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Synthesis of β-aminocarbonyl compounds catalyzed by 1-propylimidazolium trifluroacetoacetate

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ABSTRACT

A facile synthetic procedure has been reported for classical mannich reaction of aldehyde, acetophenone and aniline using catalytic quantity of 1-propylimidazolium trifluroacetoacetate. As a result, acetophenone undergo rapid reactions with a variety of halide substituted benzalaldehyde, methylbenzaldehyde, methoxybenzaldehyde, isopropylbenzaldehyde, nitrobenzaldehyde, halide substituted aniline, nitroaniline to produce β-aminocarbonyl compounds, in moderate to very good yields. Recovery of the products from the reaction mixture is very facile. Efficiency of the catalyst in terms of reusability is also discussed. The formation of the products was confirmed based on their H^1 *NMR and melting point.*

Keywords: Brønsted acidic ionic liquid, reusable, recyclable and neoteric solvent

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INTRODUCTION

The mannich reaction is one of the most classical methods for the preparation of β-aminocarbonyl compounds. It is an important carbon-carbon bond formation reaction in organic synthesis.[1] The products which are formed in mannich reaction (i.e.) β-aminocarbonyl compounds are important intermediates for various nitrogen containing natural products and pharmaceuticals. [2] The reported mannich reactions catalyzed by HCl, HBF_4[3], $InCl_3$,[4] $Y(OTf)_3$ chiral brønsted acid,[5-6] and dodecylbenzenene sulfonic acid[7] have some drawbacks, such as difficult in separation, some are corrosive, volatile, recycling of catalyst and environmental problems[8,9]. There was an urge to design a catalyst to overcome stated problems and there were several green techniques available such as microwave assisted techniques, UV radiation, ionic liquids and solvent free techniques for mannich reactions.[10-11] The ionic salts which having melting point below 100°C, fulfill the requirement and successfully used as catalyst in mannich reaction to produce β-aminocarbonyl compounds.[12-13.]

Ionic liquids serve as neoteric solvents in green technology.[14-16] The recent literature reports have prompted synthesis of new classes of ionic liquids since it has very good physico-chemical properties such as low melting point, high polarity, non flammability, non-volatility, high viscosity, negligible vapor pressure, high conductivity and reasonable thermal stability.[17] Ionic liquids have been referred as designer solvents.[18-21] The literature suggests that the use of imidazolium based ionic liquid as solvent, results in the greatest improvement towards greener processes in many fields like chemical and pharmaceutical industries.[22] The physical and chemical properties of imidazolium based ionic liquids are easily tunable[23] by means of changing substitution on nitrogen in the ring and also using different anions. In the present work 1-propylimidazolium trifluroacetoacetate has been used to perform one pot three component reactions, resulting in the formation of β- aminocarbonyl compounds.

MATERIALS AND METHODS

1-propylimidazole, trifluroaceticacid, benzaldehyde, 4-fluorobenzaldehyde, 4-chlorobenzaldehyde, 4-bromobenzaldehyde, 4-methylbenzaldehyde, 4-methoxybenzaldehyde, 4-isopropylbenzaldehyde, 3-nitrobenzaldehyde, acetophenone, aniline, 4-fluroaniline, 4-chloroaniline, 4-bromoaniline, 4-nitroaniline, ethanol, ethylacetate, hexane and toluene were supplied by Avara chemicals, Pvt. Ltd. Melting point was determined by open capillary method and corrected. ^{1}H NMR ^{13}C NMR spectra in $CDCl_3$ and DMSO-d_6 solution were recorded in Brucker ADVANCE instrument 400 FT NMR instrument, elemental analysis of the compounds were obtained from thermoquest CE instruments CHNS-O, EA/110 model. Mass spectrometry was performed on a Q-Tof premier [waters corporation] mass spectrometer operating in positive ion electro spray mode and methanol was used as a mobile phase. The solvents were dried prior to use.

Synthesis of 1-propylimidazolium trifluroacetoacetate
In a two neck flask, trifluroaceticacid (10 mmole, 0.65g) was added to a toluene (10 mL) solution of 1-propylimidazole (10 mmole, 1.15g.). The resulting mixture was heated to 80ºC stirred for 16 hours. The immiscible layers were seperated by decanting the toluene mixture and the sticky product was washed with hexane and dried over vacuum.

