

Available online at www.sciencedirect.com**ScienceDirect**

Procedia Chemistry 16 (2015) 413 – 419

Procedia
Chemistry

International Symposium on Applied Chemistry 2015 (ISAC 2015)

Microwave-assisted Fischer indole synthesis of 1,2,3,4-tetrahydrocarbazole using pyridinium-based ionic liquids

Ramon M. Eduque, Jr.^{a,*} and Evelyn C. Creencia^a^a*Mindanao State University - Iligan Institute of technology, Tibanga, Iligan City 9200, Philippines*

Abstract

Microwave-assisted organic synthesis using ionic liquids is believed to enhance efficiency of the reaction leading to a cleaner method, higher product yields and shorter reaction times. Six pyridinium-based ionic liquids were prepared from 2-methylpyridine and a series of alkyl bromides (R : *n*-C₄, *sec*-C₄, *t*-C₄, C₆, C₈ and Bn) by oil bath heating at 80, 90, 100 and 110 °C. The ionic liquids product yield efficiency has direct relationship with heating temperatures affording highest yields at 110 °C of 71.15%, 8.20%, 45.96%, 57.75%, 48.02% and 80.45% for each respective alkyl bromides. The catalytic activities of the synthesized ionic liquids in the Fischer indole synthesis of THC were examined. The highest yield of 67.82% is found to be less satisfactory compared to the use of the Lewis acid standard, ZnCl₂, which gave 79.89%. On the other hand, the use of the pyridinium-based ionic liquids in conjunction with ZnCl₂ afforded better yields than individual test catalysts resulting to 89.66% of the THC. Structural effects such as branching and chain length of the alkyl bromides for the synthesis of ionic liquids and the THC have negative effects on the product yields.

© 2015 Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Peer-review under responsibility of Research Center for Chemistry, Indonesian Institute of Sciences

Keywords: microwave-assisted synthesis; ionic liquids; Fischer indole

* Corresponding author. Cell phone:: +63- 922-218-3048
E-mail address: mon.eduque@gmail.com

Nomenclature

Bn	benzyl
THC	1,2,3,4-tetrahydrocarbazole
VOCs	volatile organic compounds

1. Introduction

Green chemistry principles require the development of cleaner processes. Among the several features of green chemistry is the reduction or replacement of VOCs. Volatile organic compounds in organic synthesis and industrial applications present a problem in their large volume of use, cleanup and environmental hazards, i.e., VOCs are very difficult to separate or remove from products, they impose problems for recycle and reuse, and incur substantial cost and adversely affecting the environment and personnel during disposal. Alternatives such as ionic liquids as solvents have recently gathered interest due to their negligible vapor pressure, thermal stability, non-flammability and non-corrosive properties. Ionic liquids have also been employed as catalysts for a wide range of organic reactions due to their tunable properties. As solvent or catalyst, modification of the ionic components of the ionic liquids leads to the emergence of new property to match required results; hence ionic liquids are also called designer solvents^{1,2,3,4,5,6}.

Organic transformations that require long ours even days to complete with catalysts or ionic liquids have limited the development of discovering novel compounds and industrial processes. With the advent of microwave technology, which is a non-conventional heating method, these limitations have been reduced. Microwave irradiation have been applied to diminish reaction times and enhance product yields by increasing selectivity and decreasing side products. This has led to the development of a broad field of research, the microwave-assisted organic chemistry (MAOS)^{1,7,8}.

Many organic reactions have utilized the combined advantages of ionic liquids and microwave irradiation. Of particular interest is the application of ionic liquids in the Fischer indole synthesis due to its diverse pharmaceutical applications^{9,10}. Different catalysts and solvents have been tested for Fischer indole synthesis to optimize product yield and enhance “greenness” of the process. The use of cheap and easily prepared pyridinium-based ionic liquids in organic reactions have shown remarkable properties, both as solvent and catalyst^{11,12}. Thus, this study presents the synthesis of pyridinium-based ionic liquids and their use to further enhance the microwave-assisted Fischer indole synthesis of THC.

