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Synthesis of *N*-methyl imines in the presence of poly(*N*-vinylpyridine) as a reusable solid base catalyst by a mechanochemical process

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Abstract The synthesis of *N*-methyl imines was performed in the presence of catalytic amounts of poly(4-vinylpyridine) in high yields and rapidly at room temperature by a ball milling process. This new method has some advantages including good yields for relatively unreactive carbonyl compounds and short reaction times as well as being green in terms of avoiding the use of toxic reagents and solvents. The major advantage of this process is that the catalyst can be easily regenerated and reused several times without any significant loss of activity.

Keywords Recyclable solid base · Mechanochemical process · *N*-methyl imine · Poly(4-vinylpyridine)

Introduction

Compounds containing an azomethine group (–CH=N–), known as Schiff bases are produced by the condensation of a primary amine with an aldehyde or ketone. Schiff bases of aromatic aldehydes, having an effective conjugation system, are substantially more stable and more readily synthesized, while those which contain alkyl substituents are relatively unstable and are readily polymerized. Schiff bases and their derivatives possess interesting biological properties viz., anti-inflammatory, analgesic, anticonvulsant, antituberculous, antitumor, anti-HIV and antimicrobial activity [1–3]. In addition, they also play an important role in the treatment

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of leishmaniasis, trypanosomiasis, and malaria [4–6]. Furthermore, they have found widespread use in asymmetric synthesis of α-aminonitriles, preparation of secondary amines by hydrogenation, and cycloaddition reactions [7–9]. These compounds have been employed as organocatalysts, ligands for metal complexes, drug design, and the syntheses of heterocyclic compounds [10, 11].

Various methods for the synthesis of imines include (a) the use of polymer-supports [12], (b) Lewis acids [13–16], (c) P_4O_{10}/SiO_2 [17], (d) molecular sieves [18], (e) $Mg(ClO_4)_2$ [19], and (f) infrared [20], microwave [21, 22] or ultrasound irradiations [23]. The synthesis of *N*-methyl imines involves the use of an aqueous solution of methylamine or its salt, i.e., methylamine hydrochloride as the methylamine scaffold source and then using classical routes [24–26].

Alternative protocols include the use of *N*,*N*-bis(trimethylsilyl) methylamine in the presence of trimethylsilyl trifluoromethanesulfonate in chlorinated solvents such as dichloromethane (DCM) or dichloroethane (DCE) [27] and methylamine gas [28] or 1,3-dimethylurea dispersed on montmorillonite K10 under microwave irradiation as the methylamine precursors [29]. In spite of this, even the most convenient methods for the synthesis of *N*-methyl imines have several inherent disadvantages, such as gas handling, the use of toxic and volatile organic solvents, and long reaction times.

Coherent efforts have over the years been made to develop chemical technologies able to reduce or eliminate the use of toxic organic solvents in protocols aimed at securing pure *N*-methyl imines. The ball milling process was introduced to manage the global problems of pollution [30, 31] and incorporated as a major component in various reactions [32–39]. The applications of solid bases are not only of interest from an environmental point of view, but in many cases, also offer considerable synthetic advantages such as their reusability and milder conditions. Application of P(4-VP) for the alkylation of isobutene to produce alkylates of high octane numbers [40], the selective methanolysis of methyl and methylene bromides [41], the chemoselective silylation of alcohols, phenols, and N-tert-butoxycarbonyl (N-Boc) protection of amines [42] has been demonstrated. The influence of the nature of a base on the synthesis of *N*-methyl imines has been reported [43].

Herein, a simple, efficient and environmentally benign method of mild reaction conditions is presented for the synthesis of various *N*-methyl aryl imines in the presence of the inexpensive solid base catalyst Poly(4-vinylpyridine) [P(4-VP)].

Experimental

General

All chemicals were purchased from either Merck or Fluka Chemical Companies. All yields refer to the isolated products. Known products were characterized by their melting point and FTIR, NMR spectral data, and comparison with the literature. Two new products were characterized by their melting point and FTIR, with NMR spectral and elemental analysis. The purity determination of the substrates and

reaction monitoring was accompanied by TLC using silica gel SIL G/UV 254 plates.

