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Cocamidopropyl Betaine Catalyzed Benzoin Condensation and Pseudo-Four-Component Reaction of the in Situ Formed Benzoin in Water

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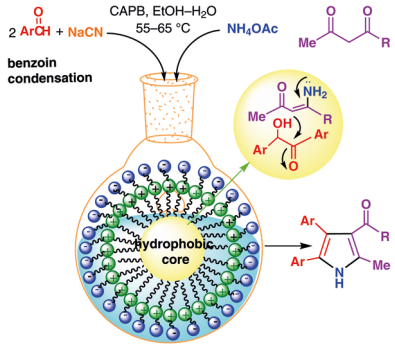

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Abstract An improved synthesis of benzoins, as key synthetic building blocks, and substituted pyrroles in micelle medium using a very small amount of cocamidopropyl betaine in water is described. In this one-pot strategy, benzoin condensation of aldehydes and further pseudo-four-component reaction of the in situ formed benzoin with 1,3-dicarbonyls, and ammonium acetate gave excellent yields of the desired pyrrole products.

Key words pseudo-four-component reaction, water, pyrrole, CAPB, zwitterionic surfactant, benzoin condensation, worm-like micelles

Organic synthesis in aqueous medium is an important challenge in modern chemistry contrasting the unique properties of water as a green solvent with the lower solubility or instability of organic compounds in water.[1] Although their hydrophobic nature may be used to speed up water-based organic reactions, surfactants provide an option to improve the solubility of organic materials in water. Surfactants, including nonionic, cationic, anionic, nano, and zwitterionic forms enhance the solubility of materials by forming micelles, reducing aqueous interfacial tension and easing the dispersion of organic molecules in water.[2] Zwitterionic surfactants are ampholites with both a cationic and an anionic head and hydrophobic tail that can self-assemble in aqueous medium to produce the network of flexible worm-like micelles[3] (WLMs; Figure 1).

Cocamidopropyl betaine (CAPB) is a biodegradable zwitterionic surfactant that creates flexible viscoelastic WLMs in water.[4] In spite of its broad industrial applications, there is only one report of the use of CAPB in organic transformations.[4f]

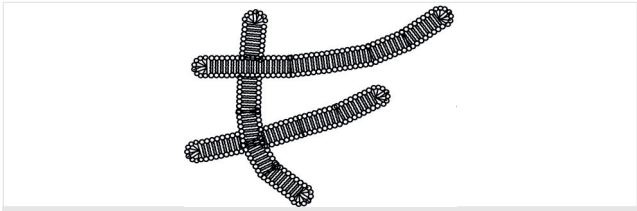

Figure 1 Schematic of entangled worm-like micelles

Aromatic α-hydroxyketones are unique synthetic building blocks[5] and access to them via the benzoin condensation has been reported using cyanide,[6] polystyrene-supported ammonium cyanide,[7] enzymes,[8] and triazolium,[9] imidazolium[10] and thiazolium[11] carbenes. However, the classical benzoin condensation is associated with the formation of side-products, long reaction times, and low yields.[12] Recently, a benzoin condensation in water has been reported using polyethylene glycol (PEG), but required extended reaction times and was limited in scope.[13]

Multicomponent reactions (MCRs) have had a notable impact in heterocyclic and combinatorial chemistry.[14] While the original MCRs focused on the starting materials and catalysts,[15] recent efforts have been directed to water-based MCRs[16] and pseudo-MCRs (*p*MCRs).[17] Given the importance of benzoins as building blocks in MCRs, their in situ generation and reaction in aqueous micellar medium is attractive.

Pyrroles are prominent in pharmaceuticals, and polymeric materials,[18] as well as are present in the cores of haemoglobin, chlorophyll and cytochromes and have been the target for one-pot MCR-based synthesis.[19] Due to the bioactivities of tetrasubstituted pyrroles,[20] we have recently developed a [2+2+1] MCR strategy for their synthesis via the three-component reaction of benzoins, 1,3-dicarbonyls, and ammonium acetate.[13,21] In continuation of our work, we have turned our synthetic strategy to a more simple

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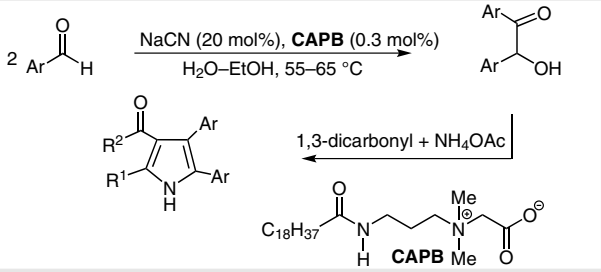
[1+1+2+1] *p*MCR by a one-pot tandem modified benzoin condensation. In this *pseudo* four-component reaction, the in situ generated benzoins react efficiently with 1,3-dicarbonyls and ammonium acetate in a micellar medium generated using CAPB. This advantageous protocol provides an efficient, one-pot, and substantially beneficial method for the synthesis of either benzoins or tetrasubstituted pyrroles (Scheme 1).



