ORIGINAL ARTICLE

A C G publications

Org. Commun. 6:1 (2013) 31-40

organic communications

Green synthesis of 2,3,4,9-tetrahydro-1*H*-carbazoles/ 2,3-dimethylindoles catalyzed by [bmim (BF_4)] ionic liquid in methanol

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(Received July 7, 2012; Revised February 2, 2013; Accepted February 4 2013)

Abstract: 1-butyl-3-methylimidazolium tetrafluoroborate [bmim (BF_4)] ionic liquid has been used as catalyst for the synthesis of tetrahydrocarbazoles and 2, 3-dimethylindoles with excellent yields in a shorter reaction time. The results show that the [bmim (BF_4)] ionic liquid is very efficient in the Fischer indole synthesis due to its operational simplicity, high yields, dual catalyst-solvent properties and reused for five consecutive reactions without significant loss of catalytic efficiency. The applicability of the methodology for large-scale reaction highlights its potentiality for industrial scale synthesis. The main advantage of this procedure is that the products could be obtained in pure form after filtration and evaporation of MeOH solvent.

Keywords: Fischer indole synthesis; 2,3,4,9-tetrahydro-1*H*-carbazoles; 2, 3-dimethylindoles; 1-butyl-3-methylimidazolium tetrafluoroborate; ionic liquid.

1. Introduction

The tetrahydrocarbazole ring system has been the structural subunit of many naturally occurring alkaloids, biologically active molecules and medicinal important synthetic analogues.[1] Tetrahydrocarbazoles condensed with indole,[2] furan, [3] pyrimidine,[4] pyrazoline,[5] and thiophene,[6] moieties have been known to processes wide spectrum biological activities.[7-9] There has been many methods of synthesis which includes cyclization of diphenylhydrazone of cyclohexane-1,2-dione or 2-phenylhydrazono cyclohexanone via Fischer indole synthesis. [10–14] However the Bischler[15-16] synthesis served as one of the simplest and attractive method to obtain tetrahydrocarbazoles and carbazoles by the condensation of α-halocyclohexanones with aromatic amines. Improved method for the synthesis of tetrahydrocarbazoles by the Bischler reaction was also reported.[17] The catalytic intra molecular alkylation of alkenyl indoles using transition metal complexes for tetrahydrocarbazoles was also studied extensively.[18] However all the reported methods has disadvantages such as harsh reaction conditions, use of corrosive acid in Fischer synthesis, modest yields in Bischler reaction and use of costlier reagents in metal catalyzed coupling reaction[19]respectively. Very recently the propylphosphonic anhydride (T3P) under microwave-assisted,[20] synthesis of substituted indoles using continuous flow micro reactors,[21] microwave-assisted one-pot synthesis of tetrahydrocarbazole,[22] facile clay-induced synthesis of 1,2,3,4-tetrahydrocarbazole and indoles,[23] have been reported. Apart from many significant features of these methods, there are certain draw backs such as use of corrosive

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The article was published by Academy of Chemistry of Globe Publications
www.acgpubs.org/OC/index.htm © Published 3/5/2013 EISSN:1307-6175

acid i.e., T3P makes isolation difficult, harsh reaction condition i.e., use of microwave condition and so on stimulated our interest to develop still milder and simple approach to synthesize these class of compounds. The 1-butyl-3-methylimidazolium tetrafluoroborate has been used as green catalyst in many organic reactions like Diels Alder reactions,[24] and Aldol condensations.[25] In spite of this, the 1-butyl-3-methylimidazolium tetrafluoroborate also been used as solvent in many reactions such as Heck reaction,[26] Suzki-Miyaura,[27] Wittig reaction,[28] Stille reaction,[29] Friedal–Crafts reaction,[30] respectively. Further, reduction reactions like hydrogenation of C-C double bond, [31] reduction of the benzaldehydes,[32] and halogenation reactions,[33] have also reported by using 1-butyl-3-methylimidazolium tetrafluoroborate as green solvent. As mentioned above, a variety of reactions utilizing 1-butyl-3-methylimidazolium tetrafluoroborate ionic liquids either as solvent and catalyst has been extensively studies. Recently, Fisher indole synthesis has been reported by using different ionic liquids.[34-35] Hence in this work, we report the application of 1-butyl-3-methylimidazolium tetrafluoroborate as a green catalyst for efficient one-pot Fischer indole synthesis of tetrahydrocarbazoles and 2, 3-dimethylindoles by using methanol as cosolvent (scheme-1) with good purity and excellent yields. The 1-butyl-3-methylimidazolium tetrafluoroborate catalyst could be easily recovered by a simple extraction process and reused for 3-5 times without decreasing its reactivity. This work is in continuation of our previous work on the synthesis Fischer indolization of arylhydrazines,[36-39] involving rapid mild and high yielding protocol and also for the simple synthesis of new heterocycles via modifications of existing methodologies and their biological activities.[40-51]

