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A SIMPLE TWO-STEP SYNTHESIS OF ETHYL 2-OXO-1,2-DIHYDRO-3-QUINOLINECARBOXYLATE

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The efficient two-step procedure for the preparation of ethyl 2-oxo-1,2-dihydro-3-quinolinecarboxylate has been proposed. The synthesis is based on using stable and available reagents, it is simple in performance and with a high yield of the target product.

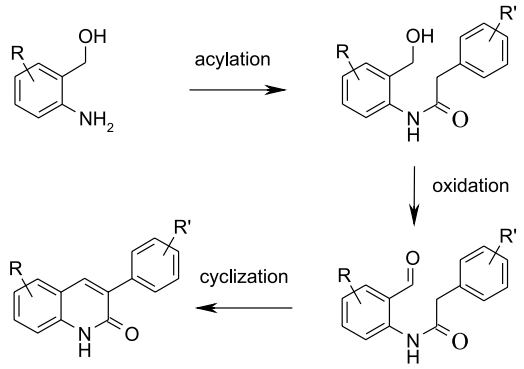
ПРОСТИЙ ДВОСТАДІЙНИЙ СИНТЕЗ ЕТИЛОВОГО ЕСТЕРУ 2-ОКСО-1,2-ДИГІДРОХІНОЛІН-3-КАРБОНОВОЇ КИСЛОТИ
І.В.Українець, О.В.Горохова
Запропоновано ефективний двостадійний метод одержання етилового естеру 2-оксо-1,2-дигідрохінолін-3-карбонової кислоти. Синтез оснований на використанні стійких і доступних реагентів, відрізняється простотою виконання та високим виходом цільового продукту.

ПРОСТОЙ ДВУХСТАДИЙНЫЙ СИНТЕЗ ЭТИЛОВОГО ЭФИРА 2-ОКСО-1,2-ДИГИДРОХИНОЛИН-3-КАРБОНОВОЙ КИСЛОТЫ
И.В.Украинец, О.В.Горохова
Предложен эффективный двухстадийный метод получения этилового эфира 2-оксо-1,2-дигидрохинолин-3-карбоновой кислоты. Синтез основан на использовании устойчивых и доступных реагентов, отличается простотой выполнения и высоким выходом целевого продукта.

For a long time the attention of scientists of different specialties has been drawn to 1,2-dihydro-2-quinolinones and their numerous derivatives unsubstituted in position 4. The sustainable interest to the compounds of this chemical group is explained by several reasons. Firstly, they are produced by many plants [1-4] and fungi [5], i.e. these are rather distributed in nature substances. Even only this fact is often sufficient to make an attempt to obtain them synthetically since nature reputedly does not create anything in vain. Secondly, 1,2-dihydro-2-quinolinone as a molecular system has a powerful synthetic potential with the possibility of unlimited chemical modification. That is why it can be a suitable matrix for fixing various elements-pharmacophores and, therefore, it allows to vary the properties of the substance created in the intended direction.

Therefore, it is not surprising that by now among 1,2-dihydro-2-quinolinones the biologically active substances with a wide spectrum of action have been found. For example, isolated from the bark of *Galipea officinalis* the alkaloids of this group are simultaneously effective against some strains of *Mycobacterium tuberculosis* [3]. Alkaloids of another plant – *Zanthoxylum hyemale* – have revealed the marked antispasmodic activity [4]. Serotonin 5-HT4 receptor agonists [6-8], inhibitors of steroid 5α reductases [9], local anesthetics [10, 11], and novel class selective of KDR kinase inhibitors [12, 13] have been found among synthetic derivatives of 1,2-dihydro-2-quinolinone. (*R*)-Indacaterol and other derivatives of 5-[(1*R*)-2-amino-1-hydroxyethyl]-8-hydroxy-1,2-dihydro-2-quinolinone related in their structure have been suggested as novel inhaled agonists of the β_2 adrenoceptor suitable for the treatment of asthma and chronic obstructive pulmonary disease [14, 15]. Of special interest is a new family of highly selective inverse agonists of cannabinoid receptor 2 (CB2), which play an important role in human physiology and pathophysiology of different diseases, including neuroinflammation, neurodegeneration, and cancer [16-18].

