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An efficient synthesis of N1-substituted 2,5-dioxo-1,2,5,6,7,8-hexahydro-3-quinolinecarboxamide via enolate salts

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Abstract

Various 2-(2-cyano-2-carbamoyl-1-ethenyl)-5,5-dimethyl-3-oxo-1-cyclohexen-1-olates substituted in the amide group with dialkylammonium or sodium cations were prepared via reactions of N-substituted cyanoacetamides with dimedone–DMFDMA adduct by a one-pot, two-step protocol. The salts obtained were used in reactions with N-nucleophiles for further synthesis of the N1-substituted 2,5-dioxo-1,2,5,6,7,8-hexahydro-3-quinolinecarboxamides that are analogues of well-known pharmaceuticals. The structure of the salts and the N1-substituted 2,5-dioxo-1,2,5,6,7,8-hexahydro-3-quinolinecarboxamides was established by means of spectroscopic and X-ray diffraction studies.

Keywords: 2-Pyridones; Dimedone; Enolates; Primary amines

1. Introduction

Compounds that contain the 2-pyridone ring exhibit different biological activities. For instance, pirfenidone **1** is an inhibitor of cytokines, which can cause death during serious inflammation[1] (Chart 1). Huperzine A **2** is a natural alkaloid that possesses cholinesterase inhibitor properties. This drug has been used worldwide for decades as a short-term memory enhancer and also in Alzheimer's disease treatment.[2,3] Ciclopirox **3** possesses antifungal activity.[4] Some 2-pyridone derivatives are also reported to be inotropic agents,[5,6] specific non-nucleoside reverse transcriptase inhibitors of human immunodeficiency virus-1 (HIV-1),[7,8] and other valuable biologically active agents.[9,10] Therefore, the synthesis of novel compounds on the basis of a 2-pyridone scaffold attracts considerable attention.[11]

One of the approaches to a range of 2-pyridone derivatives **6** uses the reactivity of methylene active nitriles **4** in their reactions with dicarbonyl compound–DMFDMA adducts **5**[12] (Scheme 1). In this reaction, however, in several cases, uncyclised salts that include 4-cyano-1,3-butadienolate moiety,

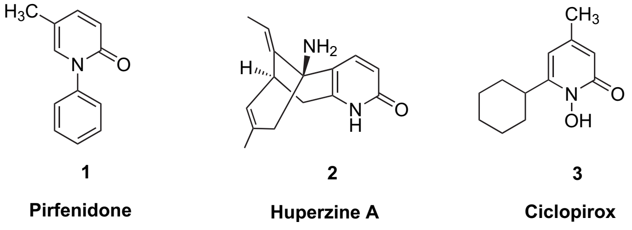
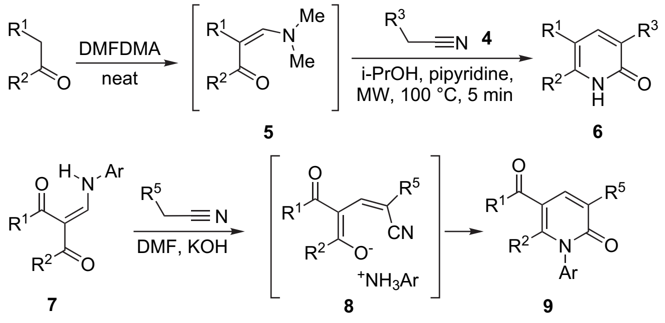


Chart 1.



Scheme 1.

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e.g., **8** (Scheme 1) were obtained as byproducts or intermediates. Analogous salts were also isolated in a number of other works.[13–23] In spite of the obvious synthetical potential of these salts, they were utilized mostly for intramolecular cyclization into the pyridones **6** or, after their hydrolysis, into 2-pyranone derivatives,[14,15,19] whereas such cyclization with participation of N-nucleophiles could lead to more diverse range of 1N-substituted 2-pyridones **9**. Thus, Ziegler and Wolfbeis postulated the formation of enolates **8** in the course of the synthesis of 1N-substituted 2-pyridones **9** starting from enamines **7** (Scheme 1). This reaction was carried out applying malonodinitrile and ethyl cyanoacetate as methylene active nitriles in a strong base medium.[18] Unfortunately, an application of more diverse building blocks such as substituted cyanoacetamides in this reaction is unlikely to be successful because, under the strong base conditions, the intramolecular cyclization may involve the amide group.[24,25]

In continuation of the work,[12] we aimed to develop a facile and efficient method for preparation of various salts **8** in the current study, and to apply these enolates as starting materials for synthesis of the N1-substituted 2,5-dioxo-1,2,5,6,7,8-hexahydro-3-quinolinecarboxamide derivatives. Whereas in the previous work,[12] attention was focused on diversity of the dicarbonyl compounds and methylene active nitriles; in the current study the 2-pyridone derivatives are diversified by various N-substituted cyanacetanilides[26,12] and aromatic/heteroaromatic amines applying dimedone as a representative dicarbonyl compound.

