β-Naphthol in Glycerol: A Versatile Pair for Efficient and Convenient Synthesis of Aminonaphthols, Naphtho-1,3-oxazines, and Benzoxanthenes

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Abstract: Three-component Betti reaction was carried out in the environmentally benign, inexpensive, non-toxic solvent glycerol. Even in the absence of a catalyst, the reaction went completion with an unprecedented high rate and the expected Betti bases were obtained in up to 91% yield. The reaction works well for representative cyclic, acyclic, aliphatic, and aromatic amines and aldehydes. A benzoxanthene was also prepared in 93% yield following the same methodology with 20 mol% methanesulfonic acid catalyst.

Key words: glycerol, Betti reaction, one-pot synthesis, naphtho-1,3-oxazine, benzoxanthenes

The Betti reaction,[1] discovered by Mario Betti is useful in the synthesis of substituted aminonaphthols. Aminonaphthols have several interesting biological applications, for example as antipain agents **1** and **2**,[2] antibacterial activity **3**,[3] and enhancing drug cytotoxicity to multidrug resistant cell lines **4**,[4] etc. (Figure 1). Betti base derivatives have been employed in the total synthesis of tropane alkaloids[5] and they have also been used as a chiral auxiliary in natural product synthesis.[6] Recently, heterogeneous copper(II) triflate–silica gel,[7] copper nanoparticle,[8] nanocrystalline magnesium oxide,[9] and non-ionic surfactant[10] catalyzed Betti reactions have been reported in literature. Novel methodologies in Betti reaction are required to avoid the use of catalysts and to reduce reaction times. Multicomponent reactions carried out in unconventional/non-organic solvents have attracted much attention to date.[11] Its inexpensive, nontoxic, biocompatible, polar nature, and easy availability makes glycerol a suitable and viable alternative to solvents such as ionic liquids and supercritical carbon dioxide. Recent review article on glycerol by Cardierno and co-workers[12] and Jérôme and co-workers[13a] provide good insight into organic transformations carried out in glycerol solvent. To the best of our knowledge, the Betti reaction in glycerol has not been reported.

We were interested in investigating the Betti reaction in glycerol solvent. Initially, a trial reaction was carried out with β-naphthol (**5**, 1 mmol), formaldehyde (2 mmol), and morpholine (2 mmol). At room temperature, β-naphthol (**5**) was sparingly soluble in glycerol. However, after stirring for one hour at room temperature, partial conversion of β-naphthol into the corresponding product **6** was observed. Encouraged by this result, we decided to further investigate the role of temperature and co-solvent on the Betti reaction in glycerol (Scheme 1, Table 1).

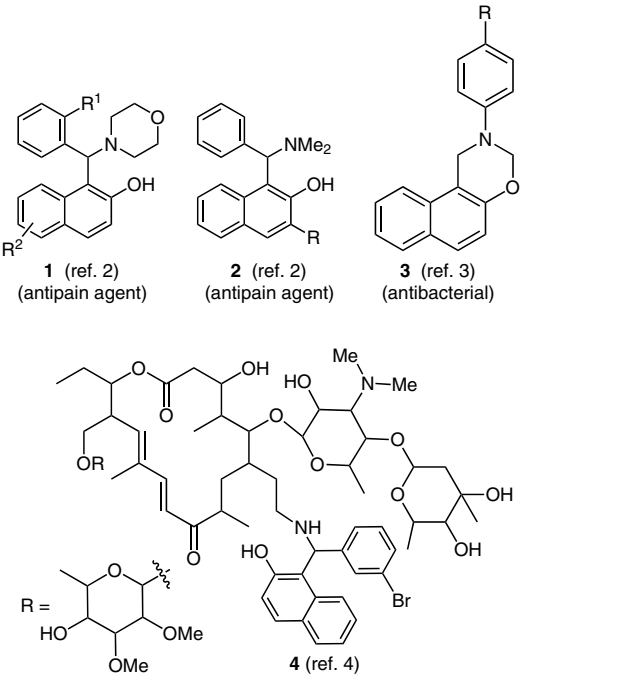
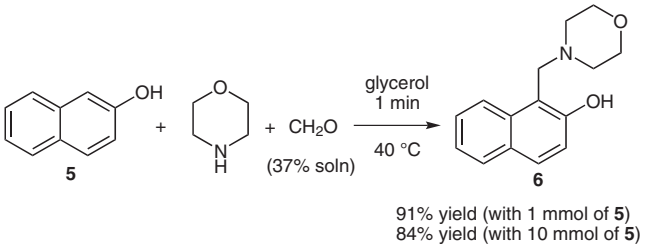


