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Graphical Abstract





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Admicellar catalysis in multicomponent synthesis of polysubstituted pyrrolidinones

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ABSTRACT

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Keywords: Pyrrolidinones TiO₂ nano-particle Admicellar catalysis Multicomponent reaction Green methodology A multicomponent green methodology was developed to synthesize 3-hydroxy-2-pyrrolidinones under admicellar catalysis by TiO_2 nano-particles at room temperature (30 °C). TiO_2 nano-particles in aqueous CTAB solution promote the formation of admicelles and the reaction occurs in admicellar environment. The methodology was successfully applied to synthesize a variety of 3-hydroxy-2-pyrrolidinones and 3'-hydroxyspiro-2'-pyrrolidinone derivatives.

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Due to increasing concern over volatile organic solvents and their toxic effects on human body, till date, a large number of reactions have been successfully investigated in aqueous medium.¹ In some cases, owing to the limited solubility of the organic compounds in water, surfactants were efficiently used to promote the organic reactions to give the desired product in high yields through the formation of micelles.²

Another very important reaction template in aqueous medium called "admicelle" is a relatively new investigated phenomenon in science. At lower surfactant concentration, admicelles are formed in aqueous medium by the adsorption of surfactant on solid-liquid interfaces of nano particles.³ Due to high surface area and small size, nano particles have very unique properties and they efficiently catalyze many reactions.⁴ However, in aqueous medium, nano heterogeneous particles are self aggregated to form larger particles having low catalytic activity and in such cases, use of a surfactant leads to the formation of admicelles.⁵ Presence of the hydrophobic core within admicelles furnishes a region which is able to solubilize the water-insoluble organic compounds. This process is termed as "adsolubilization" or "surface solubilization".⁶ A reaction template is therefore formed on the surface of the nano particles where the organic reactions can be catalyzed by the nano catalyst under admicellar environment. Formation of admicelles plays an important role in many practical applications, including ore flotation, petroleum recovery, food science, agriculture etc.⁷ and can significantly improve the outcome of many reactions through conventional admicellar catalysis.⁸

Five membered nitrogen-containing heterocyclic polysubstituted 3-hydroxy-2-pyrrolidinones are one of the most investigated class of compounds and have significant biological activities like HIV-1 integrase inhibitors,⁹ anti cancer agents,¹⁰

anti microbial activity,¹¹ antibacterial ¹² and anti inflammatory¹³ activities. In our study, we have investigated the catalytic activity of the admicelles formed by the adsorption of cetyltrimethylammonium bromide (CTAB) on the surface of TiO₂ nano-particles (TiO₂-np) at lower surfactant concentration (below critical micellar concentration, CMC) for the multicomponent¹⁴ green synthesis of the polysubstituted 3-hydroxy-2-pyrrorolidinones and its spiro derivatives also.

Initially the reaction was carried out with 4-methyl benzaldehyde, 4-chloro aniline and diethyl acetylenedicarboxylate ester in aqueous medium at room temperature (30 °C) (Scheme 1) using commercially available TiO₂ powder as a heterogeneous catalyst in the absence of CTAB. The reaction mixture was stirred around 18 h at room temperature (30 °C), but a gummy mass was obtained. This problem arises due to the limited solubility of the reactants in water. To overcome this problem, we focused our attention to utilize TiO₂ admicellar system as a reaction template. Therefore, further study was done with the aqueous admicellar system formed by commercially available TiO₂ powder in aqueous solution of CTAB (CTAB: CMC value 0.92 mM).¹⁵ At first, we carried out the reaction in 0.1 mM aqueous CTAB solution but the reaction did not take place. By using 0.8 mM aqueous solution of CTAB in the reaction medium we got polysubstituted 3-hydroxy-2-pyrrolidinone as the product, although in very low yields. Interestingly it was found that in comparison with commercially available TiO2 powder, the maximum yield of the polysubstituted 3-hydroxy-2-pyrrolidinone has been achieved by employing TiO₂ nano-particles. At 0.8 mM aqueous solution of CTAB, formation of the admicelles by TiO₂ nano-particles efficiently catalyzed the synthesis of polysubstituted 3-hydroxy-2-pyrrolidinone in high yields. In aqueous medium at low

