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Synthesis of polycyclic fused 2-quinolones in aqueous micellar system

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ABSTRACT

A high yielding green protocol has been developed for the synthesis of tri-, tetra-, and pentacyclic fused 2-quinolones in micellar medium. The method is more effective compared to phase-transfer catalytic (PTC) method in terms of the yield of the product as well as the reaction time. It is operationally simple as well as environmentally benign.

In recent years, considerable interest has been noticed among the synthetic organic chemists to perform organic reactions in water[1] because it is abundant in nature, has virtually no cost, and is safest among all available solvents, thus leading to environmentally benign chemical processes.[2] But the limited solubility of various organic compounds in water is the prime hindrance in performing reactions in aqueous media. The development that has contributed to some extent to overcome this hindrance is the introduction of aqueous surfactant solutions in the form of micelles[3] as the reaction medium. In conventional micellar catalysis, the surfactant micelles act to locally concentrate all reactants within the solution, both by solubilization due to hydrophobic effect and by counter ion binding due to electrostatic forces. The solubilization of water-insoluble reactants and products inside the micelles results not only in high concentration within the small volume, but also in different orientations of the soluble molecules that influence the reaction mechanism, resulting in remarkable differences in reaction rate and selectivity than would be observed in a homogeneous system.[4]

In recent times, quinolone antibiotics have received much attention due to their inhibitory effect on bacterial DNA gyrase,[5] an enzyme essential for DNA replication. After the discovery of nybomycin,[6] a number of quinolone antibacterials have been developed which possess either 2-quinolone or 4-quinolone moieties in their core. Considerable interest has been noticed in developing 2-quinolones as anticancer, antiviral, and antihypertensive agents.[7] 4-Substituted 3-phenyl-2-quinolones exhibit high affinity in binding to the glycine site of *N*-methyl-D-aspartate receptor, and such antagonists hold promise for the treatment of several central nervous system disorders.[8] Amides of 3-hydroxy/alkyl-4-carboxylic acids of 2-quinolones also exhibit high affinity for the 5-HT3 serotonin receptor.[8b]

In our ongoing endeavor for the syntheses of fused 2-quinolones, very recently we have developed a methodology for the synthesis of fused tri-, tetra-, and pentacyclic quinolones having six-, seven-, and eight-membered ring systems from easily available 8-hydroxyquinolines and 1,ω-dihaloalkanes/xylenes/methylquinoxalines in water–dichloromethane biphasic system using a phase-transfer catalyst[9] (TBAB). However, the methodology had some shortcomings, like low yields of the quinolones (30–50%), formation of the quinolinium cation as a mixture, long reaction time, and use of environmentally hazardous organic solvents. We have now successfully overcome these by developing a truly green protocol for the synthesis of fused tri-, tetra-, and pentacyclic-fused quinolones with excellent yields in a short reaction time using cetyltrimethylammonium bromide (CTAB) as a micellar catalyst (MC) in aqueous media, without the use of any organic solvent in the reaction.

Initially we took up the synthesis of the tricyclic fused 2-quinolone **3a**, for which we chose 8-hydroxyquinoline (**1a**) and 1,2-dibromoethane (**2a**) as model starting materials. These were reacted in the presence of aq NaOH (10%) and a surfactant in water at room temperature for different time periods to evaluate the effect of various conditions. We also investigated the reactions systematically in aqueous solutions of cationic, anionic, and nonionic surfactants well above their critical micellar concentrations (CMC) in order to study the effect of surfactant solutions. The results revealed that the reactions carried out without a surfactant was ineffective even up to 24 h (Table 1, entry 1). However, reaction using tetradecyltrimethylam-

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Table 1
Effect of concentration of the surfactants on the yield of **3a**

Entry[a]	Surfactant	Concentration (mM)	Yield[b] (%)	
			In presence of TBAB[c]	In absence of TBAB
1	None	—	NR[d]	NR[d]
2	CTAB	30	25	24
3	CTAB	40	55	53
4	CTAB	50	75	74
5	CTAB	60	95	95
6	CTAB	70	95	95
7	CTAB	80	96	95
8	TTAB	60	75	75
9	SDS	60	60	NR[d]
10	Triton X-114	60	65	NR[d]

