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Caffeine-H_3PO_4: a novel acidic catalyst for various one-pot multicomponent reactions

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Abstract Caffeine-H_3PO_4 along with caffeine-$HClO_4$ and caffeine-HNO_3 have been prepared and applied for one-pot preparation of bis(indolyl) methanes, 4,4′-(arylmethylene) bis(1*H*-pyrazol-5-ols), 3,3′-(arylmethylene) bis(4-hydroxycoumarins), 2,4,5-trisubstituted imidazoles, 1-amidoalkyl-2-naphthols, and polyhydroquinolines. The catalysts were characterized using Fourier-transform infrared (FTIR) spectroscopy, ^{1}H and ^{13}C nuclear magnetic resonance (NMR), powder X-ray diffraction (PXRD) analysis, thermogravimetric analysis (TGA), and liquid chromatography (LC)–mass spectroscopy (MS) techniques. The results indicated high product yield, short reaction time, facile separation of catalyst, and easy work-up procedure, suggesting that caffeine-H_3PO_4 can be considered to be an efficient acidic catalyst for organic transformations.

Keywords Caffeine-H_3PO_4 · One-pot reaction · Solvent-free · Bis(indolyl) methanes · 1-Amidoalkyl-2-naphthols · Multicomponent reaction

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Introduction

The design of novel catalysts for particular tasks has attracted attention due to industrial needs for higher product yield and/or purity in shorter reaction time [1, 2]. Meanwhile, research on preparation of novel acidic catalysts such as ionic liquids [3], zeolites [4], metal–organic frameworks (MOFs) [5], and organocatalysts [6] has drawn attention recently.

Multicomponent reactions (MCRs) have been a focus of interest for organic and medicinal chemists recently, due to the simplicity and diversity they offer [7, 8]. Apart from their applications in synthesis, MCRs have also been applied as criteria for benchmarking novel catalysts, including acidic [9], basic [10], magnetic nanoparticle-supported [11], SBA-15-supported [12], and MOF-supported materials [13], as well as ionic liquids [14].

Solvent-free organic reactions have been proposed as a solution to environmental concerns regarding use of organic solvents [15]. Solvent-free multicomponent synthesis enables organic and medicinal chemists to prepare biologically active scaffolds that are traditionally synthesized using a sequence of separate reaction steps. The synergism of performing multicomponent reactions under solvent-free conditions would be considered beneficial due to the simple monitoring of the reaction, ability to perform the reaction at any temperature due to the absence of solvent, simple reaction setup, and easy workup [16].

In continuation of our previous work on applications of novel catalysts in organic synthesis [17, 18], we decided to investigate one-pot preparation of bis(indolyl) methanes, 4,4′-(arylmethylene) bis(1*H*-pyrazol-5-ols), 3,3′-(arylmethylene) bis(4-hydroxycoumarins), 2,4,5-trisubstituted imidazoles, 1-amidoalkyl-2-naphthols, and polyhydroquinolines in presence of catalytic amount of caffeine-H_3PO_4 under solvent-free conditions (Scheme 1).

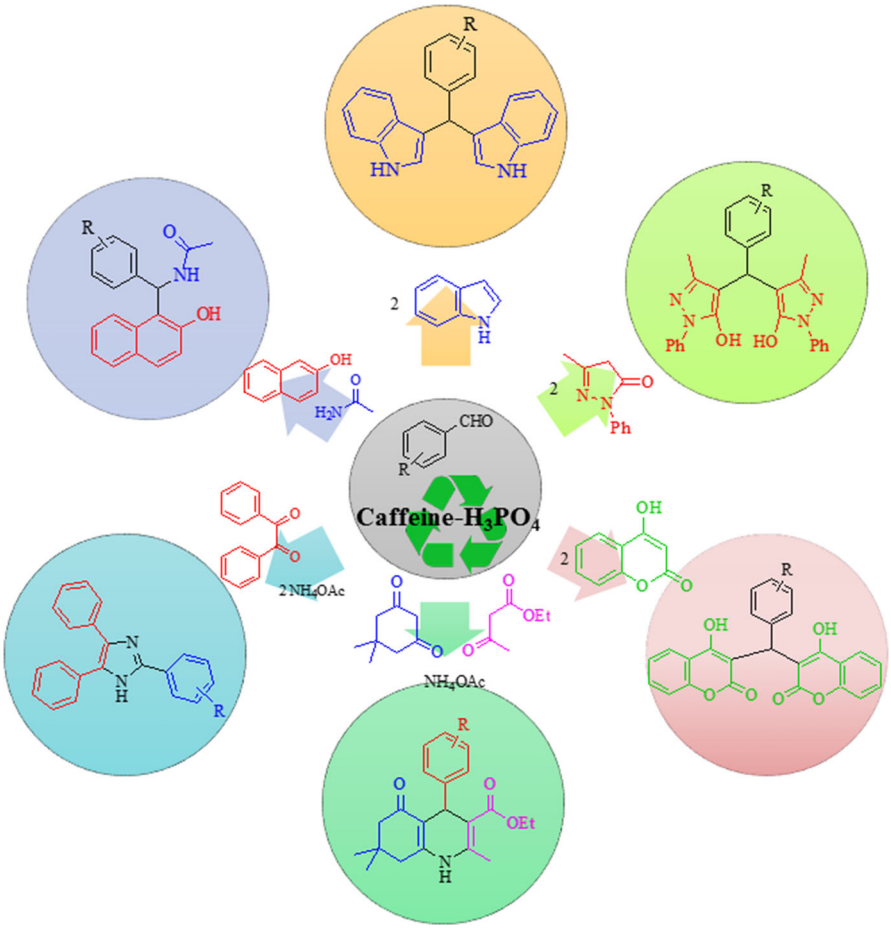
Results and discussion

In the first step, caffeine-H_3PO_4, caffeine-$HClO_4$, and caffeine-HNO_3 were prepared by dropwise addition of concentrated phosphoric acid, perchloric acid, and nitric acid, respectively, to solution of caffeine in $CHCl_3$. The mixture was stirred overnight, and the precipitate was filtered and washed with acetone (Scheme 2). The catalysts were characterized by FTIR spectroscopy. The characteristic peaks of caffeine due to amide functional groups at 1654 and 1697 cm^{-1} were apparent in the spectra, with a slight shift to higher wavenumber (Figs. 1, 2, 3).

