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Non-ionic surfactant catalyzed synthesis of Betti base in water

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ABSTRACT

We have developed an efficient non-ionic surfactant (Triton X-100) catalyzed multicomponent synthesis of Betti base from secondary amine, aromatic aldehydes, and β-naphthol using Mannich-type reaction in water. Lewis and Brønsted acid catalysts, ionic and non-ionic surfactant have been screened for the reaction. Non-ionic surfactant (Triton X-100) gave the best results and the reaction proceeds through the imine formation, which is stabilized by colloidal dispersion and undergoes nucleophilic addition to afford the corresponding N,N-dialkylated Betti base in excellent yields.

Water as solvent has attracted much attention in organic synthesis because of its unique reactivity and selectivity that are not attained in organic solvents. Water is the cheapest, safest, and most non-toxic solvent of the chemical world. Water is also considered as an ideal solvent due to economical and environmental concerns.[1] Breslow and co-workers reported acceleration of the Diels–Alder reaction 'In Water,'[2] while Sharpless and co-workers described 'On Water,'[3] reaction that triggered a more widespread interest in the field. Initially, the use of water as solvent for organic reactions was mainly restricted to simple hydrolysis reactions. Recently, water has been successfully applied to Claisen-rearrangements,[4] Aldol reactions,[5] allylation reactions,[6] Reformatsky-type reactions,[7] Mukaiyama Aldol reactions,[8] Pinacol coupling,[9] Wittig reactions,[10] Baylis–Hillman reactions,[11] Mannich reactions,[12] Heck coupling,[13] Suzuki coupling,[14] Stille coupling,[15] 1,3-dipolar cycloaddition reactions,[16] and transition-metal-catalyzed cyclization reactions.[17]

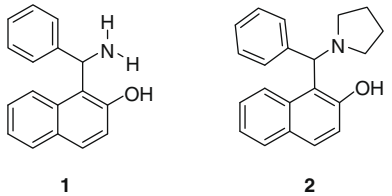
The use of water is preferred over organic solvents to decrease environmental contamination, easy work-up, and economical. However, the possibility of using water as solvent is limited because the majority of reactants are poorly soluble in water which can be overcome by the use of surfactant.

Recently, interest in the chemistry of the Betti base[18] has intensified due to their attractive catalytic[19] and biological[20] properties (Fig. 1). Betti base **1** is generally synthesized by condensation of 2-naphthol, ammonia and benzaldehyde but it is thermally unstable and therefore, it is not easy to synthesize corresponding *N,N*-dialkyl derivatives.[21] However, the alkyl derivative of Betti base **2** has been prepared by the original Betti procedure.[22] The most valuable methodology was reported by Katritzky et al. by displacement of the benzotriazole moiety from *N*-[α-(dialkylamino)alkyl]benzotriazoles with phenolate anions under refluxing toluene.[23]

In continuation of our work on multicomponent reactions (MCRs)[24] for the synthesis of various biologically important heterocyclic compounds, we wish to report herein a highly efficient procedure for the preparation of Betti base and its derivatives via one-pot three component Mannich-type reaction using non-ionic surfactant Triton X-100 in aqueous media (Scheme 1). It is important to emphasize that Lewis, and Brønsted acid surfactant catalyzed reactions are commonly reported but there are very few reports where non-ionic surfactants were used as catalyst.[25]

The non-ionic surfactant Triton X-100 (TR) is one of the most commonly used detergents in biochemistry as solubilizer with a wide range of applications to biological systems.[26] Solubilization of lipid membranes triggered by Triton X-100 is a well-described phenomenon. It is also used as an emulsifier, and complexing agent in both aqueous and non-aqueous media.

Non-ionic surfactants have the tendency to adsorb at interfaces and to form micelles beyond their critical micelle concentration (CMC) similar to the ionic surfactants.[27] However, the advantage of non-ionic surfactants (Triton X-100) is the absence of the electrical double layer as formed by the ionic surfactants. Consequently, non-ionic surfactants are desirable model adsorbents for interfacial processes. Therefore, we decided to exploit these properties of non-ionic surfactant for organic reaction.



1 2

Figure 1. Structure of Betti bases.

