European Journal of Chemistry

View Journal Online
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Ecofriendly and simple synthesis of pyrano[3,2-c]quinolone in water via an efficient one-pot three-component reaction

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RESEARCH ARTICLE

10.5155/eurjchem.9.1.44-48.1679

Received: 28 December 2017
Received in revised form: 27 January 2018
Accepted: 28 January 2018
Published online: 31 March 2018
Printed: 31 March 2018

KEYWORDS

Ethanolamine
One pot reaction
Pyranoquinolinone
4-Hydroxyquinolinone
Multicomponent reaction
Cinnamonitrile derivatives

ABSTRACT

Pyrano[3,2-c]quinolones are commonly found in alkaloids, manifesting diverse biological activities. In this work, 2-amino-6-methyl-5-oxo-4-substituted-5,6-dihydro-4*H*-pyrano[3,2-c]quinoline-3-carbonitriles and ethyl 2-amino-4-(substituted)-6-methyl-5-oxo-5,6-dihydro-4*H*-pyrano[3,2-c]quinoline-3-carboxylates have been synthesized efficiently from reaction of 4-hydroxy-1-methylquinolin-2(1*H*)-one, aldehydes and active methylene nitriles in one-pot three component reaction in aqueous medium, containing catalytic amount of ethanolamine resulting in 70-95% yields.

Cite this: *Eur. J. Chem.* **2018**, *9(1)*, 44-48 **Journal website**: www.eurjchem.com

1. Introduction

Synthesis of pyrano[3,2-c]quinolone, as the parent ring structure of pyranoquinoline alkaloids, has received significant attention in previous years due to the broad spectrum of their biological properties such as antimicrobial [1-3], anti-inflammatory [4], antimalarial [5]. Many of these alkaloids exhibit antiproliferative and anti-tubulin activities and are investigated as potential anticancer agents [6]. Examples for these cytotoxic alkaloids includes *N*-methylfindersine (**1**) and melicobisquinolinone B (**2**) which obtained via phytochemical studies on leaves of *Melicope ptelefolia* (Rutaceae) [7] as well as zanthosimuline (**3**), and huajiaosimuline (**4**) [8] (Figure 1). Nowadays, multicomponent reactions (MCR) strategy have attracted many attentions in organic and medicinal chemistry to produce biologically active compounds [9-11]. We herein report a safe, facile, fast and high yielding, eco-friendly synthesis of pyranoquinolones derivatives via an efficient one-pot three component reaction of 4-hydroxyquinolone with aldehydes and malononitrile or ethyl cyanoacetate in water.

2. Experimental

2.1. Instrumentations

Melting points were obtained on a Gallenkamp melting point apparatus. ^{1}H NMR spectra were performed on a Bruker (600 MHz) Ultra Shield Avance III spectrometer using TMS as an internal standard and $CDCl_3$ as solvents. Chemical shifts were expressed as δ ppm. The IR spectra were performed on a Jasco 4100 FTIR spectrophotometer (KBr pellet). The electron impact (EI) mass spectra were performed on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 eV. The Elemental analyses were performed on a Perkin Elmer's 2400 Series II CHN elemental analyzer.

2.2. Synthesis

2.2.1. General procedure for the synthesis of pyrano[3,2-c] quinolones (8a-c and 11a,b)

ISSN 2153-2249 (Print) / ISSN 2153-2257 (Online)
http://dx.doi.org/10.5155/eurjchem.9.1.44-48.1679

