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ORIGINAL PAPER

Three-component, solvent-free synthesis of Betti base catalyzed by sulfated polyborate

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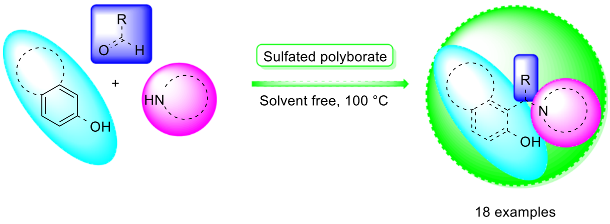
Abstract

In this work, efficient, mild, and eco-friendly procedure of 1-aminoalkyl-2-phenol/Betti base from one-pot three-component condensations of aldehyde, phenol, and morpholine in the presence of sulfated polyborate catalyst, under a solvent-free condition at 100 °C, is described. The key advantages of the present method are short reaction time, high yields, aqueous work-up procedure, low cost, stable, reusable catalyst, and solvent-free reaction conditions.

Graphical abstract



Keywords Sulfated polyborate · Betti base · Solvent free · Recyclable catalyst

Introduction

Betti base was first reported by the distinguished Italian chemist Mario Betti via a modified Mannich reaction named Betti reaction [1]. Betti base is synthesized by simple condensation of 2-naphthol with benzaldehyde and amines [2–8]. Betti base has special significant biological [9] and catalytic [10] properties. They show the activity like chiral auxiliaries for the synthesis of α-aminophosphonic acids [11] and act as chiral shift reagents for the preparation of carboxylic acids [12]. Betti base has various pharmacological active molecules like as antibacterial [13, 14], fungicidal [15, 16], antitumor [17, 18], and antitubercular [19, 20].

There are several methods which have been previously described for the analogues of aminoalkylation [21–23]. The more common is the reaction of aldehydes, amines, and phenols in ethanol at room temperature; this method suffers from long reaction times [22, 23]. The reaction of preformed iminium salts with electron-rich aromatic compounds in anhydrous acetonitrile [24]; in this condition, iminium salts are hygroscopic and sensitive to hydrolysis and must be prepared under extreme anhydrous conditions and treatment of *N*-(aminoarylmethyl)-benzotriazoles with preformed sodium phenolates in refluxing toluene in presence of a phase-transfer catalyst [25]. In this method, adducts must be prepared with azeotropic removal of water from the reaction of an appropriate aldehyde, a

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Scheme 1

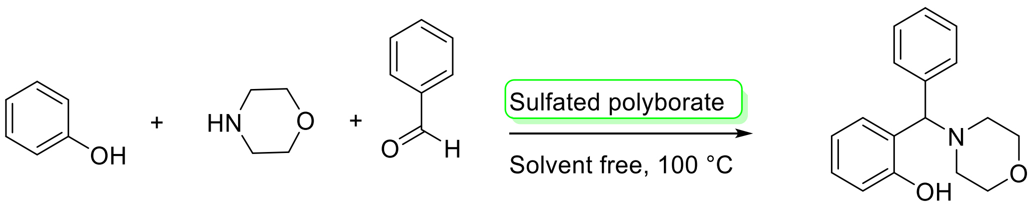


Table 1 Results of optimization studies

Entry	Catalyst/wt%	Solvent	Temperature/°C	Time/h	Yield[a]/%
1	0	Solvent free	100	12	20
2	2.5	Solvent free	100	1	40
3	5.0	Solvent free	100	1	72
4	7.5	Solvent free	100	1	85
5	10.0	Solvent free	100	1	95
6	15.0	Solvent free	100	1	93
7	10.0	Solvent free	r.t.	6	NR[b]
8	10.0	Solvent free	50	6	57
9	10.0	Solvent free	80	6	78
10	10.0	EtOH	Reflux	2	60
11	10.0	MeCN	Reflux	2	43
12	10.0	THF	Reflux	2	33
13	10.0	Water	Reflux	2	20
14	10.0	Toluene	Reflux	2	40
15	10.0	DMF	100	2	50

[a] Isolated yield

[b] No reaction

secondary amine, and benzotriazole in benzene. These disadvantages necessitate that the development of a new effective, high yielding methodology is reasonable.