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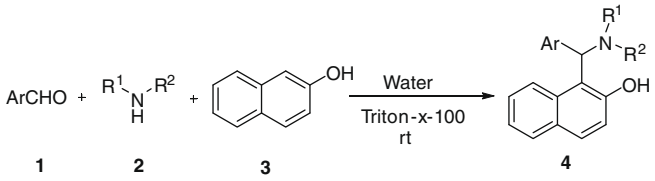


Scheme 1. Synthesis of Betti base in water.

Table 1
Screening of various types of catalysts for the synthesis of Betti base

Entry	Catalyst[a]	Time(h)	Yield[b] (%)
1	TsOH	4.0	35
2	Boric acid	4.5	15
3	SDS	4.0	40
4	TsOH + SDS	5.0	57
5	SDBS	4.5	50
6	DBSA	5.2	38
7	Triton X-100	2.5	93
8	Tween-20	3.0	90
9	Triton CF-10	3.0	86
10	CTAB	5.2	59

[a] The reaction was conducted with benzaldehyde (5 mmol), β-naphthol (3.8 mmol), and pyrrolidine (3.8 mmol) in a mixture of catalyst (5 mol %) and water (2 ml) at room temperature for given hours.
[b] Isolated yield.

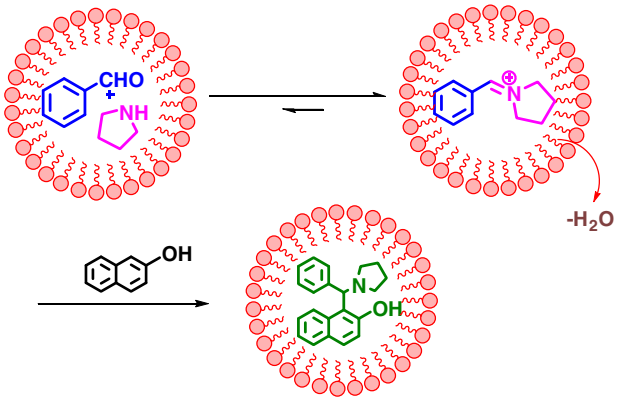


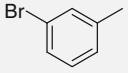
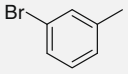
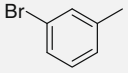
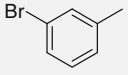
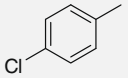
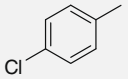
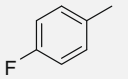
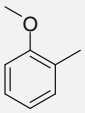
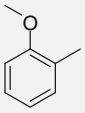
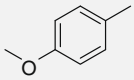
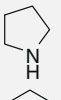
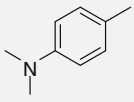
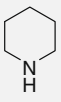
Figure 2. Micelle-promoted multicomponent Betti base synthesis.

In our preliminary study, several surfactant, Lewis, and Brønsted acid catalysts were used for optimization of reaction conditions in water. Benzaldehyde, pyrrolidine, and 2-naphthol were taken as a model substrate.

Among the catalysts tested, surfactant catalyzed the reaction most efficiently. *p*-Toluenesulfonic acid (TsOH) and boric acid did not afford the desired product in good yields. TsOH formed two immiscible layers while the surfactant formed a white turbid reaction mixture indicating that the long alkyl chain of the surfactant is necessary for the formation of the colloidal dispersion. However, it was found that the type of surfactant used influenced both the yield and the reaction time. Non-ionic surfactants (Triton X-100, Tween-20, and Triton CF-10) were effective, and required a shorter reaction time, an acidic surfactant DBSA (dodecylbenzenesulfonic acid) reduced the yield, and anionic surfactants SDS and SDBS(4-dodecylbenzenesulfonic acid) were slightly less effective than a cationic surfactant CTAB (cetyltrimethylammonium bromide). In fact, a combination of TsOH and sodium dodecyl sulfate (SDS) which formed a colloidal dispersion adduct gave the desired product in a modest yield. From these observations, it was concluded that Triton X-100 is the most efficient surfactant for this reaction (Table 1). These reactions when performed in water without any surfactant, starting materials were recovered.

