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Development of five membered heterocyclic frameworks *via* [3+2] cycloaddition reaction in an aqueous micellar system†

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A series of novel dihydropyrrolo[2,1-*a*]isoquinolines and dihydropyrrolo-[1,2-*a*]quinolines have been synthesized from isoquinolines/quinolines, various substituted phenacyl bromides and substituted dialkylacetylene-dicarboxylates *via* [3+2] cycloaddition reaction. The reaction proceeds in aqueous micellar medium with DBU as a catalyst. The present protocol offers a simple one pot sequential reaction affording products in excellent yields.

Bridgehead nitrogen heterocycles, especially pyrroloisoquinolines, are of great interest because they constitute a major class of natural products, many of which exhibit useful biological activities.[1] Pyrrolo[2,1-*a*]isoquinolines, an important series of this class, have received much attention in the last few years due to their antidepressant,[2] muscarinic agonist, cardiotonic[3] and anti-cancer activities. These compounds also serve as intermediates for the synthesis of various bioactive alkaloids.[4] Additionally, these compounds can also be used as positron emission tomography (PET) radiotracers for imaging serotonin uptake sites.[5] The various biological activities and applications of pyrrolo[2,1-*a*]-isoquinoline derivatives have attracted the attention of organic chemists and a number of synthetic methodologies have been developed for these systems.[6] However, most of these methods are multistep processes and require a long reaction time. A common protocol for the synthesis of pyrrolo[2,1-*a*] isoquinoline is 1,3-dipolar cycloaddition of isoquinolinium ylides with alkynes. Pyrrolo[2,1-*a*]isoquinolines are generally synthesized by 1,3-dipolar addition of isoquinolium ylide to limited commercially available alkynes. Active alkenes have also been used as alternatives to alkynes with some disadvantages such as long reaction time, low yield and use of metallic catalysts.[7]

As part of our interest in the development of new molecules and novel strategies in heterocyclic synthesis,[8] we herein report an efficient one-pot synthesis of novel dihydropyrroloisoquinolines *via* reaction of isoquinolines and various phenacyl bromides followed by addition of substituted dialkylacetylenedicarboxylates under various conditions.

The proposed multicomponent synthesis is very appealing due to its numerous advantages over conventional linear synthesis, such as the reduced number of synthetic steps, shorter reaction times, a high degree of atom economy, *etc.*, which allow the preparation of diverse structures in a rapid and cost-effective manner.[9] In the present work, we also found that 1,3-dipolar ylide cycloaddition reaction is an efficient and very powerful tool for the construction of dihydropyrroloisoquinolines.

Initially, we investigated optimization conditions with respect to both the catalyst and the solvent. For this purpose, isoquinoline (**1**), 4-chlorophenacylbromide (**2**) and diethylacetylenedicarboxylate (**3**) were chosen as model substrates for the synthesis of a representative compound (**4a**) (Scheme 1). We performed this reaction using DBU (10%) as a catalyst and water as the preferred solvent because it is the best green solvent for solution phase chemistry and cyclization reactions occur more easily in polar solvents.[10] The main obstacle in this procedure is related to the solubility problem which led to the formation of the product in traces even after 10 h. The key issue is the insolubility of 4-chlorophenacyl bromide in water. To overcome this problem, we used cetyltrimethylammonium bromide (CTAB: cmc value 0.92 mM)[11] as a surfactant, which contributes significantly to the promotion of the reaction,[12] since it acts as an emulsifying agent when mixed with an organic reagent to form colloidal dispersion. It can be easily removed after completion of the reaction using the powdered activated carbon method[13] or the potassium ferrate method.[14] As a trial, we performed the reaction with 5 mol% of CTAB in water but no significant change was observed. An encouraging change was noticed when the reaction was carried out with 8 mol% of CTAB in 50 mL of water. This gave only 25% yield of the product (Table 1, entry 3). Surprisingly, the reaction afforded a maximum yield of 70% (Table 1, entry 4) when performed with 10 mol% of CTAB. No change in yield was noticed when the concentration of CTAB was

