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Domino reactions between 6-ethyl-5,6-dihydro-4,5-dioxo-4*H*-pyrano[3,2-*c*]quinoline-3-carbonitrile and carbon nucleophilic reagents: Synthesis of novel heteroannulated pyridopyranoquinolines

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ABSTRACT

A variety of novel heteroannulated pyrano[3,2-*c*]quinolines **2**–**12** was efficiently synthesized *via* a domino '*Michael*/retro-*Michael*/nitrile addition/heterocyclization' reactions between 6-ethyl-5,6-dihydro-4,5-dioxo-4*H*-pyrano[3,2-*c*]quinoline-3-carbonitrile (**1**) and a diversity of carbon nucleophilic reagents. Pyrido[3′,2′:5,6]pyrano[3,2-*c*]quinolines **2**–**6** were synthesized from ring opening ring closure reactions of carbonitrile **1** with some methylene active nitrile namely malononitrile, cyanoacetamide, *N*-phenylcyanoacetamide, (phenylthio)acetonitrile and ethyl cyanoacetate, respectively. Reactions of carbonitrile **1** with dimer malononitrile and cyanoacetohydrazide showed different behavior producing the novel heteroannulated pyranoquinoline derivatives **7** and **8**, respectively. Treatment of carbonitrile **1** with some methylene active ketones namely acetylacetone, acetoacetanilide, ethyl acetoacetate and ethyl benzoylacetate afforded pyrido[3′,2′:5,6]pyrano[3,2-*c*]quinolines **9**–**12**, respectively. Structures of the synthesized products were deduced on the basis of their analytical and spectral data.

1. Introduction

Quinolinone fused with pyrane ring is of considerable biological importance [1,2] and constitutes the basic skeleton of a number of alkaloids [3]. Pyrano[3,2-*c*]quinolines has a diversity of biological activities such as antibacterial [4,5], antifungal [6], antimicrobial [7], antimalarial [8], antidiabetic [9] anticoagulant [10], antitumor [11], and anti-HIV [12,13]. Pyrano[3,2-*c*]quinolinones were examined for their optical, electrical and photoelectrical properties [14,15]. Recently, a variety of methods were utilized to synthesis pyrano[3,2-*c*]quinoline derivatives [16–20]. Quantum chemical studies, DFT calculations and electronic absorption spectra of some pyrano[3,2-*c*]quinolinones were studied [21,22]. A number of research articles were published on the chemical reactivity of γ–pyrone link cyano group at its 3-position leading to a diversity of heterocyclic systems [23–27]. Previously [28], 6-ethyl-5,6-dihydro-4,5-dioxo-4*H*-pyrano[3,2-*c*]quinoline-3-carbonitrile was synthesized from the reaction of the corresponding aldehyde with hydroxylamine hydrochloride in pyridine. Our plan is to study the interesting behavior of this carbonitrile towards different nucleophilic reagents and herein we highlight its chemical behavior towards some active methylene nitriles (−CH_2CN) and some active methylene ketones (−CH_2CO−) hoping to synthesize a novel category of heteroannulated pyrido[3′,2′:5,6]pyrano[3,2-*c*]quinolines.

2. Results and discussion

The present work aimed to study the chemical transformations of 6-ethyl-5,6-dihydro-4,5-dioxo-4*H*-pyrano[3,2-*c*]quinoline-3-carbonitrile (**1**) with a variety of active methylene compounds bearing −CH_2CN and −CH_2CO− moieties. As depicted in Scheme 1, reaction of pyrano[3,2-*c*]quinoline-3-carbonitrile **1** with malononitrile, in absolute ethanol containing 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a basic catalyst, provided 2-amino-7-ethyl-5,6-dioxo-6,7-dihydro-5*H*-pyrido[3′,2′:5,6]pyrano [3,2-*c*]quinoline-3-carbonitrile (**2**) as yellow crystals. Compound **2** may be synthesized *via* a domino process including *Michael* addition of malononitrile at C-2 position of the γ-pyrone moiety (1,4–addition) leading to intermediate **A** which underwent retro-*Michael* reaction with concomitant γ-pyrone ring opening generating open-chained intermediate **B**. Free rotation around single

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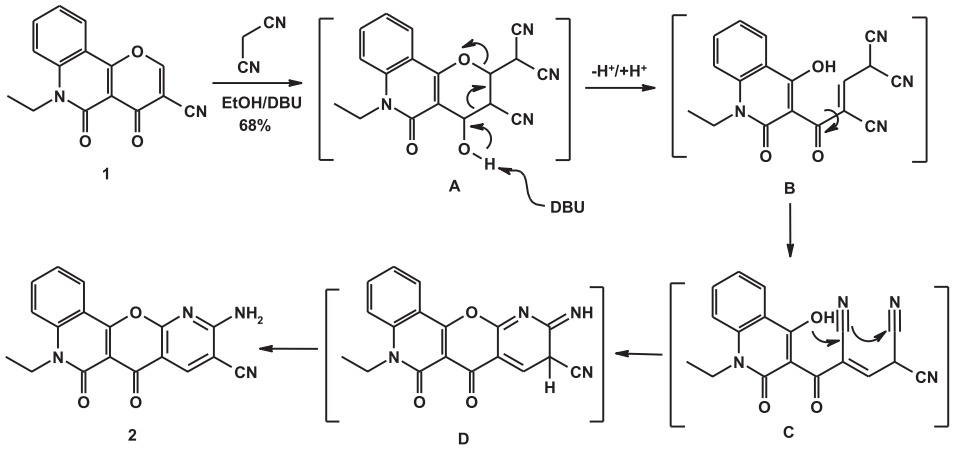