The reaction might proceed through the imine formation of the aldehyde and the 2° amine, followed by the attack of the β-naphthol. This dehydrative imine formation is a characteristic feature of colloidal dispersion system of our reactions of imines in water. Dehydration in water is really unusual and exciting because in water usually hydrolysis occurs. The equilibrium position shifts toward the imine side, because water molecules would be expelled

Table 2
Triton X-100 catalyzed synthesis of Betti base[a]

Entry	Ar	Amine	Product[b]	Time (h)	Yield[c]
1			**4a**	2.5	93
2			**4b**	2.5	90
3			**4c**	2.5	89
4			**4d**	2.0	94
5			**4e**	2.0	90
6			**4f**	2.0	90
7			**4g**	2.0	93
8			**4h**	2.0	88
9			**4i**	2.0	86
10			**4j**	2.0	90
11			**4k**	3.0	85
12			**4l**	3.0	88
13			**4m**	3.0	86
14			**4n**	4.5	80

[a] The reaction was conducted with aromatic aldehyde (5 mmol), β-naphthol (3.8 mmol), and secondary amine (3.8 mmol) in a mixture of Triton X-100 (5 mol %) and water (2 ml) at room temperature for 2–4.5 h.
[b] All products were characterized by ^{1}H and ^{13}C NMR, and mass spectroscopy.
[c] Isolated yield.

out of the droplets due to hydrophobic nature of their interior (Fig. 2).

The high solubilizing capacity of non-ionic Triton X-100 is related to its hydrophobic character, as can be evaluated from its critical micelle concentration (2.5×10^{-4} M)[28] and hydrophile–lipophile balance (13.5)[29] values. Triton X-100 solubilizes the nucleophilic reagent, as well as enhances the nucleophilicity of the counterions. Besides, the surfactant properties of Triton X-100 improve the reaction kinetics by increasing interfacial area.

The optimization reveals that Triton X-100 gives the best results hence the generality of this procedure has been examined. A series of aldehyde and amines with 2-naphthol was carried out using Triton X-100 as surfactant catalyst in water.[30,31] The results are shown in (Table 2). All the aromatic aldehydes reacted almost equally well to afford Betti base (**4a–n**) in excellent yields.

In conclusion, we have developed an efficient non-ionic surfactant, Triton X-100 catalyzed multicomponent Mannich-type reactions for the synthesis of Betti base from aldehydes, secondary amines, and 2-naphthol in water. Triton X-100 forms stable colloidal medium which plays an essential role in acceleration of the reactions in water.

The process is high yielding, eco-friendly, and demonstrates the value of the non-ionic surfactant-mediated organic solvent-free methodology in organic synthesis.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.01.056.