Several Lewis and Brønsted acids, such as $SnCl_4{\cdot}5H_2O$ [26], polymer-supported sulfonic acid [27], ionic liquids [28], nano-sulfated zirconia [29], $[HMIM]C(CN)_3$ [30], $ZrO(OTf)_2$ [31], and $Bi(NO_3)_3{\cdot}5H_2O$ [32], have been applied to catalyze this Betti reaction. Although these methods have one or more limitations such as long reaction time, low yield, harsh reaction conditions, the use of corrosive, toxic, non-reusable, expensive, difficult-to-handle and a large amount of catalysts and tedious work-up procedures. Hence, the exploration of a mild, efficient, and eco-friendly protocol for the synthesis of Betti base is highly desirable.

The development of greener, convenient, and practical catalytic methods of the current interest in organic synthesis and commercial processes is in demand. The sulfated polyborate was prepared from readily available boric acid, as an economic and non-toxic starting material, characterized and effectively applied for various organic transformations [33–47]. Herein, we report the synthesis of Betti base catalyzed by sulfated polyborate under a solvent-free condition with high yields and short duration of time (Scheme 1).

Results and discussion

For primary screening, the study was structured to investigate the suitability of sulfated polyborate as a homogeneous catalyst at different reaction conditions. For the preliminary experiment, a mixture of phenol, as a representative substrate, benzaldehyde, and morpholine was used to afford 2-[morpholino(phenyl)methyl]phenol. The results are summarized in Table 1.

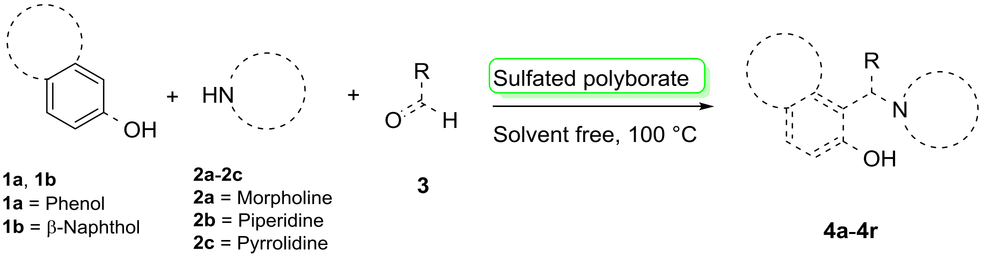
The effect of the catalyst loading on time and yields of the reaction was assessed. In the absence of a catalyst, the reaction proceeded at 100 °C, but took longer reaction time with a poor yield (Table 1, entry 1). An increase in the catalyst loading increased the product yield with significate reduction in the reaction time (Table 1, entries 2–5). The catalyst loading beyond 10 wt% was not advantageous

Table 2 Efficiency of sulfated polyborate in comparison with the literature reported catalysts for the Betti reaction

Entry	Catalyst	Condition	Time/h	Yield[a]/%	References
1	Sulfated polyborate	solvent free/100 °C	0.5	90	This work
2	Diphenylphosphine oxide	solvent free/180 °C	0.5–2	93	[48]
3	Nanocrystalline MgO catalyst	Water/r.t.	2	88	[49]
4	Non-ionic surfactant (Triton X-100)	Water/r.t.	4.5	93	[50]
5	Glycerol	50 °C	24	77	[51]

[a] Isolated yield

Table 3 Synthesis of Betti base using a variety of amines and aldehyde



Entry	Substrate	Amine	Aldehyde	Product	Time/min	Yield[a]/%	Melting point/°C	
							Obs.	References
1	**1a**	**2a**	C_6H_5	**4a**	30	90	114–115	115–116 [52]
2	**1a**	**2a**	4-Cl–C_6H_4	**4b**	40	92	114–116	114–115 [53]
3	**1a**	**2a**	4-CH_3O–C_6H_4	**4c**	35	91	101–101	102–103 [52]
4	**1a**	**2a**	4-CH_3–C_6H_4	**4d**	35	94	88–89	87–88 [52]
5	**1a**	**2a**	4-Br–C_6H_4	**4e**	35	93	100–101	99–101 [52]
6	**1a**	**2a**	2-Cl–C_6H_4	**4f**	45	90	85–87	84–86 [54]
7	**1a**	**2b**	C_6H_5	**4g**	25	95	88–89	87–88 [54]
8	**1a**	**2b**	4-CH_3O–C_6H_4	**4h**	25	94	99–100	98–99 [53]
9	**1b**	**2a**	C_6H_5	**4i**	20	95	175–177	176–178 [55]
10	**1b**	**2c**	C_6H_5	**4j**	10	98	167–169	168 [55]
11	**1b**	**2c**	2-Cl–C_6H_4	**4k**	10	98	159–161	160 [55]
12	**1b**	**2c**	4-Cl–C_6H_4	**4l**	10	97	133–135	135 [55]
13	**1b**	**2b**	C_6H_5	**4m**	15	96	193–195	194 [55]
14	**1b**	**2b**	4-CH_3O–C_6H_4	**4n**	25	94	136–138	138 [55]
15	**1b**	**2a**	4-Cl–C_6H_4	**4o**	20	93	118–120	120 [55]
16	**1b**	**2a**	2-Thienyl	**4p**	20	96	144–146	145–146 [53]
17	**1b**	**2a**	5-Methylfuran-2-yl	**4q**	20	97	160–162	–
18	**1b**	**2a**	4-Pyridyl	**4r**	20	92	187–189	–

