery was only 67%. While this recovery may be optimized, it is important to consider these losses during recovery when comparing the differences of the green-chemistry method over the conventional method. Second, performing an alkylation with bromohexane in purified ionic liquid that was used in a previous alkylation with bromopentane gave a product that contained both hexyl and pentyl products in a 13:1 ratio, by GC-MS analysis. We did not determine whether this was due to pentyl-indole product being carried over in the ionic liquid, or whether unreacted bromopentane was left over in the ionic liquid after purification, which would compete with the bromohexane to create the mixture of alkylated products. In either case, the purification scheme was insufficient to ensure the removal of impurities from prior reactions. Therefore, the current purification method would only allow the reuse of the ionic liquid for running the identical reaction; otherwise, the purification method would need significant improvement to ensure complete removal of impurities.

CONCLUSION

In our hands, the conventional synthesis produced higher yields, less waste, and more easily purified material than did the green process using ionic liquids. Our limited trials using the ionic liquid method did not produce the yields expected from the prior literature.[3] The ionic liquid method also did not perform as anticipated in terms in its ability to recover, purify, and reuse the ionic liquid. The literature suggested that ether extraction of the product gave an ionic liquid that only required filtration before reuse.[3] We experienced significant carryover from a prior reaction of either product or the bromoalkane reagent. Purification of the ionic liquid[4] required the use of conventional solvents and produced solid waste; hence, the process did not meet the objectives of reducing waste. Purification also resulted in the loss of some of the ionic liquid and was still not adequate to remove impurities that would affect the next reaction for which it was used. Besides not delivering on the expectations of comparable yields and reduced solvent use, the green process was significantly more expensive and required more time due to the extra step of solvent recovery and reprocessing. Finally, while the ionic liquid is less volatile than conventional solvents, and therefore has the possibility of presenting less inhalation hazard risk, this does not mean that the ionic liquid is less toxic for humans or the environment.[5,6] Based on all these considerations, for our purposes in efficiently creating laboratory scale precursors for the combinatorial synthesis of biologically active materials for structure-activity studies, the conventional synthesis ultimately produces less toxic waste and makes more efficient use of materials than the ionic liquid method and in that sense is more environmentally friendly of two options.

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ABOUT THE STUDENT AUTHOR

Jonathan Redrico worked on this project as part of the 2014 Summer Undergraduate Research Experience program at Keck Graduate Institute. He graduated with a Bachelor of Science degree in Biochemistry and Molecular Biology from Chapman University in May 2015. He is currently pursuing an industrial career in biotechnology.

PRESS SUMMARY

Green chemistry is the use of chemical methods that reduce environmental impact in terms of reducing hazardous waste, reducing workplace hazard, utilizing sustainable materials, or reducing energy requirements. One such approach is to replace conventional solvents with ionic liquids. We examined the indole alkylation reaction routinely done in our labs. In this particular case, we found that at the laboratory scale, the conventional method was more effective and generated less toxic waste than the ionic liquid method.