The infrared (IR) spectra were run on a Perkin–Elmer 781 spectrophotometer using KBr pellets for solid and neat for liquid samples in the range of 4000–400 cm^{-1}. The reaction conversions were measured by GC–MS on an Agilent GC-Mass-6890 instrument under 70 eV conditions. The 1H NMR spectra were recorded on a Bruker Avance 300 or 400 MHz and the 13C NMR were run on a Bruker Avance 75 or 100 MHz instrument (δ in ppm). Melting points were recorded on a Büchi B-545 apparatus. Grinding was performed in a Retsch PM 100 planetary ball mill using a 50 mL reaction chamber and 7 mm stainless steel balls with sun wheel speed of 400 min^{-1}.

General procedure for *N*-methyl imines formation

Poly(4-vinylpyridine) (1.0 g) was ground with a mixture of methylamine hydrochloride (10 mmol) and appropriate carbonyl compound (5 mmol) (molar ratio CH_3NH_2·HCl/ArCHO = 2:1) in a planetary ball mill along with two stainless steel balls of 7 mm diameter at room temperature. After completion of the reaction (monitored by TLC), hot absolute ethanol (5 mL) was added to the reaction mixture, which was then filtered. The precipitated P(4-VP)·HCl was isolated while the filtrate/supernatant was examined by GC. No signal of the catalyst P(4-VP) was detected, confirming that the catalyst was converted to its hydrogen chloride salt form. The base catalyst was recovered by neutralization using $NaHCO_3$. The filtrate was evaporated under reduced pressure, and the pure product was obtained upon recrystallization from absolute ethanol. IR and ^1H NMR spectra of known compounds were in agreement with those reported in the literature [43–45].

Recycling of P(4-VP)

After each run, P(4-VP)·HCl was neutralized via the incremental addition of sodium bicarbonate until pH >6 and then extracted with EtOAc (3 × 5 mL), dried, and evaporated to a residue, which was dried overnight at 50 °C under vacuum. The FT-IR spectra of fresh and recycled P(4-VP) were identical in all aspects.

The spectral data of new and some representative products

N-(4-nitrobenzylidene)methanamine (Table 2, entry 4) yellow solid, m.p. 104–106 °C; IR (KBr): ν_{max} 2975, 2910, 1649, 1598, 1510, 1444, 1347 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, δ ppm): δ 3.56 (d, J = 1.6 Hz, 3H, CH_3), 7.86 (d, J = 8.4 Hz, 2H, CH_2), 8.20 (d, J = 8.4 Hz, 2H, CH_2), 8.38 (q, J = 1.6 Hz, 1H, N=CH).

N,N-dimethyl-4-((methylimino)-methyl)aniline (Table 2, entry 7) yellow solid, m.p. 54–56 °C; IR (KBr): ν_{max} 3042, 1640, 1560, 1491, 1412, 1269, 1189, 1152 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, δ ppm): δ 3.02 (s, 6H, $N(CH_3)_2$), 3.38 (s,

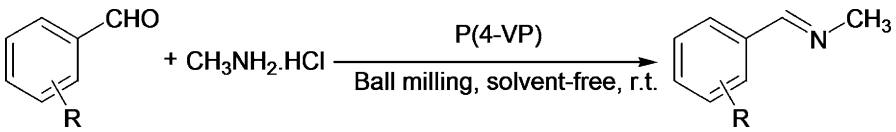
3H, N-CH_3), 6.83 (d, $J = 8.2$ Hz, 2H, Ar-H), 7.43 (d, $J = 8.2$ Hz, 2H, Ar-H), 8.16 (s, 1H, N=CH).

N-(pyridin-4-ylmethylene)methanamine (Table 2, entry 15) colorless oil; IR (neat): ν_{max} 3045, 1648, 1581, 1566, 1506, 1463, 1393, 1250, 1211, 1140, 1042 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, δ ppm): δ 3.62 (d, $J = 1.8$ Hz, 3H, CH_3), 7.56 (d, $J = 8.4$ Hz, 2H, Ar-H), 8.62 (d, $J = 8.4$ Hz, 2H, Ar-H), 8.85 (q, $J = 1.6$ Hz, 1H, N=CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz, δ ppm): δ 48.9, 120.4, 127.3, 129.9, 148.7, 159.7; Calcd for $C_7H_8N_2$: C 69.97, H 6.71, N 23.31 %; found: C 69.84, H 6.63, N 22.97 %.

