Article

Solid-Phase Synthesis of 3-Hydroxy-6-Nitroquinolin-4(1*H*)-ones with Two Diversity Positions

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The efficient solid-phase synthesis of 3-hydroxy-2,7-disubstituted-6-nitroquinolin-4(1*H*)-ones using Rink amide resin is described. Synthesis starts from immobilized 4-chloro-5-nitroanthranilic acid which, after the nucleophilic replacement of the chlorine atom with various amines and subsequent esterification with bromoacetophenones, afforded substituted phenacylanthranilates. Their cyclization by heating in sulfuric acid gave corresponding hydroxyquinolinones of excellent purity.

Introduction

3-Hydroxyquinolin-4(1*H*)-ones are an interesting group of compounds derived from the 4-quinolinone skeleton. From a historical point of view, 4-quinolinones belong among the most frequently studied synthetic as well as natural heterocycles. In contrast, synthetic derivatives of 3-hydroxyquinolin-4(1*H*)-ones only became a focus of research attention in the past decade, when a new synthetic route leading to this group of compounds was developed (Scheme 1).[1]

The procedure described was later successfully used for the preparation of various hydroxyquinolinones[2–5] and represents the simplest and also the most widely applicable solution-phase synthesis known so far. In addition, in 2007 the first solid-phase synthesis of hydroxyquinolinone-carboxamides was published[6] taking advantage of the same strategy.

The importance of synthesizing suitable hydroxyquinolinones can be illustrated by their promise as biological agents. Among the biological effects studied most frequently belongs their cytotoxicity against various cancer cell lines. In previous studies[4,5,7] we have shown that hydroxyquinolinones bearing certain specific structures/groups can exhibit in vitro cytotoxicity against cells sensitive to chemotherapy, as well as multiresistant subclones. The described cytotoxicity was observed toward selected lines (A549, K562, K562-Tax, CEM, CEM-DNRB) using the MTT test and reached, in certain cases, submicromolar concentration (IC_{50}). Patent protection has been applied for a selected group of compounds that also exhibited immunosuppresive effects.[7] In addition, other kinds of biological activities have also been described (topoisomerase inhibition,[8,9] an inhibition of inosine monophosphate dehydrogenase[10]), which stimulate our continuing interest in this group of compounds. Recently, the biological properties of hydroxyquinolinones have been reviewed.[11]

In this article, we describe the solid-phase synthesis of novel hydroxyquinolinone derivatives using 4-chloro-2-fluoro-5-nitrobenzoic acid as an excellent multifunctional building block suitable for this purpose. After immobilization via substitution of the fluorine atom with polymer supported amines, the resulting 4-chloro-5-nitroanthranilic acid offers various transformations (Figure 1) based on the chlorine atom substitution with various nucleophiles, subsequent nitro group reduction, and another possible modification of the resulting *o*-phenylenediamines.

After the esterification of the carboxylic group, the corresponding substituted anthranilates should be obtained as the starting material for the subsequent hydroxyquinolinone solution-phase preparation.

Results and Discussion

Theoretically, 4-chloro-2-fluoro-5-nitrobenzoic acid can serve as the starting material for the preparation of *N*-substituted as well as *N*-unsubstituted hydroxyquinolinones depending on the type of immobilized amine used. To evaluate our general synthetic route we first focused on the preparation of N-unsubstituted derivatives (**7**) using the Rink amide resin (Scheme 2).[12]

The difference in the reactivity of the chlorine and fluorine atom in 4-chloro-2-fluoro-5-nitrobenzoic acid toward nucleophilic substitution at moderately elevated temperature allowed the selective preparation of the immobilized 4-chloro-5-nitroanthranilic acid (**1**). The subsequent substitution of the chlorine atom was tested with a number of amino derivatives (Table 1).

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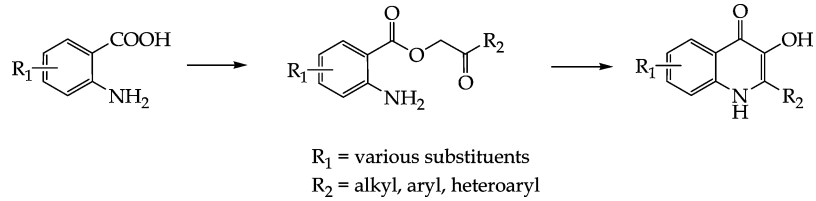
Scheme 1. General Preparation of Hydroxyquinolinones Using Rearrangement of Anthranilates



