UTILIZATION OF AROMATIC DENITROCYCLIZATION REACTION FOR THE SYNTHESIS OF 3-UNSUBSTITUTED 1,4-DIHYDROQUINOLIN-4-ONE DERIVATIVES

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Synthesis of 3-unsubstituted 1-alkyl- and 1-aryl-1,4-dihydroquinolin-4-ones from 2-nitroacetophenone via the corresponding 3-amino-1-(2-nitrophenyl)prop-2-en-1-ones and -but-2-en-1-ones by denitrocyclization reaction is described. The nucleophilic cyclization was achieved either by sodium hydride or potassium carbonate in DMF.
Keywords: Enaminones; Quinolines; Ketones; Quinolin-4-ones; Aromatic denitrocyclization; Cyclizations.

1,4-Dihydroquinolin-4-one derivatives are well known for their biological activities, the corresponding 3-carboxylic acids referred to antibacterial quinolones being the most prominent examples (for a review on the chemistry of antibacterial quinolones, see[1], for reviews on their biological activities, see[1a,2–4]). It has been recently published that some 3-carboxylic acids[5a] and/or 5-carboxamides[5b] are active against certain viruses, including HIV. Some quinolones without antibacterial activity were found active as mammalian topo-II inhibitors, including a series of 3-unsubstituted compounds[3]. 1-Methyl-1,4-dihydroquinolin-4-one, echinopsine, is a nonpoisonous alkaloid from *Echinops* species, which regulates the function of the parasympathetic autonomous nervous system[6]. Several other 2-substituted derivatives of echinopsine were isolated from natural sources as minor alkaloids and some of them were also found to be biologically active. More information and references can be found under[7].

Several 1-alkyl-3-unsubstituted derivatives were prepared by the decarboxylation of the corresponding 3-carboxylic acids[8]. This method usually requires high temperatures and the reported yields are generally low to medium. Some 1-aryl-3-unsubstituted 1,4-dihydroquinolin-4-ones were also prepared by this method but the yields were generally low[9]. Thermal rear-

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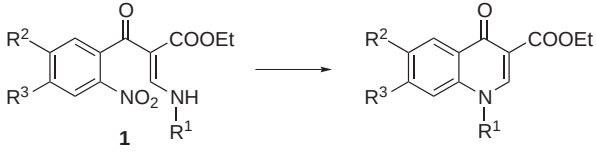
rangement of 4-methoxy- and 4-ethoxyquinoline derivatives can be used for the synthesis of the corresponding 1-methyl- and 1-ethyl-1,4-dihydroquinolin-4-one, respectively[10]. This method requires generally high temperatures (300–350 °C) and the yields are usually low. Lower temperatures and higher yields were reported when the rearrangement was done in the presence of the appropriate iodoalkane[11], alkyl tosylate[12], or trialkyl phosphate[12]. 1-Alkyl-3-unsubstituted 1,4-dihydroquinolin-4-ones having a primary alkyl group at position 1 can also be prepared by *N*-alkylation of the corresponding 1-unsubstituted 1,4-dihydroquinolin-4-ones, i.e. quinolin-4-ols. While the alkylation of 4-oxo-1,4-dihydroquinoline-3-carboxylates generally leads to 1-alkyl derivatives[1], variable amounts of the corresponding *O*-alkylation products are formed by the alkylation of 3-unsubstituted quinolin-4-ols[13]. This method cannot be used for the synthesis of compounds bearing secondary or tertiary alkyl groups as well as aryl groups at position 1.

All of the above methods were found useful in the synthesis of these compounds. However, especially for the structure–activity studies, the need for new methods of the preparation of the 3-unsubstituted compounds is evident. This is true especially for 1-*sec*-alkyl, 1-*tert*-alkyl, and 1-aryl-1,4-dihydroquinolin-4-ones.

Aromatic nucleophilic denitrocyclization reactions, where the nitro group serves as a leaving group, have been successfully emplyed in the synthesis of various heterocyclic compounds (for reviews, see[14]). There are several reports[15] on using this methodology for the synthesis of ethyl 1-alkyl- and 1-(dimethylamino)-4-oxo-1,4-dihydroquinoline-3-carboxylates **2a**–**2c** from the corresponding ethyl 2-(2-nitrobenzoyl)acrylates **1a**–**1c** (Scheme 1). Herein we report that this methodology can also be useful for the synthesis



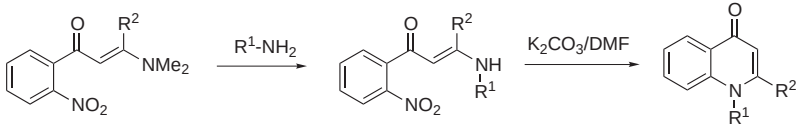
1, 2	R^1	R^2	R^3
a	cyclopropyl	H	NO_2
b	cyclopropyl	F	NO_2
c	NMe_2	H	H

SCHEME 1

of similar 3-unsubstituted derivatives, and we demonstrate this by the synthesis of both 2-unsubstituted- and 2-methyl-1,4-dihydroquinolin-4-ones **5**.