The thermal stability of the catalysts was evaluated by thermogravimetric analysis (TGA). Degradation of caffeine-H_3PO_4, caffeine-$HClO_4$, and caffeine-HNO_3 was observed to start at 268, 306, and 250 °C.

To confirm that the caffeine molecule remained intact, ^{13}C NMR of caffeine-H_3PO_4 was carried out, revealing the characteristic peaks in the spectrum (Fig. S1).

In the LC–MS spectrum, the caffeine-H^+ peak was seen at *m*/*z* of 194.9 (100 %) and 195.9 (11.4 %).

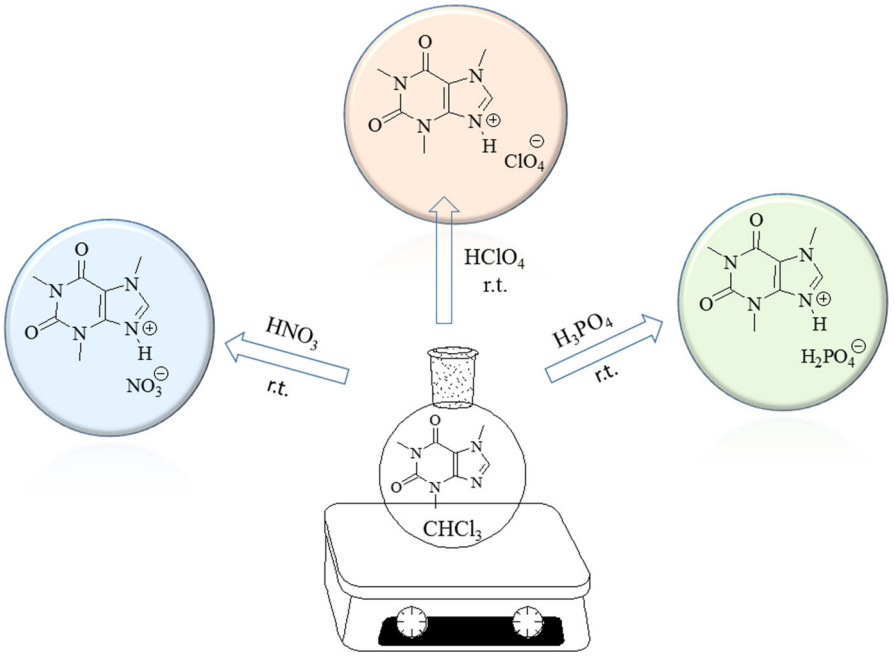


Scheme 1 One-pot preparation of bis(indolyl) methanes, 4,4′-(arylmethylene) bis(1*H*-pyrazol-5-ols), 3,3′-(arylmethylene) bis(4-hydroxycoumarins), 2,4,5-trisubstituted imidazoles, 1-amidoalkyl-2-naphthols, and polyhydroquinolines

Finally the powder X-ray diffraction (XRD) patterns of caffeine and caffeine-H_3PO_4 were recorded (Fig. 4).

After successful characterization of caffeine-H_3PO_4, caffeine-$HClO_4$, and caffeine-HNO_3, it was decided to utilize these catalysts for synthesis in various one-pot organic reactions.

First, preparation of polyhydroquinoline via reaction of benzaldehyde (1 mmol), dimedone (1 mmol), ethyl acetoacetate (1 mmol), and NH_4OAc (1.5 mmol) in presence of caffeine-H_3PO_4, caffeine-$HClO_4$, and caffeine-HNO_3 was utilized to benchmark the catalysts. The catalytic activity of caffeine-H_3PO_4 was superior compared with the other catalysts. It appears that caffeine-$HClO_4$ and caffeine-HNO_3, which have a nonacidic counterion, did not show good catalytic activity. In contrast, caffeine-H_3PO_4, which has an acidic counterion, showed excellent acidic



Scheme 2 One-pot preparation of caffeine-H_3PO_4, caffeine-$HClO_4$, and caffeine-HNO_3

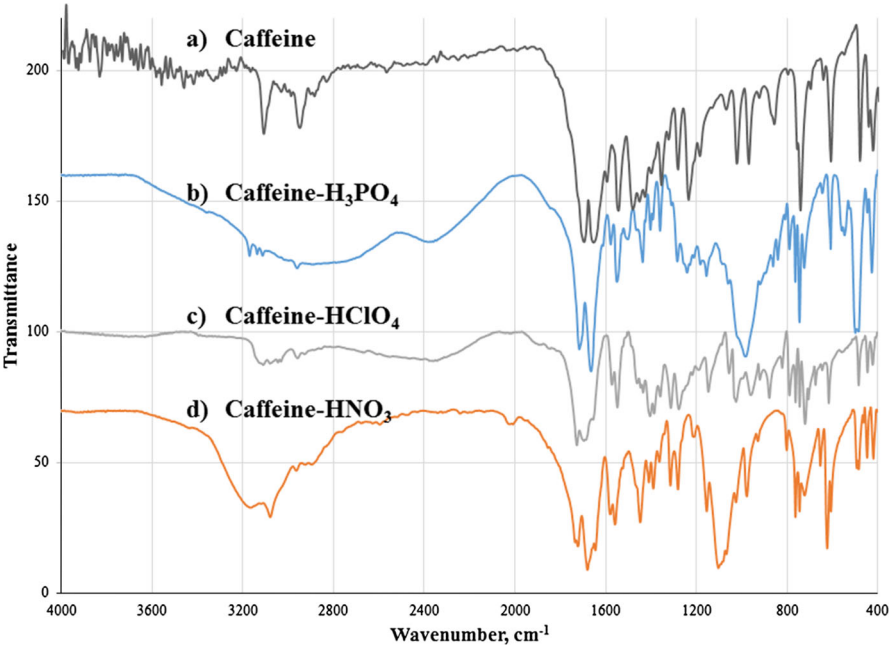


Fig. 1 FTIR spectra of *a* caffeine, *b* caffeine-H_3PO_4, *c* caffeine-$HClO_4$, and *d* caffeine-HNO_3

