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Pathways for cyclizations of hydrazine-derived 2-(2-cyanovinyl)-3-oxo-cyclohex-1-ene enolates

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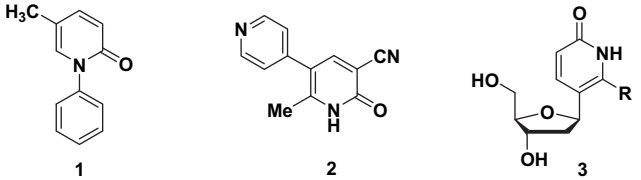
ABSTRACT

The introduction of a hydrazine functionality into 2-(2-cyanovinyl)-3-oxo-cyclohex-1-ene enolates results in their spontaneous cyclizations with participation of the hydrazine moiety. Depending on the reaction conditions used, the hydrazine-derived enolates are transformed into derivatives of 1-arylpyridine-2-one-3-carbonitriles or pyrazoloquinolinones in a one-pot synthesis. They also react with anilines to give the corresponding N1-substituted pyridine-2-one-3-carboxamides. Product characterization was performed by means of spectroscopic and X-ray diffraction studies. In addition, for structure elucidation purposes, a counter synthesis of 1-arylaminopyridine-2-one-3-carboxamide was also carried out.

1. Introduction

The development of novel methods for the synthesis of 2-pyridone derivatives[1] is of interest due to the fact that a number of compounds in this class exhibit interesting biological activities.[2,3] Namely, some 2-pyridone derivatives possess antiphlogistic (pirfenidone 1, Scheme 1),[4] antiulcer,[5] and antifungal[6] activities. Well known inotropic agents milrinone **27** and amrinone[7] also contain the 2-pyridone moiety. In the last decade, considerable attention has been also focused on investigation of nucleosides analogs **3** serving as valuable tools in structure activity studies.[8]



Scheme 1.

Enolates containing the 4-cyano-1,3-butadienolate moiety are usually formed as intermediates or byproducts during the synthesis of 2-pyridone or 2-pyranone derivatives.[9–12] In spite of obvious synthetic potential of these salts, their application as starting materials for the synthesis of 2-pyridone derivatives and other heterocycles has not been widely studied.

We have previously described several methods for the synthesis of 2-pyridone derivatives by means of reactive intermediate enolates **4** (Scheme 2).[13–16] These enolates are highly functionalized and it was possible to switch on the reactivity of their cyano and amide groups selectively for the 2-pyridone ring construction depending on the reaction conditions used. Heating of the enolates **4** in 2-propanol leads to the formation of 2-pyridones **5**. Probably this transformation takes place via the intermediate formation of an iminopyrane cycle, which is highly labile and forms 2-pyridones **5** via Dimroth-like rotation.[13] Use of basic reaction media activates the amide function of the enolates **4** resulting in the formation of N1-substituted 2-pyridines-3-carbonitriles **7**.[15] On the other hand, under acidic conditions enolates **4** react with amines forming N1-substituted 2-pyridines-3-carbonitriles **6**.[14]

The subsequent isolation of the salts **4** was very helpful for understanding of the mechanism of these transformations and now for the application of these salts as reactive building blocks for further transformations. Here we report the continuation of our study into the synthetic potential of the enolates, broadening the horizons of their reactivity by introduction of an additional reaction center; namely a hydrazine-type nitrogen, into the amide group.

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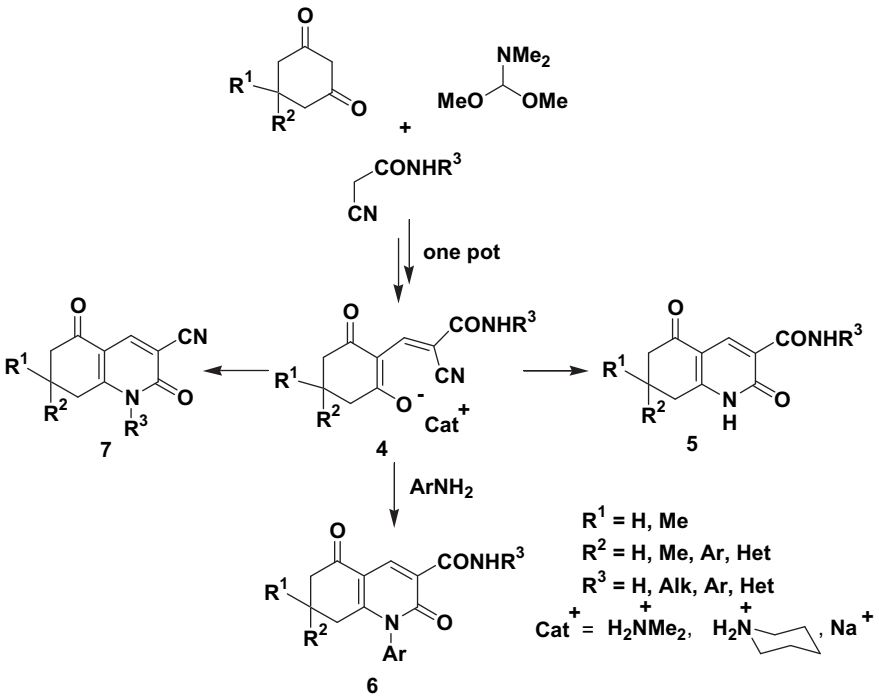
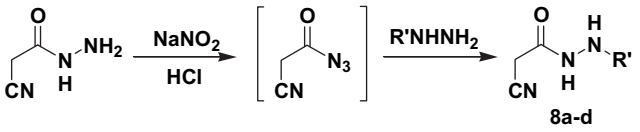


Scheme 2. Previous research on the reactivity of 2-(2-cyanovinyl)-3-oxo-cyclohex-1-ene enolates **4**.

2. Results and discussion

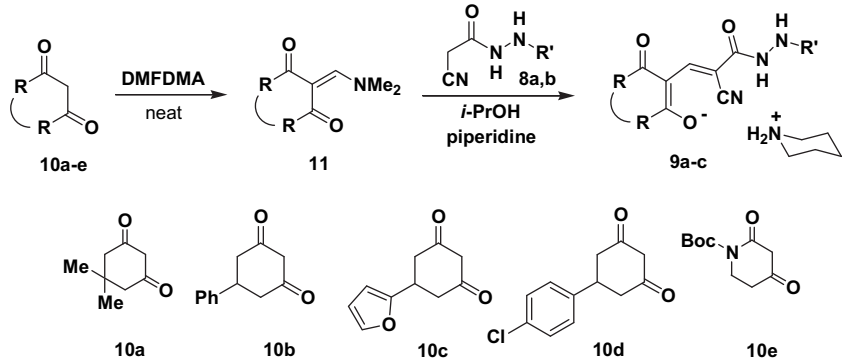
The starting active methylene nitriles **8a**–**d** bearing the hydrazine function were synthesized following a known procedure by the reaction of an in situ formed cyanoacetylazide with commercially available arylhydrazines (Scheme 3).[17]



