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REVIEW

Chemistry of 4-Hydroxy-2(1*H*)-quinolone. Part 1: Synthesis and reactions

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KEYWORDS

4-Hydroxy-2(1*H*)-quinolone;
Synthesis;
Chemical reactivity;
Tautomeric structure;
Reactions

Abstract This review summarizes results from the literature concerning the synthesis and chemical reactivity of 4-hydroxy-2(1*H*)-quinolone as well as its reactions that are reported. Most imaginable reaction types have been successfully applied and used, as many of the synthetized compounds exhibit interesting biological activity in various fields.

Contents

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1. Introduction

4-Hydroxy-2(1*H*)-quinolones are of great interest due to their roles in natural product chemistry and their fascinating pharmacological activities (Bessonova, 2000; Detsi et al., 1996; Clarke and Grundon, 1964; Grundon, 1978; Chauncey et al., 1988; Ngadjui et al., 1992; Ukrainets et al., 2007; Lager et al., 2006; Seman et al., 1997, 1998; Boteva et al., 2007, 2008; Yang, 1998a, 1998b; Cecchetti et al., 2000; Nakahira et al., 2009a, 2009b; Crespo et al., 2000; Hall et al., 1974; Suen et al., 2006; Liang et al., 2009; Meisel and Ciociola, 2004a, 2004b; Cutler (2001a,b), Chem. Abstr, 2001; Davies and Yates, 1995). These compounds have found numerous applications as antibacterial, antifungal (Arya and Agarwal, 2007; Smiley and Benkovic, 1995; O'Loughlin et al., 1999), analgesic (Ukraintos et al., 1994, 1995), dye-stuffs (Zieglar et al., 1963), herbicides (Bayer, 1956), orally active antagonists (Morsay and Lerson, 1994), anti-inflammatory (Haviv and Dewat, 1983, 1984), anti-allergenic (Ysoshizami et al., 1990a,b), antitubercular (Dodia and Shah, 1999) and cardiovascular agents (Meo et al., 1949). Additionally, these kind of compounds have been reported to show selective glycine site antagonists related to several central nervous system disorders including stroke, epilepsy, schizophrenia, Parkinson's disease, and Alzheimer's disease (Hwang, 2000; Mcleod et al., 1995; Carling et al., 1993a,b; Cai et al., 1996).

It has been impracticable to survey the literature of 4-hydroxy-2(1*H*)-quinolones completely. At the same time, the results of work on the chemistry of different derivatives of 4-hydroxy-2(1*H*)-quinolone are scattered over original papers, patents, and dissertations, unavailable to a wide circle of chemists. In the present review, I have thus chosen to summarize the most relevant advances in the construction of 4-hydroxy-2(1*H*)-quinolone, without any substituents attached, reported in the literature. It is hoped that this review will demonstrate the synthetic potential of 4-hydroxy-2(1*H*)-quinolone and generate some new ideas in this area.

2. Molecular structures and spectral properties

The structures of 4-hydroxy-2(1*H*)-quinolone have been assigned by UV (Abe et al., 2006; Fadda et al., 1991; Priya et al., 2010), IR (Bhudevi et al., 2009; Zhang, 2008; Sicker et al., 1987; Gao, 2010; Jung et al., 2001; Shobana et al., 1989; Balasubramanian et al., 1993; Pandey et al., 1989; Franck, 1971; Sterk and Ziegler, 1967; Omori et al., 1970; Price and Willis, 1959; Szorcsik et al., 2006; Bunce and Nammalwar, 2010), MS (Arya and Agarwal, 2007; Priya et al., 2010; Bhudevi et al., 2009; Zhang, 2008; Sicker et al., 1987; Hebanowska et al., 1986), fluorescence (Fabian, 1978) and NMR spectroscopy (Bessonova, 2000; Cheng et al., 2011; Ruano et al., 1991; Osborne et al., 1993; Ukrainets et al., 2006; Sterk and Holzer, 1974; Clarke, 1997). The ultraviolet spectrum of 4-hydroxy-2(1*H*)-quinolone revealed two intense bands in methanol at 269 and 314 nm (Priya et al., 2010). The analysis of IR spectrum of it showed characteristic bands in Nujol mull at 3360 cm^{-1} (OH), 1657 (C═O), and 1508 (C═C, arom.) Bunce and Nammalwar, 2010.

The proton NMR spectrum of 4-hydroxy-2(1*H*)-quinolone Ukrainets et al., 2006 revealed that only one signal is observed as a singlet at 5.77 ppm, typical chemical shift for hydrogens on non-aromatic double bonds and no other signal is observed with the exception of the four aromatic hydrogens (H-5, H-6, H-7, H-8). It shows two complex multiplets, of equal intensity, at 7.51 and 7.83 ppm due to the C-5 and C-6 protons, and two others at 7.16 and 7.30 ppm for the C-7 and C-8 protons, respectively. Also, the OH and NH signals appeared at 12.90 and 11.18 ppm, respectively.

A ^{13}C NMR study (Priya et al., 2010) of the 4-hydroxy-2(1*H*)-quinolone (Table 1) indicated that the C-2, C-4 and C-9 carbons resonate downfield, compared to the other carbons. Splitting pattern analysis showed the signal of the C-2 atom to be doublet due to its interaction with the only proton at position 3. The signals of C-4 are multiplets (doublets of doublets) due to splitting of H-3 and H-5 atoms.

Table 1 ^{13}C NMR spectra [39] of 4-hydroxy-2(1*H*)-quinolone (solvent, DMSO-d_6, chemical shifts are given in Hz).

C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
163.57,d	98.18,d	162.43,dd	121.04,dd	114.95,dd	130.82,dd	115.10,dd	115.10,dd 139.13,dd	122.62,dd

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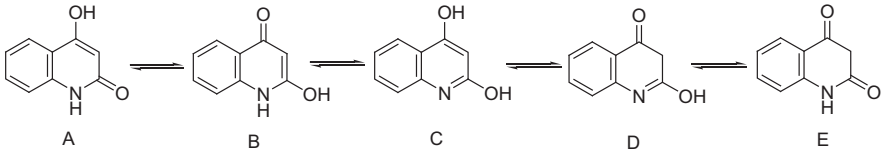


Figure 1 Possible tautomeric structures of 4-hydroxy-2(1*H*)-quinolone **1** (A-E).