2. Materials and Methods

The chemicals used in the study are reagent grade supplied by Sigma-Aldrich and were used as received. All the microwave-assisted reactions were performed using an unmodified, open-vessel multi-mode microwave reactor, Samsung household microwave oven model ME711K. The reactor is equipped with mechanical power control operating at output power of 100 to 800W in 2.45 GHz frequency. The microwave oven has a triple distribution system with ceramic enamel cavity. The reactor vessels used are 25 mL Pyrex™ test tubes standing in a 250 mL Erlenmeyer flask for support. The method of microwave irradiation were conducted by direct heating by controlling power setting and irradiation time.

The ¹H NMR spectra were measured at 500 MHz on an Agilent OneNMR Probe spectrometer using CDCl₃ and D₂O as solvents for the 1,2,3,4-tetrahydrocarbazole and the ionic liquids, respectively. Additional tool for structural elucidation of the products was performed by Fourier- Transform Infrared Spectroscopy (FTIR) measurements using Thermo Scientific Nicolet iS5 FT-IR Spectrometer equipped with iD1 transmission accessory.

2.1 General procedure for the synthesis of pyridinium-based ionic liquids

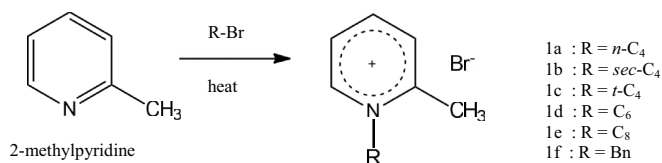


Figure 1. The general reaction for the synthesis of 2-methylpyridinium-based ionic liquids.

A 25 mL Pyrex™ test tube (15 mm i.d. x 17 mm o.d. x 105 mm h) was used as a reaction chamber for the synthesis of ionic liquids using 10.0 mmol of 2-methylpyridine and 11.0 mmol of the alkyl bromides [R : *n*-C₄, *sec*-C₄, *t*-C₄, C₆, C₈, and Bn]. Prior to oil bath heating, the reactants were mixed thoroughly using vortex mixer. Samples were heated in an oil bath at 80, 90, 100 and 110 °C for a designated time or until a change from a two-phase mixture into a clear single-phase solution was observed. The resulting solutions were then cooled to room temperature and washed with diethyl ether (3x2 mL) to remove unreacted starting materials and then purged with nitrogen gas for further cleaning to afford the ionic liquid products.

The nitrogen purging method was conducted at ambient pressure with the use of the N₂ gas cylinder, with the synthesized ionic liquids contained in a 25 mL test tube immersed in a constant temperature oil bath (70 °C). A fraction of the length of a Pasteur pipette attached to a chemical hose connected to the N₂ gas cylinder was submerged into the ionic liquid inside the test tube during the purging.

2.1 General procedure for the synthesis of THC

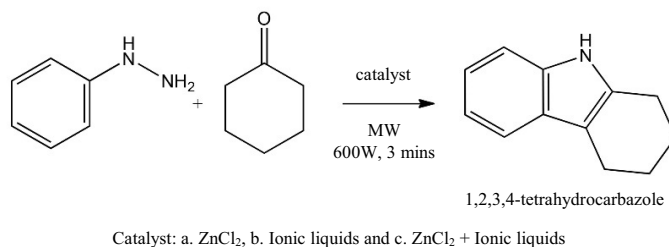


Figure 2. General reaction for the synthesis of THC.

A mixture of 1 mmol (0.1 mL) phenylhydrazine, 3 mmol (0.3 mL) mmol cyclohexanone and a catalytic amount (0.1 mmol) of ionic liquid and/or ZnCl₂ were placed in a 25 mL test tube. The test tube was plugged with quartz wool and placed in a 240 mL Erlenmeyer flask for support. Microwave irradiations were performed at 600 W for 3 mins. The resulting mixtures were dissolved in a small amount of acetone in preparation for gravity column chromatography (GCC) using hexane and ethyl acetate (1:3) as the solvent system. Fractions were analyzed for isolates using thin layer chromatography while performing several reruns of GCC as necessary to ensure complete separation of components. The indole isolates were collected and prepared for melting point determination, FT-IR and NMR analyses.