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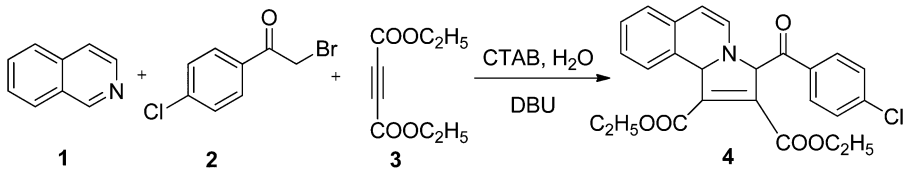


Scheme 1 Synthesis of diethyl 3-(4-chlorobenzoyl)-3,10*b*-dihydropyrrolo[2,1-*a*] isoquinoline-1,2-dicarboxylate in an aqueous micellar system.

Table 1 Effect of different surfactants on the yield of the reaction

Entry	Surfactant	Conc. (mol%)	Time (min)	Yield (%)
1	—	—	180	Traces
2	CTAB	5	180	Traces
3	CTAB	8	180	25
4	CTAB	10	30	70
5	CTAB	10	50	70
6	CTAB	15	30	70
7	SDS	10	30	30
8	TTAB	10	30	45

Table 2 Optimization of base

Entry	Base	Conc. (mol%)	Time (min)	Yield (%)
1	DBU	10	30	70
2	DBU	15	30	72
3	DBU	20	30	95
4	DBU	30	30	95
5	DBU	40	30	95
6	Et_3N	20	30	40
7	DABCO	20	30	Traces
8	DMAP	20	30	Traces
9	K_2CO_3	20	30	52

further increased. Besides CTAB, other surface active reagents like sodium dodecylsulfate (SDS: cmc value 8.1 mM)[15] and tetradecyltrimethylammonium bromide (TTAB: cmc value 3.8 mM)[16] were also used to perform the reaction (Table 1, entries 7 and 8), but no satisfactory results were obtained as compared to CTAB.

Table 3 Effect of different solvents on the yield of the reaction

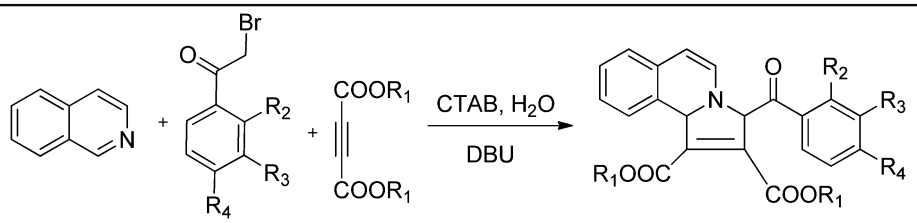
Entry	Solvent	Time (min)	Yield (%)
1	Hexane	30	25
2	CH_3CN	30	75
3	THF	30	50
4	Toluene	30	35
5	1,4-Dioxane	30	55
6	Water	30	95

With the hope of increasing the yield of the product, we performed a series of reactions by changing the concentration of the base, *i.e.*, DBU, and found that 20% DBU afforded a maximum yield (95%) in 30 minutes. Further increment of the catalyst amount (DBU) did not affect the yield of the product. We have also performed the reaction in the presence of other bases like Et_3N, DABCO, DMAP and K_2CO_3 and the results are summarized in Table 2, which clearly shows that DBU is the best catalyst for the proposed synthesis.

Lastly, to study the effect of solvents, we replaced water by other organic solvents but the results were not as good as in the case of water (Table 3). It was also noticed that a higher reaction temperature (instead of room temperature) had no effect on the yield.

