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Article

Studies on the Chemical Behavior of 3-(Nitroacetyl)-1-ethyl-4-hydroxyquinolin-2(1*H*)-one towards some Electrophilic and Nucleophilic Reagents

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Uma variedade de sistemas heterocíclicos contendo o sistema 1-etilquinolin-2(1*H*)-ona, foi preparada a partir da reação de 3-(nitroacetil)-1-etil-4-hidroxiquinolin-2(1*H*)-ona com alguns reagentes eletrofílicos e nucleofílicos. Além da sua ciclização para 5-etil-2-(hidroxiimino)-2,3,4,5-tetrahydrofuro[3,2-*c*]quinolina-3,4-diona, o composto 3-(nitroacetil)-1-etil-4-hidroxiquinolina-2(1*H*)-ona foi bromado, clorado, formilado, acetilado, e condensado com cromona-3-carbonitrila e 2-amino-3-formilcromona. Alguns novos pirazolo[4,3-*c*]quinolina,pirimido [5,4-*c*]quinolina e derivados de quinolino[4,3-*b*][1,5]benzodiazepina foram também sintetizados.

A variety of heterocyclic systems linked to 1-ethylquinolin-2(1*H*)-one was prepared from reaction of 3-(nitroacetyl)-1-ethyl-4-hydroxyquinolin-2(1*H*)-one with some electrophilic and nucleophilic reagents. Besides its cyclization to 5-ethyl-2-(hydroxyimino)-2,3,4,5-tetrahydrofuro[3,2-*c*]quinoline-3,4-dione, the 3-(nitroacetyl)-1-ethyl-4-hydroxyquinolin-2(1*H*)-one has been brominated, chlorinated, formylated, acetylated, and condensed with chromone-3-carbonitrile and 2-amino-3-formylchromone. Some new pyrazolo[4,3-*c*]quinoline, pyrimido[5,4-*c*] quinoline and quinolino[4,3-*b*][1,5]benzodiazepine derivatives were also synthesized.

Keywords: β-ketoacid, 3-nitroacetylquinolinone, pyrazolo[4,3-*c*]quinolinones, pyrimido[5,4-*c*] quinolinones, cyclocondensation

Introduction

4-Hydroxyquinolin-2(1*H*)-ones and their derivatives represent a class of heterocyclic compounds that have been associated with several biological activities.[1-6] The biological importance of quinolinones stimulated an intensive research work for the synthesis of many members of this class of compounds.[7-10] In continuation of our previous reports on the synthesis of novel 4-hydroxyquinolin-2(1*H*)-ones starting from 3-(1-ethy1-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-3-oxopropanoic acid (**1**),[11] the present work aims to synthesize the 3-(nitroacetyl)-1-ethyl-4-hydroxyquinolin-2(1*H*)-one (**4**) and to study its reactivity towards a variety of chemical reagents.

Results and Discussion

In continuation to our work on the novel β-ketoacid **1**,[11] we found that nitration of β-ketoacid **3** using a mixture of concentrated nitric acid and sulfuric acid gave the cyclized product, 6-ethyl-4-hydroxy-3-nitropyrano[3,2-*c*]quinoline-2,5(6*H*)-dione (**3**) *via* the non isolable intermediate **2** (Scheme 1).[12] The reaction proceeds *via* nitration at the active methylene carbon with concomitant cyclization under the strongly acidic reaction conditions. The mass spectrum of compound **3** reveal the molecular ion peak at *m/z* 302 which is coincident with the formula weight (302.25) and supports the identity of the structure.

Basic hydrolysis of 3-nitropyrano[3,2-*c*]quinoline derivative **3** using 2 mol L^{-1} aqueous NaOH solution yielded the 3-(nitroacetyl)-1-ethyl-4-hydroxyquinolin-2(1*H*)-one (**4**) (Scheme 1).[12] The IR spectrum of compound **4** did not revealed the α-pyrone (O–C=O) absorption band which observed at 1765 cm^{-1} in the IR spectrum of compound **3**. The ^{1}H NMR spectrum of compound **4** showed a characteristic singlet at δ 6.14 ppm due to the active methylene protons, in addition to a broad exchangeable signal at δ 14.71 ppm due to the hydroxyl proton. Formation of compound **4** takes place *via* the α-pyrone ring opening with concomitant decarboxylation.

