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Regioselective ring expansion followed by H-shift of 3-ylidene oxindoles: a convenient synthesis of N-substituted/un-substituted pyrrolo[2,3-*c*]quinolines and marinoquinolines†

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Herein, we report a simple and metal-free protocol for the synthesis of 4-oxo-4,5-dihydro-3*H*-pyrrolo[2,3-*c*]quinolines. The present method under mild reaction conditions with wide functional group compatibility gives several unexplored N-substituted/unsubstituted 4-oxo-4,5-dihydro-3*H*-pyrrolo[2,3-*c*]quinolines and marinoquinolines in good to excellent yields. Mechanistic insights for the synthesis of N-substituted pyrroloquinolines reveal the ring expansion of 3-ylideneoxindoles and H-shift as the key steps.

Introduction

Functionalized heteroarenes, particularly azaheteroarenes are indispensable structural units in a large number of natural products, pharmaceuticals, agrochemicals, and functional materials.^{1a-e} The fused azaheteroarenes such as pyrrolo[2,3-*c*]quinoline derivatives occupy an essential role, due to their wider occurrence in the pharmaceutically active compounds. These are very well explored in the literature for various medicinal applications such as a caspase 3-inhibitor,² 5HT4R antagonist,³ ATPase inhibitor,⁴ apildipsamine,⁵ and marinoquinoline A, E, and F.⁶ A few examples are shown (Fig. 1).

Owing to its huge application in various scientific fields, the development of new synthetic methodologies for the synthesis of these compounds is of high demand and attractive in the synthetic community. In the recent past, several synthetic methods have been reported for the synthesis of fused pyrrolo[2,3-*c*]quinoline derivatives. In 2009, Rossi *et al.*, developed photostimulated intramolecular S_{RN}1 reactions for 3*H*-pyrrolo[2,3-*c*]quinolin-4(5*H*)-one synthesis.⁷ Recently, palladium catalysed intramolecular cycloaddition was also explored.⁸ KO^tBu mediated synthesis of 3*H*-pyrrolo[2,3-*c*]quinolin-4(5*H*)-one was achieved by Bergman *et al.*,⁹ and Ji *et al.*,¹⁰ separately (Scheme 1). Synthesis of N-unsubstituted pyrrolo[2,3-*c*]quinoline, which in fact attempted

by Bergman *et al.*, where, isocyanate intermediate formation and H-shift are the key steps in the mechanism and it is applied only for the synthesis of N-unsubstituted pyrrolo[2,3-*c*]quinolines. Unfortunately, to the best of our knowledge no successful attempts were reported for the synthesis of N-substituted fused pyrrolo[2,3-*c*]quinolines. More recently, in our previous work, we have developed methods for the synthesis of pyrazoloquinazolinones in a single step from isatin derivatives.¹¹ Herein, we report the study on development of an effective method for the synthesis of N-unsubstituted as well as N-substituted pyrrolo[2,3-*c*]quinoline, which in fact was also attempted by Ji *et al.*, but it is applicable only for the synthesis of N-unsubstituted pyrrolo[2,3-*c*]quinolines.¹⁰ However, the synthesis of N-substituted pyrrolo[2,3-*c*]quinolines are not-feasible with this strategy as N-H cleavage is involved in the isocyanate intermediate formation. In this regard, herein our current approach, spiro ring expansion followed by H-shift are

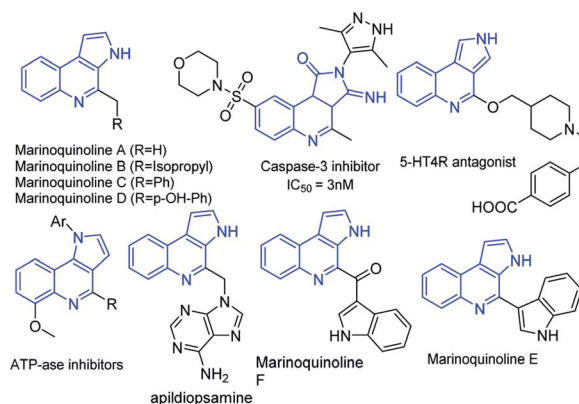


Fig. 1 Examples of biologically important pyrroloquinoline derivatives.