2. Results and discussion

The preparation of the desired salts **14** was carried out in one-pot by the reaction of dimedone **10**, dimethylformamide dimethylacetal (DMFDMA) **11**, and N-substituted cyanacetamides **13** in the presence of a base at room temperature (Scheme 2). It is necessary to perform this synthesis starting from the reaction of dimedone **10** with DMFDMA **11**, for it was shown[12] that the product of reaction between DMFDMA **11** and methylene active nitrile **13** did not react with dimedone **10**. At room temperature, the salt formation proceeded fast enough without formation of the undesired cyclization product **6**. The enolates **14** were isolated as pale yellow precipitates by simple filtration from the reaction mixture in moderate to good yields (Table 1) and used in further transformations without additional purification. The salts are stable in the solid state at least during shelf-storage for a month, however, in DMSO-d_6 solution they slowly decompose. When piperidine is used as a base in catalytic amounts, dimethylammonium salts **14b**,**c** are formed. Generally, by varying the nature of the prevalent base in the reaction mixture, it is possible to obtain the enolates **14a–j** with different cations (sodium, dimethylammonium, piperidinium cations). However, in the case of the cyanoacetamide **13** (R=H) the dimethylammonium enolate **14b** (R=H) was formed in fair amounts in the course of our attempts to synthesize a corresponding piperidinium salt, in spite of considerable prevalence of piperidine in the reaction mixture. Also, in the case of aromatic substituent R in the amide group, the application of sodium ethylate as a basic medium did not lead to isolation of the desired sodium salts.

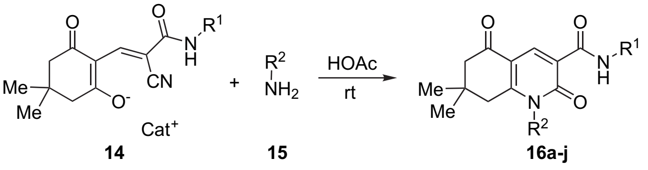
Table 1
The isolated yields for the enolates **14a–j**

	R	Cat$^+$	Yield (%)
14a[a]	H	Na^+	62
14b[b]	H	$Me_2NH_2^+$	90
14c[b]	Me	$Me_2NH_2^+$	67
14d[a]	Me	Na^+	29
14e[c]	Me	$(CH_2)_5NH_2^+$	52
14f[c]	$CH_2C_6H_5$	$(CH_2)_5NH_2^+$	62
14g[a]	$CH_2C_6H_5$	Na^+	20
14h[c]	3-Me–C_6H_4	$(CH_2)_5NH_2^+$	50
14i[c]	2-MeO–C_6H_4	$(CH_2)_5NH_2^+$	56
14j[c]	2-Thiazolyl	$(CH_2)_5NH_2^+$	77

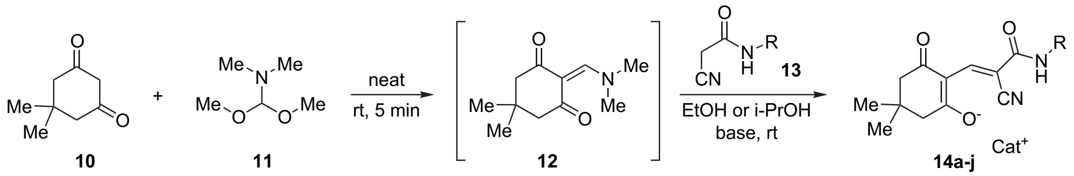
[a] Reaction conditions: EtOH, Na (1 equiv).
[b] *i*-PrOH, piperidine (0.03 equiv).
[c] *i*-PrOH, piperidine (2 equiv).

It should be pointed, that this one-pot reaction applies the same starting materials (**10**, **11**, **13**) that under microwave irradiation gave 2-pyridone derivatives,[12] however, isolation of the intermediate salts from this reaction allows them to be applied further in the synthesis of N1-substituted 2-pyridone derivatives.

The salts **14** obtained easily reacted with N-nucleophiles such as aromatic and heteroaromatic primary amines including *ortho*-phenylenediamine **15** in acetic acid at room temperature leading to N-substituted 2-pyridones **16** (Scheme 3, Table 2). The reaction yields of the 2-pyridones **16a–j** did not depend on the nature of the salt cation. However, the overall yields of these two consecutive stages were higher using the enolates with the dialkylammonium cations because of higher yields of the corresponding salts.



Scheme 3.



Scheme 2.

Table 2
The yields for quinolinecarboxamide derivatives **16a–j**

Ph	R^1	R^2	Yields (%)
16a	H	4-NEt_2–C_6H_4	73
16b	H	2-NO_2–C_6H_4	60
16c	H	2-Me–C_6H_4	78
16d	2-Thiazolyl	Ph	82
16e	H	Ph	74
16f	2-MeO–C_6H_4	4-Me–C_6H_4	74
16g	$CH_2C_6H_5$	4-MeO–C_6H_4	89
16h	Me	4-MeO–C_6H_4	77
16i	H	2-NH_2–C_6H_4	66
16j	2-Thiazolyl	3-Py	75

3. Structural elucidation

All signals in ^1H, ^{13}C NMR spectra correspond to the presumed structure of the obtained salts **14a–j**. In IR spectra, characteristic signals of the nitrile and carbonyl groups were observed. Employing mass spectrometry with EI ionization did not allow any specific signals of the salts to be observed because of their instability in such conditions. Therefore, the mass spectrometry with FAB ionization was applied successfully. In such mass spectra, peaks corresponding to the cation and the anion were observed. For the complete structural elucidation, an X-ray diffraction study of the compound **14h** was performed, which confirmed the presumed salt structure (Fig. 1). From the crystallographic data it can be assumed that the positive charge is localized on the protonated N(3) atom of the piperidine. All hydrogen atoms were located from difference maps of the electron density and the N(3)–C(20) and N(3)–C(24) bonds are longer (1.498(3) Å and 1.515(3) Å, respectively) than mean value[27] for N–Csp^3 bond in the neutral molecule (1.473 Å). The analysis of the bond lengths in the anion demonstrates that the C(1)–C(6) and C(5)–C(6) bonds have the equal value 1.465(2) Å, the O(1)–C(1), O(2)–C(5), and O(3)–C(9) bonds are longer (1.248(2) Å, 1.272(2) Å, and 1.261(2) Å, respectively) in comparison with their mean value 1.210 Å, the C(6)–C(7) bond is shortened (1.433(2) Å) (the mean value is 1.455 Å) and the C(7)–C(8) bond is 1.393(2) Å (the mean value is 1.316 Å). Such redistribution of the electron density allows to assume that the structure of this molecule is the superposition of three resonance structures (Chart 2).

