Synthesis of 1-carbamatoalkyl-2-naphthols in Tween® 20 aqueous micelles

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A facile and efficient procedure for the preparation of 1-carbamatoalkyl-2-naphthols by a one-pot multi-component reaction of 2-naphthol, aldehydes and carbamates is described. The procedure is carried out under neutral conditions at 75–80 °C in an aqueous medium catalysed by the non-ionic surfactant Tween® A loading of 20. 5 wt% of the catalyst was optimal. After the reaction, the catalyst could be simply recovered and reused directly without any further treatment. Product yields were slightly decreased after six cycles. The effect of some common solvents other than water on the reaction was explored besides the water. The generality of this multi-component condensation reaction was evaluated with various aldehydes and carbamates under the optimised conditions.

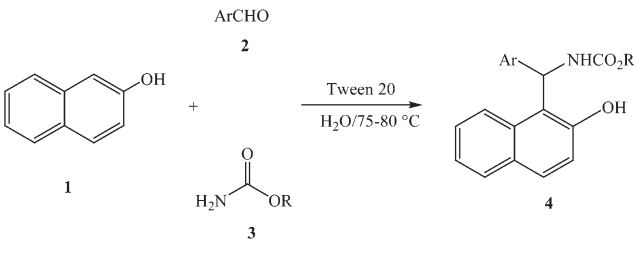
Keywords: 1-carbamatoalkyl-2-naphthols, Tween®, 2-napthol, aldehydes, alkyl carbamates

Water is becoming a more attractive solvent for economic and environmental reasons.[1] It has attracted much attention in organic synthesis because of its unique effects on reactions, which cannot be achieved using organic solvents.[2] Additionally, procedures do not requiredrying of solvents, substrates and reagents.

The poor solubility of organic reactants in water is the main obstacle to using water as a reaction medium in many cases. To solve the problem, surfactants have been applied as emulsifiers, and complexing agents in aqueous reactions, or as solubilisers for biological systems on an industrial scale.[3,4] It is known that surfactants solubilise nucleophilic reagents, enhance the nucleophilicity of anions[5] and improve rates of reaction by increasing the interfacial area.

Carbamates show important of biological activity and are Found:in drugs such as nucleoside antibiotics and HIV protease inhibitors.[6] In particular, 1-carbamatoalkyl-2-naphthol derivatives exhibit a broad spectrum of biological and pharmaceutical activities.[7] They can be prepared by the multicomponent reaction (MCR) of 2-naphthol, aldehydes and carbamates.[8] The condensation is catalysed by various homogeneous and heterogeneous Lewis or Brønsted acids including SiO_2-$NaHSO_4$,[9] SiO_2–$HClO_4$,[10] SiO_2–PPA,[11] zwitterionic-type molten salts,[12] ionic liquids,[13–14] $[MeC(OH)_2]^+ClO_4^-$,[15] SiO_2-nanoparticles,[16] magnetic nanoparticles,[17] and $Mg(OOCCF_3)_2$.[18] However, the search for new, environmentally friendly, efficient and more general kinds of catalysts, including neutral ones, to synthesise 1-carbamatoalkyl-2-naphthols is ongoing.

Continuing our work on clean MCRs,[19] and considering the importance of reactions in aqueous media, we wish to report the behavior of Tween® 20, a non-ionic surfactant, as a neutral catalyst in the synthesis of 1-carbamatoalkyl-2-naphthols by a three-component condensation (Scheme 1). The effect of the catalyst, solvent, and other conditions has been investigated. The reaction is carried out for the first time under neutral conditions.



Scheme 1 Synthesis of 1-carbamatoalkyl-2-naphthols.

Initially, to find the optimal conditions, benzaldehyde, 2-naphthol, and methyl carbamate were selected as the model reactants under various conditions and loadings of the catalyst (Table 1). No product was observed in the absence of a catalyst after 2 H, even at 100 °C. It is noteworthy that the water-catalyst system could be reused several times without an appreciable decrease in yield and reaction rate. The reaction of 2-naphthol, benzaldehyde and methyl carbamate proceeded smoothly in Tween® 20 aqueous media, and the optimal loading of the catalyst was 5 wt %.

