

1-Methylimidazolium trifluoroacetate [Hmim]Tfa: Mild and efficient Brønsted acidic ionic liquid for Hantzsch reaction under microwave irradiation

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Abstract. One pot synthesis of 1,4-dihydropyridine derivatives was achieved via condensation of various β -ketoesters with aromatic/aliphatic aldehydes and ammonium acetate. The reaction was catalysed by a stable and reusable Brønsted acidic ionic liquid (IL), 1-methyl-imidazolium trifluoroacetate ([Hmim]Tfa), under microwave (MW) irradiation. The synergistic combination of MW with IL can potentially go a long way to meet the increasing demand for chemical processes. This homogeneous catalytic procedure is simple and efficient. The catalyst can be reused at least four times with almost complete retention in its activity.

Keywords. 1,4-Dihydropyridine; Hantzsch synthesis; [Hmim]Tfa; homogeneous catalyst; microwave; multicomponent reaction.

1. Introduction

Current conventional methods of organic synthesis are orders of magnitude too slow to satisfy the ever-increasing demand for generation of organic compounds.¹ The efficiency of microwave (MW) heating has resulted in remarkable reductions in reaction times (from days and hours to minutes and seconds). The time saved by using a MW heating approach is potentially important in traditional organic chemistry and assembly of heterocyclic systems.² Not surprisingly, these features have also recently attracted interest of the drug discovery field and medicinal chemistry communities.³

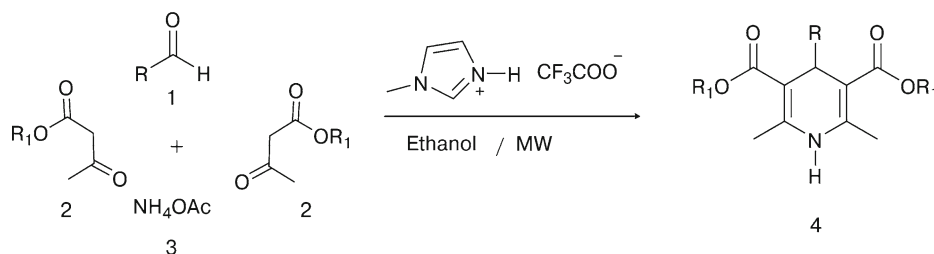
In recent years, ionic liquids (ILs) have attracted immense interest and been successfully used in a variety of catalytic reactions as dual solvents–catalysts⁴ due to their relatively low viscosities, low vapour pressure, and high thermal and chemical stability.⁵ Brønsted acidic ionic liquids consist of desired characteristics of solid acids and mineral liquid acids and are designed to replace customary mineral acids like HCl, H₂SO₄ and HNO₃.⁶

Heterocyclic rings containing nitrogen atoms are abundant in nature and of great importance to life because their structural subunit exists in many bioactive

nuclei.⁷ 1,4-DHPs represent an important class of biologically active molecules, several of which have found use in the treatment of cardiovascular disease.^{8,9} 1,4-DHPs are analogues of NADH coenzymes^{10,11} and an important class of drugs which are potent blockers of calcium (Ca²⁺) currents.¹² Hence, the development of new methods that lead to multisubstituted 1,4-DHPs via an efficient and convenient procedure are of great interest for pharmaceutical researchers.

More than a century ago, Hantzsch¹³ developed an efficient method for the synthesis of 1,4-DHPs. The classical method involves a one-pot condensation of an aldehyde with β -ketoesters and ammonia refluxing either in acetic acid or in alcohol for a longer time,¹⁴ Up till now, numerous literature exist describing various attempts to improve the Hantzsch reaction using alternative catalyst and greener methods.^{15–24} Almost all of the new methodologies of organic reactions have attempted to maximize reaction conversion and minimize reaction time. We have already demonstrated the efficient role of ionic liquids as dual solvent–catalysts in Biginelli reaction.^{25,26} In the present study, we report 1-methyl-imidazolium trifluoroacetate ([Hmim]Tfa) as an effective and reusable catalyst for Hantzsch pyridine synthesis (scheme 1).

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Scheme 1. General synthetic pathway for the synthesis of 1,4-dihydropyridines (1,4-DHPs).