[a] Isolated yield

(Table 1, entries 5 and 6). Hence, a 10 wt% catalyst loading was chosen for further study.

Temperature played an important role for the synthesis Betti base. The temperature effect was examined at ambient, 50, 80, and 100 °C using sulfated polyborate (Table 1, entries 5 and 7–9). The reaction did not proceed at room temperature (Table 1, entry 7). An increase in the temperature to 100 °C resulted in significantly increased product yield in shorter reaction time (Table 1, entries 5, 8, and 9). Therefore, 100 °C was chosen as optimum temperature for the reaction.

The effect of various solvents on time and yield of the reaction was ascertained (Table 1, entries 5 and 10–15). None of the solvents has shown an advantage over solvent-free condition. Hence, the solvent-free condition was regarded as best for the cost and environmental acceptability.

There are only a few catalysts reported for the synthesis of Betti base via reaction of phenol, benzaldehyde, and

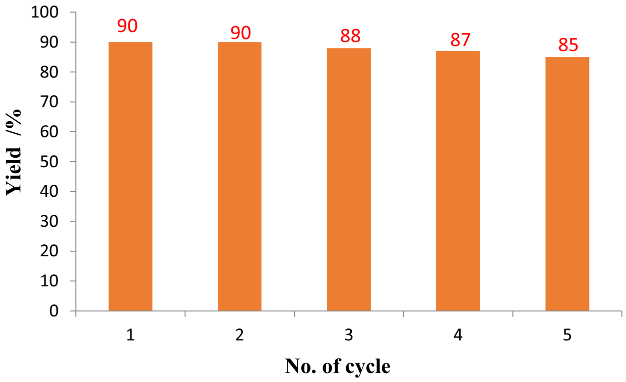


Fig. 1 Recyclability of the catalyst

morpholine. Here, in comparison with other catalysts with sulfated polyborate showed an advantage with respect to reaction conditions, work-up procedure, time, and yields (Table 2, entries 1–6).

To study the generality and scope, optimized reaction conditions were applied to various aromatic/heteroaromatic aldehydes and amines. All the substrate variants reacted well and afforded higher yields of Betti base in shorter reaction time (Table 3). In comparative phenol, β-naphthol showed higher product yield and short reaction time. Several electron-releasing or electron-withdrawing substituents at the *ortho*, *meta*, and *para* positions of aromatic aldehydes showed no significant effect on product yield and time. This protocol is also extendable to heteroaromatic, which also reacted very well and afforded good-to-high yields (Table 3, entries 16–18).

On the other hand, the applicability of this protocol on aliphatic amines was also examined using morpholine, piperidine, and pyrrolidine variants. All the amine variants were reacted well and afforded good yields of the corresponding Betti base in shorter reaction time. However, piperidine and pyrrolidine variants took lesser time than morpholine. We also attempted the reaction of aliphatic aldehydes under optimized reaction condition with no success.

The reusability of the catalyst in the model reaction under solvent-free conditions at 100 °C was evaluated. After completion of each cycle of the reaction, the catalyst was recovered by adding water and the product was filtered off. The filtrate was evaporated under reduced pressure to recover the catalyst quantitatively. The recovered catalyst was reused four times with no significant loss in a catalytic activity (Fig. 1).