The model reaction was carried out in the presence of 5 wt% catalyst in different solvents and under solvent-free conditions. The results are summarised in Table 2. The yields of the reaction in polar solvents such as H_2O, EtOH, and CH_3CN were greater than in non-polar solvents and solvent-free conditions. Of the polar solvents, water gave the best result in terms of efficiency. The product could be separated from the aqueous medium (water, catalyst, *etc*.) simply by filtration and the catalyst contained in the water could be reused directly without any treatment. Therefore removing water from products was not a highly energy-consuming process. When the reaction was completed, the catalyst could be reused at least six times without appreciable decrease in yield. Any decrease in

Table 1 Optimisation of the condensation of benzaldehyde, 2-naphthol and methyl carbamate[a]

Entry	Catalytic system	Loading /wt%	T/°C	Time /min	Yield /%
1	catalyst free	–	100	120	0
2	Tween® 20	1	75–80	45	61
3	Tween® 20	3	75–80	45	73
4	Tween® 20	5	75–80	45	89
5	Tween® 20	7	75–80	45	89
6	Tween® 20	10	75–80	45	88

[a]Reaction conditions: naphthol (2 mmol), benzaldehyde (2 mmol), methyl carbamate (2 mmol), catalyst (0.1 mmol), aqueous media (4 mL).

Table 2 Effects of solvents on reaction of benzaldehyde, 2-naphthol and methyl carbamate

Entry	Solvents	Temperature /°C	Time/min	Yield/%
1	Solvent-free	100	120	23
2	H_2O	75–80	45	89
3	EtOH	Reflux	45	34
4	CH_3CN	Reflux	45	46
5	$CHCl_3$	Reflux	45	26
6	CH_2Cl_2	Reflux	45	25
7	Benzene	Reflux	45	31
8	Toluene	100	45	42

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yield might be due to loss of the catalyst in the recycling procedures.

In order to evaluate the generality of this multi-component condensation reaction, the reactions of various aldehydes and carbamates in the presence of Tween® 20 were explored. As Table 3 shows, this one-pot, three-component reaction was completed within 30–60 min and the products were isolated in moderate to good yields. It noteworthy that aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents afforded similarly good yields of the corresponding carbamatoalkyl naphthols. In addition, methyl, ethyl and benzyl carbamates could also afford reasonable to good yields. In case of aliphatic aldehydes, the corresponding product (Table 3 entries 16–18) appeared not to be generated. This observation is general for aliphatic aldehydes, and the reason is being investigated. It is intended to extend the method to reaction of thiocarbamates, ureas, *etc*.

The results obtained with α-naphthol, benzaldehyde, and methyl carbamate under the optimised conditions were compared with those from previous work reported in recent years using other catalysts for this reaction. The data listed in Table 4 show that Tween® 20 is a good catalyst for the synthesis of carbamatoalkylnaphthols based on cost-effectiveness, post-procedure, recyclability and yields.

Table 3 Tween® 20-catalysed three-component reaction of naphthol, carbamate and various aromatic aldehydes[a]

Entry	Ar	R	Time /min	Yield/%	M.p. /°C	Lit. m.p. / °C Ref.
1	C_6H_5	Me	45	89	220–222	222–224[12]
2	4-ClC_6H_4	Me	45	90	201–203	203–205[12]
3	2-ClC_6H_4	Me	45	88	214–216	–
4	2,4-$Cl_2C_6H_3$	Me	60	86	194–196	194–196[12]
5	2-$NO_2C_6H_4$	Me	30	92	237–239	241–242[12]
6	3-$NO_2C_6H_4$	Me	30	91	247–249	253–255[12]
7	4-$CH_3C_6H_4$	Me	50	79	186–188	188[17]
8	2-$CH_3C_6H_4$	Me	60	78	229–231	230–232[12]
9	C_6H_5	$PhCH_2$	50	89	179–181	180–182[12]
10	2-$NO_2C_6H_4$	$PhCH_2$	30	93	206–208	–
11	3-$NO_2C_6H_4$	$PhCH_2$	30	92	201–203	205–207[12]
12	2-ClC_6H_4	$PhCH_2$	50	90	166–168	163–165[12]
13	C_6H_5	Et	50	91	196–198	195–196[13]
14	4-ClC_6H_4	Et	45	87	210–212	–
15	3-$NO_2C_6H_4$	Et	30	90	222–224	215–217[13]
16	CH_3CH_2	Me	120	–	–	–
17	*n*-C_3H_7	Me	120	–	–	–
18	*n*-C_4H_9	Me	120	–	–	–

[a]Reaction conditions: naphthol (2 mmol), benzaldehyde (2 mmol), carbamate (2 mmol), catalyst (5 wt. %, 4.0 mL aqueous micelles).