concentration of CTAB (below CMC), adsorption of positively charged cetyltrimethylammonium ions on negatively charged sites of TiO₂ surface (coulombic force) give hemimicelles where the hydrophobic tails are exposed towards polar water medium, then surfactant chain–chain interactions (non-coulombic force) results to the formation of another layer where the head groups of the surfactants are exposed towards water, thus a surfactant bilayer was formed on the surface of TiO₂-np, these assemblies termed as admicelle, illustrated in Figure 1.^{3e,7b,16}



Figure 1. Surfactant bilayer of TiO₂ admicelle.

Organic substrates come closer to each other in the hydrophobic region of admicelles and reaction between them is catalyzed by TiO₂. At higher concentration of CTAB (just above CMC), we noticed no increase in the yield of the product. But, at very high concentration of CTAB yield of the reaction decreases to a large extent. This is due to the reason that, at high CTAB concentration (>>CMC), formation of micelles² solubilize the organic compounds within its hydrophobic core and the reaction cannot undergo through admicellar catalysis. Use of TiO2 nanoparticles facilitated the formation of admicelles in aqueous reaction medium and improved the reaction methodology through its higher surface area, reusability and high catalytic activity. Formation of admicelles in aqueous medium was justified from analyzing the DLS data. In the absence of CTAB in aqueous medium, TiO₂ nano-particles aggregated themselves to form larger particles and DLS study shows that the sizes of these larger particles vary in a wide range from 3335.3 nm to 6539.5 nm. However, in 0.8 mM aqueous solution of CTAB, TiO₂ nano-particles formed admicelles and from DLS study we found that sizes of the maximum number of admicelles is around 162.8 nm. These two DLS results are given in the supplementary section.

After the successful application of admicellar reaction template formed by TiO₂-np in aqueous CTAB solution, we investigated the action of other surfactants in the reaction medium like TTAB (TTAB: CMC value 3.8 mM)¹⁵ and SDS (SDS: CMC value 8.1 mM)¹⁸ below their CMC but we found that 0.8 mM CTAB is the best for the conversion to the product mentioned. The effects of surfactants at different concentration are summarized in Table-1. Catalytic activity of many other catalysts were also investigated and from our study we found that 10 mol% TiO₂ in 0.8 mM aqueous CTAB solution efficiently catalyzed the reaction (Scheme 1) to produce the maximum yield, the detailed results of using different catalysts are summarized in Table-2.



Scheme 1. Synthesis of polysubstituted 3-hydroxy-2pyrrolidinone 8a.

Table 1. Effect of different surfactants on th	e yield of
pyrrolidinone 8a, in presence of 10 mol% Ti	iO ₂ -np

Entry	Surfactant	Concentration (mM)	Yield (%)
1	none	-	No reaction
2	CTAB	0.1	No reaction
3	CTAB	0.6	50
4	СТАВ	0.8	82
5	CTAB	0.9	82
6	CTAB	1.0	80
7	CTAB	8.0	40
8	CTAB	10	40
9	TTAB	3.0	15
10	SDS	7.0	20

 Table 2. Effect of different catalysts on the yield of pyrrolidinone 8a, in 0.8 mM aqueous solution of CTAB.

