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Mechanochemistry in Action: Exploitation of Internal Acid Catalysis in Solvent-Free Synthesis of Imines and Evaluation of Radical Scavenging Activities of Imino Derivatives

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Mechanochemical protocol has been exploited to accomplish the synthesis of imino derivatives from aromatic amines with acidic functionalities and different aromatic aldehydes in excellent to nearly quantitative yields. Presence of acidic groups in the aromatic amines has been found to have profound influence on the course of the reaction. The prepared imines were screened for *in vitro* antioxidant activity using 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical. Some of the prepared imino derivatives displayed good to moderate antioxidant property when compared with standard natural antioxidant (L-ascorbic acid).

Keywords: Mechanochemistry, Internal acid catalysis, Solvent-free reaction, Radical scavenging activity.

INTRODUCTION

Appearance of imino functionality in a number of pharmacologically privileged molecules prompts exploration of prolific methodologies for construction of this structural unit [1-6]. Molecules with imino function also serve as efficient heterodienophiles for the generation of nitrogen heterocycles [7-10]. Reduction of imines leads to useful primary and secondary amines. Imines with suitably designed functionalities and molecular framework are extremely important ligands for binding various metal ions [11-19]. Conventionally imines are prepared by heating a mixture of a carbonyl compound and a primary amine in a suitable solvent [20,21]. Success of the reaction often necessitates use of acid catalysis for activation of the carbonyl function [22-24]. These reactions are not only lengthy but also seldom give satisfactory yield of the product. Tedious work up also adds to the demerit of the conventional protocol.

An useful alternative of the conventional methodology is mechanochemical protocol, which involves thorough grinding of an intimate mixture of the reactants usually at room temperature [25,26]. The process has sometimes been mechanized utilizing jet milling [27,28]. This solvent-free technique appears to be superior to the conventional methodology with respect to reaction time, ease of isolation and yield of the desired product [29-32]. Such mechanochemical protocol also often involves use of acid catalysis for successful completion of the reaction [33-35]. The main objective of this work is to explore the scope of mechanochemical protocol in common laboratory set-up and find out the possibility of catalysis expected to be conferred by suitably located acidic functionalities within the reactant molecules. Synthesized imino derivatives were also screened for DPPH radical scavenging activities.

EXPERIMENTAL

Melting points were determined on an electrical melting point apparatus (S.I.) and are uncorrected. IR spectra were run on KBr pellets on a Perkin-Elmer 1330 apparatus. Solutions in $CDCl_3$ with TMS as internal standard were used to record the ^1H NMR spectra on a Bruker 300 NMR spectrometer. Elemental analyses were performed on a Perkin-Elmer instrument 2400 Series II CHN analyzer.

General procedure for the synthesis of imines (entries 1-12): A mixture of aromatic amines (1 mmol) and appropriate aromatic aldehyde (1 mmol) was ground thoroughly in a clean, dry porcelain mortar with a pestle until the mixture became sticky. The sticky mass was left in air for 15-30 min (Table-1) with a little grinding from time to time. After completion of reaction (monitored by TLC), the solid mass was taken out with the flat end of a spatula. All the compounds were purified by recrystallization from dilute aqueous ethanol.

TABLE-1
in vitro DPPH RADICAL SCAVENGING ACTIVITY OF IMINO DERIVATIVES

Compounds	IC_{50} (μM) ± S.E.	Compounds	IC_{50} (μM) ± S.E.
1	38.61 ± 1.35	**7**	24.16 ± 1.04
2	89.14 ± 0.76	**8**	30.12 ± 1.86
3	54.36 ± 1.59	**9**	18.15 ± 1.38
4	10.32 ± 1.46	**10**	21.37 ± 1.62
5	42.42 ± 1.14	**11**	62.08 ± 0.88
6	35.58 ± 1.73	**12**	27.92 ± 1.17
L-Ascorbic acid	8.44 ± 0.78		

4-(Benzylideneamino)benzoic acid (1): Yield: 88%, m.p.: 122 ºC,; IR (KBr, ν_{max}, cm^{-1}): 1490, 1595, 1602,1685, 3050; ^{1}H NMR ($CDCl_3$): 7.41 (2H, d, *J* = 8.8 Hz, ArH), 7.56-7.78 (5H, m, Ar***H***), 8.13 (2H, d, *J* = 8.8 Hz, ArH), 8.85(1H, s, N=C***H***), 12.10 (1H, s, -COO*H*). Anal. calcd. (found) % for $C_{14}H_{11}NO_2$; C, 74.65 (74.43); H, 4.92 (4.82); N, 6.22 (5.96).

