# Rapid Three-Step One-Pot Microwave-Assisted Synthesis of 2,5-Dioxo-1,2,5,6,7,8-hexahydro-3-quinolinecarbonitrile Library

Sergey A. Yermolayev, Nikolay Yu. Gorobets,* and Sergey M. Desenko

*Department of Chemistry of Heterocyclic Compounds, SSI "Institute for Single Crystals" of National Academy of Sciences of Ukraine, Lenin Avenue 60, Kharkiv 61001, Ukraine*

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Many well-known drugs contain 2-pyridone and 2-quinolone scaffolds. In the current paper, a one-pot three-step microwave-assisted method for the synthesis of N1-substituted 2,5-dioxo-1,2,5,6,7,8-hexahydro-3-quinolinecarbonitrile derivatives was developed. Employing this protocol, we quickly generated 105 compounds library from 1,3-cyclohexanediones, dimethylformamide dimethylacetal, and various cyanacetamides.

## Introduction

Various 2-pyridone and 2-quinolone analogs are well-known to exhibit antiphlogistic (pirfenidone **1**, Chart 1),[1] antiulcer,[2] and antifungal[3] properties, as well as activities useful in conditions, such as heart failure (milrinone **2**)[4,5] and Alzheimer's disease (Huperzine A **3**).[6,7] Some representatives are reported as specific non-nucleoside reverse transcriptase inhibitors of human immunodeficiency virus-1 (HIV-1)[8,9] and other valuable biologically active agents.[10,11]

Recent reviews on the 2-pyridone chemistry display an increase of the interest in this field.[12,13] In the last years, considerable attention has been also focused on the microwave-assisted synthesis of these compounds.[13a] This technology provides fast optimization of the reaction conditions that is necessary especially for combinatorial chemistry.[13] In our previous papers, we have described methodologies for the synthesis of N1-(un)substituted 2,5-dioxo-1,2,5,6,7,8-hexahydro-3-R-quinoline derivatives containing different functions in the position 3 of the 2-pyridone ring.[14−16] These methods apply the cyano function of methylene active nitriles to form the 2-pyridone ring.

In the current study, we report a facile three-step one-pot microwave-assisted protocol for the synthesis of the 2,5-dioxo-1,2,5,6,7,8-hexahydro-3-quinolinecarbonitrile combinatorial library **4**{*1*−*5*,*1*−*21*}, employing dimethylformamide dimethylacetal **5**, various cyanacetamides **6**{*1*−*21*} (Table 1) and 1,3-cyclohexanediones **7**{*1*−*5*} (Scheme 1). In this case, the reactivity of the amide group of N-substituted cyanoacetoamides **6**{*1*−*21*} is used for the 2-pyridone ring construction. A few representatives of such compounds were first obtained earlier using alternative synthetic routes.[17]

The preparation of 2,5-dioxo-1,2,5,6,7,8-hexahydro-3-quinolinecarbonitriles **4**{*1*−*5*,*1*−*21*} was based on a one-pot three-step synthesis. The first formation of the enamine **8** was generally done by stirring of 1,3-cyclohexanediones **7**{*1*−*5*} with DMFDMA **5** in a microwave process vial at room temperature for 5 min (Scheme 1). In the case of 5-(3,4-dimethoxyphenyl)-1,3-cyclohexanedione **7**{4}, to complete this reaction it was necessary to apply isopropyl alcohol as solvent at 100 °C for 2 min under microwave irradiation. The following one-pot reaction was between enamine **8** and various N-substituted cyanacetamides **6**{*1*−*21*} (Table 1) with excess of piperidine which led to piperidinium salts **9** at room temperature.[15] The microwave-assisted cyclization (120 °C for 10 min) of the salts **9** led to 2,5-dioxo-1,2,5,6,7,8-hexahydro-3-quinolinecarbonitriles **4**{*1*−*5*,*1*−*21*} in alcohol-aqueous media with good yields and acceptable purity, isolated by simple filtration, and did not require purification (Table 2). When an additional purification is required, the

**Chart 1. Biologically Active 2-Pyridone Derivatives**

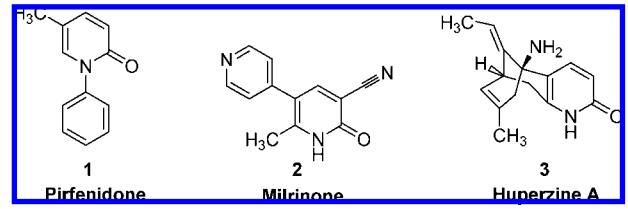
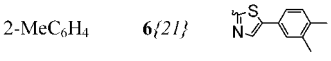



