Received: 24 December 2018 | Revised: 29 April 2019 | Accepted: 1 May 2019

DOI: 10.1002/jccs.201800486

JOURNAL OF THE CHINESE CHEMICAL SOCIETY

ARTICLE

Systematic studies on mechanochemical synthesis: Schiff bases from solid aromatic primary amines and aldehydes

Getinet Tamiru Tigineh[1,2,3] | **Ling-Kang Liu**[1,4]

[1]Institute of Chemistry, Academia Sinica, Taipei, Taiwan

[2]Department of Chemical Engineering, National Taiwan University of Science and Technology, Taipei, Taiwan

[3]Department of Chemistry, Bahir Dar University, Bahir Dar, Ethiopia

[4]Department of Chemistry, National Taiwan University, Taipei, Taiwan

Correspondence
Getinet Tamiru Tigineh, Department of Chemistry, Bahir Dar University, Bahir Dar, Ethiopia.
Email: getsh2007@gmail.com

Funding information
Academia Sinica

A versatile and robust mechanochemical route to Aldehyde–Schiff base conversions has been established for a broad range of aldehydes *via* a simple cogrinding in mortar with a pestle under a solvent-free, as well as solvent-assisted, environment. The extent of amines reactivity under these conditions has also been explored, along with an examination of the possible connection between reactivity and electronic substituent effects. Results obtained demonstrated that the solvent-free mechanochemical conversion of *p*-toluidine and aromatic aldehydes to the corresponding Schiff bases proceeded more smoothly than the corresponding synthesis with 4-aminobenzonitrile. The present approach not only provides good to excellent yields but also eliminates the disadvantages of the traditional synthesis of Schiff bases, such as the use of hazardous solvents, more or less demand of expensive catalysts, and looking for optimization on reaction conditions.

KEYWORDS
aromatic aldehydes, mechanochemistry, Schiff base, solvent-free reaction

1 | INTRODUCTION

An important incentive to study mechanochemical phenomena is their potential usefulness for making new materials and to make current or future technologies more efficient.[1] As the demand for better recovery, higher efficiency, and greener operation increases, interest in the use of mechanical activation will grow.[2]

The growing interest in mechanochemical processes has, in the past decade, provided exciting developments in the areas of supramolecular (cocrystals, capsules, catenanes, rotaxanes),[3] pharmaceuticals (screening new solid drug forms, pharmaceutical cocrystals),[4] materials (porous metal–organic frameworks, luminescent sensors),[5] and organic (solvent-free synthesis, solid-state deracemization, organic cages) chemistry[6–9] and catalysis (stereoselective organocatalysts, metal organic solvent-free catalysis, catalytic solid-state photoreactions).[10,11] These developments indicate that mechanochemistry will play a key role in future clean and sustainable technology, ranging from "green" synthesis to mineral manufacturing and nanoparticle synthesis. [4,12]

In a recent Faraday discussion-themed issue on "*Mechanochemistry: From Functional Solids to Single Molecules,*" the mechanochemistry of organic molecules, soft materials and pharmaceuticals, the mechanochemistry of inorganic compounds and coordination-based materials, sonication and macromolecular mechanochemistry, current theoretical models for mechanochemical reactions, the mechanistic and kinetic understanding, catalysis, and scaling up of mechanochemistry were broadly discussed.[13–39]

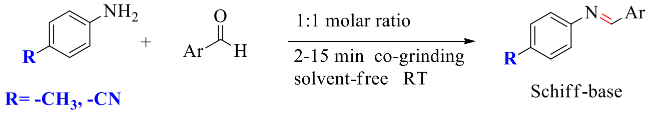
However, mechanochemical methods are a very active and promising research area, their use in organic and organometallic synthesis is relatively rare and in a very infant stage compared with other synthesis protocols, and also they are poorly communicated for the scientific society.

Furthermore, interest in Schiff base, attributed to their function as primary reagents in cycloaddition,[40] cyclization,[41,42] enantioselective oxidation,[43] metal complex synthesis for versatile application,[44,45] etc., have drastically increased. However, most current protocols for the synthesis of Schiff bases are environmentally stressful and less economical because of the extensive use of volatile organic solvents and looking for optimization on reaction conditions. [46,47] To our knowledge, many Schiff bases have been synthesized in solution, yet the corresponding synthesis in solid state is much less widespread, and no systematic investigations with detail characterization have been conducted before to address the scope.[48–50] Therefore, in this work, attempts have been made to synthesize 20 Schiff bases from 10 differently functional solid aromatic aldehydes and two solid primary aromatic amines by cogrinding in mortar with a pestle under a solvent-free, and differently under solvent-assisted, environment at room temperature in order to determine the scope of solvent-free mechanochemical synthesis of the Schiff base from systematically selected aromatic aldehyde and primary aromatic amine.

2 | RESULTS AND DISCUSSION

2.1 | Solvent-free mechanochemical synthesis

For the investigation of solvent-free mechanochemical synthesis of Schiff base, the solid primary aromatic amines used were carrying either an electron-donating substituent (-CH_3) or an electron-withdrawing substituent (-CN) at *p* position, whereas 10 solid aromatic aldehydes systematically selected and used contained *para* substituted halides (*p*-Cl, *para*-Br, *para*-I), isomeric NO_2 derivatives *(o*-, *meta*-, *p*-NO_2), disubstituted functional 2-OH-5NO_2, 3-Br-5Br derivatives, and *p*-OH (Scheme 1). The cogrinding was performed with a mortar and a pestle under a solvent-free environment at room temperature. The broad spectrum of aromatic aldehydes and two primary aromatic amines with different electronic natures examined here was meant to provide sufficient data to determine limitation, if any, of the solvent-free mechanochemical conversion of *p*-toluidine and 4-aminobenzonitrile with differently functionalized aromatic aldehydes to corresponding Schiff bases. The 20 target Schiff bases, abbreviated as **SBA1–SBA10** and **SBB1–SBB10,** are shown in Table 1. The results demonstrated that, for instance, in the reaction of *p*-toluidine with 4-bromobenzaldehyde, grinding each reactant separately does not lead to any changes in bulk physical characteristics except particle size (both are white powders). However, grinding equivalent molar quantities of the two powders together results in a dark green-colored intermediate, followed by the formation of a liquid melt that transforms in a matter of seconds into a white solid product. Similar behavior was noted for a number of analogous substrates, although the duration of transformation of liquid melt to solid product varies from one substrate to another. Overall, the solid Schiff base product begins to separate in a matter of minutes, and the entire reaction mixture turns into a wet crystalline mass within a few minutes. Note that similar behavior was hinted in a previous report of the analogous reaction of aromatic amines (vanillin and 4-chlorobenzaldehyde).[50] On the other hand, in the reaction of *p*-toluidine with 4-nitrobenzaldehyde, as soon as the reactants were mixed, an immediate color change was demonstrated. The mixtures displayed uniform color without melting for 10 min of cogrinding. Unlike the previous two situations, in the reactions such as 3, 5-dibromobenzealdehyde with 4-aminobenzonitrile, the reactants did not show melt or color change for >15 min of cogrinding. However, some were able to show color change without melting after a prolonged period of cogrinding, for example, **SBB9**.



