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Caffeine-H_2SO_4: a novel dual acidic catalyst for one-pot preparation of 2*H*-indazolo[2,1-*b*]phthalazinetriones

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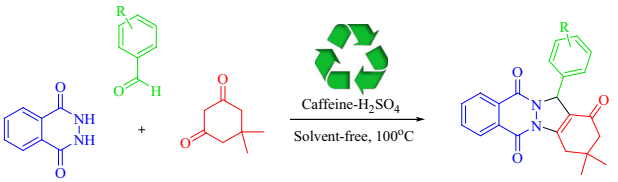
Abstract Caffeine-H_2SO_4 was prepared as a novel dual acidic catalyst. The catalytic activity of caffeine-H_2SO_4 was evaluated in one-pot preparation of 2*H*-indazolo[2,1-*b*]phthalazinetriones. The catalyst was also characterized by Fourier-transform infrared (FT-IR) and ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy and thermogravimetric analysis (TGA). According to the obtained results including reaction time, yield, and recyclability, caffeine-H_2SO_4 can be considered an efficient catalyst for organic transformations.

Graphical Abstract One-pot preparation of 2*H*-indazolo[2,1-*b*]phthalazinetriones



Keywords Caffeine-H_2SO_4 · One-pot reaction · Solvent-free · 2*H*-indazolo[2,1-*b*]phthalazinetriones · Phthalhydrazide

Introduction

Recently, organic chemists have become more interested in multicomponent reactions (MCRs) due to their simplicity, high product yield, one-pot synthesis, and ecofriendly reaction conditions [1]. Due to the great potential of MCRs in designing

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novel organic reactions [2], different strategies have been devised, including use of solvent-free conditions [3], application of homogeneous or heterogeneous catalysts [4], or performing reactions in unconventional solvents [5].

Due to environmental concerns regarding organic solvents, solvent-free organic reactions have been devised as an alternative tool for organic synthesis, particularly from the viewpoint of green chemistry. Reduced pollution, lower cost, and simplicity in process and workup are some advantages of solid-state (or solvent-free) synthesis [6]. The possibility to perform multicomponent reactions under solvent-free conditions using a heterogeneous catalyst could offer enhanced efficiency from an economic as well as ecological point of view [3, 7].

Recently, multicomponent preparation of 2*H*-indazolo[2,1-*b*]phthalazinetriones via one-pot reaction of aromatic aldehydes, phthalhydrazide, and dimedone was reported by Bazgir et al., using *p*-toluenesulfonic acid (*p*-TSA) as catalyst [8]. Due to phthalazine's pharmacological and biological effects, such as antimicrobial [9], anticonvulsant [10], antifungal [11], anticancer [12], and antiinflammatory [13] activities, different catalysts have been proposed for preparation of these derivatives [14–25].

In continuation of our previous work on applications of novel catalysts in organic synthesis [26–29], we decided to investigate synthesis of 2*H*-indazolo[2,1-*b*]phthalazinetriones in presence of catalytic amounts of caffeine-H_2SO_4 under solvent-free conditions (Scheme 1).

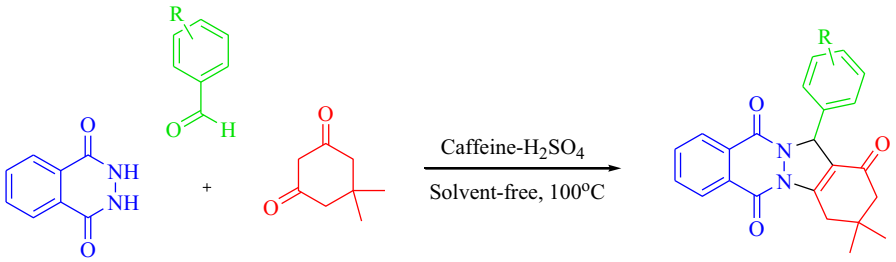
Results and discussion

Caffeine-H_2SO_4 was easily prepared by addition of conc. H_2SO_4 to solution of caffeine in CH_2Cl_2 with subsequent stirring for 24 h. Caffeine-H_2SO_4 is introduced as a novel bioinspired acidic catalyst, using preparation of 2*H*-indazolo[2,1-*b*]phthalazinetriones as a sample reaction.