4-(Benzylideneamino)benzene sulfonic acid (2): Yield: 90%, m.p.: 240 ºC; IR (KBr, ν_{max}, cm^{-1}): 1178, 1230, 1495, 1590, 1605, 3045; ^{1}H NMR ($CDCl_3$): 7.48-7.90 (9H, m, ArH), 8.75 (1H, s, N=C***H***). Anal. calcd. (found) % for $C_{13}H_{11}NO_3S$; C, 59.76 (59.54); H, 4.24 (4.02); N, 5.36 (5.21).

2-(Benzylideneamino)benzoic acid (3): Yield: 92%, m.p.: 128 ºC; IR (KBr, ν_{max}, cm^{-1}): 1495, 1595, 1612,1678, 3045; ^{1}H NMR ($CDCl_3$): 7.46-7.80 (7H, m, Ar***H***), 8.05-8.18 (2H, m, ArH), 8.72 (1H, s, N=C***H***), 11.26 (1H, s, -COO*H*). Anal. calcd. (found) % for $C_{14}H_{11}NO_2$; C, 74.65 (74.48); H, 4.92 (4.78); N, 6.22 (5.99).

4-((2-Hydroxybenzylidene)amino)benzoic acid (4): Yield: 98%, m.p.: 276 ºC; IR (KBr, ν_{max}, cm^{-1}): 1580, 1610, 1690, 3040, 3320; ^{1}H NMR ($CDCl_3$): 6.92-7.46 (4H, m, Ar***H***), 7.52 (2H, d, *J* = 8.8 Hz, Ar***H***), 8.16 (2H, d, *J* = 8.8 Hz, Ar***H***), 9.04 (1H, s, N=C***H***), 12.05 (1H, s, -COO*H*), 11.42 (1H, s, O*H*), Anal. calcd. (found) % for $C_{14}H_{11}NO_3$; C, 69.70 (69.52); H, 4.60 (4.49); N, 5.81 (5.58).

4-((2-Hydroxybenzylidene)amino)benzene sulfonic acid (5): Yield: 96%, m.p.: 260 ºC; IR (KBr, ν_{max}, cm^{-1}): 1175, 1232, 1278, 1572, 1605, 1635, 3020, 3330; ^{1}H NMR ($CDCl_3$): 6.96-7.62 (6H, m, Ar***H***), 7.92 (2H, d, *J* = 8.8 Hz, Ar***H***), 9.08 (1H, s, N=C***H***), 11.30 (1H, s, O*H*), Anal. calcd. (found) % for $C_{13}H_{11}NO_4S$; C, 56.31 (56.18); H, 4.00 (3.85); N, 5.05 (4.82).

2-((2-Hydroxybenzylidene)amino)benzoic acid (6): Yield: 97%, m.p. 210 ºC; IR (KBr, ν_{max}, cm^{-1}): 1598, 1612, 1688, 3025, 3295 cm^{-1}; ^{1}H NMR ($CDCl_3$): 6.94-7.10 (2H, m, Ar***H***), 7.56-7.75 (4H, m, Ar***H***), 8.10-8.15 (2H, m, Ar***H***), 9.04 (1H, s, N=C***H***), 11.42 (1H, s, O*H*), 11.38 (1H, s, -COO*H*), Anal. calcd. (found) % for $C_{14}H_{11}NO_3$; C, 69.70 (69.52); H, 4.60 (4.49); N, 5.81 (5.58).

4-((Furan-2-ylmethylene)amino)benzoic acid (7): Yield: 89%, m.p. > 300 ºC; IR (KBr, ν_{max}, cm^{-1}): 1582, 1614, 1680, 3035 cm^{-1}; ^{1}H NMR ($CDCl_3$): 6.48 (1H, t, *J* = 8.1 Hz, furan Ar***H***), 7.01 (1H, dd, *J* = 8.1 Hz, 1.8 Hz furan Ar***H***), 7.49 (2H, d, *J* = 8.8 Hz, Ar***H***), 7.72 (1H, dd, *J* = 8.1 Hz, 1.8 Hz furan Ar***H***), 7.79 (1H, s, N=C***H***), 8.09 (2H, d, *J* = 8.8 Hz, Ar***H***), 12.06 (1H, s, -COO*H*), Anal. calcd. (found) % for $C_{12}H_9NO_3$; C, 66.97 (66.73); H, 4.22 (4.08); N, 6.51 (6.32).

