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An efficient, expeditious, and diastereoselective one-pot pseudo-five-component reaction for the synthesis of new bis-Betti bases under catalyst-free conditions

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ABSTRACT

A novel, diastereoselective, one-pot synthesis of new bis-Betti bases via condensation of dihydroxynaphthalene, two equivalents of aryl aldehydes, and two equivalents of 3-amino-5-methylisoxazole is reported. Conversion into the adducts was almost quantitative without the use of solvent or catalyst. The reaction conditions are very simple and enable easy isolation of the product.

One-pot multi-component reactions are effective processes for the discovery of new reactions and the synthesis of complex structures.[1] They enable rapid access to large compound libraries with diverse functionalities, and avoid costly purification processes in addition to protection and deprotection steps by systematic variation of the starting material which is either commercially available or is easily prepared.[2]

One of the classic multi-component reactions is the synthesis of Betti bases.[3] The typical Betti reaction is a three-component reaction between an aldehyde, ammonia/urea, and β-naphthol.[4] Several studies have centered on the catalysis of this reaction, using different bases or metal salts.[5] The Betti reaction represents a useful method to obtain amidoalkyl naphthols.[3] These are very important precursors for the synthesis of bioactive 1-aminomethyl-2-naphthols, the bradycardiac and hypotensive effects of which have been evaluated in humans.[6] Moreover, they are attractive compounds as chiral ligands in enantioselective reactions.[7] They can be used as chiral shift reagents for carboxylic acids or as chiral auxiliaries for the synthesis of α-aminophosphonic acids.[8] Furthermore, isoxazole derivatives, especially 5-methylisoxazole represent an interesting class of heterocycles possessing a wide spectrum of biological activity.[9,10]

Thus, new hybrid moieties secured by introducing 5-methylisoxazole into Betti bases, promise to offer fascinating scaffolds.

In continuation of our work on one-pot multi-component reactions,[10] we embarked on the synthesis of novel bis-Betti bases possessing 2-amino-5-methylisoxazole, arene, and dihydroxy naphthalene moieties embedded in a fused molecular framework via a pseudo-five-component reaction under catalyst-free conditions (Scheme 1).[11]

Initially, we investigated the one-pot condensation reaction of 2-chlorobenzaldehyde (2 mmol), 5-amino-3-methylisoxazole (2 mmol), and 2,3-dihydroxynaphthalene (1 mmol) to give diastereoisomer **3b**, as a model system to study the solvent and temperature effects (Table 1).

The stereochemistry of **3b** was unambiguously assigned by X-ray crystallography (CCDC 849432) (Fig. 1). Interestingly, it was found that this transformation produced (±)-**3b** selectively.

The reaction was carried out in a range of solvents, including water, ethanol, PEG-400, acetonitrile, and toluene for a period of 3 h at 80 °C. However, the best result was obtained at 80 °C under solvent-free conditions (Table 1, entry 6). The results subsequently showed that the temperature appeared to be crucial as the reaction did not take place even after stirring for 24 h at room temperature (Table 1, entry 7). Running the reaction for 3 h at 50–70 °C did not result in any increase in the yield (Table 1, entries 8–10). Furthermore, no remarkable differences in the diastereoselectivity were apparent in this temperature range.