SCHEME 1 Solvent-free mechanochemical synthesis of Schiff base

2.2 | ^{1}H NMR ($CDCl_3$) spectra

The Schiff base product mixtures were periodically monitored by ^{1}H NMR spectroscopy in order to achieve the complete disappearance of the aldehyde and amine protons and the full emergence of the azomethine proton (Supporting Information Appendix S1). At 100% conversion, the product spectra exhibited a singlet at δ 8.35–8.98 attributed to azomethine proton (–C*H*=N–) and no signal at ca.δ10 attributed to aldehyde proton (–C*H*=O). The extra single sharp peak around δ1.56 is due to the solvent residual peak of H_2O in $CDCl_3$.[51] It is worth mentioning that, on Schiff base formation, the signal of the azomethine hydrogen is upfield relative to the original signal of the aldehyde hydrogen (–C*H*=O). For Schiff bases **SBA9** and **SBB9,** the –O*H* proton signal of aldehyde originally at ca.δ11.6 (Figure 4(b)) changed to that of the Schiff base at δ14.65 (Figure 4(d)) and δ13.61, respectively, the downfield shift being attributed to the O–H···N intramolecular H-bonding as a common feature of o-hydroxysalicylidene systems.[52,53] Among the 10 examples of **A** series Schiff base, seven reactions (**SBA1, SBA2, SBA3, SBA5, SBA6, SBA7, SBA10**) demonstrated virtually no evidence of aromatic aldehyde or *p*-toluidine in the crude product mixture taken directly from the mortar, indicating the efficiency of the conversion. The ^{1}H NMR spectrum of the ground product mixture for **SBA6** is shown in Figure 1 as a typical example, in which the dehydration reaction was completed without side products. For the Schiff bases (**SBA4** and **SBA9**) prepared with mortar and pestle, a trace amount of the aldehyde proton

TABLE 1 Series of synthesized Schiff bases using a solvent-free mechanochemical method[a]

Entry	Amine (Mp in °C)	Aldehyde (Mp in °C)	Schiff base (CODE)	Transition state	Product	Yield (%)
1	p-toluidine (41–46)	4-Chlorobenzaldehyde (45–47)	(E)-N-(4-chlorobenzylidene)-4-methylaniline **(SBA1)**	Melt	White solid	98.6
2		4-Bromobenzaldehyde (55–58)	(E)-N-(4-bromobenzylidene)-4-methylaniline **(SBA2)**	Melt	White solid	98.4
3		4-Iodobenzaldehyde (78–80)	(E)-N-(4-iodobenzylidene)-4-methylaniline **(SBA3)**	No melt	White solid	99.5
4		4-Nitrobenzaldehyde (103–106)	(E)-4-methyl-N-(4-nitrobenzylidene)aniline **(SBA4)**	No melt	Yellow solid	99.6
5		3-Nitrobenzaldehyde (57–59)	(E)-4-methyl-N-(3-nitrobenzylidene)aniline **(SBA5)**	Melt	White solid	99.0
6		2-Nitrobenzaldehyde (42–44)	(E)-4-methyl-N-(2-nitrobenzylidene)aniline **(SBA6)**	Melt	Light yellow-brown solid[b]	99.4
7		4-Cyanobenzaldehyde (100–102)	(E)-4-([p-tolylimino]methyl) benzonitrile **(SBA7)**	Sticky	White solid	99.2
8		4-Hydroxybenzaldehyde (112–115)	(E)-4-([p-tolylimino]methyl)phenol **(SBA8)**	No melt	White solid	81.0
9		2,4-Dinitrobenzaldehyde (67–70)	(E)-4-nitro-2-([p-tolylimino]methyl) phenol **(SBA9)**	No melt	Yellow solid	98.8
10		3,5-Dibromobenzaldehyde (84–86)	(E)-N-(3,5-dibromobenzylidene)-4-methylaniline **(SBA10)**	Melt	White solid	99.0
11	4-aminobenzonitrile (83–85)	4-Chlorobenzaldehyde (45—47)	(E)-4-((4-chlorobenzylidene)amino) benzonitrile **(SBB1)**	Melt	White solid	98.9
12		4-Bromobenzaldehyde (55–58)	(E)-4-((4-bromobenzylidene)amino) benzonitrile **(SBB2)**	Melt	White solid	98.1
13		4-Iodobenzaldehyde (78–80)	(E)-4-([4-iodobenzylidene]amino) benzonitrile **(SBB3)**	No melt	White solid	32.0
14		4-Nitrobenzaldehyde (103–106)	(E)-4-((4-nitrobenzylidene)amino) benzonitrile **(SBB4)**	No melt	Yellow solid	72.0
15		3-Nitrobenzaldehyde (57–59)	(E)-4-((3-nitrobenzylidene) amino)benzonitrile **(SBB5)**	Melt	White solid	84.0
16		2-Nitrobenzaldehyde (42–44)	(E)-4-methyl-N-(2-nitro benzylidene)aniline **(SBB6)**	Melt	Light yellow-brown solid[b]	99.3
17		4-Cyanobenzaldehyde (100–102)	(E)-4-([4-cyanobenzylidene]amino) benzonitrile **(SBB7)**	Sticky	White solid	99.0
18		4-Hydroxybenzaldehyde (112–115)	—	No melt	Yellow solid	No product
19		2,4-Dinitrobenzaldehyde (67–70)	(E)-4-([2-hydroxy-5-nitrobenzylidene]amino) benzonitrile **(SBB9)**	No melt	Yellow solid	64.0
20		3,5-Dibromobenzaldehyde (84–86)	(E)-4-((3,5-dibromobenzylidene) amino) benzonitrile **(SBB10)**	No melt	White solid	50.0

[a] In a mortar, accurately weighed 1.0 mmol of *p*-toluidine/4-aminobenzonitrile and 1.0 mmol of aromatic aldehyde were ground together with a pestle. The progress of the reaction was monitored using the ^{1}H NMR spectroscopic method to ensure the extent of conversion.

[b] The ground mixture changes from yellow to light yellow-brown powder with time. **SBB8** was not obtained.