Anal. Calcd. For $C_8H_{12}F_3N_2O_2$ C, 42.67; H, 5.37; N, 12.44. Found; C, 42.52; H, 5.42; N, 12.40 Pale yellow color liquid, yield 90 % , H^{1}NMR ($CDCl_3$, 400 MHz): δ 15.1 (s, 1*H*, 2-C*H*), 8.76 (s, 1H, 4-C*H*), 7.35 (t, J = 3.2Hz, 1*H*, 5-C*H*), 4.1 (t, 2*H*, CH_2-CH_2-CH_3, 1.91 (m, 2*H*, CH_2-CH_2-CH_3), 0.95 (t, 3H, CH_2-CH_2-CH_3) ;^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.06 (C-5), 135.26 (C-3), 121.90 (C-2) 120.57, 118.344, 115.3, 112.15 (CF_3-SO_3), 50.42 (N-CH_2-CH_2-CH_3), 23.66 (N-CH_2-CH_2-CH_3) 10.47 (N-CH_2-CH_2-CH_3) ES-MS m/z: 112.10 [M- CF_3-COO]$^-$

General procedure for the preparation of β-aminocarbonyl compounds
Aromaticaldehyde (1 mmole), aromaticamines (1.5 mmole), aromaticketone (1 mmole) in 0.5 mL ethanol was added 1-propylimidazolium trifluroacetoacetate (0.4 mmole). The mixture was stirred at room temperature for an appropriate amount of time. The course of the reaction was monitored by thin layer chromatographic analysis, upon reaction completion the products were collected by filtration. The products were washed with water/ethanol mixture (1:1) to give the corresponding compounds. Finally the precipitate was washed with hexane and dried in vacuum.

RESULTS AND DISCUSSION

The reported 1-propylimidazolium trifluroacetoacetate (ImPrHTFAA) was synthesized by the reported procedure and it is in liquid state at room temperature.[24] The ionic liquid was characterized by ^{1}H, ^{13}C NMR, ESI-mass and elemental analysis. The proton NMR spectrum has shown that the 2-C*H* and 4-*CH* proton resonates at 15.1 ppm and 7.35 ppm respectively. The 1-propylimidazolium trifluroacetoacetate (ImPrHTFAA) catalyzed mannich reaction was optimized in ethanolic medium by varying reaction conditions such as amount of catalyst and ratio of reactant (table 1). The optimization reveals that the ratio of the reactants (aldehyde, aniline and acetophenone) is 1:1.5:1 and the amount of catalyst is 0.4 mmole. In order to strengthen the solvent choice, we have performed the same reaction in different solvents namely acetonitrile, water, ethanol, dichloromethane, dimethylsulfoxide, dimethylformamide, toluene, ethyl acetate and tetrahydrofuran. Among them ethanol alone has given the better yield (table 2).

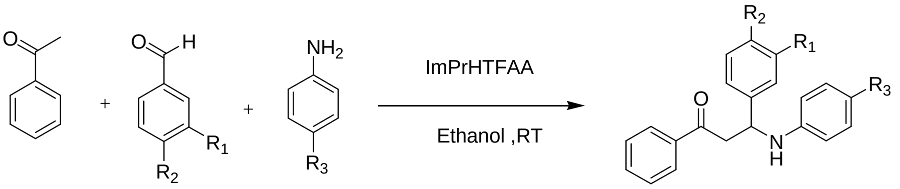
Table 1: Optimization of reaction conditions

S.No	RTILs (mmole)	Solvent	Reactants^a (mmole)	Time (hh:mm)	Yield (%)
1	0.1	Ethanol	1:1:1	01:30	70
2	0.2	Ethanol	1:2:1	00:50	75
3	0.3	Ethanol	1:1:1	00:45	75
4	0.4	Ethanol	1:1:1.5	00:25	80
5	0.4	Ethanol	1:1.5:1	00:40	95
6	0.5	Ethanol	1:1:2	00:15	85
7	0.6	Ethanol	1:2:1	00:15	80

a-Benzaldehyde: Aniline: Acetophenone; all the reaction were carried out at room temperature

