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Highly selective organocatalytic three-component reaction of 2-chloroquinoline-3-carbaldehydes, 6-aminouracils, and cyclic methylene active compounds

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ABSTRACT

An efficient synthesis of novel functionalized 4*H*-pyrano[2,3-*b*]quinoline and 1,4-dihydrobenzo[*b*][1,8]-naphthyridine derivatives via the one-pot reaction of 2-chloroquinoline-3-carbaldehydes, 6-aminouracils and dimedone or 3-methyl-1*H*-pyrazol-5(4*H*)-one was developed. The simple procedure, mild organocatalytic reaction conditions, good to high yields, and no column chromatography are important features of this protocol.

Heterocyclic nitrogen compounds have gained special attention because of their wide application in pharmaceuticals, and the design of novel heterocyclic motifs.[1] 1,8-Naphthyridines and pyrano[2,3-*b*]quinolines are of interest because they are important subunits of many natural and synthetic compounds. 1,8-Naphthyridine derivatives have shown a broad range of interesting biological activities, such as analgesic,[2] antiaggressive,[3] anti-inflammatory,[3] anticancer,[4] antibacterial,[5] antitumor,[6] antihypertensive,[7] antiallergitic,[8] and antimalarial properties.[9] Moreover, 1,8-naphthyridine derivatives are well known as fluorescent dyes[10] and sensors[11] due to their optical properties.

Although many endeavors have been devoted to the synthesis of 1,8-naphthyridine building blocks, a literature review reveals considerable scope for the refinement of existing procedures.[12] Thus, there is still a need to develop new and efficient methods for the construction of biologically active, structurally complex molecules from readily available starting materials. One of the most promising approaches to this type of efficient synthesis relies on multicomponent reactions (MCRs) which can be used to generate a library of compounds with a minimum number of steps and high atom economy.[13] Removal of the need for isolation and purification of reaction intermediates make MCRs well suited for the construction of complex organic molecules (with diverse hetero atoms)[14] or natural product scaffolds under asymmetric,[15] homogeneous,[16] and heterogeneous[17] catalysis conditions.

The reaction of 2-chloroquinoline-3-carbaldehydes with methylene active compounds has been widely investigated.[18] In some of these reactions the oxygen atom of the methylene active compound undergoes intramolecular cyclization, leading to the formation of pyranoquinolines.[19] Very recently, Fu and co-workers reported that the three component reaction of 2-chloroquinoline-3-carbaldehyde, 1,3-dicarbonyl compounds, and enaminones led solely to the formation of benzo[*b*][1,8]naphthyridine derivatives **5** (Fig. 1, Path A).[20] Most probably **5** was formed by activation of the nitrogen atom in intermediate **4** toward intramolecular nucleophilic aromatic substitution (Fig. 1, Path A). It seems that selective activation of the oxygen atom over nitrogen in a similar intermediate would lead to the formation of a new type of polycyclic azaheterocycles **6** (Fig. 1, Path B). With this proposal in mind and in continuation of our program aimed at the construction of new heterocyclic compounds via MCRs,[21] herein, we report a three component reaction of 2-chloroquinoline-3-carbaldehyde, 6-aminouracils and dimedone or 3-methyl-1*H*-pyrazol-5(4*H*)-one.

Initially, 2-chloroquinoline-3-carbaldehyde **1a**, dimedone **2a**, and 6-aminouracil **3a** were selected as model substrates.[22] As summarized in Table 1, several solvents including DMF, EtOH, CH_3CN, and CH_2Cl_2 at different temperatures in the presence of various bases including L-proline, Cs_2CO_3, and K_2CO_3 were examined in order to determine optimal reaction conditions. This study showed

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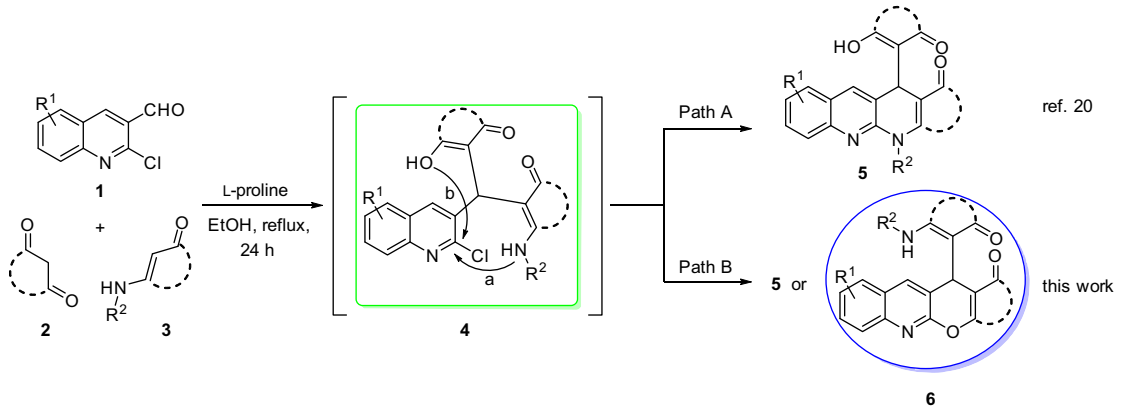


Figure 1. Selective activation of *O* or *N* atoms toward intramolecular cyclization.

