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Novel route for the synthesis of structurally diverse pyrrolo[2,1-*a*]isoquinoline in aqueous micellar medium

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ABSTRACT

A high yielding environmentally benign protocol has been developed for the synthesis of pyrrolo[2,1-*a*]isoquinoline using chromone-3-carboxaldehyde, isoquinoline and phenacyl bromide/bromoacetic acid ester as reagents in aqueous micellar medium. The method is operationally simple and more effective compared to the previous methods in terms of the yield of the products as well as the reaction time.

In recent times, synthetic organic chemists have developed considerable interest 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 basic problem in performing reaction in water is that many organic compounds are hydrophobic and are insoluble in water. The development that has contributed to some extent to overcome this problem is the introduction of aqueous surfactant solutions in the form of micelles,[3] as the reaction medium. 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 years, pyrrolo[2,1-*a*]isoquinolines have received much attention as they possess antidepressant,[5] muscarinic agonist, cardiotonic[6] and anticancer activity, and serve as intermediates for the synthesis of bioactive alkaloids.[7] Moreover, this type of compounds can be used as positron emission tomography (PET) radiotracers for imaging serotonin uptake sites.[8] The varied biological activities of pyrrolo[2,1-*a*]isoquinoline derivatives have attracted the attention of organic chemists and a number of synthetic methodologies have been developed for this system.[9] However, most of the methods are multistep processes and require long reaction time. The most common method for the synthesis of pyrrolo[2,1-*a*]isoquinoline is 1,3-dipolar cycloaddition of isoquinolinium ylides with alkynes. But the scope of this procedure has been limited due to the use of alkynes, very few of which are commercially available. As an alternative to the alkynes, olefinic dipolarophiles have been utilized, although there remain some difficulties, such as long reaction time, low yield and use of a mild dehydrogenative oxidant like TPCD to convert the tetrahydropyrrolo[2,1-*a*]isoquinoline intermediate to pyrrolo[2,1-*a*]isoquinoline.[10]

To overcome this problem, we wanted to develop a high yielding environmentally benign protocol by performing the 1,3-dipolar cycloaddition reaction of an isoquinolinium ylide (generated in situ by reacting isoquinoline and phenacyl bromide/bromoacetic acid ester in presence of a base) with chromone-3-carboxaldehyde as the 1,3-dipolarophile because the 1,3-dipolar cycloaddition reaction involving chromone-3-carboxaldehyde could generate novel heterocycles.[11] In continuation of our research on the synthesis of fused heterocycles in aqueous micellar medium,[12] we found out that carrying out the above reaction in aqueous micellar medium was crucial to ensure product formation in high yields. A library of pyrrolo[2,1-*a*]isoquinoline derivatives could thus be generated without using any additional dehydrogenative agent. The novelty of the methodology lies in its eco-friendly operation, formation of structurally unique molecules, short reaction time and excellent yield.

At the outset, we decided to condense isoquinoline (**1a**), phenacyl bromide (**2a**), and chromone-3-carboxaldehyde (**3a**) as model reagents to synthesize the pyrrolo[2,1-*a*]isoquinoline **4a**. The

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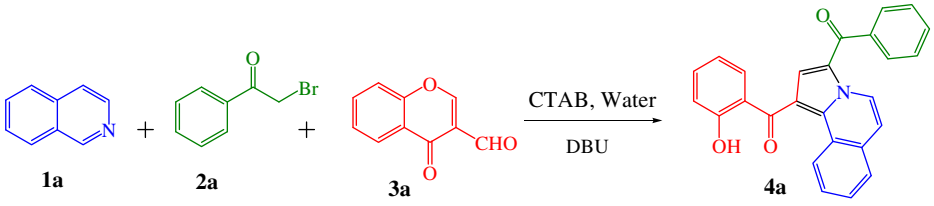
Table 1
Effect of the different surfactants on the yield of **4a**

Entry[a]	Surfactant	Concentration (mM)	Yield[b] (%)
1	None	–	NR[c]
2	CTAB	50	15
3	CTAB	60	35
4	CTAB	70	75
5	**CTAB**	**80**	**95**
6	CTAB	90	95
7	CTAB	100	95
8	SDS	80	55
9	TTAB	80	80
10	Triton X-114	80	65

[a] Reactions performed using **1a**, **2a** and **3a** in water at room temperature for 1 h.
[b] Yield of isolated pure product.
[c] No reaction.