Scheme 1 CAPB-catalyzed benzoin condensation and synthesis of tetrasubstituted pyrroles

In our initial studies, we studied the optimization of the sodium cyanide catalyzed reaction of benzaldehyde (**1**) as a model substrate using various surfactants and conditions (Table 1).

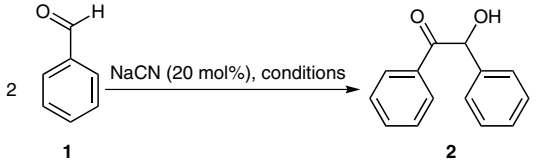
With the exception of the cationic surfactant CATB (Table 1, entry 2), the model reaction was accelerated in the presence of various neutral, anionic, and zwitterionic surfactants in water. However, a significant increase in yield and decrease in reaction time was observed using 0.3 mol% of CAPB in H_2O–EtOH (80:20; Table 1, entry 16). Increasing the proportion of ethanol as co-solvent reduced the yields (entries 17, 18, and 15), possibly due to the reduced hydrophobic effect, disrupting the micelles, disordering the system, and increasing the critical micelle concentration.[22] The superiority of CAPB may be due to a special micellar effect which is the result of the zwitterionic structure of CAPB leading to multilayer WLMs for better interaction of cyanide and benzaldehyde.

To show the superiority of the CAPB, performances of previously reported methods for benzoin condensation of benzaldehyde are compared in Table 2.

To explore the potential one-pot benzoin condensation–pyrrole synthesis, acetyl acetone (**3**) and ammonium acetate (**4**) were added to the in situ formed benzoin **2** in micellar medium which led to the desired pyrrole **5a** in an overall yield of 93% from benzaldehyde. The performance of this CAPB-catalyzed pseudo-four-component reaction in water is compared with the previous reported methods in Table 3.

The recyclability of the reaction medium was also assessed. Therefore, the reaction mixture was filtered after the first reaction run and the filtrate was used for two successive runs without significant decrease in the yield of **5a** (98%, 96%, and 95%).

Table 1 Optimization of the Benzoin Condensation



Entry	Surfactant (mol%)	Solvent	Temp (°C)	Time (min)	Yield (%)[a]
1	no surfactant	H_2O	90–100	560	45
2	CTAB[b] (0.5)	H_2O	90–100	440	35
3	SDS[c] (0.5)	H_2O	90–100	385	50
4	TritonX[d]-100 (0.5)	H_2O	90–100	210	60
5	TritonX[d]-114 (0.5)	H_2O	90–100	175	75
6	PEG-400 (0.5)	H_2O	90–100	325	80
7	CAPB (0.5)	H_2O	90–100	35	95
8	CAPB (0.8)	H_2O	90–100	20	90
9	CAPB (0.3)	H_2O	90–100	20	95
10	CAPB (0.1)	H_2O	90–100	30	85
11	CAPB (0.08)	H_2O	90–100	55	72
12	CAPB (0.3)	H_2O	70–80	18	91
13	CAPB (0.3)	H_2O	55–65	15	93
14	CAPB (0.3)	H_2O	25–35	45	90
15	CAPB (0.3)	EtOH	55–65	140	58
16	CAPB (0.3)	H_2O–EtOH (80:20)	55–65	10	98
17	CAPB (0.3)	H_2O–EtOH (50:50)	55–65	15	91
18	CAPB (0.3)	H_2O–EtOH (30:70)	55–65	20	89

[a] Isolated yield.
[b] Cetyltrimethylammonium bromide.
[c] Sodium dodecylsulfonate.
[d] Polyethylene glycol *p*-(1,1,3,3-tetramethylbutyl)phenyl ether.

Having established the optimal conditions for conjugated benzoin condensation and synthesis of pyrrole **5a**, reaction of various aromatic and heteroaromatic aldehydes was attempted to give the corresponding benzoins in high yields. Further one-pot reaction of the in situ generated benzoins with 1,3-dicarbonyls and ammonium acetate proceeded in good to excellent yields (Table 4).