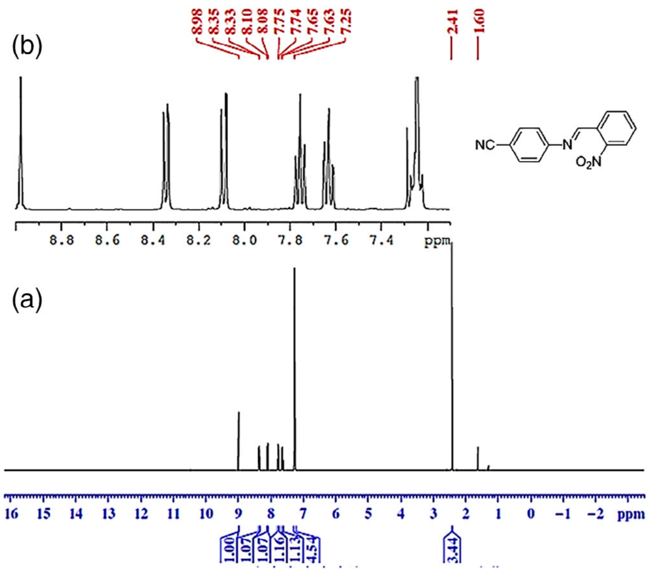


FIGURE 1 ^{1}H NMR spectra (δ −3 to 16.5, $CDCl_3$) of (a) **SBA6** directly taken from the ground product mixtures; (b) expansion (δ 7.2–9.0) of (a)

signal was observed, which could be removed by extending the grinding time or assisting with the solvent. Conversely, **SBA8**, resulted from 1:1 cogrinding between *p*-toluidine and 4-hydroxybenzaldehyde and showed mixing signals of reactants and product on both ^{1}H NMR and ^{13}C NMR spectra in both $CDCl_3$ and CD_3OD, in agreement with the previous report.[50] Remarkably, the positive mode of EI-MS used for **SBA8** after 10 days of synthesis demonstrated the molecular ion peak with best accuracy at 100% intensity of *m/z* [M+] (see Appendix S1).

Among the 10 examples of **B** series Schiff bases, four reactions (**SBB1, SBB2, SBB6, SBB7**) demonstrated trace evidence of aromatic aldehyde, but no evidence of 4-aminobenzonitrile, in the crude product mixture taken directly from the mortar. The other three (**SBB4, SBB5, SBB9**) showed a substantial amount of aldehyde on the crude product mixture directly taken from the mortar. **SBB3** and **SBB10** displayed comparable amount of both reactants and product on the ^{1}H NMR spectra of the crude Schiff base samples directly taken from ground mixture. Astonishingly, **SBB8** did not show any azometine proton on the ^{1}H NMR spectra taken in $CDCl_3$ and CD_3OD. Its ^{1}H NMR spectra was the sum of those of starting materials, indicating that there is no reaction between 4-hydroxybenzaldehyde and 4-aminobenzonitrile under the given reaction condition (see Appendix S1).

Overall, the solvent-free mechanochemical synthesis results of **A** and **B** series Schiff bases showed that better yield was obtained with *p*-toluidine (**A** series) than with *p*-aminobenzonitrile (**B** series), which is seemingly attributable to the electron-donating group ($-CH_3$) in *p*-toluidine playing a significant role in increasing the electron density on the nitrogen atom of $-NH_2$ and, accordingly, the nucleophilicity.

2.3 | Solvent-assisted mechanochemical synthesis

Attempts have been made to enhance the kinetics and yield of solvent-free mechanochemical synthesis of Schiff base using small drops of solvent in which the starting aldehyde and amine are soluble. The investigation surprisingly demonstrated that, in the case of **SBB4**, the solvent-free mechanochemical synthesis, under the given reaction circumstance, was better than the corresponding solvent-assisted grinding (Figure 2). This probably suggests that **SBB4** may not be achieved with good yield in solvents such as methanol solution. In the other experiment, both **SBB7** and **SBB8** demonstrated no significant difference in the yield via solvent-free or solvent-assisted synthesis protocols, likely because methanol has no significant effect on the kinetics and yield of such reactions at a given reaction condition. Moreover, we were also able to observe the effect, if any, (a) by looking at the ^{1}H NMR in $CDCl_3$ and CD_3OD of the freshly prepared samples after a week of mechanosynthesis of the above Schiff bases and (b) by leaving the solutions in the NMR tubes for a week in $CDCl_3$, as well as CD_3OD, at room temperature before the remeasurement. In both cases, there were no observable differences in the yield after a prolonged period of time in the solid state or in the solution phase for **B** series, obtained using both solvent-free and solvent-assisted techniques (Figure 3).

Interestingly, ^{1}H NMR and ^{13}C NMR of **SBA9** after being maintained for 4 days in $CDCl_3$ solution in the NMR tube demonstrated the disappearance of 2-hydroxy-5-nitrobenzaldehyde and *p*-toluidine, indicating that solvents such as $CHCl_3$ have significant influence on the conversion of aldehyde and amine into the corresponding Schiff bases (Figure 4).

2.4 | Mass spectra

In the HRMS-EI and HRMS-FAB mode mass spectra of Schiff bases (see experimental section), the molecular ion peaks were observed with best accuracy at *m/z* $[M + H]^+$

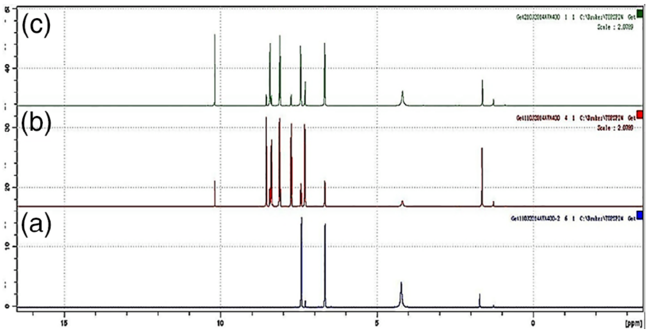


FIGURE 2 ^{1}H NMR spectra (δ −3 to 16.5, $CDCl_3$) of (a) 4-aminobenzonitrile, (b) **SBB4** obtained via solvent-free method, and (c) **SBB4** obtained via solvent-assisted method

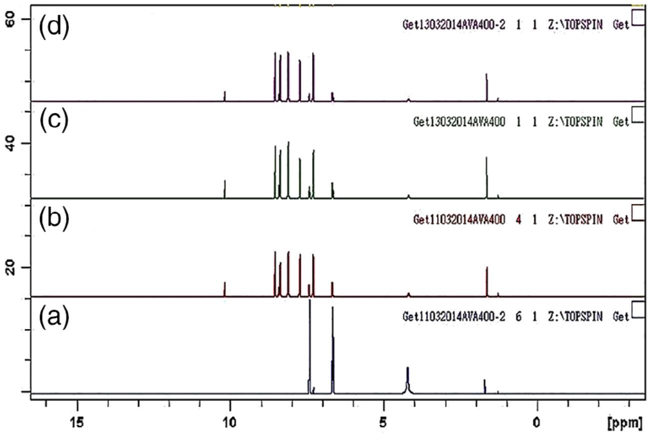


FIGURE 3 ^{1}H NMR spectra (δ −3 to 16.5, $CDCl_3$) of (a) 4-aminobenzonitrile, (b) **SBB4** freshly prepared from solid material after 5 days of mechanosynthesis, (c) **SBB4** solution after 2 days in NMR tube, and (d) **SBB4** freshly prepared solution from solid material after 7 days of mechanosynthesis

and $[M]^+$, which are in good agreement with the molecular weight of the proposed structure of corresponding Schiff bases.[54]