R_1 = various substituents
R_2 = alkyl, aryl, heteroaryl

Although a high temperature and, in the case of amines (**C**, **G**), catalysis by DIEA was required for the quantitative reaction, all building blocks used except ammonia gave the corresponding intermediates (**3**). The reaction times were highly dependent on the reactivity of the amines, but, after overnight heating, all tested substitutions were quantitative. Subsequently we focused on the reduction of the nitro group which we anticipated would lead to *o*-phenylenediamine derivatives (**4**). Since *o*-phenylenediamines are in general excellent starting materials for the synthesis of various nitrogen containing heterocyclic systems, the successful preparation of the intermediates (**4**) should dramatically increase the scope of the synthesis, especially if primary amines were used for the previous chlorine substitution. Unfortunately, we observed an interesting resistance of the nitro group toward various reducing agents (such as tin(II) chloride, lithium aluminum hydride, samarium iodide, diisobutyl aluminum hydride, sodium borohydride). In spite of this fact, we found that it was possible to smoothly reduce the intermediate (**1**) to aniline (**2**) using tin(II) chloride. This indicated that the resistance of the nitro group toward reduction was caused by the double-resonance effect of the electron donating amino groups in the ortho and para positions. Unfortunately, other powerful reducing methods,

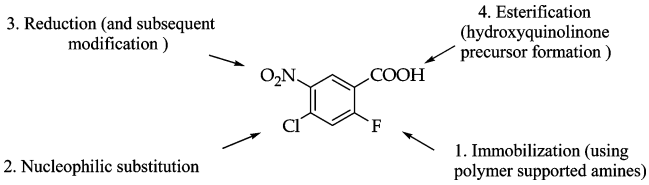
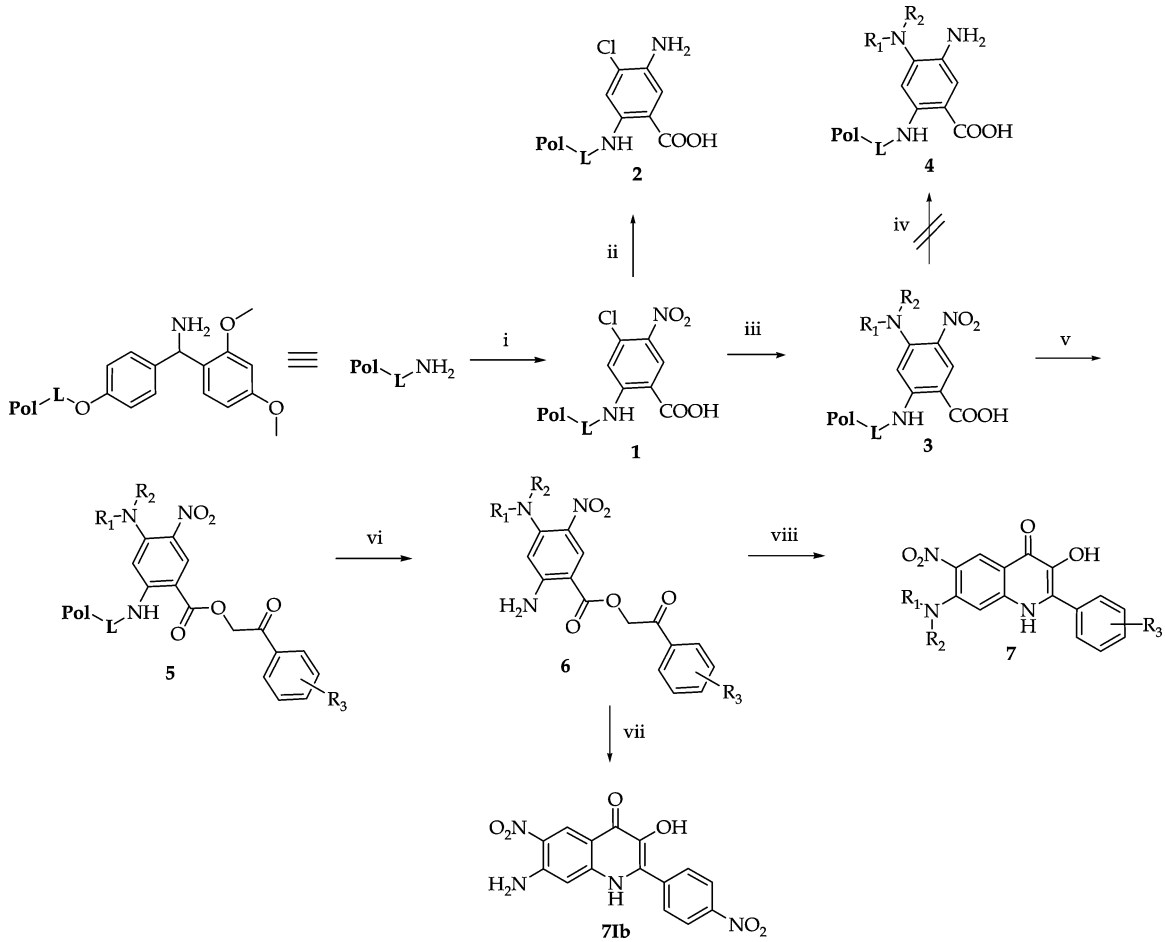