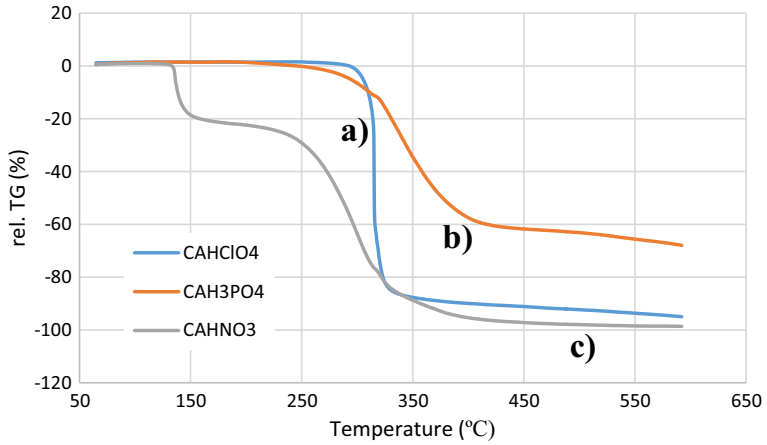


Fig. 2 Thermogravimetry of *a* caffeine-$HClO_4$, *b* caffeine-H_3PO_4, and *c* caffeine-HNO_3

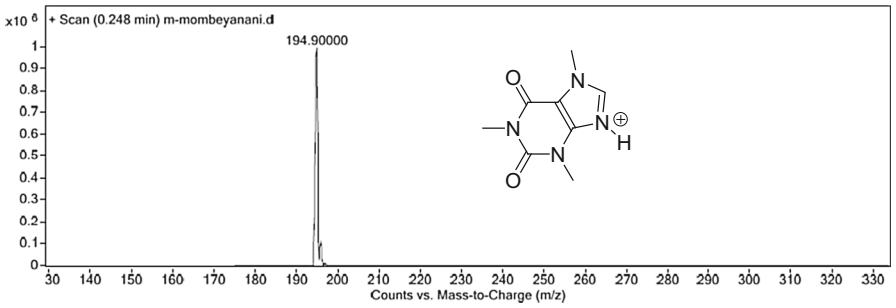


Fig. 3 LC–MS spectrum of caffeine-H^+

activity. Thus, considering that the catalyst remained intact in the reaction medium, it seems that caffeine-$HClO_4$ and caffeine-HNO_3 act as organocatalysts via the caffeine-H^+ core. On the other hand, caffeine-H_3PO_4, which has an acidic counterion, can act as both an organocatalyst and Brønsted acid. These synergistic effects make caffeine-H_3PO_4 the preferred catalyst. The optimized condition was found to be reaction temperature of 100 °C and amount of catalyst of 7.5 mol%. Increasing the amount of catalyst or temperature neither increased the yield nor shortened the time substantially (Table 1). Therefore, with the optimized reaction condition in hand, we explored the efficiency of caffeine-H_3PO_4 for one-pot preparation of polyhydroquinoline derivatives via Hantzsch condensation (Table 2).

After this successful preparation of polyhydroquinoline derivatives using the catalyst, it was decided to explore its activity in one-pot preparation of 1-amidoalkyl-2-naphthols. The results are summarized in Table 3.

Using the same method as mentioned above, the catalytic activity of caffeine-H_3PO_4 was also evaluated in one-pot synthesis of 2,4,5-trisubstituted imidazoles, showing satisfactory results (Table 4).

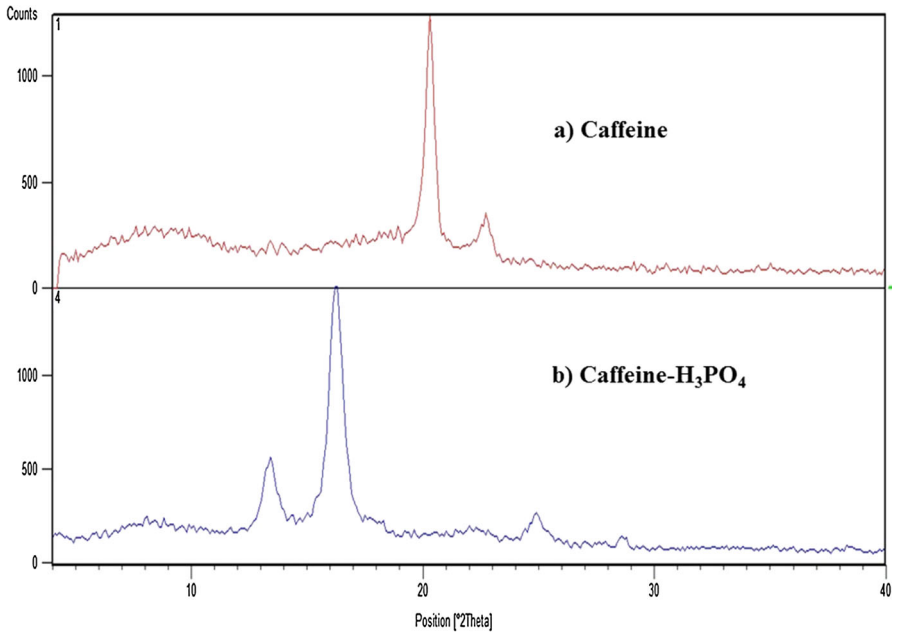


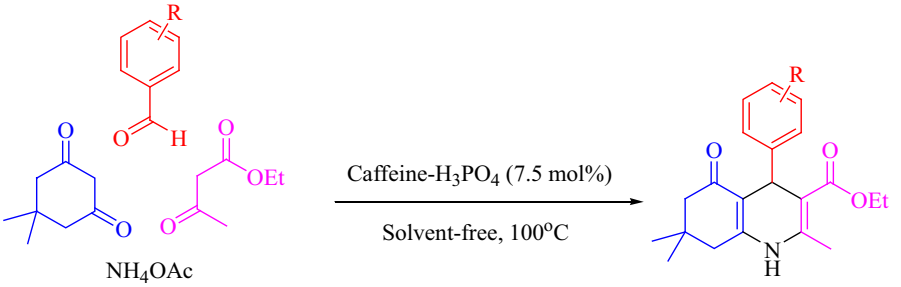
Fig. 4 Powder XRD patterns of *a* caffeine and *b* caffeine-H_3PO_4