Herein, we studied the effect of high boiling solvents on compound **4** as previously published by K.V. Rao[13] on

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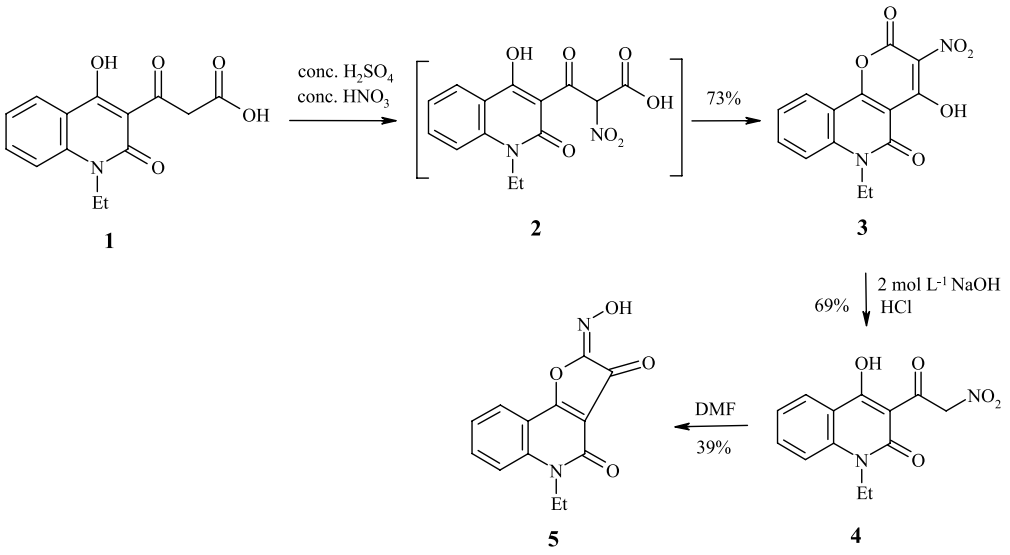


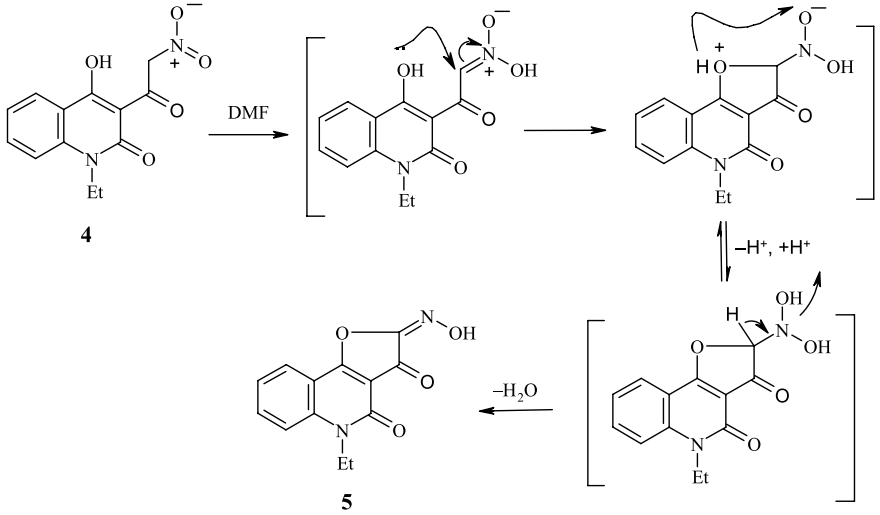
Scheme 1. Formation of 3-nitroacetylquinolinone **4** and furoquinolinone **5**.

2'-nitro-2-hydroxyacetophenone. Thus, refluxing 3-nitroacetylquinolinone **4** in DMF gave 5-ethyl-2-(hydroxyimino)furo[3,2-*c*]quinoline-3,4(2*H*,5*H*)-dione (**5**) (Scheme 1). The ^{1}H NMR spectrum of compound **5** reveal the disappearance of the active methylene protons which appeared at δ 6.14 ppm in the ^{1}H NMR spectrum of compound **4**. The proposed mechanism of dehydration of 3-nitroacetylquinolinone **4** to produce furo[3,2-*c*] quinoline **5** is depicted in Scheme 2.