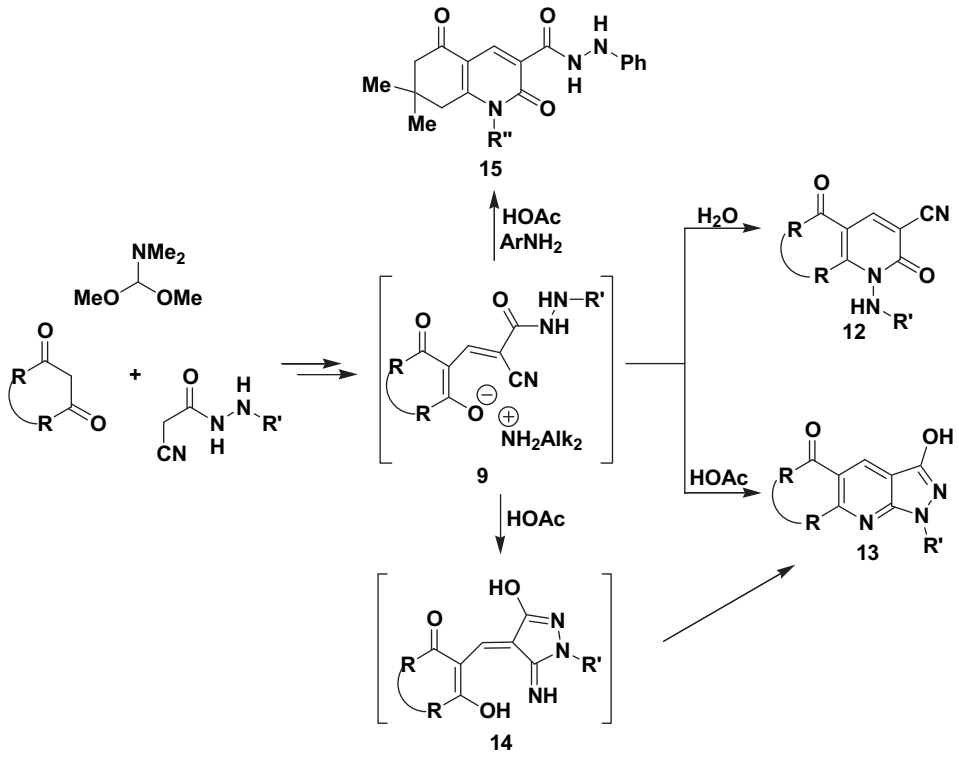
Scheme 3. Synthesis of starting nitriles **8a**–**d** (isolated yield): **a** R′=Ph (50%); **b** R′=R′=4-F–Ph (48%); **c** 4-CO_2Me–Ph (57%); **d** R′=3-Me–Ph (56%).

The previous procedure[14] used for the preparation of enolates **4** is generally suitable also for the synthesis of their hydrazine derivatives **9**. It consists of two steps carried out in one pot: initially the cyclic 1,3-dicarbonyl compound **10** is reacted with neat dimethylformamide dimethylacetal (DMF-DMA), the process being complete within a few minutes at room temperature. Then, the appropriate substituted 2-cyanoacetohydrazide **8** is added to the formed enamine **11** along with 2-propanol and 1 equiv of piperidine. After stirring for 30 min at room temperature the solid product **9** is separated as precipitate and removed upon filtration (Scheme 4). As cyclic 1,3-dicarbonyl compounds, cyclohexanediones **10a**–**d** and *N*-Boc-piperidinedione **10e** were used. With the exception of commercially available dimedone, these compounds were synthesized by known methods.[18,19] Attempts to synthesize enolates with acyclic 1,3-dicarbonyl compounds under such conditions, however, were not successful. The reason for this could be associated with the enhanced conjugation of negative charge in the cyclic enoles due to the higher acidity of the cyclic 1,3-dicarbonyl compounds as compared to their acyclic analogs.[20,21]

The enolates **9a**–**c** obtained were readily soluble in water, this meaning that aqueous conditions could be used for their further transformation. After heating at 80 °C for 5 min in water, enolates **9a**–**c** could be cyclized to give the corresponding 3-cyano-2-pyridones **12a**–**c** (Scheme 5, Table 1). Interestingly, in the case of the



Scheme 4. Hydrazine-derived enolates **9a**–**c** (isolated yield): **a** R–R=–$CH_2CMe_2CH_2$–, R′=Ph (70%); **b** R–R=–$CH_2CMe_2CH_2$–, R′=4-F–Ph (82%); **c** R–R=–*N*(Boc)CH_2CH_2–, R′=Ph (69%).



Scheme 5.

Table 1
The yields for compounds **12a**–**k**, **13a**–**d**, and **16a**–**c**

Compounds	R–R	R′	R″	Yield[a]
12a	$-CH_2C(CH_3)CH_2-$	C_6H_5	—	65% (45%[b])
12b	$-CH_2C(CH_3)CH_2-$	4-F–C_6H_4	—	80% (62%[b])
12c	$-N(Boc)CH_2CH_2-$	C_6H_5	—	50% (26%[b])
12d	$-CH_2C(CH_3)_2CH_2-$	3-CH_3–C_6H_4	—	41%
12e	$-CH_2C(CH_3)_2CH_2-$	4-COOMe–C_6H_4	—	64%
12f	$-N(Boc)CH_2CH_2-$	4-F–C_6H_4	—	72%
12g	$-CH_2CH(Furyl)CH_2-$	C_6H_5	—	64%
12h	$-CH_2CH(C_6H_5)CH_2-$	C_6H_5	—	50%
12i	$-CH_2CH(C_6H_5)CH_2-$	4-F–C_6H_4	—	45%
12j	$-CH_2CH(4\text{-}ClC_6H_4)CH_2-$	C_6H_5	—	54%
12k	$-CH_2CH(4\text{-}ClC_6H_4)CH_2-$	4-F–C_6H_4	—	44%
13a	$-CH_2C(CH_3)_2CH_2-$	C_6H_5	—	36% (28%[b])
13b	$-CH_2C(CH_3)_2CH_2-$	3-CH_3–C_6H_4	—	37%
13c	$-CH_2C(CH_3)_2CH_2-$	4-F–C_6H_4	—	34% (26%[b])
13d	$-CH_2CH(Furyl)CH_2-$	C_6H_5	—	11%
15a	$-CH_2C(CH_3)_2CH_2-$	C_6H_5	4-F–C_6H_4	64%[c]
15b	$-CH_2C(CH_3)_2CH_2-$	C_6H_5	3-Cl–C_6H_4	60%[c]
15c	$-CH_2C(CH_3)_2CH_2-$	C_6H_5	2-MeO–C_6H_4	63%[c]

[a] Isolated yields over three steps.
[b] Isolated yields of the pyridones synthesis with separation of the enolates **9** calculated over three steps.
[c] Isolated yields calculated on the amount of the starting salt **9a**.

