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ORIGINAL PAPER

A mild, efficient, and environmentally friendly synthesis of *N*,*N*′-arylidene bisamides using $B(HSO_4)_3$ under solvent-free conditions

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Abstract A green, efficient, and rapid procedure for the synthesis of *N*,*N*′-arylidene bisamide derivatives has been developed by one-pot condensation of aldehydes and amides in the presence of tris(hydrogensulfato)boron as a highly effective heterogeneous catalyst under solvent-free conditions at 100 °C. Various aromatic aldehydes, acetamide or benzamide were used in the reaction, and in all cases the desired products were synthesised successfully. This method has the advantages of high yields, a clean reaction, an environmental friendly procedure, easy workup, simple methodology, and short reaction times.

Keywords Bisamides · Tris(hydrogensulfato)boron · Aldehydes · Amides · Solvent-free

Introduction

Improving the efficiency of organic synthesis, lowering the consumption of chemicals, and constructing complex molecules from simple and available starting materials are fundamental goals in organic synthesis. In recent years, the "greening" of chemical processes to attain environmental friendliness and sustainability has become a major issue in academia and industry [1, 2]. The search for alternative reaction media to replace volatile, flammable, and often toxic solvents commonly used in organic synthesis is an important objective in the development of green chemical processes [3, 4]. Multicomponent reactions (MCRs) enjoy outstanding status in organic and medicinal chemistry because these comply with the principles of green chemistry in terms of economy of steps and applications in the diversity-oriented convergent synthesis of complex organic molecules [5–8].

Amides are widely used not only in chemical industries but also in organic synthesis. Specifically, bisamides are key fragments for the introduction of *gem*-diaminoalkyl residues in retro-inverse pseudopeptide derivatives [9]. The prevalence of the amide moiety in natural products and pharmacologically active compounds has instituted a diverse array of synthetic approaches to these compounds [10, 11]. The common approach for the synthesis of bisamides is the direct reaction of aldehydes with the corresponding amides or nitriles [12–20] using different catalysts, such as sulfuric acid (85 %, also as solvent) [12], triflic acid [13], sulfonic acid [14], sulfamic acid [15], *p*-toluenesulfonic acid [16], boric acid [17], phosphotungstic acid [18], silica-supported barium chloride [19], and $ZnCl_2$ [20]. However, in most cases the yields are good at high temperatures, and some of the reagents require longer reaction times and tedious purification procedures. Thus, there is a certain need for the development of an alternative route for the production of symmetrical *N*,*N*′-arylidene bisamides, which surpasses those limitations.

Solid acids have found increased application in organic synthesis. They also may be easily recovered and recycled. Furthermore the use of inorganic solid supports, such as clay, zeolite, alumina, and silica gel, for the generation of small organic molecules under solvent-free conditions has gained immense popularity because of its ease of set-up, mild conditions, increased yields of products, cost efficiency, and environmental friendliness compared to homogeneous counterparts.

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According to the literature, a general and green chemistry method for the synthesis of symmetrical bisamides is still demanded, and there is no report on the formation of bisamide derivatives catalyzed by eco-friendly tris(hydrogensulfato)boron catalyst. During the course of our systematic studies directed toward the development of environmentally friendly procedures for several important organic transformations [21–26], we describe herein an efficient method for the synthesis of symmetrical bisamides by condensing aryl aldehydes and amides using tris(hydrogensulfato)boron as a catalyst under solvent-free conditions at 100 °C.

Results and discussion

Tris(hydrogensulfato)boron [$B(HSO_4)_3$] was easily prepared by addition of chlorosulfonic acid to boric acid under an N_2 atmosphere at room temperature. This reaction was easy and clean, because HCl gas evolved from the reaction vessel immediately. This catalyst is safe and easy to handle (Scheme 1) [27]. It has been utilized as a catalyst for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones [25] and α,α′-benzylidenebis(4-hydroxycoumarin) derivatives by our group [26].

To optimize the reaction conditions, the reaction of benzaldehyde and benzamide was used as a model reaction. Reactions at different conditions and various molar ratios of substrates in the presence of tris(hydrogensulfato)boron revealed that the best conditions were solvent-free at 100 °C using benzaldehyde (1 mmol) and benzamide (2 mmol) in the presence of 0.015 g tris(hydrogensulfato)boron (0.05 mmol). The reaction proceeds smoothly to afford *N*,*N*′(phenylmethylene)dibenzamide in excellent yield (85 %) after 45 s. Furthermore, it was found that increasing the reaction time or reaction temperature over 100 °C did not improve the yields.