2. Experimental

2.1 General

All chemicals were of research grade and were used as obtained. The reactions were carried out by using 700 Watt CATA-R scientific microwave system. Melting points were measured in open capillaries and are uncorrected. TLC was performed on Silica Gel 60 F₂₅₄ pre-coated plates (Merck). IR spectra were recorded on a FT IR Perkin Elmer Spectrum 100 spectrometer, mass spectra on a Shimadzu LCMS 2010 spectrometer, and elemental analysis on Perkin Elmer PE 2400 elemental analyzer. ¹H NMR and ¹³C NMR spectra were recorded on Bruker Avance 400 MHz instrument with TMS as an internal standard. The IL [Hmim]Tfa was prepared according to the procedure reported in literature.²⁷

2.2 Procedure for the synthesis of 1,4-DHPs

A mixture of aldehyde **1** (1 mmol), 1,3-dicarbonyl compound **2** (2.1 mmol), ammonium acetate **3** (3 mmol), ethanol (1 ml) and [Hmim]Tfa (20 mol%) were taken in a round bottom flask containing a teflon-coated magnetic stirrer bar. It was subjected to microwave irradiation at power level 7 (455 watt) for an appropriate time shown in table 3. The completion of reaction was monitored by TLC. The reaction mixture was treated with cold water, extracted with diethyl ether and dried over anhydrous Na₂SO₄. It was then concentrated under reduced pressure to leave the crude product which was crystallized in ethanol. The compounds have been identified by comparison of spectral data and mp with those reported elsewhere.

2.3 Spectral data for selected compounds

2.3a Dimethyl 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4d): Anal. Calcd. For C₁₇H₁₈N₂O₆: C, 58.96; H, 5.24; N, 8.09. Found: C, 59.30; H, 5.10; N, 7.84. IR (KBr) cm⁻¹: 3304 (-NH

stretching of amine), 2949 (-CH stretching), 1696, 1645 (respectively due to C=O and C=C stretching of conjugate ester), 1487, 1342, 1215; ¹H NMR (400 MHz, CDCl₃): δ 2.37 (s, 6H, -CH₃), 3.66 (s, 6H, -OCH₃), 5.12 (s, 1H, aryl -CH of C4), 5.86 (s, 1H, -NH), 7.45 (d, *J* = 8.8 Hz, 2H, Ar-H), 8.10 (d, *J* = 8.8 Hz, 2H, Ar-H); ¹³C NMR (100 MHz, CDCl₃): δ 19.63 (-CH₃), 39.87, 51.14, 103.02, 123.45, 128.60, 144.91, 146.43, 154.75, 167.47 (C=O). ESI-MS: *m/z*: 346.9(M+H)⁺

2.3b Diethyl 4-(furan-2-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4k): Anal. Calcd. For C₁₇H₂₁NO₅: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.72; H, 7.01; N, 4.11. IR (KBr) cm⁻¹: 3348 (-NH stretching of amine), 2985 (-CH stretching), 1692, 1649 (respectively due to C=O and C=C stretching of conjugate ester), 1486, 1209. ¹H NMR (400 MHz, CDCl₃): δ 1.28 (t, *J* = 7.2 Hz, 6H, -CH₂CH₃), 2.34 (s, 6H, -CH₃), 4.18 (m, 4H, -CH₂CH₃), 5.22 (s, 1H, aryl -CH of C4), 5.84 (s, 1H, -NH), 5.95 (d, *J* = 3.2 Hz, 1H, Ar-H), 6.23 (dd, *J* = 2.8, 2 Hz, 1H, Ar-H), 7.23 (s, 1H, Ar-H); ¹³C NMR (100 MHz, CDCl₃): δ 14.32, 19.51, 33.43, 59.80, 100.78, 104.43, 109.98, 140.84, 145.02, 158.70, 167.46 (C=O). ESI-MS: *m/z*: 319.8(M+H)⁺