N-(Furan-2-ylmethylene)methanamine (Table 2, entry 16) colorless oil; IR (neat): ν_{max} 3052, 1652, 1588, 1561, 1501, 1461, 1389, 1254, 1208, 1146, 1038 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, δ ppm): δ 3.58 (d, $J = 1.8$ Hz, 3H, CH_3), 6.01 (d, $J = 2.8$ Hz, 1H, CH), 6.23 (dd, $J = 0.8$ and 2.8 Hz, 1H, CH), 7.22 (d, $J = 0.8$ Hz, 1H, CH), 8.94 (q, $J = 1.8$ Hz, 1H, N=CH); ^{13}C NMR ($CDCl_3$, 75 MHz, δ ppm): δ 49.3, 111.9, 112.0, 132.3, 146.5, 156.4; Calcd for C_6H_7NO: C 66.04, H 6.47, N 12.84 %; found: C 65.92, H 6.36, N 12.97 %.

Results and discussion

In order to determine the optimal reaction conditions for the ball milling protocol, 4-nitrobenzaldehyde and methylamine hydrochloride were selected as reagents in a model reaction (Scheme 1). Initially, equimolar amounts of 4-nitrobenzaldehyde and CH_3NH_2·HCl were milled together in the absence of the catalyst P(4-VP) for 1 h. (Table 1, entry 1). The yield was poor and starting aldehyde was recovered. In the presence of 0.5 g P(4-VP) as base catalyst and with milling for 30 min, there was afforded a crude product as a mixture of 4-nitrobenzaldehyde and *N*-(4-nitrobenzylidene) methanamine in the ratio 24:76 (GC–MS analysis) (Table 1, entry 2). In order to improve the yield, the reaction was carried out with a two fold excess of CH_3NH_2·HCl and variation of the amount of P(4-VP) (0.5–1.0 g) and milling time (30–60 min) was then investigated. Increasing the amount of solid base to 0.8 and 1.0 g resulted in yield increases from 88 to 94 %, respectively (Table 1, entries 3 and 4). However, further increases of the amount of catalyst, i.e., 1.2 g of P(4-VP) did not enhance the yield (Table 1, entry 6). Similarly prolonging the milling time to 60 min did little to improve the yield (Table 1, entry 5). Thus, best yields were obtained when the reaction was performed by ball milling 5 mmol of aldehyde, 10 mmol of CH_3NH_2·HCl, and 1.0 g of P(4-VP) for 30 min.



Scheme 1 Synthesis of *N*-methyl imines in the presence of P(4-VP)

Table 1 The effect of P(4-VP) and milling time for a mixture of 4-nitrobenzaldehyde and methylamine hydrochloride

Entry	Amount of catalyst (g)	Time (h)	Yield (%)[a]
1	–	1	8[b]
2	0.5	0.5	76
3	0.8	0.5	88
4	1.0	0.5	94
5	1.0	1	96
6	1.2	1	96

Reaction conditions: 4-Nitrobenzaldehyde 5.0 mmol, *N*-methylamine hydrochloride 10.0 mmol, room temperature, and solvent-free

[a] Determined by GC–MS

[b] Equimolar amounts of reactants were milled

It may be concluded that the solid base catalyst plays a crucial role, apparently through slowly scavenging liberated HCl.

To investigate the scope of this reaction, different aryl aldehydes were subjected to the optimized reaction conditions. Table 2 illustrates that the present method is most effective for formation of the *N*-methyl imines. The aldehydes bearing electron-withdrawing groups gave higher yields in shorter reaction times than those with electron-donating substituents. Aldehydes with electron-withdrawing substituents in the ortho-position such as 2-nitrobenzaldehyde gave the highest yield (Table 2, entry 11), whereas the yield of 2-methoxy benzaldehyde having an electron-releasing substituent was lower (Table 2, entry 12). Imines formed from aldehydes with electron-releasing substituents in the *ortho* position were obtained with higher yield compared to those of the corresponding *para*-position (Table 2, entries 5 and 12). It seems that the steric interaction between the *ortho*-substituent and carbonyl group of aldehyde causes the displacement of the carbonyl group out-of-plane of the aromatic ring; therefore, *ortho*-isomers have higher electrophilicity than *meta*- and *para*-isomers [43].

