



Solid-phase synthesis of arylidene and alkylidene malonates, as versatile intermediates, catalyzed using mesoporous poly-melamine–formaldehyde as a nitrogen-rich porous organic polymer (POP)

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Abstract

An efficient solid/slurry-state synthesis of arylidene and alkylidene malonates as versatile intermediates is developed in the presence of mesoporous poly-melamine–formaldehyde. The condensation reaction was conducted through a ball milling process as a non-conventional procedure and a greener methodology at room temperature under solvent-free conditions. The mesoporous heterogeneous catalyst could be recovered and reused ten times, and the results showed a negligible loss of catalytic activity. Various aryl- and heteroarylidene malonates, as well as dimethyl (cyclohexylidene)malonate, were isolated in good to high yields under optimal conditions. The use of hazardous reagents and solvents were minimized in the current method, and separation of catalyst and products, as well as the recovery and reusing of catalyst, were performed by cost-effective procedures. This work revealed that the synergistic effect of numerous Lewis base sites together with acceptor-donor hydrogen bonding functional groups in porous organic polymer (POP), and its high porosity plays a vital role to promote the carbon–carbon coupling reaction in the solid phase synthesis.

Keywords Porous materials · Solid-Slurry synthesis · Heterogeneous catalysis · Carbon–carbon coupling · Sustainable process

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Introduction

Microwave and ultrasound irradiation along with the milling process has been mentioned as non-conventional processes in organic synthesis. In particular, ball milling as a mechanochemistry process has been extensively employed in organic synthesis as an eco-friendly, and greener approach to perform the organic synthesis, which can lead to minimize and reduce environmental concerns [1, 2]. The solid-phase synthesis using milling can be easily scaled up to gram/kilogram amount of reactants, which in turn is interested in industrial processes. Many previous reports have been indicated that ball milling leads to the use of small amount catalysts, shorter reaction times, and higher yield of desired products [2].

Design and introduce more efficient and greener methods for the preparing of intermediates and fine chemicals is one of the most important areas of chemistry research; for example, (a) the avoid or minimize the use of toxic reagents and volatile solvents, or conducting a reaction under solvent-free conditions, which leads to reduce the toxic and hazard waste generation, (b) the use of a small amount of catalyst, or the use of high recyclable catalysts, (c) conducting a reaction at room temperature to enhance the energy efficiency [3, 4].

The Knoevenagel condensation products bearing a carbon–carbon double bond have been widely employed as versatile and valuable organic intermediates in academic or industry fields [5, 6]. The Knoevenagel condensation reaction is often performed by a homogeneous system viz. into a solvent using organic bases such as aliphatic or cyclic amines and their salts, amino acids. The conventional catalyst of the Knoevenagel condensation reactions is piperidine which is used with or without acetic acid in an organic solvent. Homogeneous catalysts are not environmentally benign and sustainable since their separation from the reaction mixtures, and their recovery or recycling is difficult. The conventional procedure and some reported methods have limitations such as the use of flammable, volatile, and toxic solvents for the reaction or preparation of the catalyst, preparation of the catalysts using tedious and multi-step processes, utilization of expensive metal-based catalyst and generation of metal waste, etc.

Recently, our group fabricated and characterized mesoporous poly-melamine–formaldehyde (mPMF) as a nitrogen-rich porous organic polymer, which was applied successfully in several organic syntheses [7, 8]. Owing to the presence of numerous amination functional groups and triazine rings, mPMF contains the hydrogen bond donating-accepting agent and abundant Lewis base sites. In continuation of our interest in the synthesis of versatile intermediates through the Knoevenagel condensation reaction [9], herein, the catalytic performance of mPMF is successfully demonstrated for the preparation of aryl/heteroarylidene malonates and dimethyl (cyclohexylidene)malonate, as versatile intermediates in organic chemistry, under practical and environmental-friendly conditions using a Retsch PM100 planetary ball mill in a slurry-state. The mPMF is easy to handling and storage, and it can be easily separated from the Knoevenagel's products and recycled for at least ten runs. Based on the results of this work, mPMF can be an appropriate alternative to piperidine, a toxic liquid with high flammability in liquid and vapor states.