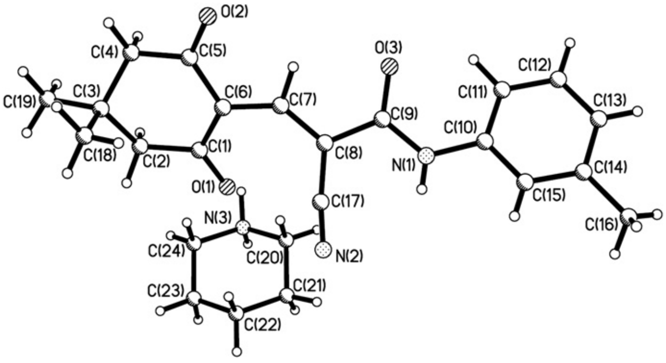


Figure 1. The molecular structure of salt **14h**. The atom numbering corresponds to that in X-ray analysis data.

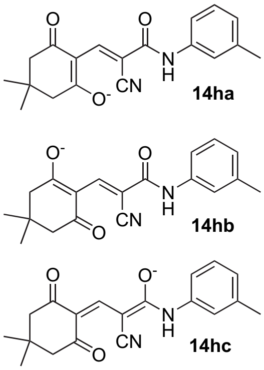


Chart 2.

The **14hb** resonance structure (Chart 2) makes the main contribution into the structure of the anion and the negative charge is localized mainly on the O(2) atom, which is connected with piperidine by intermolecular hydrogen bond N(3)–H(3Nb)··· O(2)′ (1−*x*, 1−*y*, 1−*z*) H···O 1.79 Å N–H···O 166°. The O(2)–C(5) bond (1.272(2) Å) is very similar to the mean value for the C–O^- bond (1.280 Å).

In the course of reaction between the enolates **14** and N-nucleophiles **15**, the formation of alternative products, 2,5-dioxo-1,2,5,6,7,8-hexahydro-3-quinolinecarboxamide **16** and imine **16*** is possible (Chart 3). Determination of the reaction product structure was performed by means of ^1H, ^{13}C NMR spectroscopy, and X-ray diffraction study (Fig. 2). The tetrahydrocycle of the compound **16e** has an asymmetric half-chair conformation. Deviation of the C(3) and C(4) atoms from the mean plane of remaining atoms of the cycle are 0.46 Å and −0.28 Å, respectively. The carbamide substituent lies in

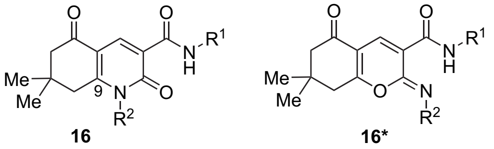


Chart 3.

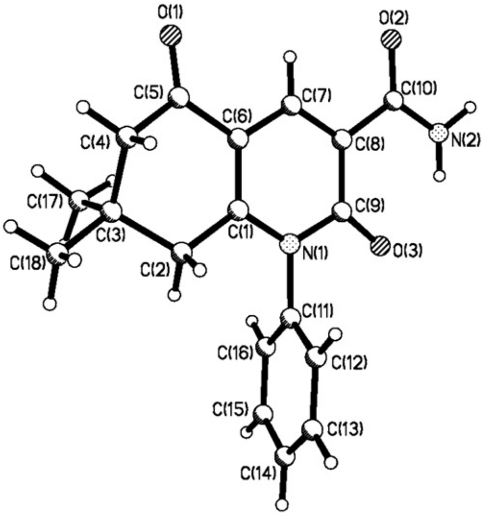


Figure 2. The molecular structure of salt **16e**. The atom numbering corresponds to that in X-ray analysis data.

the plane of pyridine ring (the C(7)–C(8)–C(10)–O(2) torsion angle is 0.1(2)°), probably, as a result of the formation of the intramolecular hydrogen bond N(2)–H(2Nb)···O(3)H···O 2.04 Å N–H···O 133°. The phenyl substituent is almost orthogonal with respect to the pyridine ring (the C(9)–N(1)–C(11)–C(12) torsion angle is 100.7(1)°).

In ^{13}C NMR spectra, the reaction product has a key signal at δ 160.3 ppm that was assigned to the carbon at position 9 (Chart 3).

4. Conclusion

In summary, a new synthetic method for *N*1-substituted 2-pyridone derivatives has been developed. Starting resonance-stabilized enolates **14a–j** were obtained by a one-pot reaction of dimedone, DMFDMA ,and different N-substituted cyanoacetamides. The isolated yields (20–90%) depend on the cation nature and substituted cyanoacetamide structure. The reaction of the salts obtained **14a–j** with different N-nucleophiles affords diverse N-substituted 2,5-dioxo-1,2,5,6,7,8-hexahydro-3-quinolinecarboxamides **16a–j**. The application of dialkylammonium salts was found to be more productive than sodium salts.

5. Experimental

5.1. General

Starting materials were obtained from commercial suppliers and used without further purification. Melting points (°C) were measured using Koeffler melting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded at 200 MHz (50 MHz for ^{13}C NMR) on a Varian Mercury VX-200 spectrometer in DMSO-d_6, using TMS as an internal standard (chemical shifts in parts per million). IR spectra were taken on a Spectrum ONE spectrophotometer in KBr pellet. Mass spectra were taken on a Varian 1200 L DIP; Ioniz. mode: EI; Electron energy: −70 eV. FAB mass-spectrometric experiments were performed using magnetic sector mass spectrometer MI-1201E ('SELMI' Works, Sumy, Ukraine) equipped with commercial FAB units; argon was used as a bombarding gas, the energy of the primary beam was 4.5 keV; the compounds were dissolved in *m*-NBA matrix.