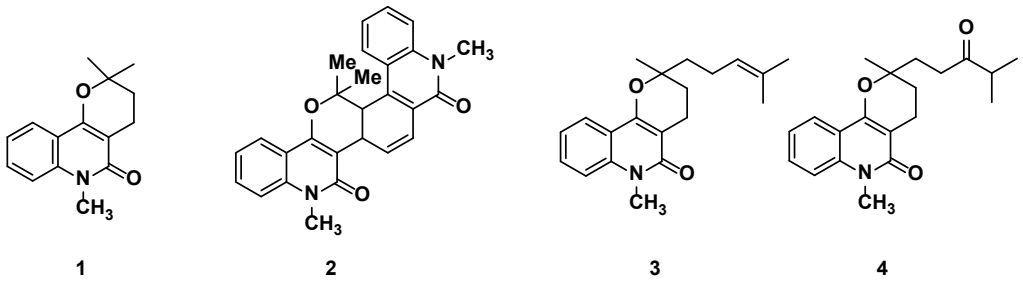
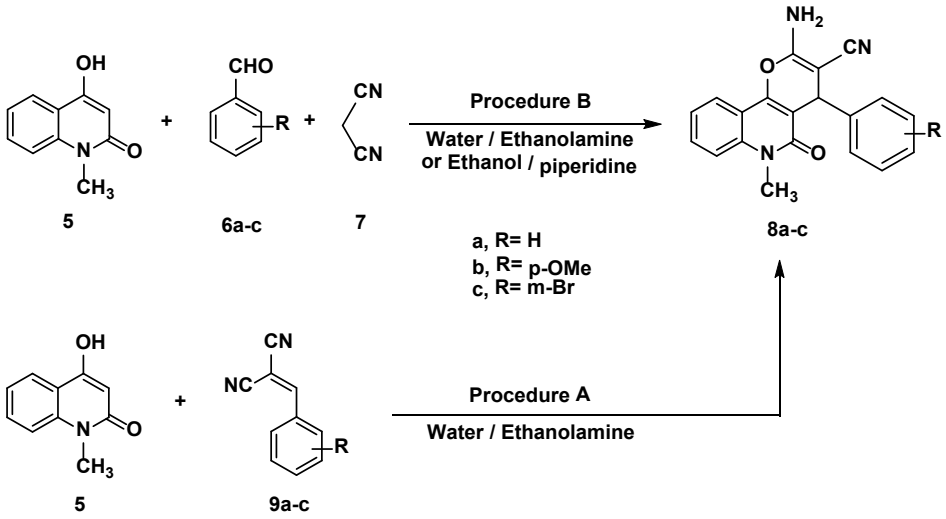


Figure 1. Examples of pyranoquinolone alkaloids exhibit cytotoxic activity.



Scheme 1

Procedure A: A cinnamonitrile derivatives (**9a-c**) (0.01 mol for each) were added to a solution of 4-hydroxy-1-methyl-quinolin-2(1*H*)-one (**5**) (0.01 mol) in 30 mL of distilled water which containing few drops of ethanolamine as a catalyst. The reaction mixture was stirred at room temperature for 20-180 minutes (Table 1). The solid product, which formed, was collected by filtration, washed by cold water and crystallized from ethanol.

Procedure B: A mixture of 4-hydroxy-1-methylquinolin-2(1*H*)-one (**5**), active methylene compound (malononitrile (**7**) and/or ethyl cyanoacetate (**10**)) and corresponding aromatic aldehyde (**6a-d**) in water and in presence of catalytic amount of ethanolamine (0.05 mmol) was stirring at room temperature. The precipitate was collected by filtration and washed with water and recrystallized from ethanol (Scheme 1 and 2).

2-Amino-6-methyl-5-oxo-4-phenyl-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carbonitrile (**8a**): Color: White. Yield: 80%. M.p.: 200-204 °C. FT-IR (KBr, ν, cm^{-1}): 3328-3319 (NH_2), 3107 (=CH), 2935 (-CH), 2198 (nitrile), 1677 (CO), 1604 (C=C). ^{1}H NMR (600 MHz, $CDCl_3$, δ, ppm): 3.86 (s, 3H, N-CH_3), 4.36 (s, 1H, pyran H-4), 4.47 (s, 2H, NH_2), 7.20-8.00 (m, 9H, ArH). MS (EI, *m/z* (%)): 329 (M^+, 53.21), 314 (M^+-CH_3, 2.61), 252 (M^+-C_6H_5, 100), 285 (M^+-CH_2NO, 29.17), 263 (M^+-$C_3H_2N_2$, 14.11), 247 (M^+-$C_3H_3N_2O$, 0.94), 201 (M^+-C_9H_6N, 1.01), 157 (M^+-$C_{10}H_8N_2O$, 0.4), 118 (M^+-$C_{12}H_9N_2O_2$, 1.81), 89 (M^+-$C_{13}H_{12}N_3O_2$, 5.65). Anal. calcd. for $C_{20}H_{15}N_3O_2$: C, 72.94; H, 4.59; N, 12.76. Found: C, 72.92; H, 4.59; N, 12.75%.