Figure 1. Strategy for using 4-chloro-2-fluoro-5-nitrobenzoic acid in the solid-phase synthesis of hydroxyquinolinones.

Scheme 2. Preparation of N-Unsubstituted Hydroxyquinolinones (**7**)[a]



[a] Reagents: (i) 4-chloro-2-fluoro-5-nitrobenzoic acid, DMSO, DIEA, 50 °C, overnight; (ii) $SnCl_2.2H_2O$, DIEA, DMF, rt, overnight; (iii) amine, DMSO (DIEA for C and G), 120 °C, overnight; (iv) $LiAlH_4$ or $SnCl_2.2H_2O$ or SmI_2 or DIBAL-H or $NaBH_4$, various conditions; (v) bromoketone, TEA, DMF, rt, 3 − 48 h; (vi) TFA, DCM, rt, 30 min; (vii) H_2SO_4, 100 °C, 2 h or TFA, reflux, 2 h; (viii) H_2SO_4, 100 °C, 2 h or TFA, reflux, 2−8 h or acetic acid (only for **6Aa**), reflux, 14 h (for details see experimental part).

Table 1. Amino Derivatives Used for the Substitution of the Chlorine Atom in Immobilized 4-Chloro-5-nitroanthranilic Acid

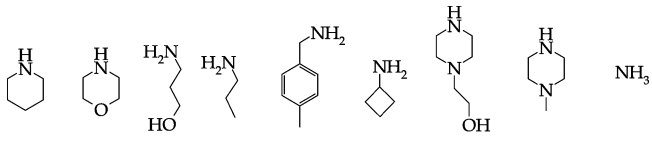
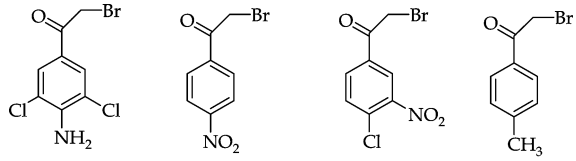


Table 2. Bromoacetophenones Used for the Esterification

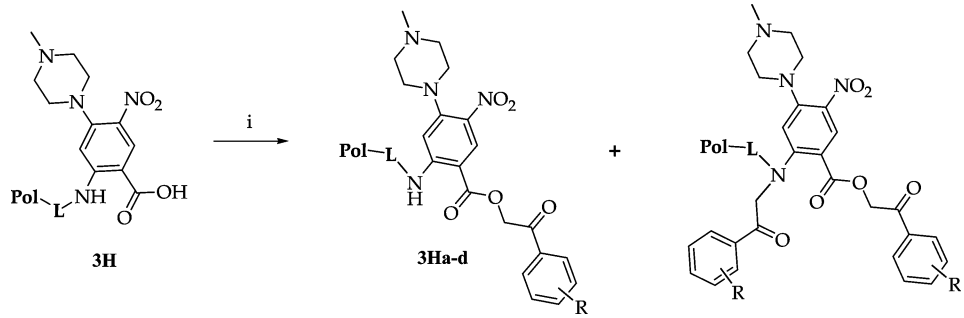


such as catalytic reduction or reduction with metals, could not be used because of their incompatibility with solid-supported reactions. To prepare the hydroxyquinolinone precursors (**5**), we subsequently esterified carboxylic acids (**3**) with four different bromoacetophenones (Table 2). The esterification times depended on the type of bromoketone used; for building blocks **a** and **d**, only a few hours were sufficient, while the reactions with bromoketones **b** and **c**, containing an electron-withdrawing nitro group, required 24−48 h for the quantitative esterification.

In most cases, the reactions afforded the pure corresponding anthranilates (**5**). However, during the esterification of the intermediate (**3H**), we observed formation of a double alkylated product (Scheme 2). The amount of the side product depended on each used bromoketone (**a**, **c**: 60%, **b**: 35%, **d**: 25%, LC-MS traces). Interestingly, except for the alkylation of intermediate (**3H**), the formation of such side products was not detected. The side products were not separated, therefore their structure estimation was based only on the MS analysis (Scheme 3).