In the first step, the catalyst was characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, and TGA. In the FT-IR spectrum of caffeine-H_2SO_4, the characteristic peaks of caffeine were apparent, while a wide peak was seen in the region of 2060–2673 cm^{-1}, as also reported for caffeine-HCl [30] (Fig. 1).

To confirm retention of the caffeine structure in the catalyst without deterioration or decomposition, ^{1}H and ^{13}C NMR spectra were used. In the ^{13}C NMR spectra, the characteristic peaks of caffeine were seen [30–32] (Fig. 2). The broad peak at δ 10.8–11.3 ppm in the ^{1}H NMR spectrum is attributed to N-9, which has accepted the proton from sulfuric acid. The peak at δ 9.2 ppm in the ^{1}H NMR spectrum is attributed to HSO_4^- counterion, displaced (along with the broad peak of NH) to δ 6.3 ppm after deuterium exchange.

Due to the importance of the thermal stability of catalysts and as a final qualification tool, thermogravimetric analysis (TGA) of caffeine-H_2SO_4 was investigated (Fig. 3). According to the TGA diagram, the catalyst started to decompose at about 290 °C. Thus, the catalyst can be used without danger of decomposition at temperatures below 290 °C.



Scheme 1 Three-component reaction of dimedone, phthalhydrazide, and aromatic aldehydes

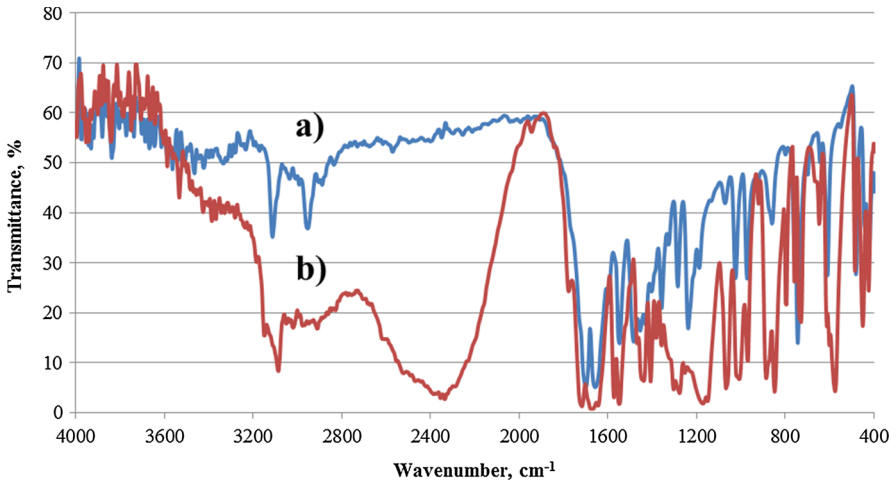


Fig. 1 FT-IR spectra of (*a*) caffeine and (*b*) caffeine-H_2SO_4

To investigate the optimal reaction conditions, solvent-free reaction of benzaldehyde (1.1 mmol), phthalhydrazide (1 mmol), and dimedone (1 mmol) was evaluated in absence and presence of caffeine-H_2SO_4. The obtained results are presented in Table 1. With different catalyst amounts of 1.7–6.8 mol% (5–20 mg) in the range from room temperature to 120 °C, the optimum reaction condition was obtained as 100 °C with 3.4 mol% catalyst. Use of greater amounts of catalyst did not lead to considerable changes in yield or reaction time. It should also be mentioned that the reaction did not proceed at room temperature, while at 60 and 80 °C the yield was not satisfactory. Although performing the reaction at 120 °C decreased the reaction time, the yield was also lowered compared with at 100 °C.

