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ORIGINAL PAPER

One-pot and solvent-free synthesis of aliphatic and aromatic 1*H*-indazolo[2,1-*b*]phthalazinetriones catalyzed by boron sulfonic acid

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Abstract An efficient and simple method for the synthesis of aliphatic and aromatic 1*H*-indazolo[2,1-*b*]phthalazinetrione derivatives through a one-pot three-component condensation of phthalhydrazide, aldehyde, and dimedone in the presence of boron sulfonic acid as a reusable and efficient catalyst under solvent-free conditions is described. The reusability of catalyst, good to excellent yields, short reaction times, and the avoidance of harsh reagents are the main advantages of this method.

Keywords Boron sulfonic acid · 1*H*-Indazolo[2,1-*b*]phthalazinetrione · Multicomponent reactions · Solvent-free

Introduction

Multicomponent reactions (MCRs) have become important tools in synthetic chemistry because of efficient access to complex molecules from readily available starting materials, construction of interesting biologically active organic compounds, and rapid generation of drug-like molecule libraries [1–7].

In recent years, synthesis of nitrogen-containing heterocyclic compounds has received growing attention because of their applications to biologically active pharmaceuticals, agrochemicals, and functional materials [8–11]. Among a large variety of heterocyclic compounds, bridgehead nitrogen heterocycles containing a phthalazine moiety are of interest because they exhibit pharmacological and biological activities [12–14]. The phthalazine unit is an important structural motif found in biologically active organic compounds. Phthalazine derivatives, which have two bridgehead nitrogen atoms in a fused ring system, were reported to possess a multiplicity of pharmacological properties including vasorelaxant cytotoxic [15], cardiotonic [16], antimicrobial [17], anticonvulsant [18], anti-inflammatory [19], antifungal [20], and anticancer [21] activities. Therefore, a number of methods have been reported for the synthesis of phthalazine derivatives using *p*-TSA [22], silica sulfuric acid [23], H_2SO_4 [24], silica-supported polyphosphoric acid [25], $Mg(HSO_4)_2$ [26], heteropoly acids [27], *N*-halosulfonamides [28], sulfonated poly(ethylene glycol) [29], cyanuric chloride [30], nano-silica sulfuric acid [31], and phosphosulfonic acid [32] as catalysts.

Recently, more attention has been paid to the application of inorganic acidic salts in organic synthesis [33, 34]. Simplicity in handling, decreased reactor and plant corrosion problems, more environmentally safe disposal in different chemical processes, and minimized or avoided wastes and by-products for the developing cleaner synthesis routes are some of the main advantages of the application of solid acids in organic synthesis. Boron sulfonic acid (BSA) is a novel solid acid catalyst that was introduced by Kiasat and Fallah-Mehrjardi [35] (Scheme 1) for the regioselective conversion of epoxides to thiocyanohydrins under solvent-free reaction conditions.

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BSA as a trifunctional inorganocatalyst is a strong acid that efficiently catalyzes many reactions.

Results and discussion

As part of our continuing studies in the use of BSA as a solid acid in organic synthesis [36–41], herein we report one-pot, three-component condensation of phthalhydrazide **1**, aldehydes **2a–2l**, and dimedone **3** for the synthesis of aliphatic and aromatic 1*H*-indazolo[2,1-*b*]phthalazinetriones **4a–4l** using BSA as a valuable catalyst under solvent-free conditions in good to excellent yields and short reaction times (Scheme 2).

In order to optimize the reaction conditions, phthalhydrazide (1.0 mmol), benzaldehyde (1.2 mmol) as an aromatic aldehyde, and dimedone (1.0 mmol) were used as model substrates (Table 2, entry **4a**). To evaluate the catalyst effect, first, the reaction was examined in the absence and presence of BSA under solvent-free conditions. In the absence of BSA, no product was formed after 60 min at 100 °C (Table 1, entry 1), but in the presence of BSA, the reaction took place with the best result. Next, to optimize the amount of BSA, the reaction was carried out using various amounts of the catalyst. As shown in Table 1, the best yield (94 %) was obtained with 5 mol% (0.05 g, 0.15 mmol H^+) of the BSA at 100 °C (Table 1, entry 3). The use of more than 5 mol% BSA did not enhance chemical yield (Table 1, entry 4). Finally, to evaluate the temperature effect, the model reaction was examined at 80 and 120 °C (Table 1, entries 5 and 6). It was observed that the reaction at 100 and 120 °C proceeded in the highest yield; thus, 100 °C was chosen as the reaction temperature (Table 1, entry 7). Also, a similar optimization was performed using phthalhydrazide (1.0 mmol), 3-phenylpropanal (1.2 mmol) as an aliphatic aldehyde and dimedone (1.0 mmol) as a model substrate (Table 2, entry **4l**). As shown in Table 1, the best condition for preparation of compound **4l** is the use of 5 mol% of BSA at 100 °C (Table 1, entry 3). The results are summarized in Table 1.