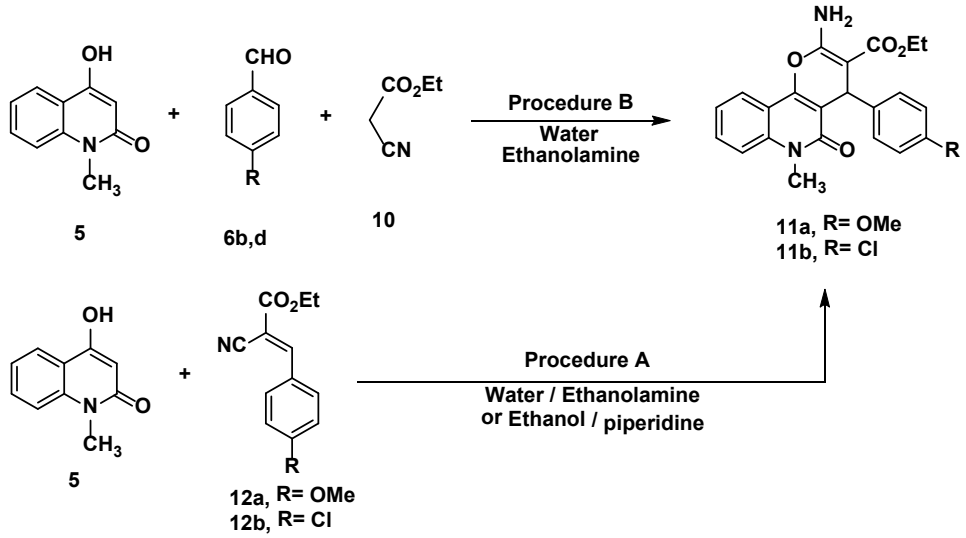
2-Amino-4-(4-methoxyphenyl)-6-methyl-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carbonitrile (**8b**): Color: White. Yield: 85%. M.p.: 230-233 °C. FT-IR (KBr, ν, cm^{-1}): 3370-3311 (NH_2), 3154 (=CH), 2217 (nitrile), 1670 (CO), 1608 (C=C), 1238 (C-N). ^{1}H NMR (600 MHz, $CDCl_3$, δ, ppm): 2.93 (s, 3H, O-CH_3), 3.91 (s, 3H, N-CH_3), 4.72 (s, 1H, pyran H-4), 4.90 (s, 2H, NH_2), (m, 8H, ArH). MS (EI, *m/z* (%)): 359 (M^+, 36.78), 328 (M^+-OMe, 5.08), 293 (M^+-$C_3H_2N_2$, 70.44), 292 (M^+-$C_3H_3N_2$, 99.65), 277 (M^+-$C_3H_2N_2O$, 5.31), 252 (M^+-C_7H_7O, 40.88), 186 (M^+-$C_{10}H_9N_2O$, 8.01), 170.05 (M^+-$C_{10}H_9N_2O_2$, 3.08), 157 (M^+-$C_{11}H_{10}N_2O_2$, 4.47), 129 (M^+-$C_{12}H_{10}N_2O_3$, 18.35), 133 (M^+-$C_{13}H_{10}N_2O_2$, 12.83), 105.05 (M^+-$C_{14}H_{10}N_2O_3$, 100), 89 (M^+-$C_{14}H_{13}N_3O_3$, 19.25), 76 (M^+-$C_{15}H_{13}N_3O_3$, 15.53). Anal. calcd. for $C_{21}H_{17}N_3O_3$: C, 70.18; H, 4.77; N, 11.69. Found: C, 70.17; H, 4.78; N, 11.70%.

2-Amino-4-(3-bromophenyl)-6-methyl-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carbonitrile (**8c**): Color: White. Yield: 70 %. M.p.: 255-257 °C. FT-IR (KBr, ν, cm^{-1}): 3324-3297 (NH_2), 3197 (=CH), 2981 (CH), 2198 (nitrile), 1670 (CO), 1619(C=C), 1254 (C-N). ^{1}H NMR (600 MHz, $CDCl_3$, δ, ppm): 3.65 (s, 3H, N-CH_3), 4.74 (s, 1H, pyran H-4), 4.77 (s, 2H, NH_2), 7.17-7.98 (m, 8H, ArH). MS (EI, *m/z* (%)): 407 (M^+, 18.02), 408 (M^+, 7.26), 409 (M^+,19.77), 363 (M^+-CH_2NO, 6.81), 362 (M^+-CH_3NO, 3.71), 341.95 (M^+ -$C_3H_3N_2$, 6.3), 328.1 (M^+-Br, 6.39), 252 (M^+-C_6H_4Br, 100), 225 (M^+-C_7H_8BrN, 2.21), 207 (M^+-C_7H_7BrNO, 3.88), 157 (M^+-$C_{10}H_7BrN_2O$, 3.41), 129 (M^+-$C_{11}H_7BrN_2O_2$, 2.77), 105 (M^+-$C_{13}H_7BrN_2O_2$, 4.72), 76 (M^+- $C_{14}H_{10}BrN_3O_2$, 12.05). Anal. calcd. for $C_{20}H_{14}BrN_3O_2$: C, 58.84; H, 3.46; N, 10.29. Found: C, 58.82; H, 3.46; N, 1028%.