Ethyl 2-oxo-1,2-dihydro-3-quinolinecarboxylate (**1**) is a suitable base for obtaining many 1,2-dihydro-2-quinolinones. Nowadays several radically different schemes for synthesis of this scaffold have been described. The most widespread is reductive cyclization of (2-nitrobenzylidene)malonic acid diethyl ester differing only in details. Unfortunately, the yields only at the final stage reach seldom 65% [6, 19-22]. A better result can be achieved with the help of condensation of diethyl malonate with anthranilic aldehyde [23]. However, complexity of obtaining the key reagent of such synthesis – anthranilic aldehyde caused by its extremely great tendency to autocondensation deprives the method of any advantages at all. As a result it can find the application only in laboratory practice. The

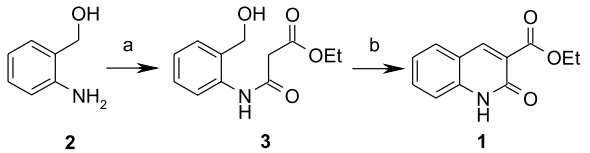


Scheme 1. The typical synthesis of 2-quinolinones that are unsubstituted in position 4 from 2-aminobenzyl alcohols.

problems connected with unstability of anthranilic aldehyde can be somewhat avoided by means of transformation of the aldehydic fragment of the initial 2-nitrobenzaldehyde, which precedes reduction, into less reactive group, for example, 1,3-dioxolan-2-ylic one [24]. But the necessity of introduction of the protective group makes this four-step procedure of obtaining ethyl 2-oxo-1,2-dihydro-3-quinolinecarboxylate (**1**) even more complex than the abovementioned reductive cyclization of (2-nitrobenzylidene)malonic acid diethyl ester. Another variant of synthesis of ethyl 2-oxo-1,2-dihydro-3-quinolinecarboxylate (**1**) – acylation of 1,2-dihydro-2-quinolinone by ethyl chloroformate [25] – is ambiguous, it gives quite a low yield and, thus, it is rather of theoretical interest than of practical one.

The original three-step assembly scheme of 1,2-dihydro-2-quinolinone core have been suggested for the synthesis of 3-aryl-substituted derivatives [26]. The method is interesting, first of all, because the use of available and stable 2-aminobenzyl alcohols as initial building-blocks is suggested. Their aromatic aminogroup is protected at once at the first stage by acylation with the corresponding arylacetyl chloride (Scheme 1). Therefore, the further oxidation of alcoholic hydroxyl into the aldehyde group with the help of pyridinium chlorochromate occurs without complications that are characteristic for synthetic works with a free anthranilic aldehyde. And, at last, the final third step is intramolecular quinolone cyclization catalyzed by bases.

We tried to use the similar synthetic scheme for obtaining ethyl 2-oxo-1,2-dihydro-3-quinolinecarboxylate (**1**). The only difference is in that we used ethyl malonyl chloride as a methylene active component instead of arylacetyl chloride, and pyridinium



Scheme 2. Synthesis of quinolone ester **1**.
Reagents and conditions: (a) $ClCOCH_2COOEt$, Et_3N, CH_2Cl_2, –15 °C, 94%; (b) MnO_2 activ., THF, 50°C, 89%.

chlorochromate as an oxidant was substituted by activated Manganese (IV) oxide. The reaction of 2-aminobenzyl alcohol (**2**) with ethyl malonyl chloride in the solution of dichloromethane at –15°C with a high yield gives ethyl 2-(2-hydroxymethylphenylcarbamoyl)acetate (**3**); it is basically optional to isolate and subject to further transformations without additional purification (Scheme 2). Though this method has some specific features directed to prevention of undesired alcoholic hydroxyl acylation, however, generally it is the common procedure for organic chemistry.

However, at first sight, unremarkable treatment of amido-ester (**3**) by activated manganese (IV) oxide in tetrahydrofuran gave rather unexpected result. Monitoring of this reaction performed with the help of thin-layer chromatography allowed to fix clearly the total absence of the initial amido-ester (**3**) in the reaction mixture already in 1.5 h after the start of the reaction. The real surprise is not this moment: it is the appearance of a new product appeared to be not the intermediate ethyl 2-(2-formylphenylcarbamoyl)acetate (that would be not surprisingly and quite logical), but the final ethyl 2-oxo-1,2-dihydro-3-quinolinecarboxylate (**1**). At first this bicyclic ester was identified by the value R_f comparing to the reference sample, then by spectral methods.