Figure 1 Bioactive Betti base derivatives



Scheme 1 Aminonaphthol synthesis in glycerol

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Table 1 Effect of Temperature and Co-solvent on the Yield of the Betti Reaction Product **6**

Entry	Method[a]	Solvent	Temp (°C)	Time (min)	Yield (%)
1	A	glycerol	r.t.	1	87
2	B	glycerol	40	1	91
3	B	glycerol	80	1	86
4	C	glycerol–EtOH (1:1)	r.t.	3	87
5	C	glycerol–MeOH (1:1)	r.t.	3	89
6	C	glycerol–H_2O (1:1)	r.t.	10	69
7	D	glycerol	80	10	81

[a] Method A: 1. β-naphthol (1 mmol), glycerol (2 mL), 90 °C (water bath), 5 min (dissolution); 2. cooled to r.t.; 3. successive addition of morpholine (2 mmol) and 37% CH_2O (2 mmol), r.t., stirring. Method B: 1. β-naphthol (1 mmol), glycerol (2 mL), indicated temperature, stirring, 10 min (homogeneous soln); 2. successive addition of morpholine (2 mmol) and 37% CH_2O (2 mmol), indicated temperature, stirring, indicated time. Method C: β-naphthol (1 mmol), glycerol–alcohol or H_2O (1:1, 2 mL) (homogeneous soln, entries 4 and 5); suspension, entry 6), successive addition of morpholine (2 mmol) and 37% CH_2O (2 mmol), r.t., stirring. Method D: β-naphthol (1 mmol), paraformaldehyde (1.5 mmol), morpholine (1.5 mmol), glycerol (2 mL), stirring, 80 °C, 10 min.

Under homogeneous conditions (Table 1, Method A), the reaction is complete within one minute and the aminonaphthol product **6** was obtained in 87% yield (entry 1). It was previously reported in the literature that as the temperature increases, the viscosity of glycerol decreases substantially and this facilitates the solubility of substrates and increases the product yield.[13] A slight increase in the reaction temperature to 40 °C only gave a marginal improvement in the yield (entry 2) while a further increase in the temperature above 40 °C reduced the product yield (entry 3). The use of methanol or ethanol as a co-solvent enabled the reaction to be performed at room temperature (entries 4 and 5). In both cases, aminonaphthol product **6** was obtained in good yields. Addition of water as a co-solvent reduced the solubility of β-naphthol (**5**) in glycerol and thus reduced the product yield (entry 6). The replacement of formaldehyde (37%) solution with paraformaldehyde did not affect the course of the reaction (entry **7**). Paraformaldehyde is insoluble in glycerol at room temperature and, hence, the reaction must be carried out at a higher temperature. The use of β-naphthol (1 mmol) in glycerol (2 mL) was necessary to obtain the optimum yield.

The sequence of Betti reaction in glycerol (Method A) is presented in Figure 2. After the addition of formaldehyde (37%) solution to the reaction mixture (d), an instantaneous exothermic reaction took place with immediate formation of the Betti base product **6**.

The formation of product **6** can be easily observed with the naked eye [Figure 2 (e)]. After one minute, the reaction was quenched with water (2 mL) and the product was filtered off.