3. Results and Discussion

3.1 Synthesis of 2-methylpyridinium-based ionic liquids

The results show that regardless of the reaction time, the rate of reaction is increased by increasing the reaction temperature due to increased collisions of the reactants. As shown in Figure 3, ionic liquid yield generally increases as the heating temperature increases that at 110 °C the highest yield is observed.

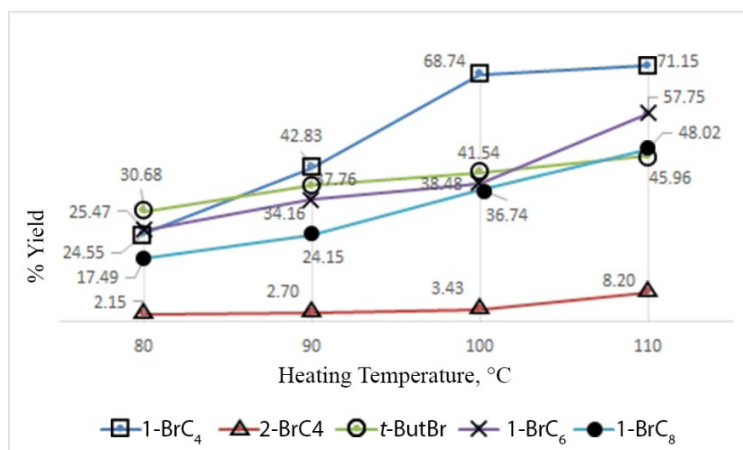


Figure 3. Summary of results in the synthesis of 2-methylpyridinium-based ionic liquids.

For the synthesis of 1-(*sec*-butyl)-2-methylpyridinium bromide, insignificant yields were obtained for all the temperature conditions. Meanwhile the respective ionic liquid produced from *t*-butyl bromide, 1-bromohexane and 1-bromooctane were significantly lower in yields than 1-bromobutane.

Table 1. Percent Yield for the Synthesis of 2-Methylpyridinium Bromide Ionic Liquids

Bromide Used	Ionic liquid	Product	Heating Conditions		Yield, %
			Temp., °C	Time, Hours	
1-bromobutane	1-butyl-2-methylpyridinium bromide	1a	80	8	24.55
			90	8	42.83
			100	8	68.74
			110	5	71.15
<i>sec</i> -butylbromide	1-(<i>sec</i> -butyl)-2-methylpyridinium bromide	1b	80	8	2.15
			90	8	2.70
			100	8	3.43
			110	5	8.20
<i>t</i> -butylbromide	1-(<i>t</i> -butyl)-2-methylpyridinium bromide	1c	80	5	30.68
			90	5	37.76
			100	5	41.54
			110	5	45.96
1-bromohexane	1-hexyl-2-methylpyridinium bromide	1d	80	10	25.47
			90	8	34.16
			100	5	38.48
			110	5	57.75
1-bromooctane	1-octyl-2-methylpyridinium bromide	1e	80	10	17.49
			90	8	24.15
			100	6	36.74
			110	5	48.02
benzylbromide	1-benzyl-2-methylpyridinium bromide	1f	room temperature		80.45

The heating time is stopped when the clear ionic liquid is formed. Generally, heating time decreases as the heating temperature increases. Reactions at higher temperature completes faster than those at lower temperatures. At temperatures beyond 110 °C, decomposition of the reactants and products was observed which resulted to the blackening of the samples and losing its viscosity and such results were discarded.

There is a decrease in the heating time with respect to heating temperature for the 1-BrC₆ and 1-BrC₈. This observation may be attributed to the faster reaction of the said primary alkyl bromides in comparison with *sec*- and *t*-butyl homologs which are bulkier and more sterically hindered for the nucleophile to attack the substrate.