Treatment of acetophenones with *N*,*N*-dialkylamide acetals is a well-known method of the preparation of the corresponding enaminones. In several cases, the *E* configuration was confirmed by various methods including X-ray crystallography[16]. Their reactions with primary amines easily provide the corresponding enaminones bearing secondary amino groups. These compounds can exist in both *E* and *Z* forms and exhibit interesting behavior in solutions, where they undergo configurational and conformational changes depending on the solvent used and/or substituents attached to the conjugated π-bonds, as discussed in[17]. Zhuo[18] reported that these forms can be easily distinguished by their ^{1}H NMR spectra since the N-H signals of the *E* form appear at a much higher field (4–8 ppm) than those of the *Z* form (9–13 ppm). This difference was explained by the strong intramolecular hydrogen bonding in the *Z* form. Various chemical shift differences of the *E* and *Z* forms have been previously observed in their ^{13}C [19], ^{15}N [19d,20], and ^{17}O NMR spectra[18] as well.

Our synthetic procedure is depicted in Scheme 2. The starting 2-nitroacetophenone provided a good yield of **3a** on treatment with *N*,*N*-dimethylformamide dimethyl acetal. The same reaction with *N*,*N*-dimethylacetamide dimethyl acetal led to a dark mixture, from which only medium yields of **3b** were isolated by flash chromatography. These compounds, treated with simple amines, e.g. methyl- or ethylamine, provided high yields of the corresponding intermediates **4**. Quite surprisingly, compound



3a, R = H
3b, R = Me

4 **5**

4, 5	R^1	R^2
a	Me	H
b	Et	H
c	cyclopropyl	H
d	*t*-Bu	H
e	Ph	H
f	Me	Me
g	Et	Me
h	cyclopropyl	Me
i	*t*-Bu	Me
j	Ph	Me

SCHEME 2

3b was found more reactive towards simple alkylamines, such as methyl- and ethylamine, than compound **3a**. When the reaction was carried out at room temperature, it was complete after 24 h with compound **3b**, while the corresponding process with compound **3a** required about 10 days. However, the reaction was very sensitive to the steric requirement of the alkyl group. The corresponding *N*-cyclopropyl derivatives **4c** and **4h**, as well as *N*-*tert*-butyl derivatives **4d** and **4i**, were obtained in low to moderate yields only after prolonged heating with amine solutions in a sealed tube. With cyclopropylamine at 85 °C, compound **3b** was completely consumed after 12 h, while with **3a** the necessary reaction time was about 14 days. The more sterically demanding *tert*-butylamine, treated with **3a** under the above mentioned conditions, required 14 days. The same reaction with **3b** did not provide compound **4i**; the starting material was gradually consumed, providing only polymeric products. However, treating at 50 °C provided a mixture of the starting compound and the required compound **4i** after 50 days; flash chromatography of the mixture afforded **4i** in 57% yield. On the other hand, no substantial differences in the reactivity of compounds **3a** and **3b** with aniline was observed. The reaction was done with acetic acid as a catalyst, and the corresponding *N*-phenyl derivatives **4e** and **4j** were obtained in high yields. It is well known for closely related compounds that both *E* and *Z* forms can be detected in solution, depending on the solvent, temperature and other factors[17–20]. In the ^{1}H NMR spectra of all compounds **4** measured in $CDCl_3$, the signals corresponding to the N–H group, if detected, were observed in the range of 10.8–11.6 ppm, indicating that the *Z* form strongly prevails under the given conditions[17]. This is especially true for but-2-en-1-one derivatives **4f**–**4i**. In the case of prop-2-en-1-ones, the *E* and *Z* isomer content can be exactly determined by the *J* values of the CO-C**H**=C**H** protons, the values for the *Z* and *E* forms being in the range of 7.2–7.5 and 12.5–12.9 Hz, respectively.