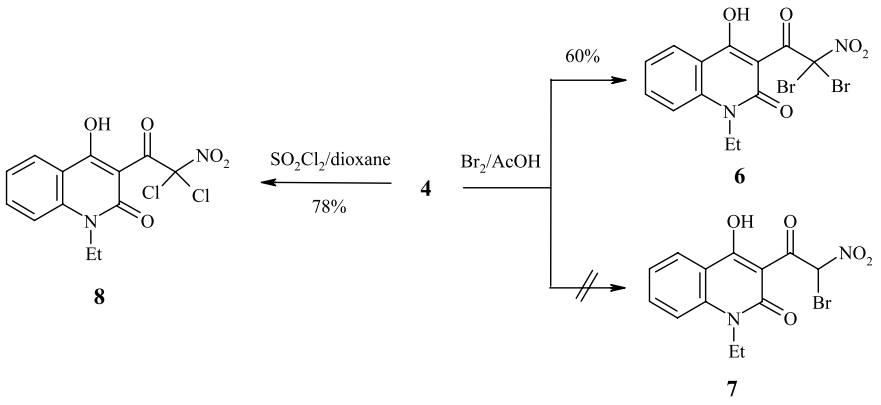
3-Nitroacetylquinolinone **4** was reacted with some electrophilic and nucleophilic reagents to obtain some new quinolin-2(1*H*)-one derivatives. Thus, bromination of compound **4** using bromine in acetic acid gave the dibromo derivative, 3-[dibromo(nitro)acetyl]-1-ethyl-4-hydroxyquinolin-2(1*H*)-one (**6**). Herein, the monobromo quinolinone derivative **7** was excluded on the basis of the ^{1}H NMR spectrum which confirms the disappearance of the two active methylene protons (Scheme 3).

Also, chlorination of compound **4** using sulfuryl chloride in dioxane afforded the 3-[dichloro(nitro)acetyl]-1-ethyl-4-hydroxyquinolin-2(1*H*)-one (**8**) (Scheme 3). The ^{1}H NMR spectrum of compound **8** showed signals attributed to the ethyl and aromatic protons.

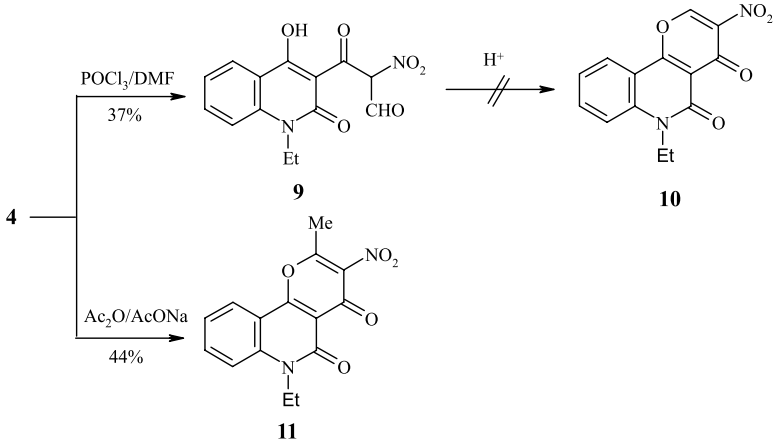
We also aimed to synthesize some new γ-pyrone rings fused with the quinolin-2(1*H*)-one moiety to produce the pyrano[3,2-*c*]quinoline-4,5(6*H*)-diones which are rarely known in literature.[14-16] Therefore, formylation of compound **4** under Vilsmeier-Haack conditions (DMF/$POCl_3$) resulted in introducing the formyl group at the active methylene carbon giving 3-(1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-2-nitro-3-oxopropanal (**9**) (Scheme 4). The IR spectrum of compound **9** showed a



Scheme 2. The suggested mechanism for dehydration of compound **4**.



Scheme 3. Bromination and chlorination of 3-nitroacetylquinolinone **4**.



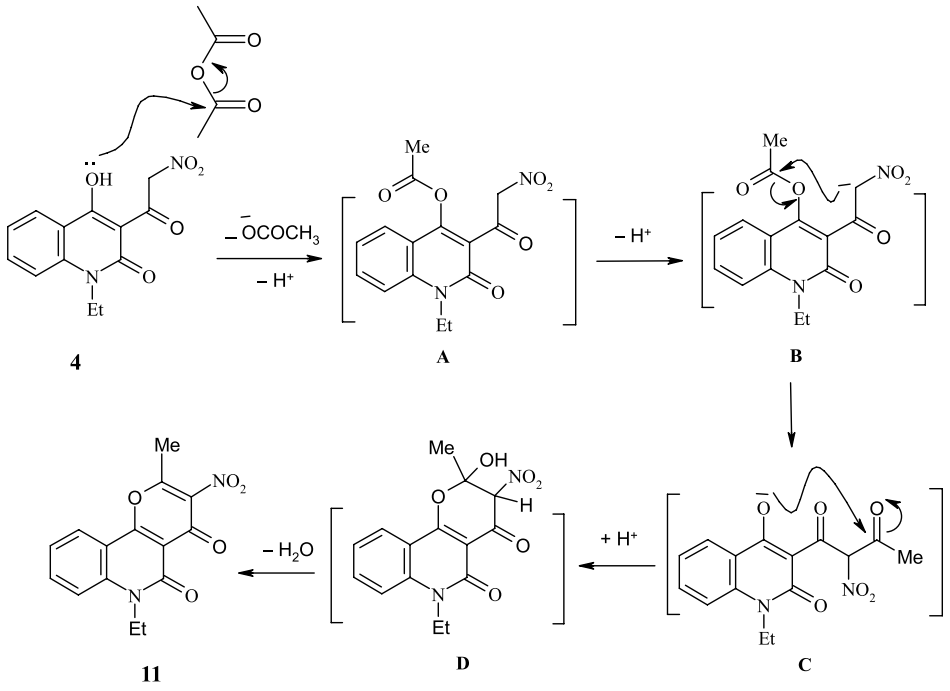
Scheme 4. Formylation and acetylation of 3-nitroacetylquinolinone **4.**