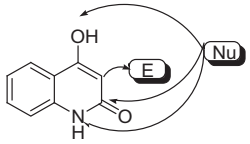
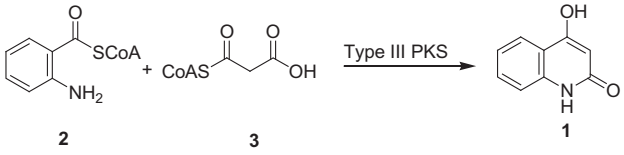
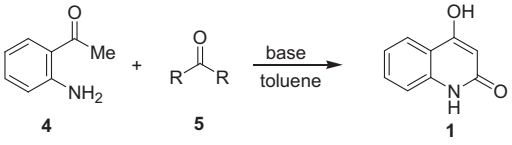


Figure 2 Chemical reactivity of 4-hydroxy-2(1*H*)-quinolone.



Scheme 1

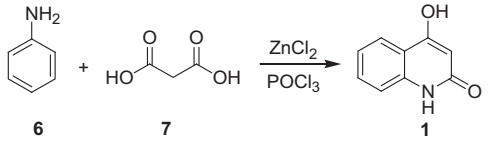


	a	b	c	d	e	f
R	OEt	OEt	OMe	OMe	Cl	Cl
Base	NaOEt	NaH	NaH	NaOEt	NaH	NaOEt
Yield (%)	76	81	79	76	65	61

Scheme 2

3. Tautomeric structure(s)

4-Hydroxy-2(1*H*)-quinolone can theortically exist in five possible tautomeric forms **1 A**–**E** (Fig. 1). However, in practice, the tautomerism is reduced to forms **1 A**–**C**. These three possible prototropic transformations have been intensively examined by various chemical reactivity, spectral, thermochemical, and computational methods (Ruano et al., 1991; Coppola et al., 1981; Elguero et al., 1976; Johnson, 1984). Additional studies by quantum chemical calculations using the LCAO-MO method in the CNDO/2 approximation showed that the dihydroxy tautomer **1c** is predicted to be slightly more stable (Hebanowska et al., 1986). The experimentally found predominance of both quinolone tautomers **1A** and **1B** in solution is explained by self-association in the latter case that stabilizes the oxo forms.



Scheme 3

4. Chemical reactivity

It is evident from the topography of 4-hydroxy-2(1*H*)-quinolone (Fig. 2) that it possesses both electrophilic and nucleophilic properties. The third position in the 4-hydroxy-2(1*H*)-quinolone ring is highly activated, because of the influence of the hydroxyl group with electron-donating properties and electron-withdrawing effects of carbonyl oxygen atom at the second place. There is a conjugation of *p*-electrons from the double bond and lone *p*-electron pairs from oxygen atom. These factors make the third position in the quinolone ring very convenient for many reactions. Thus reactions like coupling and halogenation reactions have taken place readily at such carbon. Recently Michael type addition was also described. The oxygen atom of the hydroxyl group however remains the main site for attack by acylating and alkylating agents. It seemed that hard nucleophiles attack preferentially oxygen atom and somewhat nitrogen atom, while the soft ones attack preferentially the carbon atom (Fig. 2).

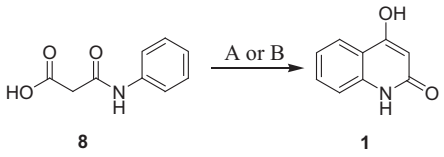
5. Synthesis

5.1. The biosynthetic pathway

Biosynthesis of 4-hydroxy-2(1*H*)-quinolone **1** involves benzalacetone synthase from Rheum palmatum efficiently catalyzed the condensation of anthraniloyl-CoA **2** with malonyl-CoA **3** to produce 4-hydroxy-2(1*H*)-quinolone **1**, a novel alkaloidal scaffold produced by a type III polyketide synthase (PKS) Abe et al., 2006 (Scheme 1).

5.2. The chemical synthetic pathway

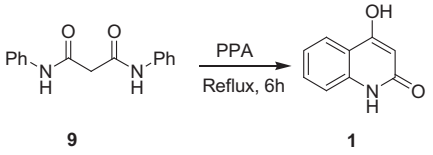
There are several methods for the synthesis of 4-hydroxy-2(1*H*)-quinolone in the literature. Most of them are not gen-



A : Eaton's reagent, 70 °C.
B : PPA, 140 °C.

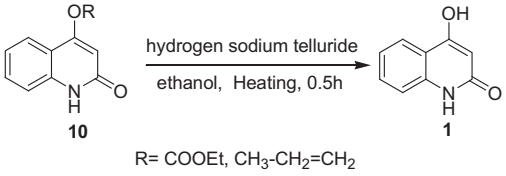
Scheme 4

eral and often involve many steps with low yields. This is probably the reason for the limited number of references in the literature regarding their reactivity. The following are some of the methods which have been used to prepare 4-hydroxy-2(1*H*)-quinolone.



9 1

Scheme 5

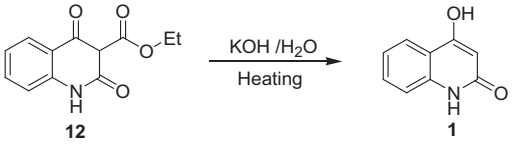


10 1

Scheme 6

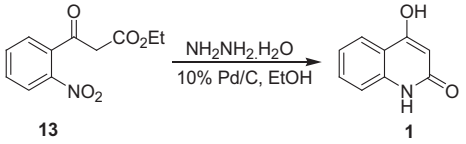
11

Scheme 7



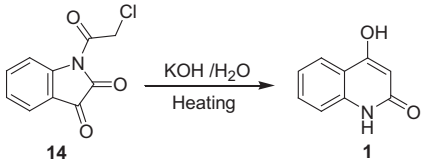
12 1

Scheme 8



13 1

Scheme 9



14 1

Scheme 10

5.2.1. Using 2-aminoacetophenone

The reaction of 2-aminoacetophenone **4** with acylating agents **5** such as phosgene, dimethylcarbonate, or diethylcarbonate in the presence of stoichiometric amount of base in anhydrous toluene afforded 4-hydroxy-2(1*H*)-quinolone **1** in variable yields (Scheme 2). It was found that sodium hydride was a more effective base than sodium ethoxide (Jung et al., 2001).