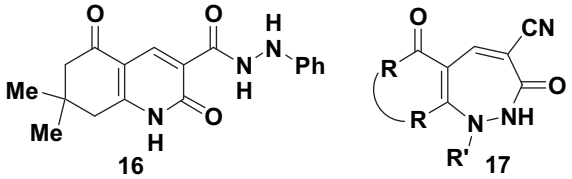
corresponding enolates bearing an amide group instead of a hydrazide group, the cyclization required a higher temperature (120 °C) and longer time (10 min) in order to obtain acceptable yields of product.[15] This is probably associated with the increase in nucleophilicity of the amide nitrogen influenced by the neighboring nitrogen in enolates **9**; the so-called alpha-effect.

Issues with isolation of **9a**–**c** cause the yields to decrease during the work-up stages. As a result, attempts were made to convert them into the desired 3-cyano-2-pyridones **12a**–**c** in one pot without separation of the enolates. This one-pot, three-step method gave significantly higher overall yields in comparison with the stage-by-stage method. Applying this method the range of 3-cyano-2-pyridones **12a**–**k** was synthesized with good overall yields (Table 1). Piperidine (1 equiv) proved essential in this cyclization. Lower loadings of piperidine caused side reactions, thereby increasing the quantities of impurities.

Changing the solvent from water to acetic acid yielded different products, namely the 1*H*-pyrazolo[3,4-*b*]pyridin-3-ol derivatives **13a**–**d** (Scheme 5). In this case, the hydrazine-type nitrogen participated in the cyclization with the cyano group, forming the iminopyrozoline intermediate **14**, which is then transformed into the corresponding 1*H*-pyrazolo[3,4-*b*]pyridin-3-ol **13**. Overall yields of this transformation were modest, a number of byproducts also being formed. However, the pyrazolo[3,4-*b*]pyridin-3-ols **13a**–**d** had the lowest solubility in acetic acid providing a simple method for their separation.

To complete the comparative investigation of chemical properties of enolates **4** and **9**, the reactivity of **9a**–**c** reacted with anilines was probed. In this case no significant differences were observed. The corresponding *N*1-substituted 2-pyridones **15a**–**c** were obtained in good yields (Scheme 4, Table 1).

During the synthesis of compounds **12** and **13** the formation of small quantities of a compound with the presumed structure of *N*1-unsubstituted 2-pyridone **16** was observed (Scheme 6).[22] Attempts were made to synthesize these interesting products in



Scheme 6.

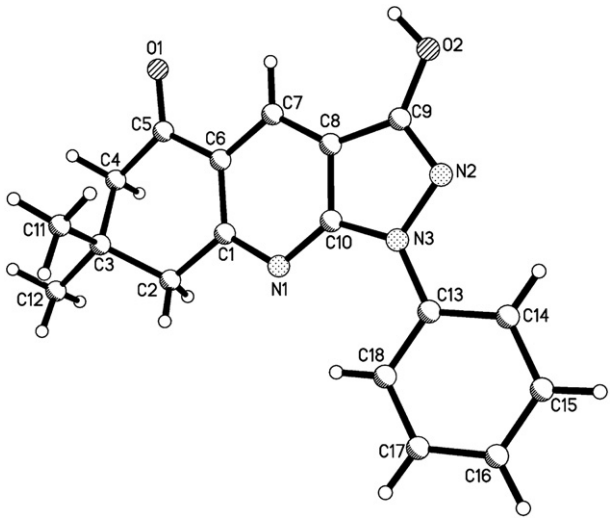


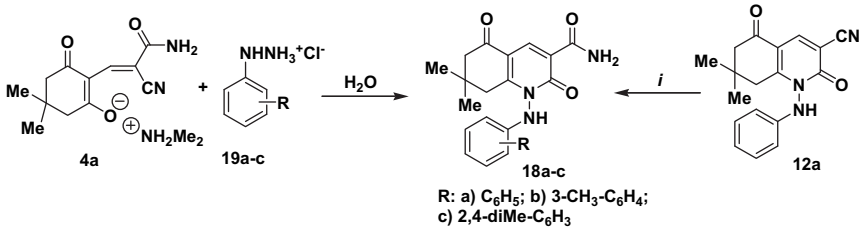
Fig. 1. The molecular structure of **13a**. The atom numbering corresponds to that in X-ray analysis data.

greater amounts by variation of the reaction conditions, but in all cases, compounds **12** and **13** predominated. The reason for these difficulties is the high nucleophilicity of hydrazine group, causing it to react faster with cyano or enol groups (Scheme 5) than Dimroth-like rotation proceeds (Scheme 2).

3. Structure elucidation

Besides 3-cyano-2-pyridone **12** and 1*H*-pyrazolo[3,4-*b*]pyridin-3-ol **13**, formation of diazepinone **17** (Scheme 6) was also possible. For this reason, considerable attention was focused on structure determination for these compounds. All the compounds have the same molecular weight and set of protons complicating structure elucidation by means of mass and ^{1}H NMR spectroscopy. Attempts to prove the structures of the obtained compounds by means of correlation NMR spectroscopy (NOESY, HMBC, and HMQC) were not successful. The structure of compound **13a** was proven by means of X-ray analysis (Fig. 1).

Unfortunately, X-ray analysis for compounds **12** could not be performed since a single crystal of suitable quality could not be successfully grown. However, the related compounds **18a**–**c** could be easily synthesized by the reaction of the salts **4a** with corresponding hydrazine hydrochlorides **19a**–**c** (Scheme 7) similarly to compounds **15a**–**c** (Scheme 5) using water as a solvent. The structure of **18c** was unequivocally determined by means of single crystal X-ray analysis (Fig. 2). In the ^{1}H NMR spectra, the coupling profiles of the methylene groups for compounds **12** and **18** were very similar. That is why we attempted to convert the nitriles **12** into the amides **18** to prove definitively the structure of compound **12**. An acceptable protocol for this conversion was a palladium-catalyzed transformation of nitriles into amides by the action of acetamide excess (Scheme 6).[23]



Scheme 7. i: Acetamide (10 equiv), $PdCl_2$ (10 mol %), durene (30 mol %), reflux in dioxane for 40 h, 30% conversion.