The capacity of the pyridine nitrogen to attack the electrophilic carbon of the alkyl bromide to form the ionic liquids depends on the availability of the electrophilic carbon. Since the reaction is thought to proceed via nucleophilic substitution, SN₂, sterically hindered bulky substrates constrains the back-side attack of the nucleophile leading to decreased reaction rates. The product yield generally decreases as branching of the alkyl group increases from primary to tertiary. The effect of steric hindrance increases from primary alkyl to tertiary alkyl hence at 110 °C, the observed yields are 71.15%, 8.20% and 45.96% for primary, secondary and tertiary butyl, respectively.

The significantly small yield of *sec*-butyl bromides in contrast to the primary and tertiary butyl bromides is attributed to the rapid evaporation of the reactant even at low temperature heating, 70 °C. This rapid evaporation is not observed for the primary and tertiary butyl bromides even if the *t*-butyl bromide has lower boiling point than the secondary analog.

The less sterically hindered substrates favor a nucleophilic substitution, SN₂, reaction. Steric effect is most observed for bulky groups or longer chained substrates. The number of carbons increases from the 1-bromobutane to 1-bromooctane and, as with the branching effects, the increase in chain length results to increased steric hindrance for nucleophilic substitution and thereby inhibiting the reaction leading to lower product yields. The increase in chain length resulted to the observed decrease in the yield at 110 °C of 71.15%, 57.75 and 48.02% from butyl, hexyl and octyl bromides, respectively.

The synthesis of ionic liquid using benzyl bromide as anion was spontaneous at room temperature and did not require heating affording a yield of 80.45%.

3.2 Synthesis of THC

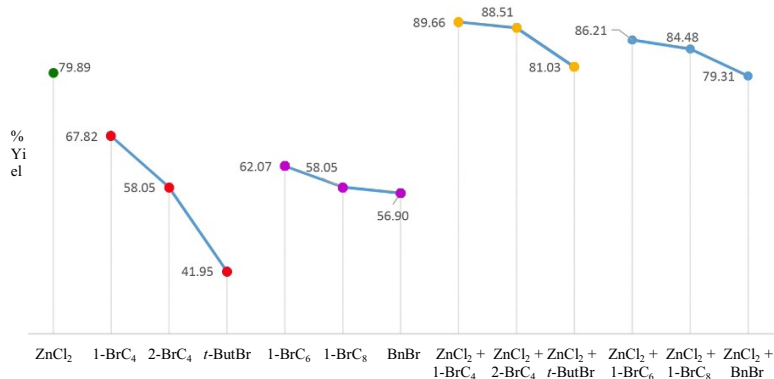


Figure 4. Summary of the THC product yields and the corresponding catalysts used.

As illustrated in Figure 4, there is a general decrease in the THC product yield as the order of alkyl bromides used to synthesize the 2-methylpyridinium ionic liquids increase. This is observed for syntheses employing pure ionic liquids alone and those that used ZnCl₂ as co-catalyst. It is also notable that the synergy of ZnCl₂ and the 2-methylpyridinium ionic liquids resulted to higher THC yields in comparison with the pure ZnCl₂ and pure ionic liquids. As the chain length of increases, the THC product yield decreases. Similarly with the *sec*- and *t*-butyl analogs of the 2-methylpyridine, bulky groups and increasing side chain may interfere with the rate of reaction to produce the THC as the bigger groups tend to occupy spaces between the phenylhydrazine and

cyclohexanone reactants reducing the collision rate leading to decreased product yield. The method employing both ZnCl_2 and 2-methylpyridinium ionic liquids generally has higher THC product yields than those that are using pure ZnCl_2 or pure ionic liquids alone.