**Table 1.** Blocks **6**{*1*−*21*}

| № | $R^3$ | № | $R^3$ |
|---|---|---|---|
| **6**{*1*} | 4-$ClC_6H_4$ | **6**{*12*} | 3-$FC_6H_4$ |
| **6**{*2*} | 3,4-di-$MeC_6H_3$ | **6**{*13*} | 4-$MeC_6H_4$ |
| **6**{*3*} | 2-$MeOC_6H_4$ | **6**{*14*} | 3-$MeC_6H_4$ |
| **6**{*4*} | 4-$FC_6H_4$ | **6**{*15*} | 2,3-di-$MeC_6H_3$ |
| **6**{*5*} | 4-$COMeC_6H_4$ | **6**{*16*} | 4-$COOEtC_6H_4$ |
| **6**{*6*} | 2-Me-3-$ClC_6H_3$ | **6**{*17*} | 4-$CF_3OC_6H_4$ |
| **6**{*7*} | 4-$EtOC_6H_4$ | **6**{*18*} | 2-$EtC_6H_4$ |
| **6**{*8*} | 2,4,6-tri-$MeC_6H_2$ | **6**{*19*} | 3,5-di-$MeC_6H_3$ |
| **6**{*9*} | 3-Cl-4-$MeOC_6H_3$ | **6**{*20*} | 3,5-di-$MeOC_6H_3$ |
| **6**{*10*} | 2-$MeC_6H_4$ | **6**{*21*} |  |
| **6**{*11*} |  | | |

* To whom correspondence should be addressed. E-mail: gorobets@isc.kharkov.com. Fax: +38 (057) 340 9343.

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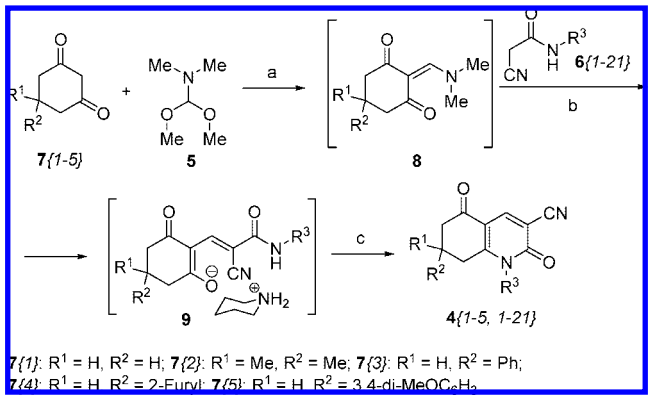
**Scheme 1**[a]



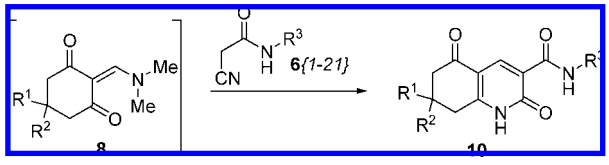

[a] Reagents and conditions: (a) rt, 5 min; (b) the same vial, *i*-PrOH, piperidine (2.0 equiv), rt, 10 min; (c) the same vial, $H_2O$, MW, 120 °C, 10 min.

**Table 2.** Yields and Purities for Random Sampling Compounds of the Library **4**{*1*−*5*,*1*−*21*}

| product | yield[a], % | purity[b], % |
|---|---|---|
| **4**{*2*,*11*} | 72 | 94 |
| **4**{*2*,*8*} | 72 | 98 |
| **4**{*2*,*9*} | 67 | 96 |
| **4**{*2*,*14*} | 64 | 98 |
| **4**{*2*,*15*} | 63 | 99 |
| **4**{*1*,*15*} | 65 | 98 |
| **4**{*1*,*6*} | 70 | 97 |
| **4**{*1*,*19*} | 62 | 94 |
| **4**{*4*,*2*} | 53 | 80 |
| **4**{*4*,*13*} | 45 | 85 |
| **4**{*4*,*3*} | 60 | 93 |
| **4**{*4*,*11*} | 54 | 96 |
| **4**{*5*,*12*} | 49 | 90 |
| **4**{*5*,*3*} | 59 | 95 |
| **4**{*5*,*4*} | 42 | 81 |
| **4**{*5*,*15*} | 40 | 80 |
| **4**{*5*,*6*} | 45 | 89 |
| **4**{*3*,*13*} | 49 | 84 |
| **4**{*3*,*11*} | 45 | 80 |
| **4**{*3*,*7*} | 41 | 95 |

[a] Isolated yield over three reaction steps. [b] Purity was determined by HPLC on 254 nm wavelength.

