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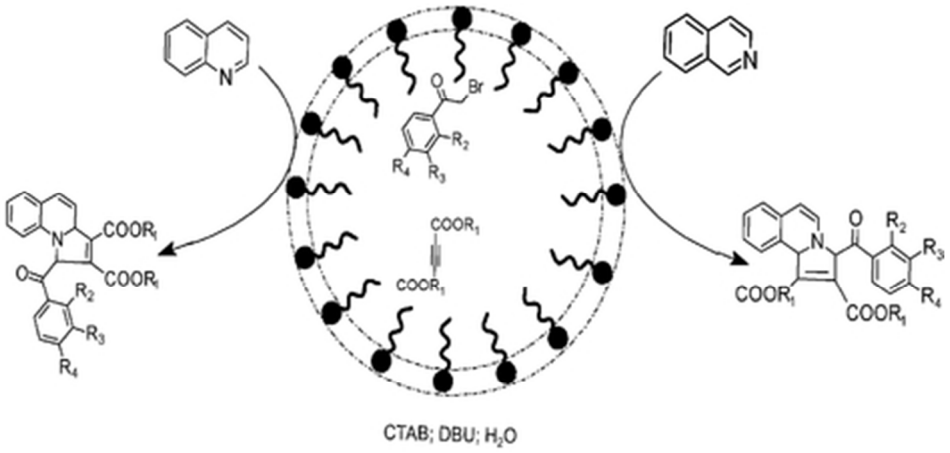


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# Development of five membered heterocyclic frameworks via [3+2] cycloaddition reaction in aqueous micellar system

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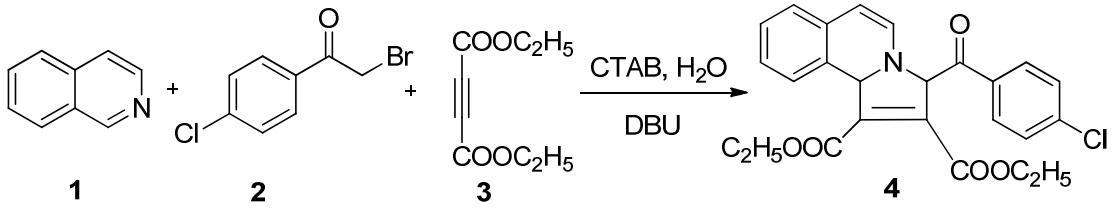
**Abstract:** A series of novel dihydropyrrolo[2,1-a]isoquinolines and dihydropyrrolo[1,2-a]quinolines have been synthesized from isoquinoline/quinoline, various substituted phenacyl bromides and substituted dialkylacetylenedicarboxylate via [3+2] cycloaddition reaction. The reaction proceeds in aqueous micellar medium with DBU as catalyst. The present protocol offers 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, received much attention in previous years due to antidepressant,[2] muscarinic agonist, cardiotonic[3] and anticancer 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] These varied 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 this system.[6] However, most of these methods are multistep processes and require 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. The scope of this procedure is limited due to the use of alkynes, very few of which are commercially available. As an alternative to the alkynes, olefinic dipolarophiles have also been used, although there remain some difficulties, such as long reaction time, low yield and use of a dehydrogenative oxidant like tetrakis-pyridino-cobalt(II) dichromate (TPCD) to convert the tetrahydropyrrolo[2,1-a]isoquinoline intermediate to pyrrolo[2,1-a]isoqunoline.[7]
As part of our interest on 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 isoquinoline and various phenacyl bromides followed by addition of substituted dialkylacetylenedicarboxylate under various conditions.
The proposed multicomponent synthesis is very appealing due to numerous advantages over conventional linear syntheses, such as reduced number of synthetic steps, shorter reaction times, 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.




**Scheme 1: synthesis of diethyl 3-(4-chlorobenzoyl)-3,10b-dihydropyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate in aqueos micellar system**

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 representative compound (**4a**) (Scheme 1). We performed this reaction using DBU (10%) as a catalyst and water as 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 solubility problem which led to the formation of product in traces even after 10 hrs. The key issue is insolubility of 4-chlorophenacyl bromide in water. To overcome this problem, we have used cetyltrimethylammonium bromide (CTAB: cmc value 0.92 mM)[11] as a surfactant, which contributes significantly to promote the reaction,[12] since it acts as emulsifying agent when mixed with 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 water. This gave only 25% yield of the product (Table 1, entry 3). Surprisingly, the reaction afforded maximum 70% yield (Table 1, entry 4) when performed with 10 mol% of CTAB. No change in yield was noticed when concentration of CTAB was 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 1 Effect of different surfactant 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 |

With the hope to increase 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 catalyst amount (DBU) did not affect the yield of 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 proposed synthesis.

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 |

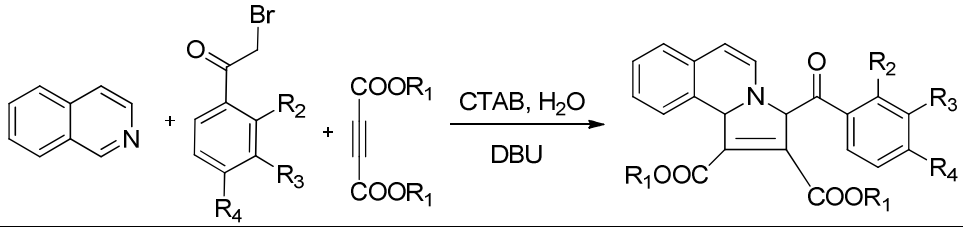
Lastly, to study the effect of solvents, we replaced water by other organic solvents but the results were not as good as in case of water (Table 3). It was also noticed that a higher reaction temperature (instead of room temperature) had no effect on the yield.