As expected, electron-releasing groups viz., $-OCH_3$ decrease the electrophilicity of the carbonyl carbon. In this regard Radulović et al. [43] reported that use of 4-methoxybenzaldehyde/CH_3NH_2·HCl/$NaHCO_3$ in the ratio of 1:5:5 afforded 65 % yield after 3 h by grinding. In the current method, a 78 % yield of the corresponding *N*-methyl imine was obtained in 1 h in the presence of P(4-VP) under optimized conditions (Table 2, entry 5). Salicylaldehyde gave much lower yields of the respective *N*-methyl imine in strong basic conditions [43], but using the current conditions, the expected imine was obtained in 82 % yield (Table 2, entry 8).

The presence of the 4-dimethylamino group in 4-dimethylaminobenzaldehyde reduces the electrophilicity of the carbonyl carbon through resonance. Thus, synthesis of *N*,*N*-dimethyl-4-[(methylimino)-methyl]aniline from the condensation between 4-dimethylaminobenzaldehyd with methylamine failed in the presence of $NaHCO_3$ as the base at room temperature [43]. Also, due to deprotonation of the

Table 2 The reaction of aryl aldehydes with methylamine hydrochloride in the presence of P(4-VP)

Entry	Aldehyde	Time (h)	Yield (%)[a]
1	C_6H_5–CHO	1	91
2	4-Cl–C_6H_4–CHO	1	94
3	4-CH_3–C_6H_4–CHO	1	92
4	4-O_2N–C_6H_4–CHO	0.5 (0.5,0.5,0.5)[b]	94 (94,93,92)[b]
5	4-CH_3O–C_6H_4–CHO	1	78
6	4-HO–C_6H_4–CHO	1	89
7	4-$(CH_3)_2N$–C_6H_4–CHO	2	86
8	Salicylaldehyde	1	82
9	2-Cl–C_6H_4–CHO	1	78
10	2-CH_3–C_6H_4–CHO	1	81
11	2-O_2N–C_6H_4–CHO	0.5	98
12	2-CH_3O–C_6H_4–CHO	1	83
13	3,4-$(CH_3O)_2$–C_6H_3–CHO	1	85
14	Vanilline	1	89
15	Pyridine-4-carbaldehyde	1	90
16	Furfural	1.16	78

IR and ^{1}H NMR spectra of known compounds were in agreement with those reported in the literature [43, 44]

Reaction conditions: aryl aldehyde 5.0 mmol, CH_3NH_2·HCl 10.0 mmol, P(4-VP) 1.0 g, room temperature, and solvent-free