2-((Furan-2-ylmethylene)amino)benzoic acid (8): Yield: 90%, m.p. 226 ºC; IR (KBr, ν_{max}, cm^{-1}): 1510,1578, 1616, 1699, 3038; ^{1}H NMR ($CDCl_3$): 6.51 (1H, t, *J* = 8.1 Hz, Furan Ar***H***), 6.96 (1H, dd, *J* = 8.1 Hz, 1.8 Hz furan Ar***H***), 7.62-7.69 (m, 2H, Ar*H*), 7.74 (1H, dd, *J* = 8.1 Hz, 1.8 Hz furan Ar***H***), 7.85 (1H, s, N=C***H***), 8.09-8.16 (2H, m, Ar***H***), 11.36 (1H, s, -COO*H*), Anal. calcd. (found) % for $C_{12}H_9NO_3$; C, 66.97 (66.78); H, 4.22 (4.12); N, 6.51 (6.35).

4-((Thiophene-2-ylmethylene)amino)benzoic acid (9): Yield: 82%, m.p.: 240 ºC; IR (KBr, ν_{max}, cm^{-1}): 1580, 1610, 1689, 3040; ^{1}H NMR ($CDCl_3$): 7.08 (1H, t, *J* = 8.1 Hz, thiophene Ar***H***), 7.46 (2H, d, *J* = 8.8 Hz, Ar***H***), 7.62-7.70 (2H, m, thiphene Ar***H***), 8.13 (2H, d, *J* = 8.8 Hz, Ar***H***), 8.92 (1H, s, N=C***H***), 12.04 (1H, s, -COO*H*), Anal. calcd. (found) % for $C_{12}H_9NO_2S$; C, 62.32 (62.11); H, 3.92 (3.75); N, 6.06 (5.82).

2-((Thiophene-2-ylmethylene)amino)benzoic acid (10): Yield: 86%, m.p.124 ºC; IR (KBr, ν_{max}, cm^{-1}): 1578, 1615, 1685, 3040; ^{1}H NMR ($CDCl_3$): 7.10 (1H, t, *J* = 8.1 Hz, thiophene Ar***H***), 7.60-7.82 (4H, m, Ar***H***), 8.05-8.18 (2H, m, Ar***H***), 8.96 (1H, s, N=C***H***), 11.34 (1H, s, -COO*H*). Anal. calcd. (found) % for $C_{12}H_9NO_2S$; C, 62.32 (62.15); H, 3.92 (3.72); N, 6.06 (5.79).

4-((2-Chlorobenzylidene)amino)benzoic acid (11): Yield: 85%, m.p. 218 ºC; IR (KBr, ν_{max}, cm^{-1}): 1515, 1580, 1620, 1688, 3020; ^{1}H NMR ($CDCl_3$): 7.38 (2H, d, *J* = 8.8 Hz, Ar*H*), 7.48-7.72 (4H, m, Ar***H***), 8.11 (2H, d, *J* = 8.8 Hz, Ar*H*), 8.79 (1H, s, N=C***H***), 12.01 (1H, s, -COO***H***). Anal. calcd. (found) % for $C_{14}H_{10}NO_2Cl$; C, 64.75 (64.59); H, 3.88 (3.73); N, 5.39 (5.21).

4-((4-Methyoxybenzylidene)amino)benzoic acid (12): Yield: 92%,m.p.224 ºC; IR (KBr, ν_{max}, cm^{-1}): 1508, 1602, 1625, 1675, 3050; ^{1}H NMR ($CDCl_3$): 3.72 (3H, s, -OC***H***$_3$), 7.02 (2H, d, *J* = 8.8 Hz, Ar***H***), 7.48 (2H, d, *J* = 8.8 Hz, Ar***H***), 7.91 (2H, d, *J* 8.8 Hz, Ar***H***), 8.16 (2H, d, *J* = 8.8 Hz, Ar***H***), 8.83 (1H, s, N=C***H***), 12.02 (1H, s, -COO***H***). Anal. calcd. (found) % for $C_{15}H_{13}NO_3$; C, 70.58 (70.42); H, 5.13 (5.02); N, 5.49 (5.27).