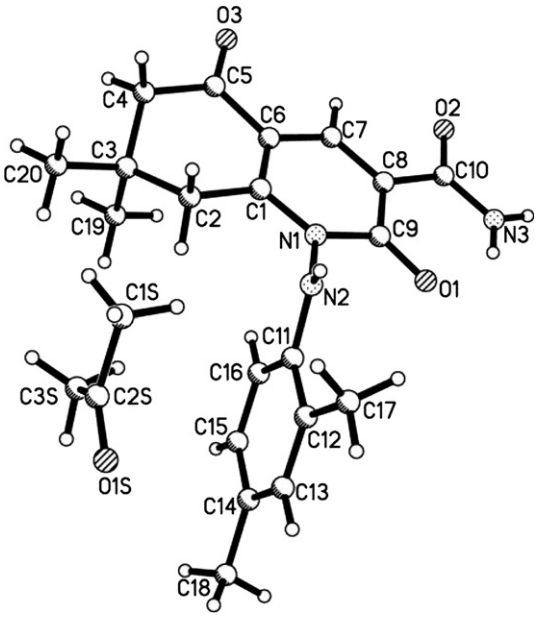


Fig. 2. The molecular structure of **18c**. The atom numbering corresponds to that in X-ray analysis data.

4. Conclusions

The addition of the hydrazine-type nitrogen into the amide group of 2-(2-cyanovinyl)-3-oxo-cyclohex-1-ene results in particular changes of their reactivity. The formation of 2-pyridone ring of compounds **12** with participation of the acylated hydrazine nitrogen of enolates **9** proceeds easier than for derivatives **4**: at lower temperature in water and without addition base. In this case, the neighboring nitrogen atom increases the nucleophilicity of the amide nitrogen due to the alpha-effect. Employing acetic acid as the solvent probably prevents the reaction of acylated hydrazine nitrogen, and the arylated nitrogen appears to be more reactive under these conditions. In this way the initial attack of the arylated hydrazine nitrogen proceeds with sequential formation of iminopyrozoline intermediate **14** and 1*H*-pyrazolo[3,4-*b*]pyridin-3-ol **13**. At the same time, the presence of the amide nitrogen does not prevent the reaction of enolates **9** with anilines in acetic acid to give *N*1-substituted 2-pyridones **16**.

5. Experimental

5.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DRX-400 (400 MHz) or Bruker DRX-300 (300 MHz) spectrometers in DMSO-d_6 and chemical shifts (δ) are expressed in parts per million relative to TMS as an internal standard. High resolution mass spectra were recorded with Q-TOF mass spectrometer operating in ESI$^+$ mode

unless otherwise indicated. Starting materials were obtained from commercial suppliers and used without further purification. The enolate **4a** was synthesized by the described method.[13]

5.2. Preparation of cyano-acetic acid *N′*-aryl-hydrazides 8

Cyano-acetic acid hydrazide (5.64 g, 57 mmol) was dissolved in water (20 mL) and acidified using concentrated hydrochloric acid (4.8 mL). The mixture was cooled to 0 °C and diethyl ether (20 mL) was added. A solution of sodium nitrite (3.86 g, 56 mmol in 7 mL of water) was added dropwise over the period of 15 min to the mixture of hydrazide hydrochloride, maintaining the temperature below 5 °C and using vigorous stirring. After complete addition of the sodium nitrite, the reaction mixture was stirred for an additional 30 min at the same temperature. The corresponding arylhydrazine (0.056 mmol) was added to the solution of formed azide and the reaction mixture was stirred for an additional hour. Application of hydrazines hydrochlorides requires neutralization by sodium hydroxide and neutralized solution can be used in the reaction with azide.

The precipitated cyano-acetic acid *N′*-aryl-hydrazide was filtered off, washed with 5 mL of water and then with 5 mL of ether. For additional purification recrystallization in water or in ethanol–water mixture (1:1) can be used.

5.3. General procedure for the synthesis of enolates 9

The corresponding methylenactive 1,3-dicarbonyl compound **10** (1.4 mmol) was mixed with DMF-DMA (1.4 mmol) and stirred for 5 min at room temperature. The resulting enamine **11** was diluted with 2-propanol (1 mL). To the solution of enamine **11** in 2-propanol was added the requisite hydrazide **8** (1.3 mmol) and piperidine (0.119 g, 1.4 mmol). The mixture was stirred for 10–30 min at room temperature until a pale yellow precipitate of the salt **9** was formed. The precipitate was filtered, washed with diethyl ether (5 mL), and dried at room temperature. The obtained pale yellow compound did not require additional purification.

*5.3.1. Piperidinium 2-[2-cyano-2-(N′-phenyl-hydrazinocarbonyl)-vinyl]-5,5-dimethyl-3-oxo-cyclohex-1-enate (**9a**).* Yield: 430 mg, 70%; mp: 154–156 °C (dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.95 (s, 6H), 1.49–1.71 (m, 6H), 2.13 (s, 4H), 2.94–3.06 (m, 4H), 6.62–6.75 (m, 3H), 7.12 (t, J=8.0 Hz, 2H), 7.59 (s, 1H), 8.06 (s, 1H), 8.91 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 22.4, 23.0, 29.1, 31.1, 44.5, 52.4, 86.4, 100.2, 110.8, 112.9, 118.9, 120.0, 129.2, 146.1, 150.5, 167.5, 192.9.

*5.3.2. Piperidinium 2-{2-cyano-2-[N′-(4-fluoro-phenyl)-hydrazinocarbonyl]-vinyl}-5,5-dimethyl-3-oxocyclohex-1-enolate (**9b**).* Yield: 486 mg, 82%; mp: 154–156 °C (dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.95 (s, 6H), 1.49–1.70 (m, 6H), 2.13 (s, 4H), 2.94–3.07 (m, 4H), 6.64–6.77 (m, 2H), 6.89–7.03 (m, 2H), 7.57 (s, 1H), 8.06 (s, 1H), 8.97 (s, 1H).

*5.3.3. Piperidinium 1-tert-butoxycarbonyl-5-[2-cyano-2-(N′-phenyl-hydrazinocarbonyl)-vinyl]-6-oxo-1,2,3,6-tetrahydropyridin-4-olate (**9c**).* Yield: 433 mg, 69%; mp: 149–151 °C (dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.45 (s, 9H), 1.52–1.60 (m, 2H), 1.60–1.69 (m, 4H), 2.28 (t, J=6.0 Hz, 2H), 2.99–3.02 (m, 4H), 3.64 (t, J=6.0 Hz, 2H), 6.63–6.75 (m, 3H), 7.12 (t, J=7.0 Hz, 2H), 7.60 (s, 1H), 8.16 (s, 1H), 8.20 (br s, 2H), 8.96 (s, 1H).

5.4. General procedure for the synthesis of 2-pyridone-3-carbonitiles 12

The corresponding methylenactive 1,3-dicarbonyl compound **7** (1.4 mmol) was mixed with DMF-DMA (1.4 mmol) and stirred for 5 min at room temperature. The resulting enamine **11** was diluted with 2-propanol (1 mL). To the solution of enamine **11** in 2-propanol was added the requisite hydrazide **8** (1.3 mmol) and piperidine (120 g, 1.4 mmol). The mixture was stirred for 10–30 min at room temperature until a pale yellow precipitate of the salt **9** was formed. Then, water (2 mL) was added, this dissolving enolate **9**, and then reaction mixture was placed into heated oil bath and refluxed for 5 min. After heating, the 2-propanol solvent was almost completely evaporated and an oily residue was left. After cooling the residue crystallized. The product was filtered and dried under vacuum. In most cases the product did not require additional purification. Recrystallization of the crude product using a mixture of 2-propanol and water (2:1) was used if needed.