Table 2: Solvent Studies

S.No	Solvent	Time (hh:mm)	Yield (%)	S.No	Solvent	Time (hh:mm)	Yield (%)
1	Methanol	01:00	80	6	Difluoromethane	01:10	75
2	Ethanol	00:40	95	7	Toluene	01:20	75
3	Acetonitrile	03:00	80	8	Dichloromethane	01:20	70
4	Tetrahydrofuran	01:20	85	9	Ethyl acetate	001:00	70
5	Water	08:00	65	10	Neat	08:00	40



R_1 = H and Br
R_2 = H, F, Cl, Br, CH_3, OCH_3 and $CH(CH_3)_2$
R_3 = H,F, Cl, Br and NO_2

Scheme 1: Synthesis of β-carbonyl compounds

Table-3 -Results of 1-propylimidazolium trifluroacetoacetate catalyzed Mannich reaction

S No	R_1	R_2	R_3	Time (hh:mm)	Yield^a (%)	Melting point (°C)
1	H	H	H	00:40	95	165-167[25]
2	H	F	H	01:00	70	110-111[25]
3	H	Cl	H	24:00	40	116-117[25]
4	H	Br	H	01:45	85	132-133[25]
5	H	CH_3	H	00:50	80	130-132[25]
6	H	OCH_3	H	01:45	85	152-153[26]
7	H	$CH(CH_3)_2$	H	01:45	85	132-133[25]
8	Br	H	H	08:00	75	133-134[27]
9	H	H	F	00:50	80	163-164[25]
10	H	F	F	01:00	80	113-114[25]
11	H	Cl	F	10:00	60	109-110[25]
12	H	Br	F	01:00	75	136-137[25]
13	H	CH_3	F	03:00	80	141-143[25]
14	H	OCH_3	F	08:00	NR	--
15	H	$CH(CH_3)_2$	F	00:10	80	132-134[25]
16	Br	H	F	08:00	NR	--
17	H	H	Cl	00:25	90	168-170[25]
18	H	F	Cl	00:45	80	136-137[25]
19	H	Cl	Cl	00:10	70	120-121[25]
20	H	Br	Cl	03:40	85	138-139[25]
21	H	CH_3	Cl	00:40	80	163-165[25]
22	H	OCH_3	Cl	00:30	80	119-120[26]
23	H	$CH(CH_3)_2$	Cl	03:45	75	135-138[25]
24	Br	H	Cl	06:00	NR	-------
25	H	H	Br	00:25	76	180-182[25]
26	H	F	Br	00:05	68	155-156[25]
27	H	Cl	Br	00:05	80	130-132[25]
28	H	Br	Br	00:40	75	134-135[25]
29	H	CH_3	Br	00:15	70	175-176[25]
30	H	OCH_3	Br	02:30	69	131-132[26]
31	H	$CH(CH_3)_2$	Br	00:30	72	153-154[25]
32	Br	H	Br	08:00	NR	--
33	H	H	NO_2	02:00	75	140-142[27]
34	H	F	NO_2	00:50	75	116-118[27]
35	H	Cl	NO_2	00:40	70	149-150[27]
36	H	Br	NO_2	00:20	75	128-130[27]
37	H	CH_3	NO_2	00:30	70	177-179[27]
38	H	OCH_3	NO_2	00:20	70	114-116[26]
39	H	$CH(CH_3)_2$	NO_2	01:30	75	118-120[27]
40	Br	H	NO_2	01:00	65	130-132[27]

NR-No reaction, ^{a}-isolated yield.

1-propylimidazolium trifluroacetoacetate has been used as catalyst for the synthesis of β-aminocarbonyl compounds. The results were tabulated in the (table 3). The catalytic reaction was monitored by thin layer chromatographic analysis. Upon the completion of reaction course, the mixture was quenched with water and the product was precipitated. The precipitate was filtered off and the filtrate contains ionic liquid and which may be recovered and reused. The precipitate washed with hexane and dried in vacuum. The reaction of aniline with benzaldehyde results in good yields of about 90% (entry 17) however the yield was less in the case of chlorobenzaldehyde. The reaction between 3-bromobenzaldehyde and halo-substituted aniline results in no reaction (entry 16, 24, 32) and with 4-NO_2 aniline good yield of corresponding β-aminocarbonyl compounds (entry 40) are obtained. Often the reaction completion takes less than two hours. Overall the yield of β-aminocarbonyl compounds catalyzed by 1-propylimidazolium trifluroacetoacetate is moderate to good yields.