Scheme 1. Synthesis of **4a** in aqueous micellar medium.

Table 2
Effect of different bases on the yield of **4a**

Entry[a]	Base	Amount (mmol)	Time (h)	Yield[b] (%)
1	DBU	0.25	12	54
2	DBU	0.50	12	78
3	DBU	0.75	12	82
4	**DBU**	**1**	**1**	**95**
5	Et_3N	1	8	55
6	DABCO	1	10	40
7	K_2CO_3	1	8	NR[c]
8	DMAP	1	12	NR[c]
9	Piperidine	1	12	NR[c]

[a] Reactions performed using **1a**, **2a** and **3a** in water (50 ml) at room temperature in presence of CTAB (4 mmol) for 1 h.
[b] Yield of isolated pure product.
[c] No reaction.

results (Table 1) reveal that reactions carried out in absence of a surfactant were ineffective even up to 24 h (Table 1, entry 1). An encouraging change in the outcome was however noticed when 50 mM of cetyltrimethylammonium bromide (CTAB, cmc 0.92 mM)[13a] was introduced in the system. Carrying out the reaction in water at room temperature for 1 h (Scheme 1) now ensured its completion (monitored by TLC) but gave low yield (15%) of the product **4a**.

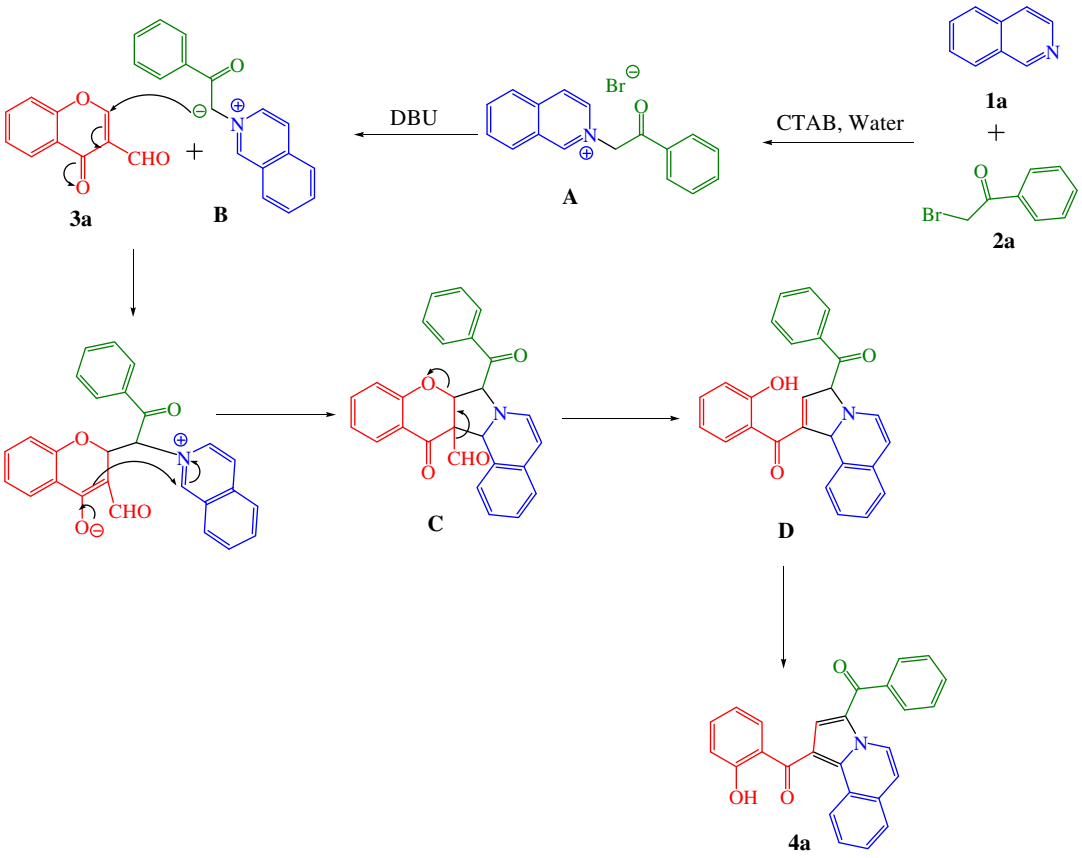
The structure of the product as (3-benzoyl-pyrrolo[2,1-*a*]isoquinolin-1-yl)-(2-hydroxy-phenyl)-methanone **4a** was determined from NMR and mass spectral studies. Single crystal X-ray crystallographic analysis then led to the confirmation of the assumed structure (see Fig. 1, Supplementary data).