Conclusion

In conclusion, the present procedure is a rapid, efficient and eco-friendly protocol for the Betti reaction of phenol/β-naphthol with a variant of aldehyde, and amines under optimized conditions are high yields, shorter reaction time, and mild reaction conditions, easy of work-up procedure and recyclability of the catalyst are the key features of this protocol. Moreover, the present method has the ability to tolerate a wide variety of substituents along with enhanced product purity which promises economical as well as ecological rewards.

Experimental

Melting points of all the compounds were recorded by Analab ThermoCal melting point apparatus in the open capillary tube. ^{1}H and ^{13}C NMR spectra were recorded on MR400 Agilent Technology NMR spectrometer using tetramethylsilane (TMS) as an internal standard and $CDCl_3$ and DMSO-d_6 as a solvent. Chemicals and solvents used were of LR grade and purchased from SD fine, Avra Synthesis, and Spectrochem and used without purification. The purity determination of the starting materials and reaction monitoring was accomplished by thin-layer chromatography (TLC) on Merck silica gel G F_{254} plates.

Preparation of sulfated polyborate

Boric acid was heated in a petri dish at 200 °C for 4 h to convert it to the polyboric acid; resultant glassy solid was then ground into fine powder. Polyboric acid powder (5 g) was suspended in 20 cm^3 chloroform in 250 cm^3 round bottom flask, and then 4.23 cm^3 chlorosulfonic acid was added dropwise over a period of 30 min at room temperature. The mixture was further stirred for 120 min. The reaction was quenched by adding 10 cm^3 ethanol. Residual HCl gas was flushed with nitrogen, the solid was filtered, washed several times with chloroform. Finally, solid sulfated polyborate was dried at 100 °C in hot air oven until constant weight. The catalyst was characterized by various analytical techniques such as potentiometric analysis, Fourier transform infrared spectroscopy (FTIR), X-ray diffraction (XRD), and scanning electron microscopy (SEM) energy dispersive X-ray spectroscopy (EDAX) [36].

General procedure for the Betti reaction

A mixture of a phenol (1 mmol), aldehyde (1 mmol), and amine (1.2 mmol) was added sulfated polyborate (10 wt%). The mixture was heated at 100 °C in an oil bath. The reaction was monitored by thin-layer chromatography. After completion of the reaction, the mixture was cooled to room temperature and quenched with 5 cm^3 water. Solid was filtered at vacuum pump, washed with water (3 × 5 cm^3), dried under vacuum to get the products in pure form, or recrystallized from methanol. The products obtained were known compounds and were identified by melting point, ^{1}H and ^{13}C NMR spectroscopy. The spectral data were compared with those in the literature.

1-[(5-Methylfuran-2-yl)(morpholino)methyl]naphthalen-2-ol (4q, $C_{20}H_{21}NO_3$) ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 12.480$ (brs,1H), 7.803–7.782 (d, $J = 8.4$ Hz, 1H), 7.732–7.662 (m, 2H), 7.422–7.384 (t, $J = 7.6$ Hz, 1H), 7.266–7.230 (m, 1H), 7.120–7.098 (d, $J = 8.8$ Hz, 1H), 6.190–6.183 (d, $J = 2.8$ Hz, 1H), 5.812–5.807 (d, $J = 1.9$ Hz, 1H), 5.216 (s, 1H), 3.815–3.745 (m, 4H), 2.857–2.402 (m, 4H), 2.226 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 155.4$, 152.1, 149.5, 132.3, 129.7, 129.8, 128.6, 126.6, 122.5, 120.8, 119.6, 112.4, 110.6, 106.6, 66.8, 63.6, 13.7 ppm.

1-[Morpholino(pyridin-4-yl)methyl]naphthalen-2-ol (4r, $C_{20}H_{20}N_2O_2$) ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 12.7$ (brs, 1H), 8.514–8.499 (d, $J = 6$ Hz, 2H), 7.803–7.782 (d, $J = 8.4$ Hz, 1H), 7.712–7.675 (t, $J = 7.4$ Hz, 2H), 7.505–7.490 (d, $J = 6$ Hz, 2H), 7.425–7.387 (t, $J = 7$ Hz, 1H), 7.274–7.239 (t, $J = 7$ Hz, 1H), 7.138–7.116 (d, $J = 8.8$ Hz, 1H), 5.089 (s, 1H), 3.964–3.616 (m, 4H), 3.222–2.225 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 154.8$, 150.5, 147.4, 132.0, 130.4, 129.1, 128.8, 126.8, 123.6, 122.9, 120.4, 119.7, 113.6, 70.78, 66.6 ppm.

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