The cyclization of compounds **4** leading to **5** was slower than with the corresponding (2-nitrobenzoyl)acetates and the yields were lower under the same conditions. Nevertheless, useful yields of the corresponding 1,4-dihydroquinolin-4-ones **5** could be obtained in a number of cases. The ease of the cyclization was found to be dependent on the steric requirements of the *N*-1 substituents; *N*-methyl, *N*-ethyl and *N*-phenyl substituted compounds cyclized under much milder conditions than those bearing *N*-cyclopropyl and *N*-*tert*-butyl substituents. We usually used potassium carbonate–DMF at elevated temperatures; heating to 100 °C (method *A*) was satisfactory for the synthesis of both 2-unsubstituted quinolones, e.g. **5a**, **5b**, **5c** and **5e**, and their 2-methyl derivatives, e.g. **5f**, **5g**, **5h** and **5j**. However, the reaction

time necessary for the cyclization of *N*-cyclopropyl derivative **4c** to **5c** was about 24 h, while the corresponding *N*-methyl and *N*-ethyl derivatives required only 2–4 h for complete cyclization. However, the reaction at reflux DMF (method *B*) led to complete cyclization of **4c** and **4h** in 8 h. These conditions were not sufficient for the cyclization of *N*-*tert*-butyl derivatives **4d** and **4i**, and we failed to develop a useful cyclization protocol that would lead to compounds **5d** and **5i**. In several cases, e.g. preparation of **5b** and **5e**, sodium hydride–DMF at room temperature (method *C*) was also used. Summary of the obtained yields of compounds **4** and **5** is given in Table I.

In summary, we have explored the scope and utility of the aromatic nucleophilic denitrocyclization reaction for the synthesis of 1,4-dihydroquinolin-4-ones. The method is especially useful for the synthesis of 1-aryl- and 1-alkyl-1,4-dihydroquinolin-4-ones bearing primary alkyl groups at position 1.

EXPERIMENTAL

Melting points were measured on a Kofler block and are uncorrected. The IR spectra were measured on a Perkin Elmer Spectrum BX FT-IR device in KBr pellets, wavenumbers are given in cm^{-1}. The UV spectra were recorded on a Shimadzu UV-260 spectrophotometer in the range 190–400 nm. ^1H NMR spectra were recorded on a Bruker instrument (250 MHz) in $CDCl_3$, if not otherwise stated. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. The purity of the substances prepared was evaluated by TLC on silica gel

TABLE I
Yields of compounds **4** and **5**

R^1	R^2	Compound	Yield of **4**, %	Compound	Yield of **5**, % (method)
H	Me	**4a**	85	**5a**	94 (*A*)
H	Et	**4b**	91	**5b**	76 (*A*), 74 (*C*)
H	Cyclopropyl	**4c**	76	**5c**	61 (*A*), 57 (*B*)
H	*t*-Bu	**4d**	55	**5d**	–
H	Ph	**4e**	80	**5e**	66 (*A*), 68 (*C*)
Me	Me	**4f**	90	**5f**	81 (*A*), 83 (*B*)
Me	Et	**4g**	81	**5g**	80 (*B*)
Me	Cyclopropyl	**4h**	91	**5h**	85 (*B*)
Me	*t*-Bu	**4i**	50	**5i**	72 (*A*)
Me	Ph	**4j**	74	**5j**	–

(FP KG F 254, Merck). Flash chromatography was performed on silica gel Merck, particle size 0.04–0.063 mm.

(*E*)-3-(Dimethylamino)-1-(2-nitrophenyl)prop-2-en-1-one (**3a**)

A mixture of 2-nitroacetophenone (8.25 g, 50 mmol), *N*,*N*-dimethylformamide dimethyl acetal (9 g, 75 mmol) and toluene (100 ml) was heated at reflux under nitrogen for 20 h, then an additional amount of the acetal was added (3 g, 25 mmol) and the reaction continued for additional 30 h. The mixture was cooled and left to stand in a refrigerator overnight. The separated yellow crystals were filtered off to provide 72% yield of **3a**; m.p. 126–129 °C (lit.[21], 127–130 °C). For $C_{11}H_{12}N_2O_3$ (220.2) calculated: 59.99% C, 5.49% H, 12.72% N; found: 59.65% C, 5.33% H, 13.01% N. IR: 1638.4 (C=O); 1526.6, 1362.6, 777.4 (NO_2). UV (ethanol), λ_{max} (log ε): 301.8 (4.56), 205.6 (4.77). ^{1}H NMR ($CDCl_3$): 2.87 bs, 3 H (CH_3); 3.09 bs, 3 H (CH_3); 5.28 d, J_{trans} = 12.6, 1 H (CO-CH=); 7.38–7.63 m, 4 H (arom. H, -CH=); 7.91 m, 1 H (H-3′).