[a] All the reactions were performed using **1a** and **2a** in water at room temperature for 1 h.
[b] Yield of isolated pure products.
[c] Catalytic amount (0.05 mmol) of TBAB was used in all cases.
[d] No reaction.

monium bromide (TTAB: cmc value 3.8 mM)[10a] at a concentration of 60 mM yielded 75% of the product **3a** (entry 8). The most striking yield (95%) was obtained when the reaction was performed using cetyltrimethylammonium bromide (CTAB: cmc value 0.92 mM)[10b] at 60 mM concentration for 1 h (entry 5). However, following the same protocol but using a 30 mM concentration of CTAB, the yield of the product was diminished to 24% (entry 2). On the other hand no significant increase in the yield was observed on enhancement of the concentration of CTAB beyond 60 mM (entry 6). When the reaction was carried out in the presence of the anionic surfactant sodium dodecylsulfate (SDS: cmc value 8.1 mM)[10c] at the same concentration (60 mM) no product was isolated (Table 1, entry 9). This may be due to the mutual repulsion of the negatively charged phenoxide groups of 8-hydroxyquinolines and sulfate groups of SDS resulting in minimal interaction (between phenoxide group of 8-hydroxyquinoline and micelle) with the other reactant (1,2-dibromoethane) located in the reaction system. In order to overcome this limitation, we used a catalytic amount (0.05 mmol) of tetrabutylammonium bromide (TBAB) as phase-transfer catalyst along with the anionic surfactant. Gratifyingly, we obtained the fused quinolone **3a** in 60% yield (Table 1, entry 9). In this case the role of the phase-transfer catalyst was to shuttle the hydrophilic reactant into the micellar pseudophase for reaction with the solubilized lipophile.[11] Nonionic surfactant like Triton X-114 (cmc 0.28 mM)[10d] also failed to yield **3a** even at concentration 60 mM**,** but the yield was better compared to anionic surfactant when the catalytic amount (0.05 mmol) of the phase-transfer catalyst was used (Table 1, entry 10). In the case of cationic surfactants like CTAB or TTAB, no significant changes in yields were observed in the presence of phase-transfer catalyst (Table 1, entries 2–8), as the cationic surfactant itself could perform a dual role.

The plausible mechanism for the formation of fused quinolone is depicted in Figure 1. In micellar media the reactants (**1a** and **2a**) are in very close proximity and it is presumed that the initial formation of the quinoline ether (**A**) is formed through condensation of 8-hydroxyquinoline (**1a**) and 1,2-dibromoethane (**2a**) is followed by intramolecular attack of the quinoline ring nitrogen to form the quinolinium salt (**B**), as described earlier,[9a] which on arial oxidation leads to **3a**.

In order to establish the generality and scope of this new methodology, we used different derivatives of 8-hydroxyquinoline and 1,ω-dihaloalkanes/xylenes/methyl-quinoxalines as alkylating agents. The results, summarized in Table 2, reveal that the yields of the fused quinolones were reduced with increase in the ring size (i.e., the yield of 6,6,6 > 6,6,7 > 6,6,8 ring system), and no product formation was observed in case of 1,5-dibromopentane or

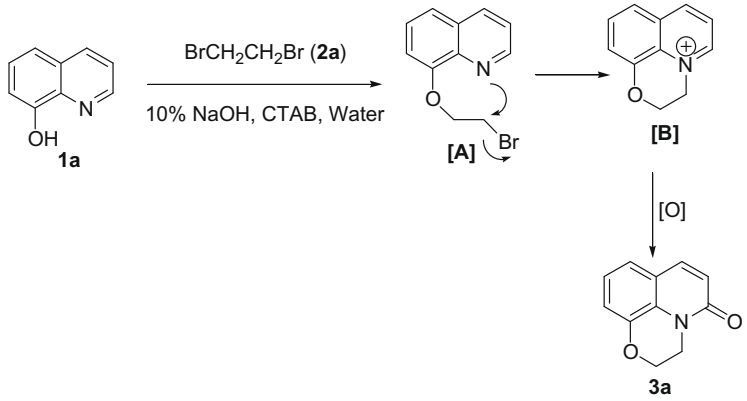


Fig. 1. Plausible pathway for the formation of **3a**.