*5.4.1. 7,7-Dimethyl-2,5-dioxo-1-phenylamino-1,2,5,6,7,8-hexahydro-quinoline-3-carbonitrile (**12a**).* Yield: 260 mg, 65%; mp: 175–177 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.02 (s, 6H), 2.50 (d, J=9.0 Hz, 2H), 2.79 (d, J=18.0 Hz, 1H), 3.23 (d, J=18.0 Hz, 1H), 6.70 (d, J=8.0 Hz, 2H), 6.91 (t, J=8.0 Hz, 1H), 7.24 (t, J=8.0 Hz, 2H), 8.56 (s, 1H), 9.36 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 27.5, 37.8, 38.9, 39.5, 48.8, 99.3, 101.6, 112.6, 115.0, 120.9, 129.1, 143.8, 145.5, 158.9, 164.5, 192.4; HRMS (ESI) calculated for $C_{18}H_{18}N_3O_2$ (M+H$^+$) 308.1399; found, 308.1420; IR (KBr), cm^{-1}: 1538, 1641, 1671, 2230, 2959, 3259.

*5.4.2. 1-(4-Fluoro-phenylamino)-7,7-dimethyl-2,5-dioxo-1,2,5,6,7,8-hexahydro-quinoline-3-carbonitrile (**12b**).* Yield: 338 mg, 80%; mp: 175–177 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.03 (s, 6H), 2.47 (br s, 2H), 2.85 (br s, 1H), 3.21 (br s, 1H), 6.69–6.79 (m, 2H), 7.03–7.14 (m, 2H), 8.54 (s, 1H), 9.32 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 28.4, 28.6, 32.8, 49.9, 113.3, 115.0, 116.5, 126.6, 139.8, 143.3, 162.1, 163.0, 164.2, 194.3; HRMS (ESI) calculated for $C_{18}H_{16}N_3O_2FNa$ (M+Na$^+$) 348.1124; found, 348.1069; IR (KBr), cm^{-1}: 1507, 1534, 1671, 2230, 2891, 2964, 3270, 3380.

*5.4.3. 3-Cyano-2,5-dioxo-1-phenylamino-1,5,7,8-tetrahydro-2H-[1,6]naphthyridine-6-carboxylic acid tert-butyl ester (**12c**).* Yield: 247 mg, 50%; mp: 156–158 °C (dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.49 (s, 9H), 2.91–3.11 (m, 1H), 3.26–3.47 (m, 1H), 3.79–4.07 (m, 2H), 6.73 (d, J=8.0 Hz, 2H), 6.91 (t, J=7.3 Hz, 1H), 7.23 (d, J=7.3 Hz, 2H), 8.62 (s, 1H), 9.38 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.8, 25.0, 27.1, 82.0, 101.4, 108.5, 111.6, 112.6, 114.7, 120.7, 128.7, 145.2, 151.4, 158.1, 159.5, 161.6; HRMS (ESI) calculated for $C_{20}H_{20}N_4O_4Na$ (M+Na$^+$) 403.1382; found, 403.1383; IR (KBr), cm^{-1}: 1671, 1689, 1715, 1759, 2233, 3049, 3260.

*5.4.4. 7,7-Dimethyl-2,5-dioxo-1-m-tolylamino-1,2,5,6,7,8-hexahydro-quinoline-3-carbonitrile (**12d**).* Yield: 171 mg, 41%; mp: 166–168 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.00 (s, 6H), 2.21 (s, 3H), 2.45 (s, 2H), 2.76 (d, J=13.0 Hz, 2H), 3.21 (d, J=13.0 Hz, 1H), 6.39–6.54 (m, 2H), 6.71 (d, J=8.0 Hz, 2H), 7.09 (t, J=8.0 Hz, 1H), 8.53 (s, 1H), 9.23 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.7, 25.1, 31.6, 38.5, 48.6, 101.4, 109.5, 112.4, 112.9, 114.8, 121.5, 128.7, 138.3, 143.6, 145.2, 158.6, 164.3, 192.2; HRMS (ESI) calculated for $C_{19}H_{19}N_3O_2Na$ (M+Na$^+$) 344.1375; found, 344.1366; IR (KBr), cm^{-1}: 1639, 1678, 2227, 2870, 2952, 3048, 3271.

*5.4.5. 4-(3-Cyano-7,7-dimethyl-2,5-dioxo-5,6,7,8-tetrahydro-2H-quinolin-1-ylamino)-benzoic acid methyl ester (**12e**).* Yield: 388 mg, 64%; mp: 217–219 °C (dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.99 (s, 6H), 2.45 (s, 2H), 2.72 (d, J=19.0 Hz, 2H), 3.17 (d, J=19.0 Hz, 1H), 3.78 (s, 3H), 6.77 (d, J=9.0 Hz, 2H), 6.82 (d, J=9.0 Hz, 2H), 8.54 (s, 1H), 9.72 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 27.1, 27.4, 31.6, 48.5, 51.3, 101.6, 111.8, 112.7, 114.7, 121.5, 130.5, 143.9, 149.6, 158.4, 164.2, 165.4, 192.1; HRMS (ESI) calculated for $C_{20}H_{19}N_3O_4Na$ (M+Na$^+$) 388.1273; found, 388.1260; IR (KBr), cm^{-1}: 1646, 1675, 1709, 2230, 2952, 3263.

*5.4.6. 3-Cyano-1-(4-fluoro-phenylamino)-2,5-dioxo-1,5,7,8-tetrahydro-2H-[1,6]naphthyridine-6-carboxylic acid tert-butyl ester (**12f**).* Yield: 310 mg, 60%; mp: 193–195 °C (dec); ^{1}H NMR (300 MHz, DMSO-d_6)

δ 1.49 (s, 9H), 2.95–3.47 (m, 2H), 3.80–4.03 (m, 2H), 6.73–6.84 (m, 2H), 7.00–7.11 (m, 1H), 8.61 (s, 1H), 9.35 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 25.3, 27.6, 41.6, 48.8, 82.4, 101.8, 108.9, 112.0, 113.0, 115.0, 121.1, 129.0, 145.6, 145.9, 151.8, 158.5, 160.0, 162.1; HRMS (ESI) calculated for $C_{20}H_{19}N_4O_4NaF$ (M+Na$^+$) 421.1288; found, 421.1335; IR (KBr), cm^{-1}: 1670, 1690, 1758, 2230, 2913, 2978, 3048, 3217, 3257.

