American Journal of Clinical Microbiology and Antimicrobials

Mini Review
Published: 28 Jun, 2022

Strategies to Prepare Quinol-4-Ones

Milata V and Zálupsky P*

Department of Organic Chemistry, Institute of Organic Chemistry, Catalysis and Petrochemistry, Slovak

Abstract

This article is aiming at comprehensive simple review of main strategies for preparation of (substituted) quinol-4-one-3-carboxylic acids possessing antibacterial properties. On the background of many other reviews about detailed aspects of the synthesis, biological properties of products or relation structure-biological activity here we wish to present historical background of this group of drugs, used also in many other therapies, not only in those fighting bacteria.

Keywords: Quinol-4-one (I); Chemical structure and antibacterial; N-methylisatoic acid

Introduction

Quinol-4-one (I) without N- or O-substitution represent a tautomeric system in prototropic equilibria with its enol form – 4-hydroxyquinoline: Research and deep interest on quinol-4-ones started due to accidental discovery of the antibacterial activity [1] of the mother liquors after target synthesis of the antimalarics chloroquine in 60's [2]. Thus started the era of antibacterial quinolones or nalidixic acid type antibacterials, such as the first known antibacterial drug discovered by Lesher in 1962 [3]. Despite much effort to introduce newly prepared compounds into clinical praxis, many quinolones were rejected for both human and veterinary applications. Nevertheless, strategies to prepare new derivatives keep focusing on modification of substitution pattern skeleton by transformation of its substituent's. Another approach we first presented in [4] is based on classification of the synthesis of the quinol-4-ones on the basis of the last built bond of the skeleton. Due to enormous number of examples used to prepare the target substance we have used only selected few examples documenting this method, believing to be representative of this group (preferring the oldest one). From preparations we have selected those leading to quinol-4-one-3-carboxylic acid (derivatives).

Bond Creation N1-C8a

This strategy is the most popular one, suitable and mostly used for the preparation of 1-cyclopropyl-, and 1-aryl-substituted quinol-4-ones. In the key-step of the ring cyclisation starting from 2-X-nitrobenzoates/acetylbenzenes is required [5,6]: Alkylaminomethylene derivatives are also prepared from 3-oxoacetates by reaction with dialkylformamide dialkylacetales and following substitution of the dialkylamino group by alkyl/cycloalkyl/aryl amine or by analogous benzoylation of appropriate enaminoesters [5].

Bond Creation N1-C2

This approach exploits isatoic acid anhydride or 2-nitrobenzoyl chlorides thus producing 2-methyl-3-alkoxycarbonyl-quinol-4-ones from 2-(2´-aminoaroyl)-3-oxopropanoates [7]: (2´-aminoaroyl)-3-arylprop-2-enones after Michael-type addition or 2-iodo/bromoanilines with terminal alkynes under palladium (0) catalyzed carbonylation produce only 3-unsubstituted compounds.

Bond Creation C2-C3

Antranilates are exploited in this modified von Niementowski reaction [8]: A similar process, involving the reaction of the lithium salt of substituted acetophenone with N- methylisatoic acid anhydride, gives rise to 3-unsubstituted 1-metyl-2-aryl-quinol-4-one [9].

Bond Creation C3-C4

A similar approach based also on antranilic acid and α-oxomethylene compounds and followed by Dieckmann cyclization 1894CB1394. Some intermediates used by this methodology require (electro) oxidation: Snieckus extended this von Niementowski reaction to amides cyclized by lithium diisopropylamide [10].

Correspondence:
Viktor Milata, Department of Organic Chemistry, Institute of Organic Chemistry, Catalysis and Petrochemistry, Faculty of Chemistry and Food Technology, Slovak University of Technology in Bratislava, Radlinského Street 9, SK-812 37 Bratislava, Slovakia,
E-mail: viktor.milata@stuba.sk

Received Date: *12 May 2022*
Accepted Date: *23 Jun 2022*
Published Date: *28 Jun 2022*

Citation:
Milata V, Zálupsky P. Strategies to Prepare Quinol-4-Ones. Am J Clin Microbiol Antimicrob. 2022; 5(1): 1061.

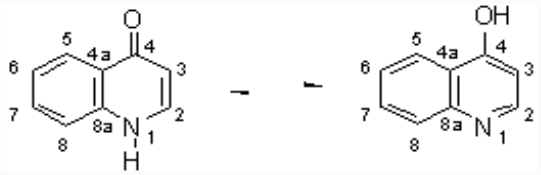

Figure 1: Quinol-4-one (I) without *N*- or *O*-substitution represent a tautomeric system in prototropic equilibria with its enol form – 4-hydroxyquinolin