(*E*)-3-(Dimethylamino)-1-(2-nitrophenyl)but-2-en-1-one (**3b**)

By the same procedure as described for the preparation of **3a**, but using *N*,*N*-dimethylacetamide dimethyl acetal, a dark reaction mixture containing **3b** was obtained after a 50-h reaction time. Toluene was evaporated and the residue purified by flash chromatography (hexane–ethyl acetate, 2:1). The selected combined fractions provided 54% yield of **3b** as slightly orange crystals after crystallization from ethyl acetate; m.p. 115–116 °C. For $C_{12}H_{14}N_2O_3$ (234.3) calculated: 61.53% C, 6.02% H, 11.96% N; found: 61.37% C, 5.82% H, 12.27% N. IR: 1606.1 (C=O); 1515.9, 1353.3, 778.8 (NO_2). UV (ethanol), λ_{max} (log ε): 317.6 (4.38), 208.2 (4.93). ^{1}H NMR ($CDCl_3$): 2.64 s, 3 H (CH_3); 3.03 bs, 6 H ((CH_3)$_2$N); 5.13 s, 1 H (-CH=); 7.39–7.61 m, 3 H (arom. H); 7.86 dd, *J* = 8.0, 0.9, 1 H (H-3′).

3-(Methylamino)- and 3-(Ethylamino)-1-(2-nitrophenyl)alk-2-en-1-ones **4a**, **4b**, **4f**, and **4g**. General Procedure

Compound **3a** or **3b** (10 mmol) was added to a 10% solution of the corresponding amine in ethanol (50 ml) and the mixture was left to stand at room temperature in a sealed flask. When the reaction was complete (TLC; hexane–acetone, 7:3), the mixture was evaporated and the residue was crystallized from ethanol to provide yellow crystalline products.

3-(Methylamino)-1-(2-nitrophenyl)prop-2-en-1-one (**4a**). Reaction time 10 days, yield 85%; m.p. 114–120 °C. For $C_{10}H_{10}N_2O_3$ (206.2) calculated: 58.25% C, 4.89% H, 13.59% N; found: 57.93% C, 4.73% H, 13.81% N. IR: 3261.3 (amine); 1617.9 (C=O); 1553.6, 1275.0, 782.2 (NO_2). UV (ethanol), λ_{max} (log ε): 296.6 (4.23), 202.0 (4.11). ^{1}H NMR ($CDCl_3$ + DMSO-d_6): 2.79 bs, 3 H (CH_3); 5.30 d, J_{cis}= 7.5, ≈0.1 H (CO-CH=); 5.39 d, J_{trans} = 12.9, ≈0.9 H (CO-CH=); 6.80 b, 1 H (NH); 7.47–7.67 m, 4 H (arom. H, -CH=); 7.96 d, *J* = 7.9, 1 H (H-3′).

3-(Ethylamino)-1-(2-nitrophenyl)prop-2-en-1-one (**4b**). Reaction time 10 days, yield 91%; m.p. 119–121 °C. For $C_{11}H_{12}N_2O_3$ (220.2) calculated: 59.99% C, 5.49% H, 12.72% N; found: 59.79% C, 5.56% H, 12.85% N. IR: 3247.5 (amine); 1606.3 (C=O); 1518.0, 1271.5, 782.2 (NO_2). UV (ethanol), λ_{max} (log ε): 301.0 (4.23), 207.4 (4.72). ^{1}H NMR (DMSO-d_6): 1.28 t, *J* = 7.2, 3 H (CH_3); 3.37 m, 2 H (CH_2); 5.30 d, J_{cis} = 7.2, ≈0.65 H (CO-CH=); 5.37 d, J_{trans} = 12.6, ≈0.35 H (CO-CH=); 7.09 dd, *J* = 7.3, 13.3, 1 H (-CH=); 7.47–7.63 m, 3 H (arom. H); 7.78 m, 1 H (H-3′), 10.06 bs, ≈0.85 H (NH).

3-(Methylamino)-1-(2-nitrophenyl)but-2-en-1-one (**4f**). Reaction time 24 h, yield 90%; m.p. 133–136 °C. For $C_{11}H_{12}N_2O_3$ (220.2) calculated: 59.99% C, 5.49% H, 12.72% N; found: 59.63% C, 5.59% H, 12.47% N. IR: 3195.7 (amine); 1599.0 (C=O); 1543.1, 1324.4, 763.3 (NO_2). UV (ethanol), λ_{max} (log ε): 318.2 (4.20), 203.4 (4.13). ^{1}H NMR ($CDCl_3$): 2.03 s, 3 H (CH_3); 3.01 d, *J* = 5.3, 3 H (CH_3); 5.27 s, 1 H (-CH=); 7.44–7.56 m, 3 H (arom. H); 7.78 m, 1 H (H-3′); 11.00 bs, ≈1 H (NH).