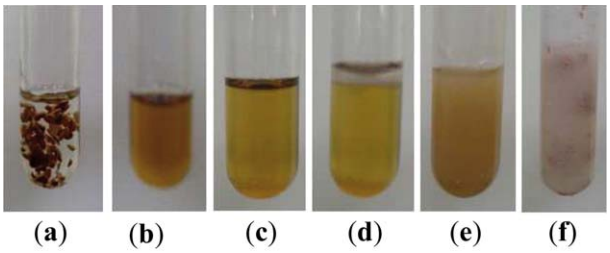
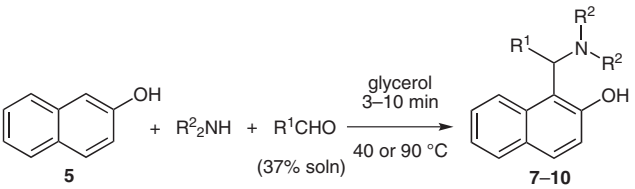


Figure 2 Sequence: (a) β-Naphthol in glycerol at r.t. (b) After heated in a water bath at 90 °C for 5 min. (c) After the addition of morpholine. (d) Immediately, after the addition of 37% formaldehyde solution. (e) Reaction mixture after 1 min. (f) Reaction mixture after quenching with H_2O.

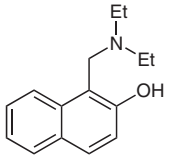
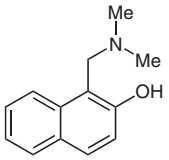
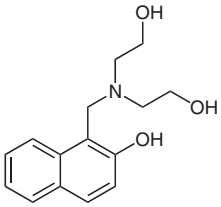
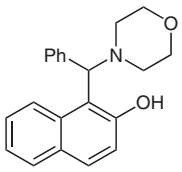
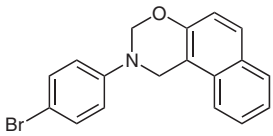
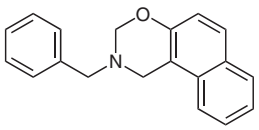
A stock solution of β-naphthol (**5**) in glycerol solvent could be prepared by heating β-naphthol (10 mmol) in glycerol (20 mL) in a water bath at 90 °C for approximately 30 minutes. The homogeneous solution thus obtained was kept undisturbed at room temperature. However, after eight hours, β-naphthol (**5**) began to crystallize from the solution. Hence, it is essential use a freshly prepared solution of β-naphthol (**5**) in glycerol in this reaction. In order to investigate the scope of reaction during the scale-up process, the following reaction was performed. To a homogeneous solution of β-naphthol (**5**, 10 mmol) in glycerol (20 mL) at 40 °C, morpholine (20 mmol) and 37% formaldehyde (20 mmol) were added successively in each in one portion and the reaction mixture was further vigorously stirred at 40 °C for a further 10 minutes. TLC analysis of reaction mixture revealed the clean and complete conversion of β-naphthol (**5**) to the corresponding Betti base product **6** in 84% yield. This observation shows that the reaction can be scaled up without difficulty. After standardizing the reaction conditions in glycerol, the reaction was screened with different amines and aldehyde (Schemes 2 and 3, Table 2). Acyclic aliphatic amines gave comparable yields to that of morpholine. However, after quenching, dimethylamine, diethylamine, and diethanolamine products **7**–**9** could not be isolated by simple filtration. The products were extracted with ethyl acetate (2 × 2 mL) using a cyclomixer.



$R^2{}_2NH$ = Me_2NH, Et_2NH, $[HO(CH_2)_2]_2NH$, morpholine
R^1CHO = CH_2O, PhCHO

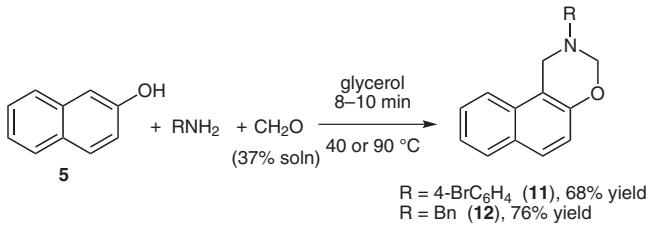
Scheme 2 Betti reaction in glycerol

Table 2 Betti Reaction of β-Naphthol (**5**), Amine, and Aldehyde in Glycerol Medium[a]