Results and discussion

The catalytic efficiency of mPMF in carbon–carbon coupling

The mPMF was fabricated according to the previous report in the literature [8]. The Brunauer–Emmett–Teller (BET) surface area and pore volume were determined to be 972.9 and 2.34 cm³ g^{−1} (See supplementary information, Figure S1). As seen in Figure S2, mPFM contains the micropores and mesopores based on its pore size distribution curve (See supplementary information).

The catalytic performance of mPMF was investigated for the synthesis of arylidene malonates via the Knoevenagel condensation of dimethyl malonate with aryl/ heteroaryl aldehydes and cyclohexane carboxaldehyde. We selected dimethyl malonate ($pK_a = 15.87$) [10] because it is a much weaker acid than malononitrile ($pK_a = 11.1$) [11], acetylacetone ($pK_a = 8.99$) [12], 5,5-dimethyl-1,3-cyclohexanedione (dimedone) ($pK_a = 5.23$) [13], Meldrum acid ($pK_a = 4.83$) [14], and barbituric acid ($pK_a = 4.01$) [15]. The Knoevenagel condensation of the 4-chlorobenzaldehyde and dimethyl malonate was studied under different conditions to find the optimized reaction conditions (Table 1).

Initially, the milling of model reactants was carried out using four balls (diameter 45 mm) at 600 revolutions per minute (rpm) by a planetary ball mill at room temperature in the absence of catalyst and solvent. The dimethyl 2-(4-chlorobenzylidene) malonate **2a** was detected in 35% conversion after six hours (Table 1, entry 1). In the presence of the porous organic polymers mPMF (50 mg, 7.6 wt. % based on dimethyl malonate) at room temperature after six hours, the conversion was improved to 75% (Table 1, entry 2). A conversion of 100% was obtained by increasing the amount of mPMF to 100 mg (Table 1, entry 3).

By shortening the milling time to three hours, there was no drop in the conversion (Table 1, entry 4), however, a sudden drop was observed in the conversion of **2a** within two hours (Table 1, entry 5). As shown in Table 1 entries 6–8,

Table 1 The results of Knoevenagel condensation of model reactants at different conditions.^a

Entry	(wt. % based on methyl malonate)	Number of ball mill	Revolutions per minute (rpm)	Ball diameter (mm)	Milling time (h)	Conversion (%)
1	0	4	600	5	6	35
2	7.6	4	600	5	6	75
3	15.1	4	600	5	6	100
4 ^b	15.1	4	600	5	3	100
5	15.1	4	600	5	2	72
6	15.1	4	400	5	3	78
7	15.1	2	600	5	3	56
8	15.1	2	600	7	3	62

^a Reaction conditions: 4-chlorobenzaldehyde **1a** (5.0 mmol), dimethyl malonate (5.0 mmol), room temperature

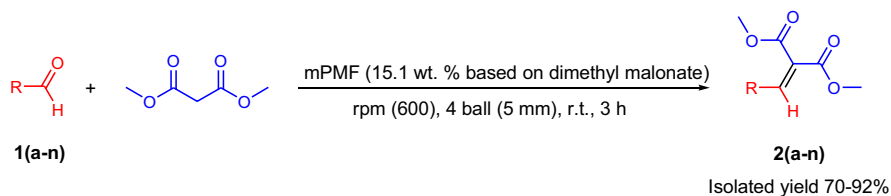
^b Selected optimal condition

the technical parameters also influence the conversion. Decreasing the speed and number of balls to 400 revolutions per minute (rpm) and two balls, respectively, led to a significant drop in conversion (Table 1, entries 6 and 7). The increase of the diameter of balls up to 7 mm also resulted in a 62% conversion (Table 1, entry 8). Entry 4 was chosen as the optimized reaction conditions (Table 1).

The substrate scope of the current method for the preparation of versatile intermediates **2(a–n)** was evaluated through the solid/slurry condensation of various aldehydes **1(a–n)** with dimethyl malonate in optimal conditions using a non-conventional process (Scheme 1). The reaction mixture often formed a dispersion of the catalyst in the liquid phase of reactants (slurry phase) rather than a solid phase because dimethyl malonate is a liquid and most of the aldehydes are liquid or have low melting points such as benzaldehyde, 4-methylbenzaldehyde, 4-methoxybenzaldehyde, 4-fluorobenzaldehyde, 4-(trifluoromethyl)benzaldehyde, cinnamaldehyde, cyclohexanecarboxaldehyde, and 4-chlorobenzaldehyde.