3-(Ethylamino)-1-(2-nitrophenyl)but-2-en-1-one (**4g**). Reaction time 24 h, yield 81%; m.p. 88–90 °C. For $C_{12}H_{14}N_2O_3$ (234.3) calculated: 61.53% C, 6.02% H, 11.96% N; found: 61.29% C, 5.73% H, 12.31% N. IR: 3088.0 (amine); 1597.8 (C=O); 1555.5, 1312.0, 744.0 (NO_2). UV (ethanol), λ_{max} (log ε): 318.8 (4.22), 203.6 (4.14). ^{1}H NMR ($CDCl_3$): 1.27 t, *J* = 7.3, 3 H (ethyl CH_3); 2.03 s, 3 H (CH_3); 3.35 dq, *J* = 7.3, 5.8, 2 H (CH_2); 5.23 s, 1 H (-CH=); 7.40–7.60 m, 3 H (arom. H); 7.77 ddd, *J* = 7.9, 1.2, 0.6, 1 H (H-3′); 11.00 bs, ≈1 H (NH).

3-(Cyclopropylamino)- and 3-(*tert*-Butylamino)-1-(2-nitrophenyl)alk-2-en-1-ones **4c**, **4d**, and **4h**. General Procedure

A mixture of **3a** (1.1 g, 5 mmol), the corresponding amine (1 g) and methanol (15 ml) was magnetically stirred in a sealed tube (pressure tube with threaded plug, Aldrich) at bath temperature 85 °C for 12 h (**4h**), 14 h (**4c**) or 20 days (**4d**) . The residue after solvent evaporation was purified by flash chromatography (hexane–acetone, 20:1) and crystallized from appropriate solvents to provide the products as yellow crystals. In the case of **4d**, 35% of unreacted starting compound **3a** was recovered.

3-(Cyclopropylamino)-1-(2-nitrophenyl)prop-2-en-1-one (**4c**). Yield 76%; m.p. 129–134 °C (ethanol). For $C_{12}H_{12}N_2O_3$ (232.2) calculated: 62.06% C, 5.21% H, 12.06% N; found: 61.93% C, 5.07% H, 12.34% N. IR: 3249.9 (amine); 1605.5 (C=O); 1516.7, 1271.5, 781.0 (NO_2). UV (ethanol), λ_{max} (log ε): 297.6 (4.23), 210.6 (4.09). ^{1}H NMR ($CDCl_3$): 0.51–0.85 m, 4 H (CH_2); 2.48 m, 1 H (cyclopropyl CH); 5.66 bd, J_{trans} = 12.5, 1 H (-CH=); 7.30 b, ≈1 H (NH); 7.48–7.65 m, 4 H (arom. H, -CH=); 7.93 d, *J* = 7.8, 1 H (H-3′).

3-(tert-Butylamino)-1-(2-nitrophenyl)prop-2-en-1-one (**4d**). Yield 55%; m.p. 71–73 °C (cyclohexane). For $C_{13}H_{16}N_2O_3$ (248.3) calculated: 62.89% C, 6.50% H, 11.28% N; found: 62.62% C, 6.28% H, 11.53% N. IR: 3088.4 (amine); 1624.2 (C=O); 1530.3, 1230.4, 782.4 (NO_2). UV (ethanol), λ_{max} (log ε): 301.8 (4.56), 205.6 (4.77). ^{1}H NMR ($CDCl_3$ + ≈15% DMSO-d_6): 1.36 s, 9 H (CH_3); 5.29 d, J_{cis} = 7.3, ≈0.95 H (-CH=); 5.52 d, J_{trans} =12.5, ≈0.05 H (-CH=); 7.14 ddd, *J* = 13.6, 7.4, 0.8, 1 H (N-CH=); 7.45–7.64 m, 3 H (arom. H); 7.79 d, *J* = 7.9, 1 H (H-3′); 10.38 bd, 1 H (NH).

3-(Cyclopropylamino)-1-(2-nitrophenyl)but-2-en-1-one (**4h**). Yield 91%; m.p. 99–102 °C (ethanol). For $C_{13}H_{14}N_2O_3$ (246.3) calculated: 63.40% C, 5.73% H, 11.38% N; found: 63.03% C, 5.55% H, 11.52% N. IR: 3050.7 (amine); 1599.0 (C=O); 1530.3, 1313.5, 739.0 (NO_2). UV (ethanol), λ_{max} (log ε): 321.6 (4.21), 203.2 (4.15). ^{1}H NMR ($CDCl_3$): 0.74 m, 2 H (CH_2); 0.85 m, 2 H (CH_2); 2.17 d, 3 H (CH_3); 2.69 m, 1 H (cyclopropyl CH); 5.26 s, 1 H (-CH=); 7.45 ddd, *J* = 7.9, 6.8, 2.1, 1 H (H-4′); 7.50 ddd, *J* = 7.6, 2.1, 0.5, 1 H (H-6′); 7.56 ddd, *J* = 7.7, 6.8, 1.3, 1 H (H-5′); 7.80 ddd, *J* = 7.9, 1.3, 0.5, 1 H (H-3′); 10.86 bs, ≈1 H (NH).