With optimum reaction conditions in hand, it was decided to evaluate the ability of caffeine-H_2SO_4 to catalyze some phthalazinetrione derivatives. Accordingly, the reaction with some electron-withdrawing as well as electron-donating groups was examined under optimum reaction conditions. Fortunately, the corresponding products were prepared in minimum reaction time and high yield (Table 2).

Although different aldehydes were used, the reaction times for electron-withdrawing and electron-donating groups were comparable. According to the

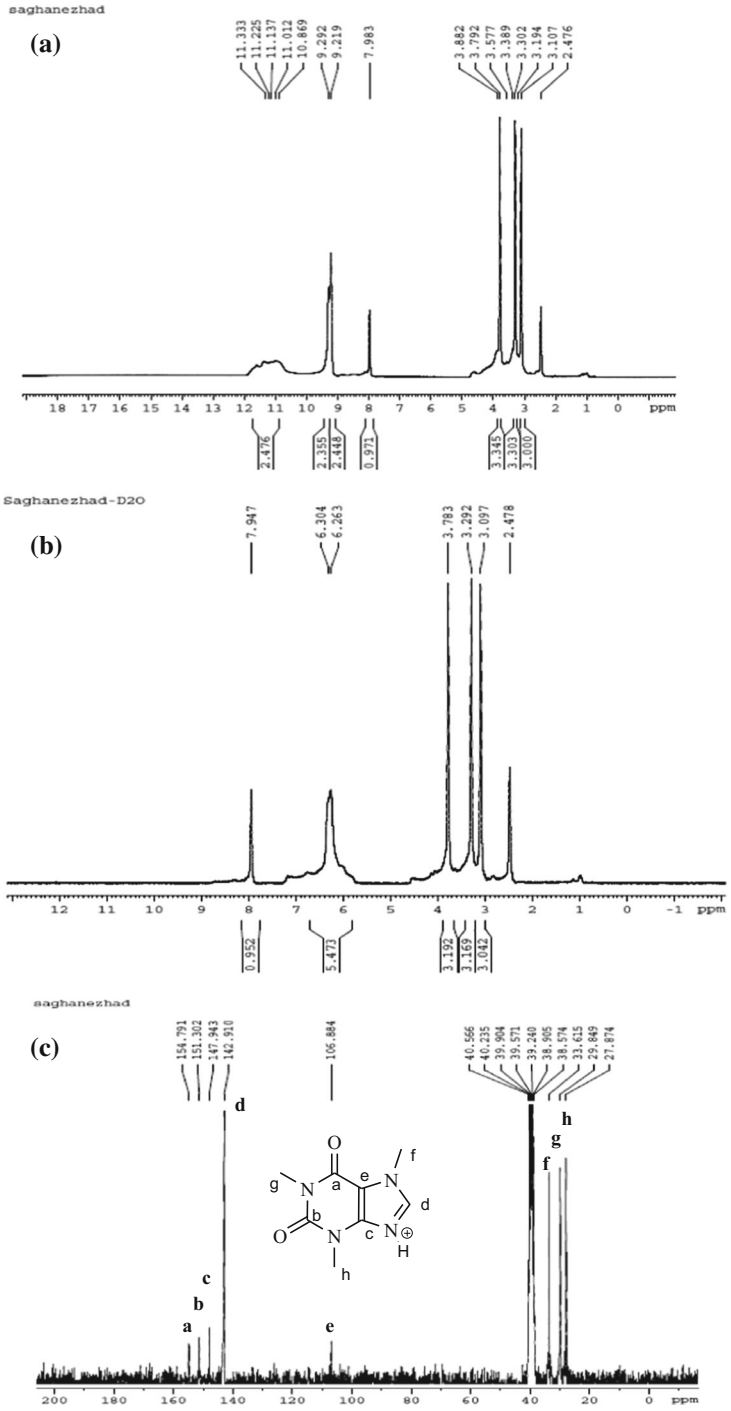


Fig. 2 **a** ^{1}H NMR, **b** ^{1}H NMR (D_2O addition), and **c** ^{13}C NMR (in DMSO-d_6) spectra of caffeine-H_2SO_4