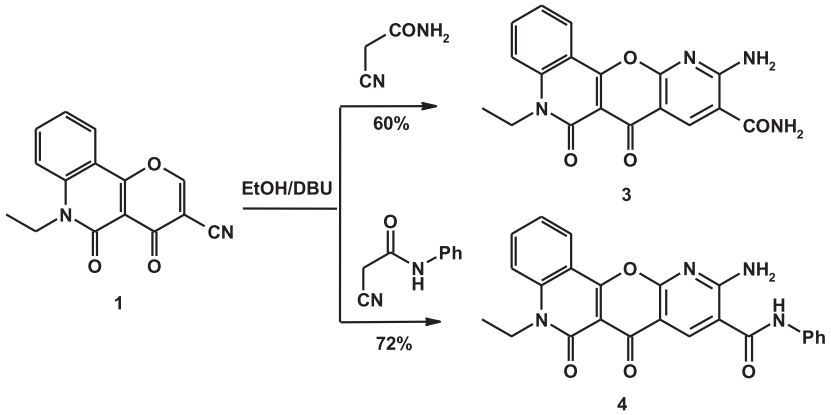
Scheme 1. Formation of pyrido[3′,2′:5,6]pyrano[3,2-*c*]quinoline-3-carbonitrile **2**.

bond gave intermediate **C** which underwent two consecutive cycloaddition reactions giving intermediate **D** that upon proton transfer afforded the final product **2**. Elemental analysis and spectral data of the synthesized compound agree well with the assigned structure **2**. Conversion of carbonitrile **1** into pyridopyranoquinoline **2** can be regarded as a domino '*Michael*/retro-*Michael*/nitrile additions' reactions. The IR spectrum of compound **2** showed characteristic absorption bands at 3358, 3240 (NH_2), 2221 (C≡N), 1658 ($C{=}O_{\gamma\text{-pyrone}}$), 1632 ($C{=}O_{quinolinone}$) and 1609 cm^{-1} (C=N). The ^1H NMR spectrum of compound **2** displayed characteristic singlet at chemical shift (δ 8.90 ppm) distinctive for H-$4_{pyridine}$, in addition to D_2O-exchangeable signal at δ 8.45 ppm assigned to NH_2 protons. The ^{13}C NMR spectrum of compound **2** displayed characteristic signals at δ 95.2 (C-3), 116.5 (C≡N), 140.5 (C-4), 154.2 (C-2), 161.5 (C-6), 175.1 (C-5). The mass spectrum of compound **2** showed the molecular ion peak, as the base peak, at *m*/*z* 332 and confirms the postulated structure.

In the same manner, pyrido[3′,2′:5,6]pyrano[3,2-*c*]quinolines **3** and **4** were efficiently synthesized from treatment of carbonitrile **1** with cyanoacetamide and *N*-phenylcyanoacetamide, respectively (Scheme 2). The IR spectra of compounds **3** and **4** presented characteristic absorption bands at 1662/1669 ($C{=}O_{amide}$), 1651/1657 ($C{=}O_{\gamma\text{-pyrone}}$) and 1635/1633 cm^{-1} ($C{=}O_{quinolinone}$), respectively. The ^1H NMR spectra showed specific singlet corresponds to H-$4_{pyridine}$ at δ 8.75 and 8.69 ppm for compounds **3** and **4**, respectively. ^{13}C NMR spectrum of compound **3** revealed significant signals at δ 95.6 (C-3), 141.3 (C-4), 154.4 (C-2), 161.9 (C-6), 175.4 (C-5) and 178.6 ($C{=}O_{amide}$). Furthermore, the mass spectra for compounds **3** and **4** revealed their molecular ion peaks at *m*/*z* 350 and 426 that agree well with their formula weights 350.33 and 426.42, respectively.

Moreover, ring opening ring closure (RORC) reactions of carbonitrile **1** with (phenylthio)acetonitrile and ethyl cyanoacetate yielded 2-amino-3-substituted-pyrido[3′,2′:5,6]pyrano[3,2-*c*]quinolines **5** and **6**, respectively (Scheme 3). The IR spectrum of compound **5** exhibited characteristic absorption bands at 3332, 3250 (NH_2), 1649 ($C{=}O_{\gamma\text{-pyrone}}$) and 1633 cm^{-1} ($C{=}O_{quinolinone}$). While IR spectrum of compound **6** detected absorption bands at 3331, 3210 (NH_2), 1697 ($C{=}O_{ester}$), 1661 ($C{=}O_{\gamma\text{-pyrone}}$) and 1641 cm^{-1} ($C{=}O_{quinolinone}$).

On the other hand, treatment of pyrano[3,2-*c*]quinoline-3-carbonitrile **1** with malononitrile dimer (2-aminoprop-1-ene-1,1,3-tricarbonitrile) as 1,3-C,*N* binucleophile showed different behavior than the above active methylene nitrile producing the novel quinolino[3′,4′:5,6]pyrano[4,3-*b*]pyridine derivative **7** (Scheme 4). Formation of compound **7** occurs through a domino process including deprotonation of malononitrile dimer and nucleophilic attack at C-2 position with γ-pyrone ring opening, producing intermediate **E**, followed by free rotation around the single bond leading to intermediate **F**. Cycloaddition and cyclodehydration reactions of the later intermediate yielded intermediate **G** which hydrolyzed to produce the final product **7** as depicted in Scheme 4. The IR spectrum of compound **7** showed characteristic absorption bands at 3422 (NH), 2220, 2191, 2170 (3C≡N), 1714



Scheme 2. Formation of pyrido[3′,2′:5,6]pyrano[3,2-*c*]quinoline-3-carboxamides **3** and **4**.