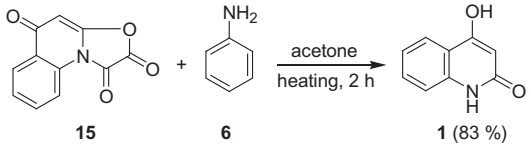
5.2.2. Using aniline

Condensation of aniline **6** with malonic acid **7** in the presence of a mixture of anhydrous zinc chloride and phosphorus oxychloride as the condensing agent furnished **1** (Seman et al., 1997, 1998; Boteva et al., 2007, 2008; Yang, 1998a) (Scheme 3). This environmentally unacceptable procedure suffers from many disadvantages like long reaction period, use of dehydrating agents ($ZnCl_2$) and hazardous reagent ($POCl_3$). Recently, it was found that, the yield was improved to be carried out under microwave condensation in the presence of *N*,*N*-dimethylformamide, which acts as an energy transfer agent and homogenizer to increase the reaction (Arya and Agarwal, 2007; Ahmed et al., 2010; Ahmed et al., 2011).

5.2.3. Using phenyl malonamides

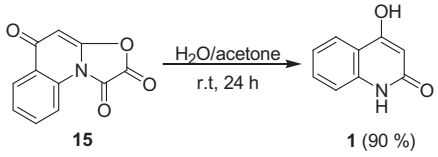
Intramolecular cyclization of malonic acid monophenyl amide **8** to form 4-hydroxy-2(1*H*)-quinolone **1** is a convenient procedure; the crucial problem to be solved is to reduce or eliminate the decarboxylation of the intermediates. Thus, Eaton's reagent (phosphoric anhydride and methyl sulfonic acid) (Gao, 2010; Im et al., 2009) or polyphosphoric acid (PPA) (Pandey et al., 1989; Patel and Mehta, 1960, 1961) was chosen as cyclization reagents in mild reaction condition (Scheme 4).

The synthesis of 4-hydroxy-2(1*H*)-quinolone **1** is also observed *via* cyclization of *N*,*N*$^{-}$-diphenyl malonamide **9** in the presence of polyphosphoric acid (PPA) at 140–150 °C



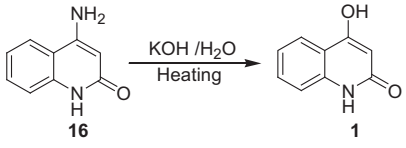
15 6 1 (83 %)

Scheme 11



15 1 (90 %)

Scheme 12



16 1

Scheme 13

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(Scheme 5) (Shobana et al., 1989; Cheng et al., 2011; Balasubramanian et al., 1996; Subramanian et al., 1992).

5.2.4. Using cleavage of 4-allyl quinoloneyl ether

Shobana et al. have described an efficient procedure for the synthesis of **1** *via* the cleavage of 4-allyl quinoloneyl ether (Shobana and Shanmugam, 1986) or quinoloneyl ethyl carbonate (Shobana et al., 1988) using a catalytic amount of hydrogen sodium telluride in acetic acid and ethanol (Scheme 6).

5.2.5. Hydrolysis and decarboxylation of 3-carbethoxy-4-hydroxy-2(1*H*)-quinolone

Short term (30 min) boiling of the ethyl ester of 4-morpholino-2-oxo-1,2-dihydroquinoline-3-carboxylic acid **11** in concentrated hydrochloric acid afforded 4-hydroxy-2(1*H*)-quinolone **1** Ukrainets et al., 2006 (Scheme 7).

In a similar manner, the base-catalyzed hydrolysis and decarboxylation of ethyl-4-hydroxyquinolin-2(1*H*)-one-3-carboxylate **12** in aqueous potassium hydroxide furnished 4-hydroxyquinolin-2(1*H*)-one **1** Koller, 1927 (Scheme 8).

5.2.6. Reduction cyclization

The reduction of ethyl 3-(2-nitrophenyl)-3-oxopropanoate **13** with hydrazine hydrate and 10% Pd/C in ethanol at 23 °C and subsequent cyclization lead to the formation of **1** in 86% yield (Scheme 9) Bunce and Nammalwar, 2010. Also, this reduction can be successfully carried out by means of hydrogen in the presence of platinum black catalyst (Sicker et al., 1987).

Huntress and Bornstein (1949), claimed that the reaction of *N*-chloroacetylisatin **14** with alkali gives 4-hydroxy-2(1*H*)-quinolone **1** (Scheme 10).

5.2.7. Using oxazoloquinolone

Aminolysis of oxazoloquinolone **15** with aniline **6** under heating in acetone for two hours gave 4-hydroxyquinolone **1** in 83% yield (El-Nabi, 1997) (Scheme 11).

Similarly, oxazoloquinolone **15** was easily hydrolyzed by a mixture of acetone/water at room temperature to give 4-hydroxyquinolone **1** in 90% yield (El-Nabi, 1997) (Scheme 12).

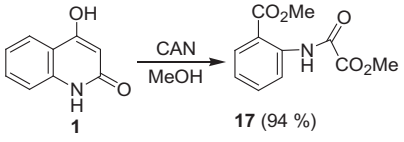
5.2.8. Hydrolysis of 2-amino-4-hydroxyquinoline

4-Amino-2-hydroxyquinoline **16** on heating with aqueous potassium hydroxide was smoothly hydrolyzed and converted into 4-hydroxyquinolone **1** (Hardman and Partridge, 1958) (Scheme 13).

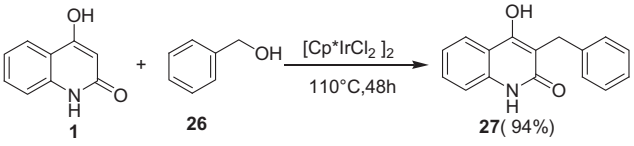
6. Reactions

6.1. Reactions involving cleavage of lactam ring

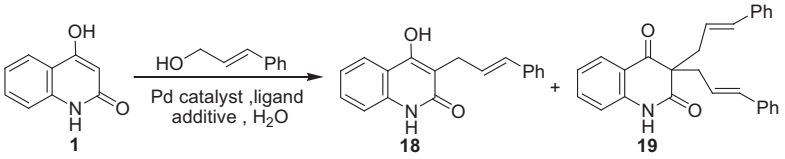
Reaction of **1** with two equivalents of cerium(IV) ammonium nitrate (CAN) in methanol at room temperature afforded