2.3c Diisopropyl 4-(furan-2-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4l): Anal. Calcd. For C₁₉H₂₅NO₅: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.86; H, 7.57; N, 3.79. IR (KBr) cm⁻¹: 3347 (-NH stretching of amine), 2978 (-CH stretching), 1696, 1649 (respectively due to C=O and C=C stretching of conjugate ester), 1483, 1208. ¹H NMR (400 MHz, CDCl₃): δ 1.22 (dd, *J* = 6.0, 0.8 Hz, 6H, -CH₃), 1.28 (dd, *J* = 6.4, 1.2 Hz, 6H), 2.33 (s, 6H), 5.05 (m, 2H), 5.2 (s, 1H), 5.76 (s, 1H), 5.95 (s, 1H), 6.22 (m, 1H), 7.22 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 19.52, 22.07, 33.59, 67.02, 101.15, 104.47, 109.92, 140.67, 144.54, 158.92, 167.01 C=O. ESI-MS: *m/z*: 347.9 (M+H)⁺

3. Results and discussion

Our first objective was to develop a set of working conditions for the microwave mediated process. Initially we optimized the reaction conditions with respect to microwave power (P). The reaction of *p*-nitro benzaldehyde, methyl acetoacetate and ammonium acetate was performed as the model reaction in the presence of catalytic amount of [Hmim]Tfa in ethanol as co-solvent. The results are given in table 1.

It could be observed that with increase in microwave power from 280 W to 700 W, the yield of **4d** is linearly increased from 55% to 93%. At higher power level (700 W) reaction completed in 3 min but resulted in moderate yield. The optimized microwave power and the irradiation time were 455 W and 2 min, respectively.

The model reaction was also screened to know the effect of a range of different solvents as shown in table 2. It was noted that in ethanol, the yield of desired product **4d** was achieved exclusively up to 93% (table 2, entry 5). When we carried out the reaction in other solvent such as acetonitrile, DMF, THF and 1, 4-dioxane the yield of **4d** was 80, 63, 70 and 75% respectively.

Above experimental results encouraged us to extend the scope of reaction condition to apply on a range of variously substituted aldehydes (table 3). Both electron-deficient and electron-rich aldehydes were well-tolerated. The reaction of heteroaromatic aldehydes and formaldehyde proceeded in very short reaction time (entry 4j–4o). Ethyl acetoacetate and isopropyl acetoacetate were also employed for the Hantzsch reaction in place of methyl acetoacetate to afford appropriate 1,4-DHPs in good yield. All the reactions were completed in 1–4 min. Increase in the equivalent of IL did not improve the conversion, use of just 20 mol% IL is found to be sufficient to accelerate the reaction forward.

Table 1. Effect of the microwave power and the irradiation time on the model reaction (4d)^a.

Entry	Time (min) ^b	P (watt)	Yield (%) ^c
1	8	280	55
2	6	350	65
3	5	420	80
4	2	455	93
5	3	490	89
6	3	700	80

^aReaction conditions: Aldehyde (1 mmol), β -ketoester (2.1 mmol), ammonium acetate (3 mmol), ethanol (1 ml), [Hmim]Tfa 20 mol%; ^bReaction progress was monitored by TLC; ^cAll yields refer to isolated yield

Table 2. Effect of solvent on model reaction (4d)^a.

Entry	Solvent	Time (min) ^c	Yield (%) ^b
1	Acetonitrile	3	80
2	DMF	2	63
3	THF	4	70
4	1,4-Dioxane	3	75
5	Ethanol	2	93

^aReaction conditions: Aldehyde (1 mmol), β -ketoester (2.1 mmol), ammonium acetate (3 mmol), [Hmim]Tfa 20 mol%, $P = 455$ W; ^bIsolated yield; ^cReaction progress was monitored by TLC