In order to increase the yield of **4a**, we then used higher amounts of the surfactant. Use of 60 or 70 mM CTAB indeed improved the product yield. The most striking result (95%) was obtained when the reaction was performed using CTAB at 80 mM concentration (Table 1, entry 5). However, no significant increase in the yield was observed on enhancement of concentration of CTAB beyond 80 mM (Table 1, entries 6 and 7). Also, extension of the reaction time did not improve the yield of the products. Changing to other surface active agents, the reaction yielded only 55% of the product **4a** (Table 1, entry 8) with sodium dodecylsulfate (SDS: cmc value 8.1 mM)[13b] and 80% (Table 1, entry 9) with tetradecyltrimethylammonium bromide (TTAB: cmc value 3.8 mM),[13c] both at the concentration of 80 mM.

Even the use of a nonionic surfactant like Triton X-114 (cmc 0.28 mM)[13d] proved less effective compared to CTAB (Table 1, entry 10).

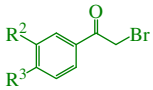
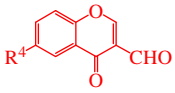
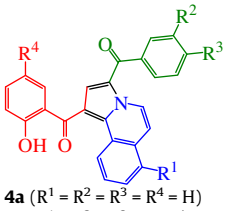
The above reactions were also performed in the presence of different bases, viz. DBU, Et_3N, DABCO, DMAP, piperidine and K_2CO_3; however, DBU appeared to be the most effective when employed in molar equivalent (Table 2), affording the product in maximum yield.

A plausible mechanism for the formation of pyrrolo[2,1-*a*]isoquinoline **4a** is depicted in Scheme 2. It is presumed that initially the reaction of isoquinoline (**1a**) and phenacyl bromide (**2a**) generates the isoquinolinium salt (**A**), which is converted to the isoquin-



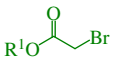
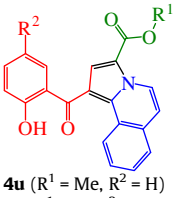
Scheme 2. Plausible pathway for the formation of **4a**.

Table 3
Synthesis of pyrrolo[2,1-*a*]isoquinolines in aqueous micellar medium

Entry[a]	Isoquinoline	Phenacyl bromide/bromoacetic acid ester	Chromone-3-carboxal-dehyde	Pyrrolo[2,1-*a*] isoquinoline	Yield[b] (%)
					
1	**1a** (R^1 = H)	**2a** (R^2 = R^3 = H	**3a** (R^4 = H)	**4a** (R^1 = R^2 = R^3 = R^4 = H)	95
2	**1a**	**2a**	**3b** (R^4 = Me)	**4b** (R^1 = R^2 = R^3 = H, R^4 = Me)	90
3	**1a**	**2a**	**3c** (R^4 = Cl)	**4c** (R^1 = R^2 = R^3 = H, R^4 = Cl)	92
4	**1a**	**2b** (R^2 = H, R^3 = F)	**3a**	**4d** (R^1 = R^2 = R^4 = H, R^3 = F)	90
5	**1a**	**2b**	**3b**	**4e** (R^1 = R^2 = H, R^4 = Me, R^3 = F)	93
6	**1a**	**2b**	**3c**	**4f** (R^1 = R^2 = H, R^4 = Cl, R^3 = F)	90
7	**1a**	**2c** (R^2 = H, R^3 = NO_2)	**3a**	**4g** (R^1 = R^2 = R^4 = H, R^3 = NO_2)	95
8	**1a**	**2c**	**3b**	**4h** (R^1 = R^2 = H, R^4 = Me, R^3 = NO_2)	94
9	**1a**	**2c**	**3c**	**4i** (R^1 = R^2 = H, R^4 = Cl, R^3 = NO_2)	94
10	**1a**	**2d** (R^2 = H, R^3 = Me)	**3a**	**4j** (R^1 = R^2 = R^4 = H, R^3 = Me)	90
11	**1a**	**2d**	**3b**	**4k** (R^1 = R^2 = H, R^4 = Me, R^3 = Me)	90
12	**1a**	**2d**	**3c**	**4l** (R^1 = R^2 = H, R^4 = Cl, R^3 = Me)	92
13	**1a**	**2e** (R^2 = H, R^3 = Ph)	**3a**	**4m** (R^1 = R^2 = R^4 = H,	90