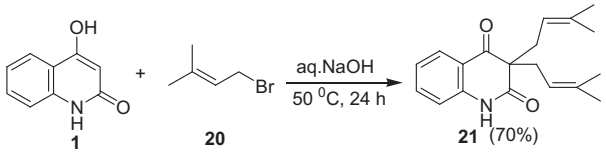
Scheme 14



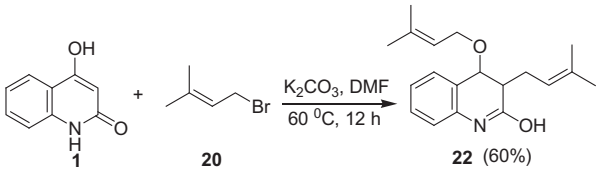
Scheme 19



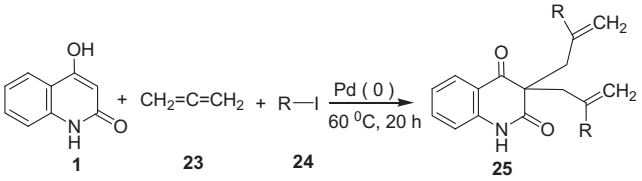
Scheme 15



Scheme 16

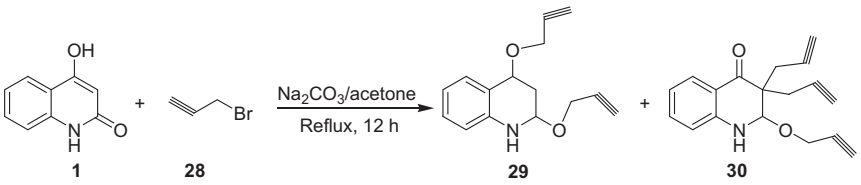


Scheme 17

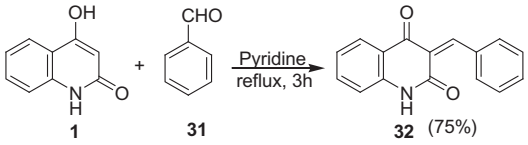


24, 25	a	b	c
R	I	I—OMe	I—CO_2Me
Yield (%)	56	41	75

Scheme 18



Scheme 20



Scheme 21

methyl-*N*-(2-methoxycarbonylphenyl)oxalamate **17** as the sole product in 94% yield (Ye et al., 1999) (Scheme 14).

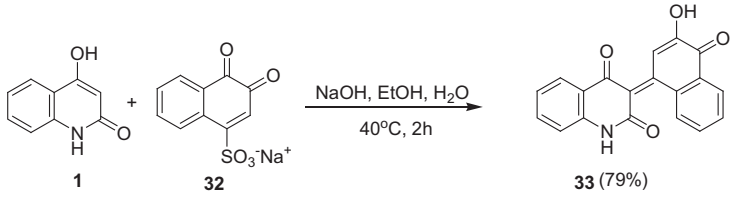
6.2. Reactions involving carbon–carbon bond formation

6.2.1. C-C Bond formation

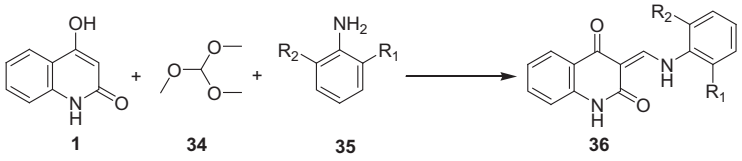
6.2.1.1. C_3-Allyation reaction. The allyation of 4-hydroxy-2(1*H*)-quinolone **1** is an important strategy for the formation of C–C bonds in organic synthesis. Recently, considerable interest has been focused on the allyation of **1** using alcohols as electrophiles, since it offers several potential advantages, such as the wide availability of the starting materials and the generation of water as the only side product. Such strategy has been elegantly applied to the synthesis of allyl and benzyl-substituted 4-hydroxy-2(1*H*)-quinolone compounds.

Activator-free and one-pot C-allylation of 4-hydroxy-2(1*H*)-quinolone **1** by simple palladium catalyst in water is now a well-documented process (Gan et al., 2008; Shue and Yang, 2012). Palladium-catalyzed allyation of **1** using cinnamyl alcohol directly gave the corresponding mono- and diallylated products **18**, **19** (Scheme 15).

The allylation of 4-hydroxy-2(1*H*)-quinolone **1** with prenyl bromide **20** in aqueous sodium hydroxide (Shobana et al.,

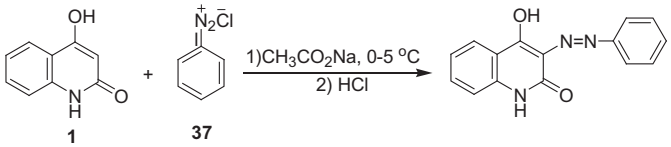


Scheme 22



35, 36	a	b	c
R_1	H	OCH_3	CH_3
R_2	H	H	CH_3
Yield %	60	59	77

Scheme 23



Scheme 24

1989) or aqueous lithium hydroxide (Ahmed et al., 2010) afforded only diprenylated quinolone **21** (Scheme 16).

However, Ahmed et al. investigated that the same reaction afforded natural product 3-(3-methylbut-2-enyl)-4-(3-methylbut-2-enyloxy) quinolin-2-ol **22** when carried out with dimethylformide in the presence of potassium carbonate at 60 °C (Ahmed et al., 2010) (Scheme 17).

Bis-C-allylated of 4-hydroxy-2(1*H*)-quinolone **25** was produced in 3-component cascade reaction involving aryliodides **24**, 4-hydroxy-2(1*H*)-quinolone **1**, and allene **23** using tris(dibenzylideneacetone) dipalladium, tris(2-furyl)-phosphine as catalyst with potassium carbonate in DMF at 60 °C for 20 h. (Grigg et al., 2004) (Scheme 18).

6.2.1.2. C3-Benzylation. Iridium catalyzed alkylation of 4-hydroxy-2(1*H*)-quinolone **1** with benzyl alcohol **26** under solvent free thermal condition afforded the corresponding 3-benzyl-4-hydroxyquinolin-2(1*H*)-one **27** Grigg et al., 2009 (Scheme 19).

6.2.1.3. Propargylation and allenylation. Propargylation of 4-hydroxy-2(1*H*)-quinolone **1** with propargyl bromide **28** in the presence of anhydrous potassium carbonate, under reflux conditions for 12 h in acetone, afforded a mixture of O,O-dialkylated quinolone **30**, and C,C,O-trialkylated quinolone **31** (Majumdar and Choudhury, 1087) (Scheme 20).

6.2.1.4. Olefination. One of the most successful strategies for constructing 3-benzylidene quinolone in only one diastereoisomeric form (*Z*) is the Knovenagel condensation. Heterocondensation reaction between 4-hydroxy-2(1*H*)-quinolone **1** and benzaldehyde **31** in pyridine (Refouvelet et al., 2004) under gave (*Z*)-2,4-dihydro-3-benzylidenquinolin-2,4-dione **32** (Scheme 21).