5.2. General procedure for the preparation of the dimethylammonium 2-(2-carbamoyl-2-cyano-1-ethenyl)-5,5-dimethyl-3-oxo-1-cyclohexen-1-olate (*14b*,*c*)

For the preparation of the enamine **12**, a mixture of dimedone **10** (5.00 g, 36.0 mmol) and DMFDMA (4.28 g, 36.0 mmol) was stirred for 5 min. Then 2-propanol (15 mL), corresponding cyanacetamide **13** (36.0 mmol), and piperidine (0.1 g, 0.11 mmol) were added consecutively to the reaction mixture and stirred at room temperature for 5 h. A pale yellow precipitate of the salt was formed, removed by filtration, washed with ether, and dried.

5.2.1. Dimethylammonium 2-(2-carbamoyl-2-cyano-1-ethenyl)-5,5-dimethyl-3-oxo-1-cyclohexen-1-olate (*14b*)

Yield 9.04 g, 90%. Spectral data for the product was same as described in Ref 12; FABMS *m/z*: 235 (An+2H^{+}), 280 (An+Cat+H^{+}).

5.2.2. Dimethylammonium 2-(2-cyano-2-methylcarbamoyl-1-ethenyl)-5,5-dimethyl-3-oxo-1-cyclohexen-1-olate (*14c*)

Yield 6.54 g, 62%; mp 111–113 °C (dec); δ_H (200 Hz, DMSO-d_6) 0.91 (6H, s, Me), 2.07 (4H, s, CH$_2$), 2.53 (6H, s, NMe$_2$), 2.63 (3H, d, *J* 4.6 Hz, NMe), 6.97 (1H, q, *J* 4.6 Hz, NH), 8.03 (1H, s, CH), 8.18 (2H, br s, NH$_2$); δ_C (50 MHz, DMSO-d_6) 27.1, 29.0, 30.1, 35.2, 52.2, 88.5, 110.1, 120.1, 145.1, 167, 192.6; ν_{max} (KBr) 1246, 1395, 1486, 1531, 1647, 2186, 2763, 2948, 3172, 3381; FABMS *m/z*: 249 (An+2H^{+}), 294 (An+Cat+H^{+}). Purification caused decomposition of the salt that is why the CHN analysis was not representative.

5.3. General procedure for the preparation of the hexahydropyridinium 2-(2-carbamoyl-2-cyano-1-ethenyl)-5,5-dimethyl-3-oxo-1-cyclohexen-1-olates (*14e*, *f*, *h–j*)

The enamine **12**, obtained as described above from dimedone **10** (5.00 g, 0.036 mol) and DMFDMA (4.28 g, 0.036 mol), was dissolved in 2-propanol (30 mL). Then piperidine (6.19 g, 0.072 mol), corresponding cyanacetamide **13** (0.036 mol) were added consecutively to the solution and stirred at room temperature for 1 h. A pale yellow precipitate of the salt was formed, removed by filtration, washed with ether, and dried.

5.3.1. Hexahydropyridinium 2-(-2-cyano-2-methylcarbamoyl-1-ethenyl)-5,5-dimethyl-3-oxo-1-cyclohexen-1-olate (*14e*)

Yield 6.23 g, 52%; mp 121–123 °C (dec); δ_H (200 MHz, DMSO-d_6) 0.91 (6H, s, Me), 1.51–1.73 (6H, m, (CH$_2$)$_3$), 2.08 (4H, s, CH$_2$), 2.64 (3H, d, *J* 4.5 Hz, NMe), 2.93–3.09 (4H, m, N(CH$_2$)$_2$), 6.98 (1H, q, *J* 4.5 Hz, NH), 8.04 (1H, s, CH), 8.18 (2H, br s, NH$_2$); FABMS *m/z*: 249(An+2H^{+}), 334(An+Cat+H^{+}); ν_{max} (KBr) 1235, 1397, 1497, 1618, 1660, 2183, 2942, 3120, 3444. Purification caused decomposition of the salt that is why the CHN analysis was not representative.

5.3.2. Hexahydropyridinium 2-(2-benzylcarbamoyl-2-cyano-1-ethenyl)-5,5-dimethyl-3-oxo-1-cyclohexen-1-olate (*14f*)

Yield 9.12 g, 62%; [Found: C, 70.4; H, 7.6; N, 10.0. $C_{24}H_{31}N_3O_3$ requires C, 70.4; H, 7.6; N, 10.3%]; mp 145–147 °C; δ_H (200 MHz, DMSO-d_6) 0.92 (6H, s, Me), 1.48–1.68 (6H, m, (CH$_2$)$_3$), 2.10 (4H, s, CH$_2$), 2.89–3.07 (4H, m, N(CH$_2$)$_2$), 4.33 (2H, d, *J* 5.7 Hz, CH$_2$), 7.17–7.32 (5H, m, Ph), 7.58 (1H, t, *J* 5.7 Hz, NH), 8.08 (1H, s, CH); ν_{max} (KBr) 1229, 1271, 1394, 1485, 1534, 1603, 1618, 1655, 2187, 2955, 2932, 3345; FABMS *m/z*: 325 (An+2H+), 410 (An+Cat+H^{+}).

