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Regioselective synthesis of pyrano[3,2-*f*]quinoline and phenanthroline derivatives using molecular iodine ☆

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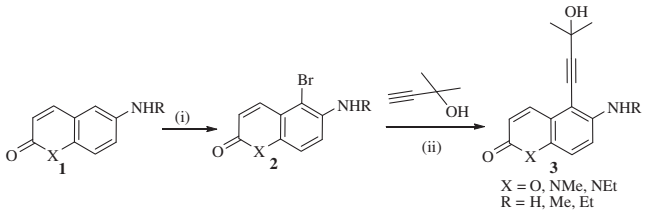
ABSTRACT

A series of polysubstituted pyrano[3,2-*f*]quinoline and phenanthroline derivatives have been synthesized by molecular iodine-catalyzed tandem reaction of various propargylic alcohols with or without substituted amines in excellent yields. Moreover, the cyclized side products are also pyrano[3,2-*f*]quinoline and phenanthroline derivatives.

The heterocyclic ring system tetrahydroquinoline represents an important class of alkaloids and are often found as structural frameworks in a large number of biologically active natural products and pharmaceuticals.[1] Quinoline nucleus has found broad application in drug development material science,[2] bioorganometallic processes,[3] and agrochemicals and effect chemicals such as dyestuffs, corrosion inhibitors, and medicinal chemistry.[1] Substituted quinolines show numerous biological activities as antagonists of endothelin,[4] $5HT_3$,[5] and NK-3 receptors[6] and also function as inhibitors of gastric (H^+/K^+)-ATP-ase[7] and dihydroorotate dehydrogenase.[8] Moreover, pyrano[3,2-*f*] quinoline shows unique biological activities, such as psychotropic,[9] antiallergic,[10] anti-inflammatory,[11] and estrogenic[12] activities and are used as potential pharmaceuticals.[13] Helietidine, dutadrupine, and geibalansine[14] are examples of natural products containing pyranoquinoline core structure. 4,7-Phenanthroline derivatives and its analogs exhibit a high antibacterial activity and are used for the treatment of gastrointestinal disease.[15–20] Because of the significance of these scaffolds in drug discovery and medicinal chemistry, efficient synthesis of pyranoquinoline and phenanthroline derivatives continues to attract the interest of synthetic chemists. However, most classical methods for the synthesis of the complex substituted tetrahydroquinolines need expensive metals, high temperatures or extended reaction times.[21] To overcome the above limitations, an efficient, and environmentally friendly method with short reaction time is always welcomed.



Reagent and condition: (i) NBS, CH_3CN, r.t. stirring (ii) $Pd(PPh_3)_2Cl_2$, CuI, NEt_3, DMF, 90 °C, 3h

Scheme 1. Preparation of starting materials. Reagent and condition: (i) NBS, CH_3CN, rt stirring (ii) $Pd(PPh_3)_2Cl_2$, CuI, NEt_3, DMF, 90 °C, 3 h.

Recently, molecular iodine has received considerable attention as an inexpensive, non-toxic, readily available reagent for the preparation of a variety of five- and six-membered carbocyclic and heterocyclic ring systems. Thus, iodine-promoted tandem reactions continue to be an area of active research in synthetic chemistry due to efficient, mild, and clean reaction conditions.[22] As a part of our continuing efforts toward the development of new protocols for the expeditious synthesis of biologically relevant heterocyclic compounds,[23] we undertook a simple molecular iodine-induced tandem cyclization reaction of propargylic alcohols with amines for the preparation of potentially bioactive substituted pyranoquinoline or phenanthroline derivatives.

The starting materials **3** for this study were prepared easily according to the reactions outlined in Scheme 1. The process

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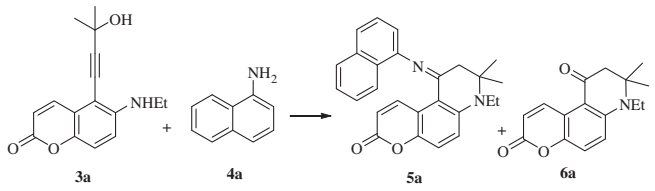
involves bromination of compound **1** by NBS followed by the Sonogashira coupling of brominated derivative **2** with 2-methyl but-3-yn-2-ol using 5 mol % $Pd(PPh_3)_2Cl_2$ and 5 mol % CuI in a mixture of DMF and NEt_3 (7 ml: 3 ml) at 90 °C in 77–91% yield. 2-Methyl but-3-yn-2-ol has been used widely as a readily available, cheap, non-volatile, protected form of acetylene which is unmasked via thermolysis in the presence of a base with the expulsion of acetone. Iodine-catalyzed cyclization of the resulting **3a** with aromatic amine to give **5a** in 92% yield along with **6a** (6%) as side product.