2.5 | Comparative outlook of solvent-free and solvent-assisted syntheses of Schiff bases

Experimentally, the solvent-free mechanochemical conversion of *p*-toluidine and aromatic aldehydes to the corresponding Schiff bases proceeded more smoothly than the corresponding synthesis with 4-aminobenzonitrile. As a result, the yield and reaction kinetics of **A** series Schiff base synthesis are better than those of the corresponding **B** series Schiff base synthesis. This is because the presence of the electron-withdrawing –*CN* group on the aromatic ring of amine decreases the reactivity, and hence nucleophilicity, of the $–NH_2$.[55]

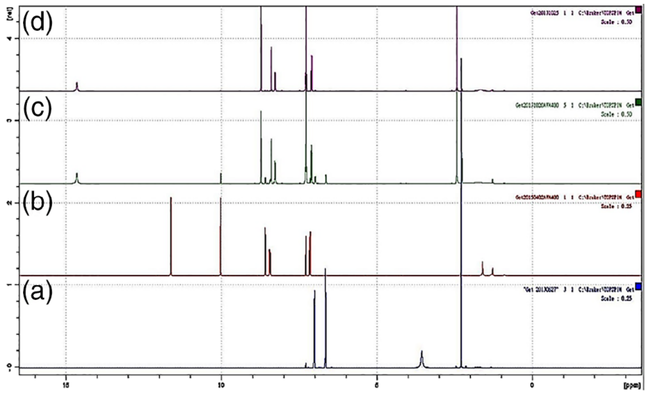


FIGURE 4 ^{1}H NMR spectra (δ −3 to 16.5, $CDCl_3$) of (a) *p*-toluidine, (b) 2-hydroxy-5-nitrobenzaldehyde, (c) **SBA9** fresh solution, and (d) **SBA9** after staying in $CDCl_3$ solution for 4 days

A solvent-free mechanochemical reaction proceeding through a melt transition state gave better yield and showed fast kinetics compared with those proceeding without melt during cogrinding in both **A** and **B** series Schiff bases.

For **SBA8**, a significant amount of azomethine proton signal was observed for the product obtained via solvent-free mechanochemical synthesis, but not for **SBB8**. The reaction between 4-hydroxybenzaldehyde and 4-aminobenzonitrile, expected to form **SBB8,** showed no azomethine proton signal, neither through solvent-free nor solvent-assisted mechanochemical synthesis (see Appendix S1). This is most likely due to the synergistic effect of both the electron-donating –OH group on aldehyde and the electron-withdrawing –CN group on amine.

The observation for **SBB4**, the solvent-free mechanochemical synthesis, under the given reaction circumstance was found to be better than the corresponding solvent-assisted grinding, suggesting that solvent-free mechanochemical synthesis is important for the isolation of species, which cannot be obtained in solution.

The observation in solvent-assisted cogrinding at room temperature showed that solvents like chloroform and methanol presumably have no significant effect on the reaction kinetics, as well as yield of the **B** series Schiff bases reported in this paper, unless an otherwise external energy is supplied and/or grinding time is prolonged.

3 | EXPERIMENTAL

3.1 | General information

Starting chemicals used were from commercial sources, for example, Aldrich, RDH, Fluka, Acros, Matrix scientific and were used directly without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded using BRUKER 400 and 300 MHz machines, with chemical shifts in δ units, downfield positive, and referenced to the residual peak of deuterated solvents ($CDCl_3$ δ 7.24, $CDCl_3$ δ 77, correspondingly) and CD_3OD. EI + MS spectra were recorded with a JMS-700 double-focusing mass spectrometer (JEOL, Tokyo, Japan) with a resolution of 8000 (3000) (5% valley definition). Melting points were determined by using a PERKIN ELMER differential scanning calorimeter DSC 7 modules in sealed aluminum pans, heated in flowing nitrogen (20.0 mL/min) at 10°C/min.

3.2 | General procedure for solvent-free mechanochemical synthesis of Schiff-base

The solid reactants *p*-toluidine (1.0 mmol) and aromatic aldehyde (1.0 mmol) were ground individually until finely divided solids were formed; they were then mixed at a 1:1

FIGURE 5 Photos of the 20 target Schiff bases, abbreviated as **SBA1–SBA10** and **SBB1–SBB10,** obtained from a solvent-free mechanochemical reaction between 10 differently functionalized aromatic aldehydes with *p*-toluidine and with 4-aminobenzonitrile

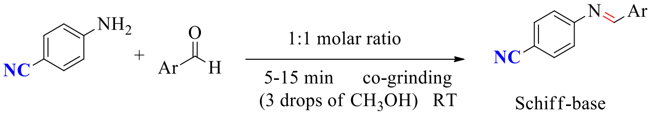
stoichiometric molar ratio at room temperature for cogrinding. As soon as the reactants were mixed, some exhibited immediate color change, whereas the others did not. The mixtures that displayed immediate color change also melted after few minutes of cogrinding. Then, the melt was further mixed and ground to solidify or otherwise left in open air for about half a day at room temperature for drying. Finally, the dried products were ground for an extra 1–3 min and weighed. The resultant crude products without further purification were investigated directly by DSC, ^{1}H NMR, ^{13}C NMR, and EI + MS. The other set of mixes that did not melt took 5–15 min more of cogrinding to show color change, if any, without melting, and the obtained products were treated in a similar fashion, without further purification. The same procedure was used for 4-aminobenzonitrile with aromatic aldehyde (Figure 5).

3.3 | General procedure for solvent-assisted mechanochemical synthesis of Schiff base

The solid reactants 4-aminobenzonitrile (1.0 mmol) and aromatic aldehyde (1.0 mmol) were ground individually until finely divided solids were formed; they were then mixed at a 1:1 stoichiometric molar ratio, and three drops of solvent were added to the mixture at room temperature for cogrinding. The rest reaction progress and the obtained products were treated in a fashion similar to the solvent-free mechanochemical synthesis of Schiff base (Scheme 2 and Figure 6).

3.3.1 | SBA1 (E)-N-[4-chlorobenzylidene]-4-methylaniline

Yield: 0.2263 g (98.6%); color: white solid; ^{1}H NMR (400 MHz, CDCl$_3$, 27°C, TMS): δ = 8.46 (s, 1H; C*H*=N), 7.87 (d, *J*[H,H] = 8 Hz, 2H). 7.48 (d, *J*[H,H] = 8 Hz, 2H), 7.24 (d, *J*[H,H] = 8 Hz, 2H), 7.17 (d, *J*[H,H] = 8 Hz, 2H), 2.40 ppm (s, 3H; C*H*$_3$); ^{13}C NMR (300 MHz; CDCl$_3$, 27°C, TMS): δ = 158.0 (*C*H=N), 149.1, 137.2, 136.1, 134.9, 129.8, 129.5, 129.0, 120.8, 21.0 (*C*H$_3$) ppm; HRMS (EI+): *m/z* calcd for $C_{14}H_{12}ClN^+$: 229.0658 [M+]; found: 229.0654.



