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The catalyst-free syntheses of pyrazolo[3,4-*b*]quinolin-5-one and pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidin-5,7-dione derivatives by one-pot, three-component reactions

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ABSTRACT

Herein we report the syntheses of pyrazolo[3,4-*b*]quinolin-5-one and pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidin-5,7-dione derivatives by cyclocondensation of 1,3-diketones, 3-methyl-1-phenyl-1*H*-pyrazole-5-amine and arylglyoxals, under catalyst-free conditions in H_2O/EtOH at reflux in 65–98% and 73–96% yields respectively. This protocol provides mild reaction conditions, good to high yields, non-catalytic, simple procedures and easy isolation of products to structurally diverse tricyclic pyrazolo[3,4-*b*]quinolin-5-one and pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidin-5,7-dione derivatives, which may have biological and pharmacological activities.

1. Introduction

The green synthesis of nitrogen-containing heterocyclic compounds using environmentally friendly chemical procedures has attracted much attention due to their various biological and pharmaceutical activities. One-pot, multicomponent reactions (MCRs), which combine three or more substrates concurrently or in sequential addition, lead to domino processes,[1] without isolating intermediate species or changing the solvent. MCRs offer benefits such as simple and convenient operation, facile automation and minimized waste generation due to the decrease in the number of work-up, extraction and purification stages. They play an important role in the synthesis of heterocyclic compounds through environmentally and economically useful one-pot procedures.

Water is the ideal green solvent and the best alternative to organic solvents, because of being non-flammable, non-hazardous, non-toxic, uniquely redox-stable, inexpensive, readily available and environmentally benign.[2] Pyrazoles are important because of their wide range of pharmacological effects[3] and biological activities,[4] such as antidepressant,[5] antibacterial,[6] antihyperglycemic,[7] antimalarial,[8] antiinflammatory,[9] antimicrobial,[10] antitumor,[11] anticancer,[12] antiviral,[13] and analgesic[14] properties. They also have a wide range of applications in the agrochemicals industry,[15,16] but are relatively scarce in nature.

Pyrazolo[3,4-*b*]quinolones have attracted more attention than other derivatives due to their bioactivities,[17] such as antimycobacterial,[18] antimicrobial,[19] and antiviral.[20] Examples of their use are as inhibitors of herpex simplex virus,[21] oncogenic ras-inhibitors,[22] cyclooxygenase inhibitors,[23] replication,[24] activators of caspases and inducers of apoptosis.[25] Among the several methods available for the synthesis of pyrazolo[3,4-*b*]quinolones,[26–28] the one-pot, three-component reaction of 1,3-diketons, 5-aminopyrazoles and aromatic aldehydes has received much attention.[29]

Pyrazolo[3,4-*b*]pyridines are present in numerous natural products and biologically active molecules, such as the anxiolytic drugs cartazolate, etazolate and tracazolate.[30]

Several methods for the synthesis of pyrazoloquinoline derivatives have been reported by diverse procedures,[31–34] but some of the reported methods are limited by the use of expensive reagents, time-consuming multi-step procedures, use of toxic solvents or catalysts. In continuation of our interests in the synthesis

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of new heterocyclic compounds by one-pot, multi-component reactions,[35–40] herein we report a convenient and rapid method for the synthesis of novel pyrazolo[3,4-*b*]quinoline and pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine derivatives via a one-pot, three-component reaction, involving intramolecular cyclocondensation of arylglyoxals, 3-methyl-1-phenyl-1*H*-pyrazol-5-amine, 1,3-dicarbonyl compounds such as cyclohexane-1,3-dione, dimedone (5,5-dimethylcyclohexane-1,3-dione) and 1,3-dimethylbarbituric acid using H_2O/EtOH as solvent, without any catalyst.

2. Results and discussion

In attempting to develop a simple, one-pot and short reaction route for the synthesis of various heterocyclic compounds, we reported earlier the syntheses of arylquinoxalines, cinnolines, 1*H*-indol-4(5*H*)-ones, acridinediones and diindenopyridine-10,12-diones starting from arylglyoxals.[35–40]

We found that reaction of arylglyoxals **1** with 1,3-diketones [(cyclohexane-1,3-dione (**2a**) and dimedone (**2b**)] and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **3**, in H_2O/EtOH at 50 °C afforded pyrazolo[3,4-*b*]quinolone derivatives **4a-k** by a one-pot, three-component reaction in good to excellent yields. When the reaction was carried out under reflux conditions in the presence of air, the corresponding pyrazolo[3,4-*b*]quinolones **5a-k** were obtained in good to excellent yields (Scheme 1).

Similarly, the reaction of arylglyoxals **1** with 1,3-dimethylbarbituric acid (**2c**) and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**3**) in H_2O/EtOH under reflux conditions gave the desired pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-diones **6a-e** in 73–96% yields (Scheme 2).