Entry	Aldehyde	Amine	Product	Temp (°C)	Time (min)	Yield (%)
1[b]	CH_2O	Et_2NH	 **7**	40	5	85 (80)[c]
2[b]	CH_2O	Me_2NH	 **8**	40	5	87 (76)[c]
3[b]	CH_2O	$[HO(CH_2)_2]_2NH$	 **9**	40	3	85 (81)[c]
4[d]	PhCHO	morpholine	 **10**	90	10	71
5[b,e]	CH_2O	$4\text{-}BrC_6H_4NH_2$	 **11**	90	10	68
6[b,f]	CH_2O	$BnNH_2$	 **12**	40	8	76 (63)[c]

[a] Conditions: β-naphthol (**5**, 1 mmol), glycerol (2 mL), amine (2 mmol), CH_2O (2 mmol), stirring.
[b] After quenching with H_2O, the mixture was extracted with EtOAc.
[c] Reaction carried using Method A (Table 1).
[d] After quenching with H_2O, the mixture was filtered and the product was recrystallized (EtOAc).
[e] Conditions: β-naphthol (**5**, 1 mmol), glycerol (2 mL), amine (1.1 mmol), 37% CH_2O (3 mmol); the crude product **11** was recrystallized (EtOAc).
[f] Conditions: β-naphthol (**5**, 1 mmol), glycerol (2 mL), amine (1.5 mmol), 37% CH_2O (3 mmol). The crude product **12** was recrystallized (EtOAc) and further confirmed by single crystal XRD.[14]

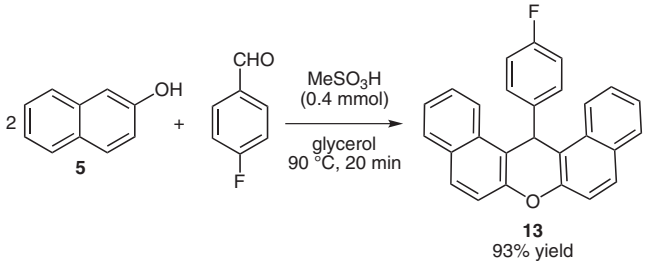
The Betti reaction in glycerol solvent was also screened with a representative aromatic aldehyde. With benzaldehyde, at room temperature only partial conversion of the β-naphthol to the corresponding product **10** was observed. Hence, reaction mixture was stirred in an oil bath at 90 °C for 10 minutes and the product **10** was formed in 71% yield (Table 2, entry 4). The Betti reaction of both aromatic amine (4-bromoaniline) and aliphatic primary amine (benzylamine) were carried out in glycerol solvent. With excess formaldehyde, 4-bromoaniline and benzylamine gave the corresponding naphtho-1,3-oxazine derivatives **11** and **12**, respectively (Scheme 3). It has been previously reported in the literature that with excess formaldehyde, primary amine Betti bases will be converted into the cor-



Scheme 3 Synthesis of naphthoxazine in glycerol

responding naphthoxazine derivatives.[3] The rate of the Betti reaction in glycerol is unusually very high. The high reaction rate could be attributed to the high polarity and strong hydrogen-bonding network of glycerol solvent.

We were interested in extending this methodology further to the synthesis of xanthenes. Xanthenes are interesting class of heterocyclic molecules with good antiproliferation properties.[15] In the presence of methanesulfonic acid (0.4 mmol), β-naphthol (**5**, 2 mmol), and 4-fluorobenzaldehyde (1.1 mmol) in glycerol (1 mL) at 90 °C for 20 minutes gave the expected xanthene **13** in 93% yield (Scheme 4).