SCHEME 2 Solvent-assisted mechanochemical synthesis of Schiff base

3.3.2 | SBA2 (E)-N-[4-bromobenzylidene]-4-methylaniline

Yield: 0.2698 g (98.4%); color: white solid; ^{1}H NMR (400 MHz, CDCl$_3$, 27°C, TMS): δ = 8.44 (s, 1H; C*H*=N), 7.80 (d, *J*[H,H] = 8 Hz, 2H). 7.63 (d, *J*[H,H] = 8 Hz, 2H), 7.24 (d, *J*[H,H] = 8 Hz, 2H), 7.18 (d, *J*[H,H] = 8 Hz, 2H), 2.40 ppm (s, 3H; C*H*$_3$); ^{13}C NMR (300 MHz; CDCl$_3$, 27°C, TMS): δ = 158.0 (*C*H=N), 149.0, 136.2, 135.3, 132.0, 130.1, 129.8, 125.7, 120.8, 21.0 (*C*H$_3$) ppm; HRMS (EI+): *m/z* calcd for $C_{14}H_{12}BrN^+$: 273.0153 [M+]; found: 273.0159.

3.3.3 | SBA3 (E)-N-(4-iodobenzylidene)-4-methylaniline

Yield: 0.3194 g (99.5%); color: white solid; ^{1}H NMR (400 MHz, CDCl$_3$, 27°C, TMS): δ = 8.42 (s, 1H; C*H*=N), 7.85 (d, *J*[H,H] = 8 Hz, 2H). 7.65 (d, *J*[H,H] = 8 Hz, 2H), 7.24 (d, *J*[H,H] = 8 Hz, 2H), 7.17 (d, *J*[H,H] = 8 Hz, 2H), 2.40 ppm (s, 3H; C*H*$_3$); ^{13}C NMR (300 MHz; CDCl$_3$, 27°C, TMS): δ = 158.2 (*C*H=N), 149.0, 138.0, 136.2, 135.8, 130.1, 129.8, 120.8, 97.9, 21.0 (*C*H$_3$) ppm; HRMS (EI+): *m/z* calcd for $C_{14}H_{12}IN^+$: 321.0015 [M+]; found: 321.0012.

3.3.4 | SBA4 (E)-4-methyl-N-[4-nitrobenzylidene]aniline

Yield: 0.2392 g (99.6%); color: yellow solid; ^{1}H NMR (400 MHz, CDCl$_3$, 27°C, TMS): δ = 8.59 (s, 1H; C*H*=N),

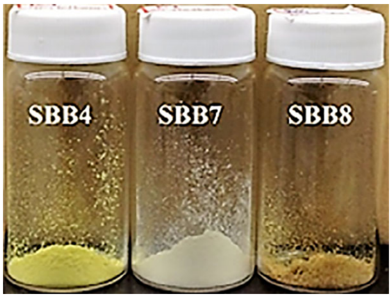


FIGURE 6 Photos of three Schiff bases, **SBB4, SBB7,** and **SBB8,** obtained from a solvent-assisted mechanochemical reaction between 4-aminobenzonitrile with 4-nitrobenzaldehyde, 4-cyanobenzaldehyde, and 4-hydroxybenzaldehyde, respectively

8.35 (d, *J*[H,H] = 8 Hz, 2H). 8.10 (d, *J*[H,H] = 8 Hz, 2H), 7.27–7.23 (m, 4H), 2.42 ppm (s, 3H; C*H*$_3$); ^{13}C NMR (300 MHz; CDCl$_3$, 27°C, TMS): δ = 156.3 (*C*H=N), 149.2, 148.3, 141.8, 137.3, 130.0, 129.3, 124.0, 121.0, 21.1 (*C*H$_3$) ppm; HRMS (EI+): *m/z* calcd for $C_{14}H_{12}N_2O_2^+$: 240.0899 [M+]; found: 240.0896.

3.3.5 | SBA5 (E)-4-methyl-N-[3-nitrobenzylidene]aniline

Yield: 0.2378 g (99.0%); color: white solid; ^{1}H NMR (400 MHz, CDCl$_3$, 27°C, TMS): δ = 8.75 (s, 1H; C*H*=N), 8.58 (s, 1H), 8.34 (d, *J*[H,H] = 8 Hz, 1H), 8.27 (d, *J*[H,H] = 8 Hz, 1H), 7.69 (t, *J*[H,H] = 8 Hz, 1H), 7.25–7.20 (m, 4H), 2.42 ppm (s, 3H; C*H*$_3$); ^{13}C NMR (300 MHz; CDCl$_3$, 27°C, TMS): δ = 156.2 (*C*H=N), 148.7, 148.2, 138.1, 137.0, 134.0, 130.0, 129.8, 125.4, 123.4, 121.0, 21.1 (*C*H$_3$) ppm; HRMS (EI+): *m/z* calcd for $C_{14}H_{12}N_2O_2^+$: 240.0899 [M+]; found: 240.0896.

3.3.6 | SBA6 (E)-4-methyl-N-(2-nitrobenzylidene)aniline

Yield:0.2389 g (99.4%); color: light yellow-brown solid; ^{1}H NMR (400 MHz, CDCl$_3$, 27°C, TMS): δ = 8.98 (s, 1H; C*H*=N), 8.35 (d, *J*[H,H] = 8 Hz, 1H), 8.10 (d, *J*[H,H] = 8 Hz, 1H), 7.77 (t, *J*[H,H] = 8 Hz, 1H), 7.65 (t, *J*[H,H] = 8 Hz, 1H), 7.27–7.23 (m, 4H), 2.41 ppm (s, 3H; C*H*$_3$); ^{13}C NMR (300 MHz; CDCl$_3$, 27°C, TMS): δ = 154.8 (*C*H=N), 149.3, 148.5, 137.0, 133.5, 131.3, 131.0, 129.9, 129.7, 124.5, 121.2, 21.1 (*C*H$_3$) ppm; HRMS (EI+): *m/z* calcd for $C_{14}H_{12}N_2O_2^+$: 240.0899 [M+]; found: 240.0901.

3.3.7 | SBA7 (E)-4-([p-tolylimino]methyl) benzonitrile

Yield: 0.2185 g (99.2%); color: white solid; ^{1}H NMR (400 MHz, CDCl$_3$, 27°C, TMS): δ = 8.53 (s, 1H; C*H*=N), 8.03 (d, *J*[H,H] = 8 Hz, 2H), 7.78 (d, *J*[H,H] = 8 Hz, 2H), 7.26 (d, *J*[H,H] = 8 Hz, 2H), 7.21 (d, *J*[H,H] = 8 Hz, 2H), 2.41 ppm (s, 3H; C*H*$_3$); ^{13}C NMR (300 MHz; CDCl$_3$, 27°C, TMS): δ = 156.8 (*C*H=N), 148.4, 140.2, 137.0, 132.5, 129.9, 129.0, 120.9, 118.5, 114.2, 21.1 (*C*H$_3$) ppm; HRMS (EI+): *m/z* calcd for $C_{15}H_{12}N_2^+$: 220.1000 [M+]; found: 220.0999.