Ethyl 2-amino-4-(4-methoxyphenyl)-6-methyl-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carboxylate (**11a**): Color: White. Yield: 78 %. M.p.: 225-227 °C. FT-IR (KBr, ν, cm^{-1}): 3297-3216 (NH_2), 3085 (=CH), 2985 (CH), 1681 (CO), 1623 (CO), 1604 (C=C), 1234 (C-N).

Table 1. Yield percentage and reaction time for the synthesized compounds.

Compound	Procedure A		Procedure B	
	t (min)	Yield (%)	t (min)	Yield (%)
8a	65	86	70	80
8b	75	80	90	85
8c	20	77	50	70
11a	120	65	180	78
11b	40	92	60	95



Scheme 2

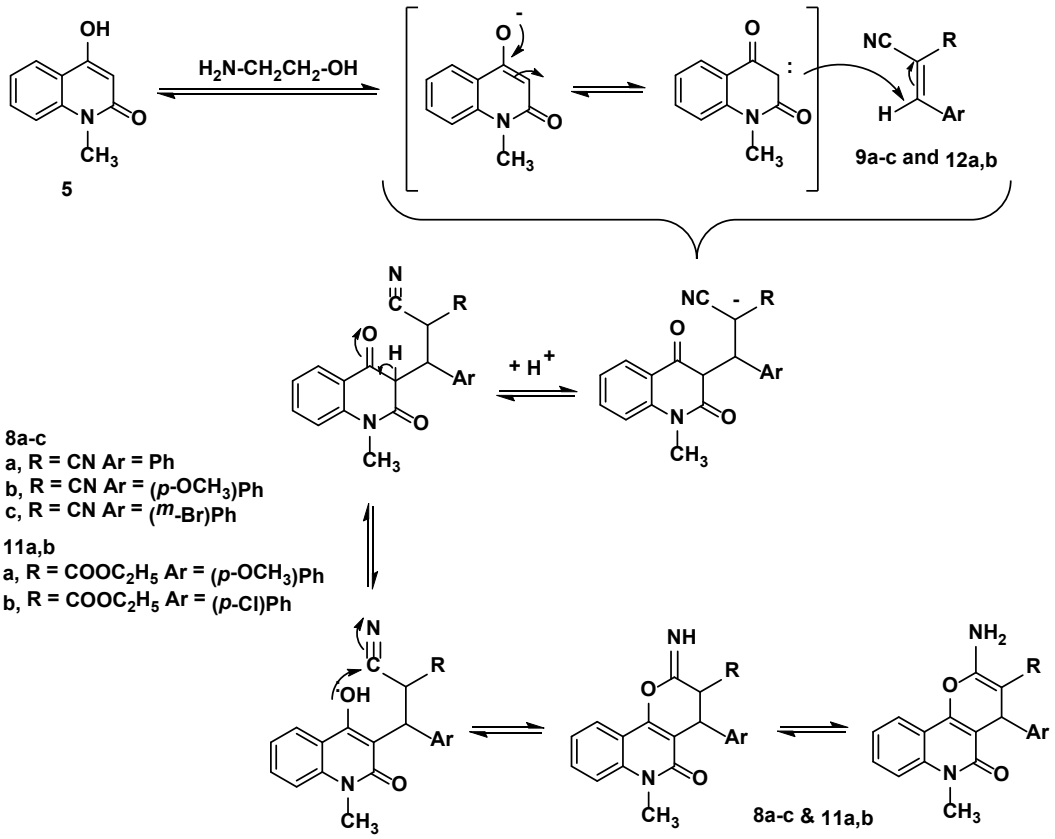
^{1}H NMR (600 MHz, $CDCl_3$, δ, ppm): 1.21 (t, 3H, *J* = 6.9 Hz, CH_3), 3.63 (s, 3H, N-CH_3), 3.76 (s, 3H, O-CH_3), 4.14 (q, 2H, *J* = 6.9 Hz, CH_2), 5.04 (s, 1H, pyran H-4), 6.35 (s, 2H, NH_2), 6.65-8.00 (m, 8H, ArH). MS (EI, *m/z* (%)): 406 (M^+, 55.3), 361 (M^+-C_2H_5O, 4.82), 360 (M^+-C_2H_6O, 12.07), 333 (M^+-$C_3H_5O_2$, 30.43), 332 (M^+-$C_3H_6O_2$, 10.8), 299 (M^+-C_7H_7O, 100), 293(M^+-$C_5H_7NO_2$, 8.13), 277 (M^+-$C_5H_7NO_3$, 1.42), 254 (M^+-$C_9H_{12}O_2$, 13.87), 253 (M^+-$C_9H_{13}O_2$, 82.8), 226 (M^+-$C_{10}H_{12}O_3$, 5.16), 170 (M^+-$C_{12}H_{14}NO_4$, 7.83), 157 (M^+-$C_{13}H_{15}NO_4$, 2.36), 142 (M^+-$C_{13}H_{14}NO_5$, 2.17), 105 (M^+-$C_{16}H_{15}NO_4$, 3.4), 104 (M^+-$C_{16}H_{16}NO_5$, 11.92), 76 (M^+-$C_{17}H_{18}N_2O_5$, 3.52). Anal. calcd. for $C_{23}H_{22}N_2O_5$: C, 67.97; H, 5.46; N, 6.89. Found: C, 67.98; H, 5.46; N, 6.90%.