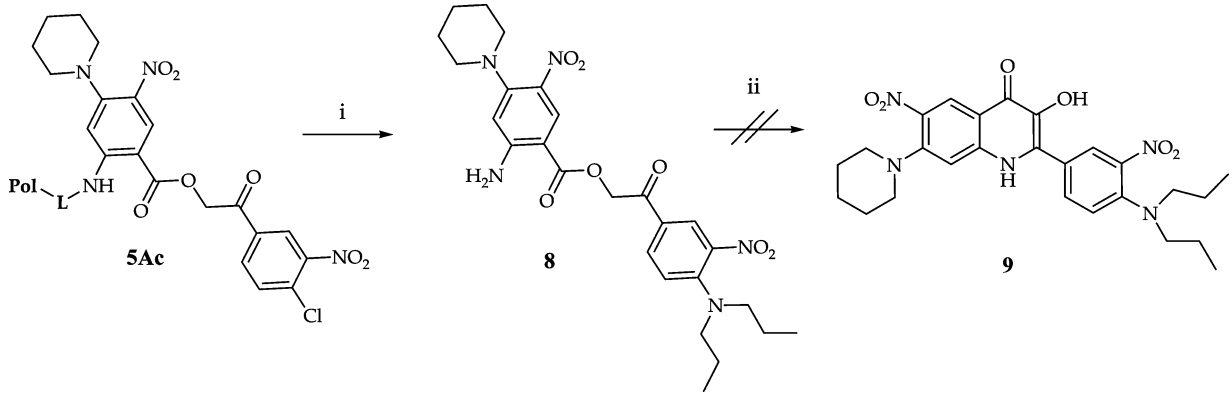
Intermediates **5** were then cleaved from the resin, and their cyclization to the corresponding hydroxyquinolinones (**7**) was tested by heating in acids. Surprisingly, the already described protocols with polyphosphoric acid,[2–5] trifluoroacetic acid,[6] or *N*-methylpyrrolidone[3] were not universally applicable. Polyphosphoric acid and *N*-methylpyrrolidone were unreactive while trifluoroacetic acetic furnished relatively better results: intermediates (**6Cd**), (**6Dd**), (**6Gd**), (**6Hd**), (**6Ca**), (**6Da**), (**6Ga**), and (**6Ha**) were successfully cyclized. However, the rest of the intermediates did not afford the corresponding hydroxyquinolinones which demonstrated the structure−reactivity dependence of the TFA cyclization. Hence we tested other potentially suitable cyclizing agents. When heated in acetic acid, only one hydroxyquinolinone **7Aa** from the whole set resulted. Finally we developed a new, generally applicable procedure using sulfuric acid and tested it successfully for all intermediates **6**. The derivative **7Eb** was not obtained because of the debenzylation following the cyclization of the intermediate **6Eb**, which produced 7-aminoderivative **7Ib** (cyclization in sulfuric acid and trifluoroacetic acid) (Scheme 2). The dealkylated product **7Ib** was obtained also when phenacylanthranilate **6Fb** was

Scheme 3. Formation of a Double Alkylated Products[a]



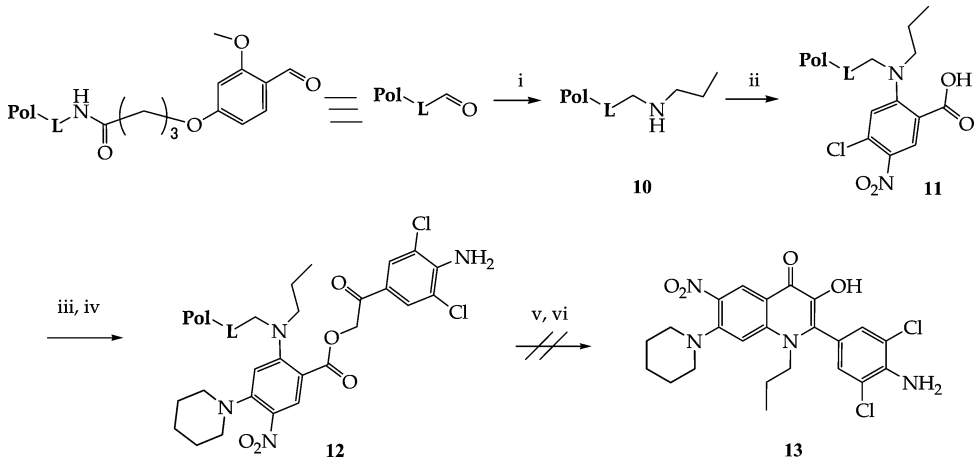
[a] Reagents: (i) bromoketone, TEA, DMF, rt, overnight for bromoketone **a** and **d**, 2 days for bromoketone **b** and **c**.