3.3.8 | SBA8 (E)-4-([p-tolylimino]methyl) phenol

Yield: 81% (^{1}H NMR estimation); color: white solid; ^{1}H NMR (400 MHz, CD$_3$OD, 27°C, TMS): δ = 8.44 (s, 1H; C*H*=N), 7.78 (d, *J*[H,H] = 8 Hz, 2H), 7.23 (d, *J*[H,H] = 8 Hz, 2H), 7.14 (d, *J*[H,H] = 8 Hz, 2H), 6.91 (d, *J*[H,H] = 8 Hz, 2H), 2.36 ppm (s, 3H; C*H*$_3$); HRMS (EI+): *m/z* calcd for $C_{14}H_{13}ON^+$: 211.0997 [M+]; found: 211.0993. Note: neither reactants nor Schiff-base signals were observed on both ^{1}H NMR and ^{13}C NMR spectra in CD$_3$OD. **SBA8** is insoluble in CDCl$_3$.

3.3.9 | SBA9 (E)-4-nitro-2-([p-tolylimino] methyl)phenol

Yield: 0.2531 g (98.8%); color: yellow solid; ^{1}H NMR (400 MHz, CDCl$_3$, 27°C, TMS): δ = 14.65 (s, 1H; O*H*), 8.72 (s, 1H; C*H*=N), 8.40 (s, 1H), 8.28–8.25 (m, 1H), 7.30–7.25 (m, 4H), 7.11 (d, *J*[H,H] = 8 Hz, 1H), 2.43 ppm (s, 3H; C*H*$_3$); ^{13}C NMR (300 MHz; CDCl$_3$, 27°C, TMS): δ = 167.05, 159.5 (*C*H=N), 143.9, 139.9, 138.4, 130.3, 128.2, 128.1, 121.1, 118.3, 118.2, 21.1 (*C*H$_3$) ppm; HRMS (EI+): *m/z* calcd for $C_{14}H_{12}O_3N_2^+$: 256.0848 [M+]; found: 256.0846.

3.3.10 | SBA10 (E)-N-[3,5-dibromobenzylidene]-4-methylaniline

Yield: 0.3494 g (99.0%); color: white solid; ^{1}H NMR (400 MHz, CDCl$_3$, 27°C, TMS): δ = 8.37 (s, 1H; C*H*=N), 8.00 (s, 2H), 7.77 (s, 1H), 7.25 (d, *J*[H,H] = 8 Hz, 2H), 7.17 (d, *J*[H,H] = 8 Hz, 2H), 2.41 ppm (s, 3H; C*H*$_3$); ^{13}C NMR (300 MHz; CDCl$_3$, 27°C, TMS): δ = 155.8 (*C*H=N), 148.3, 139.7, 136.8, 136.2, 131.2, 130.2, 129.9, 123.4, 120.9, 21.0 (*C*H$_3$) ppm; HRMS (EI+): *m/z* calcd for $C_{14}H_{11}(79)Br_2N^+$: 350.9250 [M+]; found: 350.9258.

3.3.11 | SBB1 (E)-4-([4-chlorobenzylidene] amino) benzonitrile

Yield: 0.2380 g (98.9%); color: white solid; ^{1}H NMR (400 MHz, CDCl$_3$, 27°C, TMS): δ = 8.39 (s, 1H; C*H*=N), 7.88 (d, *J*[H,H] = 8 Hz, 2H). 7.71 (d, *J*[H,H] = 8 Hz, 2H), 7.50 (d, *J*[H,H] = 8 Hz, 2H), 7.25 (d, *J*[H,H] = 8 Hz, 2H); ^{13}C NMR (300 MHz; CDCl$_3$, 27°C, TMS): δ = 160.9, 155.6 (*C*H=N), 138.4, 134.0, 133.8, 133.4, 130.9,130.3, 129.5, 129.3, 121.5, 118.9, 114.5, 109.3 ppm; HRMS (FAB+): *m/z* calcd for $C_{14}H_9ClN_2 + H^+$: 241.0533 $[M + H]^+$; found: 241.0527.

3.3.12 | SBB2 (E)-4-([4-bromobenzylidene] amino) benzonitrile

Yield: 0.27970 g (98.1%); color: white solid; ^{1}H NMR (400 MHz, CDCl$_3$, 27°C, TMS): δ = 8.38 (s, 1H; C*H*=N), 7.80 (d, *J*[H,H] = 8 Hz, 2H). 7.71 (d, *J*[H,H] = 8 Hz, 2H), 7.67 (d, *J*[H,H] = 8 Hz, 2H), 7.25 (d, *J*[H,H] = 8 Hz, 2H); ^{13}C NMR (300 MHz; CDCl$_3$, 27°C, TMS): δ = 161.1, 155.6 (*C*H=N), 134.4, 133.8, 133.4, 132.5, 132.3,131.0, 130.5, 127.0, 121.5, 118.9, 114.5, 109.4 ppm; HRMS (FAB+): *m/z* calcd for $C_{14}H_9(79)BrN_2 + H^+$: 285.0027 [M + H]$^+$; found: 285.0033.

3.3.13 | SBB3 (E)-4-([4-Iodobenzylidene] amino) benzonitrile

Yield: 32% (^{1}H NMR estimation); color: white solid; ^{1}H NMR (400 MHz, CDCl$_3$, 27°C, TMS): δ = 8.35 (s, 1H; C*H*=N), 7.88 (d, *J*[H,H] = 8 Hz, 2H). 7.71 (d, *J*[H,H] = 8 Hz, 2H), 7.65 (d, *J*[H,H] = 8 Hz, 2H), 7.25 (d, *J*[H,H] = 8 Hz, 2H); HRMS (FAB+): *m/z* calcd for $C_{14}H_9N_2I + H^+$: 332.9889 [M + H]$^+$; found: 332.9885.

3.3.14 | SBB4 (E)-4-([4-nitrobenzylidene] amino)benzonitrile

Yield: 72% (^{1}H NMR estimation); color: yellow solid; ^{1}H NMR (400 MHz, CDCl$_3$, 27°C, TMS): δ = 8.53 (s, 1H; C*H*=N), 8.38 (d, *J*[H,H] = 8 Hz, 2H). 8.13 (d, *J*[H,H] = 8 Hz, 2H), 7.75 (d, *J*[H,H] = 8 Hz, 2H), 7.31 (d, *J*[H,H] = 8 Hz, 2H); HRMS (FAB+): *m/z* calcd for $C_{14}H_9N_3O_2 + H^+$: 252.0773 [M + H]$^+$; found: 252.0778.