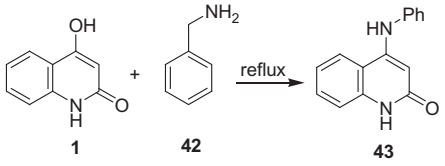
Michael addition of **1** with the sodium salt of 1,2-naphthoquinone-4-sulfonate **32** in alcoholic sodium hydroxide at 40 °C by crushing in a mortar or traditional heating gave 3-(3-hydroxy-4-oxonaphthalen-1-ylidene)quinoline-2,4-dione **33** (Villemin et al., 2010) (Scheme 22).

6.2.1.5. Synthesis of enaminones. The reaction of 4-hydroxy-2(1*H*)-quinolone **1** with trimethyl orthoformate **34** and anilines **35** afforded the corresponding 3-arylaminomethylenquinolin-2,4-diones **36** (Chilin et al., 2009; Trathnigg et al., 1984; Fiala and Stadlbauer, 1993) (Scheme 23).

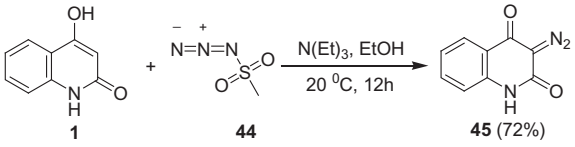
6.3. Reactions involving carbon-heteroatom bond formation

6.3.1. C–N Bond formation

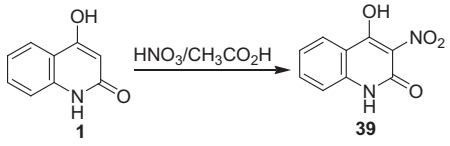
6.3.1.1. Coupling reactions. 3-(2-Phenylhydrazono)quinoline-2,4(1*H*,3*H*)-dione **38** was prepared by coupling of basic solution (sodium acetate) of 4-hydroxy-2(1*H*)-quinolone **1** with diazotized aniline **37** (Manvar et al., 2011, 2013) (Scheme 24).



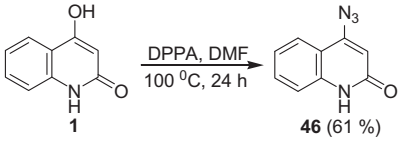
Scheme 28



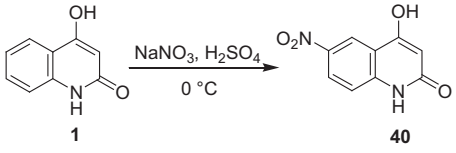
Scheme 29



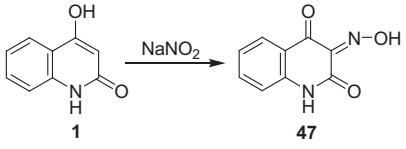
Scheme 25



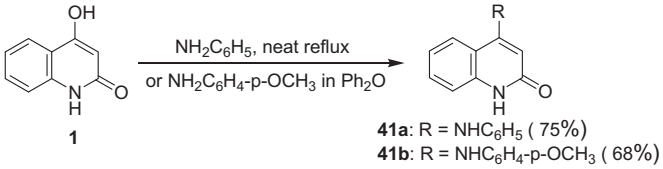
Scheme 30



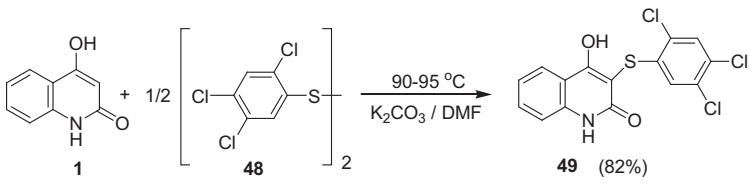
Scheme 26



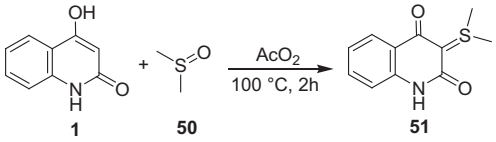
Scheme 31



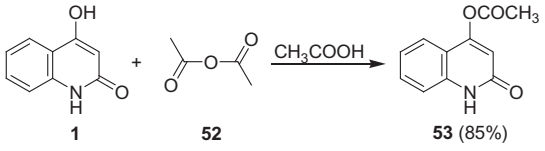
Scheme 27



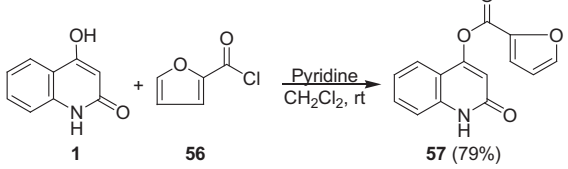
Scheme 32



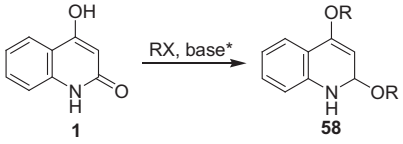
Scheme 33



Scheme 34



Scheme 36



* base : Ag_2CO_3 or K_2CO_3

RX :MeI, EtI, $C_5H_{11}I$, Me_2CHI, ICH_2CO_2Et, C_4H_9Br, $CH_2{=}CHCH_2Br$, $BrCH_2CH{=}C(CH_3)CH_2CH_2CH(CH_3)_2$, $BrCH_2CHCH_3$, $BrCH_2CH_2CH{=}C(CH_3)_2$, $BrCH_2CH_2OCH_2CH_3$, $BrCH_2CH_2CH(CH_3)_2$.

Scheme 37

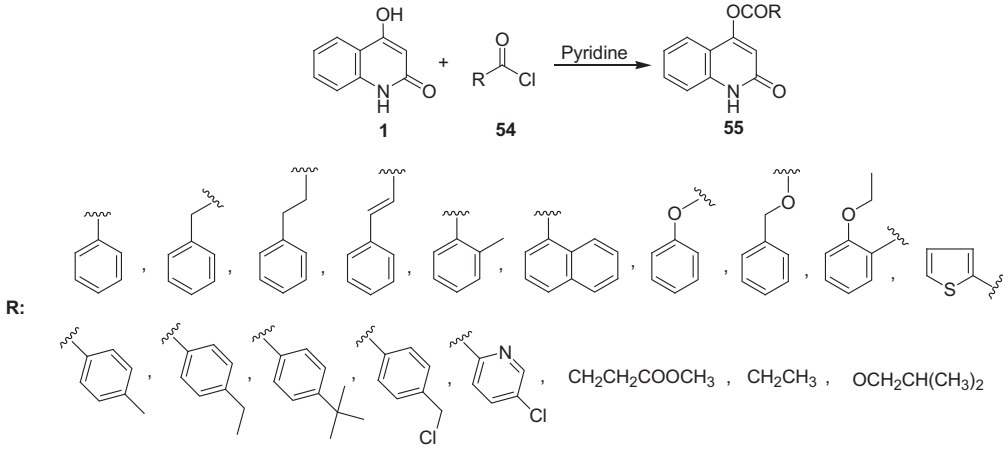
6.3.1.2. Nitration reaction. Nitration of **1** with neat nitric acid or a mixture of glacial acetic acid and concentrated nitric acid afforded 4-hydroxy-3-nitroquinolin-2(1*H*)-one **39** Dolle et al., 1995; Audisio et al., 2011; Buckle et al., 1975; Cai et al., 1996; Shukla et al., 2010 (Scheme 25).