Scheme 4. Unsuccessful Preparation of Hydroxyquinolinones **9**[a]



[a] Reagents: (i) dipropylamine, DMSO, rt, overnight; TFA, DCM, rt, 30 min; (ii) TFA, reflux or AcOH, reflux or H_2SO_4, 100 °C.

Scheme 5. Attempt to Prepare *N*-Alkyl Hydroxyquinolinones **13**[a]



[a] Reagents: (i) propylamine, 10% AcOH in DMF, rt, overnight, then $NaBH(OAc)_3$, 5%AcOH in DMF, rt, 180 min; (ii) 4-chloro-2-fluoro-5-nitrobenzoic acid, DMSO, DIEA, 50 °C; (iii) piperidine, DMSO, 120 °C, overnight; (iv) 4-amino-3,5-dichloro-2′-bromacetophenone, TEA, DMF, rt, overnight; (v) TFA, DCM, rt, 30 min; (vi) TFA, reflux or AcOH, reflux or H_2SO_4, 100 °C or PPA 100 °C.

cyclized in sulfuric acid, however, the cyclization of phenacylanthranilate **6Fa** in TFA afforded required derivate **7Fa**. This indicates that cycloaliphatic amines can be used for the preparation of the corresponding hydroxyquinolinones, but they are not compatible with bromoacetophenones that contain electron-withdrawing nitro group as they do not undergo the cyclization in trifluoroacetic acid. After the cyclization, most of the products were isolated in an excellent crude purity of about 90−95%. A small number of hydroxyquinolinones were contaminated with side products (about 10−15%, LC-MS traces) which were identified as hydrolysis products **3** and discarded after sonification of the crude products **7** in potassium carbonate solution or diethyl ether. Products prepared using the building block **H** were not isolated because of their contamination after the esterification step (as described above).

In theory, the diversity of the intermediates **5A**−**G**,**c** can be extended by reaction with nucleophiles, for example, amino derivatives leading to nitroanilines **8**. Some hydroxyquinolinones with this kind of 2-phenyl-substitution have been described earlier as promising cytotoxic and imunosuppresive agents.[7] We tested the possible preparation of the similar hydroxyquinolinones **9** using dipropylamine as the model building block. The nucleophilic substitution of the chlorine atom took place under mild conditions; however, the cyclization of the intermediate **8** was unsuccessful. Heating in various acids, such as acetic acid, trifluoroacetic acid, or sulfuric acid, unfortunately did not give the required hydroxyquinolinone **9** (Scheme 4).

Finally, we were interested in the utilization of our synthetic route for the preparation of *N*-alkylated hydroxyquinolinones. Synthesis of *N*-methyl and *N*-phenyl derivatives using rearrangement of the corresponding phenacylanthranilates has been described only once.[3] In our previous article, we described an unsuccessful attempt to synthesize similar derivatives with use of TFA cyclization.[6] Concerning the biological effects, *N*-alkylated 2-arylhydroxyquinolinones are totally unexplored group of derivatives; hence, they still represent focus our interest. For the synthesis of *N*-alkylated hydroxyquinolinones, we used aminomethylated polystyrene resin equipped with BAL linker, and after reductive alkylation with propylamine **10**, we immobilized 4-chloro-2-fluoro-5-nitrobenzoic acid as *N*-propyl-4-chloro-5-nitroanthranilic acid **11**. After the chlorine substitution with piperidine and subsequent esterification with bromoketone **a**, we tried to cyclize the intermediate **12** to the corresponding *N*-propyl hydroxyquinolinone **13**. Unfortunately, the required rearrangement did not take place using any above-described procedure (Scheme 5).

In conclusion, we have developed an efficient and simple synthesis of 3-hydroxy-6-nitro-2-phenylsubstituted-quinolin-4(1*H*)-ones with two diversity positions. All reaction steps were completed with excellent purity including the final cyclization which afforded only minor impurities easily removable by simple purification methods. Thus, the described procedure contributes a powerful tool for the library synthesis of diverse target molecules from the large number of commercially available building blocks such as amines and bromoketones.

The unsuccessful reduction of the nitro group of immobilized intermediates is a challenge for more focused research. In addition, the unclear structure−reactivity relationship at play during the cyclization of phenacylesters to final hydroxyquinolinones will receive further attention.

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Supporting Information Available. Details of experimental procedures and spectroscopic data for synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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