Table 2
Synthesis of fused quinolones using micellar catalyst (MC) in water at different conditions[a]

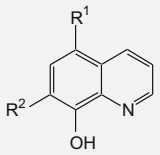
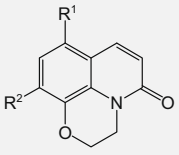
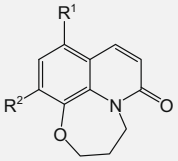
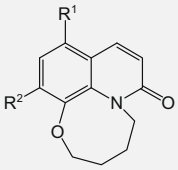
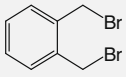
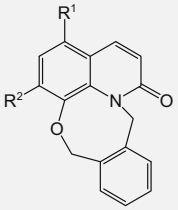
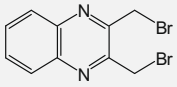
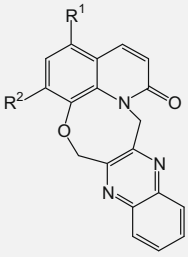
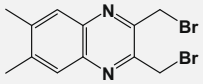
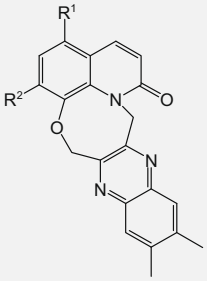
8-Hydroxy quinoline	Alkylating agent	Fused 2-quinolone	Yields[b] (%)	Ref.
	$BrCH_2CH_2Br$ **2a**			
1a ($R^1 = R^2 = H$)		**3a**	95	[9a]
1b (R^1 = Cl, R^2 = H		**3b**	92	[9a]
1c ($R^1 = R^2$ = Cl)		**3c**	92	—
1d ($R^1 = R^2$ = Br)		**3d**	95	[9a]
1e (R^1 = Cl, R^2 = I		**3e**	95	—

Table 2 (*continued*)

8-Hydroxy quinoline	Alkylating agent	Fused 2-quinolone	Yields[b] (%)	Ref.
	$BrCH_2CH_2CH_2Br$ **2b**			
1a		**4a**	95	[9b]
1b		**4b**	92	[9b]
1c		**4c**	92	—
1d		**4d**	90	[9b]
1e		**4e**	95	—
1f ($R^1 = R^2 = I$)		**4f**	90	—
	$BrCH_2CH_2CH_2CH_2Br$ **2c**			
1a		**5a**	95	[9b]
1b		**5b**	92	[9b]
1d		**5c**	94	[9b]
	 **2d**			—
1a		**6a**	90	[9c]
1b		**6b**	92	[9c]
1c		**6c**	92	—
1d		**6d**	90	[9c]
1e		**6e**	95	[9c]
	 **2e**			
1a		**7a**	95	[9d]
1b		**7b**	90	[9d]
1d		**7c**	90	[9d]
	 **2f**			
1a		**8a**	92	[9d]
1b		**8b**	94	[9d]
1d		**8c**	90	[9d]

[a] Reaction conditions: 8-hydroxyquinoline derivatives (1 mmol), alkylating agent (1 mmol), 50 ml 10% NaOH solution, CTAB (3 mmol), 1 h in air.
[b] Yield of isolated pure products.

1,6-dibromohexane used as alkylating agent even after a long reaction time (5 days), most probably due to the ring strain involved in the formation of fused 6,6,9 or 6,6,10 system. Next we attempted to use α,α′-dibromo-ortho-xylene as alkylating agent in order to synthesize tetracyclic benzoxazocino ring system. In this case the formation of the benzoxazocino quinolone was relatively faster than the previous cases since the substitution reaction at benzylic position is faster. Finally, we used bicyclic 2,3-bis-bromomethyl-

quinoxaline as alkylating agent for the formation of pentacyclic oxazocino quinolones. In this case also the yields were excellent.

In summary, we have developed an environmentally benign protocol for the synthesis of fused tricyclic, tetracyclic, and pentacyclic quinolones with excellent yields using micellar catalyst (MC) in aqueous medium.[12,13] The scope of the study demonstrates minimization of reaction time with maximization of the yields of the products.