Fischer indole synthesis requires an acid catalyst to have a significant yield and in the absence of the Lewis acid ZnCl_2 , apparent decrease in the yield is observed for the synthesis of THC. The observed increase in the THC yield when both ZnCl_2 and ionic liquids are employed can be attributed to the ionic liquids acting as hot spots during the microwave irradiation, increasing the temperature of the solution in a short time thereby increasing the rate of reaction leading to higher product yields. Furthermore, the presence of ionic liquids is assumed to facilitate the condensation reaction between the phenylhydrazine and cyclohexanone producing resulting to better yields¹³.

3.3 ¹H NMR and IR Spectral Data

1-butyl-2-methylpyridinium bromide (1a)

(500 MHz, D_2O) δ = 2.77 (s, 3H), 7.82 (bd, $J=7.8$ Hz, 1H), 8.27 (td, $J=8.1, 1.5$ Hz, 1H), 7.76 (t, $J=6.8$ Hz, 1H), 8.63 (bd, $J=6.4$ Hz, 1H), 4.46 (m, 2H), 1.84, (m, 2H), 1.35 (m, 2H), 0.87 (t, $J=7.3$ Hz, 3H).

1-(*sec*-butyl)-2-methylpyridinium bromide (1b)

(500 MHz, D_2O) δ = 2.78 (s, 3H), 7.75-7.81 (m, 2H), 8.23 (td, $J=7.8, 1$ Hz, 1H), 8.69 (d, $J=6.4$ Hz, 1H), 4.90 (m, 1H), 1.52, (d, $J=6.4$ Hz, 3H), 1.90-1.93 (m, 2H), 0.67 (t, $J=7.6$ Hz, 3H).

1-(*t*-butyl)-2-methylpyridinium bromide (1c)

(500 MHz, D_2O) δ = 2.64 (s, 6H), 7.69-7.75 (m, 2H), 8.31 (bt, $J=7.8$ Hz, 1H), 8.45 (bd, $J=4.9$ Hz, 1H).

1-hexyl-2-methylpyridinium bromide (1d)

(500 MHz, D_2O) δ = 2.72 (s, 3H), 7.77 (bd, $J=7.8$ Hz, 1H), 8.22 (bt, $J=7.1, 1$ Hz, 1H), 7.72 (bt, $J=6.8$ Hz, 1H), 8.59 (bd, $J=6.4$ Hz, 1H), 4.72 (t, $J=7.6$ Hz, 2H), 1.81, (m, 2H), 1.15-1.30 (m, 6H), 0.725 (t, $J=6.4$ Hz, 3H).

1-octyl-2-methylpyridinium bromide (1e)

(500 MHz, D_2O) δ = 2.72 (s, 3H), 7.71-7.79 (m, 2H), 8.23 (m, 1H), 8.59 (bd, $J=6.4$ Hz, 1H), 4.41 (m, 2H), 1.81 (m, 2H), 1.11-1.29 (m, 10H), 0.725 (t, $J=6.4$ Hz, 3H).

1-benzyl-2-methylpyridinium bromide (1f)

(500 MHz, D_2O) δ = 2.63 (s, 3H), 7.82 (bd, $J=7.8$ Hz, 1H), 8.29 (t, $J=7.8$ Hz, 1H), 7.76 (t, $J=7.1$ Hz, 1H), 8.63 (bd, $J=6.4$ Hz, 1H), 5.66 s, 2H), 7.12 (d, $J=6.8$ Hz, 2H), 7.31-7.35 (m, 3H).

1,2,3,4-tetrahydrocarbazole

[pale yellow crystals, mp 112-116 °C (lit.^{9,14} m.p. 112-116 °C)] (500 MHz, CDCl_3) δ = 2.75 (t, $J=5.4$ Hz, 4H), 1.88-1.98 (m, 4H), 7.5 (d, $J=7.8$ Hz, 1H), 7.10-7.13 (m, 1H), 7.14-7.17 (m, 1H), 7.29 (d, $J=7.3$ Hz, 1H), 7.66 (bs, 1H). IR (cm⁻¹) 3412 (N-H stretch), 3004 (aromatic C-H stretch), 1738-1440 (C=C ring stretch), 1366-1228 (aromatic C-N stretch), 1217 (C-H bend).