Ethyl 2-amino-4-(4-chlorophenyl)-6-methyl-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carboxylate (**11b**): Color: White. Yield: 95%. M.p.: 222-225 °C. FT-IR (KBr, ν, cm^{-1}): 3293-3215 (NH_2), 3085 (=CH), 2985 (CH), 1685 (CO), 1654 (CO), 1619 (C=C),1226(C-N). ^{1}H NMR (600 MHz, $CDCl_3$, δ, ppm): 1.18 (t, 3H, *J* = 6.9 Hz, CH_3), 3.64 (s, 3H, N-CH_3), 4.13 (q, 2H, *J* = 6.9, CH_2), 5.05 (s, 1H, pyran H-4), 6.40 (s, 2H, NH_2), 7.16-8.00 (m, 8H, ArH). MS (EI, *m/z* (%)): 410 (M^+, 30.77), 411 (M^+, 7.73), 412 (M^+, 9.98), 365 (M^+-C_2H_5O, 4.3), 364 (M^+-C_2H_6O, 3.55), 337 (M^+-$C_3H_5O_2$, 17.42), 299 (M^+-C_6H_4Cl, 100), 281 (M^+-$C_5H_7NO_3$, 0.55), 226 (M^+-$C_9H_9ClO_2$, 2.58), 170 (M^+-$C_{11}H_{11}ClNO_3$, 4.11), 157 (M^+-$C_{12}H_{12}ClNO_3$, 0.25), 129 (M^+-$C_{13}H_{12}ClNO_4$, 1.44), 118 (M^+-$C_{14}H_{13}ClNO_4$, 1.13), 89 (M^+-$C_{15}H_{16}ClN_2O_4$, 2.18), 76 (M^+-$C_{16}H_{16}ClN_2O_4$, 2.9). Anal. calcd. for $C_{22}H_{19}Cl\,N_2O_4$: C, 64.32; H, 4.66; N, 6.82. Found: C, 64.33; H, 4.64; N, 6.83%.

3. Results and discussion

It has been reported that the reaction of 4-hydroxy-2-quinolinone with α,β-unsaturated nitriles, as two component system, had afforded pyrano[3,2-c]quinolone derivatives. This reaction was carried out in refluxing ethanol for 50 minutes, using triethylamine as catalyst, and the pyranoquinolones were obtained in 64-95% yields [12,13]. Herein, we present the reobtaining pyrano[3,2-c]quinolone derivatives through modified facile, fast, higher yielding and ecofriendly procedure. In this procedure, we have used ethanolamine instead of triethylamine and replaced ethanol by water, the most clean, greenest and economic solvent (procedure A, Scheme 1). Thus, stirring of 4-hydroxy-1-methylquinolin-2(1*H*)-one (**5**) and α-cyano-cinnamonitriles (**9a-c**) in water containing catalytic amount of ethanolamine, at room temperature, afforded the expected solid products (**8a-c**) in 70-95% yields based on the isolated products, which were in considerable degrees of purity. On the other hand, pyrano[3,2-c]quinolone derivatives (**8a-c**) were also prepared by efficient technique of one-pot three component reaction (procedure B, Scheme 1). Thus, compound **5**, the appropriate aldehyde **6a-c** and malononitrile **7** were allowed to react together, under the suitable reaction conditions, to afford the same respective pyrano[3,2-c]quinolone derivatives (**8a-c**). This confirmation reaction was carried out twice, once in water and once, else, in ethanol (procedure B, Scheme 1) as the reaction solvent and, always, the planned pyrano[3,2-c]quinolone derivatives were obtained.