3.3.15 | SBB5 (E)-4-([3-nitrobenzylidene] amino)benzonitrile

Yield: 84% (^{1}H NMR estimation); color: white solid; ^{1}H NMR (400 MHz, CDCl$_3$, 27°C, TMS): δ = 8.78 (s, 1H; C*H*=N), 8.53 (s, 1H), 8.41 (d, *J*[H,H] = 8 Hz, 1H), 8.28 (d, *J*[H,H] = 8 Hz, 1H), 7.75–7.21 (m, 3H), 7.30 (d, *J*[H,H] = 8 Hz, 2H); HRMS (FAB+): *m/z* calcd for $C_{14}H_9N_3O_2 + H^+$: 252.0773 [M + H]$^+$; found: 252.0769.

3.3.16 | SBB6 (E)-4-methyl-N-(2-nitrobenzylidene)aniline

Yield: 0.2493 g (99.3%); color: light yellow-brown solid; ^{1}H NMR (400 MHz, CDCl$_3$, 27°C, TMS): δ = 8.93 (s, 1H; C*H*=N), 8.31 (d, *J*[H,H] = 8 Hz, 1H), 8.15 (d, *J*[H,H] = 8 Hz, 1H), 7.82 (t, *J*[H,H] = 8 Hz, 1H), 7.75–7.69 (m, 3H) 7.33 (d, *J*[H,H] = 8 Hz, 2H); HRMS (FAB+): *m/z* calcd for $C_{14}H_9N_3O_2 + H^+$: 252.0773 [M + H]$^+$; found: 252.0778.

3.3.17 | SBB7 (E)-4-([4-cyanobenzylidene] amino)benzonitrile

Yield: 0.2298 g (99.0%); color: white solid; ^{1}H NMR (400 MHz, CDCl$_3$, 27°C, TMS): δ = 8.47 (s, 1H; C*H*=N), 8.06 (d, *J*[H,H] = 8 Hz, 2H), 7.82 (d, *J*[H,H] = 8 Hz, 2H), 7.74 (d, *J*[H,H] = 8 Hz, 2H), 7.28 (d, *J*[H,H] = 8 Hz, 2H); HRMS (FAB+): *m/z* calcd for $C_{15}H_9N_3 + H^+$: 232.0875 [M + H]$^+$; found: 232.0878.

3.3.18 | SBB8 (E)-4-([4-hydroxybenzylidene] amino) benzonitrile

No product.

Note: **SBB8** did not show any azometine proton on the ^{1}H NMR spectra taken from CDCl$_3$ and CD$_3$OD.

3.3.19 | SBB9 (E)-4-([2-hydroxy-5-nitrobenzylidene]amino) benzonitrile

Yield: 64% (^{1}H NMR estimation); color: yellow solid; ^{1}H NMR (400 MHz, CDCl$_3$, 27°C, TMS): δ = 13.61 (s, 1H; O*H*), 8.74 (s, 1H; C*H*=N), 8.46 (s, 1H), 7.81 (d, *J*[H,H] = 8 Hz, 2H), 7.43 (d, *J*[H,H] = 8 Hz, 2H), 7.19–7.17 (m, 1H), 6.68 (d, *J*[H,H] = 8 Hz, 1H); HRMS (FAB+): HRMS (FAB+): *m/z* calcd for $C_{14}H_9O_3N_3 + H^+$: 268.0722 [M + H]$^+$; found: 268.0715.

3.3.20 | SBB10 (E)-4-([3,5-dibromobenzylidene]amino) benzonitrile

Yield: 50% (^{1}H NMR estimation); color: white solid; ^{1}H NMR (400 MHz, CDCl$_3$, 27°C, TMS): δ = 8.31 (s, 1H; C*H*=N), 8.00 (s, 2H), 7.95 (s, 1H), 7.44 (d, *J*[H,H] = 8 Hz, 2H), 7.25 (d, *J*[H,H] = 8 Hz, 2H); HRMS (FAB+): *m/z* calcd for $C_{14}H_8(79)Br_2N_2 + H^+$: 362.9132 [M + H]$^+$; found: 362.9135.

4 | CONCLUSIONS

In this work, attempts have been made to synthesize Schiff bases mechanochemically under solvent-free and solvent-assisted environments from systematically selected aromatic amines and aldehydes. Among the 20 solvent-free mechanochemical reactions between solid aromatic primary amines and aldehydes, 13 Schiff bases were produced with a greater than 98% yield, four Schiff bases obtained with good yield (60%–85%), and two Schiff bases were synthesized with less than 60% yield. However, one among 20 did not give any Schiff base product. Based on our previous study[8] and the investigation thereon**,** solvent-free mechanochemical synthesis is a powerful method for Schiff base synthesis; it is however, not the universal standard in Schiff base formation.

ACKNOWLEDGMENTS

This research was supported by Academia Sinica, Institute of Chemistry, Taiwan. The authors thank Dr. Jer-Yeu Lee at the Structural Chemistry laboratory, Institute of Chemistry, Academia Sinica, for his valuable support.