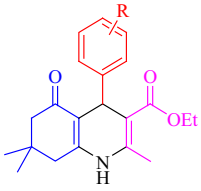
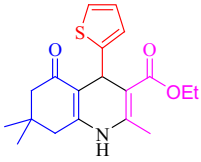
Table 1 Optimization of conditions for preparation of polyhydroquinoline via reaction of benzaldehyde (1 mmol), dimedone (1 mmol), ethyl acetoacetate (1 mmol), and NH_4OAc (1.5 mmol)

Entry	Catalyst	Catalyst (mol%)	Temp. (°C)	Time (min)	Yield (%)
1	–	–	R.T.	120	–
2	Caffeine-H_3PO_4	5	60	60	68
3	Caffeine-$HClO_4$	5	60	60	35
4	Caffeine-HNO_3	5	60	60	42
5	Caffeine-H_3PO_4	5	100	30	85
6	Caffeine-$HClO_4$	5	100	30	54
7	Caffeine-HNO_3	5	100	30	50
8	Caffeine-H_3PO_4	7.5	100	25	96
9	Caffeine-H_3PO_4	10	100	20	91
10	Caffeine-H_3PO_4	15	100	20	97

For the last set of reactions to assess the catalyst's activity, we selected one-pot preparation of bis(indolyl) methanes (Table 5), 4,4′-(arylmethylene) bis(1*H*-pyrazol-5-ols) (Table 6), and 3,3′-(arylmethylene) bis(4-hydroxycoumarins) (Table 7). The optimum reaction temperature was found to be 80 °C. The corresponding products were prepared in presence of caffeine-H_3PO_4.

Table 2 Conditions for preparation of polyhydroquinolines via reaction of aromatic aldehydes (1 mmol), dimedone (1 mmol), ethyl acetoacetate (1 mmol), and NH_4OAc (1.5 mmol) in presence of caffeine-H_3PO_4 (7.5 mol%) at 100 °C under solvent-free conditions



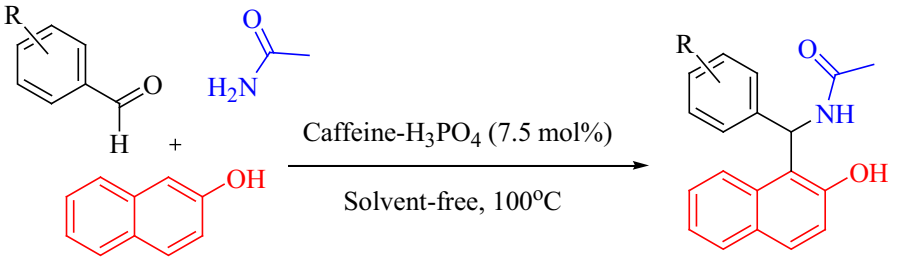
Entry	Product	R	Time (min)	Yield (%)	Melting point (°C)	
					Obtained	Reported
1a		H	25	96	203–205	202–204 [19]
2a		4-Me	18	94	261–263	260–262 [19]
3a		4-OMe	19	91	256–257	255–257 [19]
4a		4-OH	22	89	229–231	230–231 [19]
5a		2-Cl	27	86	208–210	207–209 [19]
6a		4-Cl	24	90	231–233	230–232 [19]
7a		$2,4\text{-}Cl_2$	18	92	242–244	242–243 [20]
8a		$4\text{-}NO_2$	18	95	237–239	238–240 [19]
9a		$3\text{-}NO_2$	17	92	182–184	178–180 [19]
10a		4-Br	21	89	254–255	252–254 [19]
11a			22	87	233–235	239–240 [20]

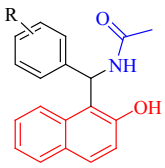
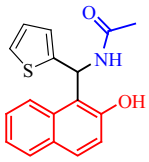
Given the increasing regard being paid to green chemistry, we decided to study the recyclability and reusability of the catalyst in preparation of 3,3′-(aryl-methylene) bis(4-hydroxycoumarins). After completion of the reaction, water was evaporated and the catalyst was reused for four subsequent cycles. A small decrease in performance of the catalyst was observed in subsequent cycles (Fig. 5).

To confirm the intactness of the catalyst, the FTIR spectrum of caffeine-H_3PO_4 was recorded (Fig. 6). The catalyst did not change during the course of the reaction. Thus, caffeine-H_3PO_4 can be considered to be an efficient recyclable green catalyst for organic synthesis.

To identify the advantages of using caffeine-H_3PO_4 compared with reported catalysts, the model reaction of aromatic aldehydes, dimedone, ethyl acetoacetate, and NH_4OAc for preparation of polyhydroquinolines was considered as a

Table 3 Conditions for preparation of 1-amidoalkyl-2-naphthols via reaction of aromatic aldehydes (1 mmol), β-naphthol (1 mmol), and acetamide (1.5 mmol) in presence of caffeine-H_3PO_4 (7.5 mol%) at 100 °C under solvent-free conditions



Entry	Product	R	Time (min)	Yield (%)	Melting point (°C)	
					Obtained	Reported
1b		H	40	90	244–246	242–243 [21]
2b		4-CH_3	40	87	217–219	220–221 [21]
3b		4-OCH_3	40	88	181–183	184–186 [21]
4b		3-OCH_3	60	88	204–206	203–205 [22]
5b		2-Cl	40	90	215–217	210–211 [21]
6b		4-Cl	30	92	223–224	224–226 [21]
7b		2,4-Cl_2	30	90	229–230	225–227 [22]
8b		4-Br	40	95	226–227	226–229 [23]
9b		3-NO_2	30	88	237–238	243–245 [21]
10b		4-NO_2	30	89	244–245	245–246 [21]
11b			25	85	222–223	222–224 [33]