Biological assay

DPPH radical scavenging activity: Method described by Blois along with some modifications was used for the determination of DPPH radical scavenging activity of all the imino compounds [36,37]. Minimum volume of DMSO was used to dissolve the synthesized imines and dilution of the solutions was done with PBS buffer. Various concentrations of the synthesized imines ranging between (1-100 mM) were mixed with 0.1 mM methanolic solution of DPPH (SRL, India). The resulting solutions were incubated in dark for 30 min at 37 ºC. The absorbance of the solution was measured with a digital colorimeter (Labtronics) at λ = 517 nm. L-Ascorbic acid and DMSO were taken as standard positive and negative controls respectively. The following equation was used for the calculation of the percentage of DPPH radical scavenging activity:

$$\text{DPPH scavenging (\%)} = \frac{A_{control} - A_{sample}}{A_{control}} \times 100$$

where $A_{control}$ stands for the absorbance of the control reaction (with all reagents except the test compound) and A_{sample} is the

absorbance of the test sample. Concentration of the compound showing 50% radical inhibitory activity (IC_{50}) was calculated by linear regression analysis. The experiment was carried out thrice and the data presented as the mean of three independent measurements.

RESULTS AND DISCUSSION

Mechanistic rationalization of the reaction between a carbonyl compound and a primary amine involves the following steps (Fig. 1).

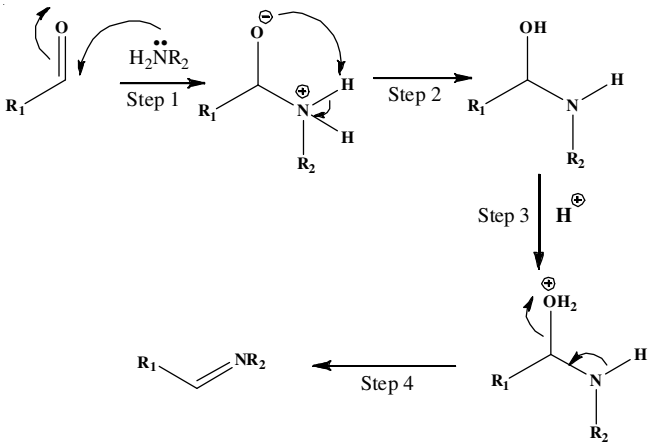


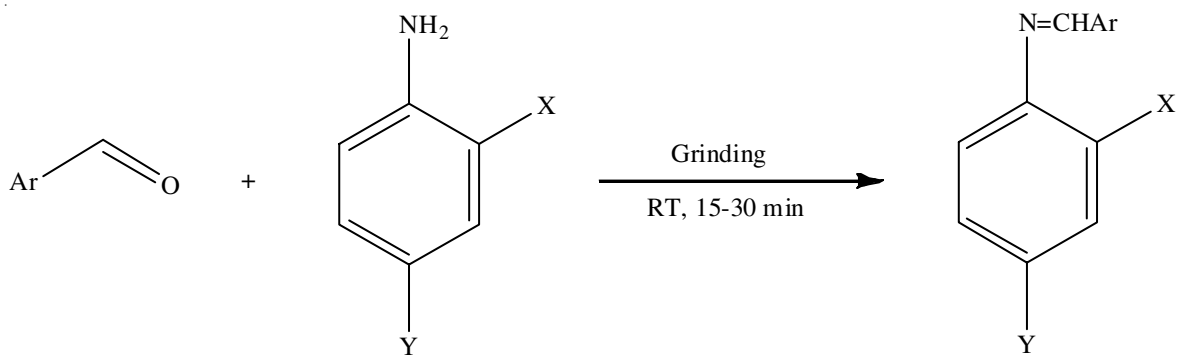
Fig. 1. Mechanism of imine formation

In the presence of electron releasing groups in the carbonyl compound step 1 appears to be the rate limiting step [38,39]. This corroborates from a positive Hammett ρ value for the reaction, which indicates the development of a negative charge around the reaction centre (here carbonyl oxygen) in the transition state for the rate limiting step. Step 4 becomes rate limiting in presence of electron withdrawing groups in the carbonyl compound. The Hammett ρ value for such cases is negative which is indicative of the generation of a positive charge around the reaction centre in the transition state for the rate determining step. Thus breakage of C-O bond is slightly more advanced than that of N-H bond. Apart from the electronic nature of the substituents present in the carbonyl compound pH of the reaction medium also profoundly influences the rate of the reaction. At low pH step 1 becomes rate limiting whereas at higher pH step 4 appears to be rate limiting. For the study of catalysis by the 'in-built' functionalities, we used aromatic amines with carboxylic acid and sulfonic acid moieties in the nucleus. All the reactions occurred smoothly at room temperature without external acid catalysis (**Scheme-I**).