2. Results and Discussion

In a typical experiment the mole equivalent of phenylhydrazine hydrochloride 2.0g (0.013mol) and cyclohexanone 1.36g (0.016mol) with 11.3g of [bmim (BF_4)] (5 mole equivalent) as catalyst and solvent was taken in a round bottom flask. The whole reaction mixture was refluxed on water bath for 1 hr and the progress of the reaction was monitored by TLC. The yield about 95% of tetrahydrocarbazole (3a) was obtained in the model reaction in which [bmim (BF_4)] served as both catalyst and solvent. Further, we carried out the same reaction with catalytic amount (20 mol% and 50 mol %) of [bmim (BF_4)] with MeOH as cosolvent (10 ml) in order to use only catalytic amount and to avoid the use of excess of catalyst as impressed by our earlier report [29-32] and expecting the same result from the [bmim (BF_4)] as catalyst. As a result, both 20 mol% and 50 mol % of [bmim (BF_4)] catalyst load gave good yield with the model reaction. However, there is only noticeable change in reaction time and not with the yield of the product between 20 mol% and 50 mol % of [bmim (BF_4)] catalyst load (Table 1). Further, the solvent effect on this reaction was also studied and it was found that MeOH and absolute EtOH gave a best result as a cosolvent when compared to other solvents (Table 2). Most of the products were immiscible with ionic liquid and soluble with MeOH, hence they could be separated by a simple decantation at the end of the reaction and the small catalyst could be discarded. Thus by adopting optimized reaction conditions the various tetrahydrocarbazoles and 2,3-dimethylindoles were also prepared with various phenylhydrazine hydrochlorides and ethyl methyl ketone in presence of 20 mol % of [bmim(BF_4)] in MeOH (10 ml) as a solvent (scheme 1&2) and the results are reported in Table 3&4. The possible catalytic assistance by 1-butyl-3-methylimidazolium tetrafluoroborate in this *Fischer* indole synthesis is as shown in scheme-3. It presumes that the traces of BF_3 present in cluster of 1-butyl-3-methylimidazolium tetrafluoroborate may facilitate the condensation reaction between phenylhydrazine hydrochlorides and ketones. Further, the *Fischer* cyclization of intermediates occurs thermally in presence of high boiling 1-butyl-3-methylimidazolium tetrafluoroborate. The Postulated structures of the newly synthesized compounds were in good agreement with their ^{1}H NMR, ^{13}C NMR and Mass spectral data. The ^{1}H NMR spectra of the compounds **3a-k & 5a-g**, in particular **3j** showed the 3Ar protons at δ 6.74-7.15 ppm. In this, two aromatic protons appears as doublet of doublet, one in the range of δ 6.98-7.01 ppm with two coupling constants, *J*=2.80 Hz and *J*=10.0 Hz and another one in the range of δ 7.12-7.15 ppm with two coupling constants, *J*=8.80 Hz and *J*=4.40 Hz is due to interaction with adjacent Fluorine atom. The aliphatic protons appeared as doublet, triplet and multiplet at δ 1.39-2.69 ppm and three methyl proton showed doublet at δ 1.03-1.04 ppm with coupling constant, *J*=6.40 Hz. The broad peak of NH appears

at 10.6 ppm. ^{13}C NMR spectra of the compounds showed the signals in the respective regions. The mass spectra of the compounds exhibited molecular ion peaks at their respective molecular weights which confirmed their formation.