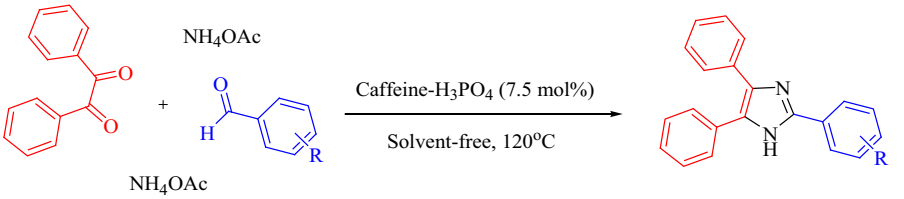
representative example (Table 8). Compared with the caffeine-H_3PO_4-catalyzed procedure, some of the reported procedures required prolonged reaction time (entries 1, 2, 5) or gave lower product yield (entries 1, 2, 4, 5). These results obviously demonstrate that caffeine-H_3PO_4 could be used as a novel catalyst for organic transformations.

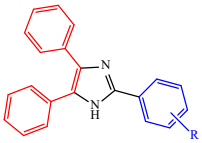
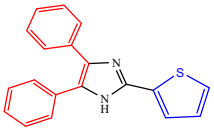
Experimental

General

All commercially available chemicals were purchased from Sigma and Merck companies and used without further purification. Products were characterized based

Table 4 Conditions for preparation of 2,4,5-trisubstituted imidazoles via reaction of aromatic aldehydes (1 mmol), benzil (1 mmol), and NH_4OAc (1.5 mmol) in presence of caffeine-H_3PO_4 (7.5 mol%) at 120 °C under solvent-free conditions

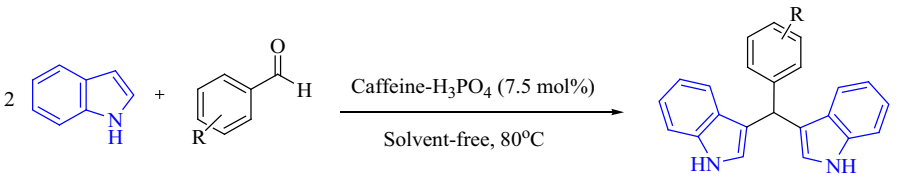


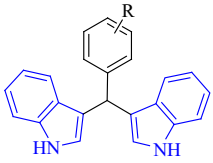
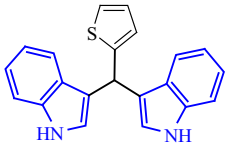
Entry	Product	R	Time (min)	Yield (%)	Melting point (°C)	
					Obtained	Reported
1c		H	50	93	269–270	272–274 [24]
2c		4-CH_3	100	91	229–230	232–234 [24]
3c		4-OCH_3	100	95	226–228	230–231 [24]
4c		3-OCH_3	100	89	258–260	259–262 [25]
5c		2-Cl	100	94	192–193	192–193 [26]
6c		4-Cl	100	92	260–261	261–263 [24]
7c		2,4-Cl_2	110	93	175–177	170–172 [25]
8c		4-Br	90	94	261–263	263–265 [25]
9c		3-NO_2	55	94	261–262	262–264 [24]
10c		4-NO_2	100	92	232–264	236–238 [26]
11c			40	74	260–262	261–264 [25]

on their physical constants and comparison with authentic samples. Reaction monitoring was carried out by TLC on silica gel POLYGRAM SIL G/UV254 plates. FTIR spectra were recorded on a BOMEM MB-Series 1998 spectrophotometer using KBr pellets as samples in the range of 4000 to 400 cm^{-1}. ^1H and ^{13}C NMR spectra were recorded in dimethylsulfoxide (DMSO)-d_6 on a Bruker 250 MHz spectrometer using tetramethylsilane (TMS) as internal standard. The thermal stability of the supported catalyst was examined using a BÄHR SPA 503 thermogravimetric analyzer at heating rate of 10 °C min^{-1} over the temperature range of 40–600 °C under nitrogen atmosphere. The LC-MS spectrum was recorded using an Agilent 6410 triple-quadrupole LC/MS.

General procedure for preparation of caffeine-H_3PO_4, caffeine-$HClO_4$, and caffeine-HNO_3 In a 25-mL round-bottomed flask, caffeine (1.94 g, 10 mmol) was dissolved in 20 mL $CHCl_3$, and the solution was stirred for 1 h. Concentrated phosphoric/perchloric/nitric acid (10 mmol) was added to the flask. The mixture was stirred overnight at room temperature. The precipitate was centrifuged and

Table 5 Conditions for preparation of bis(indolyl) methanes via reaction of aromatic aldehydes (1 mmol) and indole (2 mmol) in presence of caffeine-H_3PO_4 (7.5 mol%) at 80 °C under solvent-free conditions



Entry	Product	R	Time (min)	Yield (%)	Melting point (°C)	
					Obtained	Reported
1d		H	75	95	129–131	128–130 [27]
2d		4-Me	70	80	96–98	90–92 [28]
3d		4-OMe	64	82	185–187	186–188 [27]
4d		3-OMe	70	89	164–166	163–165 [27]
5d		2-Cl	65	93	91–92	94–95 [27]
6d		4-Cl	60	92	82–84	86–88 [27]
7d		2,4-Cl_2	55	94	105–108	103–106 [28]
8d		4-NO_2	65	96	236–238	237–239 [27]
9d		3-NO_2	70	93	219–221	220–222 [27]
10d		4-Br	65	89	110–112	110–112 [27]
11d			55	85	144–146	140–143 [28]

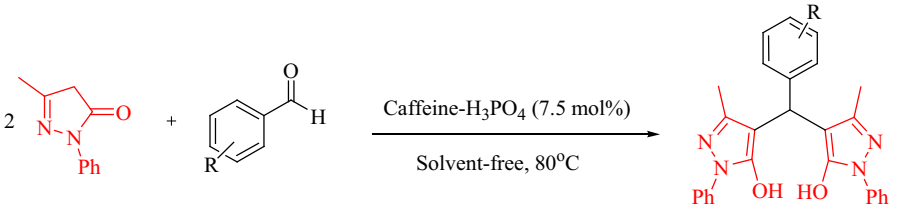
washed several times with $CHCl_3$ and finally with acetone. Finally, white solid powder (caffeine-H_3PO_4, caffeine-$HClO_4$, or caffeine-HNO_3) was obtained and dried at 60 °C for 12 h.