In contrast, Oeveren et al. Oeveren et al. (2007) observed that the nitration of **1** in the presence of a solution of nitric acid and sulfuric acid at 0 °C was successful at the 6-position and afforded 4-hydroxy-6-nitro-quinolin-2-(1*H*)-one **40** (Scheme 26).

6.3.1.3. Formation of substituted amine (Amination). A simple and facile amination of **1** with equimolar amounts of aniline (neat) or *p*-anisidine (in Ph_2O) afforded 4-anilino-2-quinolinone **41a** or 4-methoxy derivative **41b**, respectively (Chen et al., 2004) (Scheme 27).

Stadlbauer and Kappe described the condensation of **1** with phenylmethanamine **42** in various solvents under reflux condition which gave the 4-(phenylamino)quinolin-2(1*H*)-one **43** Stadlbauer and Kappe, 1981 (Scheme 28).

6.3.1.4. Formation of azide. The formation of 3-diazo-1*H*-quinolin-2,4-dione **45** is observed when 4-hydroxy-2(1*H*)-quinolone **1** is reacted with mesyl azide **44** in ethanol in the presence of triethyl amine (Pirrung and Blume, 1999) (Scheme 29).



Scheme 35

Please cite this article in press as: Abdou, M.M. Chemistry of 4-Hydroxy-2(1*H*)-quinolone. Part 1: Synthesis and reactions Arabian Journal of Chemistry (2014), http://dx.doi.org/10.1016/j.arabjc.2014.01.012

Aizikovich et al. demonstrated a new application of diphenylphosphoryl azide (DPPA) as a reagent for the transformation of **1** into its corresponding azide **46** (Aizikovich et al., 2004) (Scheme 30).

6.3.1.5. Formation of oxime. The main method for the synthesis of the quinolone oxime **47** is based on the reaction of sodium nitrite with **1** in the presence of acetic acid (Brown et al., 1954; Cai et al., 1996), or hydrogen chloride (Fadda et al., 1991) (Scheme 31).

6.3.2. C–S Bond formation

6.3.2.1. Sulfides (Thioethers) formation. Treatment of 4-hydroxy-2(1*H*)-quinolone **1** with diaryl disulfides **48** in dimethylformide in the presence of potassium carbonate yielded 4-hydroxy-1-methyl-3-(2,4,5-trichlorophenylthio)-2(1*H*)-quinolone **49** Yadav et al., 2007 (Scheme 32).

6.3.2.2. Thionation reaction. 4-Hydroxy-2(1*H*)-quinolinone **1** reacts with dimethylsulfoxide **50** in acetic anhydride at 100 °C to afford 3-dimethylsulfonioquinoline-2,4-dionate **51** as the main product (Khan and Shoeb, 1985; Kappe et al., 1983) (Scheme 33).

6.3.3. C–O Bond formation

6.3.3.1. Esterification. The direct esterfication of 4-hydroxy-2(1*H*)-quinolone **1** with acetic anhydride **52** using triethylamine (Selig and Bach, 2008), pyridine (Brown et al., 1954; Ashley et al., 1930), or acetic acid (Priya et al., 2010) afforded 4-acetoxyquinolin-2-one **53** in good yield (Scheme 34).

In addition, the base catalyzed O-acylation of 4-hydroxy-2(1*H*)-quinolone **1** with various acyl chlorides **54** in the presence of pyridine at ambient temperature afforded the corresponding esters **55** (Stadlbauer and Kappe, 1981; Sun et al., 2013) (Scheme 35).

Im et al. noted that the esterification of 4-hydroxy-2(1*H*)-quinolone **1** with 2-furoyl chloride **56** in pyridine and dichloromethane afforded 2-oxo-1,2-dihydroquinolin-4-yl-furan-2-carboxylate **57** as human rhinovirus 3C protease inhibitors (Im et al., 2009) (Scheme 36).

6.3.3.2. O-Alkylation reaction. The highly regioselective O-alkylation reaction of **1** with alkyl iodides, benzyl bromides and allyl bromides in the presence of silver carbonate (Morel et al., 2005) or potassium carbonate (Ahmed et al., 2010; Cravotto et al., 2004) afforded 2,4-dialkoxyquinolines **58** in moderate to excellent yields. (Scheme 37).

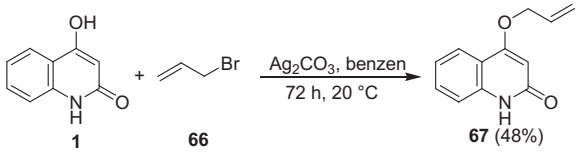
O-methylation of 4-hydroxy-2(1*H*)-quinolone **1** is readily performed upon treatment of it with dimethyl sulfate in the presence of anhydrous silver carbonate in acetone (Chen et al., 2004) or sodium hydroxide in methanol (Reisch and Mester, 1980) to give 4-methoxyquinolone **59** (Scheme 38). However, it was reported that this reaction gave a mixture of 4-methoxyquinolone **59** and l-methyl-4-methoxy-2-quinolon **60** (Lamberton, 1953).

Morel and coworkers showed that the reaction of **1** with methyl iodide **61** and silver carbonate in boiling benzene afforded 2,4-dimethoxyquinoline **62** as the only product (Bodendiek et al., 2009). However, Morel et al. (2005) observed that this reaction when carried in the presence of potassium hydroxide in boiling acetone gave a mixture of 1,3,3-trimethyl-2,4-dioxo-1,2,3,4-tetrahydroquinoline **63**, 1,3-dimethyl-4-methoxy-2-quinolone **64**, and l-methyl-4-methoxy-2-quinolone **65**. Also, by-product 2,4-dimethoxy quinoline **62** was identified (Morel et al., 2005) (Scheme 39).