*5.4.7. 7-Furan-2-yl-2,5-dioxo-1-phenylamino-1,2,5,6,7,8-hexahydro-quinoline-3-carbonitrile (**12g**).* Yield: 287 mg, 64%; mp: 112–114 °C (dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.75–2.96 (m, 2H), 3.00–3.28 (m, 1H), 3.62–3.84 (m, 2H), 6.15 (d, *J*=3.0 Hz, 1H), 6.30–6.39 (m, 1H), 6.51–6.82 (m, 2H), 6.89 (t, *J*=8.0 Hz, 1H), 7.10–7.31 (m, 2H), 7.52 (br s, 1H), 8.56 (s, 1H), 9.38 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 26.0, 31.6, 62.5, 102.5, 106.1, 110.9, 113.5, 114.0, 115.6, 121.7, 129.6, 142.6, 144.5, 146.1, 155.5, 159.3, 164.9, 192.8; HRMS (ESI) calculated for $C_{20}H_{15}N_3O_3Na$ (M+Na$^+$) 368.1011; found, 368.1051; IR (KBr), cm^{-1}: 1537, 1600, 1667, 2232, 29,653,052, 3122, 3265.

*5.4.8. 2,5-Dioxo-7-phenyl-1-phenylamino-1,2,5,6,7,8-hexahydro-quinoline-3-carbonitrile (**12h**).* Yield: 230 mg, 50%; mp: 227–229 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.64–2.76 (m, 1H), 2.88–3.17 (m, 2H), 3.34–3.71 (m, 2H), 6.71 (d, *J*=8.0 Hz, 2H), 6.90 (t, *J*=7.0 Hz, 1H), 7.16–7.36 (m, 7H), 8.62 (s, 1H), 9.37 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 26.2, 33.9, 38.2, 114.2, 115.8, 116.3, 116.6, 127.6, 127.7, 129.4, 142.7, 143.0, 144.8, 156.7, 159.1, 159.6, 165.8, 192.9; HRMS (ESI) calculated for $C_{22}H_{17}N_3O_2Na$ (M+Na$^+$) 378.1218; found, 378.1215; IR (KBr), cm^{-1}: 1657, 1673, 2230, 3266.

*5.4.9. 1-(4-Fluoro-phenylamino)-2,5-dioxo-7-phenyl-1,2,5,6,7,8-hexahydro-quinoline-3-carbonitrile (**12i**).* Yield: 218 mg, 45%; mp: 127–129 °C (dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.69 (d, 1H), 2.90–3.11 (m, 2H), 3.49–3.65 (m, 2H), 6.70–6.80 (m, 2H), 7.21–7.38 (m, 5H), 8.61 (s, 1H), 9.34 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 33.9, 38.0, 114.2, 115.3, 115.8, 116.3, 116.6, 127.6, 127.7, 129.4, 142.7, 143.0, 144.9, 156.7, 159.1, 159.6, 165.8; HRMS (ESI) calculated for $C_{22}H_{16}N_3O_2NaF$ (M+Na$^+$) 396.1124; found, 396.1139; IR (KBr), cm^{-1}: 1505, 1671, 2231, 3031, 3260.

*5.4.10. 7-(4-Chloro-phenyl)-2,5-dioxo-1-phenylamino-1,2,5,6,7,8-hexahydro-quinoline-3-carbonitrile (**12j**).* Yield: 273 mg, 54%; mp: 217–219 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.68 (d, 1H), 2.89–3.20 (m, 2H), 3.51–3.69 (m, 2H), 6.68–6.80 (m, 2H), 7.21–7.38 (m, 5H), 8.61 (s, 1H), 9.34 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 33.6, 37.6, 113.7, 114.1, 115.8, 121.9, 129.3, 129.6, 129.9, 132.3, 142.0, 144.8, 146.3, 159.6, 165.7, 192.6; HRMS (ESI) calculated for $C_{22}H_{16}N_3O_2NaCl$ (M+Na$^+$) 412.0829; found, 412.0855; IR (KBr), cm^{-1}: 1649, 1673, 2229, 2874, 2952, 3052, 3267.

*5.4.11. 7-(4-Chloro-phenyl)-1-(4-fluoro-phenylamino)-2,5-dioxo-1,2,5,6,7,8-hexahydro-quinoline-3-carbonitrile (**12k**).* Yield: 233 mg, 44%; mp: 165–167 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.68 (d, 1H), 2.89–3.21 (m, 2H), 3.50–3.68 (m, 2H), 6.67–6.80 (m, 2H), 6.95–7.12 (m, 2H), 7.30–7.45 (m, 4H), 8.61 (s, 1H), 9.34 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 33.8, 37.6, 114.2, 115.8, 116.3, 116.6, 129.3, 129.6, 132.3, 142.0, 142.7, 144.9, 159.6, 165.7, 193.0; HRMS (ESI) calculated for $C_{22}H_{15}N_3O_2NaClF$ (M+Na$^+$) 430.0735; found, 430.0754; IR (KBr), cm^{-1}: 1647, 16,734, 2231, 2891, 2952, 3052, 3274.

5.5. General procedure for the synthesis of pyrazoloquinolinones 13

The corresponding methylenactive 1,3-dicarbonyl compound **7** (1.4 mmol) was mixed with DMF-DMA (167 mg, 1.4 mmol) and stirred for 5 min at room temperature. The resulting enamine **11** was diluted with 2-propanol (1 mL). To the solution of enamine **11** in 2-propanol was added the requisite hydrazide **8** (1.3 mmol) and piperidine (120 mg, 1.4 mmol). The mixture was stirred for 10–30 min at room temperature until a pale yellow precipitate of the salt **9** was formed. Following this, acetic acid (1 mL) was added and the reaction mixture placed into heated oil bath and refluxed for 5 min. The product precipitated during heating or after cooling. The precipitate was filtered, washed with water, and then dried under vacuum. In most cases further purification was not necessary.

*5.5.1. 3-Hydroxy-7,7-dimethyl-1-phenyl-1,6,7,8-tetrahydro-pyrazolo [3,4-b]quinolin-5-one (**13a**).* Yield: 144 mg, 36%; mp: 260–262 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.04 (s, 6H), 2.57 (s, 2H), 3.09 (s, 2H), 7.23 (t, *J*=7.0 Hz, 1H), 7.50 (t, *J*=7.0 Hz, 2H), 8.23 (d, *J*=7.0 Hz, 2H), 8.66 (s, 1H), 11.80 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ27.4, 32.2, 46.2, 51.1, 106.8, 119.2, 121.0, 124.5, 128.7, 129.5, 138.7, 150.0, 155.4, 163.0, 195.9; HRMS (ESI) calculated for $C_{18}H_{18}N_3O_2$ (M+H$^+$) 308.1399; found, 308.1387; IR (KBr), cm^{-1}: 1590, 1658, 3089.