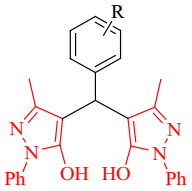
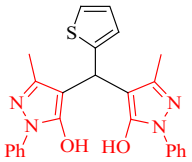
Spectra of catalysts

Caffeine-H_3PO_4, white powder, M.P. 138 °C, IR (KBr, cm^{-1}): 3171, 2960, 2857, 2360, 1717, 1666, 985, 745, 484; ^{1}H NMR (250 MHz, DMSO-*d6*): δ (ppm) 3.12 (s, 3H, CH_3), 3.31 (s, 3H, CH_3), 3.79 (s, 3H, CH_3), 7.8 (s, 1H, ArH), 9.1 (s, 3H, H_3PO_4); ^{13}C NMR (62.5 MHz, DMSO-*d6*): δ (ppm) 155.2, 151.72, 148.7, 143.4, 107.3, 33.8, 30.1, 28.2; LC-MS (ESI, positive mode) *m*/*z* (%): 194.9 (M^+, 100), 195.9 ($M+1^+$, 11).

Caffeine-HNO_3, white powder, M.P. 145 °C (color change to orange), IR (KBr, cm^{-1}): 3083, 2958, 2344, 1726, 1688, 1549, 1406, 1390, 1110, 763, 623; ^{1}H NMR (250 MHz, DMSO-*d6*): δ (ppm) 3.11 (s, 3H, CH_3), 3.31 (s, 3H, CH_3), 3.79 (s, 3H,

Table 6 Conditions for preparation of 4,4′-(arylmethylene) bis(1*H*-pyrazol-5-ols) via reaction of aromatic aldehydes (1 mmol) and 3-methyl-5-pyrazolone (2 mmol) in presence of caffeine-H_3PO_4 (7.5 mol%) at 80 °C under solvent-free conditions



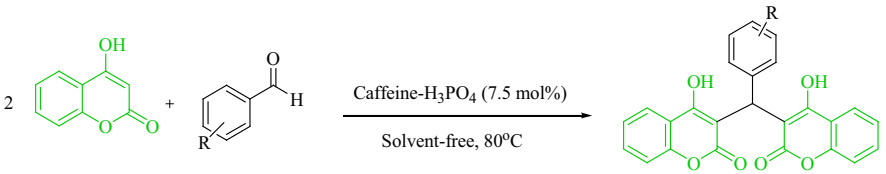
Entry	Product	R	Time (min)	Yield (%)	Melting point (°C)	
					Obtained	Reported
1e		H	75	91	167–169	167–169 [27]
2e		4-Cl	65	92	206–208	206–208 [27]
3e		3-NO_2	60	80	148–150	148–150 [27]
4e		4-NO_2	55	83	224–226	224–226 [27]
5e		4-CH_3	60	85	201–202	202–204 [29]
6e		3-CH_3O	70	85	192–194	192–194 [27]
7e		4-CH_3O	70	91	173–175	173–175 [27]
8e		2,4-Cl_2	60	82		228–230 [30]
9e			60	90	183–184	181–183 [29]

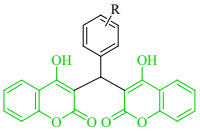
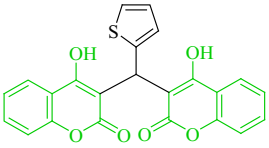
CH_3), 7.94 (s, 1H, ArH), 11.85 (s, 1H, HNO_3); ^{13}C NMR (62.5 MHz, DMSO-*d6*): δ (ppm) 155.8, 152.4, 149.2, 144.0, 107.9, 34.5, 30.8, 28.8; LC-MS (ESI, positive mode) *m*/*z* (%): 194.9 (M^+, 100), 195.9 ($M+1^+$, 11).

Caffeine-$HClO_4$, white powder, M.P. >150 °C, IR (KBr, cm^{-1}): 3165, 3076, 2960, 2890, 1723, 1680, 1646, 1540, 1448, 1100, 763, 622; ^{1}H NMR (250 MHz, DMSO-*d6*): δ (ppm) 3.15 (s, 3H, CH_3), 3.35 (s, 3H, CH_3), 3.82 (s, 3H, CH_3), 6.43 (s, 1H, $HClO_4$), 7.95 (s, 1H, ArH); ^{13}C NMR (62.5 MHz, DMSO-*d6*): δ (ppm) 155.9, 152.4, 149.4, 144.1, 107.9, 34.6, 30.8, 28.9; LC-MS (ESI, positive mode) *m*/*z* (%): 194.9 (M^+, 100), 195.9 ($M+1^+$, 11).

General procedure for preparation of polyhydroquinolines Mixture of dimedone (0.14 g, 1 mmol), ethyl acetoacetate (0.13 g, 1 mmol), aromatic aldehydes (1 mmol), ammonium acetate (0.115, 1.5 mmol), and caffeine-H_3PO_4 (0.022 g, 7.5 mol%) was heated at 100 °C. Reaction completion was indicated by TLC [EtOAc/*n*-hexane (3:10)], after which the mixture was washed with water and the crude product was recrystallized in hot ethanol to afford the pure product.