Table-4 Reuse of 1-propylimidazoliumtrifluroacetoacetate in Mannich Reactions

S. No	Cycle	Time (hh:mm)	Yield (%)
1	Fresh	00:30	90
2	First	00:35	85
3	Second	00:40	83
4	Third	00:45	80
5	Fourth	00:50	75

Isolated yield;

The efficiency of the catalyst in reusability had checked and the catalyst can be reused four times without loss of notable catalytic activity.

CONCLUSION

1-propylimidazolium trifluoroacetoacetate was synthesized and characterized and their application in mannich reaction as a catalyst. The yield of β-aminocarbonyl compounds catalyzed by 1-propylimidazolium trifluroacetoacetate is moderate to good yields. The choice of reaction medium was ethanol and it provides good yield of β-carbonyl compounds. Also, the reusability of the 1-propylimidazolium trifluoroacetoacetate was reported.

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REFERENCES

[1] C. Allemann, R. Gordillo, F. R. Clemente, P. H. Cheong, K. N. Houk, *Acc. Chem. Res.,*. **2004**, 37, 558.
[2] T. Akiyama, K. Matsuda, K. Fuchibe, *Synlet.*, **2005,** 322.
[3] T. Akiyama, J. Itoh, K. Fuchibe, *Synlett*., **2002,** 1269.
[4] T.P. Loh, S.L. Chen, *Org.Lett., 4,* **2002**, 3647.
[5] T.Akiyama, J. Itoh, K.Yokota, K. Fuchibe, *Angew. Chem. Int. Ed 43,* **2004**, 1566.
[6] A. Hasegwa, Y. Naganawa M. Fushimi, K. Ishihara, H. Yamamato, *Org.Lett.8,* **2006**, 3175.
[7] K. Manabe, Y. Mori and Kobayashi, *Tetrahedran.*, **2001**,57,2537.
[8] Guaving Zhoa,Tao Jiang, Haixiang Goa, Buxing Han, Jun Huang and Donghai Sun, *Green Chem*., **2004**, 6, 75-77.
[9] T. Welton, *Chem rev.*, **1999**, 99, 2071.
[10] K .Manabe, S. Kobayshi, *Org.Lett.*1, **1999, 1965**
[11] T.Okuhara , *Chem. rev*., **2002**, 102, 3641.
[12] A.C.Cole, J.L. Jensen, I. Ntai, K.L. T.Tran, K.J. Weaver, D.C Forbes and J.H Jr. Davis. *J.Am.Chem.Soc.,* **2002**, 124, 5962.
[13] L. Jizong, P. Yanqing, S. Gonghua, *Catal. Lett.*, **2005,** 102, 3-4.
[14] (a) P. Wasserscheid and T.Welton, wiley-vcit,weinheim, *Ionic liquids in synthesis*.,ed **2003**; (b) R. D. Roger, K. R. Seddon, *science*, **2003**, 302, 702; (c) J. S. Wikes, *Green chem*., **2002**, 4, 73.
[15] L. A. Blanchard, D. Hancu, E. J. Beckmann, J. F. Brennecke, *Nature*, **1999**, 399, 28.
[16] R. Sheldon, *Chem. Commun*., **2001**, 23, 2399
[17] M. Freemantle, *C&EN*, March 30, **1998**, .32; May 15, **2000**, 37; January 1, **2001**, 20.

[18] K. Elang,.R. Srirambalaji, G. Anantharaman, *Tetrahedron lett.*, **2007**, 48, 9059.
[19] G. Anantharaman, K. Elango, *synch. React*. *Inorg. metal-org. Nano metal chem*., **2007**,7,719.
[20] S. Nagarajan, K. Elango,*Catal. Lett.*, **2014**, 144, 1507.
[21] S. G. Kazarian, B. J. Briscoe, T. Welton, *Chem.commun.*, **2000**, 2047.
[22] L. A. Blanchard, J. F. Brennecke, *Ind. Eng. Chem. Res*., **2001** ,40, 287.
[23] J. C. Xiao, J. M. Shreeve, *J.org.chem***., 2005**, 70, 3072-3078.16
[24] D. Fang, Z. Fei, Z. Liu *Catal. Commun.* 10, **2009** 1267.
[25] L. Zheng, M. Xuelin, X. Zinglin. *J.mole .catal.* A, **2007** 132.