Very high regioselectivity was observed for unsymmetrical 1,3-dicarbonyls as evidenced by ^{1}H NMR, and ^{13}C NMR spectroscopy, with single regioisomers **5d** and **5h** being isolated from the reaction of the in situ formed benzoin with benzoylacetone, and ammonium acetate (Table 4, entries 4 and 8). As an exception, tandem benzoin condensation and pyrrole synthesis was not successful for 3-pyridinecarbaldehyde (entry 16). Similarly, using sterically hindered 1,3-dicarbonyls such as 4,4,4-trifluoro-1-(thiophen-2-yl)butane-1,3-dione or ethyl 3-oxohexanoate led to high yields of 2,3,5,6-tetraphenyl pyrazine (**6a**) instead of the desired pyr-

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Table 2 Comparative Performances of the Methods for Synthesis of Benzoin **2**

Entry	Catalyst (mol%)	Solvent	Base (amount)	Temp (°C)	Time (h)	Yield (%)	TOF
1	O-silylated triazolium salt (10)	1,4-dioxane	*t*-BuOK (10 mol%)	r.t.	15	75[9b]	0.005
2	1,3-didodecylbenzimidazolium bromide (20)	H_2O	Et_3N (3.6 mmol)	r.t.	20	98[10a]	0.122
3	1-butyl-3-methylimidazolium bromide (50)	CH_2Cl_2	K_2CO_3 (152 mg)	r.t.	12	76[10d]	0.126
4	1-octyl-2,3-dimethylimidazolium triflate (40)	–	DBU (60 mg)	80	1	72[10c]	0.018
5	C12(MIM)2-2Br (0.1)[a]	THF	NaOH (20 mol%)	reflux	0.25	96[10f]	3.84
6	PEG (50)	EtOH	KCN (30 mol%)	reflux	5	85[13]	0.34
7	Amberlite IRA-910CN (0.5 g)	H_2O	–	reflux	2.5	80[7]	10.66
8	CAPB (0.3)	H_2O–EtOH (80:20)	NaCN (20 mol%)	55–65	0.16	98 (this work)	20.41

[a] 1,12-Bis(3-methylimidazolium-1-yl)dodecyldecan dibromides.

Table 3 Comparative Performances of Methods for the Synthesis of **5a**

Entry	Catalyst (mol%)	Solvent	Temp (°C)	Time (min)	Yield (%)
1	MSA (5)	H_2O	80	60	50[21a,b]
2	MSA (5)	EtOH	80	40	80[21a,b]
3	–	H_2O–EtOH (50:50)	60–70	240	98
4	–	–	90	120	90[23]
5	CAPB (0.3)	H_2O–EtOH (80:20)	55–65	25	98 (this work)

role (Table 4, entries 17 and 18). This pyrazine can be formed by condensation of two in situ generated α-amino ketones (Scheme 2).

We assume that the zwitterionic property of the surfactant CAPB is the main factor for catalytic roles in this one-pot multistep reaction. The CAPB-derived WLMs accelerate the tandem benzoin condensation, formation of enaminones, and condensation of the in situ formed benzoin with an enaminone.

In summary, we have developed a zwitterionic surfactant catalyzed, one-pot synthesis of tetrasubstituted pyrroles via the generation of benzoins from aldehydes and their in situ reaction with 1,3-dicarbonyl compounds, and ammonium acetate using CAPB in water.[24,25] Due to the atom economy, short reaction times, simple manipulation and isolation of products, this protocol is advantageous over the previously reported procedures.

Acknowledgment

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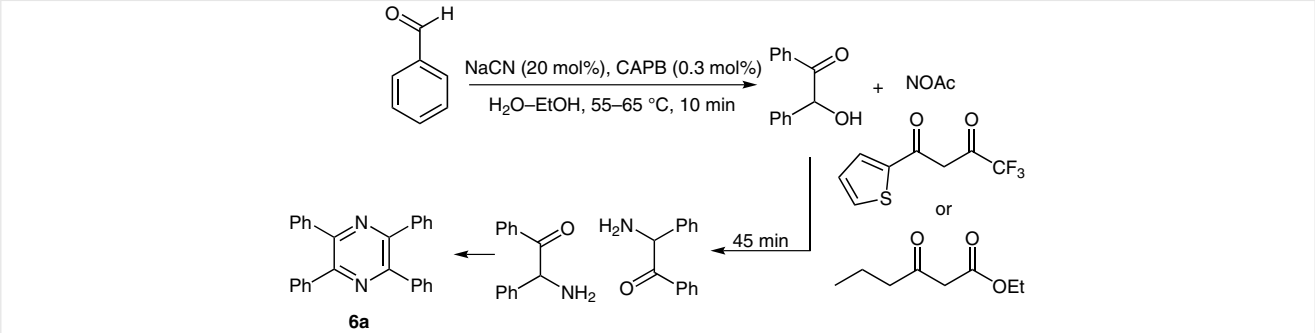