Initially we have used the reaction of 6-(ethylamino)-5-(3-hydroxy-3-methylbut-1-ynyl)-2*H*-chromen-2-one (**3a**) and naphthalen-1-amine (**4a**) as a model reaction to optimize the reaction condition and the results are presented in Table 1.

The reaction was first carried out in moist dichloromethane without any catalyst at room temperature for 10 h. The reaction failed to give any product in the absence of any catalyst (Table 1, entry 1).

A similar reaction was carried out in the presence of 10 mol % of AcOH (entry 2) and the reaction was completed in 30 min. to give 7-ethyl-8,8-dimethyl-8,9-dihydro-3*H*-pyrano[3,2-*f*]quinoline-3,10(7*H*)-dione (**6a**) in 90% yield. In the presence of 10 mol % $BF_3{\cdot}Et_2O$ at rt in DCM (5 ml) for 30 min. afforded **6a** as major product along with 7-ethyl-8,8-dimethyl-10-(naphthalen-1-ylimino)-7,8,9,10-tetrahydro-3*H*-pyrano[3,2-*f*]quinolin-3-one (**5a**) in 10% yield (entry 3). Various catalysts such as TfOH, $FeCl_3$, $AlCl_3$, CuI, $AgSbF_6$, and $InCl_3$ were investigated in DCM at rt and all of them gave **6a** as the major products and **5a** as minor product (entries 4–9) in 30 min. When we carried out the same reaction in the presence of 10 mol % I_2 **5a** was obtained as the major product (92%) along with a small amount of **6a** (6%) (entry 10). I_2 gives better yield compared to other Lewis acids. Brönsted acids give only the cyclized product **6a**. Lower loading of the catalyst (5 mol %) gives lower yield (72%) but higher loading of the catalyst (20, 50 or 100 mol %) had no significant effect on the reaction yield (entries 11–14). To establish the optimum reaction conditions THF, CH_3OH, CH_3CN, DCE, and $CHCl_3$ (entries 15–19) were also tested as solvents under the same reaction condition. Variation of the catalyst and solvent showed that running the reaction in DCM at rt using 10 mol % I_2 provides the best result.

Table 1
Optimization of reaction conditions



Entry	Catalyst (mol %)	Solvent[b]	Time	% Yield (**5a**:**6a**)[a]
1	—	CH_2Cl_2	10 h	0
2	AcOH (10)	CH_2Cl_2	30 min	90 (0:90)
3	$BF_3{\cdot}OEt_2$ (10)	CH_2Cl_2	30 min	96 (10:86)
4	TfOH (10)	CH_2Cl_2	30 min	95 (0:95)
5	$FeCl_3$ (10)	CH_2Cl_2	30 min	97 (16:81)
6	$AlCl_3$ (10)	CH_2Cl_2	30 min	94 (12:82)
7	CuI (10)	CH_2Cl_2	30 min	96 (17:79)
8	$AgSbF_6$ (10)	CH_2Cl_2	30 min	87 (22:65)
9	$InCl_3$ (10)	CH_2Cl_2	30 min	90 (21:69)
10	**I_2(10)**	**CH_2Cl_2**	**30 min**	**98 (92:6)**
11	I_2 (5)	CH_2Cl_2	30 min	76 (72:4)
12	I_2 (20)	CH_2Cl_2	30 min	98 (92:6)
13	I_2 (50)	CH_2Cl_2	30 min	98 (92:6)
14	I_2 (100)	CH_2Cl_2	30 min	98 (92:6)
15	I_2 (10)	THF	30 min	68 (56:12)
16	I_2 (10)	CH_3OH	30 min	86 (72:14)
17	I_2 (10)	CH3CN	30 min	63 (52:11)
18	I_2 (10)	DCE	30 min	94 (82:12)
19	I_2 (10)	$CHCl_3$	30 min	97 (91:6)

[a] Isolated yield.
[b] All solvents were moist.