**Scheme 2**[a]




[a] Reagents and conditions: *i*-PrOH, piperidine (catalytic amounts), MW, 100 °C, 5 min.[14]

product generally can be recrystallized from acetone. In the most cases the major impurities detected by $^1$H NMR spectroscopy were intermediate salts **9** or the products of alternative reactions, for example, 2-pyridones **10** (see Scheme 2). The quantity of the latter impurity is increased when the reaction is carried out in the presence of less than 2.0 equiv of piperidine. The lower reaction temperature (MW, 100 °C, 10 min) is not enough for the cases of ortho-substituted building-blocks (e.g **6**{*3*}, **6**{*6*}, **6**{*10*}). Compared with the pure *i*-PrOH, the use of water as the major solvent component in the last stage (Scheme 1) appeared to be reliable because the intermediate salts **9** are soluble in water, and the target compounds **4**{*1*−*5*,*1*−*21*} are not.

Building blocks **7**{*1*}, **7**{*2*}, and DMFDMA are commercially available. The other 1,3-cyclohexanediones were prepared by the same way as described by Vorlander.[18] All the employed N-substituted cyanacetamides **6**{*1*−*21*} were prepared by cyanoacetylation of the corresponding amines with 1-cyanoacetyl-3,5-dimethylpyrazole in refluxing toluene following the known strategies.[14,19]

Formation of the target 2,5-dioxo-1,2,5,6,7,8-hexahydro-3-quinolinecarbonitriles **4**{*1*−*5*,*1*−*21*} occurred via intermediate hexahydropyridinium 2-[2-cyano-2-(2-arylcarbamoyl)-1-ethenyl]-5,5-dimethyl-3-oxo-1-cyclohexen-1-olates **9**. The isolation of the salts of the type **9** under the analogous conditions was described in our previous papers.[14−16]

Thereby, under the conditions proposed (Scheme 1), the amide group of the salts **9** reacts with the enol function and the target 3-quinolinecarbonitriles **4**{*1*−*5*,*1*−*21*} are formed. In contrast, the previously described protocol[14] applies the same starting materials and similar conditions leading to formation of corresponding 2,5-dioxo-1,2,5,6,7,8-hexahydro-3-quinolinecarboxamides **10** in the presence of only catalytic amounts of piperidine (Scheme 2).

The latter reaction applies the reactivity of the cyano group in the intermediates of type **9**. Apparently, the excessive amount of piperidine has a crucial role in the reaction mechanism alteration, increasing the amide group reactivity (Scheme 1). Also, strong basic catalysts, such as sodium hydride or alkoxides, are known to promote participation of unsubstituted amide group in the 2-pyridone ring formation.[20] However, in the presence of water the application of the strong bases is not acceptable and application of alcohols or DMF as solvents results in significantly lower yields of the products.

The structures of all the synthesized compounds were established by means of $^1$H NMR spectroscopy. The singlet of the 2-pyridone C−H is observed at 8.49−8.64 ppm. The spectra do not contain exchangeable NH protons, which are observed for compounds **10**. In the cases when $R^1$ and $R^2$ are not equal, the appearance of a chiral center in the molecules leads to coupling of $CH_2$ proton signals into complex multiplets. Also, in several cases, a hindered rotation of the N1-aryl radical probably causes the observed doubling of the singlets of the methyl groups in the radical (e.g., **4**{*5*,*3*}, **4**{*5*,*6*}). $^{13}$C NMR and mass spectra measured for a random sampling of the library do not contradict the product structures proposed. Purity of the compounds obtained was determined by means of HPLC and exceeded 80% (see Table 2 and Supporting Information for details).

In conclusion, we have developed a facile microwave-assisted protocol for generation of 7,7-dimethyl-2,5-dioxo-1,2,5,6,7,8-hexahydro-3-quinolinecarbonitriles library by the one-pot reaction between 1,3-cyclohexanediones **7**, DMFDMA **5**, and various cyanacetamides **6**. This synthesis represents an instance of a controlled mechanism reaction when the same reagents furnish different products dependently on the reaction conditions applied. In this way, by the change of basicity of the medium it is possible to involve amide or nitrile function into the 2-pyridon ring formation.

Thus, the application of the N-substituted cyanoacetamide building blocks in the reactions with enamines of type **8**

allows the synthesis of three types of products: 3-quinolinecarbonitriles **4** (Scheme 1), 3-quinolinecarboamides **10** (Scheme 2), and N1-substituted 3-quinolinecarboamides[15] via reaction of the isolated intermediates **9** with N-nucleophiles. These reactions enlarge the diversity of synthetically available potentially bioactive 2-pyridone derivatives that can be further applied for multiple target screening.

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**Supporting Information Available.** A general procedure for the synthesis of 7,7-dimethyl-2,5-dioxo-1,2,5,6,7,8-hexahydro-3-quinolinecarboxamide derivatives **4**{*1*−*5*,*1*−*21*} and $^{1}$H, $^{13}$C NMR, and HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

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