Entry	Catalyst	Amount	Time	Yield	
		(mol %)	(h)	$(\%)^{\mathrm{a}}$	
	TiO ₂	10	18	40	
2	nano TiO ₂	5	18	50	
3	nano TiO ₂	8	18	70	
4	nano TiO ₂	10	18	82	
5	nano TiO ₂	15	18	82	
6	SiO_2	10	18	10	
7	Alumina (acidic)	10	18	20	
8	InCl ₃	10	18	10	
9	$MgSO_4$	10	18	5	
10	P-TsOH	10	18	30	
11	AcOH	10	18	35	

^a Isolated yield

Analyzing the results of our study, we were finally able to optimize the reaction condition¹⁷ using 10 mol% nano-TiO₂ catalysts in 0.8 mM aqueous CTAB solution and this optimized reaction condition was adapted for future study. After optimization of the reaction condition and in order to access a range of polysubstituted 3-hydroxy-2-pyrrolidinone, we investigated the scope of the reaction by varying electron-withdrawing and electron-donating arylamines and aromatic aldehydes with both the ester dimethyl acetylenedicarboxylate (Scheme 2, Table 3, entries 1-14). In all the reactions, the yields were highly satisfactory.



Scheme 2. General synthesis of poly substituted 3-hydroxy-2-pyrrolidinone (8a-8r).

Table 3. Synthesis of poly substituted pyrrolidinones 8a-8r ^b .						
Entry	Ar	R^1	R	Product	Yield (%) ^a	
1	p-CH ₃ C ₆ H ₄	p-ClC ₆ H ₄	Et	H ₃ C Sa	82	
2	p-MeOC ₆ H ₄	p-CH ₃ C ₆ H ₄	Me	CI MeO ₂ C N O MeO Sb CH ₃	80	
3	p-ClC ₆ H ₄	p-ClC ₆ H ₄	Me		85 ^{9c}	
4	p-MeOC ₆ H ₄	p-CH ₃ C ₆ H ₄	Et	CI EtO ₂ C OH MeO 8d CH ₃	82	
5	C_6H_4	C_6H_4	Me	MeO ₂ C OH N O 8e	75 ^{9c}	
6	p-ClC ₆ H₄	p-BrC₀H₄	Ме	MeO ₂ C OH Cl Sf Br	80	
7	m-O ₂ NC ₆ H ₄	C_6H_4	Me		72 ^{9c}	
8	p-BrC₀H₄	p-BrC₀H₄	Ме	MeO ₂ C OH Br N O Br Sh Pr	83	
9	p-CH ₃ C ₆ H ₄	p-ClC ₆ H ₄	Me		78	
10	p-MeOC ₆ H ₄	C ₆ H ₄	Et		75 ^{9c}	
11	p-BrC₀H₄	p- MeOC ₆ H ₄	Me	MeO ₂ C OH N O Br Sk	80	
12	C_6H_4	C ₆ H ₄	Et	EtO ₂ C OH N O	72 ^{9c}	



^a Isolated yield; ^b Reaction conditions: amine (1.2 mmol), dialkyl acetylenedicarboxylate (1.2 mmol), aldehyde (1.2 mmol) in 10 ml 0.8 mM aqueous CTAB solution at rt (30 °C) for 18 h

After successful application of the methodology for aryl amine and aromatic aldehyde, we improved the reaction scope by using isatin as a reactant (Scheme 3). Reaction of isatin with various aryl amines gave 3'-hydroxyspiro [indoline-3,5'-pyrroline]-2,2'-diones (Table 4, products **9a-9e**).



Scheme 3. General synthesis of 3'-hydroxyspiro-2'pyrrolidinone (9a-9e).

Table 4.	Synthesis	of 3'-hyd	lroxyspire	o-2'-pyrro	olidinone	9a-
1-						



3



^a Isolated yield; ^b Reaction conditions: amine (1.2 mmol), dialkyl acetylenedicarboxylate (1.2 mmol), isatin (1.2 mmol) in 10 ml 0.8 mM aqueous CTAB solution at rt (30 °C) for 18 hours;

All the synthesized compounds were characterized by NMR, IR, HRMS, CHN analysis and melting points. Finally we confirmed the structure of polysubstituted 3-hydroxy-2-pyrrolidinone and 3'-hydroxyspiro-2'-pyrrolidinone by a single-crystal X-ray diffraction study of the compound **8b** and compound **9a**. ORTEP structure of these two representative compounds **8b** (CCDC 918014) and **9a** (CCDC 918013) are given in the supplementary section. The spectral and analytical data of these two representative compounds have been cited in this manuscript¹⁸ while those for the remaining compounds are given in the supplementary section also.