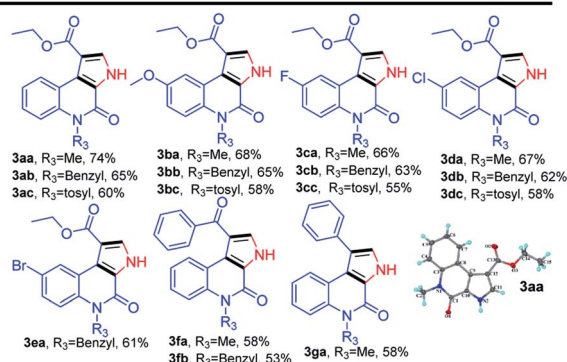
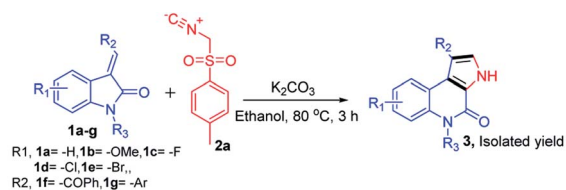
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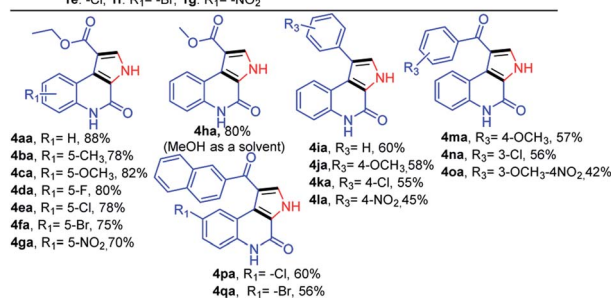
Scheme 2 Substrate scope for synthesis of N-substituted-4-oxo-4,5-dihydro-3H-pyrrolo[2,3-c]quinolines.

reaction with TosMIC 2a, and produced the required products in moderate to good yields 3ca–3ga.

From the above results, there is no such general trend was observed with the substrates having substitution on the phenyl ring of (*E*)-2-(2-oxindolin-3-ylidene)acetate 1a, whereas a remarkable impact on the yields was observed with the N-protected substrates. Electron donating groups on the N-atom produced the better yields than the electron withdrawing groups.

Next, we further extended the use of the present optimized base-mediated synthesis of ethyl 4-oxo-4,5-dihydro-3H-pyrrolo[2,3-c]quinoline-1-carboxylate 4aa to explore unprotected ethyl (*E*)-2-(2-oxindolin-3-ylidene)acetate with TosMIC 2a. We then examined the scope of the reaction using a variety of structurally diverse unprotected ethyl (*E*)-2-(2-oxindolin-3-ylidene)acetates 1a precursors (Scheme 3). Further, a range of functional groups such as electron donating ($R_1 = -\text{OMe}$, and $-\text{Me}$) as well as electron withdrawing groups on the phenyl ring of oxindole ($R_1 = -\text{F}$, $-\text{Cl}$, $-\text{Br}$ and $-\text{NO}_2$) were also compatible with the reaction. These underwent the desired transformation efficiently and furnished the corresponding product (Scheme 3, 4aa–4ga) in good to excellent yields. It was found that various substitutions on the olefinic position of the oxindole ($R_2 = -\text{CO}_2\text{Et}$, $-\text{CO}_2\text{Me}$, substituted aryl and phenacyl) are amenable to the present reaction and also afforded good to high yields (Scheme 3). It is to be noted that, the electronic nature of substituents on the olefinic position of (*E*)-2-(2-oxindolin-3-ylidene)acetate has discernible impact on the reaction efficacy where electron donating ($R_3 = -\text{substituted aryl}$) groups provided corresponding products in slightly better yields than the electron withdrawing groups ($R_2 = -\text{substituted phenacyl}$) (Scheme 3, 4ha–4qa).

To further explore the synthetic utility of this reaction, a gram scale reaction was performed under optimized reaction conditions which delivered ethyl 5-methyl-4-oxo-4,5-dihydro-3H-pyrrolo

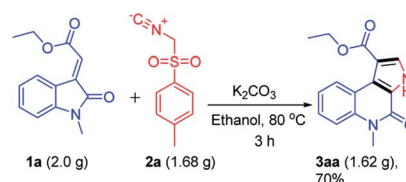


Scheme 3 Substrate scope for synthesis of N-unsubstituted 4-oxo-4,5-dihydro-3H-pyrrolo[2,3-c]quinolines.

[2,3-c]quinoline-1-carboxylate 3aa without affecting the reaction efficacy showing its potential in bulk scale utility (Scheme 4).