At the first stage alcoholic hydroxyl of amido-ester (**3**) under the action of activated manganese (IV) oxide is no doubt oxidized in the aldehyde group. However, the question about the catalyst of the further quinolone cyclization remains open. At present we only state the fact of occurance of two successive processes under the similar conditions – oxidation and intramolecular cyclization, the later is possible only due to the function appear as the result of the first reaction. Therefore, transformation of ethyl 2-(2-hydroxymethylphenylcarbamoyl)-acetate (**3**) into ethyl 2-oxo-1,2-dihydro-3-quinolinecarboxylate (**1**) in the presence of activated manganese (IV) oxide is domino reaction [27], and synthetic chemists are always take an active interest in it.

Experimental

The ^1H NMR spectra were recorded on a Varian Mercury VX-200 (200 MHz) instrument using DMSO-d_6 with TMS as internal standard. Mass spectra were obtained on a Varian 1200L spectrometer in full scanning mode in the range 35-700 *m/z* and EI ionization 70 eV. Elemental analysis was performed on EuroVector EA-3000 microanalyzer. The melting point was determined in a capillary on a Stuart SMP10 digital melting point analyzer. Chromatographic studies were performed on plates Sorbfil, developer – iodine vapor. Commercial activated manganese (IV) oxide from Aldrich was used in the work.

Ethyl 2-oxo-1,2-dihydro-3-quinolinecarboxylate (1). To the solution of 2-aminobenzyl alcohol (**2**)

(1,23 g, 0,01 mol) and triethylamine (1,40 mL, 0,01 mol) cooled to –15°C in 20 ml of CH_2Cl_2 dropwise add ethyl malonyl chloride (1,51 g, 0,01 mol) while mixing vigorously. In 4 h to the reaction mixture add 50 mL of water and acidify with 1N HCl to pH 4.5 stirring vigorously. Separate the organic layer and distill the solvent off (finally under reduced pressure). Dissolve the residue of crude amido-ester **3** in 30 mL of THF, add activated manganese (IV) oxide (85% 2,61 g, 0,03 mol) and boil while mixing for 2 h. Filter the hot reaction mixture through a fine-mesh filter, wash the filter residue several times with a hot THF. Purify the combined filtrate with activated charcoal, then evaporate to ~ 15 mL and cool in the ice bath. Filter the colorless crystals of quinolone ester **1** obtained and dry. The yield: 1.93 g (89%). Mp – 161-163°C (mp 160-161°C [23]). R_f 0.35 (Sorbfil, acetone-hexane, 2:3). ^{1}H NMR (200 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 12.03 (1H, s, NH); 8.46 (1H, s, H-4); 7.80 (1H, d, *J* = 8.0, H-5); 7.58 (1H, t, *J* = 7.8, H-7); 7.30 (1H, d, *J* = 8.3, H-8); 7.19 (1H, t, *J* = 7.5, H-6); 4.25 (2H, q, *J* = 7.3, OCH_2); 1.28 (3H, t, *J* = 7.3, CH_3). MS (EI) *m/z*: 217 $[M]^+$. A mixed sample of the quinolone ester **1** with the known sample prepared by condensation of diethyl malonate with anthranilic aldehyde [23] did not give a depression of the melting point. The ^{1}H NMR and mass spectra for these compounds were identical.

Ethyl 2-(2-hydroxymethylphenylcarbamoyl)acetate (3) can be isolated in a pure form, if necessary, and characterized. For this purpose the crude product (see the previous example) was recrystallized from aqueous ethanol. Colorless needles. Mp – 89-90°C. R_f 0.58 (Sorbfil, acetone-hexane, 2:3). ^{1}H NMR (200 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 9.55 (1H, s, NH); 7.48-7.39 (2H, m, H-3,6); 7.30-7.12 (2H, m, H-4,5); 5.22 (1H, t, *J* = 5.4, OH); 4.48 (2H, d, *J* = 5.4, $C\underline{H}_2OH$); 4.12 (2H, q, *J* = 7.0, OCH_2); 3.47 (2H, s, $COCH_2CO$); 1.21 (3H, t, *J* = 7.0, CH_3). MS (EI) *m/z*: 237 $[M]^+$. Elemental analysis: calcd. for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90%; found: C, 60.84; H, 6.44; N, 5,82%.

Conclusion

In conclusion it should be noted that this research presents a new and effective two-step synthesis of ethyl 2-oxo-1,2-dihydro-3-quinolinecarboxylate developed by us. Thanks to simplicity of carrying out the experiment, the use of stable and and available reagents, as well as a high yield of the target product, the suggested method for obtaining of this scaffold widely used in the synthesis of biologically active substances is more attractive than the previously known ones.

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