Lastly, we propose the following possible mechanism to account for the reaction (Fig. 1). In the micelle neutral aqueous micelles of Tween® 20, the hydrophobic moieties escape from the water molecules that encircle the micelle core of the surfactant. The reactants are hydrophobic molecules in aqueous media; they are activated by hydrogen bonding and migrate into the hydrophobic core of the micellar droplets,[20] where the reactions take place more easily and solid products thus formed immediately precipitate.

In conclusion, an efficient procedure for the preparation of 2-carbamatoalkyl-2-naphthols by the one-pot three-component condensation reaction catalysed by Tween® 20 has been established. The reaction can be carried out at 75–80 °C in an aqueous medium. The methodology gives advantages such as mild conditions, recyclability of the catalyst and easy work-up and isolation of the products.

Experimental

Melting points were measured on an X-6 melting point apparatus with microscope. ^{1}H NMR spectra were recorded on a Bruker DRX300 (300 MHz) spectrometer and ^{13}C NMR spectra on Bruker DRX300 (75.5 MHz) spectrometer. Mass spectra were obtained with an automated Fininigan TSQ Quantum Ultra AM (Thermal) LC/MS spectrometer. Elemental analyses were recorded on a Perkin-Elmer C, analyser. Tween® 20 (polyoxyethylene 20 sorbitan monolaurate, $C_{58}H_{114}O_{26}$; M 1227.5) and other chemicals (AR grade) were commercially available from the Sinopharm Chemical Reagent Co., Ltd, and were used directly without further treatment.

Synthesis of 1-carbamatoalkyl-2-naphthols; general procedure

In a typical experiment (Scheme 1), β-naphthol (2 mmol), aldehyde (2 mmol) and carbamate (2 mmol) were added to a round-bottomed flask charged with a solution of 5 wt% Tween® 20 aqueous micelles (4.0 mL) under stirring. The mixture was then vigorously stirred at 75–80 °C. After completion of the condensation (monitored by TLC),

Table 4 Comparison of our results with previously reported methods

Entry	Catalyst	Reaction conditions	Time /min	Yields /% Ref.
1	SiO_2-$NaHSO_4$	Neat/ 100 °C	3.5	81[8]
2	SiO_2-$HClO_4$	Neat/ 85 °C	5	90[9]
3	SiO_2-PPA	Neat/ 100 °C	6	90[10]
4	Zwitterionic salt	Neat/ 80 °C	120	80[11]
5	Acid ionic liquids	Neat/ 90 °C	2	87[12]
6	$[MeC(OH)_2]^+ClO_4^-$	Neat/ 80 °C or EtOAc/rt	27	85[14]
7	$Mg(OOCCF_3)_2$	Neat/ 100 °C	21	85[17]
8	Tween® 20	H_2O /75–80 °C	45	89[this work]

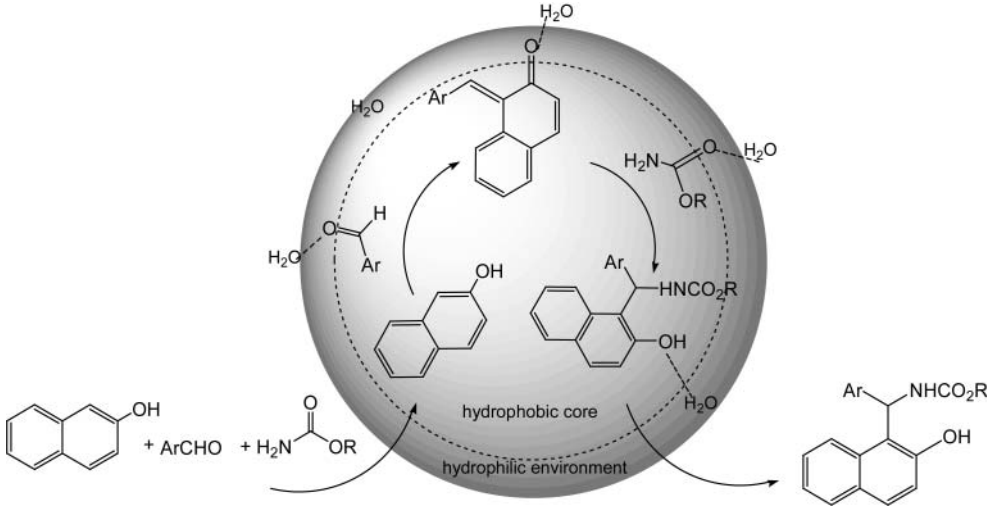

Fig. 1 Suggested mechanism for the formation of 1-carbamatoalkyl naphthol.