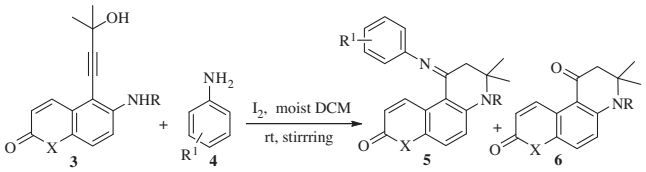
To explore the scope and generality of this simple iodine-induced tandem cyclization reaction of propargylic alcohols with amines, a range of pyrano[3,2-*f*]quinoline or phenanthroline derivatives were synthesized from a variety of substrates under the optimized reaction condition. Different types of substituted propargylic alcohol derivatives (**3a–f**), and a wide range of amines (aromatic and heterocyclic), **1a**, **1c**, and **4a–l** were examined. All of them gave excellent yields of the desired products under the optimized reaction conditions. Table 2 shows that this protocol can be applied not only to electron rich but also to electron-deficient aromatic amines and heterocyclic amines as electronic nature of the substituents on the aromatic ring of the aldehydes did not show any influence on the yield of the products of the reaction, thus demonstrating the wide scope of this protocol. But the reaction does not give desired product when a strongly electron withdrawing NO_2 group is present at the *para* position of the aromatic ring of aniline derivatives (entry 11). In this case exclusively the cyclized product **6b** was obtained, which is the side product in other cases. However NO_2 substitution at the *meta* position ofthe aromatic ring of amine derivatives (**4j**) gives exclusively desired product **5k** in just 60 min, without the formation of any side product **6b** (entry 12). But, ^1H NMR spectra of the product **5k** showed that it is mixture of two products which are inseparable by simple column chromatography. The reaction does not give any cyclized product when prop-2-yn-1-ol or but-3-yn-2-ol was used as propargylic alcohols instead of 2-methyl but-3-yn-2-ol limiting the scope to some extent.

Further, to expand the scope of this reaction, we have also carried out the same reaction without any aniline derivatives and with those propargylic alcohols which contain a free amine group (**3c**, **3e**, **3f**). Surprisingly in the presence of 10 mol % I_2 pyranoquinoline or phenanthroline derivatives **7a**, **7b**, and **7c** were obtained in excellent yields, without the formation of any type of side product **6** as depicted in Table 3. But when **3a**, **3b**, and **3d** were treated with 10 mol % I_2 in the absence of aniline derivatives, solely the cyclized derivatives pyranoquinoline or phenanthroline derivatives **6a**, **6b**, or **6d** were obtained. From the aforesaid examples, it is clear that propargylic alcohol derivatives **3** contain free amine group give the pyranoquinoline or phenanthroline derivatives in the presence or absence of another aniline derivative. In the absence of aniline derivatives another molecule of **3** behaves as the aniline component.

The structures of the products were determined from their elemental analyses and spectroscopic data. The ^1H NMR spectra of the compound **5a** as well as two peaks in ^{13}C NMR spectra at δ_c = 160.9 and 163.8 ppm show the presence of an ester and an imine group. This is further supported by the mass spectral data of compound **5a** at 397.1910. The hydrolysis of compound **5a** to the corresponding carbonyl compound **6a** by H^+ (Scheme 2) showed the presence of an imine group in the products **5**.

Two possible pathways may be considered (Scheme 3) for the iodine-catalyzed tandem cyclization reaction which is similar to that outlined by Ye et al.[25] Path a: first, in the presence of trace amounts of H^+ (formed by I_2 and H_2O), the propargylic alcohols **3** easily lose the hydroxy group to afford the intermediate propargyl carbocations **A**, aniline then subsequently captures the allene cation to give intermediate **B**. Intermediate **B** loses a proton to form the intermediate **C**. I_2 coordinates with the carbon–nitrogen double bond and generates intermediate **D**. Intramolecular nucleophilic attack of the nitrogen of the amino group gave the intermediate **E**, which on deprotonation and protonation afforded the enamine

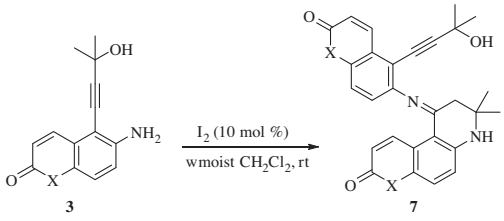
Table 2
Synthesis of various pyranoquinoline and phenanthroline derivatives