Table 1. Results of Fischer indole synthesis of Phenylhydrazine hydrochloride and Cyclohexanone in different concentration of ionic liquid [a]

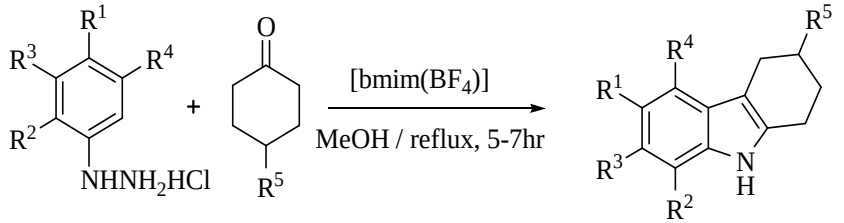
Entry	$PhNHNH_2.HCl$ Mol %	Cyclohexanone Mol %	[bmim (BF_4)] mol	Time (h)	Yield [b] %
1	1	1	5	1	95
2	1	1	50 mol%	4	90
3	1	1	20 mol%	6	90

[a] All reactions were carried out at reflux temperature [b] isolated yields.

Table 2. Effect of solvent on the synthesis of compounds 3a-k & 5a-g [a]

Entry	Solvent	[bmim(BF_4)] Mol %	Time (h)	Yield [b] (%)
1	MeOH	20	7	90-95
2	MeOH	20	6	90-91
3	EtOH	20	4	78-80
4	CH_3CN	20	3	71-73
5	THF	20	3	55-58
6	CH_2Cl_2	20	2	50-52
7	EtOAc	20	2	30-35
8	Toluene	20	1	35-40

[a] All reactions were carried out at reflux temperature [b] isolated yields.

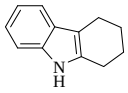
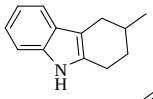
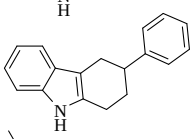
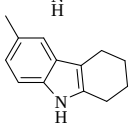
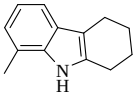
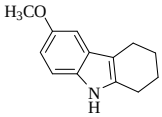
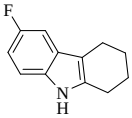
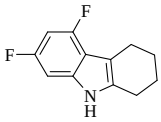
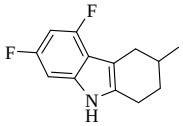
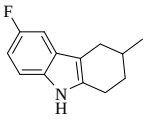
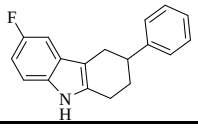


1a 2a 3a - k

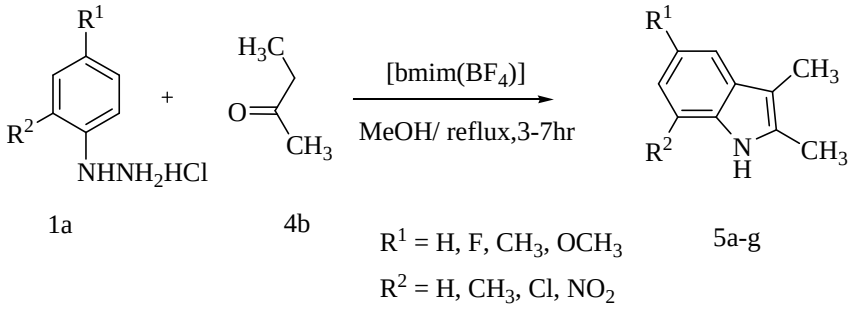
R^1= H, F, CH_3,OCH_3,Cl
R^2= H, F, CH_3, Cl
R^3= H,F
R^4= H,F
R^5= H,CH_3, Ph