Scheme 2 Formation of tetraphenylpyrazine

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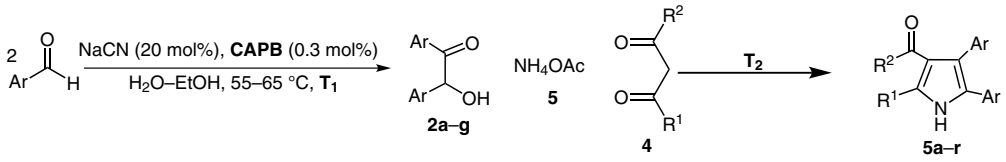
Table 4 Pseudo-Four-Component Reaction for the Synthesis of Substituted Pyrroles **5**



Entry	R^1	R^2	Ar	Benzoin product				Pyrrole product			
				2	T_1 (min)	Yield (%)[a]	Mp (°C): Found (Lit.)[Ref]	**5**	T_2 (min)	Yield (%)[a]	Mp (°C): Found (Lit.)[Ref]
1	Me	Me	Ph	**2a**	10	98	133–134 (131–131.9)[9b]	**5a**	15	98	173–174 (170–172)[21,22]
2	OEt	Me	Ph	**2a**	10	98	133–134 (131–131.9)[9b]	**5b**	30	93	207–209 (206–207)[21b,22]
3	OMe	Me	Ph	**2a**	10	98	133–134 (131–131.9)[9b]	**5c**	30	91	178–180 (178–180)[21b]
4	Ph	Me	Ph[b]	**2a**	10	98	133–134 (131–131.9)[9b]	**5d**	50	90	223–226 (221–223)[21b]
5	Me	Me	4-ClC_6H_4	**2b**	20	96	86–88 (89.6–90.1)[9b]	**5e**	35	95	233–236 (234–235)[21]
6	OEt	Me	4-ClC_6H_4	**2b**	20	96	86–88 (89.6–90.1)[9b]	**5f**	15	92	156–158 (155–156)21
7	OMe	Me	4-ClC_6H_4	**2b**	20	96	86–88 (89.6–90.1)[9b]	**5g**	15	90	212–215 (213–214)[21b]
8	Ph	Me	4-ClC_6H_4[b]	**2b**	20	96	86–88 (89.6–90.1)[9b]	**5h**	45	93	247–250 (247–249)[21]
9	CF_3	Me	4-ClC_6H_4	**2b**	20	96	86–88 (89.6–90.1)[9b]	**5i**	45	89	257–260 (259–260)[21]
10	OMe	Me	4-FC_6H_4	**2c**	10	94	78–79 (80.5–80.9)[9b]	**5j**	10	94	215–218 (216–218)[21]
11	OEt	Me	4-FC_6H_4	**2c**	10	94	78–79 (80.5–80.9)[9b]	**5k**	15	92	161–163 (160–162)[21]
12	Me	Me	4-MeC_6H_4	**2d**	20	90	80–81 (88.5–89.1)[9b]	**5l**	60	87	236–238 (237–238)[21]
13	Me	Me	4-$MeOC_6H_4$	**2e**	40	91	118–119 (120–121)[9c]	**5m**	90	83	155–161 (154–160)[21]
14	OMe	Me	2-furyl	**2f**	15	91	134–135 (88.5–89.1)[9b]	**5n**	35	91	187–191 (188–190)[21]
15	OEt	Me	2-furyl	**2f**	15	91	134–135 (88.5–89.1)[9b]	**5o**	35	92	169–172 (168–170)[21]
16	OEt	Me	3-pyridyl[c]	**2g**[c]	–	–	–	**5p**[c]	–	–	–
17	C_4H_4S	CF_3	Ph	**2a**	10	98	133–134 (131–131.9)[9b]	**6a**[d]	45	87	255–256
18	OEt	Pr	4-ClC_6H_4	**2b**	20	96	86–88 (89.6–90.1)[9b]	**6a**[d]	100	73	255–256

[a] Isolated pure products.
[b] Single regioisomer.
[c] No benzoin or pyrrole product was obtained
[d] 2,3,5,6-Tetraphenylpyrazine was obtained instead of the desired pyrrole, and 1,3-dicarbonyls remained unreacted.