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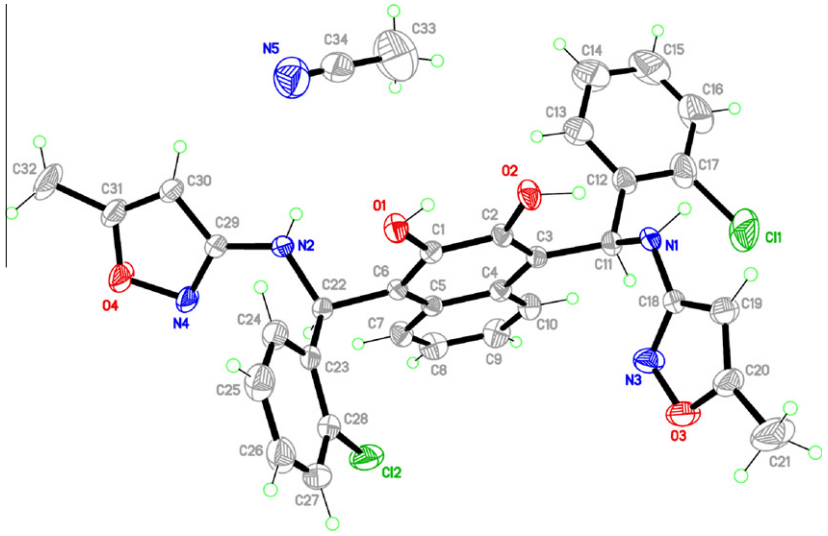
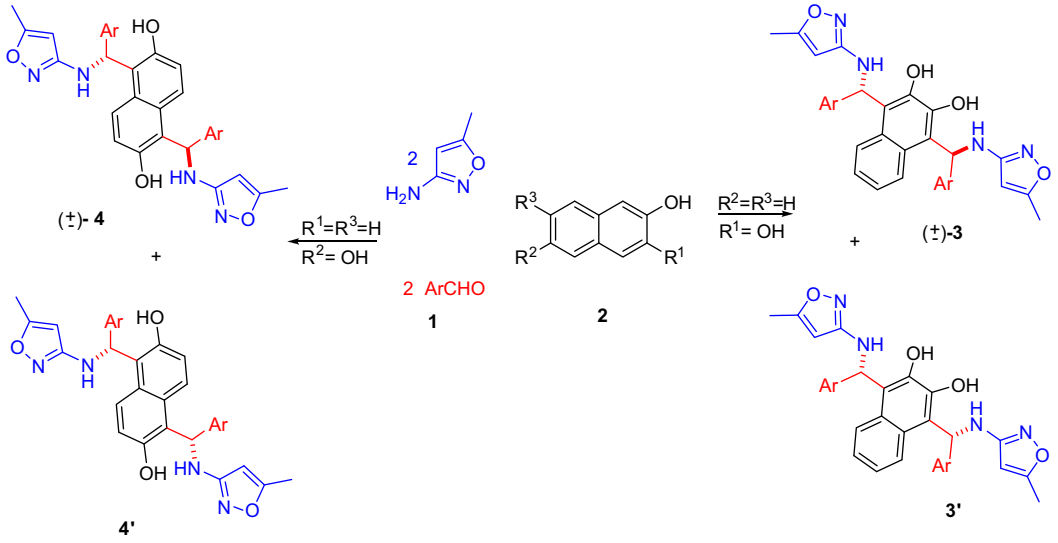


Figure 1. ORTEP view of compound **3b**.



Scheme 1. Synthesis of new bis-Betti bases.

We found that performing the reaction at 80 °C under solvent-free conditions provided the best result. The reaction was rapid, and achieved satisfactory conversion without any significant side reactions.

Next, we considered the introduction of additional diversity to this new class of Betti bases via the one-pot reaction. We examined several aryl aldehydes for the synthesis of Betti bases based on 2,6- or 2,3-dihydroxynaphthalene (Table 2). It is worthwhile to note that compounds **3** and **4** were obtained as the major products in racemic form for all the reactions examined in Table 2.

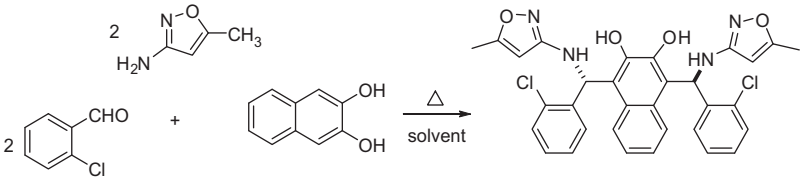
It was generally observed that high to excellent yields of the products were obtained with moderate to excellent diastereoselectivity in all cases (Table 2). The stereochemistry of compounds **3a–e** and **4a–i** was established by correlation of the spectroscopic data with those obtained for **3b**. Also, it was found that aryl aldehydes possessing electron-withdrawing groups could be converted into the desired products in higher isolated yields and shorter reaction times (Table 2, compare entries 4 and 5). Moreover, this reaction worked well with heteroaromatic carbaldehydes such as thiophene-2-carbaldehyde (Table 2, entry 14). Identification of the structures of the products was achieved by spectral analysis.[12]