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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.2010.01.030.

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11. Siswanto, C.; Battal, T.; Schuss, O. E.; Rathman, J. F. *Langmuir* **1997**, *13*, 6047.
12. *General reaction procedure for the synthesis of fused 2-quinolones*: Appropriate amount (1 mmol) of 8-hydroxyquinoline derivative (**1a–f**) was taken in a 250 ml RB flask treated with 50 ml 10% NaOH solution and the mixture was stirred at room temperature for about 10 min. Dibromoalkanes/xylenes/methyl-quinoxalines (**2a–f**) were added (1 mmol each) successively to the stirred solution followed by the addition of CTAB (3 mmol). The reaction mixture was stirred continuously for 1 hour at room temperature. After completion of the reaction (monitored by TLC), the contents were filtered and the residue was washed thoroughly with water until free from alkali and CTAB. Finally, the residue was crystallized from chloroform–petroleum ether mixture to afford the fused quinolones in excellent yields. The characterizations of the products were accomplished by spectroscopic analysis (^{1}H, ^{13}C NMR and mass) and also by comparison of the data reported in the literature.
13. (a) *Spectral data of* **3c***:* White needles (yield: 92%); mp 177–178 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.31 (2H, m), 4.47 (2H, m), 6.77 (1H, d, J = 9.6 Hz), 7.27 (1H, s), 8.06 (1H, d, J = 9.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 39.8 (CH_2), 64.2 (CH_2), 117.1 (C), 122.2 (CH), 122.4 (C), 123.6 (CH), 124.2 (C), 128.4 (C), 135.3 (CH), 138.3 (C), 159.6 (C); MS [ESI]: m/z 257 $[M+H]^+$, 259 $[M+2+H]^+$, 279 $[M+Na]^+$. HRMS (ESI): m/z calcd for $C_{11}H_7Cl_2NO_2Na$ $[M+Na]^+$: 277.9751, found 277.9742; (b) *spectral data of* **4e***:* Brownish needles (yield: 95%); mp 186–188 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.35 (2H, m), 4.35 (2H,m), 4.60 (2H, m), 6.76 (1H, d, J = 9.9 Hz), 7.65 (1H, s), 8.00 (1H, d, J = 9.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 27.3 (CH_2), 42.3 (CH_2), 71.2 (CH_2), 92.2 (C), 120.3 (C), 123.0 (CH), 127.0 (C), 132.2 (CH), 134.0 (C), 135.2 (CH), 147.0 (C), 161.7 (C); MS [ESI]: m/z 362 $[M+H]^+$, 364 $[M+2+H]^+$, 384 $[M+Na]^+$, 386 $[M+2+Na]^+$. HRMS (ESI): m/z calcd for $C_{12}H_9ClINO_2Na$ $[M+Na]^+$: 383.9264, found 383.9233; (c) *spectral data of* **6c***:* White needles (yield: 92%); mp 180–182 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.38 (1H, d, J = 14.7 Hz), 5.77 (1H, d, J = 15 Hz), 5.86 (1H, d, J = 13.5 Hz), 6.35 (1H, d, J = 13.5 Hz), 6.75 (1H, d, J = 9.9 Hz), 7.06 (1H, m), 7.24 (2H, m), 7.30 (1H, s), 7.53 (1H, m), 7.95 (1H, d, J = 9.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.2 (CH_2), 76.1 (CH_2), 119.1 (C), 122.7 (CH), 124.2 (CH), 125.9 (CH), 128.5 (CH), 128.6 (CH), 128.8 (C), 131.6 (C), 132.4 (CH), 134.3 (C), 134.5 (CH), 135.5 (C), 135.9 (C) 141.0 (C), 161.9 (C); MS [ESI]: m/z 333 $[M+H]^+$, 335 $[M+2+H]^+$, 355 $[M+Na]^+$, 357 $[M+2+Na]^+$. HRMS (ESI): m/z calcd for $C_{17}H_{11}Cl_2NO_2Na$ $[M+Na]^+$: 354.0064, found 354.0054.