Various substituted aromatic aldehydes, as well as heteroaromatic aldehydes and cyclohexane carboxaldehyde, afforded high to excellent yields of the corresponding dimethyl malonates under optimized reaction conditions (Table 2). The heteroaromatic aldehydes such as pyridine-4-carboxaldehyde and 2,6-dichloropyridine-3-carboxaldehyde gave the desired arylidene malonates in 82 and 78% yield, respectively (Table 2, entries 6 and 12). The conjugated aldehyde such as cinnamaldehyde gave 84% yield with no isomerization (Table 2, entry 11). 4-Methoxybenzaldehyde, 4-dimethyl amino benzaldehyde, and 3,4,5-trimethoxybenzaldehyde were converted to the corresponding arylidene malonates in a somewhat lower yield due to their electron-rich rings (Table 2, entries 4, 9, and 13). A lower yield for 3,4,5-trimethoxybenzaldehyde can be also attributed to the steric hindrance of three methoxy groups. Dimethyl (cyclohexylidene)malonate was successfully isolated in 72% yield (Table 2, entry 14).

Based on a survey of the literature [18, 19], a possible catalytic mechanism is illustrated as shown in Scheme 2. The mMPF can act as a nucleophile and base toward the aldehyde and the dimethyl malonate through H-bonding, which resulted in the stability of the corresponding intermediate (**I**) (Scheme 2). In the second step, the water is eliminated from intermediate (**II**) which gives the corresponding arylidene or alkylidene malonates.



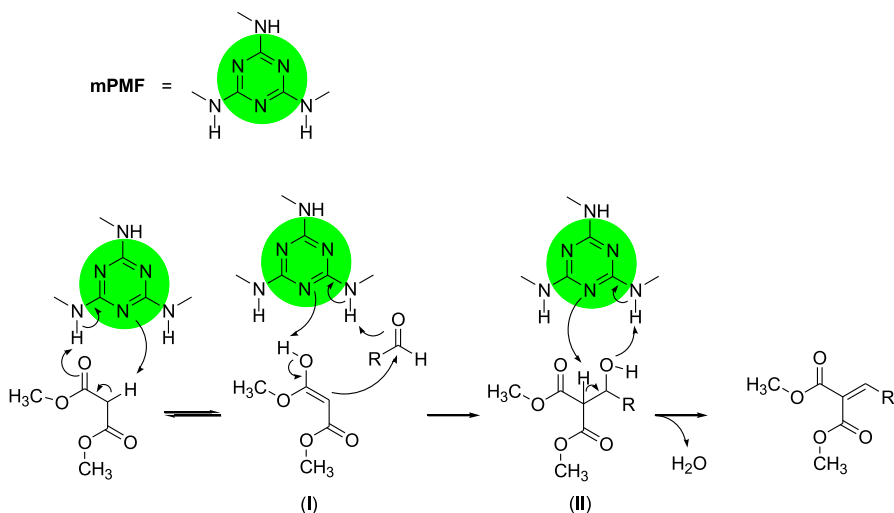
Scheme 1 Reaction conditions and isolated yield of desired products through the current protocol

Table 2 Substrate-scope of the Knoevenagel condensation of various aldehydes with methyl malonate using porous organic polymer mMPF.^a

Entry	Aldehydes 1(a-n)	Product 2(a-n)	Yield (%) ^b	Melting point (°C)		MS (ESI)
				Found	Reported [16, 17]	m/z [M + H] ⁺
1	4-Cl-C ₆ H ₄ -	a	92	36–38	36–37	255.0 and 257.0
2	C ₆ H ₅ -	b	88	39–40	40–41	221.1
3	4-CH ₃ -C ₆ H ₄ -	c	87	Oil	Oil	235.1
4	4-CH ₃ O-C ₆ H ₄ -	d	76	Oil	Oil	251.1
5	4-NO ₂ -C ₆ H ₄ -	e	92	134–136	135–136	266.1
6	4-Pyridinecarboxaldehyde	f	82	71–73	72–73	222.1
7	4-NC-C ₆ H ₄ -	g	86	95–96	97–98	246.1
8	4-CF ₃ -C ₆ H ₄ -	h	91	41–42	43–44	289.1
9	4-(CH ₃) ₂ N-C ₆ H ₄ -	i	74	85–87	86–87	264.1
10	4-F-C ₆ H ₄ -	j	88	36–38	38–39	239.1
11	C ₆ H ₅ -CH=CH-	k	84	80–82	81–82	247.1
12	2,6-Dichloropyridine-3-carboxaldehyde	l	78	75–77	–	290.1
13	3,4,5-(CH ₃ O) ₃ -C ₆ H ₂ -	m	70	36–37	–	311.3
14	(CH ₂) ₅ CH-	n	72	Oil	Oil	227.1