Table 1
Examination of different conditions for the reaction of 2-chloroquinoline-3-carbaldehyde **1a**, dimedone **2a**, and 6-aminouracil **3a**[a]

Entry	Catalyst	Solvent	Yield **6a** (%)
1	K_2CO_3	DMF	40
2	K_2CO_3	CH_3CN	50
3	Cs_2CO_3	DMF	45
4	L-proline	EtOH	87
5	K_2CO_3	CH_2Cl_2	15

[a] Reagents and Conditions: 2-chloroquinoline-3-carbaldehyde **1a** (1.5 mmol), dimedone **2a** (1.5 mmol), 6-aminouracil **3a** (1 mmol), catalyst (0.1 mmol), solvent (5 mL), reflux, 24 h.

that the reaction leading to **6a** proceeded in high yield in ethanol at reflux in the presence of L-proline.

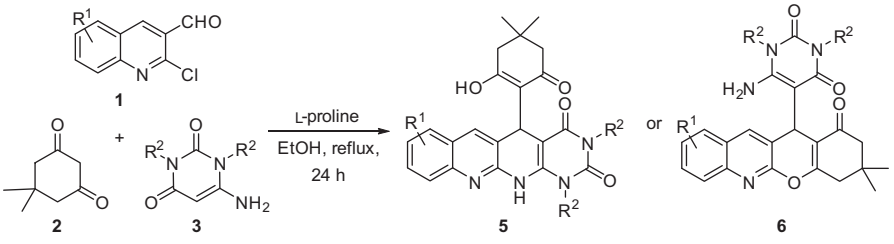
These are the same conditions employed by Fu and co-workers in their cyclization reactions.[20] With optimal conditions established, the scope of this reaction was explored by variation of the 2-chloroquinoline-3-carbaldehyde and 6-aminouracil components (Table 2).

As shown in Table 2, this protocol was efficient with dimedone as the methylene active compound, and the corresponding products were obtained in good to high yield. Interestingly, the 6-Me and 6-OMe substituted quinoline aldehydes gave rise to products proceeding via intramolecular nucleophilic attack by nitrogen, while the other aldehydes gave products resulting from attack by oxygen. The exact reason for this selectivity is at present unclear.

It was also found that 2-chloroquinoline-3-carbaldehydes bearing either electron-withdrawing or electron-donating groups on the aldehyde ring were tolerated under the reaction conditions. To the best of our knowledge, no analogous products have been reported in the literature. Although the construction of new heterocyclic compounds using *ortho*-haloarylaldehyde enamines and active methylene compounds has been reported,[19,23] in the present method when R^1 = H, 8-methyl, 6-chloro, or 6-bromo, uracil does not participate in the construction of the new heterocycle and a new ring is produced by the active methylene compounds and the aldehyde (Table 2, Entries 1–4).

The newly synthesized products were characterized by melting point, FT-IR, ^{1}H NMR, and ^{13}C NMR spectroscopy, as well as elemental analysis. Although compounds **5** and **6** are isomers they could be readily distinguished by ^{1}H NMR spectroscopy. A distinguishing peak for compounds **6** is a broad singlet at ~7 ppm attributed to the NH_2 group, for example: **6a** (6.51 ppm, 1.45 H, integral

Table 2
Selective synthesis of compounds **5** and **6**[a,22]



Entry	R^1	R^2	Yield **5** (%)	Yield **6** (%)
1	H	H	–	**6a** (87)
2	8-Me	H	–	**6b** (91)
3	6-Cl	Me	–	**6c** (88)
4	6-Br	Me	–	**6d** (93)
5	6-Me	H	**5a** (87)	–
6	6-Me	Me	**5b** (85)	–
7	6-OMe	Me	**5c** (79)	–

[a] Reagents and Conditions: aldehyde **1** (1.5 mmol), dimedone **2** (1.5 mmol), 6-aminouracil **3** (1 mmol), L-proline (0.1 mmol), EtOH (5 mL), reflux, 24 h.