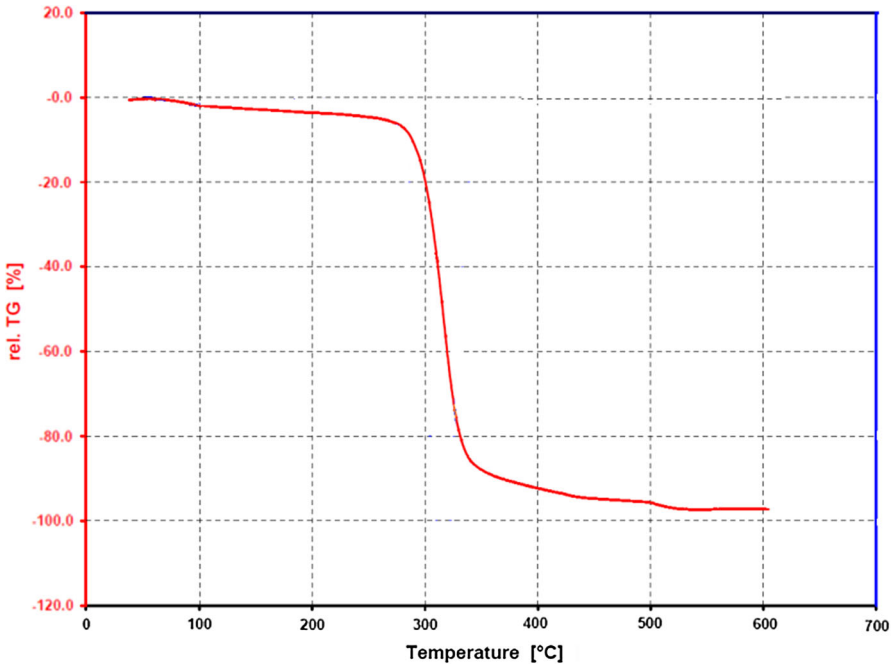


Fig. 3 TGA of caffeine-H_2SO_4

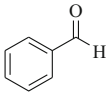
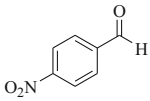
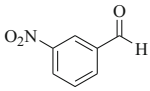
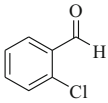
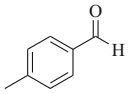
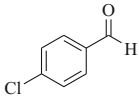
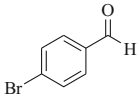
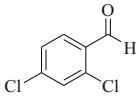
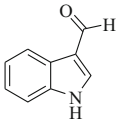
Table 1 Optimization of reaction conditions for reaction of benzaldehyde, dimedone, and phthalhydrazide in presence of caffeine-H_2SO_4 under solvent-free condition

Entry	Catalyst (mol%)	Temp. (°C)	Time (min)	Yield (%)
1	–	100	60	–
2	1.7	100	45	88
3	3.4	100	15	96
4	5.1	100	15	94
5	6.8	100	10	92
6	3.4	25	60	–
7	3.4	60	60	42
8	3.4	80	60	73
9	3.4	120	10	91

postulated mechanism, the reaction starts with keto–enol tautomerization of dimedone with subsequent Knoevenagel condensation. In the second step, Michael addition of phthalhydrazide is probable. The last step includes cyclization with subsequent dehydration to yield the product. Thus, because of the negligible impact of aldehyde substituted groups in this process, the reaction time was almost similar for all substituted groups (Scheme 2).