*5.5.2. 3-Hydroxy-7,7-dimethyl-1-m-tolyl-1,6,7,8-tetrahydro-pyrazolo [3,4-b]quinolin-5-one (**13b**).* Yield: 154 mg, 37%; mp: 250–253 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.04 (s, 6H), 2.38 (s, 3H), 2.57 (s, 2H), 3.09 (s, 2H), 7.05 (d, *J*=7.0 Hz, 1H), 7.37 (t, *J*=7.0 Hz, 1H), 8.00 (s, 1H), 8.06 (d, *J*=7.0 Hz, 1H), 8.65 (s, 1H), 11.90 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.1, 27.5, 32.3, 46.4, 51.2, 106.9, 116.6, 119.8, 121.1, 125.4, 128.7, 129.6, 138.2, 138.8, 150.1, 155.5, 163.1, 196.0; HRMS (ESI) calculated for $C_{19}H_{19}N_3O_2Na$ (M+Na$^+$) 344.1375; found, 344.1389; IR (KBr), cm^{-1}: 1598, 1656, 2865, 2953, 3126.

*5.5.3. 1-(4-Fluoro-phenyl)-3-hydroxy-7,7-dimethyl-1,6,7,8-tetrahydro-pyrazolo[3,4-b]quinolin-5-one (**13c**).* Yield: 144 mg, 34%; mp: 262–264 °C after recrystallization from ethyl acetate; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.06 (s, 6H), 2.60 (s, 2H), 3.12 (s, 2H), 3.09 (s, 2H), 7.33–7.43 (m, 2H), 8.22–8.29 (m, 2H), 8.69 (s, 1H), 12.10 (br s, 1H); HRMS (ESI) calculated for $C_{18}H_{16}N_3O_2Na$ (M+Na$^+$) 348.1124; found, 348.1157; IR (KBr), cm^{-1}: 1658, 1738, 2969, 3026, 3091.

*5.5.4. 7-Furan-2-yl-3-hydroxy-1-phenyl-1,6,7,8-tetrahydro-pyrazolo [3,4-b]quinolin-5-one (**13d**).* Yield: 49 mg, 11%; mp: 230–232 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.78–3.06 (m, 2H), 3.40–3.65 (m, 2H), 3.65–3.83 (m, 1H), 6.16 (d, *J*=3.0 Hz, 1H), 6.34 (dd, J^{I}=7.0 Hz, J^{II}=3.0 Hz, 1H), 7.23 (t, *J*=7.0 Hz, 1H), 7.42–7.60 (m, 3H), 8.22 (d, *J*=8.0 Hz, 2H), 8.67 (s, 1H), 12.00 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 31.5, 36.8, 41.4, 104.6, 106.8, 109.7, 118.9, 121.2, 124.2, 128.4, 129.4, 138.3, 141.3, 149.3, 155.2, 155.4, 162.0, 194.2; HRMS (ESI) calculated for $C_{20}H_{15}N_3O_2Na$ (M+Na$^+$) 368.1011; found, 368.1049; IR (KBr), cm^{-1}: 1593, 1656, 3132.

5.6. General procedure for the synthesis of *N*-substituted 2-pyridone-3-carboxylic acid amides 15

The requisite aniline (7.2 mmol) was dissolved in acetic acid (15 mL). Piperidinium 2-[2-cyano-2-(*N*′-phenyl-hydrazinocarbonyl)-vinyl]-5,5-dimethyl-3-oxo-cyclohex-1-enate **9a** (2.89 g, 6.6 mmol) was added and the solution stirred at room temperature for 10–15 min. Following this, water (15 mL) was added to precipitate the product. The solid product was filtered off, washed with water, and dried. Generally, the product obtained in this manner did not require additional purification.

*5.6.1. 1-(4-Fluoro-phenyl)-7,7-dimethyl-2,5-dioxo-1,2,5,6,7,8-hexahydro-quinoline-3-carboxylic acid N′-phenyl-hydrazide (**15a**).* Yield: 1.77 g, 64%; mp 191–195 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.97 (s, 6H), 2.44 (s, 4H), 6.71–6.76 (m, 3H), 7.15 (t, *J*=8.1 Hz, 2H), 7.49 (t, *J*=8.8 Hz, 2H), 7.51–7.55 (m, 2H), 8.08 (d, *J*=3.6 Hz, 1H), 8.78 (s, 1H), 10.45 (d, *J*=3.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 28.4, 33.2, 42.6, 50.0, 112.9, 114.0, 117.5, 119.1, 119.5, 129.5, 130.9, 134.0, 140.1, 149.5, 160.6, 161.6, 163.2, 163.5, 194.2; HRMS (ESI) calculated for

$C_{25}H_{26}N_3O_4Na$ ($M+Na^+$) 432.1923; found, 432.1930; IR (KBr), cm^{-1}: 1657, 1710, 2959, 3301.

*5.6.2. 1-(3-Chloro-phenyl)-7,7-dimethyl-2,5-dioxo-1,2,5,6,7,8-hexahydro-quinoline-3-carboxylic acid N′-phenyl-hydrazide (**15b**).* Yield: 1.72 g, 60%; mp 212–214 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 0.99 (s, 6H), 2.44 (s, 4H), 6.72–6.75 (m, 3H), 7.16 (t, J=7.8 Hz, 2H), 7.48 (s, 1H), 7.65–7.72 (m, 3H), 8.08 (d, J=3.7 Hz, 1H), 8.78 (s, 1H), 10.41 (d, J=3.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 28.4, 33.3, 42.5, 50.1, 113.0, 114.1, 119.2, 119.5, 127.6, 128.8, 129.8, 130.4, 132.2, 134.7, 139.0, 140.2, 149.5, 160.2, 163.0, 163.4, 194.2. Anal. Calcd ($C_{24}H_{22}ClN_3O_3$): C, 66.13; H, 5.09; N, 9.64. Found: C, 66.02; H, 5.00; N, 9.69; IR (KBr), cm^{-1}: 1637, 1677, 2918, 3437.

*5.6.3. 1-(2-Methoxy-phenyl)-7,7-dimethyl-2,5-dioxo-1,2,5,6,7,8-hexahydro-quinoline-3-carboxylic acid N′-phenyl-hydrazide (**15c**).* Yield: 1.79 g, 63%; mp 165–167 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 0.97 (d, J=23.6 Hz, 6H), 2.21 (d, J=17.8 Hz, 1H), 2.47 (d, J=6.2 Hz, 2H), 2.60 (d, J=17.8 Hz, 1H), 3.82 (s, 3H), 6.70–6.76 (m, 3H), 7.13–7.21 (m, 3H), 7.32 (d, J=7.9 Hz, 1H), 7.40 (d, J=7.9 Hz, 1H), 7.59 (t, J=7.9 Hz, 1H), 8.05 (d, J=3.6 Hz, 1H), 8.78 (s, 1H), 10.43 (d, J=3.6 Hz, 1H); HRMS (ESI) calculated for $C_{24}H_{23}N_3O_3Na$ ($M+Na^+$) 420.1723; found, 420.1627; IR (KBr), cm^{-1}: 1601, 1672, 2957, 3281.