Scheme 1. Synthesis of tetrahydrocarbazoles 3a-k

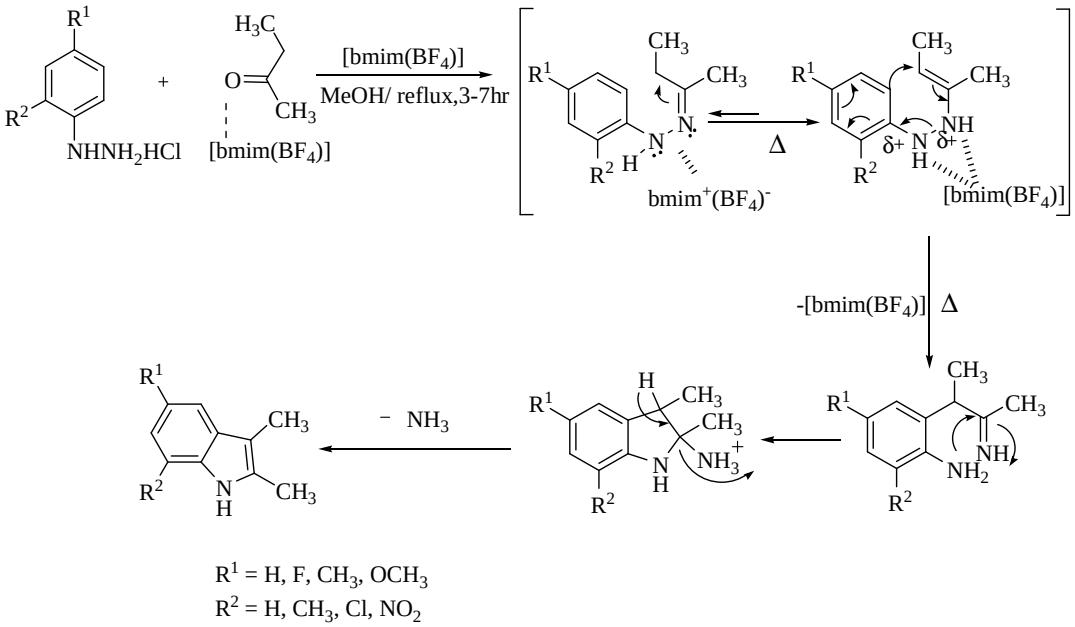
Table 3. Physical data of tetrahydrocarbazole derivatives [a] 3a-k

Entry	Product	Time (h)	Yield [b] (%)	Mp °C Found	Mp °C Report
3a		7.0	95	118-117	116-118[35]
3b		6.0	88	108-110	109-110[35]
3c		7.0	88	118-120	121-123[53]
3d		5.5	85	92-93	98-100[36]
3e		5.5	88	95-97	93-94[35]
3f		6.0	80	87-89	88-90[36]
3g		7.0	90	94-95	93-95[36]
3h		5.5	90	110-115	-
3i		6.0	89	98-100	-
3j		6.5	90	105-106	-
3k		7.0	87	115-120	-

[a] All reactions were carried out at reflux temperature. [b] isolated yields

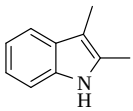
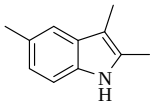
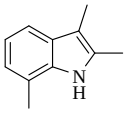
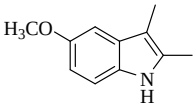
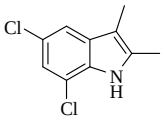
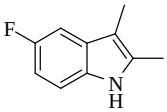
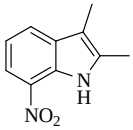


Scheme 2. Synthesis of 2,3-dimethylindoles 5a-g



Scheme 3. Possible mechanism in which the role of [bmim (BF_4)] catalyst has been described

Table 4. Physical data of 2,3-dimethylindole derivatives [a] 5a-g

Entry	Product	Time (h)	Yield [b] (%)	Mp °C Found	Mp °C Report
5a		7.0	95	103-105	106-107[35]
5b		5.0	90	97-98	98-99[36]
5c		5.0	85	78-79	75-76[35]
5d		3.0	88	63-65	60-61[36]
5e		3.5	80	89-91	95-96[52]
5f		7.0	92	61-62	60-61[36]
5g		3.0	80	96-97	95-96[35]

[a] All reactions were carried out at reflux temperature. [b] isolated yields

3. Conclusion

1-butyl-3-methylimidazolium tetrafluoroborate [bmim (BF_4)] has become an efficient catalyst for the synthesis of tetrahydrocarbazoles and 2,3-dimethylindoles due to its environmentally friendly, stability to water, air, low toxicity and reusability. The applicability of the methodology for large-scale reaction highlights its potentiality for industrial scale synthesis. The main advantage of this procedure is that the products could be obtained in pure form after filtration and evaporation of MeOH solvent.