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29. Neugebauer, J. *A Guide to the Properties and Uses of Detergents in Biology and Biochemistry*; Calbiochem-Novabiochem Int: La Jolla, 1994.
30. *General procedure for the synthesis of compound* (**4**). In a typical experiment, the aldehyde (5 mmol), β-naphthol (3.8 mmol) and pyrolidine (3.8 mmol) were taken in a mixture of Triton X-100 (5 mol %) and water (2 ml) to a round-bottomed flask. The reaction mixture was vigorously stirred at room temperature. After the reaction was completed (monitored by TLC) the reaction mixture was extracted with ethylacetate, the aqueous-phase was back extracted with ethylacetate (3×15 ml). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to leave the crude product as a white solid which was purified by silica gel column chromatography (EtoAc/hexane mixtures).
31. *Analytical data for few representative compounds*. *1-(Phenyl(pyrrolidin-1-yl)methyl)naphthalen-2-ol* (**4a**) white solid; mp 178–179 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.85 (br s, 4H), 2.43 (br s, 4H), 5.12 (s, 1H), 7.13–7.38 (m, 6H, ArH), 7.58–7.70 (m, 4H), 7.86 (d, J = 9 Hz,1H), 13.82 (br s, 1H), ^{13}C NMR (50 MHz, $CDCl_3$) δ = 23.81, 54.20, 71.25, 120.20, 120.31, 121.54, 122.80, 126.81, 127.25, 128.01, 128.26, 128.91, 129.0, 129.1, 129.91, 129.30, 132.32, 141.71, 156.00. IR (KBr): 3120, 3058, 2972, 2843, 1621, 1453, 1239, 750 cm^{-1}. ESIMS: m/z 304 (M+H)$^+$. *1-((3-Bromophenyl)(diethylamino)methyl)naphthalen-2-ol* (**4e**) white solid; mp 157 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.02 (t, J = 7.05 Hz, 6H, CH_3), 2.74 (br, d, J = 6.42 Hz, 4H, –NCH_2), 5.39 (s, 1H, CH), 7.09–7.14 (m, 2H, ArH), 7.20–7.24 (m, 1H, ArH), 7.30–7.33 (m, 1H, ArH), 7.36–7.42 (m, 1H, ArH), 7.58–7.60 (d, J = 7.62 Hz, 1H, ArH), 7.67–7.77 (m, 2H, ArH), 7.81 (d, J = 8.58 Hz, 2H, ArH), 14.01 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 300 MHz) δ = 9.91, 42.86, 66.97, 115.89, 120.19, 120.58, 122.44, 122.65, 126.60, 127.64, 128.62, 129.05, 129.68, 130.38, 131.07, 131.87, 132.03, 142.41, 156.02. IR (KBr): 3140, 3061, 2965, 2839, 1617, 1450, 1235, 749 cm^{-1}. ESIMS: m/z 384 (M+H)$^+$. *1-((4-Chlorophenyl)(dimethylamino)methyl)naphthalen-2-ol* (**4h**) white solid; mp 128–130 °C. ^{1}H NMR ($CDCl_3$, 300 MH_Z) δ = 2.34 (s, 6H, NCH_3), 4.95 (s, 1H, CH), 7.08–7.45 (m, 4H, ArH), 7.50–7.53 (m, 3H, ArH), 7.65–7.83 (m, 3H, ArH), 9.98 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 41.54, 72.76, 116.32, 119.85, 121.14, 122.38, 126.42, 127.70, 128.48, 128.67, 128.83, 128.89, 129.75, 131.21, 142.37, 155.20. IR (KBr): 3129, 3061, 2976, 2848, 1629, 1462, 1240, 758 cm^{-1}. ESIMS: m/z 312 (M+H)$^+$. *1-((2-Methoxyphenyl)(piperidin-1-yl)methyl)naphthalen-2-ol* (**4k**) mp 181 °C, white solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.42–1.73 (m, 6H, -CH_2), 2.07–2.25 (m, 2H, –NCH_2), 2.25 (d, J = 4.35 Hz, 1H, –(NCH), 3.27 (d, J = 11.7 Hz, 1H, –(NCH), 3.99 (s, 3H -OCH_3), 5.81 (s, 1H, CH), 6.81 (t, J = 7.56 Hz, 1H, ArH), 6.85 (d, J = 8.16 Hz, 1H, ArH), 7.11–7.21 (m, 3H, ArH), 7.26–7.32 (m, 1H, ArH), 7.46–7.51 (m, 1H, ArH), 7.61–7.66 (m, 2H, ArH), 7.75 (d, J = 8.58 Hz, 1H, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 24.14, 25.93, 26.31, 49.37, 54.76, 55.55, 62.15, 110.33, 116.67, 119.93, 121.43, 121.48, 122.15, 126.19, 127.61, 128.42, 128.49 128.53, 128.87, 128.92, 130.00, 132.89, 156.45, 156.77 ppm. IR (KBr): 3131, 3054, 2961, 2854, 1652, 1449, 1238, 747 cm^{-1}. ESIMS: m/z 348 (M+H)$^+$. *1-((4-(Dimethylamino)phenyl)(piperidin-1-yl)methyl)-naphthalen-2-ol* (**4n**) Oil, ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 1.25 (br s, 6H, CH_2), 1.66 (br s, 4H, –NCH_2), 2.85 (s, 6H, NCH_3), 4.98 (s, 1H, CH), 6.65 (d, J = 8.00 Hz, 2H, ArH), 7.11–7.68 (m, 8H, ArH), 7.80 (d, J = 8.46 Hz, 1H, ArH), 14.18 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 4.24, 26.11, 29.68, 40.04, 40.34, 71.46, 110.98, 112.34, 116.72, 119.90, 121.22, 122.10, 126.16, 127.09, 128.61, 128.74, 128.92, 129.90, 131.97, 132.43, 149.96, 155.44. IR (neat): 3119, 3052, 2969, 2848, 1628, 1461, 1232, 745 cm^{-1}. ESIMS: m/z 361 (M+H)$^+$.