With the encouraging results we employed different derivatives of phenacyl bromide and acetylenedicarboxylate to prepare a series of dihydropyrroloisoquinolines (Table 4). This protocol well tolerates phenacyl bromides containing both electron-withdrawing and

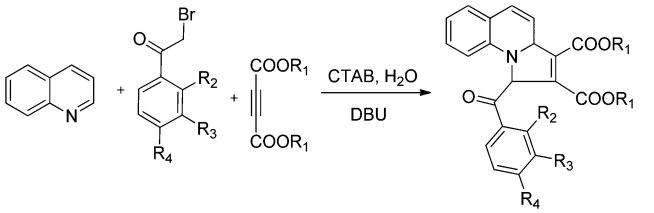
Table 4 Synthesis of dihydropyrroloisoquinoline derivatives



Entry	R_1	$R_2/R_3/R_4$	Time (min)	Product[a]	Yield[b] (%)
1	Me	H/H/Cl	30	**4a**	94
2	Me	Cl/H/H	30	**4b**	94
3	Me	H/H/OMe	40	**4c**	90
4	Me	OH/H/H	35	**4d**	92
5	Me	H/OH/OMe	40	**4e**	88
6	Me	$H/H/NO_2$	15	**4f**	95
7	Et	H/H/Cl	30	**4g**	95
8	Et	H/H/OMe	40	**4h**	92
9	Et	$H/H/NO_2$	20	**4i**	96
10	Et	OH/H/H	35	**4j**	94

[a] Reaction conditions: isoquinoline (1 mmol), phenacyl bromides (1.1 mmol), DBU (20 mol%), dialkyl acetylenedicarboxylate (1 mmol), CTAB (10 mol%); RT. [b] Isolated yield.

Table 5 Synthesis of dihydropyrroloquinoline derivatives



Entry	R_1	$R_2/R_3/R_4$	Time (min)	Product[a]	Yield[b] (%)
1	Me	H/H/Cl	40	**5a**	85
2	Me	Cl/H/H	40	**5b**	85
3	Me	H/H/OMe	60	**5c**	75
4	Me	OH/H/H	50	**5d**	80
5	Me	H/OH/OMe	50	**5e**	80
6	Me	$H/H/NO_2$	30	**5f**	88
7	Et	H/H/Cl	45	**5g**	86
8	Et	H/H/OMe	50	**5h**	82
9	Et	$H/H/NO_2$	45	**5i**	86
10	Et	OH/H/H	50	**5j**	80

[a] Reaction conditions: quinoline (1 mmol), phenacyl bromides (1.1 mmol), DBU (20 mol%), dialkyl acetylenedicarboxylate (1 mmol), CTAB (10 mol%); RT. [b] Isolated yield.

electron donating substituents. The electronic effect and the nature of the substituents in phenacyl bromide show some obvious effects in terms of the yield of the reaction. Phenacyl bromide with electron-withdrawing groups gives better results as compared to electron-donating groups.

To explore the scope and generality of the reaction with the optimized conditions, we also employed quinolines with different phenacyl bromides and dialkylacetylenedicarboxylates under optimized conditions to obtain several dihydropyrroloquinolines (**5a–j**). We got almost the same results as compared to isoquinolines. The results are summarized in Table 5.