5.3.3. Hexahydropyridinium 2-[2-cyano-2-(3-methylphenylcarbamoyl)-1-ethenyl]-5,5-dimethyl-3-oxo-1-cyclohexen-1-olate (**14h**)

Yield 7.36 g, 50%; [Found: C, 70.2; H, 7.8; N, 10.1. $C_{24}H_{31}N_3O_3$ requires C, 70.4; H, 7.6; N, 10.3%]; mp 135–137 °C (dec); δ_H (200 MHz, DMSO-d_6) 0.93 (6H, s, Me), 1.49–1.69 (6H, m, $(CH_2)_3$), 2.12 (4H, s, CH_2), 2.24 (3H, s, Me), 2.87–3.06 (4H, m, $N(CH_2)_2$), 6.80 (1H, d, *J* 7.8 Hz, CH), 7.12 (1H, t, *J* 7.8 Hz, CH), 7.35–7.45 (2H, m, CH), 8.08 (1H, s, CH), 8.80 (1H, s, CH); ν_{max} (KBr) 1230, 1300, 1368, 1396, 1484, 1545, 1606, 1642, 2193, 2725, 2857, 2955, 3033, 3322; FABMS *m*/*z*: 325 (An+$2H^+$), 410(An+Cat+H^+).

5.3.4. Hexahydropyridinium 2-[2-cyano-2-(2-methoxyphenylcarbamoyl)-1-ethenyl]-5,5-dimethyl-3-oxo-1-cyclohexen-1-olate (**14i**)

Yield 8.57 g, 56%; [Found: C, 67.8; H, 7.7; N, 9.8. $C_{24}H_{31}N_3O_4$ requires C, 67.7; H, 7.3; N, 9.9%]; mp 135–137 °C; δ_H (200 MHz, DMSO-d_6) 0.93 (6H, s, Me), 1.50–1.68 (6H, m, $(CH_2)_3$), 2.14 (4H, s, CH_2), 2.91–3.07 (4H, m, $N(CH_2)_2$), 3.87 (3H, s, OMe), 6.84–7.07 (3H, m, CH), 7.34–7.46 (2H, m, CH), 8.20 (1H, s, CH), 8.30 (1H, d, *J* 7.7 Hz, CH), 8.68 (1H, s, NH); ν_{max} (KBr) 1415, 1460, 1534, 1602, 1647, 2176, 2531, 2858, 2957, 3385; FABMS *m*/*z*: 341 (An+$2H^+$), 426 (An+Cat+H^+).

5.3.5. Hexahydropyridinium 2-[2-cyano-2-(1,3-thiazol-2-carbamoyl)-1-ethenyl]-5,5-dimethyl-3-oxo-1-cyclohexen-1-olate (**14j**)

Yield 11.14 g (77%); [Found: C, 59.2; H, 6.5; N, 13.7; S, 7.9. $C_{20}H_{26}N_4O_3S$ requires C, 59.7; H, 6.5; N, 13.9; S, 8.0%]; mp 156–158 °C (dec); δ_H (200 MHz, DMSO-d_6) 0.93 (6H, s, Me), 1.49–1.69 (6H, m, $(CH_2)_3$), 2.16 (4H, s, CH_2), 2.89–3.07 (4H, m, $N(CH_2)_2$), 7.12 (1H, d, *J* 3.6 Hz, CH), 7.41 (1H, d, *J* 3.6 Hz, CH), 8.13 (1H, s, CH); ν_{max} (KBr) 1205, 1272, 1403, 1476, 1532, 1567, 1655, 2192, 2537, 2862, 2954, 3062, 3395; FABMS *m*/*z*: 318 (An+$2H^+$), 403 (An+Cat+H^+).

5.4. A general procedure for the preparation of sodium 2-(2-carbamoyl-2-cyano-1-ethenyl)-5,5-dimethyl-3-oxo-1-cyclohexen-1-olates (**14a**,**d**,**g**)

Metallic sodium (0.92 g, 0.04 mol) was dissolved in anhydrous ethyl alcohol (90 mL). Corresponding cyanacetamide **13** (0.036 mol) was added to the solution of sodium ethoxide and stirred for 10 min. The mixture was added to the enamine **12** obtained from dimedone **10** (5.00 g, 0.036 mol) and DMFDMA (4.28 g, 0.036 mol). The reaction mixture was stirred at room temperature for 30 min. A pale yellow precipitate was formed and removed by filtration, washed with ether, and dried.

5.4.1. Sodium 2-(2-carbamoyl-2-cyano-1-ethenyl)-5,5-dimethyl-3-oxo-1-cyclohexen-1-olate (**14a**)

Yield 5.71 g, 62%; mp 190–192 °C (dec); δ_H (200 MHz, DMSO-d_6) 0.91 (6H, s, Me), 2.09 (4H, s, CH_2), 6.57 (2H, br s, NH_2), 8.05 (1H, s, CH); ν_{max} (KBr) 1284, 1352, 1487, 1557, 1665, 2182, 2958, 3173, 3358, 3484; FABMS *m*/*z*: 176 (NBA+Cat^+), 257 (An+Cat+H^+), 279 (An+2Cat). The CNH analysis of the sodium salts was not representative in all cases.

5.4.2. Sodium 2-(-2-cyano-2-methylcarbamoyl-1-ethenyl)-5,5-dimethyl-3-oxo-1-cyclohexen-1-olate (**14d**)

Yield 2.82 g, 29%; mp 250–253 °C (dec); δ_H (200 MHz, DMSO-d_6) 0.92 (6H, s, Me), 2.08 (4H, s, CH_2), 2.64 (3H, d, *J* 4.6 Hz, NCH_3), 6.98 (1H, br q, *J* 4.6 Hz, NH), 8.04 (1H, s, CH); δ_C (50 MHz, DMSO-d_6) 27.1, 28.9, 30.1, 52.1, 88.3, 110.0, 120.8, 145.4, 166.9, 192.7 (APT); ν_{max} (KBr) 1268, 1415, 1506, 1567, 1628, 1651, 2180, 2866, 2951, 3390, 3444; FABMS *m*/*z*: 176 (NBA+Cat^+), 249 (An+H^+), 271 (An+Cat+H^+), 293 (An+2Cat). The CNH analysis of the sodium salts was not representative in all cases.