Based on the optimized reaction conditions, the reactions of phthalhydrazide, dimedone, and various aromatic and aliphatic aldehydes were investigated. As shown in Table 2, aromatic aldehydes carrying either electron-withdrawing or electron-donating substituents afforded excellent yields of products with high purity at 100 °C under solvent-free conditions (Table 2, entries **4a–4g**). Also, aliphatic aldehydes afforded the desired product with lower yields than aromatic aldehydes (Table 2, entries **4h–4l**).

A suggested mechanism for the formation of the 1*H*-indazolo[2,1-*b*]phthalazinetriones is shown in Scheme 3. BSA as an acid catalyst in situ generates H^+; thus, it is reasonable to assume that aldehyde **2** and dimedone **3** through a Knoevenagel condensation are converted to intermediate **5**. Then, the subsequent Michael-type addition of phthalhydrazide **1** to this intermediate followed by cyclization affords 1*H*-indazolo[2,1-*b*]phthalazine-triones **4**.

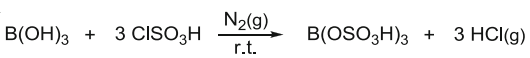
The reusability of BSA as catalyst was investigated for the synthesis of compounds **4a** and **4l** as two aromatic and aliphatic models, respectively. After each run, ethanol was added, and the catalyst was filtered. The recycled BSA was dried and reused for further runs. A mild depression in the

Table 1 Optimization of the reaction conditions for the synthesis of **4a** and **4l** under solvent-free conditions

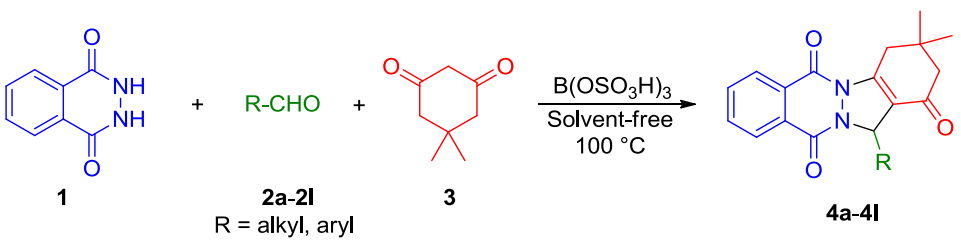
Entry	BSA/mol%	Temp./°C	Time/min	Yield/%[a]	
				4a	**4l**
1	0	100	60	0	0
2	2.5	100	15	74	52
3	5	100	15	94	78
4	10	100	15	92	78
5	5	120	15	94	77
6	5	80	15	82	64
7	5	100	10	94	72
8	5	100	5	90	70

[a] Yield of isolated product

Scheme 1



Scheme 2



catalytic activity of the catalyst was observed after four runs (Fig. 1). This shows that the BSA is an effective and recyclable catalyst for the synthesis of 1*H*-indazolo[2,1-*b*]phthalazinetriones.

Conclusion

BSA is an extremely efficient acidic catalyst for the preparation of aliphatic and aromatic 1*H*-indazolo[2,1-*b*] phthalazinetriones using one-pot, three-component condensation of phthalhydrazide, aldehyde, and dimedone under solvent-free conditions. The simplicity of the starting materials, good to excellent yields, short reaction times, easy workup, reusability of the catalyst, and use of solvent-free conditions are main advantages of this method.

Table 2 Synthesis of 1*H*-indazolo[2,1-*b*]phthalazinetrione derivatives using BSA as a catalyst (Scheme 2)

Entry	R	Time/min	Yield/%[a]	M.p./°C	
				Found	Reported
4a	C_6H_5-	10	94	201–203	204–206 [22]
4b	4-CH_3-C_6H_4-	10	90	223–225	227–228 [32]
4c	4-CH_3O-C_6H_4-	12	86	216–218	218–220 [32]
4d	4-NO_2-C_6H_4-	8	96	224–225	223–225 [22]
4e	4-Cl-C_6H_4-	8	92	260–261	262–264 [22]
4f	2,4-Cl_2-C_6H_3-	10	91	218–220	219–221 [28]
4g	2-Naphthyl	10	89	252–254	251–253 [28]
4h	CH_3CH_2-	15	65	145–147	145–147 [28]
4i	$CH_3(CH_2)_2$-	18	71	133–135	136–138 [28]
4j	$CH_3(CH_2)_4$-	20	65	135–137	138–140 [28]
4k	$(CH_3)_2CH$-	20	68	133–135	132–134 [28]
4l	$C_6H_5(CH_2)_2$-	15	78	170–172	171–173 [28]