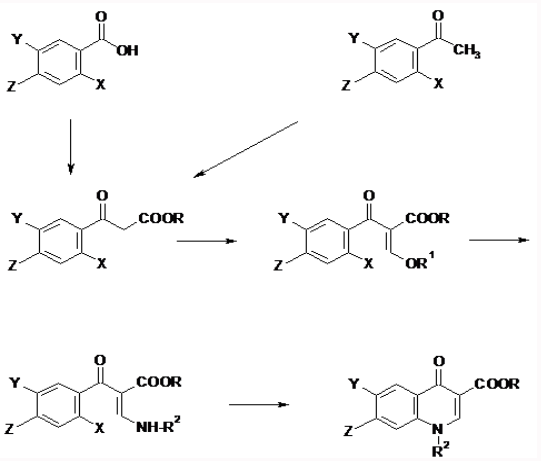

Figure 2: Aromatic nucleophilic denitrocyclization reactions in Adv. Heterocyclic.
X= F, Cl, Br, NO_2, RO, RS; Z, Y= Halogen N<; R, R^1, R^2= H, alkyl, aryl

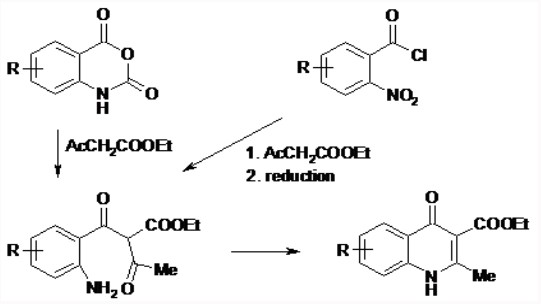

Figure 3: Approach exploits isatoic acid anhydride or 2-nitrobenzoyl chlorides thus producing 2-methyl-3-alkoxycarbonyl-quinol-4-ones from 2-(2´-aminoaroyl)-3-oxopropanoates.

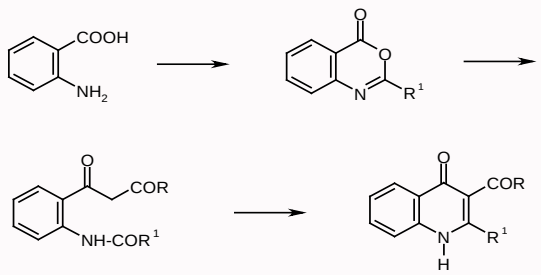

Figure 4: Involving the reaction of the lithium salt of substituted acetophenone with *N*-methylisatoic acid anhydride, gives rise to 3-unsubstituted 1-metyl-2-aryl-quinol-4-one.

Propynones, butyndioates or 2,3-pentanedienoate with or without palladium (0) catalyzed oxocarbonylation step produce 2,3-disubstituted-4-quinol-4-ones [11].

Bond Creation C4-C4a

This bond creation is the oldest method for the preparation of 3-substituted-quinol-4-ones. There exist therefore a number of reactions, frequently named according to their discoverer. The oldest reaction is the Just reaction exploiting imidoyl chlorides [12].

Conrad-Limpach reaction [13] produces 3- unsubstituted quinol-4-ones, but it is also superbly suitable for the preparation of the 2-alkyl- or 2- aryl analogues too. The youngest member of this strategy is the Gould-Jacobs reaction – the second most frequently

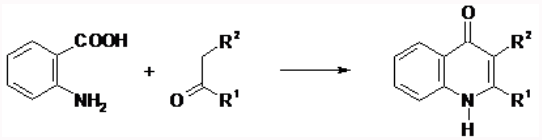

Figure 5: A similar approach based also on antranilic acid and α-oxomethylene compounds and followed by Dieckmann cyclization.

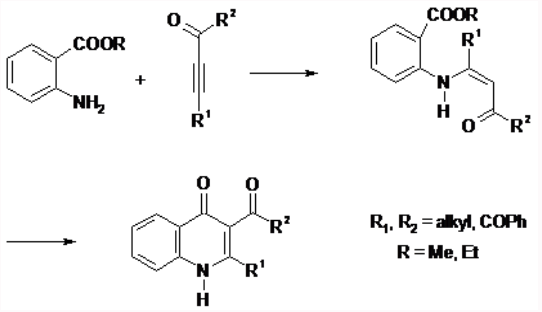

Figure 6: Catalyzed oxocarbonylation step produce 2,3-disubstituted-4-quinol-4-ones.

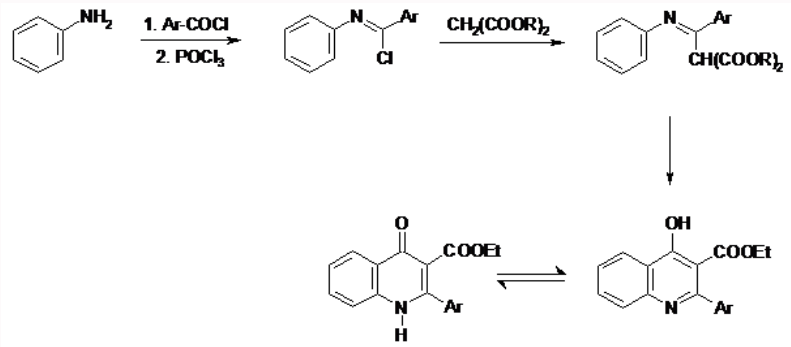

Figure 7: The oldest reaction is the Just reaction exploiting imidoyl chlorides Bond creation C4-C4a.