5.4.3. Sodium 2-(2-benzylcarbamoyl-2-cyano-1-ethenyl)-5,5-dimethyl-3-oxo-1-cyclohexen-1-olate (**14g**)

Yield 2.49 g, 20%; mp 164–166 °C; δ_H (200 MHz, DMSO-d_6) 0.91 (6H, s, Me), 2.09 (4H, s, CH_2), 4.32 (2H, d, *J* 6.0 Hz, CH_2), 7.20–7.30 (5H, m, Ph), 7.53 (1H, t, *J* 6.0 Hz, NH), 8.08 (1H, s, Ch); ν_{max} (KBr) 1236, 1408, 1490, 1535, 1654, 2190, 2953, 3418; FABMS *m*/*z*: 176 (NBA+Cat^+), 347 (An+Cat+H^+), 369 (An+2Cat). The CNH analysis of the sodium salts was not representative in all cases.

5.5. General procedure for the preparation of the 7,7-dimethyl-2,5-dioxo-1-aryl-1,2,5,6,7,8-hexahydro-3-quinolinecarboxamides (**16a–i**) and 7,7-dimethyl-2,5-dioxo-1-pyridyl-1,2,5,6,7,8-hexahydro-3-quinolinecarboxamide (**16j**)

Aromatic or heterocyclic amine **15** (7.2 mmol) was dissolved in acetic acid (15 mL). An appropriate dialkylammonium or sodium 2-(2-carbamoyl-2-cyano-1-ethenyl)-5,5-dimethyl-3-oxo-1-cyclohexen-1-olate **14** (6.6 mmol) was added to the solution and stirred at room temperature for 10–15 min. A yellow product was formed after 5–15 min. Then water (15 mL) was poured into the reaction mixture. The solid product was filtered off, washed with water, and dried. Generally, the product obtained in this manner had no additional signals in NMR spectra. To prepare a sample for elemental analysis some products needed to be recrystallized from solvent mentioned below.

5.5.1. 1-(4-Diethylaminophenyl)-7,7-dimethyl-2,5-dioxo-1,2,5,6,7,8-hexahydro-3-quinolinecarboxamide (**16a**)

The title compound was obtained following the general procedure, using 6.6 mmol of enolate **14b**. The product was recrystallized from 1-butanol, yielding 1.84 g (73%); [Found: C, 68.9; H, 6.9; N, 11.1, $C_{22}H_{27}N_3O_3$ requires C, 69.2; H, 7.1; N, 11.0%]; mp 283–285 °C (dec); δ_H (200 MHz, DMSO-d_6) 0.93 (6H, s, Me), 1.11 (6H, t, *J* 7.0 Hz, $N(CH_2\mathit{CH_3})$), 2.38 (2H, s, CH_2), 2.46 (2H, s, CH_2), 3.37 (4H, q, *J* 7.0 Hz, $N(\mathit{CH_2}CH_3)$), 6.74 (2H, d, *J* 8.9 Hz, CH), 7.03 (2H, d, *J* 8.9 Hz, CH), 7.65 (1H, s, NH), 8.56 (1H, s, NH), 8.76 (s, 1H, CH); ν_{max} (KBr) 1406, 1519, 1607, 1674, 2970, 3357; MS (EI) *m/z*: 381(M+), 367, 366, 380, 382, 349, 280, 321.

*5.5.2. 7,7-Dimethyl-1-(4-nitrophenyl)-2,5-dioxo-1,2,5,6,7,8-hexahydro-3-quinolinecarboxamide (**16b**)*

The title compound was obtained following the general procedure, using 6.6 mmol of enolate **14b**. The product was recrystallized from 1-butanol, yielding 1.41 g (60%); [Found: C, 61.1; H, 5.0; N, 11.7, $C_{18}H_{17}N_3O_5$ requires C, 60.8; H, 4.8; N, 11.8%]; mp 340–342 °C (dec); δ_H (200 MHz, DMSO-d_6) 0.93 (6H, s, Me), 2.37 (2H, s, CH_2), 2.40 (2H, s, CH_2), 7.67–7.77 (3H, m, CH and NH), 8.40 (1H, s, NH), 8.45 (2H, d, *J* 9.0 Hz, CH), 8.79 (1H, s, CH); δ_C (50 MHz, DMSO-d_6) 30.4, 35.3, 44.5, 52.2, 116.1, 122.1, 127.7, 132.5, 142.5, 145.5, 150.7, 161.6, 165.1, 166.2, 196.0; ν_{max} (KBr) 1531, 1675, 3379, 3459; MS (EI) *m/z*: 355 (M^+), 356, 340, 339, 312, 298, 283.

*5.5.3. 7,7-Dimethyl-1-(2-methylphenyl)-2,5-dioxo-1,2,5,6,7,8-hexahydro-3-quinolinecarboxamide (**16c**)*

The title compound was obtained following the general procedure, using 6.6 mmol of enolate **14b**. The product was recrystallized from 1-butanol, yielding 1.68 g (78%); [Found: C, 70.6; H, 6.4; N, 9.0. $C_{19}H_{20}N_2O_3$ requires C, 70.4; H, 6.2; N, 8.6%]; mp 262–264 °C; δ_H (200 MHz, DMSO-d_6) 0.92 (6H, d, *J* 6.7 Hz, Me), 1.98 (3H, s, Me), 2.07(1H, d, *J* 18.2 Hz, $C\mathit{H}_aH_b$), 2.42 (2H, s, CH_2), 2.52(1H, d, *J* 18.2 Hz, $CH_a\mathit{H}_b$), 7.21–7.31 (1H, m, CH), 7.43 (3H, m, CH), 7.71 (1H, s, NH), 8.47 (1H, s, NH), 8.81 (1H, s, CH); ν_{max} (KBr) 1535, 1688, 2951, 3131, 3334; MS (EI) *m/z*: 324 (M^+), 325, 309, 307, 293, 292, 280.