This simple, straightforward, and atom-economic method represents an advantageous alternative to the laborious syntheses of this class of Betti bases. Thus, the reaction developed represents a short and expedient route to a family of Betti bases for the design of metal complex catalysts, and building blocks for organic synthesis.

Also, it was found that under the above reaction conditions, 2,7-dihydroxynaphthalene gave the corresponding mono-Betti base, exclusively (Table 3), which can be attributed to the steric hindrance which would be present in the corresponding bis-Betti base.

In conclusion, we have described a novel and efficient strategy for the diastereoselective synthesis of new bis-Betti bases. To our

Table 1
The effect of solvent and temperature on the yield of **3b**[a]



Entry	Solvent[b]	Temp (°C) **3b**	Yield[c] (%)
1	H_2O	80	60
2	EtOH	80	13
3	PEG-400	80	9
4	CH_3CN	80	10
5	Toluene	80	50
6	—	80	90
7	—	25	—
8	—	50	17
9	—	60	33
10	—	70	59
11	—	90	91

[a] Reaction conditions: 2-Chlorobenzaldehyde (2 mmol), 5-amino-3-methylisoxazole (2 mmol), 2,3-dihydroxynaphthalene (1 mmol), 2.5 h.
[b] 2 ml of solvent.
[c] Isolated yield.

Table 2
Synthesis of novel bis-Betti bases via a pseudo-five-component reaction under catalyst-free conditions

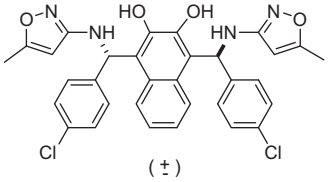
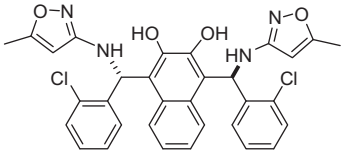
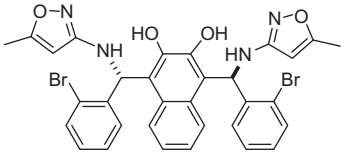
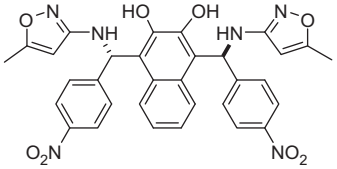
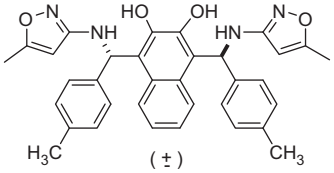
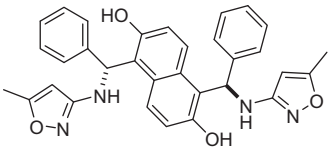
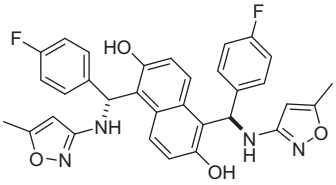
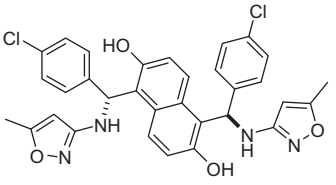
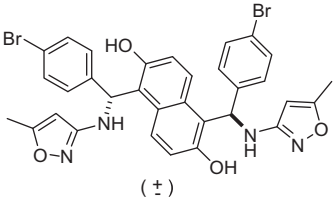
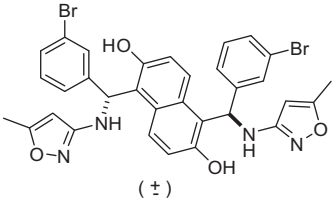
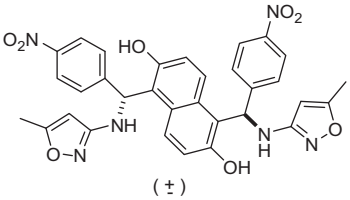
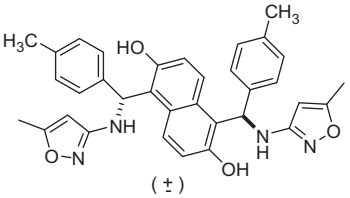
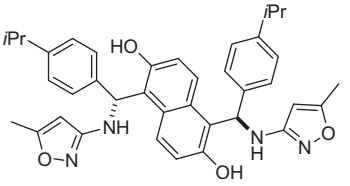
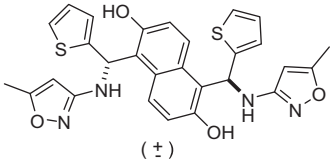
Entry	Ar	R^1	R^2	R^3	Product	Time (h)	Yield[a] (%)	d.r.[b]
1	4-ClC_6H_4	OH	H	H	**3a**  (±)	2	95	91:9
2	2-ClC_6H_4	OH	H	H	**3b** 	2.5	90	95:5
3	2-BrC_6H_4	OH	H	H	**3c** 	2.5	89	94:6
4	4-$O_2NC_6H_4$	OH	H	H	**3d** 	2	95	90:10
5	4-$H_3CC_6H_4$	OH	H	H	**3e**  (±)	3	85	95:5