characteristic absorption band at 1735 cm^{-1} which might be attributed to the C=O of the aldehydic function. The ^{1}H NMR spectrum showed two characteristic singlet signals at δ 6.90 and 10.29 ppm due the $CHNO_2$ and CHO protons, respectively. Further, the mass spectrum of compound **9** revealed the molecular ion peak at *m/z* 304 which resembles the formula weight (304.22). Trials to cyclise compound **9** to form compound **10** under different acidic conditions (EtOH/HCl, gl. AcOH, or conc. H_2SO_4) failed and compound **9** was recovered.

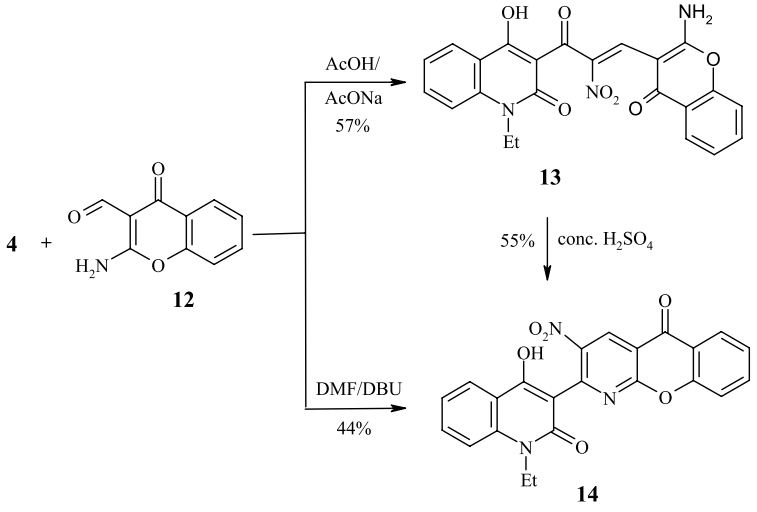
Also, acetylation of 3-nitroacetylquinolinone **4**, using acetic anhydride in the presence of freshly fused sodium acetate, led to the formation of 6-ethyl-2-methyl-3-nitropyrano[3,2-*c*]quinoline-4,5(6*H*)-dione (**11**) (Scheme 5).[17,18] The proposed mechanism for the formation of compound **11** is depicted in that Scheme.

The condensation reaction of 3-nitroacetylquinolinone **4** with 2-amino-3-formylchromone (**12**) was studied under various reaction conditions.[19] Thus, condensation of **4** with 2-amino-3-formylchromone (**12**), in glacial acetic acid containing freshly fused sodium acetate, afforded the Knoevenagel condensation product identified as 3-[3-(2-amino-4-oxo-4*H*-chromen-3-yl)-2-nitroprop-2-enoyl]-1-ethyl-4-hydroxyquinolin-2(1*H*)-one (**13**). When the latter reaction takes place in boiling DMF containing few drops of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a basic catalyst afforded the Friedländer condensation product identified as 2-(1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-y)-3-nitro-5*H*-benzopyrano[2,3-*b*] pyridin-5-one (**14**) (Scheme 6).[20,21] Compound **14** was obtained authentically by dehydration of compound **13** by stirring in concentrated sulfuric acid (the same mp, mmp and spectral data were observed) (Scheme 6). The ^{1}H NMR spectrum of compound **13** showed a characteristic singlet at δ 5.46 ppm attributed to the methine proton, while the cyclized product **14** showed a characteristic singlet at δ 8.69 ppm assigned to the H-4 of the pyridine ring. Also, the ^{1}H NMR spectrum of compound **14** reveal the disappearance of the NH_2 proton signals which appeared in the ^{1}H NMR spectrum of compound **13** at δ 9.57 and 10.04 ppm. Moreover, the IR spectrum of compound **14** did not revealed the absorption bands which appeared at 3298, 3152 cm^{-1} (assigned to NH_2 vibrational frequencies) in the IR spectrum of compound **13**.