Table 3 Effect of different solvent 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 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 electron donating substituents. The electronic effect and the nature of the substituents on phenacyl bromide show some obvious effects in terms of yield of reaction. Phenacyl bromide with electron-withdrawing groups gives better results as compared to electron-donating groups.

Table 4 Synthesis of dihydropyrroloisoquinolenes derivatives.

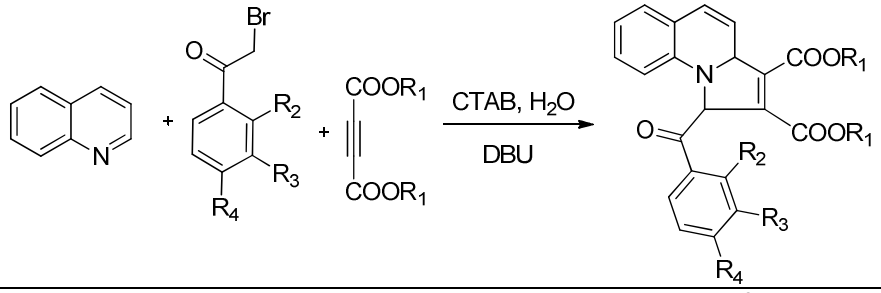



| Entry | $R_1$ | $R_2/R_3/R_4$ | Time (min) | Product[a] | Yield[b](%) |
|---|---|---|---|---|---|
| 1 | Me | H/H/Cl | 30 | 4a | 94 |
| 2 | Me | Cl/H/H | 30 | 4b | 94 |
| 3 | Me | H/H/OMe | 40 | 4c | 90 |
| 4 | Me | OH/H/H | 35 | 4d | 92 |
| 5 | Me | H/OH/OMe | 40 | 4e | 88 |
| 6 | Me | $H/H/NO_2$ | 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

To explore the scope and generality of the reaction with the optimized conditions, we also employed quinoline with different phenacyl bromides and dialkylacetylenedicarboxylates under optimized condition to obtain several dihydropyrroloquinolines (5a-j). We got almost same results as compared to isoquinoline. The results were summarized in table 5

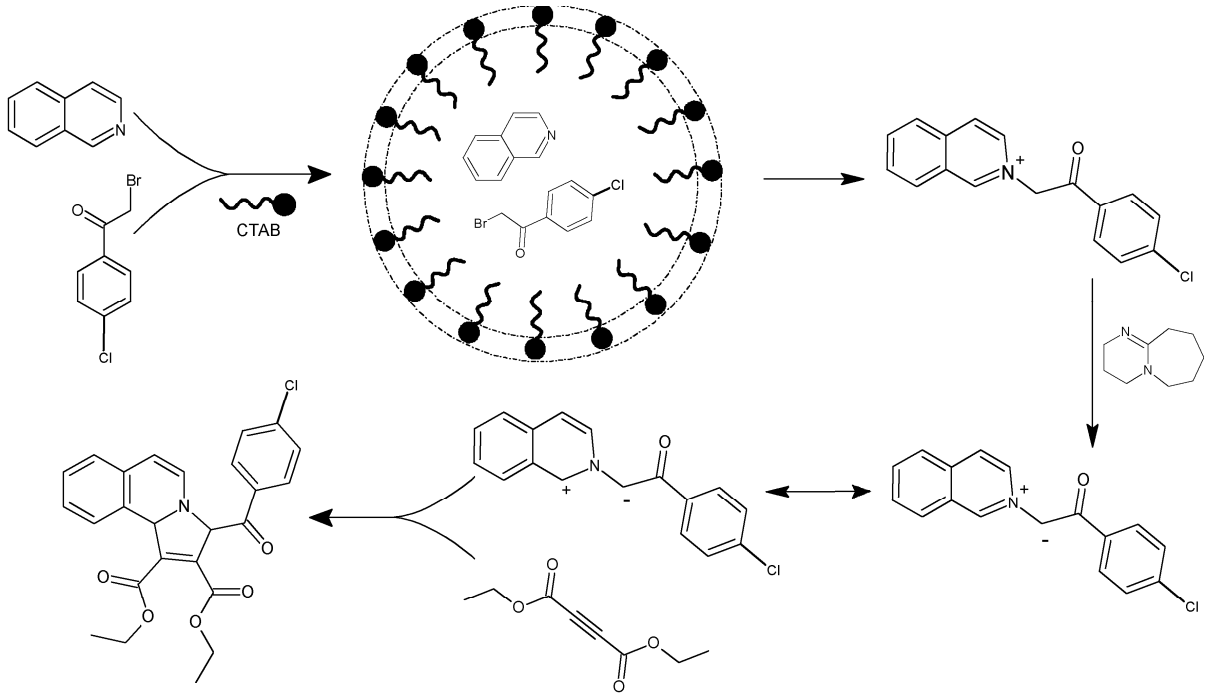
Table 5 Synthesis of dihydropyrroloquinolenes derivatives.




| 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

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 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 and gives cycloaddition reaction with diethylacetylenedicarboxylate and the desired product is obtained (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]




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

We have synthesized a number of novel dihydropyrrolo[2,1-a]isoquinolines and dihydropyrrolo[1,2-a]quinoline 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, isoquinoline/quinoline (1 mmol) and phenacyl bromides (1.1 mmol) were added and stirred at room temperature for 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 mentioned in table 4 and table 5. Progress of reaction was monitored by TLC. On completion of 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.

Electronic Supplementary Information (ESI) available: Supporting information contains spectral data of synthesized compounds.

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