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An Effective Method for One-Pot Synthesis of Betti Bases using Phenylboronic Acid as Catalyst

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Abstract: An effective method has been developed for the synthesis of Betti bases by the reaction of aromatic aldehydes, aromatic amine and 2-naphthol using phenylboronic acid as an efficient catalyst under ambient condition. The mild reaction condition and excellent yield are the notable features of this method.

Keywords: Betti base, one-pot synthesis, phenylboronic acid, aromatic amine, 2-naphthol.

Introduction

Multi-component reactions are of rising significance in synthetic organic chemistry, because the strategies of MCR offer significant advantages over conventional linear-type synthesis [1-4]. MCRs leading to interesting heterocyclic scaffolds are particularly useful for the synthesis of drug-like molecules with several degrees of structural diversity, since the combination of three or more building blocks in a single operation leads to a high combinatorial efficiency [5-6].

In terms of green chemistry, the development and application of multi-component coupling reactions in water is favourable, as they provide simple and rapid access to a large number of organic molecules via a tolerable method [7-8]. But the Betti reaction is difficult to be initiated in water because the activity of amine is inhibited by the strong hydrogen bond with water. Various methods are developed using rare earth and lanthanide triflates [9], sulfanilic acid-functionalized silica-coated magnetite nanoparticles [10], surfactants [11] or iminium salts [12-13] as catalysts for direct-type Mannich reactions in water or under solvent-free conditions have been successfully applied [14-15]. Nowadays it is necessary to develop environmentally benign reactions and atom-economic catalytic processes for Betti reaction. Herein we describe a one-pot three-component synthesis of Betti bases via the reaction of aromatic aldehyde, aromatic amine and 2-naphthol using phenylboronic acid as an efficient catalyst under ambient condition (**Scheme 1).**

Experimental Section

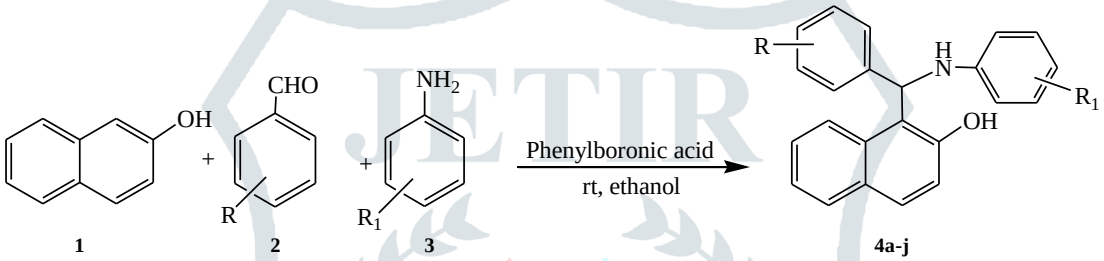
All solvents were utilized as commercial anhydrous grade without further purification. Melting points were determined in open capillary tube and are uncorrected.

General procedure for synthesis of aminobenzyl naphthol derivatives (Betti base): Substituted aniline (1 mmol), aromatic aldehyde (1 mmol) and β-naphthol (1 mmol) were mixed together in ethanol (15ml). Catalytic

amount of phenylboronic acid (0.2 mmol) was added. Then reaction mixture was stirred at room temperature for appropriate time (Table-2). After the completion of reaction indicated by TLC, reaction mixture was poured into crushed ice and then obtained precipitate was filtered and dried and melting points were recorded.

1-((4-Chlorophenylamino)(4-nitrophenyl)methyl)naphthalen-2-ol (4e): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78-8.02 (m, 4H), 7.45-7-56 (m, 4H), 7.05-7.20 (m, 4H), 6.32-6.38 (m, 2H), 5.21 (s, 1H, OH), 4.65 (s, 1H), 4.28 (s, 1H, NH); **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 52.4, 112.6, 114.0, 116.9, 118.5, 120.3, 123.0, 123.4, 123.9, 125.4, 128.0, 129.2, 129.9, 134.2, 143.5, 144.8, 149.7, 155.0**; MS: *m/z*** 405.4 (M^+) obtain; expected 404.8 (M^+).

1-((Phenylamino)(phenyl)methyl)naphthalen-2-ol (4g): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58-7.66 (m, 4H), 7.10-7.21 (m, 4H), 6.84-7.01 (m, 6H), 6.42-6.60 (m, 2H), 5.28 (s, 1H, OH), 4.72 (s, 1H), 4.20 (s, 1H, NH); **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 51.2, 112.8, 114.9, 117.0, 119.2, 123.0, 123.9, 125.8, 128.0, 128.9, 129.7, 130.2, 134.8, 140.7, 146.5, 154.2,**; MS: *m/z*** 326.0 (M^+) obtain; expected 325.4 (M^+).



Scheme 1

Results and discussion

Firstly, a model reaction of 4-chloro benzaldehyde, 4-chloro aniline and 2-naphthol was carried out in different solvent using 10 mol % of catalyst phenylboronic acid at room temperature condition. In solvent acetonitrile, the reaction afforded 59% product yield in 9 hours (Table 1, entry 1). The reaction in solvent methanol and ethanol gave 64 % and 86% product yield (Table 1, entry 2 and 3 respectively). The study show best results in solvent ethanol, reaction afforded 86% yield in reaction time 4.30 hours (Table 1, entry 3). Again we continue this reaction in solvent DMF but it requires elongated time with low yield (Table 1, entry 4). From this study we have concluded that ethanol is suitable and excellent solvent for this synthesis.

Table 1: Effect of solvent on synthesis of of aminobenzyl naphthol derivatives

Sr. No.	Catalyst (mol %) Phenylboronic acid	Solvent	Reaction time (hrs)	Yield[a] (%)
1	10	CH_3CN	7.00	59
2	10	MeOH	6.00	64
3	10	EtOH	4.30	86
4	10	DMF	8.00	42

[a]Isolated Yield

Table2: Synthesis of aminobenzyl naphthol derivatives via Betti reaction

Entry	R	R_1	Product	Reaction time. (hrs)	M. P. (^oC)	Yield[a] (%)
1.	4-Cl	4-Cl	4-a	4.30	165	86
2.	2-Cl	4-Cl	4-b	5.00	146	88
3.	3-NO_2	4-Cl	4-c	5.30	209	89
4.	4-F	4-Cl	4-d	4.00	176	88
5.	4-NO_2	4-Cl	4-e	5.00	139	84
6.	4-OH	-H	4-f	5.00	140	90
7.	-H	-H	4-g	6.00	155	84
8.	4-OCH_3	-H	4-h	5.30	178	86
9.	4-OH, 3-OCH_3	-H	4-i	6.00	188	88
10.	4-CN	-H	4-j	5.00	205	87

[a]Isolated Yield

With this optimized condition, we have employed several aromatic aldehydes having different substituents with different anilines. Result of substituent revealed short distinction in yield and reaction time (Entry 1-10, Table 2).

Conclusion:

In conclusion, we have presented simple and facile method for the synthesis of Betti base by using phenylboronic acid as catalyst in ethanol solvent under ambient temperature condition. The mild reaction condition, easy experimental operation and good to excellent yield with a wide range of aldehydes are some of the striking features of this protocol.

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