According to our previous report,[21] chromone-3-carbonitrile (**15**) was found to be chemically equivalent



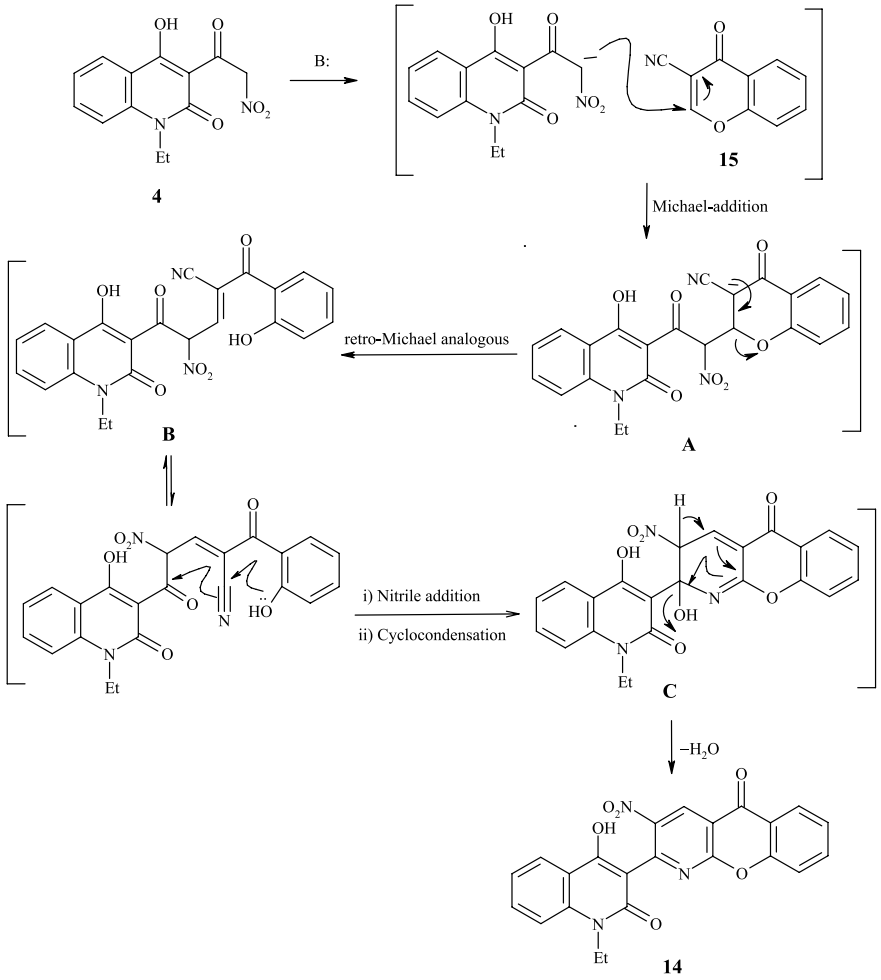
Scheme 5. The proposed mechanism for the formation of compound **11**.



Scheme 6. Condensation of **4** with 2-amino-3-formylchromone (**12**).

to 2-amino-3-formylchromone under certain nucleophilic conditions. Herein again, we found that treating 3-nitroacetylquinolinone **4** with chromone-3-carbonitrile (**15**)[19] in boiling DMF containing few drops of DBU afforded benzopyrano[2,3-*b*]pyridine derivative **14**. Formation of compound **14** from carbonitrile **15** was accomplished *via* a tandem cyclization reaction through Michael addition of the active methylene group in compound **4** to the γ-pyrone moiety of carbonitrile **15** producing intermediate **A** (non-isolable). The base-mediated retro-Michael analogous reaction of **A** gave the open chain intermediate **B** (non-isolable), the addition of hydroxyl group onto the nitrile function with concomitant cyclocondensation gave intermediate **C** (non-isolable) which underwent dehydration under the reaction conditions leading to the novel quinolinone bearing benzopyrano[3,2-*b*]pyridine **14**. The transformation of **4** into **14** can be regarded as a domino "Michael/retro-Michael/nitrile-addition/ cyclocondensation" as shown in Scheme 7.[22]