Table 7 Conditions for preparation of 3,3′-(arylmethylene) bis(4-hydroxycoumarins) via reaction of aromatic aldehydes (1 mmol) and 4-hydroxycoumarin (2 mmol) in presence of caffeine-H_3PO_4 (7.5 mol%) at 80 °C under solvent-free conditions



Entry	Product	R	Time (min)	Yield (%)	Melting point (°C)	
					Obtained	Reported
1f		H	60	95	228–230	232–234 [27]
2f		4-Cl	60	87	256–258	257–259 [27]
3f		3-NO_2	48	86	235–236	236–238 [27]
4f		4-NO_2	45	90	227–231	233–235 [27]
5f		4-CH_3	60	80	266–268	266–268 [31]
6f		3-CH_3O	50	92	255–257	256–258 [27]
7f		4-CH_3O	65	88	244–246	249–251 [27]
8f		2,4-Cl_2	60	95	201–203	200–202 [32]
9f			60	89	199–201	210–212 [32]

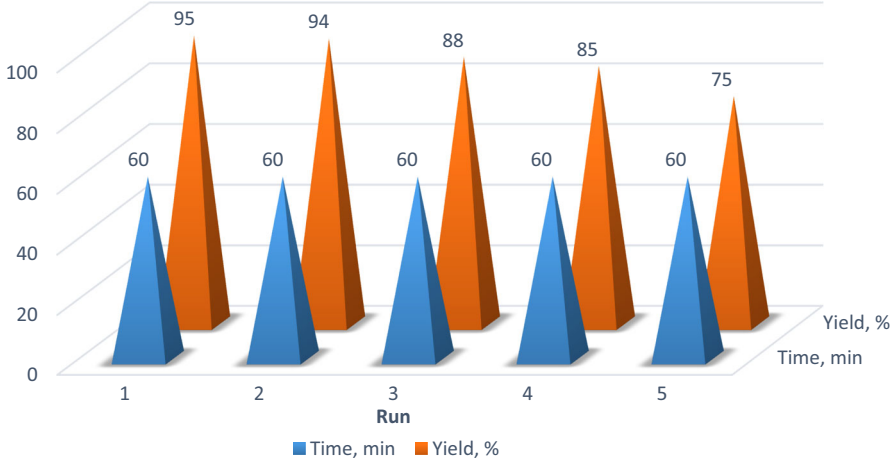


Fig. 5 Reusability of catalyst in reaction of 4-hydroxycoumarin (2.0 mmol) and benzaldehyde (1.0 mmol) in presence of caffeine-H_3PO_4 (7.5 mol%) at 80 °C under solvent-free conditions

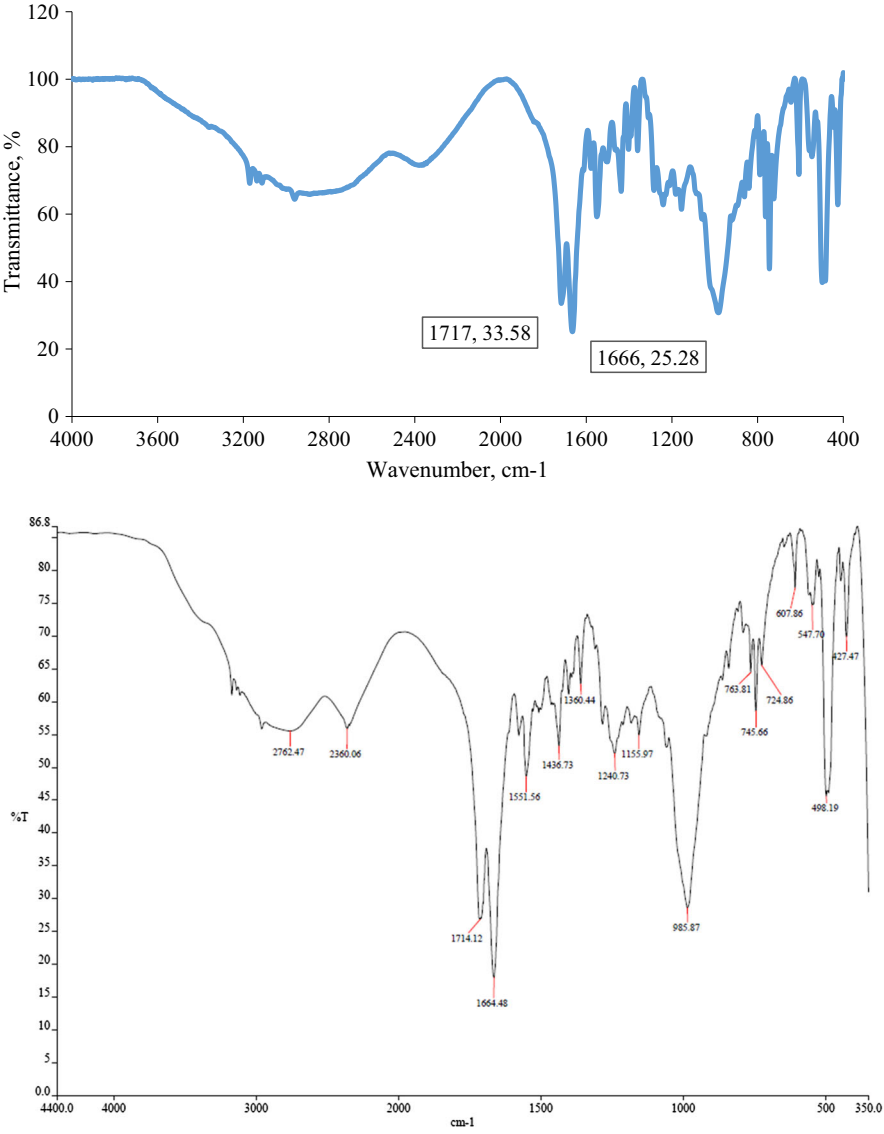


Fig. 6 FTIR spectra of fresh (*above*) and recycled (*below*) caffeine-H_3PO_4 catalyst

2,7,7-Trimethyl-5-oxo-4-thiophen-2-yl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester ***(11a)*** ^{1}H NMR (DMSO-d_6, 250 MHz): δ 0.92 (s, 3H), 0.99 (s, 3H), 1.16 (t, $J = 7$ Hz, 3H, -$OCH_2\underline{CH_3}$), 2.12 (dd, $J = 22$ Hz, 2H), 2.27 (s, 3H), 2.41 (dd, $J = 15$ Hz, 2H), 4.04 (q, $J = 7$ Hz, 2H, -$OCH_2\underline{CH_3}$), 5.18 (s, 1H), 6.65–7.14 (m, 3H, thiophene), 9.23 (s, 1H); ^{13}C NMR (DMSO-d_6, 62.5 MHz): δ 194.7, 167.1, 152, 150.3, 145.9, 126.7, 123.7, 123, 109.9, 103.5, 59.6, 50.6, 32.5, 31, 29.6, 27, 18.7, 14.7.