*5.5.4. 2-(7,7-Dimethyl-2,5-dioxo-1-phenyl-1,2,5,6,7,8-hexahydro-3-quinolinylcarboxamido)-1,3-thiazole (**16d**)*

The title compound was obtained following the general procedure, using 6.6 mmol of enolate **14j**. Yield 2.12 g (82%); [Found: C, 64.1; H, 4.9; N, 11.1; S, 8.3. $C_{21}H_{19}N_3O_3S$ requires C, 64.1; H, 4.9; N, 10.7; S, 8.2%]; mp 293–295 °C; δ_H (200 MHz, DMSO-d_6) 0.94 (6H, s, Me), 2.44 (4H, s, CH_2), 7.31 (1H, d, *J* 3.6 Hz, CH), 7.40–7.46 (1H, m, CH), 7.51 (1H, d, *J* 3.6 Hz, CH), 7.55–7.68 (3H m, CH), 8.91 (1H, s, CH), 12.58 (1H, s, NH); ν_{max} (KBr) 1522, 1637, 1678, 2953, 3061, 3429; MS (EI) *m/z*: 393 (M^+), 295, 294, 238.

*5.5.5. 1-Phenyl-7,7-dimethyl-2,5-dioxo-1,2,5,6,7,8-hexahydro-3-quinolinecarboxamide (**16e**)*

The title compound was obtained following the general procedure, using 6.6 mmol of enolate **14b**. Yield 1.51 g (74%); [Found: C, 70.2; H, 5.9; N, 9.1. $C_{18}H_{18}N_2O_3$ requires C, 70.0; H, 5.9; N, 9.0%]; mp 250–252; δ_H (200 MHz, DMSO-d_6) 0.91 (6H, s, Me), 2.36 (2H, s, CH_2), 2.39 (2H, s, CH_2), 7.37 (2H, d, *J* 7.0 Hz, CH), 7.50–7.62 (3H, m, CH), 7.71 (1H, s, NH), 8.49 (1H, s, NH), 8.79 (1H, s, CH); ν_{max} (KBr) 3366, 2951, 1674, 1593, 1532.

*5.5.6. N3-(2-Methoxyphenyl)-7,7-dimethyl-1-(4-methylphenyl)-2,5-dioxo-1,2,5,6,7,8-hexahydro-3-quinolinecarboxamide (**16f**)*

The title compound was obtained following the general procedure, using 6.6 mmol of enolate **14i**. Yield 2.10 g (74%); [Found: C, 72.6; H, 6.4; N, 6.5. $C_{26}H_{26}N_2O_4$ requires C, 72.5; H, 6.1; N, 6.5%]; mp 267–269 °C (dec); δ_H (200 MHz, DMSO-d_6) 0.93 (6H, s, Me), 2.42 (4H, s, CH_2), 2.40 (3H, s, Me), 3.78 (3H, s, OMe), 6.90–7.00 (1H, m, CH), 7.00–7.09 (2H, m, CH), 7.28 (2H, d, *J* 8.2 Hz, CH), 7.42 (2H, d, *J* 8.2 Hz, CH), 8.47 (1H, d, *J* 8.1 Hz, CH), 8. 91 (1H, s, CH), 11.62 (1H, s, NH); ν_{max} (KBr) 1525, 1597, 1672, 2923, 3506, 3594; MS (EI) *m/z*: 430 (M^+), 309, 308, 254.

*5.5.7. N3-Benzyl-1-(4-methoxyphenyl)-7,7-dimethyl-2,5-dioxo-1,2,5,6,7,8-hexahydro-3-quinolinecarboxamide (**16g**)*

The title compound was obtained following the general procedure, using 6.6 mmol of enolate **14f**. Yield 2.52 g (89%); [Found: C, 72.3; H, 6.3; N, 6.8. $C_{26}H_{26}N_2O_4$ requires C, 72.5; H, 6.1; N, 6.5%]; mp 192–194 °C; δ_H (200 MHz, DMSO-d_6) 0.92 (6H, s, Me), 2.39 (4H, s, CH_2), 3.80 (3H, s, OMe), 4.49 (2H, d, *J* 5.0 Hz, CH_2), 7.10 (2H, d, *J* 8.9, CH), 7.20–7.34 (7H, m, CH and Ph), 8.79 (1H, s, CH), 9.59 (1H, t, *J* 5.6 Hz, NH); ν_{max} (KBr) 1509, 1680, 2960, 3057, 3296; MS (EI) *m/z*: 430 (M^+), 431, 413, 325, 324, 297, 254, 106.

*5.5.8. N3,7,7-Trimethyl-1-(4-methoxyphenyl)-2,5-dioxo-1,2,5,6,7,8-hexahydro-3-quinolinecarboxamide (**16h**)*

The title compound was obtained following the general procedure, using 6.6 mmol of enolate **14c**. The product was recrystallized from 1-butanol, yielding 1.80 g (77%); [Found: C, 67.5; H, 6.4; N, 8.0. $C_{20}H_{22}N_2O_4$ requires C, 67.8; H, 6.3; N, 7.9.]; mp 212–214 °C; δ_H (200 MHz, DMSO-d_6) 0.92 (6H, s, Me), 2.39 (4H, s, CH_2), 2.78 (3H, d, *J* 4.5 Hz, NMe), 3.83 (3H, s, OMe), 7.11 (2H, d, *J* 9.4 Hz, CH), 7.27 (2H, d, *J* 9.4 Hz, CH), 8.77 (1H, s, CH), 9.07 (1H, q, *J* 4.5 Hz, NH); ν_{max} (KBr) 1508, 1674, 2834, 2955, 3309; MS (EI) *m/z*: 354 (M^+), 355, 324, 298, 297.