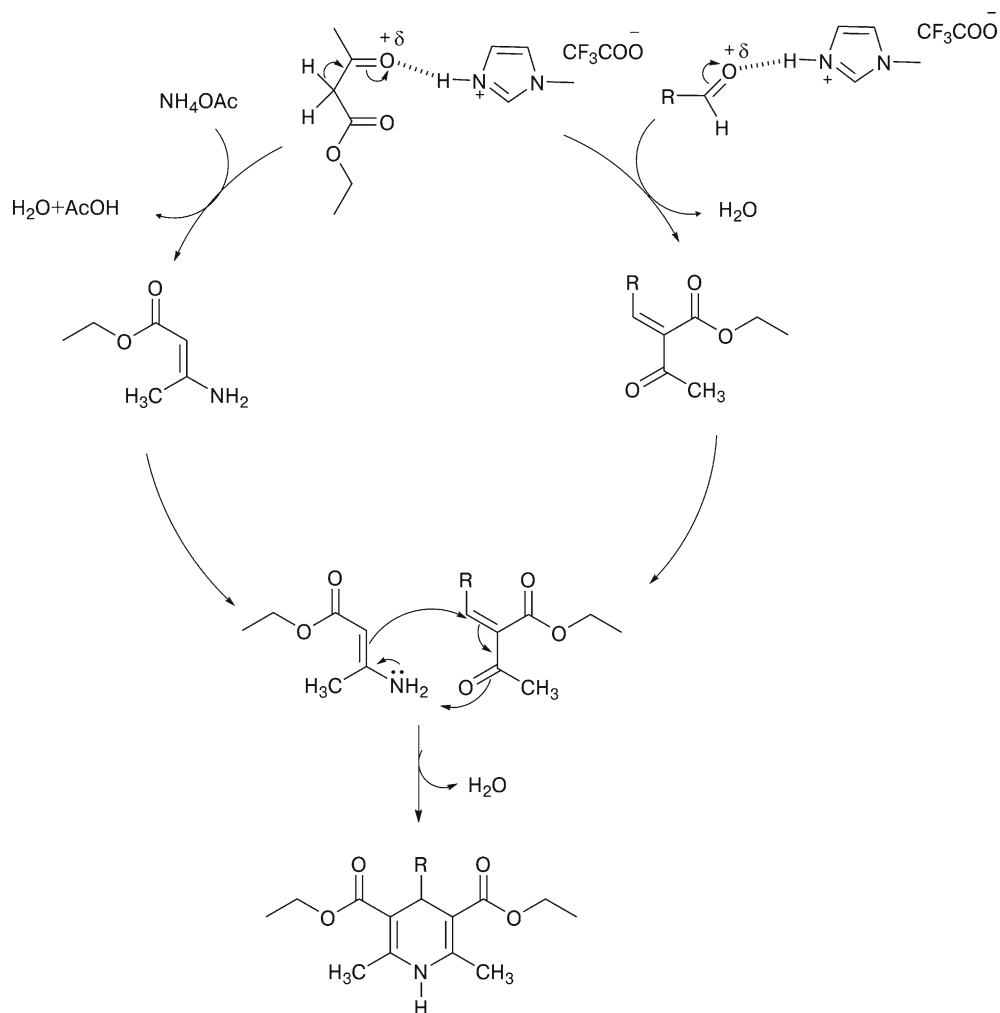
The IL, [Hmim]Tfa may promote this reaction by virtue of its inherent Brønsted acidity conferred by the most acidic N–H hydrogen [chemical shift δ 10.93]. This makes the IL capable of bonding with the carbonyl oxygen of aldehydes and β -ketoesters increasing the reactivity of the parent carbonyl compounds. Crowhursts *et al.* demonstrated that imidazolium ILs are able to act as strong hydrogen bond acids as well as bases at the same time.²⁸ Many current studies have established that hydrogen bonding can occur between the reactant and the cationic or anionic components of ILs.^{29,30} Based on this, the following mechanistic pathway has been postulated (scheme 2).

The IR spectrum of the product showed strong band around 3300–3350 cm^{-1} due to N–H stretching and bands around 1645 and 1696 cm^{-1} respectively due to C=C and C=O stretching of conjugated ester moieties whereas the aromatic C=C was found at 1483–1487 cm^{-1} . In the ¹H NMR spectrum, singlet was observed around δ 5.12–5.22 due to aryl-CH moiety of the C-4 of the dihydropyridine skeleton. In case of all the products described in table 3, broad singlet appeared around δ 5.75–5.86 confirming the presence of N–H group. In all the aforesaid cases, six-proton singlet was observed due to olefinic-CH₃ around δ 2.32–2.37 corroborated with the 1,4-DHPs skeleton. In the ¹³C NMR spectra, peak around δ 167.00–167.50 was due to carbonyl carbon of ester moiety.