3-(*tert*-Butylamino)-1-(2-nitrophenyl)but-2-en-1-one (**4i**)

A mixture of **3b** (1.17 g, 5 mmol), *tert*-butylamine (2 g) and methanol (15 ml) was magnetically stirred in a sealed tube (pressure tube with threaded plug, Aldrich) at bath temperature 50 °C for 50 days. According to TLC (hexane–acetone, 7:3), the mixture contained the start-

ing compound **3b** and a new spot. The residue after evaporation was separated by flash chromatography (hexane–acetone, 20:1) providing unreacted **3b** (0.42 g; 36%) and **4i** (0.66 g; 57%). The crude compound **4i** was crystallized from hexane to provide yellow crystals (0.58 g; 50%); m.p. 101–106 °C. For $C_{14}H_{18}N_2O_3$ (232.2) calculated: 64.11% C, 6.92% H, 10.68% N; found: 64.48% C, 6.77% H, 10.96% N. IR: 3079.7 (amine); 1595.3 (C=O); 1526.7, 1335.2, 749.9 (NO_2). UV (ethanol), λ_{max} (log ε): 324.6 (4.15), 207.8 (4.01). ^{1}H NMR ($CDCl_3$): 1.47 s, 9 H (CH_3); 2.17 s, 3 H (CH_3); 5.13 s, 1 H (-CH=); 7.27–7.55 m, 3 H (arom. H); 7.80 ddd, *J* = 8.0, 1.2, 0.6, 1 H (H-3′); 11.49 bs, ≈1 H (NH).

3-(Arylamino)-1-(2-nitrophenyl)alk-2-en-1-ones **4e** and **4j**. General Procedure

A mixture of **3a** or **3b** (10 mmol), aniline (1 g, 11 mmol), ethanol (20 ml), and acetic acid (1 ml) was heated at reflux for 20 h. The mixture was then cooled down and left to stand in a refrigerator overnight. The insoluble portion was filtered off and crystallized from ethanol (**4e**) or washed with ether (**4j**) to give the products as slightly yellow or brownish crystals.

3-Anilino-1-(2-nitrophenyl)prop-2-en-1-one (**4e**). Yield 80%; m.p. 123–128 °C (ethanol). For $C_{15}H_{12}N_2O_3$ (268.3) calculated: 67.16% C, 4.51% H, 10.44% N; found: 66.87% C, 4.76% H, 10.68% N. IR: 124.2 (C=O); 1527.5, 1284.1, 747.2 (NO_2). UV (ethanol), λ_{max} (log ε): 351.6 (4.30), 202.8 (4.30). ^{1}H NMR ($CDCl_3$): 5.56 d, J_{cis} = 7.7, 1 H (-CH=); 7.07–7.17 m, 3 H (arom. H); 7.32–7.40 m, 2 H (arom. H); 7.44–7.68 m, 4 H (arom. H, N-CH=); 7.90 ddd, *J* = 7.9, 1.2, 0.6, 1 H (H-3′); 11.79 bd, ≈1 H (NH). ^{1}H NMR (DMSO-d_6): 5.76 d, J_{cis}= 7.8, ≈0.55 H (-CH=); 5.91 d, J_{trans} = 12.9, ≈0.45 H (-CH=); 6.98–7.20 m, 2 H (arom. H); 7.27–7.45 m, 3 H (arom. H); 7.61–7.88 m, 4 H (arom. H, N-CH=); 7.93–8.07 m, 1 H (H-3′); 10.22 bd, *J* = 13.0, ≈0.45 H (NH); 11.64 bd, *J* = 12.9, ≈0.55 H (NH).

3-Anilino-1-(2-nitrophenyl)but-2-en-1-one (**4j**). Yield 74%; m.p. 113–115 °C. For $C_{16}H_{14}N_2O_3$ (282.3) calculated: 68.08% C, 5.00% H, 9.92% N; found: 67.79% C, 5.33% H, 10.31% N. IR: 1591.7 (C=O); 1523.1, 1317.1, 757.1 (NO_2). UV (ethanol), λ_{max} (log ε): 310.4 (4.24), 202.2 (4.33). ^{1}H NMR ($CDCl_3$): 2.09 s, 3 H (CH_3); 5.45 s, 1 H (-CH=); 7.14–7.30 m, 3 H (arom. H); 7.38–7.59 m, 5 H (arom. H); 7.86 d, *J* = 7.9, 1 H (H-3′); 12.62 bs, 1 H (NH).