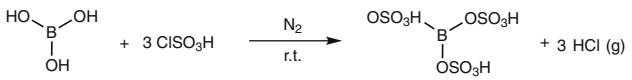
To study the scope of the reaction, a series of aldehydes and amides were applied (Scheme 2) and the results are summarized in Table 1. Aromatic aldehydes substituted with either electron-donating groups (such as alkyl, alkoxyl, hydroxyl) or electron-withdrawing groups (such as halide, nitro) were employed and reacted well to give the corresponding products **3** in good to excellent yields under these reaction conditions, so we conclude that no obvious effect of the electronic nature of substituents on the aromatic ring was observed. The reaction is also compatible with acetamide to afford the corresponding bisamides in excellent yields (Table 1, **3u**–**3z**). Therefore it was found that in all cases the reaction times are very short (15–45 s) with high yields (83–96 %) compared to other existing procedures. The structures of all products were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis.

However, pyridine-4-carbaldehyde (Table 1, **3r**), 4-hydroxybenzaldehyde (Table 1, **3s**), and 4-(dimethylamino)benzaldehyde (Table 1, **3t**) failed to give the corresponding bisamides under the same conditions. It is important to note that no product was detected in the absence of the catalyst.

Interestingly, the catalyst was effectively used for the synthesis of the corresponding bisamide **3q** through the condensation reaction between terephthalaldehyde and benzamide for the first time. In addition it was found that when terephthalaldehyde was exposed to excess benzamide in the presence of $B(HSO_4)_3$, compound **3q** was obtained as the sole product (Scheme 3).

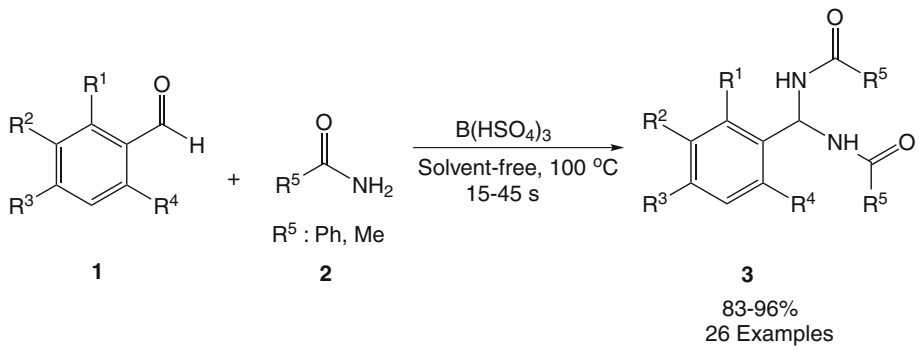
In order to show the merits of $B(HSO_4)_3$ over other catalysts reported in the literature, results with this catalyst were compared with other catalysts utilized for the synthesis of symmetrical bisamides. From Table 2, it can be seen that $B(HSO_4)_3$ appears to promote the reaction more effectively than a number of other catalysts, particularly in terms of the time and yield required to complete the reaction.

In summary, we have described an efficient and convenient synthesis strategy for the preparation of *N*,*N*′-



Scheme 1

Scheme 2



1 **2** **3**

83-96%
26 Examples

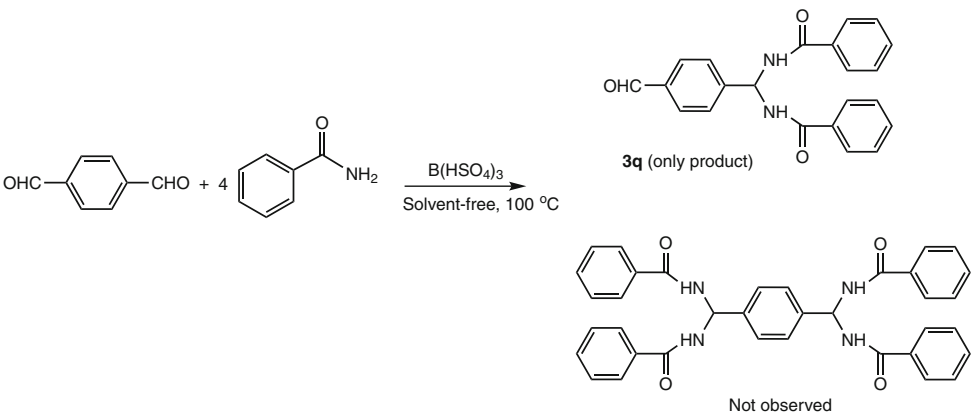
Table 1 Synthesis of symmetrical bisamides **3a–3z** in the presence of $B(HSO_4)_3$