^a Chemicals including aldehyde **1(a-n)** (5.0 mmol), dimethyl malonate (5.0 mmol), and mMPF (100 mg) were ground at room temperature for 3 h by the use of four balls (5 mm) with revolution rate (600 rpm)

^b Isolated yield

**Scheme 2** A possible catalytic mechanism for the Knoevenagel condensation reaction using mMPF

Easy separable and recyclability of mPMF

The mPMF could be separated by vacuum filtration using a Büchner funnel after adding hot ethanol to the milling jar. The separated mPMF was washed with hot ethanol several times and dried at 50 °C overnight. The recovered mPMF was reused for ten successive runs. Dimethyl 2-(4-chlorobenzylidene)malonate **2a** was isolated in 88% yield after the 10th run which demonstrated high recyclability of mPMF.

Scale-up model Knoevenagel condensation reaction

Furthermore, a scale-up of the model reaction was investigated by the condensation of 4-chlorobenzaldehyde (7.03 g, 50 mmol) and dimethyl malonate (6.60 g, 50 mmol) in the presence of the mPMF (1.0 g) at room temperature under optimized mechanical parameters. The corresponding product **2a** was afforded in 78% yield (9.93 g) after three hours.

The superiority of the current protocol

In order to verify any advantage of using the mPMF, a comparison of the catalytic activity of mPMF and a few catalytic protocols was performed for some substrates in Table 2. Nanteuil and Waser reported a 76% yield of **2n** using a stoichiometry ratio of ammonium acetate/acetic acid at 60 °C after 20 h [17], whereas our protocol gave the same product in 72% yield at room temperature after 3 h using only 15 wt. % of mPMF. Sakai et al. obtained **2d** and **2 g** in 66 and 69% yield, respectively, using metal-containing catalyst viz. Indium(III) chloride/acetic anhydride in a toxic and flammable solvent (toluene) at 60 °C after 6 h [16]. The present protocol gave the same product of **2d** and **2 g** in 76 and 74% yields, respectively, at room temperature within 3 h under solvent-free conditions.

Experimental

Synthesis of dimethyl 2-(4-chlorobenzylidene)malonate (**2a**) by the current protocol

A mixture of 4-chlorobenzaldehyde (0.703 g, 5.0 mmol) (**1a**), dimethyl malonate (0.660 g, 5.0 mmol), and mPMF (100 mg) was added into a milling jar, and the slurry mixture was ground at 600 rpm in the presence of four balls (5 mm). The mPMF was separated by vacuum filtration using a Büchner funnel after adding 5 mL of hot ethanol to the milling jar. After washing of catalyst by ethanol (5 × 2 mL), mPMF was dried at 50 °C overnight under vacuum and reused in the subsequent runs. The crude products were purified by column chromatography (90:10 hexane/EtOAc) which gave the corresponding arylidene and alkylidene

malonates. All known products were approved by comparison of their melting point and ^1H NMR with the ones reported in the literature (Table 2, entries 1–11 and 14) [16, 17].

The spectra data of the new products

2-[2-(2,6-Dichloro-pyridine-3-yl)-vinyl]-dimethyl malonate (Table 2, entry 12): IR (KBr): ν_{max} 3095, 3052, 3016, 2961, 2854, 1730, 1710, 1637, 1574, 1544, 1454, 1440, 1426, 1368, 1347, 1274, 1228, 1195, 1140, 1077, 1069, 967 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.90 (s, 1H), 7.73 (d, $J=8.2$ Hz, 1H), 7.28 (dd, $J=8.0, 0.7$ Hz, 1H), 3.85 (s, 3H), 3.75 (s, 3H) ppm; ^{13}C NMR (150 MHz, CDCl_3) δ 165.2, 163.2, 151.5, 150.4, 139.5, 136.7, 130.8, 127.3, 123.2, 52.2, 52.0 ppm; $^{\text{I}}\text{MS}$ (ESI): m/z $[\text{M} + \text{H}]^+$ 290.1.