However, use of appreciably nucleophilic aromatic amines like *p*-toluidine and *p*-anisidine rendered the reaction sluggish (except with salicylaldehyde) and completion of the reaction was not achieved even in 2 h. It, therefore, appears that catalysis conferred by the internal acidic functions has played more vital role than nucleophilicity of the amine for successful occurrence of the reaction. For anthranilic acid the ortho carboxyl function is believed to activate the carbonyl group as shown below (Fig. 2):

For *p*-amino benzoic acid and sulfanilic acid catalysis may occur as shown in Fig. 3. In these cases, distance between amino and acid groups is too large to allow activation of the carbonyl function in the same way as that of anthranilic acid (Fig. 3).

Among the various aromatic and heteroaromatic aldehydes used for the reaction, salicylaldehyde is found to undergo



Entry	Ar	X	Y	Time (min)	Yield (%)	m.p. (°C) (Obs.)	m.p. (°C) (Lit.)
1	Phenyl	H	COOH	30	88	122	121-123 [23]
2	Phenyl	H	SO_3H	30	90	240	–
3	Phenyl	COOH	H	28	92	128	126 [40]
4	2-Hydroxyphenyl	H	COOH	18	98	276	276-278 [23]
5	2-Hydroxyphenyl	H	SO_3H	15	96	260	262 [41]
6	2-Hydroxyphenyl	COOH	H	20	97	210C	209-211 [42]
7	2-Furyl	H	COOH	25	89	> 300	> 300 [43]
8	2-Furyl	COOH	H	25	90	226	227 [44]
9	2-Thienyl	H	COOH	28	82	240	242-244 [45]
10	2-Thienyl	COOH	H	28	86	124	125 [44]
11	2-Chlorophenyl	H	COOH	30	85	218	217 [43]
12	4-Methoxyphenyl	H	COOH	30	92	224	224-226 [45]

Scheme-I: Mechanochemical syntheses of imines

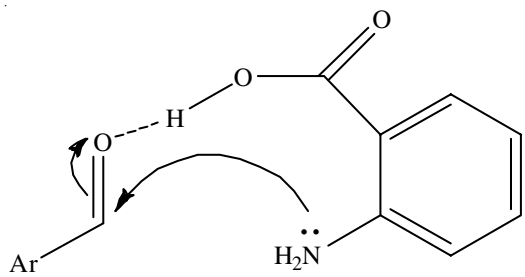


Fig. 2. Activation of carbonyl by anthranilic acid

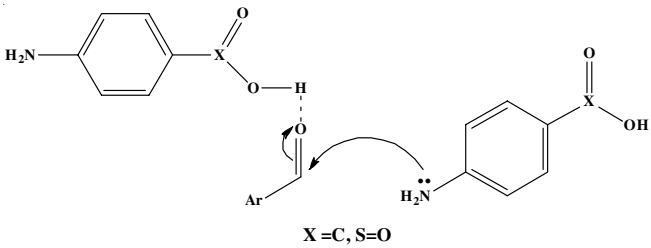


Fig. 3. Activation of carbonyl by sulfanilic acid and *p*-amino benzoic acid

the fastest reaction with the maximum yield of the corresponding imines. Stabilization of the transition states through intramolecular hydrogen bonding may lurk behind this enhanced rate of the reaction. Intramolecular hydrogen bonding may also contribute to the thermodynamic stability of the corresponding imines leading to very high yield of them (Fig. 4).

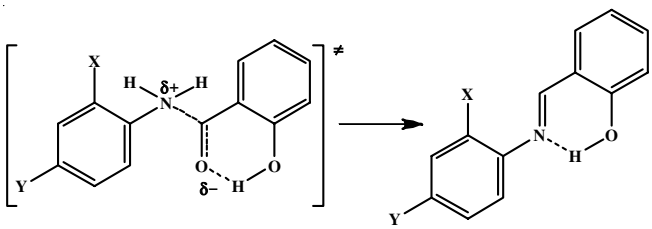


Fig. 4. Stabilisation of transition state and the product through hydrogen bonding

Superiority of this mechanochemical protocol over the conventional procedure may be attributed to entropy assistance for the former. In the solid phase molecular motion becomes restricted. Hence, further decrease in entropy during the formation of transition state is expected to be much lower than for solution phase reactions.