Comp.	R^1	R^2	R^3	R^4	R^5	Time/s	Yield/%[a]	M.p./°C	Lit. m.p./°C
3a	H	H	H	H	Ph	45	85	235–238	236–238 [19]
3b	Cl	H	H	H	Ph	45	85	240–242	242–244 [19]
3c	OMe	H	H	H	Ph	20	90	229–230	–
3d	NO_2	H	H	H	Ph	30	83	256–257	256–258 [19]
3e	H	Me	H	H	Ph	40	87	210–212	–
3f	H	NO_2	H	H	Ph	45	83	232–235	235–237 [19]
3g	H	H	Br	H	Ph	15	87	252–254	–
3h	H	H	Cl	H	Ph	20	95	232–235	230–232 [17]
3i	H	H	CN	H	Ph	40	90	235–238	230–234 [17]
3j	H	H	F	H	Ph	45	95	226–228	226–228 [17]
3k	H	H	Me	H	Ph	20	85	242–243	240 [17]
3l	H	H	OMe	H	Ph	40	90	225–227	227–229 [19]
3m	H	H	NO_2	H	Ph	40	85	259–261	260–262 [19]
3n	Cl	H	Cl	H	Ph	40	96	195–197	195–197 [19]
3o	Cl	H	H	Cl	Ph	45	93	203–206	–
3p	H	NO_2	Cl	H	Ph	40	90	252–254	–
3q	Terephthalaldehyde				Ph	30	90	317–318	–
3r	Pyridine-4-carbaldehyde				Ph	7 min	Trace	–	
3s	H	H	OH	H	Ph	10 min	N.R.[b]	–	
3t	H	H	$(CH_3)_2N$	H	Ph	10 min	N.R.[b]	–	
3u	H	H	H	H	Me	40	94	251–252	251–253 [19]
3v	H	H	Cl	H	Me	45	85	260–263	260–262 [16]
3w	H	H	F	H	Me	35	93	252–254	257–259 [19]
3x	H	H	Me	H	Me	30	95	265–267	270–272 [16]
3y	H	H	OMe	H	Me	45	85	221–223	221–223 [16]
3z	H	H	NO_2	H	Me	45	90	244–246	244–246 [19]

[a] Isolated yields

[b] No reaction

Scheme 3



arylidene bisamide derivatives via a condensation of aldehydes and amides using the inexpensive, non-toxic, and easily prepared $B(HSO_4)_3$ catalyst. This method offers some advantages in terms of very low reaction times, simplicity of performance, solvent-free condition, low cost, and it advances along the line of green chemistry. Six new desired products were synthesised and characterized for the first time. The yields are excellent and the reactions go to completion within 15–45 s.

Table 2 Comparison of results using $B(HSO_4)_3$ with other catalysts for synthesis of symmetrical bisamides

Entry	Conditions	Time	Yield/%	Reference
1	CF_3SO_3H (0.04 equiv.), CH_2Cl_2, 46 °C	0.25–48 h	67–99	[13]
2	*p*-TSA (0.1 mmol), solvent-free, 100 °C	1 h	85–99	[16]
3	H_3BO_3 (0.3 mmol), toluene, reflux	16–70 h	38–92	[17]
4	Phosphotungstic acid (0.3 mmol), toluene, 110 °C	15–40 h	44–94	[18]
5	SiO_2–$BaCl_2$ (0.025 g), solvent-free, 100 °C	10–360 min	67–91	[19]
6	$B(HSO_4)_3$ (0.015 g), solvent-free, 100 °C	15–45 s	83–96	This work

Experimental

All chemicals were commercially available and used without further purification. Melting points were determined in open capillary tubes. IR measurements were carried out using KBr pellets on a Shimadzu FTIR spectrometer. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker Avance 400 spectrometer in DMSO-d_6 as a solvent. The elemental analysis was performed with an Elementar Analysensysteme GmbH VarioEL CHNS mode. The progress of reactions was followed with thin-layer chromatography (TLC) using silica gel 60 GF_{245} precoated sheets 20 × 20 cm, layer thickness 0.2 mm (E-Merck) and were visualized by UV light at 254 nm wavelength.

Preparation of tris(hydrogensulfato)boron [B(HSO$_4$)$_3$]

A 50 cm^3 suction flask was equipped with a constant pressure dropping funnel. The gas outlet was connected to a vacuum system through an adsorbing solution (water) and an alkali trap. Boric acid (1.55 g, 25 mmol) was charged in the flask and 8.74 g chlorosulfonic acid (ca. 5 cm^3, 75 mmol) was added dropwise over a period of 1 h at room temperature. HCl evolved immediately. After completion of the addition, the mixture was shaken for 1 h, while the residual HCl was eliminated by suction. Then the mixture was washed with diethyl ether to remove the unreacted chlorosulfonic acid. Finally, 7.0 g of a grayish solid material was obtained (93 % yield). ^{1}H NMR (400 MHz, acetone-d_6): δ = 12.22 ppm [27, 28].