(*continued on next page*)

Table 3 (*continued*)

Entry[a]	Isoquinoline	Phenacyl bromide/bromoacetic acid ester	Chromone-3-carboxaldehyde	Pyrrolo[2,1-*a*] isoquinoline	Yield[b] (%)
				(R^3 = Ph)	
14	**1a**	**2e**	**3b**	**4n** (R^1 = R^2 = H, R^4 = Me, R^3 = Ph)	94
15	**1a**	**2e**	**3c**	**4o** (R^1 = R^2 = H, R^4 = Cl, R^3 = Ph)	90
16	**1a**	**2f** (R^2 = R^3 = Cl)	**3a**	**4p** (R^1 = R^4 = H, R^2 = R^3 = Cl)	90
17	**1a**	**2f**	**3c**	**4q** (R^1 = H, R^2 = R^3 = R^4 = Cl)	90
18	**1b** (R^1 = NO_2)	**2a**	**3a**	**4r** (R^1 = NO_2, R^2 = R^3 = R^4 = H)	92
19	**1b**	**2a**	**3b**	**4s** (R^1 = NO_2, R^2 = R^3 = H, R^4 = Me)	94
20	**1b**	**2g** (R^2 = H, R^3 = Cl)	**3a**	**4t** (R^1 = NO_2, R^2 = R^4 = H, R^3 = Cl)	90
					
21	**1a**	**2h** (R^1 = Me)	**3a**	**4u** (R^1 = Me, R^2 = H)	92
22	**1a**	**2i** (R^1 = Et)	**3a**	**4v** (R^1 = Et, R^2 = H)	92
23	**1a**	**2i**	**3c**	**4w** (R^1 = Et, R^2 = Cl)	90
24	**1a**	**2j** (R^1 = ^{t}Bu)	**3a**	**4x** (R^1 = ^{t}Bu, R^2 = H)	90

[a] Reaction conditions: isoquinoline (1 mmol), phenacyl bromide/bromoacetic acid ester (1 mmol), chromone-3-carboxaldehyde (1 mmol), water (50 ml), DBU (1 mmol), CTAB (4 mmol), 1 h in air.
[b] Yield of isolated pure products.

olinium ylide (**B**) by reacting with a base. A regioselective 1,3-dipolar cycloaddition reaction occurs between the electron deficient C_2–C_3 π bond of chromone-3-carboxaldehyde (**3a**) and the isoquinoline ylide (**B**), forming an unstable intermediate **C**, which after deformylation[11a] and ring opening[14] leads to dihydro-pyrrolo[2,1-*a*]isoquinoline derivative **D**, which readily aromatizes to give **4a**.

In order to establish the generality and scope of this new methodology, we used different derivatives of isoquinoline, phenacyl bromide/bromoacetic acid ester and chromone-3-carboxaldehyde. The results are summarized in Table 3.

In summary, we have developed an environmentally benign protocol for the synthesis of pyrrolo[2,1-*a*]isoquinolines[15,16] with excellent yields and in a short reaction time using easily available starting materials in aqueous micellar medium. The study demonstrates the feasibility of preparation of libraries of biologically active pyrrolo[2,1-*a*]isoquinoline analogues for lead discovery and/or optimization in medicinal chemistry.

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Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra of all new compounds. Crystallographic data in CIF format are available free of charge via the Internet at CCDC 796010 & 796011. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk)) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.01.141.