The reusability of the catalyst in the reaction of dimedone, phthalhydrazide, and benzaldehyde, under solvent-free condition at 100 °C, was evaluated. In this

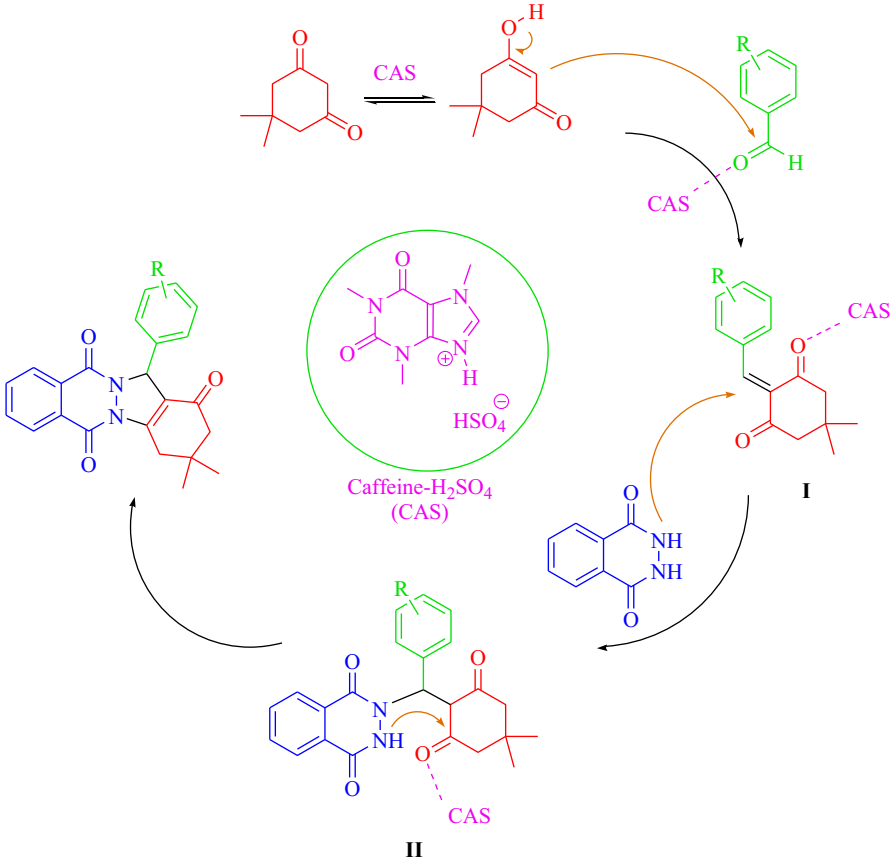
Table 2 One-pot preparation of 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione derivatives promoted by caffeine-H_2SO_4 under solvent-free condition at 100 °C

Entry	RCHO	Time (min)	Yield (%)
1		15	96
2		10	90
3		10	93
4		15	94
5		20	89
6		10	95
7		10	90
8		15	88
9		15	89
10[a]		120	45

[a] Due to the low boiling point of such aliphatic aldehydes, the components should be mixed at room temperature for 15 min in presence of the catalyst prior to reaction

procedure, after completion of each reaction, 5 mL water was added and the mixture was stirred for 5 min. After centrifuging the mixture, water was decanted. The catalyst was obtained by evaporation of water under reduced pressure. The recovered catalyst was washed with acetone, dichloromethane, dried, and reused for five times. Mild depression in the catalytic activity of the catalyst was observed after the fifth time of reuse (Fig. 4).