Scheme 4 Xanthene synthesis in glycerol solvent

In conclusion, glycerol was found to be a versatile and environmentally benign solvent for the rapid, catalyst-free, efficient, one-pot synthesis of Betti bases. A representative xanthene derivative was also prepared in good yield in glycerol. This method offers several advantages such as exploiting an environmentally benign solvent, shorter reaction times, easy product isolation etc.

All the reactions were carried out in 98% glycerol (Merck). All the solvents and reagents were used without further purification.

1-(Morpholinomethyl)naphthalen-2-ol (6); Typical Procedure (Method B)
A dispersion of β-naphthol (**5**, 144 mg, 1 mmol) in glycerol (2 mL) was stirred in an oil bath at 40 °C for 10 min. After complete dissolution, morpholine (174 μL, 2 mmol) and 37% CH_2O soln (160 μL, 2 mmol) were added successively and the mixture was stirred at this temperature for 1 min. The mixture was quenched with cold H_2O (3 mL). For products **6** and **10**, the precipitate was filtered, dried, and recrystallized (EtOAc). For products **7**–**9**, **11**, and **12**, after completion of the reaction, the mixture was quenched with H_2O (3 mL) and extracted with EtOAc (2 × 2 mL) using a cyclomixer. The organic extract was separated, washed with brine, dried (anhyd Na_2SO_4), and solvents were evaporated under reduced pressure. Products **7** and **9** were purified by column chromatography (silica gel, hexanes–EtOAc, 95:5) and products **8**, **11**, and **12** were recrystallized (EtOAc).

1-(Morpholinomethyl)naphthalen-2-ol (6)
White solid; yield: 221 mg (91%); mp 107–109 °C (Lit.[16] 113–115 °C).

IR (KBr): 3431, 2946, 2845, 1656, 1120, 780 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.68 (br s, 4 H), 3.80 (s, 4 H), 4.15 (s, 2 H), 7.09 (d, *J* = 8.7 Hz, 1 H), 7.25–7.32 (m, 1 H), 7.43–7.48 (m, 1 H), 7.70 (d, *J* = 8.7 Hz, 1 H), 7.76 (d, *J* = 7.8 Hz, 1 H), 7.83 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 53.2, 56.8, 66.8, 110.4, 119.1, 121.0, 122.6, 126.5, 128.6, 129.0, 129.5, 132.8, 156.2.

MS (ESI): *m/z* = 244 (M + 1).

1-[(Diethylamino)methyl]naphthalen-2-ol (7)
Gummy solid; yield: 195 mg (85%).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.07 (t, *J* = 6.9 Hz, 6 H), 2.59 (q, *J* = 6.6 Hz, 4 H), 4.09 (s, 2 H), 7.07 (d, *J* = 8.7 Hz, 1 H), 7.18–7.23 (m, 1 H), 7.33–7.38 (m, 1 H), 7.60 (d, *J* = 8.7 Hz, 1 H), 7.66–7.69 (m, 2 H), 12.18 (br s, 1 H).

MS (ESI): *m/z* = 230 (M + 1).

1-[(Dimethylamino)methyl]naphthalen-2-ol (8)
Light brown solid; yield: 175 mg (87%); mp 57–59 °C.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.42 (s, 6 H), 4.10 (s, 2 H), 7.10 (d, *J* = 8.7 Hz, 1 H), 7.28–7.31 (m, 1 H), 7.41–7.46 (m, 1 H), 7.69 (d, *J* = 9.0 Hz, 1 H), 7.76 (d, *J* = 8.1 Hz, 1 H), 7.82 (d, *J* = 8.7 Hz, 1 H).

MS (ESI): *m/z* = 202 (M + 1).

1-{[Bis(2-hydroxyethyl)amino]methyl}naphthalen-2-ol (9)
Gummy solid; yield: 222 mg (85%).