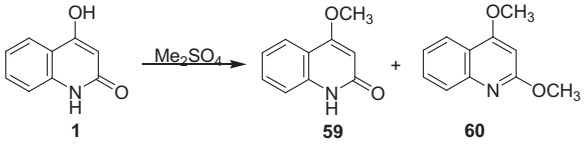
4-Allyloxyquinolone **67** was obtained by the reaction of 4-hydroxy-2(1*H*)-quinolone **1** with allylic bromide **66** and silver carbonate in benzene for 72 h at room temperature (Guo et al., 2009) (Scheme 40).

Acylation of 4-hydroxyquinolin-2-(1*H*)-one **1** with undec-10-enoyl chloride **68** afforded 2-oxo-1,2-dihydroquinolin-4-ylundec-10-enoate **69** (Cravotto et al., 2006) (Scheme 41).

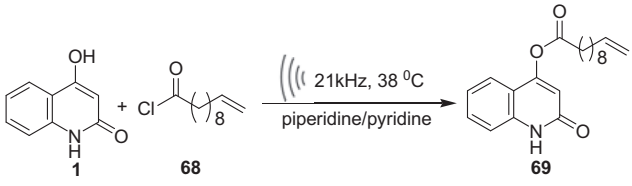
Heating 4-hydroxy-2(1*H*)-quinolone **1** with various substituted benzyl chlorides **70** in acetone (Chen et al., 2005) or dimethylformide (Chen et al., 2004; Deng et al., 2010; Ahvale



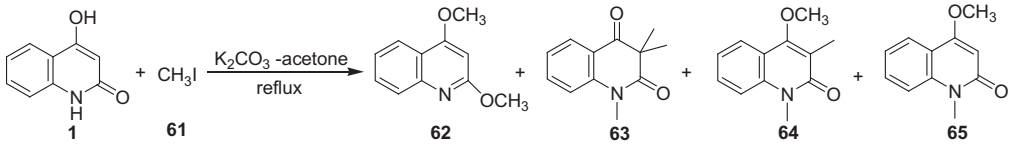
Scheme 40



Scheme 38



Scheme 41



Scheme 39

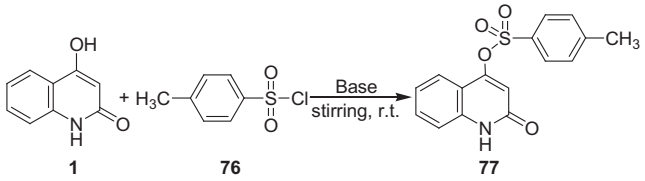
et al., 2008) containing anhydrous potassium carbonate afforded 4-alkoxy quinolinones **71** (Scheme 42).

6-[3-(1-Cyclohexyl-5-tetrazolyl)propoxy]-1,2-dihydro-2-oxoquinoline **73** was prepared by the reaction of 5(ω-chloroalkyl)-tetrazole **72** and **1** in the presence of a base (Nishi et al., 1983) (Scheme 43). This compound was found to have potent inhibitory activity toward collagen- and adenosine diphosphate (ADP)-induced aggregation of rabbit blood platelets *in vitro*.

6.3.3.3. Glucosylation reaction. Selective glucosylation of **1** into 4-(β-D-glucopyranosyloxy)quinoline-2(1*H*)-one was proceeded via treatment of **1** with tetra-acetobromo-α-D-glucose **74** in combination with cesium carbonate in acetonitrile at room temperature to give 4-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyloxy)-quinolin-2(1*H*)-one **75** in 74% yield (Kimmel et al., 2010) (Scheme 44).

6.3.3.4. Hetero ether formation. 6.3.3.4.1. Sulfonate ether formation. Two groups have reported the one step formation of 4-(*p*-toluenesulfonyloxy)-2(1*H*)-quinolone **77** *via* tosylation reaction of 4-hydroxy-2(1*H*)-quinolone **1** with tosyl chloride **76** in pyridine and 4-(*N,N*-dimethlyamino)pyridine (Ahvale et al., 2008) or triethylamine in dichloromethane (Valente and Kirsch, 2011) at room temperature (Scheme 45).

Gogsig et al. tosylation reaction of **1** with tosyl chloride **76** in dichloromethane containing catalytic amount of triethylamine at room temperature afforded 2,4-ditosylated hydroxyquinoline **78** (Gogsig et al., 2009) (Scheme 46).



Scheme 45

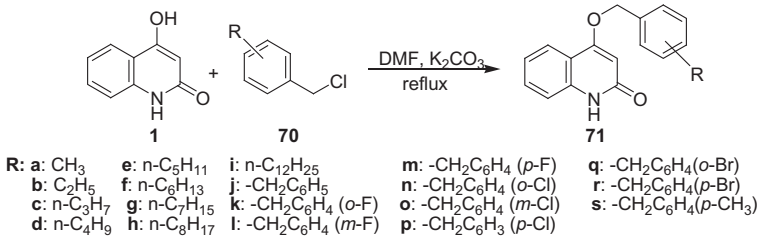
4-Trifluoromethylsulfonyloxyquinoline **80** was prepared through the treatment of **1** with phenyltrifluoromethane sulfonamide **79** and sodium hydride in anhydrous *N,N*-dimethyl-formamide at room temperature (Cacchi et al., 1997) (Scheme 47).

The synthesis of 2,4-ditrifluoromethylsulfonyloxyquinoline **82** was carried through treatment of **1** with triflic anhydride **83** under reflux in pyridine (Bissember and Banwell, 2009) (Scheme 48).

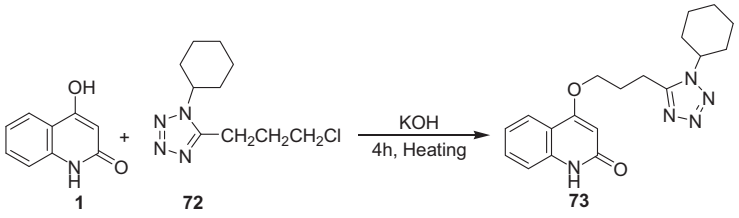
6.3.3.4.2. Phosphorylation reaction. A series of new piperazine phosphoramide derivatives of 4-hydroxyquinoline **85** were synthesized through a facile phosphorylating reaction starting from 4-hydroxy-2(1*H*)-quinolone **1** and various phosphorylating agents **84** in the presence of triethylamine at room temperature (Chen et al., 2012) (Scheme 49).