To compare the advantages of use of caffeine-H_2SO_4 over reported catalysts, the model reaction of dimedone, phthalhydrazide, and benzaldehyde was considered as



Scheme 2 Plausible reaction mechanism for preparation of 2*H*-indazolo[2,1-*b*]phthalazinetriones in the presence of caffeine-H_2SO_4 at 100 °C

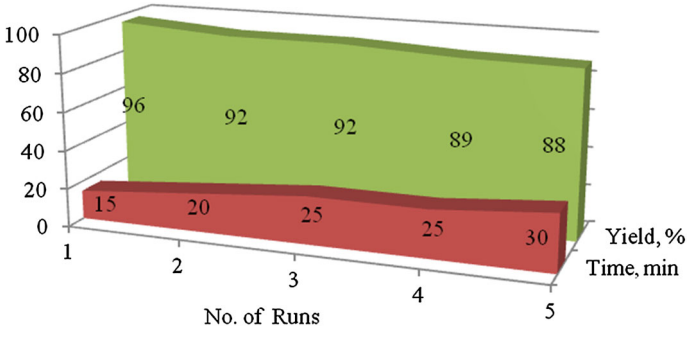


Fig. 4 Recyclability of caffeine-H_2SO_4

a representative example (Table 3). Compared with the caffeine-H_2SO_4-catalyzed procedure, some of the reported procedures required high catalyst loading (entries 1, 3) or had lower product yield (entries 1, 3, 5). These results clearly demonstrate that caffeine-H_2SO_4 can be considered an efficient catalyst for this three-component reaction.

Experimental

General

All commercially available chemicals were purchased from Fluka and Merck companies and used without further purification. Products were characterized by their physical constant and comparison with authentic samples. Reaction monitoring was accomplished by thin-layer chromatography (TLC) on silica gel Polygram SILG/UV 254 plates. IR spectra were recorded on a BOMEM MB-Series 1998 FT-IR spectrophotometer using KBr pellets for the samples and catalyst in the range of 4000–400 cm^{-1}. ^1H and ^{13}C NMR spectra were recorded in 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 40–950 °C.

General procedure for preparation of caffeine-H_2SO_4

In a 25-mL round-bottomed flask, caffeine (1.94 g, 10 mmol) was dissolved in 20 mL CH_2Cl_2 and the solution was stirred for 1 h. Concentrated sulfuric acid (0.98 g, ca. 0.55 mL, 10 mmol) in CH_2Cl_2 (10 mL) was added dropwise over a period of 30 min at room temperature. After completion of the addition, the mixture was stirred for 24 h at room temperature. The precipitate was centrifuged and washed several times with CH_2Cl_2 and finally with acetone. Finally, white solid powder (caffeine-H_2SO_4) was obtained, which was dried at 60 °C for 5 h.

Table 3 Comparison of caffeine-H_2SO_4 with reported catalysts in the reaction of dimedone, phthalhydrazide, and benzaldehyde under solvent-free condition

Entry	Catalyst/temp. (°C)	Catalyst loading (mol %)	Time (min)	Yield (%)	References
1	*p*-Toluenesulfonic acid/80	30	10	86	[8]
2	Cyanuric chloride/100	3	15	96	[23]
3	$Mg(HSO_4)_2$/100	11.5	10	85	[19]
4	$H_4SiW_{12}O_{40}$/100	1	16	92	[20]
5	PSA/100	7	10	91	[26]
6	Caffeine-H_2SO_4/100	3.4	15	96	This work

Typical procedure for preparation of 2H-indazolo[2,1-b]phthalazinetrione

A mixture of dimedone (0.14 g, 1 mmol), phthalhydrazide (0.16 g, 1 mmol), aromatic aldehyde (1.1 mmol), and caffeine-H_2SO_4 (0.01 g, 3.4 mol%) was heated at 100 °C. Completion of the reaction was indicated by TLC [TLC acetone/*n*-hexane (3:10)]. After completion of the reaction, the mixture was washed with water and the crude product recrystallized in hot ethanol to afford the pure product.

Conclusions

Caffeine-H_2SO_4 was applied as a novel dual acidic catalyst in one-pot preparation of 2*H*-indazolo[2,1-*b*]phthalazinetriones. The catalyst was characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, and TGA. According to the obtained results including reaction time, yield, and recyclability, caffeine-H_2SO_4 can be considered an efficient catalyst for this reaction and other organic transformations.

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