*General procedure for the preparation of symmetrical bisamides **3a–3z***

Aldehyde (1 mmol), amide (2 mmol), $B(HSO_4)_3$ (0.05 mmol), and 0.006 g silica gel were mixed and the mixture was stirred and heated in an oil bath at 100 °C for appropriate time. Completion of the reaction was indicated by TLC. After the reaction was completed, ethanol was added and the heterogeneous catalyst was isolated from the reaction mixture by simple filtration. The filtrate was concentrated and allowed to yield the desired product as white crystals.

N,N′-(2-Methoxyphenylmethylene)dibenzamide
(**3c**, $C_{22}H_{20}N_2O_3$)
White crystals; IR (KBr): $\bar{\nu}$ = 3,296, 2,926, 1,647, 1,511, 1,484, 1,050, 649 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.83 (3H, s, CH_3), 6.98 (1H, t, J = 7.6 Hz, CH), 7.05 (1H, d, J = 8.4 Hz, ArH), 7.19–7.20 (m, 1H, ArH), 7.31–7.56 (m, 8H, ArH), 7.92 (4H, d, J = 7.2 Hz, ArH), 8.89 (2H, d, J = 2 Hz, 2 NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 55.6, 56.1, 111.5, 120.4, 128.0, 128.3, 128.6, 129.6, 131.8, 134.5, 134.6, 157.3, 165.8 ppm.

N,N′-(3-Methylphenylmethylene)dibenzamide
(**3e**, $C_{22}H_{20}N_2O_2$)
White crystals; IR (KBr): $\bar{\nu}$ = 3,286, 3,028, 1,653, 1,549, 1,484, 707 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.38 (3H, s, CH_3), 7.04 (1H, t, J = 7.6 Hz, CH), 7.14 (1H, s, ArH), 7.28–7.59 (9H, m, ArH), 7.94 (4H, d, J = 7.6 Hz, ArH), 9.02 (2H, d, J = 7.6 Hz, 2 NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.6, 59.1, 124.1, 127.5, 128.0, 128.7, 128.8, 129.0, 132.0, 134.3, 137.8, 140.7, 165.9 ppm.

N,N′-(4-Bromophenylmethylene)dibenzamide
(**3g**, $C_{21}H_{17}BrN_2O_2$)
White crystals; IR (KBr): $\bar{\nu}$ = 3,265, 2,923, 1,649, 1,543, 1,506, 720 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.99 (1H, t, J = 7.6 Hz, CH), 7.44–7.61 (10H, m, ArH), 7.93 (4H, d, J = 7.2 Hz, ArH), 9.07 (2H, d, J = 7.2 Hz, 2 NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 58.9, 121.3, 128.0, 128.8, 129.3, 131.6, 132.1, 134.1, 140.1, 166.1 ppm.

N,N′-(2,6-Dichlorophenylmethylene)dibenzamide
(**3o**, $C_{21}H_{16}Cl_2N_2O_2$)
White crystals; IR (KBr): $\bar{\nu}$ = 3,269, 2,943, 1,640, 1,534, 1,510, 715 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.37 (1H, t, J = 8 Hz, CH), 7.47–7.58 (10H, m, ArH), 7.92 (3H, d, J = 7.2 Hz, ArH), 9.07 (2H, d, J = 6.0 Hz, 2 NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 58.6, 128.1, 128.7, 130.6, 132.0, 134.1, 134.2, 134.4, 135.4, 166.0 ppm.

N,N′-(4-Chloro-3-nitrophenylmethylene)dibenzamide (**3p**, $C_{21}H_{16}ClN_3O_4$)

White crystals; IR (KBr): $\bar{\nu}$ = 3,270, 2,925, 1,647, 1,530, 1,482, 730, 710 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): $\delta = 7.05$ (1H, t, $J = 7.2$ Hz, CH), 7.49–7.60 (6H, m, ArH), 7.80–7.85 (2H, m, ArH), 7.95 (4H, d, $J = 7.2$ Hz, ArH), 8.22 (1H, s, ArH), 9.25 (2H, d, $J = 7.2$ Hz, 2 NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 58.7$, 124.3, 124.6, 128.1, 128.7, 131.9, 132.2, 132.8, 134.0, 141.7, 148.0, 166.4 ppm.

N,N′-(4-Formylphenylmethylene)dibenzamide (**3q**, $C_{22}H_{18}N_2O_3$)

White crystals; IR (KBr): $\bar{\nu}$ = 3,264, 3,062, 1,652, 1,543, 1,483, 1,281, 696 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): $\delta = 7.10$ (1H, t, $J = 7.6$ Hz, CH), 7.49–7.58 (10H, m, ArH), 7.91–7.96 (4H, m, ArH), 9.08 (2H, d, $J = 7.6$ Hz, 2 NH), 10.03 (1H, s, CH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 64.0$, 126.9, 127.9, 128.07, 128.14, 128.8, 132.2, 134.2, 140.5, 167.0, 193.3 ppm.

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