4. Experimental

4.1 Methods and materials

The purity of the compounds was checked by TLC and was further purified by column chromatography. Melting points were obtained on a B-540 Buchi melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Brucker AM 400-MHz spectrometer (300, 400 and 100 MHz, respectively) with TMS as the internal standard in $CDCl_3$ or dimethyl sulfoxide (DMSO-d_6). Mass spectra were recorded on a Jeol SX 102=DA-6000 (10 kV) FAB mass spectrometer.

4.2. General procedure for the synthesis of tetrahydrocarbazoles and 2, 3–dimethylindoles:

The equivalent mole of phenylhydrazine hydrochloride 2.0g (0.013mol) and cyclohexanone 1.36g (0.016mol) or ethyl methyl ketone 0.99 g (1.22 mol) with 0.62g of [bmim (BF_4)] (20 mol %) as catalyst and 20 ml MeOH solvent was taken in a round bottom flask. The whole reaction mixture was refluxed on water bath for the appropriate time. After the completion of the reaction, reaction mixture was cooled to room temperature, it was poured into water (10 mL) and extracted with EtOAc (3-10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude solid. The crude product was purified by column chromatography with silica gel (60–120 mesh, petroleum ether: ethyl acetate, 8:2 v/v) furnished the analytically pure products. All the products were characterized by ^{1}H NMR, ^{13}C-NMR, LC-MS and analytical techniques.

4.3. Spectral Data for Selected Compounds

2,3,4,9-tetrahydro-1H-carbazole (3a, $C_{12}H_{13}N$): Crystalline brown solid; m.p. 118-117 ^{o}C; MS. *m/z* = 172.2 (M^++1).

3-methyl-2,3,4,9-tetrahydro-1H-carbazole (3b, $C_{13}H_{15}N$): Crystalline brown solid; m.p. 108-110 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6,):(δ/ppm,):10.58 (s,1H), 7.30 (d, 1H, *J*=7.6 Hz,), 7.21 (d, 1H ,*J*=8.0 Hz,), 6.91 (m, 2H), 2.70-2.71 (m, 3H), 2.18 (t, 1H, *J*=9.60 Hz,), 1.84-1.85 (m, 2H), 1.45-1.46 (m, 1H), 1.09 (d, 3H, *J* = 6.40 Hz,). ^{13}C NMR (100, MHz, DMSO-d_6):(δ/ppm,):135.8, 134.0, 127.1, 119.8, 117.8, 116.9, 110.4, 107.9, 31.0, 29.1, 29.1, 22.3, 21.6 ; MS. *m/z* =186.4 (M^++1).

3-phenyl-2,3,4,9-tetrahydro-1H-carbazole (3c, $C_{18}H_{17}N$): Brown solid; m.p.118-120^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) :(δ/ppm,): 7.80 (s, 1H), 7.40 (d, 1H *J*=7.6 Hz,), 7.34-7.28 (m, 5H), 7.25-7.11 (m, 1H), 7.09-7.05 (m, 2H), 3.09-3.05 (m, 2H), 2.85-2.80 (m, 3H), 2.21-2.13 (m, 2H); MS. *m/z* = 248.2 (M^+ +1).

6-methyl-2,3,4,9-tetrahydro-1H-carbazole (3d, $C_{13}H_{15}N$): *C*rystalline solid: mp 92-93^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) :(δ/ppm,): 10.40 (s, 1H), 7.10 (d, 1H, *J* = 8.60 Hz), 6.80 (s, 1H), 6.60 (d, 1H, *J*=8.4 Hz), 2.54 - 2.71 (m, 4H), 2.34 (s, 3H) 1.77 - 1.96 (m, 4H); MS. *m/z* = 186.2 (M^++1).