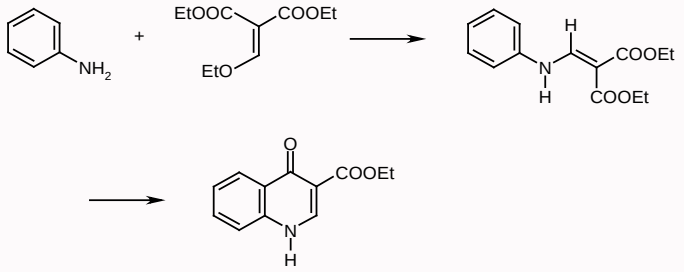

Figure 8: The reaction is suitable for preparation of 1-ethyl substituted quinol-4one-3-carboxylic acids. In the case of the use of unsymmetrically 3-substituted anilines reaction could lead to mixture of two products.

exploited type of reaction [14]. As a tandem of two reactions, starting with a nucleophilic substitution, followed by a thermal cyclization it has been known since 1939, although its first step was first carried out already in 1897 by Claisen [15]. Thermal ring-closure, the second step, was added by Camps in 1901 [16].

The mechanism of this reaction was first described [4]. The main advantage of this strategy is the use of cheap reagents, on the down side high temperature in the key-step are needed (about 250°C), but in inert media. The reaction is suitable for preparation of 1-ethyl substituted quinol-4one-3-carboxylic acids. In the case of the use of unsymmetrically 3-substituted anilines reaction could lead to mixture of two products [4,17].

Conclusion

Naturally numerous strategies to synthesize 3-substituted-quinol-4-ones combine profits with drawbacks. The most frequent used one is the N1-C8a bond creation strategy having no limitation with N-substituent, but on the other hand requires polyhalogenated precursors (mostly fluoro- and chloro-) which are required for subsequent substitution with secondary amine, naming at improving solubility (in position 7). Some additional fluorine atom(s) are also required in the target structure in position(s) 5-/6- or 8- in order to lower melting points and thus enhance solubility. Building benzene ring attached to pyrid-4-one is a rare strategy; so far only two examples have been described in literature.

Acknowledgement

This article was written thanks to the generous support under the Operational Program Integrated Infrastructure for the project: "Strategic research in the field of SMART monitoring, treatment and preventive protection against Coronavirus (SARS-CoV-2)", Project no. 313011ASS8, co-financed by the European Regional Development and with Fund Science and Technology Assistance Agency under contract No. APVV-17-0513 and APVV-20-0213.

References

1. Radl S. From chloroquine to antineoplastic drugs? The story of antibacterial quinolones. Arch Pharm. 1996;329:115-9.
2. Andersag H. Elberfeld: Bayer laboratories; 1934.
3. Lesher GY, Froelich EJ, Gruett MD, Bailey JH, Brundag RP. 1, 8-Naphthyridine derivatives. A new class of chemotherapeutic agents. J Med Pharm Chem. 1962;91:1063-5.
4. Milata V, Claramunt RM, Elguero J, Zálupský P. Chemical structure and antibacterial activity of 4- quinolones: Incidence in nature, preparations and properties. In: Attanasi OA, Spinelli D, editors. Targets in Heterocyclic Systems. 2000;4:167-203.
5. Grohe K, Heitzer H. Cycloaracylierung von Enaminen, II. Synthese von 1-Amino-4-chinolon-3-carbonsäuren. Liebigs Ann Chem. 1987;10:871-9.
6. Radl S. Aromatic nucleophilic denitrocyclization reactions. Adv Heterocycl Chem. 2002;83:189-257.
7. Agui H, Mitani T, Izawa A, Komatsu T, Nakagome T. Studies on quinoline derivatives and related compounds. VI. A novel displacement reaction of 1-ethylquinolinium iodides with nucleophiles. J Med Chem. 1977;20:791.
8. Clémence F, Le Martret O, Collard J. J Heterocyclic Chem. 1984;21:1345.
9. Kuo SC, Lee HZ, Juang JP, Lin YT, Wu TS, Chang JJ, et al. Synthesis and cytotoxicity of 1,6,7,8-substituted 2-(4'-substituted phenyl)-4-quinolones and related compounds: Identification as antimitotic agents interacting with tubulin. J Med Chem. 1993;36(9):1146-56.
10. Chong RJ, Siddiqui MA, Snieckus V. Tetrahedron Lett. 1986;27(44):5323.
11. Sinsky MS, Bass RG. The reactions of some ortho-substituted anilines with various α,β-acetylenic ketones. A route to substituted quinolines. J Heterocyclic Chem. 1984;21:759.
12. Just F. Chem Ber. 1985;18:2632.
13. Conrad M, Limpach L. Chem Ber. 1987;20:944.
14. Gould RG, Jacobs WA. The synthesis of certain substituted quinolines and 5,6-Benzoquinolines. J Amer Chem Soc. 1939;61(10):2890-5.
15. Claisen L. Justus Liebigs Ann Chem. 1897;297:77.
16. Camps R. Chem Ber. 1901;34:2714.
17. Albrecht R. Development of antibacterial agents of the nalidixic acid type. Prog Drug Res. 1977;21:9-104.