4. Conclusion

Six new ionic liquids based on 2-methylpyridinium were synthesized and characterized. The ionic liquids product yield efficiency has direct relationship with heating temperatures while structural effects such as branching and chain length of the alkyl bromides have inverse effects. The catalytic activities of the synthesized ionic liquids in the Fischer indole synthesis of THC were examined and less satisfactory results were obtained as compared to the use of Lewis acid, ZnCl_2 . On the other hand, the use of the pyridinium-based ionic liquids in conjunction with ZnCl_2 afforded better yields than individual test catalysts.

Acknowledgements

The author would like to thank CHED-FDP II for the funding of this research through MSU-IIT and MSU-GSC.

References

1. Martínez-Palou, Rafael. Microwave-assisted synthesis using ionic liquids. *Molecular diversity* 2010;14(1): 3-25.
2. Seddon, K.R., Earle, M.J. Ionic Liquids. *Green Solvents for the Future. Pure Appl. Chem.* 2000;72(7): 1391-1398.
3. Arco, S.D., Laxamana, R.T., Giron, O.D., Obliosca, J.M. Synthesis of [RMIM] Acetate Halogen-Free Ionic Liquids for use as Greener Solvents in Diels-Alder Reaction. *Phil. J. Sci.* 2009;132(2): 133-139.
4. Leveque, J-M., Estager, J., Draye, M., Cravotto, G., Boffa, L., Bonrath, W. Synthesis of Ionic Liquids Using Non-Conventional Activation Methods: An Overview. *Monatshefte für Chemie* 2007;138: 1103-1113.
5. Rogers, R.D., Hough, W.L. Ionic Liquids Then and Now: From Solvents to Materials to Active Pharmaceutical Ingredients. *Bull. Chem. Soc. Jpn.* 2007;80(12): 2262-2269.
6. Pandey, S. Analytical applications of room-temperature ionic liquids : A review of recent efforts. *Analytica Chimica Acta.* 2006;556(1): 38-45.
7. Rebeiro, G.L., Khadilkar, B.M. Chloroaluminate ionic liquid for Fischer indole synthesis. *Synthesis* 2001;3: 370-372.
8. Kappe, O.C., Horeis, G., Pichler, S., Stadler, A., Gossler, W. Microwave-Assisted Organic Synthesis – Back to the Roots. Fifth International Electronic Conference on Synthetic Organic Chemistry (ECSOC-5). [Online] 2001, <http://www.mdpi.org/ecsoc-5/e0000/e0000.htm> (accessed January 27, 2012).
9. Humphrey, G.R., Kuethe, J. Practical Methodologies for the Synthesis of Indoles. *Chem. Rev.* 2006;106: 2875-2911.
10. Creencia, E.C., Tsukamoto, M.; Horaguchi, T. One-Pot-One-Step, Microwave-Assisted Fischer Indole Synthesis. *J. Heterocyclic Chem.* 2011;48: 1095-1101.
11. Deng, Y., Duan, Z., Gu, Y., Zhang, J., Zu, L. Protic pyridinium ionic liquids: Synthesis, acidity determination and their performances for acid catalysis. *J. of Mol. Catalysis A: Chemica* 2006; 250: 163-168.
12. Scammels, P.J., Harjani, J.R., Singer, R.D., Garcia, M.T. The design and synthesis of biodegradable pyridinium ionic liquids. *Green Chem.* 2008;10: 436-438.
13. Kumar, Tamatakallu O.S., Madevan, Kittapa M. Green synthesis of 2,3,4,9-tetrahydro-1*H*-carbazoles / 2,3-dimethylindoles catalyzed by [bmim (BF₄)] ionic liquid in methanol. *Org. Comm.* 2013;6(1): 31-40.
14. Beheshtiha, Y., Heravi, M., Saeedi, M., Fallah, A., Bamoharram, F. Heteropolyacid catalysed synthesis of indole derivatives via Fischer indole synthesis. *GU J Sci* 2011;24(4): 709-714.