With the aforementioned experimental results and the literature precedents, we propose a plausible reaction mechanism for the base-mediated synthesis of 4-oxo-4,5-dihydro-3H-pyrrolo[2,3-c]quinolines (Fig. 2). The reaction starts with, TosMIC 2a reacts with base K_2CO_3 and generates anionic intermediate 2a'. The generated anionic intermediate 2a' participates in the 3 + 2 cycloaddition with (*E*)-2-(2-oxindolin-3-ylidene)acetate 1a to form the corresponding intermediate 1b, which undergoes 5-membered spiro ring formation and generates 1c. Next, formation of 1d occurs with the elimination of TsOH. Here, in the literature, Isocyanate formation occurs with the $-\text{H}$ -shift on the $-\text{N}$ atom of 1d. Whereas the groups like $-\text{Me}$, $-\text{Bn}$, $-\text{Tos}$ shift could be a tedious process and difficult to form isocyanate intermediate.⁹ In our current strategy, 1d undergoes ring expansion to form 6-membered quinoline 1e. Here, the compound 1e will undergo rearrangement *via* H-shift to form the required product 3aa (Fig. 2).

Next, our curiosity further extended to show the utility of the synthetic derivatives obtained from the current protocol, the synthesized compounds were demonstrated for the synthesis of natural products such as marinoquinolines. Reaction of 4aa with POCl_3 under reflux conditions gave the corresponding product 5 in 85% yield.¹² Next, the compound 5 was subjected to decarboxylation in presence of con. HCl (12 h).¹³ The compound 6 further treated with *p*-tolylboronic acid under Suzuki condition furnished the desired compound 7 which are having skeletal



Scheme 4 Gram scale synthesis of compound 3aa.



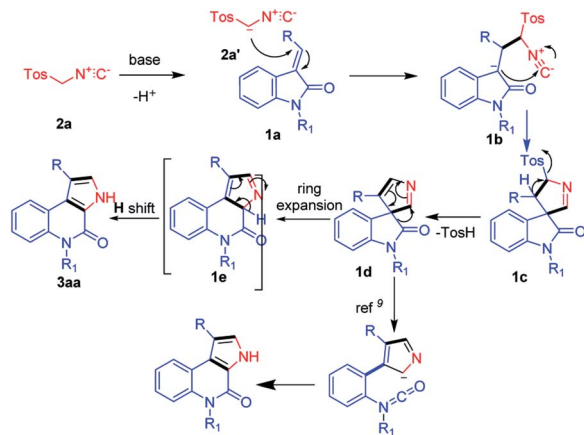
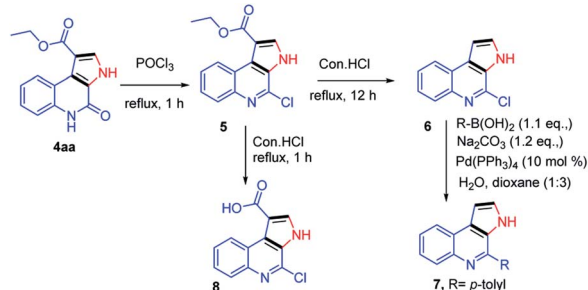


Fig. 2 Plausible reaction mechanism for the synthesis of pyrrolo[2,3-c]quinolines.



Scheme 5 Synthetic route for marinoquinolines and its derivatives.

similarities of marinoquinolines in 80% yield.¹⁴ When the compound 5 was refluxed in con. HCl for 1 h, gave the required acid derivative 8, which is a very useful precursor to participate in amide coupling with a variety of amines to synthesize novel amide derivatives of marinoquinolines (Scheme 5).

Conclusions

We have developed an efficient, metal-free and greener approach for the synthesis of N-substituted and N-unsubstituted 4-oxo-4,5-dihydro-3H-pyrrolo[2,3-c]quinolines. A range of unexplored N-substituted and unsubstituted 4-oxo-4,5-dihydro-3H-pyrrolo[2,3-c]quinolines were synthesized via ring expansion and H-shift as the key steps in the mechanism. Further, the present methodology was also compatible with variety of substituents on both phenyl and olefinic positions on the oxindole, demonstrated the gram scale as well as marine natural product synthesis. Having prominent highlights, for example, readily available substrates, mild reaction conditions, helpful synthetic protocols, and the depicted one-pot reaction is relied upon to discover wide applications in the development of potential pharmacological candidates.

Conflicts of interest

There are no conflicts to declare.

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