The recovery and reusability of the ionic liquid was investigated. After completion of the reaction, ice cold water was added to the reaction mixture and product was extracted with diethyl ether. The aqueous layer consisting the acidic IL, was recovered after removal of water under reduced pressure and was reused for subsequent reactions. It showed the same activity as that of the fresh catalyst without any loss of activity in terms of yield and purity. The ionic liquid was recycled and reused in the same reaction for at least

Table 3. Synthesis of 1,4-dihydropyridines in the presence of 20 mol% [Hmim]Tfa.

Entry	R	R ¹	Time (Min)	Yield (%)	M.P. (°C) (observed)	M.P. (°C) (reported)
4a	C ₆ H ₅	CH ₃	3	90	194	195–197 ³¹
4b	C ₆ H ₅	CH ₃ CH ₂	3	92	156–158	158–160 ³²
4c	4-ClC ₆ H ₄	CH ₃	2	86	198	196–197 ³³
4d	4-O ₂ NC ₆ H ₄	CH ₃	2	93	196–198	195–196 ³⁴
4e	4-FC ₆ H ₅	CH ₃	3	82	170	170–171 ³⁷
4f	3-O ₂ NC ₆ H ₄	CH ₃ CH ₂	3	86	162	160–162 ³²
4g	3-O ₂ NC ₆ H ₄	(CH ₃) ₂ CHCH ₂	4	85	128	123–125 ³⁸
4h	4-OH-3-OMe-C ₆ H ₃	CH ₃	4	80	225–228	231–232 ³⁵
4i	4-OHC ₆ H ₄	CH ₃ CH ₂	4	82	200–202	198–199 ³⁶
4j	2-Furyl	CH ₃	1	92	192	194–195 ³³
4k	2-Furyl	CH ₃ CH ₂	1	90	164–166	166–168 ³²
4l	2-Furyl	(CH ₃) ₂ CHCH ₂	1	88	112–114	–
4m	H	CH ₃	1	90	202–204	208–210 ³²
4n	H	CH ₃ CH ₂	1	84	168–170	170–172 ³²
4o	H	(CH ₃) ₂ CHCH ₂	1	80	120–122	–

**Scheme 2.** Suggested mechanism for the synthesis of 1,4-DHPs in the presence of [Hmim]Tfa.

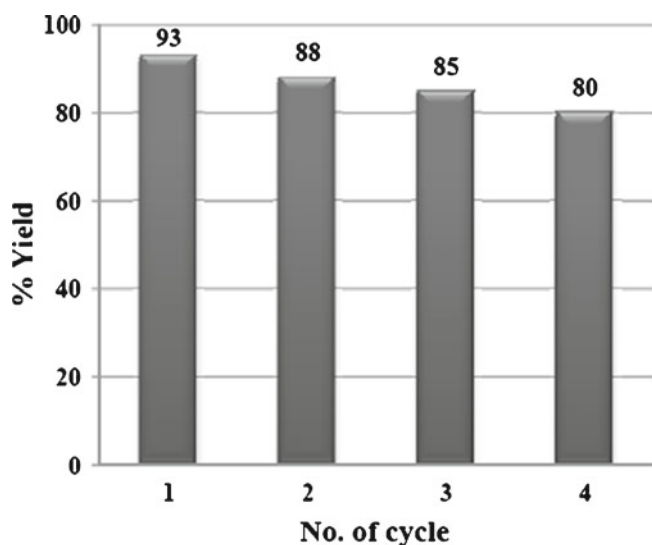


Figure 1. Recyclability study of ionic liquid on model reaction.

four times with remarkable retention in its activity (figure 1).

4. Conclusion

We have demonstrated the utility of [Hmim]Tfa in Hantzsch dihydropyridine reaction. This IL obviates the need for an additional catalyst and has allowed the preparation of a range of 1,4-DHPs in good to excellent yields (80–93%). This procedure permits recycling of the IL with almost retention in activity. On the basis of these current efforts, it is likely that a number of organic reactions could be performed equally well or perhaps even more effectively using this ionic liquid. Studies to determine the applicability to other catalytic reactions are currently underway in our laboratory.

Supporting information

^1H NMR and ^{13}C NMR spectra of ionic liquid and some selected compounds are available as supporting information in the journal of Chemical Sciences Website (www.ias.ac.in/chemsci).

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