*5.5.9. 1-(2-Aminophenyl)-7,7-dimethyl-2,5-dioxo-1,2,5,6,7,8-hexahydro-3-quinolinecarboxamide (**16i**)*

The title compound was obtained following the general procedure, using 6.6 mmol of enolate **14b**. The product was recrystallized from 1-butanol, yielding 1.42 g (66%); [Found: C, 66.4; H, 6.0; N, 13.1. $C_{18}H_{19}N_3O_3$ requires C, 66.5; H, 5.9; N, 12.9%]; mp 273–275 °C (dec); δ_H (200 MHz, DMSO-d_6) 0.93 (6H, d, *J* 2.4 Hz, Me), 2.18 (1H, d, *J* 18.1 Hz, $C\mathit{H}_aH_b$), 2.34–2.44 (2H, m, CH_aH_b), 2.55 (1H, d, *J* 18.1 Hz, $CH_a\mathit{H}_b$), 5.37 (2H, s, NH_2), 6.67 (1H, t, *J* 7.7 Hz, CH), 6.81 (1H, d, *J* 8.2 Hz, CH), 6.99 (1H, d, *J* 7.7 Hz, CH), 7.16 (1H, t, *J* 8.2 Hz, CH), 7.68 (1H, s, NH), 8.60 (1H, s, NH), 8.75 (1H, s, CH); ν_{max} (KBr) 1538, 1635, 1684, 2957, 3159, 3236, 3343, 3434; MS (EI) *m/z*: 325 (M^+), 326, 308, 294, 293, 252.

*5.5.10. 2-[7,7-Dimethyl-2,5-dioxo-1-(3-pyridyl)-1,2,5,6,7,8-hexahydro-3-quinolinylcarboxamido]-1,3-thiazole (**16j**)*

The title compound was obtained following the general procedure, using 6.6 mmol of enolate **14j**. The product was recrystallized from 1-butanol, yielding 1.95 g (75%); [Found: C, 61.2; H, 4.7; N, 14.2; S, 7.4. $C_{21}H_{19}N_3O_3S$ requires C, 60.9; H, 4.6; N, 14.2; S, 8.1%]; mp 264–266 °C; δ_H (200 MHz, DMSO-d_6) 0.95 (6H, s, Me), 2.45 (4H, s, CH_2), 7.32 (1H, d, *J* 4.1 Hz, CH), 7.51 (1H, d, *J* 4.1 Hz, CH), 7.66–7.76 (1H, m, CH), 7.99 (1H, d, *J* 9.2 Hz, CH), 8.68 (1H, s, CH), 8.79 (1H, d, *J* 4.9 Hz, CH), 8.91(1H, s, CH), 12.46 (1H, s, NH); δ_C (200 MHz, DMSO-d_6) 28.2, 33.0, 42.6, 49.8, 114.6, 115.0, 117.1, 125.3, 134.1, 136.4, 138.5, 141.1, 148.9, 151.0, 157.2, 160.7, 161.2, 163.4, 193.6 (APT); ν_{max} (KBr) 1524, 1635, 1678, 2967, 3421; MS (EI) *m/z*: 394 (M^+), 296, 295, 239.

5.6. X-ray diffraction study

Crystals of **14h** are monoclinic. At 293 K a=13.276(6), b=17.181(5), c=10.440(2) Å, β=96.45(2)°, V=2366(1) $Å^3$, M_r=409.52, Z=4, space group $P2_1/c$, d_{calcd}=1.150 g/cm^3, μ(Mo Kα)=0.076 mm^{-1}, $F(000)$=880.

Crystals of **16e** are triclinic. At 100 K a=8.473(1), b=9.128(2), c=12.145(1) Å, α=103.52(2)°, β=93.31(1)°, γ=116.96(2), V=799.4(2) $Å^3$, M_r=310.34, Z=2, space group $P\bar{1}$, d_{calcd}=1.289 g/cm^3, μ(Mo Kα)=0.089 mm^{-1}, $F(000)$=328.

Intensity of 9613 reflections (4066 independent, R_{int}=0.037) for **14h** and intensity of 5939 reflections (2798 independent, R_{int}=0.018) for **16e** were measured on the 'Xcalibur-3' diffractometer (graphite monochromated Mo Kα radiation, CCD detector, ω-scaning, $2\Theta_{max}$=50°). Both structures were solved by direct method using SHELXTL package.[28] Positions of hydrogen atoms were located from electron density difference maps and refined using isotropic approximation. Full-matrix least-squares refinement against F^2 in anisotropic approximation for non-hydrogen atoms of **14h** using 4047 reflections was converged to wR_2=0.107 (R_1=0.044 for 2340 reflections with $F>4\sigma(F)$, S=0.854). Atomic coordinates and crystallographic parameters have been deposit to the Cambridge Crystallographic Data Centre (CCDC 676521). Full-matrix least-squares refinement against F^2 in anisotropic approximation of **16e** for non-hydrogen atoms using 2726 reflections was converged to wR_2=0.092 (R_1=0.036 for 2285 reflections with $F>4\sigma(F)$, S=1.050). Atomic coordinates and crystallographic parameters have been deposit to the Cambridge Crystallographic Data Centre (CCDC 676522).

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