the precipitate was filtered off to give the corresponding products. The crude products were recrystallised from ethanol:H_2O (2:1) to afford pure 1-carbamatoalkyl-2-naphthols. The products obtained were identified by ^{1}H NMR, and physical data (m.p.) compared with those reported in the literature (Table 3). The filtrate containing the catalyst could be reused directly for the next run without any treatment.

Selected spectroscopic data for new compounds are given below.

Methyl[(2-hydroxynaphthalen-1-yl)(2-chlorophenyl)methyl]carbamate (Table 3, entry 3): White solid, mp 214-216 °C; ^{1}H NMR (300 MHz, DMSO-d_6), δ 9.96 (s, 1H, OH), 8.04 (d, J = 8.1 Hz, 1H, NH), 7.86 (d, J = 7.2 Hz, 1H, ArH), 7.77–7.26 (m, 8H, ArH), 7.16 (d, J = 8.4 Hz, 1H, ArH), 6.91 (d, J = 7.8 Hz, 1H, CH), 3.54 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 156.5, 153.9, 139.7, 133.0, 132.9, 130.3, 129.9, 129.7, 129.0, 128.8, 128.7, 126.9, 126.7, 123.3, 122.7, 118.9, 117.4, 51.9, 50.1. LC-MS *m/z* (%): 340 ([M-H]$^-$, 100 {for^{35}Cl}). Anal. Calcd for $C_{19}H_{16}ClNO_3$: C, 66.77; H, 4.72; N, 4.10. Found: C, 66.89; H, 4.63; N, 4.04%.

Benzyl[(2-hydroxynaphthalen-1-yl)(2-nitrophenyl)methyl]carbamate (Table 3, entry 10): White solid, m.p. 206–208 °C; ^{1}H NMR (300 MHz, DMSO-d_6), δ 10.16 (s, 1H, OH), 8.08 (d, J = 7.9 Hz, 1H, NH), 7.94 (d, J = 8.1 Hz, 1H, ArH), 7.79 (d, J = 8.0 Hz, 1H, ArH), 7.74 (t, J = 7.3 Hz, 2H, ArH), 7.62–7.26 (m, 11H, ArH), 7.08 (d, J = 8.5 Hz, 1H, CH), 5.12 (d, J = 12.3 Hz, 1H, CH_2), 5.06 (d, J = 12.3 Hz, 1H, CH_2). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 156.3, 154.1, 149.0, 137.5, 136.8, 133.3, 132.5, 130.4, 129.7, 129.4, 128.9, 128.7, 128.5, 128.2, 128.1, 127.8, 127.2, 127.0, 124.5, 123.0, 122.9, 118.8, 116.3, 65.9, 48.3. LC-MS *m/z* (%): 427 ([M-H]$^-$, 100). Anal. Calcd for $C_{25}H_{20}N_2O_5$: C, 70.09; H, 4.71; N, 6.54. Found: C, 70.21; H, 4.60; N, 6.46%.

Ethyl[(2-hydroxynaphthalen-1-yl)(4-chlorophenyl)methyl]carbamate (Table 3, entry 14): White solid, m.p. 210–212 °C; ^{1}H NMR (300 MHz, DMSO-d_6), δ 10.15 (s, 1H, OH), 7.93 (d, J = 8.3 Hz, 1H, NH), 7.80–7.22 (m, 10H, ArH), 6.87 (d, J = 8.1 Hz, 1H, CH), 4.05 (m, 2H, CH_2), 1.17 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 156.5, 153.3, 141.9, 132.3, 131.4, 129.9, 129.0, 128.7, 128.4, 128.2, 127.4, 127.1, 123.6, 123.0, 118.8, 60.7, 50.2, 14.9. LC-MS *m/z* (%): 354 ([M-H]$^-$, 100 {for ^{35}Cl}). Anal. Calcd for $C_{20}H_{18}ClNO_3$: C, 67.51; H, 5.10; N, 3.94. Found: C, 67.70; H, 5.01; N, 3.79%.

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