Based on previously reported reactions¹⁹ a plausible reaction mechanism involving CTAB and TiO₂-np in aqueous admicellar environment was proposed for the formation of polysubstituted 3-hydroxy-2-pyrrolidinone (product 8a-8r), which is illustrated in Scheme 4. In admicellar environment, lewis acidic character of Ti⁴⁺ promotes the reaction between aldehyde and amine, which is also facilitated by CTAB to produce the corresponding imine (A). At the same time, Ti⁴⁺ from TiO₂-np and CTAB catalyzed the addition of water molecule to dialkyl acetylenedicarboxylate to form the intermediate (B). After that in admicellar environment, the Michael addition of intermediate (B) to imine (A) catalyzed by Ti^{4+} and CTAB, gave the intermediate (C). Next, the ring cyclization occurs by the intramolecular reaction of arylamine group to the ester carbonyl activated by TiO₂-np and the intermediate (D) was formed. Finally, elimination of corresponding alcohol from D gave the poly substituted 3hydroxy-2-pyrrolidinone (E). In each step of the reaction course Ti⁴⁺ from admicelle formed by TiO₂-np actively participated to catalyze the reaction and the reaction occurs in admicellar environment. Hence the role of admicelles formed by TiO₂-np in the formation of poly substituted 3-hydroxy-2-pyrrolidinones is very significant and essential. Formation of 3'-hydroxyspiro-2'pyrrolidinone (product 9a-9e) follow the similar reaction mechanism under admicellar environment.



Scheme 4. Formation mechanism of poly substituted 3-hydroxy-2-pyrrolidinone.

 TiO_2 -np was prepared by the previously reported gel combustion method²⁰ and successfully reused with the standard reaction for up to five cycles with a slight decrease in the yield of the reaction (Table 5).

Table 5. Recycling of TiO_2 nano-particles for the
multicomponent coupling reaction between 4-methyl
benzaldehyde, 4-chloro aniline and diethyl
acetylenedicarboxylate ester in aqueous medium (product 8a)RunTime (h)Yield (%)^a

Kull	Time (ii)	1 leid (78)
1	18	82
2	18	82
3	18	82
4	18	82
5	18	80
6	18	76

^a Isolated yield

In conclusion, we have successfully developed an inexpensive, green and expeditious multicomponent reaction methodology for the synthesis of polysubstituted 3-hydroxy-2-pyrrolidinones using an admicellar system as a reaction template. Water as a reaction medium improves the scope of the reaction methodology to a large extent and the use of many hazardous organic solvents can be avoided by using this methodology. Formation of admicelles and catalytic activity of TiO_2 -np in this multicomponent reaction protocol were very significant and are extremely advantageous over many other heterogeneous and organo catalysts. Finally, in our study, we illustrated the ability of TiO_2 admicellar system to subsidize the formation of poly substituted 3-hydroxy-2-pyrrolidinones through multicomponent

reaction between dialkyl acetylenedicarboxylate and a variety of amines and aldehydes or isatin in aqueous medium at room temperature (30 °C). To the best of our knowledge, using admicellar system as a reaction template based on TiO₂-np in aqueous medium for the multicomponent synthesis of poly substituted 3-hydroxy-2-pyrrolidinones at room temperature (30 °C), have never been investigated so far.

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Supplementary Information

Spectral and analytical data of all the compounds in Table 3 and Table 4 along with characterization data of TiO_2 -np are given in the Supplementary Section. Crystallographic data of compound **8b** (CCDC 918014) and compound **9a** (CCDC 918013) also been deposited at the Cambridge Crystallographic Database Centre and these data can be obtained free of charge via www.ccdc.ac.ck./data_request/cif.