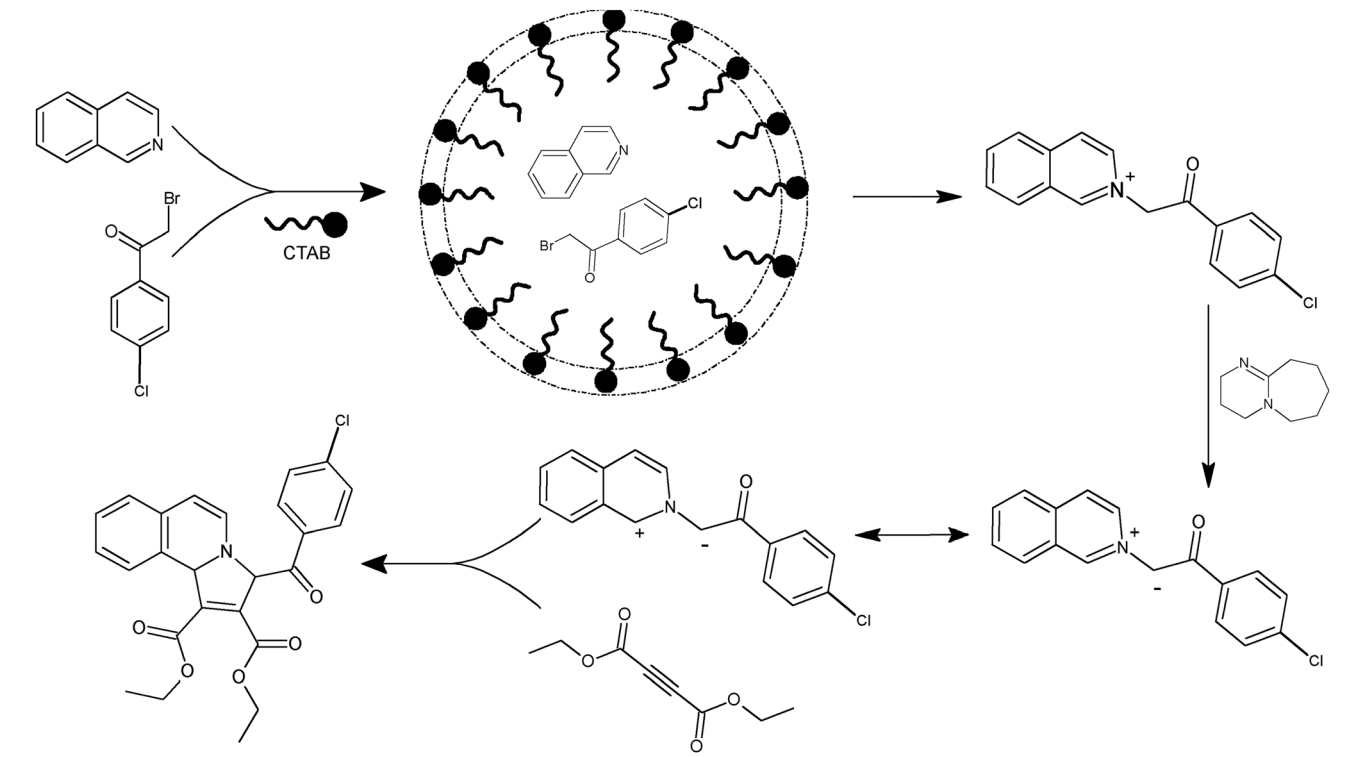
Mechanistically, the first step of the reaction is a nucleophilic substitution reaction between isoquinoline and 4-chlorophenacyl bromide under micellar conditions, leading to the formation of a quaternary ammonium salt. This salt is then converted into nitrogen ylide in the presence of the base DBU. This intermediate behaves as a carbon nucleophile in cycloaddition reaction with diethylacetylenedicarboxylate giving the desired product (Scheme 2). This is a good example of (3+2) coupling of nitrogen ylide and diethylacetylenedicarboxylate. This mechanism is also supported by Dekamin *et al.*[17]

We have synthesized a number of novel dihydropyrrolo[2,1-*a*]-isoquinolines and dihydropyrrolo[1,2-*a*]quinolines *via* 1,3-dipolar ylide cycloaddition reaction. The reaction is one pot sequential addition, which operates in basic aqueous micellar medium under mild conditions. The method described here is simple and efficient involving green protocols to obtain five membered ring systems. The yield of the products obtained is also excellent.

Experimental

General procedure for synthesis

To a homogeneous solution of CTAB (10 mol%) in water, isoquinolines/quinolines (1 mmol) and phenacyl bromides (1.1 mmol) were added and stirred at room temperature for



Scheme 2 Plausible mechanism for the synthesis of diethyl-3-(4-chlorobenzoyl)-3,10*b*-dihydropyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate in aqueous micellar medium.

half an hour. Now DBU (20 mol%) and dialkyl acetylenedicarboxylate (1 mmol) were added to the reaction mixture and stirred at room temperature for appropriate time periods mentioned in Tables 4 and 5. Progress of the reaction was monitored by TLC. Upon completion of the reaction, the product was extracted with ethyl acetate. The organic layer was washed thoroughly with water until free from CTAB and base and then dried under reduced pressure. The products were isolated by column chromatography.

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