Entry	Substrate	Amine	Time (min)	Products	% Yield (5:6)[a]
1	X = O,R = Et (**3a**)[24]	Naphthalen-1-amine (**4a**)	30	**5a**[24] + **6a**[24]	98 (92:6)
2	X = O, R = Et (**3a**)	Naphthalen-2-amine (**4b**)	30	**5b** + **6a**	97 (91:6)
3	X = O, R = Et (**3a**)	2,4-Dimethylaniline (**4c**)	30	**5c** + **6a**	97 (89:8)
4	X = O, R = Et (**3a**)	6-Amino-2*H*-chromen-2-one (**1a**)	30	**5d** + **6a**	93 (82:11)
5	X = O, R = Me (**3b**)	*o*-Toluidine (**4d**)	30	**5e** + **6b**	95 (88:7)
6	X = O, R = Me (**3b**)	p-Toluidine (**4e**)	30	**5f** + **6b**	96 (90:6)
7	X = O, R = Me (**3b**)	2-Chloroaniline (**4f**)	30	**5g** + **6b**	96 (84:12)
8	X = O, R = Me (**3b**)	5-Chloro-2-methylaniline (**4g**)	30	**5h** + **6b**	98 (87:11)
9	X = O, R = Me (**3b**)	3-Chloro-2-methylaniline (**4h**)	30	**5i** + **6b**	97 (86:11)
10	X = O, R = Me (**3b**)	2-Bromo-4-methylaniline (**4i**)	30	**5j** + **6b**	97 (89:8)
11	X = O, R = Me (**3b**)	4-Nitroaniline (**4j**)	30	**6b**	84 (0:84)
12	X = O, R = Me (**3b**)	3-Nitroaniline (**4k**)	60	**5k** + **6b**	98 (84:14)
13	X = O, R = Me (**3b**)	Naphthalen-1-amine (**4a**)	30	**5l** + **6b**	98 (88:10)
14	X = O, R = H (**3c**)	4-Methoxyaniline (**4l**)	30	**5m** + **6c**	96 (68:28)
15	X = O, R = H (**3c**)	4-Chloroaniline (**4m**)	30	**5n** + **6c**	93 (64:29)
16	X = NEt, R = Et (**3d**)	*p*-Toluidine (**4e**)	30	**5o** + **6d**	96 (83:13)
17	X = NEt, R = Et (**3d**)	2,4-Dimethylaniline (**4c**)	30	**5p** + **6d**	95 (82:13)

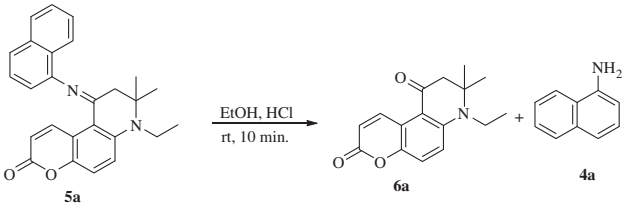
[a] Isolated yields.

Table 3
Synthesis of pyranoquinoline and phenanthroline derivatives from propargylic alcohols



Entry	Substrate	Time (h)	Product	% Yield[a]
1	X = O, R = H (**3c**)	3	**7a**	88
2	X = NMe, R = H (**3e**)	3	**7b**	86
3	X = NEt R = H (**3f**)	3	**7c**	87

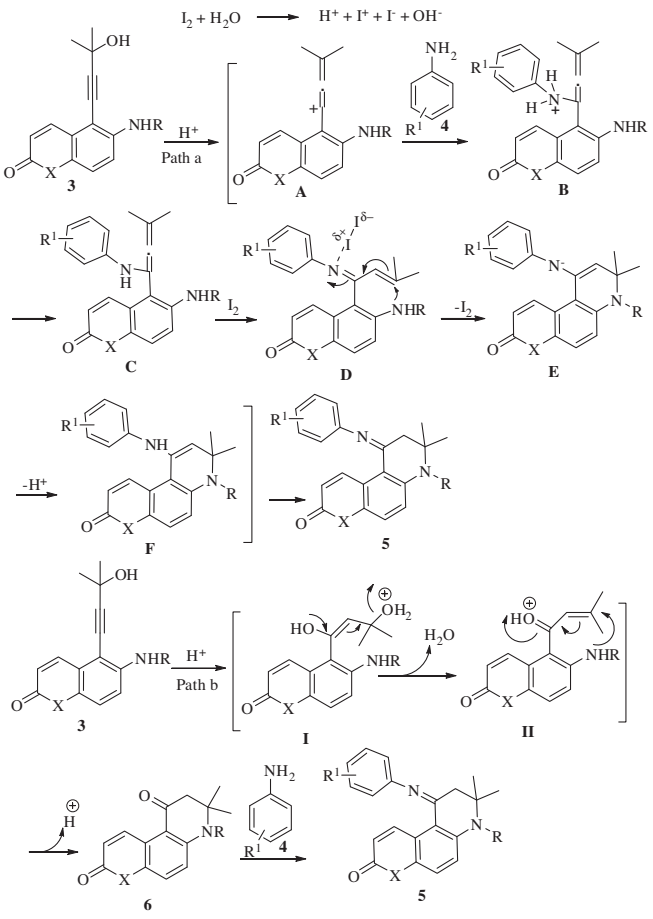
[a] Isolated yields.