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15. *General reaction procedure for the synthesis of pyrrolo[2,1-a]isoquinolines*: One mmol each of the isoquinoline (**1a–b**), phenacyl bromide/bromoacetic acid ester (**2a–j**), and chromone-3-carboxaldehyde (**3a–c**) derivatives were taken in a 100 ml RB flask. Then water (50 ml), CTAB (4 mmol) and DBU (1 mmol) were added and the mixture was stirred continuously for 1 h at room temperature. After completion of the reaction (monitored by TLC), the contents of the reaction mixture were poured into a separating funnel and extracted with ethyl acetate (3 × 25 ml). The organic layer was washed thoroughly with water until free from CTAB and base, dried over sodium sulfate, and evaporated to dryness in a rotary evaporator under reduced pressure. The residue was chromatographed over a column of silica gel (60–120 mesh) eluting with a mixture of hexane and ethyl acetate in different ratios, to yield the pyrrolo[2,1-*a*]isoquinolines (**4a–x**).
16. (a) *Spectral data of [3-(Biphenyl-4-carbonyl)-pyrrolo[2,1-a]isoquinolin-1-yl]-(5-chloro-2-hydroxy-phenyl)-methanone* (**4o**): Yellow needles (yield: 90%); mp 216–218 °C; R_f (hexane/EtOAc 9:1) 0.55; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.05 (1H, d, J = 9 Hz), 7.37 (1H, d, J = 7.2 Hz), 7.41 (1H, m), 7.45 (1H, dd, J_1 = 2.4 Hz, J_2 = 9 Hz), 7.48 (2H, m), 7.50 (1H, s), 7.59 (1H, m), 7.66 (3H, m), 7.74 (2H, m), 7.79 (1H, m), 7.82 (1H, d, J = 7.8 Hz), 7.97 (2H, m), 8.65 (1H, d, J = 8.4 Hz), 9.68 (1H, d, J = 7.2 Hz), 12.10 (1H, s); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 115.6 (2 × C), 116.1 (CH), 120.0 (CH), 121.5 (C), 123.5 (C), 123.7 (C), 124.0 (C), 125.1 (CH), 126.0 (CH), 127.2 (CH), 127.30 (2 × CH), 127.34 (2 × CH), 128.09 (CH), 128.15 (CH), 129.0 (2 × CH), 129.4 (CH), 129.6 (2 × CH), 129.9 (CH), 130.5 (C), 132.4 (CH), 136.0 (CH), 138.2 (C), 139.9 (C), 145.0 (C), 161.7 (C), 185.5 (CO), 196.1 (CO); MS [ESI]: m/z 524, 526 $[M+2+Na]^+$. HRMS [ESI] m/z calcd for $C_{32}H_{20}ClNO_3Na$ $[M+Na]^+$: 524.1029, found 524.1018; (b) *Spectral data of 1-(2-Hydroxy-benzoyl)-pyrrolo[2,1-a]isoquinoline-3-carboxylic acid tert-butyl ester* (**4x**): Yellow needles (yield: 90%); mp 186–188 °C; R_f (hexane/EtOAc 9:1) 0.79; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.62 (9H, s), 6.89 (1H, m), 7.11 (1H, d, J = 8.4 Hz), 7.20 (1H, d, J = 7.5 Hz), 7.51 (4H, m), 7.75 (2H, m), 8.48 (1H, d, J = 8.1 Hz), 9.40 (1H, d, J = 7.5 Hz), 12.35 (1H, s); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 28.4 (3 × CH_3), 81.7 (C), 114.9 (CH), 115.5 (C), 117.3 (C), 118.3 (CH), 118.8 (CH), 120.8 (C), 124.3 (CH), 124.4 (CH), 124.5 (C), 125.6 (CH), 127.1 (CH), 127.7 (CH), 128.7 (CH), 129.4 (C), 133.6 (CH), 134.3 (C), 136.1 (CH), 160.5 (C), 163.3 (C), 197.8 (CO); MS [ESI]: m/z 388 $[M+H]^+$, 410 $[M+Na]^+$. HRMS [ESI] m/z calcd for $C_{24}H_{21}NO_4Na$: 410.1368, found 410.1357.