5.7. General procedure for the synthesis of 2-pyridone-3-carboxylic acid amides 18

Dimethylammonium 2-(2-carbamoyl-2-cyano-1-ethenyl)-5,5-dimethyl-3-oxo-1-cyclohexen-1-olate **4a**[14] (500 mg, 1.8 mmol) was dissolved in water (10 mL). The requisite arylhydrazine hydrochloride (1.8 mmol) was dissolved in water (10 mL) at 40 °C. The two solutions were combined and stirred vigorously. The oily residue came out of the aqueous reaction mixture and crystallized during stirring for 1 h. The resulting reddish precipitate was filtered out, washed by 2 mL of 2-propanol and dried under vacuum.

Alternatively, 2-pyridone-3-carboxylic acid amide **18c** can be obtained via hydration of 2-pyridone-3-carbonitrile **9c** (307 mg, 1.0 mmol) by heating at reflux temperature in dioxane (3 mL) with an excess of acetamide (590 mg, 10.0 mmol), $PdCl_2$ (17.6 mg, 10 mol %), and durene (40 mg, 30 mol %). A 30% conversion was observed by HPLC and ^1H NMR.

*5.7.1. 7,7-Dimethyl-2,5-dioxo-1-phenylamino-1,2,5,6,7,8-hexahydro-quinoline-3-carboxylic acid amide (**18a**).* Yield: 240 mg, 41%; mp 230–232 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 1.04 (s, 6H), 2.49 (s, 2H), 2.80 (d, J=15 Hz, 1H), 3.23 (d, J=15 Hz, 1H), 6.66 (d, 2H), 6.89 (t, 1H), 7.24 (t, 2H), 7.74 (s, 1H), 8.39 (s, 1H), 8.80(s, 1H), 9.29 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 28.4, 28.6, 32.8, 44.9, 113.2, 113.4, 119.7, 121.6, 120.9, 130.0, 139.9, 146.9, 158.9, 162.2, 163.1, 164.2, 194.2; HRMS (ESI) calculated for $C_{18}H_{19}N_3O_2Na$ ($M+Na^+$) 348.1324; found, 348.1354; IR (KBr), cm^{-1}: 1672, 2887, 2959, 3280, 3389.

*5.7.2. 7,7-Dimethyl-2,5-dioxo-1-m-tolylamino-1,2,5,6,7,8-hexahydro-quinoline-3-carboxylic acid amide (**18b**).* Yield: 214 mg, 35%; mp 212–214 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 1.01 (s, 6H), 2.20 (s, 3H), 2.47 (s, 2H), 2.75 (d, J=19 Hz, 1H), 3.20 (d, J=19 Hz, 1H), 6.37–6.50 (m, 2H), 6.89 (d, 1H), 7.08 (d, 1H), 7.73 (s, 1H), 8.38 (s, 1H), 8.77(s, 1H), 9.20 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 28.5, 28.6, 30.1, 33.2, 43.8, 110.2, 113.0, 118.0, 120.6, 122.9, 135.3, 141.9, 147.9, 160.0, 163.2, 165.0, 166.2, 193.0; HRMS (ESI) calculated for $C_{19}H_{21}N_3O_2Na$ ($M+Na^+$) 362.1114; found, 362.1124; IR (KBr), cm^{-1}: 1680, 1695, 2880, 2959, 3045, 3246, 3370.

*5.7.3. 1-(2,4-Dimethyl-phenylamino)-7,7-dimethyl-2,5-dioxo-1,2,5,6,7,8-hexahydro-quinoline-3-carboxylic acid amide (**18c**).* Yield: 234 mg, 37%; mp 218–220 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 1.00 (s, 6H), 2.15 (s, 3H), 2.28 (s, 3H), 2.46 (s, 2H), 2.80 (br s, 1H), 3.15 (br s, 1H), 6.01 (d, J=8 Hz, 1H), 6.76 (d, J=8 Hz, 1H), 6.95 (s, 1H), 7.70 (s, 1H), 8.39 (s, 1H), 8.40 (s, 1H), 8.78 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 28.4, 28.6, 29.3, 30.1, 34.4, 43.3, 109.6, 113.0, 119.1, 122.3, 122.9, 137.5, 144.7, 148.9, 161.0, 163.7, 164.9, 167.0, 194.0; IR (KBr), cm^{-1}: 1509, 1544, 1695, 2953, 3148, 3350; MS (EI) m/z: 353(M^+), 354, 336, 321, 218. Anal. Calcd ($C_{20}H_{23}N_3O_3$): C, 67.97; H, 6.56; N, 11.89. Found: C, 68.19; H, 6.62; N, 11.87.

5.8. X-ray study for the compounds 13a and 18c

The compound **18c** exists in the crystal phase as the hemisolvate with acetone (Fig. 2). The cyclohexenone ring in the molecules **13a** and **18c** adopts a sofa conformation where the deviation of the C3 atom from plane of remaining atoms of ring is 0.68 Å in molecule **13a** and −0.64 Å in molecule **18c** (Figs. 1 and 2). The phenyl substituent in the molecule **13a** is almost coplanar to the plane of pyrazole heterocycle (the C10–N3–C13–C18 torsion angle is −12.1 (2)°) due to the formation of the C14–H···N2 and C18–H···N1 weak intramolecular hydrogen bonds (H···N 2.40 Å, C–H···N 101° and H···N 2.41 Å, C–H···N 126°, respectively). The carbamide group in the molecule **18c** is coplanar to the pyridine ring (the C7–C8–C10–O2 torsion angle is 1.6 (3)°). Such conformation of this substituent is stabilized by the N3–H···O1 intramolecular hydrogen bond (H···O 2.05 Å, N–H···O 128°). Dimethylphenyl group of the substituent at the N1 atom is orthogonal to the pyridine ring and is slightly turned relatively the hydrazine fragment (the C1–N1–N2–C11 and N1–N2–C11–C16 torsion angles are 103.1 (2)° and −21.8 (3)°, respectively). The N2 atom of the hydrazine fragment has pyramidal configuration where the sum of bond angles centered on this atom is 348°.

In the crystal phase the molecules **13a** and **18c** has similar main packing motif forming the centrosymmetric dimers due to the formation of the O2–H···O1″ (2−x, 1−y, 1−z) H···O 1.74 Å O–H···O 176° and C7–H···O1″ (2−x, 1−y, 1−z) H···O 2.31 Å C–H···O 142° intermolecular hydrogen bonds in the case of **13a** and the N3–H···O2″ (2−x, 3−y, 1−z) H···O 1.98 Å N–H···O 170° in the case of **18c**.

Atomic coordinates and crystallographic parameters have been deposited to the Cambridge Crystallographic Data Centre (CCDC 799081 for **13a** and 799080 for **18c**).

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.02.052.

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