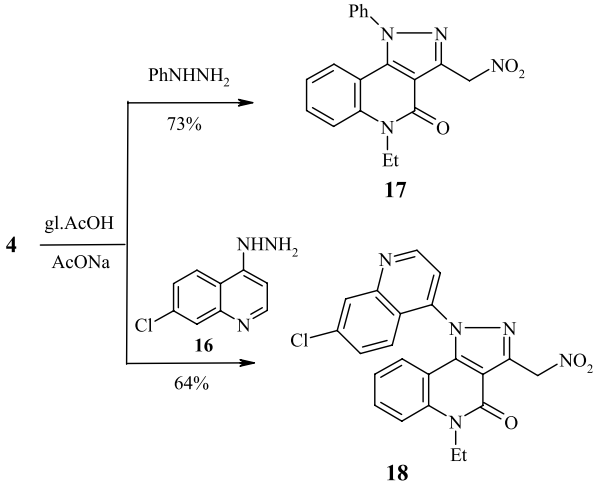
The combination of the pyrazole or the pyrimidine nucleus with the quinoline moiety, in one molecular framework, is reported in the literature to possess biological activity.[23-25] Herein, the nitroacetyl derivative **4** was allowed to react with some nucleophilic reagents.



Scheme 7. Reactions of compound **4** with chromone-3-carbonitrile **15**.

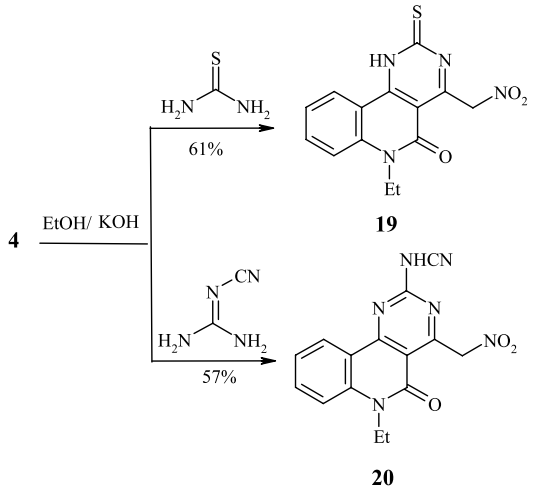
Therefore, condensation of **4** with phenyl hydrazine and 7-chloro-4-hydrazinoquinoline (**16**), in glacial acetic acid containing freshly fused sodium acetate, afforded 5-ethyl-3-(nitromethyl)-1-phenyl-1,5-dihydro-4*H*-pyrazolo[4,3-*c*] quinolin-4-one (**17**) and 1-(7-chloroquinolin-4-yl)-5-ethyl-3-(nitromethyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*] quinolin-4-one (**18**), respectively (Scheme 8).

Recently,[26] it was reported that pyrimido[5,4-*c*]quinolin-5(1*H*)-ones showed antioxidant and toxicological activities. For this reason and because of the well known biological activity of these ring systems, the nitroacetylquinoline **4** was employed as promising building block for the synthesis of this category of fused quinolinones. Thus, condensation of **4** with thiourea and cyanoguanidine in ethanolic potassium hydroxide solution led to 6-ethyl-4-(nitromethyl)-2-thioxo-2,6-dihydropyrimido[5,4-*c*] quinolin-5(1*H*)-one (**19**) and [6-ethyl-4-(nitromethyl)-5-oxo-5,6-dihydropyrimido[5,4-*c*]quinolin-2-yl]cyanamide (**20**), respectively (Scheme 9). The mass spectrum of compound **19** revealed the molecular ion peak at m/z 316 which resembles the formula weight (316.34).

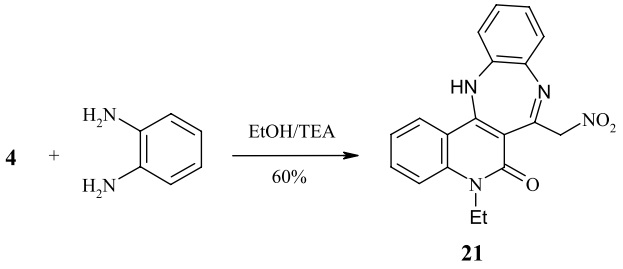


Scheme 8. Formation of pyrazolo[4,3-*c*]quinolinones **17** and **18**.

Finally, condensation of **4** with *o*-phenylenediamine in ethanol containing few drops of TEA gave 5,13-dihydro-5-ethyl-7-nitromethyl-6*H*-quinolino[4,3-*b*][1,5] benzodiazepin-6-one (**21**) (Scheme 10). The ^{1}H NMR spectrum of compound **21** showed a characteristic singlet



Scheme 9. Formation of pyrimido[5,4-*c*]quinolinones **19** and **20**.



Scheme 10. Formation of quinolino[4,3-*b*][1,5]benzodiazepine **21**.

at δ 4.93 ppm due the CH_2NO_2 protons, in addition to eight aromatic protons and ethyl protons.