6.3.4. Carbon–halogen bond formation

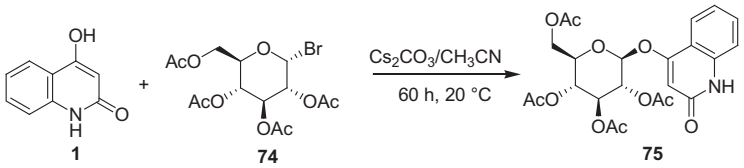
Halogenoheteroarenes are useful intermediates for the syntheses of bioactive natural products and pharmaceutical drugs.



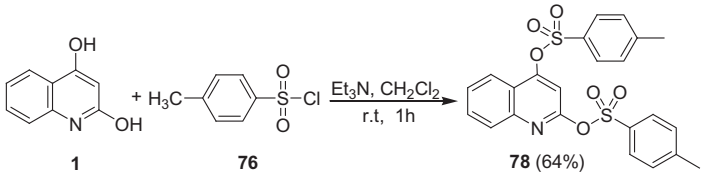
Scheme 42



Scheme 43

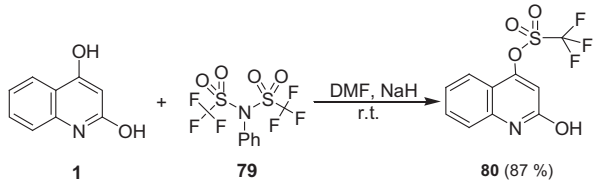


Scheme 44



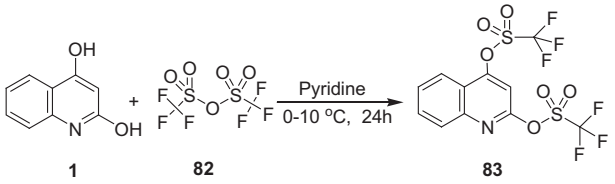
1 76 **78** (64%)

Scheme 46



1 79 **80** (87 %)

Scheme 47



1 82 83

Scheme 48

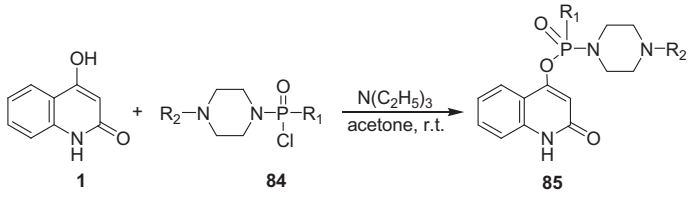
6.3.4.1. Bromination. Bromination of 4-hydroxy-2(1*H*)-quinolone **1** with bromine in formic acid (Osborne et al., 1993), acetic acid (Reisch et al., 1993; Nishimura et al., 2001), or phosphorus oxytribromide (Hardman and Partridge, 1955) yields 3,4-dibromo quinoline **86** (Scheme 50).

Gaston et al. (1985) have repeated this reaction in formic acid, but isolated only 3-bromo-4-hydroxy-2(1*H*)-quinolone **87** (Scheme 51), the structure of which was firmly established by conversion into the known 3-bromo-2,4-dimethoxyquinoline which was identified by ^{1}H NMR spectroscopy.

6.3.4.2. Chlorination. Chlorination of 4-hydroxy-2(1*H*)-quinolone **1** with phosphorous oxychloride under reflux condition afforded 2,4-dichloroquinoline **88** in good yield (Scheme 52) (Subramanian et al., 1992). Also, microwave-assisted reaction using chlorophosphonium salt was examined for this reaction, and it shortened the reaction time (5 min) as compared with a thermal reaction (Engen et al., 2010; Friedlaender and Weinberg, 1882; Baeyer and Bloem, 1882; Tanji et al., 1983; Takahashi et al., 1973).

While such a protocol may be adequate for small scale synthesis in a research laboratory, it becomes an environmental burden to deal with the excess $POCl_3$ in large scale preparations. Furthermore, even the process of quenching excess $POCl_3$ in large scale needs safety attention due to the potential for latent exothermic events.

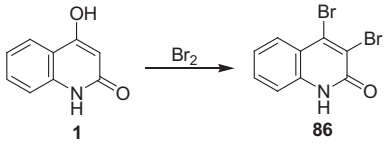
Therefore, improvements in reducing the amount of $POCl_3$ used in large scale chlorination procedures would be welcomed for economic, environmental, and safety considerations. Wang et al recently reported (Wang et al., 2012) a protocol for large scale (milligram to kilogram batches). Chlorination of 4-hydroxy-2(1*H*)-quinolone **1** using equimolar or less $POCl_3$ with



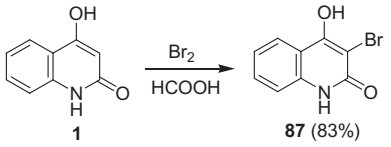
1 84 85

84,85	R_1	R_2	Yield %
a	C_6H_5O	4-CH_3 C_6H_4	85
b	C_6H_5O	4-Cl C_6H_4	85
c	C_6H_5O	CH_3	80
d	C_6H_5O	$(CH_3)_3$C-O-CO	83
e	$(ClCH_2CH_2)_2N$	4-CH_3 C_6H_4	83
f	$(ClCH_2CH_2)_2N$	4-Cl C_6H_4	85
g	$(ClCH_2CH_2)_2N$	CH_3	87
h	$(ClCH_2CH_2)_2N$	$(CH_3)_3$C-O-CO	84

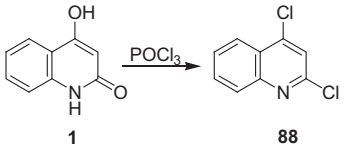
Scheme 49



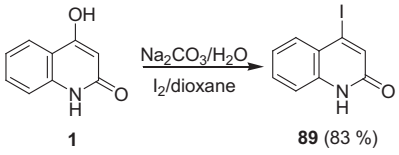
Scheme 50



Scheme 51



Scheme 52



Scheme 53

heating in a sealed reactor under solvent-free conditions using one equivalent of pyridine as base.

6.3.4.3. Iodination. Iodination of 4-hydroxy-quinolin-2(1*H*)-one 1 with iodine in aqueous dioxane afforded 4-hydroxy-3-iodoquinolin-2(1*H*)-one **89** in 83% yield (Snider and Wu, 2006; Ziegler et al., 1963) (Scheme 53).

7. Conclusion

The literature survey presented herein indicates that the synthesis, tautomerism and chemical reactivity of 4-hydroxy-2(1*H*)-quinolone as well as its reactions have attracted the interest of many research groups all over the world. This great interest of chemists in such compound is confirmed by the fact that 138 articles cited in this review are dated. Finally, I hope that this review serves as a stimulus for ongoing research in the area of 4-hydroxy-2(1*H*)-quinolone chemistry.

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