^1H NMR (300 MHz, $CDCl_3$): δ = 2.75 (t, *J* = 5.1 Hz, 4 H), 3.72 (t, *J* = 5.1 Hz, 4 H), 4.19 (s, 2 H), 5.84 (br s, 3 H), 7.04 (d, *J* = 9 Hz, 1 H), 7.24–7.28 (m, 1 H), 7.37–7.42 (m, 1 H), 7.61 (d, *J* = 8.7 Hz, 1 H), 7.69–7.76 (m, 2 H).

MS (ESI): *m/z* = 262 (M + 1).

1-[Morpholino(phenyl)methyl]naphthalen-2-ol (10)
Off-white solid; yield: 227 mg (71%); mp 175–177 °C (Lit.[17a] 177–179 °C).

^1H NMR (300 MHz, $CDCl_3$): δ = 2.45 (br s, 4 H), 3.83 (br s, 4 H), 5.14 (s, 1 H), 7.16–7.86 (m, 11 H), 13.18 (br s, 1 H).

MS (ESI): *m/z* = 320 (M + 1).

2-(4-Bromophenyl)-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine (11)
White crystals; yield: 230 mg (68%); mp 118–120 °C (Lit.[17b] 118–120 °C).

^1H NMR (300 MHz, $CDCl_3$): δ = 4.93 (s, 2 H), 5.39 (s, 2 H), 7.02–7.07 (m, 3 H), 7.34–7.43 (m, 3 H), 7.53–7.54 (m, 1 H), 7.65–7.70 (m, 2 H), 7.80 (d, *J* = 8.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 48.4, 79.4, 112.3, 114.2, 118.8, 120.4, 120.9, 123.9, 126.9, 128.6, 128.9, 129.2, 131.2, 132.3, 147.9, 152.3.

MS (ESI): *m/z* = 340 (M^+).

2-Benzyl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine (12)
White crystals; yield: 209 mg (76%); mp 123–125 °C.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.00 (s, 2 H), 4.33 (s, 2 H), 4.97 (s, 2 H), 7.10 (d, *J* = 9.0 Hz, 1 H), 7.26–7.46 (m, 7 H), 7.55 (d, *J* = 8.4 Hz, 1 H), 7.69 (d, *J* = 8.7 Hz, 1 H), 7.79 (d, *J* = 8.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 47.4, 56.2, 82.1, 111.8, 118.7, 121.2, 123.6, 126.6, 127.5, 128.1, 128.6, 128.7, 129.1, 132.0, 138.3, 151.9.

MS (ESI): *m/z* = 276 (M + 1).

14-(4-Fluorophenyl)-14*H*-dibenzo[*a*,*j*]xanthene (13)
A dispersion of β-naphthol (288 mg, 2 mmol) in glycerol (1 mL) was stirred in an oil bath at 90 °C for 5 min. After complete dissolution, 4-fluorobenzaldehyde (116 μL, 1.1 mmol) and MsOH (26 μL, 0.4 mmol) were added successively and the mixture was stirred at 90 °C for 20 min. After completion of the reaction, the mixture was quenched with cold H_2O (3 mL) and the product was extracted with EtOAc (3 × 5 mL). The solvents were evaporated, and the product was recrystallized (EtOH) to give white crystals; yield: 350 mg (93%); mp 240–242 °C (Lit.[18] 239–240 °C).

IR (KBr): 3072, 3005, 2882, 1593, 1502, 1240, 834 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.43 (s, 1 H), 6.74–6.82 (m, 2 H), 7.36–7.46 (m, 6 H), 7.50–7.58 (m, 2 H), 7.72–7.82 (m, 4 H), 8.26–8.31 (m, 2 H).

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(14) Crystal data: For compound **12**: Molecular formula: $C_{19}H_{17}NO$, MW = 275.34, monoclinic, space group: *P*21/*n*, *a* = 9.8559(6), *b* = 5.2439(3), *c* = 27.8100(16), α = 90.00, β = 98.750(3), γ = 90.00 (CCDC Deposition Number: 903651). The crystal structure of the compound **12** has already been reported: Yang, X.-H.; Chen, X.-L.; Diao, X.-J.; Wu, M.-H. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2007**, *63*, o3312.
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