[a] Isolated yields

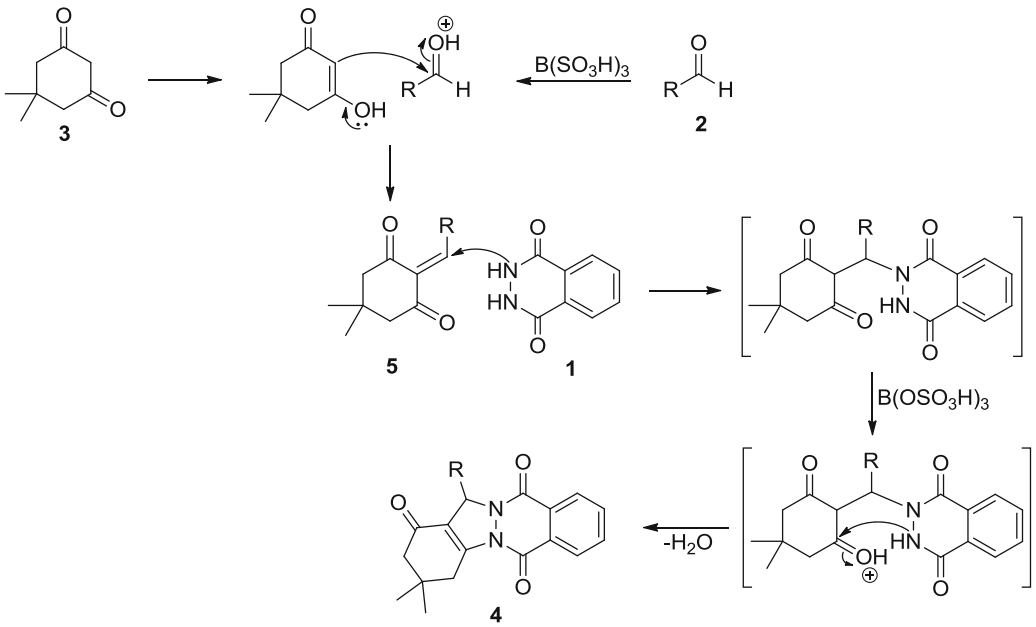
Experimental

All chemicals were purchased from Merck and Fluka companies. All yields refer to isolated products. IR spectra of the compounds were obtained on a Perkin-Elmer GX FT-IR spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 MHz NMR spectrometer using tetramethylsilane (TMS) as internal standard. Melting points were determined in a capillary tube. The progress of reaction was followed with TLC using silica gel SILG/UV 254 and 365 plates. All products are known compounds and were characterized by comparing the IR, ^1H, and ^{13}C NMR spectroscopic data and their melting points with the literature values.

General procedure for the preparation of 1H-indazolo[2,1-b]phthalazinetriones ***4a–4l***

A mixture of 0.16 g phthalhydrazide (1.0 mmol), aldehyde (1.2 mmol), 0.14 g dimedone (1.0 mmol), and 0.05 g BSA (5 mol%) was heated at 100 °C for the time indicated in Table 2. After completion of the reaction as indicated by TLC, the reaction mixture was cooled, quenched by

Scheme 3



Scheme 3 .

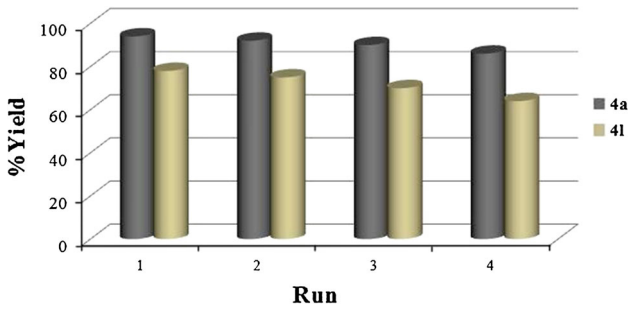


Fig. 1 The reusability of the BSA for the synthesis of **4a** and **4l** in four cycles

adding 10 cm^3 water, and extracted with chloroform (3 × 20 cm^3), and the extract was dried with Na_2SO_4. The filtrate was evaporated under vacuum, and the crude product was recrystallized from ethyl acetate/*n*-hexane to afford the pure products.

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