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(24) **General Procedure for the Benzoin Condensation**: Aldehyde (2 mmol) and sodium cyanide (20 mol%) were added to a stirred solution of H_2O–EtOH (80:20) and CAPB (0.3 mol%) and the mixture was stirred for the time stated at 55–65 °C. After completion of condensation [TLC monitoring with hexane–EtOAc (8:2)], the precipitated benzoin was washed with H_2O and filtered.
(25) **General Procedure for Tandem Benzoin Condensation and *p*MCR Synthesis of Tetrasubstituted Pyrroles**: After completion of the reaction of aldehyde (5 mmol), sodium cyanide (20 mol%), and CAPB (0.3 mol%) in H_2O–EtOH (80:20; TLC monitoring), the requisite 1,3-dicarbonyl compound (5 mmol) and ammonium acetate (6 mmol) were added to the stirred reaction mixture at 55–65 °C. After completion of the second step, cold H_2O (40 mL) was added and the pyrrole product was isolated by filtration without need for further purification.

Spectroscopic data of representative compounds follows.

2-Hydroxy-1,2-bis(4-methylphenyl)ethanone (2d): white powder; mp 80–81 °C. FT-IR (KBr): 3446 (OH stretching), 2920, 1609 (C=O), 1574, 1511, 1418, 1284, 1183, 1117, 1083, 971, 806, 754, 724, 667 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 7.85 (d, *J* = 6.8 Hz, 2 H, H_{Ar}), 7.25 (d, *J* = 10.8 Hz, 4 H, H_{Ar}), 7.01 (d, *J* = 7.2 Hz, 2 H, H_{Ar}), 6.10 (s, 1 H, CH), 5.80 (d, 1 H, OH), 2.30 (s, 3 H, Me), 2.21 (s, 3 H, Me). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 197.0, 141.55, 136.0, 135.96, 129.9, 128.1, 127.4, 124.8, 75.8, 21.7, 21.3.

2-Hydroxy-1,2-bis(4-methoxyphenyl)ethanone (2e): white powder; mp 118–119 °C. FT-IR (KBr): 3464 (OH stretching), 1666 (C=O), 1597, 1514, 1468, 1386, 1313, 1265, 1240, 1170, 1116, 1023, 979, 832, 794, 733 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 7.91 (d, *J* = 8.4 Hz, 2 H, H_{Ar}), 7.25 (d, *J* = 8.4 Hz, 2 H, H_{Ar}), 7.86 (t, *J* = 7.2 Hz, 4 H, H_{Ar}), 5.87 (d, *J* = 5.2 Hz, 1 H), 4.60 (d, *J* = 5.2 Hz, 1 H, OH), 3.83 (s, 3 H, Me), 3.76 (s, 3 H, Me). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 195.7, 162.8, 158.2, 131.0, 130.8, 128.5, 120.3, 113.5, 74.4.

Ethyl 2-Methyl-4,5-diphenyl-1*H*-pyrrole-3-carboxylate (5b): yellow solid; mp 207–209 °C. FT-IR (KBr): 3306 (NH stretching), 1673 (C=O), 1598, 1442, 1480, 1181, 1098, 758, 693 cm^{-1}.^1H NMR (400 MHz, DMSO-d_6): δ = 11.56 (br s, 1 H, NH), 7.11–7.24 (m, 10 H), 3.91 (q, 2 H, CH_2), 3.34 (s, 3 H, Me), 0.98 (s, 3 H, Me). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.1, 137.1, 136.3, 132.7, 131.1, 128.6, 127.9, 127.3, 127.2, 126.5, 123.0, 111.9, 50.8, 14.3, 13.7.

1-[4,5-Bis(4-chlorophenyl)-2-phenyl-1*H*-pyrrol-3-yl]ethanone (5h): yellow crystals; mp 247–251 °C. FT-IR (KBr): 3302 (NH stretching), 1616, 1595, 1495, 1202, 1094, 1012, 972, 831 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 11.85 (s, 1 H, NH), 7.18–7.48 (m, 13 H, H_{Ar}), 2.21 (s, 3 H, Me). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 193.0, 140.2, 135.1, 134.7, 132.4, 131.97, 131.58, 131.05, 129.3, 128.9, 128.4, 128.3, 126.4, 121.7, 62.0, 13.2.

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