Table 2 (*continued*)

Entry	Ar	R^1	R^2	R^3	Product		Time (h)	Yield[a] (%)	d.r.[b]
6	C_6H_5	H	OH	H		**4a**	5.5	75	56:34
7	4-FC_6H_4	H	OH	H		**4b**	4	90	67:33
8	4-ClC_6H_4	H	OH	H		**4c**	4.5	85	60:40
9	4-BrC_6H_4	H	OH	H		**4d**	4.5	80	67:33
10	3-BrC_6H_4	H	OH	H		**4e**	4	83	68:32
11	4-$O_2NC_6H_4$	H	OH	H		**4f**	4	89	70:30
12	4-$H_3CC_6H_4$	H	OH	H		**4g**	6	70	66:34
13	4-*i*PrC_6H_4	H	OH	H		**4h**	6	72	68:32

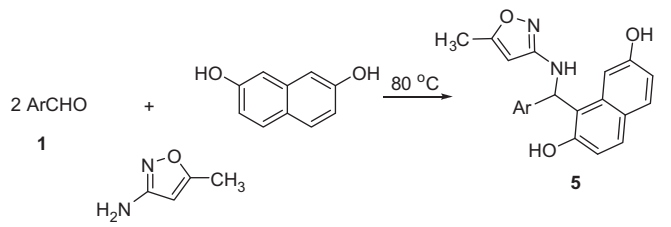
(*continued on next page*)

Table 2 (*continued*)

Entry	Ar	R^1	R^2	R^3	Product	Time (h)	Yield[a] (%)	d.r.[b]
14	2-thienyl	H	OH	H	 **4i** (±)	5	80	71:29

[a] Isolated yield.
[b] Diastereomeric ratio was determined by ^{1}H NMR and ^{13}C NMR spectroscopy of the crude product.

Table 3
Synthesis of mono-Betti bases from 2,7-dihydroxynaphthalene under catalyst-free conditions[a]



Entry	Ar		Time (h)	Yield[b] (%)
1	4-FC_6H_5	**5a**	0.5	98
2	4-ClC_6H_5	**5b**	0.6	95
3	2-ClC_6H_5	**5c**	0.6	93
4	4-$O_2NC_6H_5$	**5d**	0.5	97
5	4-$H_3CC_6H_5$	**5e**	0.7	89

[a] Reaction conditions: Arylaldehyde (2 mmol), 5-amino-3-methylisoxazole (2 mmol), 2,7-dihydroxynaphthalene (1 mmol).
[b] Isolated yield.

knowledge, this is the first example of a pseudo-five-component reaction under solvent-free conditions in the absence of any catalyst for the synthesis of bis-Betti bases under conventional heating.