Experimental

Melting points were determined on a digital Stuart SMP3 apparatus. Infrared spectra were measured on Perkin-Elmer 293 spectrophotometer (cm^{-1}), using KBr disks. ^1H NMR spectra were measured on a Mercury-300BB (300 MHz), and Jeol Eca-500 MHz using DMSO-d_6 as a solvent and TMS (δ) as the internal standard. Mass spectra were obtained using a GC-2010 Shimadzu Gas chromatography instrument mass spectrometer (70 eV). Elemental microanalyses were performed on a Perkin-Elmer CHN-2400 analyzer.

3-(1-Ethy1-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-3-oxopropanoic acid (**1**)

This compound was prepared according to our published method.[11]

6-Ethyl-4-hydroxy-3-nitropyrano[3,2-*c*]quinoline-2,5(6*H*)dione (**3**)

A mixture of β-ketoacid **1** (0.55 g, 2 mmol) in concentrated nitric acid (5 mL) and concentrated sulfuric acid (5 mL) was stirred at room temperature for 2h, then left overnight and poured onto ice/water. The solid obtained was filtered off, washed with water and crystallized from DMF/MeOH to give **3** as yellow crystals, yield 0.44 g (73%).

1-Ethyl-4-hydroxy-3-(nitroacetyl)quinolin-2(1*H*)-one (**4**)

Compound **3** (0.91 g, 3 mmol) was dissolve in 2 mol L^{-1} aqueous sodium hydroxide solution (50 mL) and heated under reflux for 3h. The solution so obtained after cooling was acidified with conc. hydrochloric acid. The precipitate so formed was filtered off, washed with water, air dried and crystallized from AcOH/H_2O to give **4** as white crystals, yield 0.57 g (69%).

5-Ethyl-2-(hydroxyimino)-2,3,4,5-tetrahydrofuro[3,2-*c*]quinoline-3,4-dione (**5**)

Compound **4** (0.55 g, 2 mmol) was dissolved in DMF (10 mL) and heated under reflux for 4h. After cooling to room temperature, the reaction mixture was poured onto ice/water. The precipitate so formed was filtered off, washed with water, air dried and crystallized from DMF/EtOH to give **5** as yellow crystals, yield 0.20 g (39%).

3-[Dibromo(nitro)acetyl]-1-ethyl-4-hydroxyquinolin-2(1*H*)-one (**6**)

A solution of bromine (0.2 mL, 2 mmol) in acetic acid (10 mL) was added dropwise to a solution of 3-nitroacetylquinoline **4** (0.55 g, 2 mmol) in acetic acid (10 mL). The reaction mixture was heated under reflux for 2 h. The yellow crystals obtained after cooling were filtered off and recrystallized from AcOH to give **6** as yellow crystals, yield 0.52 g (60%).

3-[Dichloro(nitro)acetyl]-1-ethyl-4-hydroxyquinolin-2(1*H*)-one (**8**)

To a suspension of compound **4** (0.55 g, 2 mmol) in 1,4-dioxane (20 mL), sulfuryl chloride (2 mmol) was added portionwise, while the temperature was not allowed to rise above 40 °C. Then, the reaction mixture was stirred for 1 h at room temperature and poured onto ice-H_2O (200 mL). The formed precipitate was collected by filtration and crystallized from ethanol to give compound **8** as yellow crystals, yield 0.54 g (78%).

3-(1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-2-nitro-3-oxopropanal (**9**)

Phosphoryl chloride (3 mL) was added dropwise with continuous stirring to the pre-cooled dimethylformamide (10 mL) in an ice bath. After complete addition, the mixture was further stirred for 30 min at ambient temperature, then 3-nitroacetyl derivative **4** (1.10 g, 4 mmol) in dimethylformamide (10 mL) was added dropwise with

continuous stirring at ambient temperature. After complete addition, the reaction mixture was heated on a boiling water bath under reflux for 2 h and left over night. The reddish orange solution was poured onto crushed ice and the precipitate so formed was filtered off, washed several times with water, air dried and crystallized from ethanol to give **9** as white crystals, yield 0.45 g (37%).

6-Ethyl-2-methyl-3-nitro-4*H*-pyrano[3,2-*c*]quinoline-4,5(6*H*)-dione (**11**)

3-Nitroacetylquinolinone **4** (0.83 g, 3 mmol) in acetic anhydride (10 mL) and freshly fused sodium acetate was heated under reflux for 4 h. After cooling, the reaction mixture was poured onto ice/water. The solid obtained was filtered off, washed several times with water, air dried and crystallized from ethanol to give **11** as pale yellow crystals, yield 0.40 g (44%).