Scheme 2. Convertion of imine to carbonyl.

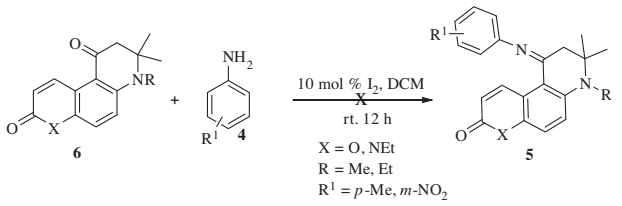
F. The unstable enamine **F**, may immediately isomerize to form the desired products **5**. Formation of the other cyclized product **6** may be explained through pathway b. In the presence of H^+, the propargylic alcohols **3** first form aldols **I** via regioselective dehydrative rearrangement of the alkyne moiety. The α,β−unsaturated ketones **II** are formed from **I** which on 6-'*endo-trig*' Michael-type ring closure give the products **6**.[26]

Subsequently, a condensation reaction of the aniline derivative with **6** may give the pyranoquinoline or phenanthroline derivatives



Scheme 3. Possible reaction pathway.

5. Ye et al. did not establish the exact pathway from the two probable routes. However, we have carried out further investigation to identify the more probable one out of the two pathways suggested



Scheme 4. Unsuccessful reaction to find out the reaction pathway.

by them. We have conducted a series of reactions of **6** with various aniline derivatives (**4**) using 10 mol % I_2 in DCM at rt for 12 h (Scheme 4). But the reaction failed to give product **5**. Since, the desired products **5** were not formed by the above mentioned reactions we may conclude that the reactions follow path 'a' and formation of the other cyclized products **6** through pathway 'b' and thus, we were able to rule out the involvement of pathway in the reactions.

In conclusion, we have demonstrated a mild and efficient, environmentally friendly strategy for the synthesis of potentially bioactive pyrano[3,2-*f*]quinoline or phenanthroline derivatives by molecular iodine-catalyzed tandem reaction of various propargylic alcoholic derivatives and with or without the use of substituted amine. The starting materials can be easily prepared and this reaction occurs with a wide range of substrates in high efficiency with shorter reaction time. While for a similar reaction Ye et al. proposed two pathways for the formation of products, we have been able to eliminate one and identify the more probable mechanism for the reaction. The methodology is simple, rapid, and inexpensive affording high yields of the cyclized products with operational simplicity.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.07.163.