***6-methoxy-2,3,4,9-tetrahydro-1H-carbazole(3f, $C_{13}H_{15}NO$)*:** Crystalline solid: mp 87-89 ^{o}C; ^{1}H NMR (400 MHz, DMSO d_6) :(δ/ppm,): 10.40 (s, 1H), 7.10 (d, 1H, *J* = 8.4 Hz), 6.80 (s, 1H), 6.60 (dd, 1H, *J* = 8.4 Hz, *J* = 2.08 Hz), 3.70 (s, 3H), 2.56 -2.74 (m, 4H), 1.74 - 1.94 (m, 4H); MS. *m/z* = 202.1 (M^++1).

6-fluoro-2,3,4,9-tetrahydro-1H-carbazole (3g, $C_{12}H_{12}FN$): Crystalline solid; mp. 94-95^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6) :(δ/ppm,): 10.72 (s, 1H), 7.18-7.21 (m, 1H), 7. 04-7.07 (m, 1H), 6.76-6.81 (m, 1H) , 2.56-2.70 (m, 4H),1.77-1.83 (m, 4H); MS. *m/z* = 190.2 (M^++1).

5,7-difluoro-2,3,4,9-tetrahydro-1H-carbazole(3h, $C_{12}H_{12}FN$): Brown solid, m.p.110-115 ^{0}C; ^{1}H-NMR (300 MHz, $CDCl_3$) :(δ/ppm,): 7.73 (s, 1H), 6.76 (dd, 1H, *J*=12.1 Hz, *J*= 2.0 Hz), 6.49-6.57 (m, 1H), 2.86 (s, 2H), 2.67 (s, 2H), 1.86 (s, 4H), MS. *m/z* = 208.2 (M^++1).

6-fluoro-3-methyl-2,3,4,9-tetrahydro-1H-carbazole (3j, $C_{13}H_{14}FN$): Brown solid, m.p.105-106 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6) :(δ/ppm,):10.66 (s,1H), 7.15 (dd, 1H *J*=8.8 Hz,*J*=4.40 Hz), 7.00 (dd, 1H, *J*=2.80 Hz, *J*= 10.0Hz), 6.70-6.76 (m, 1H), 2.68 (d, 3H, *J*=2.40 Hz), 2.10 (t, 1H, *J*=9.60 Hz), 1.79-1.81 (m, 2H), 1.40-1.41 (m,1H), 1.04 (d, 3H, *J*=6.40 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) :(δ /ppm,):158.9, 156.6, 135.9, 132.3, 128.1, 110.5, 108.7, 102.8, 31.2, 29.5, 29.2, 22.9, 21.6; MS. *m/z* = 204.2 (M^++1).

***6-fluoro-3-phenyl-2,3,4,9-tetrahydro-1H-carbazole (3k, $C_{18}H_{16}FN$)*:** Brown solid; m.p.115-120 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6) :(δ/ppm,): 10.81 (s, 1H), 7.33-6.38 (m, 4H), 7.31-7.24 (m, 2H), 7.11-7.08 (m, 1H), 6.84-6.79 (m, 1H), 3.02-3.00 (m, 1H), 2.99-2.85 (m, 3H), 2.70-2.63 (m, 1H) 2.51-2.50 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) :(δ /ppm,): 160.8, 158.7, 153.1, 147.8, 138.6, 135.6, 131.8, 130.0, 128.1, 127.3, 109.8, 96.6, 45.1, 30.5, 12.4 ; MS. *m/z* = 266.2 (M^+ +1).

Acknowledgement

We are thankful to the Department of Postgraduate Studies and Research in Chemistry, Kuvempu University, Shankaraghatta, for providing laboratory facilities and Indian Institute of Science, Bangalore for spectral analysis. One of the authors (Shrungesh Kumar. T. O.) thankful to SC/ST Cell, Kuvempu University, for granting Junior Research Fellowship.

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