2-(3,4,5-Trimethoxy-benzylidene)-dimethyl malonate (Table 2, entry 13): IR (KBr): ν_{max} 3090, 3056, 3010, 2965, 2859, 1735, 1718, 1634, 1571, 1538, 1451, 1437, 1417, 1363, 1342, 1271, 1222, 1198, 1141, 1081, 1072, 965 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.61 (s, 1H), 6.64 (s, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 3.78 (s, 9H) ppm; ^{13}C NMR (150 MHz, CDCl_3) δ 167.37, 164.54, 153.31, 142.75, 140.44, 128.05, 124.61, 106.87, 60.96, 56.12, 52.71, 52.68 ppm; $^{\text{I}}\text{MS}$ (ESI): m/z $[\text{M} + \text{H}]^+$ 311.3.

^1H NMR of some known products

2-(4-chlorobenzylidene)-dimethyl malonate (Table 2, entry 1): ^1H NMR (600 MHz, CDCl_3) δ 7.71 (s, 1H), 7.35 (s, 4H), 3.85 (s, 6H) ppm.

2-(4-methyl-benzylidene)-dimethyl malonate (Table 2, entry 3): ^1H NMR (600 MHz, CDCl_3) δ 7.75 (s, 1H), 7.33 (d, $J=8.0$ Hz, 2H), 7.20 (d, $J=8.0, 0.7$ Hz, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 2.38 (s, 3H) ppm.

2-(4-methoxy-benzylidene)-dimethyl malonate (Table 2, entry 4): ^1H NMR (600 MHz, CDCl_3) δ 7.73 (s, 1H), 7.41 (d, $J=8.0$ Hz, 2H), 6.91 (d, $J=8.0, 0.7$ Hz, 2H), 3.88 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H) ppm.

2-(4-cyanobenzylidene)-dimethyl malonate (Table 2, entry 7): ^1H NMR (600 MHz, CDCl_3) δ 7.77 (s, 1H), 7.70 (d, $J=8.0$ Hz, 2H), 7.55 (d, $J=8.1$ Hz, 2H), 3.89 (s, 3H), 3.85 (s, 3H) ppm.

2-[4-(trifluoromethyl)benzylidene]-dimethyl malonate (Table 2, entry 8): ^1H NMR (600 MHz, CDCl_3) δ 7.78 (s, 1H), 7.66 (d, $J=8.0$ Hz, 2H), 7.54 (d, $J=8.0$ Hz, 2H), 3.88 (s, 3H), 3.85 (s, 3H) ppm.

(E)-2-(3-phenylallylidene)-dimethyl malonate (Table 2, entry 11): ^1H NMR (600 MHz, CDCl_3) δ 7.54 (d, $J=11.4$ Hz, 1H), 7.48 (d, $J=6.0$ Hz, 2H), 7.36–7.33 (m, 3H), 7.25 (dd, $J=15.6, 15.0$ Hz, 1H), 7.03 (d, $J=16.0$ Hz, 1H), 3.89 (s, 3H), 3.80 (s, 3H) ppm.

Cyclohexylidene-dimethyl malonate (Table 2, entry 14): ^1H NMR (600 MHz, CDCl_3) δ 6.86 (t, $J=10.2$ Hz, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 2.41–2.37 (m, 1H), 1.80–1.62 (m, 5H), 1.36–1.09 (m, 5H) ppm.

Conclusion

In conclusion, a new catalytic application of mesoporous poly-melamine–formaldehyde (mPMF) was demonstrated for the Knoevenagel condensation reaction at room temperature by a solid/slurry phase process. Avoid toxic, flammable, and corrosive reagents and solvents, a catalytic amount of the catalyst, easy separation of porous polymer catalyst, good to high yields of the desired products, wide scope of the substrate, metal-free, acid-free and solvent-free conditions are among most-valuable merits of the current methodology. Moreover, the cost-effectiveness and high recyclability of mPMF make it an interesting heterogeneous base catalyst for solid-phase organic synthesis. The conversion, selectivity, and catalytic efficiency of the current protocol were superior to some previous reports in the literature.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s11164-021-04476-w>.

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Declarations

Conflict of interest There are no conflicts of interest to declare.

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