The reaction conditions were then applied to a range of different arylglyoxals. The results with various arylglyoxals and product yields and melting points are summarized in Tables 1–3 (Entry 14). Arylglyoxals with both electron-rich and electron-deficient substituents were well tolerated. Spectral data, TLC and melting points were used to establish that only one product was formed in all cases.

A plausible mechanism for this reaction is shown in Scheme 3. It involves the initial *Knoevenagel* condensation of arylglyoxals **1** and *β*-diketones **2a,b** or 1,3-dimethylbarbituric acid (**2c**) to form the corresponding intermediates, followed by Michael addition of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**3**) to these intermediates to form the corresponding pyrazolo[3,4-*b*]quinoline and pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine derivatives through intermolecular cyclization followed by subsequent tautomerization. The initial products were dehydrogenated to give the desired products **5a-k** and **6a-e** under reflux conditions or treatment with ethanolic KOH in the presence of air.

The substituted 4-aroyl-3-methyl-1-phenyl-6,7,8,9-tetrahydro-1*H*-pyrazolo[3,4-*b*]-5(4*H*)-ones **4a-k** were characterized using ^{1}H NMR, ^{13}C NMR and FT-TR spectral data and microanalysis. The characteristic singlet at δ = 5.61–5.82 ppm was ascribed to the CH of the dihydropyridine ring, which was present in all products, and a singlet at δ = 1.67–1.86 ppm which was due to the methyl group attached to the pyrazole ring. In the ^{13}C NMR spectra of products **4a-k**, signals located around δ = 200.4–202.9 and δ = 194.5–195.7 ppm were attributed to the quinolone and aroyl carbonyl groups respectively. The characteristic absorption bands at 1662–1695 and 1602-1624 cm^{-1} could be assigned to the vibrations of quinolone and aroyl carbonyl groups respectively.

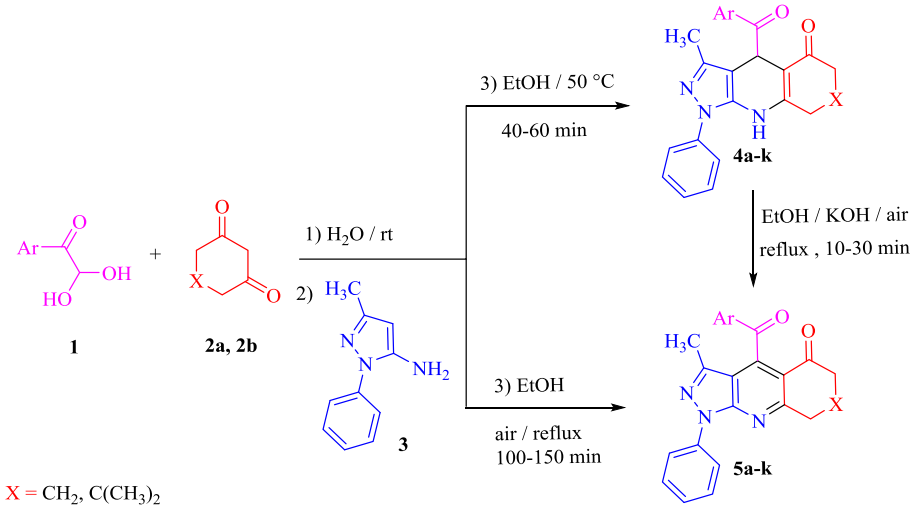
The characteristic singlet at around δ = 2.26–2.29 ppm was attributed to the methyl group attached to the pyrazole moiety and were present in all new products. In the ^{13}C NMR spectra of the products **5a-k**, signals located around δ = 196.6–199.7 and 192.3–195.1 ppm were due to the quinolone and aroyl carbonyl groups respectively. The absorption bands at around 1662-1679 cm^{-1} could be assigned to the two different carbonyl groups.

In the ^{1}H NMR spectra of the products **6a-e**, the singlets at around δ = 3.86–3.87, 3.39–3.42 and 2.26–2.27 ppm are attributed to the 3-methyl, 1-methyl and the methyl of pyrazole ring respectively and were present in all new products. In the ^{13}C NMR spectra of products **6a-e**, signals located around δ = 180.6–192.1 and 159.6–173.5 ppm were due to aroyl and C-4 carbonyl groups respectively. In the FT-IR spectra, the characteristic absorption bands at 1665-1707 cm^{-1} could be assigned to the vibrations of three different carbonyl groups.

The structures of compound **4a** and **4i** were confirmed by single-crystal X-ray analysis (Fig. 1).

The X-ray single crystal diffraction analysis showed that the carbonyl group of arylglyoxal and the carbonyl group of 1,3-diketones and also the aryl ring of the arylglyoxal and pyrazole moieties are not collimated together.

In the X-ray crystallographic data of compound **4a** the bond lengths of N1–N2, C9–C10, C18–O2 were 1.381, 1.362, 1.222 Å



Scheme 1. Synthesis of pyrazolo[3,4-*b*]quinolones **5a-k**.