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24. *General Procedure for synthesis of **3a–f**:* To a stirred solution of 6-amino-5-bromo-2*H*-chromen-2-one or 6-amino-5-bromo-1-methylquinolin-2(1*H*)-one or 6-amino-5-bromo-1-ethylquinolin-2(1*H*)-one or *N*-(5-bromo-2-oxo-2*H*-chromen-6-yl)acetamide (1 equiv) in DMF (7 mL) and NEt_3 (3 mL) 2-methyl but-3-yn-2-ol (1.2 equiv) was added at room temperature. Then $Pd(PPh_3)_2Cl_2$ (0.05 equiv) and CuI (0.05 equiv) were to the added under reaction mixture in nitrogen atmosphere and stirred at 90 °C for 3 h. After completion of the reaction (monitored by TLC) the reaction mixture was cooled and extracted with dichloromethane (25 mL × 3). The combined organic extract was washed with brine (25 mL × 4) and dried over Na_2SO_4. The solvent was distilled off. The resulting crude product was purified by filtration through a pad of silica gel (60–120 mesh) using petroleum ether-ethyl acetate mixture as eluent to give the pure compound (**3**).
6-(Ethylamino)-5-(3-hydroxy-3-methylbut-1-ynyl)-2H-chromen-2-one: (**3a**) Yield = 91%, yellow colored solid, mp 72–74 °C. IR (KBr): ν_{max} = 1701, 2978, 3481 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ_H = 1.31 (t, 3H, *J* = 7.2 Hz), 1.71 (s, 6H), 2.81 (bs, 1H), 3.23 (q, 2H, *J* = 7.2 Hz), 4.47 (br s, 1H), 6.40 (d, 1H, *J* = 9.6 Hz), 6.75 (d, 1H, *J* = 9.2 Hz), 7.14 (d, 1H, *J* = 9.2 Hz), 7.93 (d, 1H, *J* = 9.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 14.7, 31.0, 31.7, 38.3, 65.8, 74.9, 102.3, 106.4, 113.6, 117.0, 117.8, 119.6, 141.9, 145.6, 146.4, 161.3. MS: *m*/*z* = 294.06 $[M+Na]^+$. Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16; Found: C, 70.68; H, 6.35; N, 5.27.
*General procedure for the preparation of compound **5a–p**:*
A mixture of **3** (1 mmol.) and appropriate amine (1 equiv) was dissolved in dichloromethane 5 mL. Molecular iodine (10 mol %) was added to the stirring reaction mixture and continued for 30–60 min. After completion of the reaction as monitored by TLC, the reaction mixture was cooled, extracted with dichloromethane (3 × 25 mL) and washed by saturated aqueous sodium thiosulfate. The combined organic extract was washed with brine solution and dried over anhydrous Na_2SO_4. The solvent was distilled off. The crude product was purified by column chromatography over silica gel (60–120 mesh) using appropriate petroleum ether–ethyl acetate mixture as eluent to give compounds (**5a–p**) and (**6a–d**).
7-Ethyl-8,8-dimethyl-10-(naphthalen-1-ylimino)-7,8,9,10-tetrahydro-3H-pyrano[3,2-f]quinolin-3-one: (**5a**) Yellow colored solid; mp 172–174 °C, yield = 92%, IR (KBr): 1564, 1613, 1724 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ_H = 1.16 (s, 6H), 1.28 (t, 3H, *J* = 6.8 Hz), 2.53 (s, 2H), 3.39 (q, 2H, *J* = 6.8 Hz), 6.39

(d, 1H, J = 10.0 Hz), 6.76 (d, 1H, J = 7.2 Hz), 6.99 (d, 1H, J = 9.6 Hz), 7.34 (d, 1H, J = 9.6 Hz), 7.40–7.53 (m, 3H), 7.63 (d, 1H, J = 8.0 Hz), 7.78 (d, 1H, J = 8.4 Hz), 7.88 (d, 1H, J = 8.0 Hz), 9.64 (d, 1H, J = 10.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 15.3, 25.2, 40.4, 42.8, 56.6, 114.1, 116.9, 117.2, 121.0, 123.5, 123.7, 125.7, 125.8, 126.3, 128.0, 143.5, 145.4, 146.3, 146.8, 160.9, 163.8. HRMS: m/z calcd for $C_{26}H_{24}N_2O_2$ $[M+H]^+$: 397.1875; found; 397.1910.

7-Ethyl-8,8-dimethyl-8,9-dihydro-3H-pyrano[3,2-f]quinoline-3,10(7H)-dione: (**6a**) Yield = 6%, light yellow colored solid, mp 156–158 °C. IR (KBr): ν_{max} = 1514, 1720, 2954, 3108 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 1.32 (t, 3H, J = 6.8 Hz), 1.35 (s, 6H), 2.66 (s, 2H), 3.43 (q, 2H, J = 7.36 Hz), 6.47 (d, 1H, J = 10.0 Hz), 7.00 (d, 1H, J = 9.6 Hz), 7.36 (d, 1H, J = 9.6 Hz), 9.38 (d, 1H, J = 10.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 15.3, 24.7, 40.5, 53.0, 58.2, 111.2, 117.7, 118.1, 118.2, 124.2, 142.5, 146.5, 148.8, 160.5, 195.0. MS: m/z = 294 $[M+Na]^+$. Anal. Calcd For $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16; Found: C, 70.66; H, 6.38; N, 5.25.

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