Thin layer chromatography (TLC), melting points and mixed melting points of pyrano[3,2-*c*]quinolone prepared by mixing of equal amounts of compound **8** obtained out of procedures A and B (Scheme 1), have been used to confirm obtaining the same respective derivative **8** through the different procedures. Also, structures of compound **8a-c** are established for the reaction product based on the ^{1}H NMR spectra which revealed the presence of a signal at δ 4.5-5.0 ppm for one proton linked with a sp^3 carbon as 4H-pyran. Infrared spectrum of compound **8a**, as an example, revealed absorption bands at 3319-3328 cm^{-1} for NH_2 and at 2198 cm^{-1} for cyano group. On replacing the α-cyano-cinnamonitrile derivatives **9a-c** by the, relatively lesser reactive α-carboethoxycinnamonitriles (**12a**,**b**) in the above mentioned reactions A and B, Scheme 2, the corresponding pyrano[3,2-*c*]quinolone derivatives (**11a**,**b**) were obtained, but after a



Scheme 3

much larger reaction time of 150-180 minutes and in a good yield of products of 78-90%. The same trend of results was, generally, obtained on carrying out the one-pot three-component reactions of compound **5**, the appropriate aldehyde (**6b**,**d**) and ethyl cyanoacetate (**10**) (procedure B, Scheme 2) as an unambiguous synthesis, confirming the formation of the respective pyrano[3,2-*c*]quinolone derivatives. The postulated structure of compound **11a**,**b** was based on the following arguments: a) mixed melting point ; b) TLC; c) ^{1}H NMR spectra of compound **11b**, as an example, showed signals at δ 1.18 (t, 3H, *J* = 6.9, CH_3), 3.64 (s, 3H, N-CH_3), 4.13 (q, 2H, *J* = 6.9, CH_2), 5.05 (s, 1H, pyran H-4), 6.40 (s, 2H, NH_2) and 7.16-8.00 ppm (m, 8H, ArH); d) FT-IR spectra of compound **11a**-**c** exhibited absorption bands at 3297-3215 cm^{-1} for amino group, 1685 cm^{-1} for carbonyl ester group and at 1654 cm^{-1} for carbonyl of quinolone.

Using two component condensation, the formation of compounds **8a**-**c** and **11a**,**b** were assumed to proceed via addition of quinolinyl C-3 to the activated double bond in α,β-unsaturated nitriles (**9a**-**c**) and (**12a**,**b**) followed by cycloaddition of the Michael adduct (Scheme 3). Using three component condensations, the mechanism may occur by Knoevenagel condensation, Michael addition, intramolecular cyclization, and isomerization. α,β-Unsaturated nitriles is formed by Knoevenagel condensation of aldehyde (**6a**-**d**) and malononitrile (**7**) or ethyl cyanoacetate (**10**) by the action of ethanolamine. Then, the proton of 4-hydroxy-2(1*H*)-quinolone (**5**) is abstracted by ethanolamine to form carbanion which in Michael addition on compounds **9a**-**c** and **12a**,**b** leads to the formation of 2-amino-4*H*-pyrano[3,2-c]quinolin-5(6*H*)-one derivatives (**8a**-**c**) and (**11a**,**b**) through cyclization and isomerization.

4. Conclusion

In this study 2-amino-6-methyl-5-oxo-4-substituted-5,6-dihydro-4*H*-pyrano[3,2-c]quinoline-3-carbonitriles and ethyl 2-amino-4-(substituted)-6-methyl-5-oxo-5,6-dihydro-4*H*-pyrano[3,2-c]quinoline-3-carboxylates were prepared through modified facile, fast, high-yield and eco-friendly procedure.

Acknowledgment

The authors extend their appreciation to the Deanship of Scientific Research at Jazan University for funding this paper through the research group Project no. 019-FS3.

Disclosure statement

Conflict of interests: The authors declare that they have no conflict of interest.
Author contributions: All authors contributed equally to this work.
Ethical approval: All ethical guidelines have been adhered.
Sample availability: Samples of the compounds are available from the author.

Funding

Jazan University
http://dx.doi.org/10.13039/100009388

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