1-Substituted 1,4-Dihydroquinolin-4-one **5a**–**5**. General Procedures

A) A mixture of **4** (2 mmol), dry potassium carbonate (0.5 g) and dry dimethylformamide (5 ml) was stirred at 100 °C for 2–8 h (TLC monitoring). The mixture was then evaporated to dryness, the residue was triturated with water (10 ml) and extracted with dichloromethane (5 × 10 ml). The combined extracts were washed with brine (10 ml) and water (10 ml) and dried with anhydrous magnesium sulfate. If necessary, the residue after evaporation was dissolved in methanol (25 ml) and decolorized with charcoal. Crystallization from suitable solvents then provided white to off-white crystalline products.

B) The same mixture was stirred at reflux temperature and worked-up as in method *A*.

C) Sodium hydride (50% suspension in mineral oil; 0.25 g, 5 mmol) was added to a stirred solution of the corresponding compound **4** (2 mmol) in dimethylformamide (10 ml) and the resultant mixture was stirred at room temperature for 1 h and then at 100 °C for 2 h. The cold mixture was poured into water (100 ml) and the mixture was worked-up as in *A*).

1-Methyl-1,4-dihydroquinolin-4-one (**5a**). Yield 94% (method *A*); m.p. 150–152 °C (toluene) (lit.[22a], 151 °C; lit.[22b], 152 °C). For $C_{10}H_9NO$ (159.2) calculated: 75.45% C, 5.70% H, 8.80% N; found: 75.16% C, 5.33% H, 8.43% N. IR: 1648.8 (C=O). UV (ethanol), λ_{max} (log ε):

337.6 (4.16), 324.4 (4.11), 238.0 (4.25), 212.0 (4.41). ^{1}H NMR ($CDCl_3$): 3.79 s, 3 H (CH_3); 6.25 d, *J* = 7.7, 1 H (H-3); 7.38 m, 1 H (arom. H); 7.40 m, 1 H (arom. H); 7.50 d, *J* = 7.7, 1 H (H-2); 7.68 m, 1 H (arom. H); 8.45 m, 1 H (H-5).

1-Ethyl-1,4-dihydroquinolin-4-one (**5b**). Yields 76% (method *A*) and 74% (method *C*); m.p. 101–103 °C (hexane) (lit.[23], 100–102 °C; lit.[22a], 102–103 °C). For $C_{11}H_{11}NO$ (173.2) calculated: 76.28% C, 6.40% H, 8.09% N; found: 75.86% C, 6.47% H, 7.89% N. IR: 1620.6 (C=O). UV (ethanol), λ_{max} (log ε): 338.0 (4.19), 324.8 (4.15), 237.8 (4.30), 213.0 (4.43). ^{1}H NMR ($CDCl_3$): 1.47 t, *J* = 7.2, 3 H (CH_3); 4.16 q, *J* = 7.2, 2 H (CH_2); 6.24 d, *J* = 7.7, 1 H (H-3); 7.35 m, 1 H (arom. H); 7.43 d, *J* = 8.5, 1 H (H-8); 7.54 d, *J* = 7.8, 1 H (H-2); 7.65 m, 1 H (arom. H); 8.45 dd, *J* = 8.1, 0.5, 1 H (H-5).

1-Cyclopropyl-1,4-dihydroquinolin-4-one (**5c**). Yields 61% (method *A*) and 57% (method *B*); m.p. 85–88 °C (cyclohexane). For $C_{12}H_{11}NO$ (185.3) calculated: 77.81% C, 5.99% H, 7.56% N; found: 77.57% C, 6.12% H, 7.73% N. IR: 1613.4 (C=O). UV (ethanol), λ_{max} (log ε): 336.6 (4.20), 3234.4 (4.14), 238.4 (4.28), 212.8 (4.39). ^{1}H NMR ($CDCl_3$): 1.06 m, 2 H (CH_2); 1.28 m, 2 H (CH_2); 3.39 m, 1 H (cyclopropyl CH); 6.22 d, *J* = 7.8, 1 H (H-3); 7.39 m, 1 H (arom. H); 7.68 m, 1 H (arom. H); 7.68 d, *J* = 7.8, 1 H (H-2); 7.91 ddd, *J* = 8.6, 1.0, 0.6, 1 H (H-8); 8.42 ddd, *J* = 8.1, 1.7, 0.5, 1 H (H-5).