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11. *General procedure*: A mixture of aryl aldehyde **1** (2 mmol), 5-amino-3-methylisoxazole (196 mg, 2 mmol), and dihydroxynaphthalene (1 mmol) was stirred at 80 °C for 0.5–6 h. After the reaction was completed (monitored by TLC), the mixture was cooled to room temperature and diluted with H_2O. The precipitated solid was collected by filtration, washed with H_2O, and was purified as appropriate by recrystallisation from acetonitrile.
12. Selected spectral data for compounds **3b**, **4i,** and **5d**: *1,4-Bis[(2-chlorophenyl)(5-methylisoxazol-3-ylamino)methyl]naphthalene-2,3-diol* (***3b***): White solid; mp 165–166 °C. FTIR (KBr, solid):3512, 3402, 3073, 1622, 1447, 1039, 752 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.59 (s, 2H), 7.80–7.83 (m, 2H), 7.51–7.53 (m, 2H), 7.39–7.41 (m, 2H), 7.25–7.32 (m, 4H), 7.15–7.18 (m, 2H), 7.07 (d, J = 5.6 Hz, 2H), 6.67 (d, J = 5.6 Hz, 2H), 5.77 (s, 2H), 2.22 (s, 6H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 167.9, 163.5, 145.3, 138.9, 132.7, 129.5, 128.7, 127.0, 126.7, 123.0, 117.8, 94.03, 53.2, 11.9. CHN: Anal. Calcd for $C_{32}H_{26}N_4O_4Cl_2$: C, 63.90; H, 4.36; N, 9.31. Found: C, 64.10; H, 4.53; N, 9.09. *1,5-Bis[(5-methylisoxazol-3-ylamino)(thiophen-2-yl)methyl]naphthalene-2,6-diol* (***4i***): White solid, mp 224–226 °C. FTIR (KBr, solid):3346, 3085, 2713, 1611, 1518, 1295, 701 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.84 (s, 2H), 7.93 (s, 2H), 7.28–7.30 (m, 2H), 7.09–7.11 (m, 2H), 6.86–6.88 (m, 4H), 6.78–6.80 (m, 2H), 6.73–6.74 (m, 2H), 5.85 (s, 2H), 2.20 (s, 6H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 167.51, 164.08, 150.00, 148.03, 127.08, 126.43, 124.13, 123.77, 119.94, 118.38, 93.92, 52.21, 12.02. CHN: Anal. Calcd for $C_{28}H_{24}N_4O_4S_2$: C, 61.75; H, 4.44; N, 10.29; S, 11.77. Found: C, 61.29; H, 4.51; N, 10.48, S, 11,61. *1-[(5-Methylisoxazol-3-ylamino)(4-nitrophenyl)methyl]naphthalene-2,7-diol* (***5d***): Yellow solid, mp 190 °C. FTIR (KBr, solid):3488, 3396, 1626, 1514, 1342, 1189, 845 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.02 (s, 1H), 9.65 (s, 1H), 8.15 (d, J = 8.8 Hz, 2H), 7.64 (d, J = 8.8 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.50 (d, J = 8.8 Hz, 2H), 7.18 (s, 1H), 6.99 (d, J = 8.8 Hz, 1H), 6.82–6.86 (m, 2H), 6.62 (d, J = 6 Hz, 1H), 5.86 (s, 1H), 2.23 (s, 3H).^{13}C NMR (100 M Hz, DMSO-d_6): δ = 167.42, 164.33, 155.89, 153.06, 151.90, 145.72, 133.61, 130.19, 129.50, 127.27, 123.17, 123.09, 117.33, 114.93, 114.74, 94.05, 52.56, 12.01. CHN: Anal. Calcd for $C_{21}H_{17}N_3O_5$: C, 64.45; H, 4.38; N, 10.74. Found: C, 64.29; H, 4.51; N, 10.65.