3-[3-(2-Amino-4-oxo-4*H*-[1]benzopyran-3-yl)-2-nitroprop-2-enoyl]-1-ethyl-4-hydroxyquinolin-2(1*H*)-one (**13**)

A mixture of compound **4** (0.55 g, 2 mmol) and 2-amino-3-formylchromone (**12**) (0.38 g, 2 mmol), in glacial acetic acid (10 mL) and freshly fused sodium acetate (0.2 g), was heated under reflux for 4h. The yellow crystals obtained after cooling were filtered off and recrystallized from acetic acid to give **13** as yellow crystals, yield (0.51 g, 57%).

2-(1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-3-nitro-5*H*-benzopyrano[2,3-*b*]pyridin-5-one (**14**)

Method A

A mixture of compound **4** (0.55 g, 2 mmol) and 2-amino-3-formylchromone (**12**) (0.38 g, 2 mmol) or chromone-3-carbonitrile (**15**) (0.34 g, 2 mmol), in DMF (10 mL) containing few drops of DBU, was heated under reflux for 3h. The yellow crystals obtained after cooling were filtered off and recrystallized from DMF/EtOH to give **14** as yellow crystals, yield 44-48%.

Method B

Compound **13** (0.45 g, 1 mmol) in concentrated H_2SO_4 (5 mL) was stirred at room temperature for 1h. The dark brown solution was poured onto ice/water, the precipitate so formed was filtered off, washed several times with water and crystallized from DMF/EtOH to give **14** as yellow crystals, yield 0.24 g (55%).

5-Ethyl-3-(nitromethyl)-1-phenyl-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one (**17**)

A mixture of compound **4** (0.55 g, 2 mmol) and phenyl hydrazine (0.2 mL, 2 mmol), in glacial acetic acid (15 mL) and freshly fused sodium acetate (0.2 g), was heated under reflux for 4h. The yellow crystals obtained after cooling were filtered off and recrystallized from *n*-butanol to give **17** as yellow crystals, yield 0.48 g (73%).

1-(7-Chloroquinolin-4-yl)-5-ethyl-3-(nitromethyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one (**18**)

A mixture of compound **4** (0.55 g, 2 mmol), 7-chloro-4-hydrazinoquinoline (**16**) (0.36 g, 2 mmol), in glacial acetic acid (15 mL) and freshly fused sodium acetate (0.2 g), was heated under reflux for 4h. The yellow crystals obtained after cooling were filtered off and recrystallized from DMF/EtOH to give **18** as yellow crystals, yield 0.42 g (64%).

6-Ethyl-4-(nitromethyl)-2-thioxo-1,2,5,6-tetrahydro-pyrimido[5,4-*c*]quinolin-5(1*H*)-one (**19**)

A mixture of 3-nitroacetylquinoline **4** (0.55 g, 2 mmol) and thiourea (0.15 g, 2 mmol) in ethanolic potassium hydroxide solution (15 mL, 10%) was heated under reflux for 4h. After cooling at room temperature, the reaction mixture was poured onto crushed ice and neutralized with concentrated HCl. The precipitate so formed was filtered off, washed with water and crystallized from acetic acid/water to afford **19** as yellow crystals, yield 0.38 g (61%).

[6-Ethyl-4-(nitromethyl)-5-oxo-5,6-dihydropyrimido[5,4-*c*]quinolin-2(1*H*)-yl]cyanamide (**20**)

A mixture of 3-nitroacetylquinoline **4** (0.55 g, 2 mmol) and cyanoguanidine (0.17 g, 2 mmol) in ethanolic potassium hydroxide solution (15 mL, 10%) was heated under reflux for 4 h. After cooling at room temperature, the reaction mixture was poured onto crushed ice and neutralized with concentrated HCl. The precipitate so formed was filtered off, washed with water and crystallized from ethanol to afford **20** as yellow crystals, yield 0.37 g (57%).

5,13-Dihydro-5-ethyl-7-nitromethyl-6*H*-quinolino[4,3-*b*][1,5]benzodiazepin-6-one (**21**)

A mixture of 3-nitroacetylquinoline **4** (0.55 g, 2 mmol) and *o*-phenylenediamine (0.22 g, 2 mmol), in ethanol containing few drops of triethylamine, was heated under reflux for 3 h. The solid obtained during heating was filtered off and crystallized from ethanol to afford **21** as yellow crystals, yield 0.42 g (60%).

Supplementary Information

Data spectra and spectra of synthesized compounds are available free of charge at http://jbcs.sbq.org.br as PDF file.

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