REFERENCES

[1] D. Margetic, V. Štrukil, *Mechanochemical Organic Synthesis*, 1s ed., Amsterdam: Elsevier, **2016**.
[2] T. K. Achar, A. Bose, P. Mal, *Beilstein J. Org. Chem.* **2017**, *13*, 1907.
[3] T. Friscic, *Chem. Soc. Rev.* **2012**, *41*, 3493.
[4] A. Delori, T. Friščić, W. Jones, *CrystEngComm* **2012**, *14*, 2350.
[5] O. Barreda, G. A. Taggart, C. A. Rowland, G. P. A. Yap, E. D. Bloch, *Chem. Mater.* **2018**, *30*, 3975.
[6] C. B. Aakeröy, A. S. Sinha, *RSC Adv.* **2013**, *3*, 8168.
[7] N. S. Radulović, A. B. Miltojević, R. D. Vukićević, *C. R. Chim.* **2013**, *16*, 257.
[8] G. T. Tigineh, Y.-S. Wen, L.-K. Liu, *Tetrahedron* **2015**, *71*, 170.
[9] M. Safarzaei, M. T. Maghsoodlou, E. Mollashahi, N. Hazeri, M. Lashkari, *J. Chin. Chem. Soc.* **2019**, *66*, 1.
[10] G. N. Hermann, P. Becker, C. Bolm, *Angew. Chem. Int. Ed. Engl.* **2016**, *55*, 3781.
[11] M. Tireli, M. Juribasic Kulcsar, N. Cindro, D. Gracin, N. Biliskov, M. Borovina, M. Curic, I. Halasz, K. Uzarevic, *ChemCommun (Camb)* **2015**, *51*, 8058.
[12] J. L. Do, T. Friscic, *ACS Central Sci.* **2017**, *3*, 13.
[13] P. Balaz, M. Balaz, M. Caplovicova, A. Zorkovska, L. Caplovic, M. Psotka, *Faraday Discuss.* **2014**, *170*, 169.
[14] L. Beraldo da SilveiraBalestrin, D. Del Duque, D. Soares da Silva, F. Galembeck, *Faraday Discuss.* **2014**, *170*, 369.
[15] R. G. Blair, K. Chagoya, S. Biltek, S. Jackson, A. Sinclair, A. Taraboletti, D. T. Restrepo, *Faraday Discuss.* **2014**, *170*, 223.
[16] P. J. Bygrave, D. H. Case, G. M. Day, *Faraday Discuss.* **2014**, *170*, 41.
[17] D. Daurio, K. Nagapudi, L. Li, P. Quan, F. A. Nunez, *Faraday Discuss.* **2014**, *170*, 235.
[18] A. Anonymous, *Faraday Discuss.* **2014**, *170*, 287.
[19] A. Anonymous, *Faraday Discuss.* **2014**, *170*, 71.
[20] A. Anonymous, *Faraday Discuss.* **2014**, *170*, 181.
[21] L. Ma, A. H. Hart, S. Ozden, R. Vajtai, P. M. Ajayan, *Faraday Discuss.* **2014**, *170*, 9.
[22] I. Halasz, T. Friscic, S. A. Kimber, K. Uzarevic, A. Puskaric, C. Mottillo, P. Julien, V. Strukil, V. Honkimaki, R. E. Dinnebier, *Faraday Discuss.* **2014**, *170*, 203.
[23] I. Z. Hlova, S. Gupta, J. F. Goldston, T. Kobayashi, M. Pruski, V. K. Pecharsky, *Faraday Discuss.* **2014**, *170*, 137.
[24] W. Jones, M. D. Eddleston, *Faraday Discuss.* **2014**, *170*, 9.
[25] L. Maini, P. P. Mazzeo, F. Farinella, V. Fattori, D. Braga, *Faraday Discuss.* **2014**, *170*, 93.
[26] A. A. Michalchuk, I. A. Tumanov, V. A. Drebushchak, E. V. Boldyreva, *Faraday Discuss.* **2014**, *170*, 311.
[27] D. W. Peters, R. G. Blair, *Faraday Discuss.* **2014**, *170*, 83.
[28] A. Politov, O. Golyazimova, *Faraday Discuss.* **2014**, *170*, 345.
[29] M. J. Rak, T. Friscic, A. Moores, *Faraday Discuss.* **2014**, *170*, 155.
[30] A. L. Ramirez, A. K. Schmitt, M. K. Mahanthappa, S. L. Craig, *Faraday Discuss.* **2014**, *170*, 337.
[31] S. W. Schmidt, M. F. Pill, A. Kersch, H. Clausen-Schaumann, M. K. Beyer, *Faraday Discuss.* **2014**, *170*, 357.
[32] V. Sepelak, M. Myndyk, R. Witte, J. Roder, D. Menzel, R. H. Schuster, H. Hahn, P. Heitjans, K. D. Becker, *Faraday Discuss.* **2014**, *170*, 121.
[33] T. Shiraki, C. E. Diesendruck, J. S. Moore, *Faraday Discuss.* **2014**, *170*, 385.
[34] H. Shy, P. Mackin, A. S. Orvieto, D. Gharbharan, G. R. Peterson, N. Bampos, T. D. Hamilton, *Faraday Discuss.* **2014**, *170*, 59.
[35] J. Stojakovic, B. S. Farris, L. R. MacGillivray, *Faraday Discuss.* **2014**, *170*, 35.
[36] A. Stolle, R. Schmidt, K. Jacob, *Faraday Discuss.* **2014**, *170*, 267.
[37] K. S. Suslick, *Faraday Discuss.* **2014**, *170*, 411.
[38] L. Takacs, *Faraday Discuss.* **2014**, *170*, 251.
[39] L. Trobs, F. Emmerling, *Faraday Discuss.* **2014**, *170*, 109.
[40] Y. Yamashita, L. C. Nam, M. J. Dutton, S. Yoshimoto, S. Kobayashi, *ChemCommun (Camb)* **2015**, *51*, 17064.
[41] K. G. Ozokan, M. K. Gumus, S. Kaban, *J. Heterocyclic Chem.* **2008**, *45*, 1831.
[42] J. Y. Mak, W. Xu, R. C. Reid, A. J. Corbett, B. S. Meehan, H. Wang, Z. Chen, J. Rossjohn, J. McCluskey, L. Liu, D. P. Fairlie, *Nat. Commun.* **2017**, *8*, 14599.
[43] K. K. Bania, G. V. Karunakar, L. Satyanarayana, *RSC Adv.* **2015**, *5*, 33185.
[44] A. M. Abu-Dief, I. M. A. Mohamed, *Beni-Suef University Journal of Basic and Applied Sciences* **2015**, *4*, 119.
[45] S. Kumar, D. N. Dhar, P. N. Saxena, *J. Sci. Ind. Res.* **2009**, *68*, 181.
[46] J. Zhang, F. Zhao, X. Zhu, W.-K. Wong, D. Ma, W.-Y. Wong, *J. Mater. Chem.* **2012**, *22*, 16448.
[47] H. F. Abd El-Halim, M. M. Omar, G. G. Mohamed, M. A. El-ElaSayed, *Eur. J. Chem.* **2011**, *2*, 178.
[48] E. Ali, M. R. Naimi-Jamal, M. G. Dekamin, *Scientia IranicaTrans. C: Chem. Chem. Eng.* **2013**, *20*, 592.
[49] J. Schmeyers, F. Toda, J. Boy, G. Kaupp, *J. Chem. Soc. Perkin Trans.* **1998**, *2*, 989.
[50] G. Rothenberg, A. P. Downie, C. L. Raston, J. L. Scott, *J. Am. Chem. Soc.* **2001**, *123*, 8701.
[51] H. E. Gottlieb, V. Kotlyar, A. Nudelman, *J. Org. Chem.* **1997**, *62*, 7512.
[52] A. Filarowski, A. Koll, T. Głowiak, *J. Mol. Struct.* **2003**, *644*, 187.
[53] M. Yıldız, Z. Kılıç, T. Hökelek, *J. Mol. Struct.* **1998**, *441*, 1.
[54] R. M. Silverstein, F. X. Webster, D. J. Kiemle, D. L. Bryce, *Spectrometric Identification of Organic Compounds* (8th, John Wiley & Sons, New York **2014**.
[55] G. T. Tigineh, L.-K. Liu, *J. Chin. Chem. Soc.* **2014**, *61*, 1180.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Tigineh GT, Liu L-K. Systematic studies on mechanochemical synthesis: Schiff bases from solid aromatic primary amines and aldehydes. *J Chin Chem Soc*. 2019;1–9. https://doi.org/10.1002/jccs.201800486