Biological activity

***in vitro* DPPH radical scavenging activity:** Degenerative diseases like cancer, asthma, diabetes, inflammation in joints *etc*. mostly originate from free radical reactions. Damage of genetic materials, lipid peroxidation in cell membranes and inactivation of membrane-bound enzymes may also be caused by free radicals [46]. Free radicals may also be responsible for the process of biological ageing. Some of the natural antioxidants or free radical scavengers include ascorbic acid, α-tocopherol, β-carotene, coenzyme Q 10, *etc*., which play crucial role in defense mechanism against cellular impairment. Biological properties of imines are often ascribed to the presence of unshared pair of electrons on imino nitrogen. Ability of suitably designed imino derivatives to undergo facile chelation plays a vital role in their antioxidant activities [47]. The efficiency of the synthesized imino derivatives to scavenge DPPH radical was evaluated and expressed in terms of IC_{50} values (Table-1). The assay is based on the estimation of the electron or hydrogen transfer ability of compounds to the DPPH radical to form the corresponding hydrazine and the activity of each compound depends on the stabilization of the resulting free radical species [48].

Table-1 established the moderate to strong antioxidant property of some of the prepared imino compounds, which indicates their radical scavenging as well as reducing abilities.

Remarkable DPPH scavenging activity was exhibited by compound **4**, derived from salicylaldehyde and 4-aminobenzoic acid with IC_{50} value close to that of the natural antioxidant L-ascorbic acid. In fact most of the azomethine derivatives of 4-aminobenzoic acid showed fairly strong antioxidant activities. 4-Aminobenzoic acid is involved in a number of metabolic processes [49]. So, it is not unlikely that imines derived from it may be endowed with some interesting biological properties. Again the imines from heterocyclic aldehydes (compounds **7**, **8**, **9** and **10**) also displayed relatively high activities compared to other analogues. Compound **2** exhibited very poor activity and compounds **3** and **11** showed moderate activities when compared to the standard antioxidant L-ascorbic acid. Interestingly at a particular concentration (100 mM) the percentage of radical scavenging abilities of these imines is approximately reflected in the respective IC_{50} values (Fig. 5).

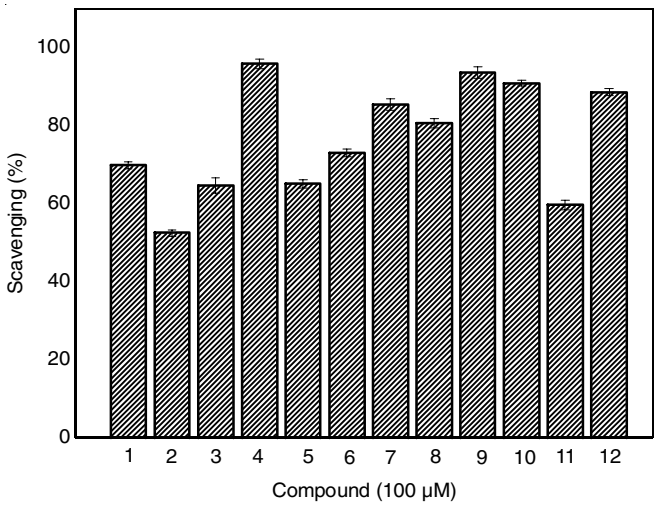


Fig. 5. *in vitro* DPPH radical scavenging activity of azomethine derivatives (100 µM). Error bars represent the standard error in each compound of three separate determinations

Conclusion

A number of imines were prepared in good to nearly quantitative yields from aromatic amines containing acidic functionalities and various aromatic and heteroaromatic aldehydes through mechanochemical protocol. Short reaction time, mild reaction conditions, high yield of the desired product and operational simplicity add strength to this methodology over the conventional solution-phase procedure. Presence of acidic

functions within the reactant molecules was found to catalyze the reactions efficiently and use of external acid catalysis was not needed. Promising radical scavenging activity was found in some of the prepared imines.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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