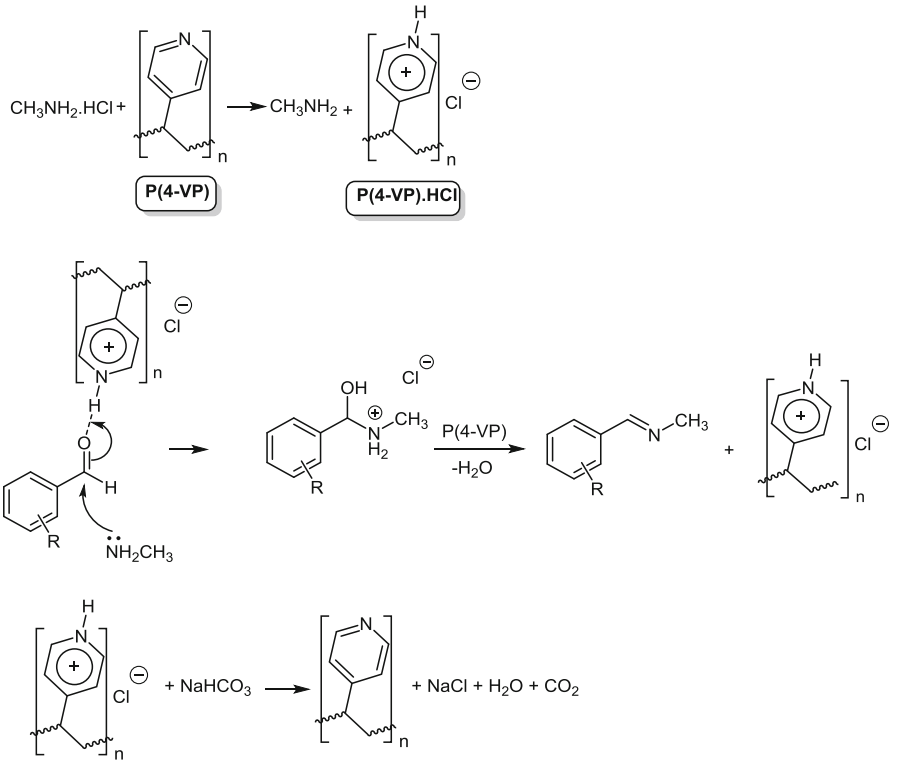
[a] Isolated yields

[b] The reaction time and product yield after three consecutive recycles in presence of recovered solid acid

phenolic group and forming the sodium salt of salicylaldehyde, the poorest yield was reported for the grinding of salicylaldehyde with CH_3NH_2·HCl in presence of $NaHCO_3$ in a molar ratio ArCHO/CH_3NH_2·HCl/$NaHCO_3$ = 1:5:5 [43]. However, using the current method, 4-dimethylaminobenzaldehyd and salicylaldehyde react with solid amine CH_3NH_2·HCl in a ball-mill at room temperature within 2 and 1 h to give 86 and 82 % yield of product, respectively (Table 2, entries 7 and 8). It was interesting to note that heteroaromatic aldehydes (Table 2, entry 15 and 16) were smoothly converted to their corresponding *N*-methyl imines without any by-products [46].

The reusability of recovered P(4-VP) was exemplified by a model reaction which afforded the *N*-methyl imine product in 94–92 % yield after four consecutive runs. The average time for four consecutive runs was 30 min and a 100 % conversion in all cases (monitored by GC–MS), which clearly demonstrates the practical recyclability of this reagent (Table 2, entry 4). The P(4-VP) catalyst remains active even after the fourth cycle, confirming the stability of the polymer under the reaction conditions. Also in the present method, the catalyst does not contain any metal ion [43].

Although a detailed mechanism for the current transformation has not yet been established, a plausible catalytic cycle for the regeneration of P(4-VP) has been proposed, as shown in Scheme 2. Thus, P(4-VP) acts as a proton scavenger to facilitate the liberation of methyl amine in the first step. The nucleophilic attack on the carbonyl group by methyl amine is catalysed by a base catalyst in the second step. Dehydration of the intermediate hydroxyl amine then affords the product. Recovery of the base catalyst is performed by neutralization of the used catalyst by



Scheme 2 Proposed mechanism for the preparation of *N*-methyl imines in the presence of P(4-VP)

the incremental addition of $NaHCO_3$ as the cheapest chemical available for neutralization. Neutralized waste is primarily water and dissolved sodium chloride, which is non-hazardous. Further investigations aimed at fully elucidating the precise mechanism of this reaction are currently underway in our laboratory.

Conclusion

A simple and efficient method for the preparation of various *N*-methyl imines by using P(4-VP) as a solid base catalyst has been developed. Methylamine hydrochloride and P(4-VP) are commercially available and safe to handle. The ethanolic mixture of P(4-VP)·HCl is readily separated from the reaction mixture by filtration and recovered without any significant loss in activity. The methodology has several other advantages viz., the use of ethanol for extracting and recrystallization, the elimination of hazardous solvents during the reaction, the obviation of handling an anhydrous gas in an evacuated container, mild reaction conditions delivering good to excellent yields, and simple experimental procedures. The major advantage of this process is the use of an environmentally benign catalyst

that can be easily regenerated and reused several times without any significant loss of its activity.

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