Table 8 Comparison of caffeine-H_3PO_4 with reported catalysts for preparation of polyhydroquinolines via reaction of aromatic aldehydes, dimedone, ethyl acetoacetate, and NH_4OAc

Entry	Catalyst/temp. (°C)	Catalyst loading (mol%)	Time (min)	Yield (%)	Refs.
1	Glucosulfonic acid@Fe_3O_4/ethanol, reflux	0.05 g	240	90	[34]
2	$Sc(OTf)_3$/ethanol, R.T.	5	240	93	[35]
3	Fe_3O_4–DETA–Cu(II)/90 °C solvent-free	0.22	50	96	[36]
4	PPA-SiO_2/80 °C solvent-free	0.03 g	45	92	[37]
5	*p*-TSA, ethanol, R.T.	10	120	90	[38]
6	Caffeine-H_3PO_4/100 °C solvent-free	7.5	25	96	This work

General procedure for preparation of 2,4,5-trisubstituted imidazoles Mixture of benzil (0.21 g, 1 mmol), aromatic aldehydes (1 mmol), ammonium acetate (0.19 g, 2.5 mmol), and caffeine-H_3PO_4 (0.022 g, 7.5 mol%) was heated at 120 °C. Reaction completion was indicated by TLC [EtOAc/*n*-hexane (3:10)], after which the mixture was washed with water and the crude product was recrystallized in hot ethanol to afford the pure product.

4,5-Diphenyl-2-(thiophen-2-yl)-1H-imidazole ***(11c)*** ^{1}H NMR (DMSO-d_6, 250 MHz): δ 7.11–8.64 (m, 13H, ArH), 12.76 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 62.5 MHz): δ 192.2, 142, 137.6, 135.9, 134.4, 131.3, 130, 129.9, 128.9, 128.6, 128.3, 127.5, 126.7, 124.7, 124.5.

General procedure for preparation of 1-amidoalkyl-2-naphthols Mixture of β-naphthol (0.14 g, 1 mmol), aromatic aldehydes (1 mmol), acetamide (0.09 g, 1.5 mmol), and caffeine-H_3PO_4 (0.022 g, 7.5 mol%) was heated at 100 °C. Reaction completion was indicated by TLC [EtOAc/*n*-hexane (3:10)], after which the mixture was washed with water and the crude product was recrystallized in hot ethanol to afford the pure product.

N-((2-Hydroxynaphthalen-1-yl)(thiophen-2-yl)methyl)acetamide ***(11b)*** ^{1}H NMR (DMSO-d_6, 250 MHz): δ 1.92 (s, 3H), 6.71 (s, 1H), 6.86–7.79 (m, 9H, ArH), 8.6 (d, 1H, ArOH), 12.76 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 62.5 MHz): δ 192.3, 169.3, 153.5, 147.5, 135.3, 132.4, 131.4, 129, 128.8, 124.8, 124.5, 123.5, 122.9, 118.8, 45.4, 23.

General procedure for preparation of bis(indolyl) methanes, 4,4′-(arylmethylene) bis(1H-pyrazol-5-ols), or 3,3′-(arylmethylene) bis(4-hydroxycoumarins) In a test tube, a mixture of indole or 3-methyl-1-phenyl-5-pyrazolone or 4-hydroxycoumarin (2 mmol), aromatic aldehydes (1 mmol), and caffeine-H_3PO_4 (0.022 g, 7.5 mol%) was heated at 80 °C in an oil bath. Reaction completion was indicated by TLC [EtOAc/*n*-hexane (3:10)], after which the mixture was washed with water and the crude product was recrystallized in hot ethanol to afford the pure product.

Selected spectra

4,4′-[(2-Thienyl)methylene]bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (9e) ^{1}H NMR (DMSO-d_6, 250 MHz): δ 2.30 (s, 6H), 5.12 (s, 1H), 6.74–7.71 (m, 13H, ArH), 13.99 (brs, 2H); ^{13}C NMR (DMSO-d_6, 62.5 MHz): δ 147.91, 146.29, 137.70, 129.39, 127.22, 126.11, 124.60, 1211.02, 105.46, 29.9, 11.93.

3,3′-(Thiophen-2-ylmethylene)bis(4-hydroxy-2H-chromen-2-one) ***(9f)*** ^{1}H NMR (DMSO-d_6, 250 MHz): δ 6.50 (s, 1H), 6.71–7.92 (m, 11H, ArH), 10.33 (brs, 2H); ^{13}C NMR (DMSO-d_6, 62.5 MHz): δ 166.1, 164.8, 152.6, 145.8, 132.4, 126.9, 124.5, 124.4, 124.2, 124.1, 118.4, 116.4, 104.7, 33.14.

3,3′-(Thiophen-2-ylmethylene)bis(1H-indole) (**11d**) ^{1}H NMR (DMSO-d_6, 250 MHz): δ 6.16 (s, 1H), 6.86–7.42 (m, 11H, ArH), 10.89 (s, 2H); ^{13}C NMR (DMSO-d_6, 62.5 MHz): δ 150.0, 136.9, 126.8, 125.1, 124.2, 123.7, 121.4, 119.6, 118.7, 118.6, 111.9, 35.4.

Conclusions

Caffeine-H_3PO_4 was prepared and applied for one-pot preparation of bis(indolyl) methanes, 4,4′-(arylmethylene) bis(1*H*-pyrazol-5-ols), 3,3′-(arylmethylene) bis(4-hydroxycoumarins), 2,4,5-trisubstituted imidazoles, 1-amidoalkyl-2-naphthols, and polyhydroquinolines. The high product yield, short reaction time, facile separation of catalyst, and easy workup procedure indicate that caffeine-H_3PO_4 can be considered to be an efficient acidic catalyst for organic transformations.

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