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- of polysubstituted-3-hydroxy-2-17. General synthesis (8a-8r): Amine pyrrolidinones (1.2 mmol). dialkvl acetylenedicarboxylate (1.2 mmol), aromatic aldehyde (1.2 mmol) and TiO2-np (10 mol %) were sequentially added to a 10 ml of 0.8 mM aqueous CTAB solution in a 50 ml round bottomed flask and stirred the mixture for next 18 h at room temperature (30 °C). Reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with 10 ml ethyl acetate and the catalyst was separated from the mixture by filtering through a sintered funnel. Recovered TiO2-np was washed with DCM (2 ml \times 4) to remove any adhering organic compound and finally by water (2 ml). It was next vacuum dried and reused for upto five cycles. After that the organic layer was separated out and washed with brine solution (7 mL \times 2) and evaporated under vacuum to result in a crude product. The crude product was purified by column chromatography over silica gel [ethyl acetate/ petroleum ether (60-80°C)]. No further purification was needed.
- 4-Hydroxy-2-(4-methoxy-phenyl)-5-oxo-1-p-tolyl-2,5-18 (a) dihydro-1H-pyrrole-3-carboxylic acid methyl ester (8b) (Table 3, entry 2): White solid, 80%, m. p. 152-154 °C (EtOAc); R_f [30 % EtOAc / petroleum ether (60-80 °C)]: 0.29; ¹H NMR (300 MHz, DMSO- d_6) δ :7.42 (d, J = 8.4Hz, 2H, ArH), 7.16-7.07 (m, 4H, ArH), 6.76(d, J = 8.4Hz, 2H, ArH), 5.97 (s, 1H, CH), 3.65 (s, 3H, OCH₃), 3.58 (s, 3H, OCH₃), 2.20 (s, 3H, CH₃); ¹³C NMR (75 MHz, DMSO-d₆) δ: 163.8, 162.6, 158.8, 152.6, 134.6, 133.8, 129.1, 128.8, 128.2, 122.6, 113.7, 111.9, 60.2, 54.9, 51.1, 20.4; IR (KBr) v: 3186, 2955, 1720, 1669, 1513, 1424, 1383, 1306, 1230, 1172, 1112, 1037, 1009, 928, 835, 765 cm⁻¹; HRMS (ESI-TOF): m/z calcd. for C₂₀H₁₉NO₅ [M+H]⁺: 354.1341. found: 354.1324; Anal. calcd. for C₂₀H₁₉NO₅; C: 67.98; H: 5.42; N: 3.96%. Found: 67.91; H: 5.41; N: 3.89%. (b) **3'-Hydroxy-4'-**C. methoxycarbonyl-1'-4-methylphenylspiro[indoline-3,5'-

pyrroline]-2,2'-dione (9a) (Table 4, entry 1): Yellow solid, 78%, m.p. 230-232 °C (MeOH); R_f [75 % EtOAc / petroleum ether (60-80°C)]: 0.28; ¹H NMR (300 MHz, DMSO-*d*₆) δ : 10.76 (s, 1H, NH), 7.27 (d, *J* = 7.2Hz, 1H, ArH), 7.18 (t, *J* = 7.2Hz, 1H, ArH), 7.08 (d, *J* = 8.1Hz, 2H, ArH), 6.92 (t, *J* = 7.8Hz, 1H, ArH), 6.84 (d, *J* = 8.1, 2H, ArH), 6.74 (d, *J* = 7.8Hz, 1H, ArH), 3.55 (s, 3H, OCH₃), 2.21(s, 3H, CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆) δ : 173.6, 165.4, 161.8, 155.2, 143.3, 137.6, 132.2, 130.1, 129.6, 126.8, 125.0, 124.4, 122.2, 110.2, 109.2, 69.8, 51.2, 20.6; IR (KBr) v: 3262, 2952, 1722, 1688, 1620, 1515, 1466, 1419, 1364, 1284, 1204, 1162, 1131, 1093, 1025, 944, 924, 803, 760 cm⁻¹; HRMS (ESI-TOF): *m*/z calcd. for C₂₀H₁₆N₂O₅; C: 65.93; H: 4.43; N: 7.69%. Found: C: 65.81; H: 4.52; N: 7.78%.

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