1-Phenyl-1,4-dihydroquinolin-4-one (**5e**). Yields 66% (method *A*) and 68% (method *C*); m.p. 118–123 °C (ethyl acetate). For $C_{15}H_{11}NO$ (221.3) calculated: 81.43% C, 5.01% H, 6.33% N; found: 81.22% C, 5.29% H, 6.01% N. IR: 1628.7 (C=O). UV (ethanol), λ_{max} (log ε): 335.8 (4.25), 323.4 (4.20), 239.0 (4.31), 209.0 (4.85). ^{1}H NMR ($CDCl_3$): 6.37 d, *J* = 7.8, 1 H (H-3); 7.00 ddd, *J* = 8.5, 1.1, 0.5, 1 H (H-8); 7.60 d, *J* = 7.8, 1 H (H-2); 7.32–7.65 m, 7 H (arom. H); 8.47 ddd, *J* = 8.0, 1.7, 0.5, 1 H (H-5).

1,2-Dimethyl-1,4-dihydroquinolin-4-one (**5f**). Yields 81% (method *A*) and 83% (method *B*); m.p. 176–178 °C (toluene) (lit.[24a], 174–175 °C; lit.[10b], 175 °C; lit.[24b], 177.5–178 °C). For $C_{11}H_{11}NO$ (173.2) calculated: 76.28% C, 6.40% H, 8.09% N; found: 76.11% C, 6.13% H, 8.24% N. IR: 1595.3 (C=O). UV (ethanol), λ_{max} (log ε): 335.4 (4.14), 322.2 (4.12), 239.4 (4.38), 211.8 (4.47). ^{1}H NMR ($CDCl_3$): 2.42 d, *J* = 0.4, 3 H (CH_3); 3.68 s, 3 H (N-CH_3); 6.16 d, *J* = 0.4, 1 H (H-3); 7.34 m, 1 H (H-6); 7.44 d, *J* = 8.5, 1 H (H-8); 7.62 m, 1 H (H-7); 8.41 ddd, *J* = 8.0, 1.7, 0.4, 1 H (H-5).

1-Ethyl-2-methyl-1,4-dihydroquinolin-4-one (**5g**). Yield 80% (method *B*); m.p. 116–118 °C (ethyl acetate). For $C_{12}H_{13}NO$ (187.2) calculated: 76.98% C, 7.00% H, 7.48% N; found: 76.54% C, 6.83% H, 7.66% N. IR: 1595.3 (C=O). UV (ethanol), λ_{max} (log ε): 335.0 (4.15), 321.8 (4.17), 239.2 (4.37), 210.0 (4.67). ^{1}H NMR ($CDCl_3$): 1.43 t, *J* = 7.2, 3 H (ethyl CH_3); 2.48 s, 3 H (CH_3); 4.22 q, *J* = 7.2, 2 H (CH_2); 6.21 s, 1 H (H-3); 7.35 m, 1 H (H-6); 7.49 d, *J* = 8.7, 1 H (H-8); 7.65 m, 1 H (H-7); 8.45 dd, *J* = 8.0, 1.7, 1 H (H-5).

1-Cyclopropyl-2-methyl-1,4-dihydroquinolin-4-one (**5h**). Yield 85% (method *B*); m.p. 164–168 °C (ethyl acetate). For $C_{13}H_{13}NO$ (199.3) calculated: 78.36% C, 6.58% H, 7.03% N; found: 78.05% C, 6.37% H, 7.29% N. IR: 1595.3 (C=O). UV (ethanol), λ_{max} (log ε): 333.8 (4.16), 321.8 (4.13), 239.2 (4.39), 215.2 (4.32). ^{1}H NMR ($CDCl_3$): 0.96 m, 2 H (CH_2); 1.39 m, 2 H (CH_2); 2.57 d, *J* = 0.6, 3 H (CH_3); 3.21 m, 1 H (cyclopropyl CH); 6.16 d, *J* = 0.6, 1 H (H-3); 7.31 m, 1 H (H-6); 7.59 m, 1 H (H-7); 7.87 ddd, *J* = 8.7, 1.0, 0.5, 1 H (H-8); 8.36 ddd, *J* = 8.0, 1.7, 0.5, 1 H (H-5).

2-Methyl-1-phenyl-1,4-dihydroquinolin-4-one (**5j**). Yield 72% (method *A*); m.p. 265–267 °C (ethyl acetate). For $C_{16}H_{13}NO$ (235.3) calculated: 81.68% C, 5.57% H, 5.95% N; found: 81.19% C, 5.33% H, 6.29% N. IR: 1622.7 (C=O). UV (ethanol), λ_{max} (log ε): 332.6 (4.22), 320.0 (4.19), 238.8 (4.38), 209.0 (4.49). ^{1}H NMR ($CDCl_3$): 2.07 s, 3 H (CH_3); 6.33 s, 1 H

(H-3); 6.68 d, *J* = 8.5, 1 H (H-8); 7.30 m, 3 H (arom. H); 7.41 m, 1 H (H-7); 7.63 m, 3 H (arom. H); 8.43 dd, *J* = 8.0, 1.6, 1 H (H-5).

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