Review Article

2-Chloroquinoline-3-carbaldehyde II:
Synthesis, Reactions, and Applications

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This review deals with synthesis and reactions of 2-chloroquinoline-3-carbaldehyde during the period from 1979 to 1999. The reactions are subdivided in groups that cover the reactions of chloro- and aldehyde substituent as well as reactions which involve both groups. Some of these reactions have been applied successfully to synthesis of biologically important compounds. The main purpose of this review is to present a survey of the literature on 2-chloroquinoline-3-carbaldehyde chemistry and provide useful and up-to-date data for organic and medicinal chemists since such compound has not been previously reviewed in this period.

1. Introduction

Over the past two decades, 2-chloroquinoline-3-carbaldehydes and their derivatives have attracted much attention due to their considerable biological and pharmacological activities as antimicrobial \cite{1,2,3,4,5,6,7}, anti-inflammatory \cite{8,9}, antimalarial \cite{10}, and antivirus activities \cite{11}. Despite this versatile importance and in continuation of our previous review articles \cite{12,13,14,15,16}, 2-chloroquinoline-3-carbaldehydes have not been previously reviewed in the period from 1979 to 1999. The present review aims to complete our review article about these compounds \cite{14}.

2. Synthetic Methods

2.1. Vilsmeier-Haack Reaction. 2-Chloroquinoline-3-carbaldehydes and 2-chloro-4-methyl-quinoline-3-carbaldehyde were prepared from acetanilide \cite{11,17,18,19,20,21} and acetooacetanilide \cite{17} via a Vilsmeier-Haack reaction (Scheme 1).

It was reported that one-pot synthesis of pyrido[2,3-b]quinolin-2-ones \textit{2} in moderate yields (22–59\%) was archived by treatment of substituted acetanilide with DMF and POCl\textsubscript{3}, to produce compound \textit{1}; to this reaction mixture a secondary amide was added in POCl\textsubscript{3} solution containing one drop of DMF, and the mixture was heated for a further 2–3 h at 75 °C (Scheme 2) \cite{22}.

3. Chemical Reactions

3.1. Substitution Reactions. 3-Formylquinoline-2(1H)-thione (X = S) and -seleno \textit{I} (X = Se) \textit{3} have been prepared from reaction of \textit{1} with NaXH (X = S, Se). Compounds \textit{3} reacted with primary amine to produce Schiff’s bases \textit{4} (Scheme 3) [23].

Treatment of 2-(3-(1,3-dioxolan-2-yl)quinolin-2-yl)-N-substituted hydrazinecarbothioamide \textit{7}, which is prepared by two steps: first reaction of \textit{1} with ethylene glycol followed by reaction with hydrazine hydrate to afford 3-(1,3-dioxolan-2-yl)-2-hydrazinoquinoline \textit{6}. The latter compound reacted with substituted isothiocyanates and with \(\alpha\)-halocarbonyl compounds which yielded thiazolidinone \textit{8} and thiazoline derivatives \textit{9}. The antimicrobial and inotropic and chronotropic activities of the prepared compounds were studied (Scheme 4) \cite{3}.
Cyclization of compound 1 with CS₂ in EtOH/NaOH or pyridine gave the triazolo[4,3-a]quinoline-1-thione 10. Treatment of 10 with 60% HCO₂H gave the corresponding aldehyde 11. [1,2,4]Triazolo[4,3-a]quinolines 15a–c were prepared and screened as antimicrobial, inotropic, and chromatropic agents. Thus, reaction of 2-hydrazino-3-(1,3-dioxolan-2-yl)quinoline 6 with aromatic aldehyde or benzoyl chloride followed by fusion in presence of air underwent cyclodehydrogenation to give the target compounds. The latter compounds were also prepared directly from reaction of compound 1 with aldehyde by fusion (Scheme 5) [24].

Reaction of compound 1 with acetic acid at reflux temperature leads to formation of quinolone 16 which was condensed with ethyl bromoacetate to give ethyl 6-methylfuro[2,3-b]quinoline-2-carboxylate 17 (Scheme 6) [25].

2H-Pyrano[2,3-b]quinolin-2-ones 20 were prepared in 46–95% by treating compound 1 with HCl to give quinolones 18, which reacted with malonic acid in ethanol in the presence of pyridine and piperidine followed by cyclization in polyphosphoric acid [26]. In a similar manner the related cyanoacrylic acid and its ethyl ester 21 both gave pyranoquinoline-3-carboxylic acid 22 in 90% yield on treatment with PPA (Scheme 7) [18].

Meth-Cohn and coworkers reported replacement of 2-Cl group of compound 1 by H, iodo, OH, SR (R = alkyl, phenyl), CO₂H, Ph, CHO, and N₃ (giving the tetrazole) as described in Scheme 8 [18].
Compounds 1 reacted with alkylthiol to afford 2-(alkylthiol)quinoline-3-carbaldehydes 31. In an alternate method compound 31 was also obtained by the reaction of 2-mercaptoquinoline-3-carbaldehyde with allyl bromide. Allyl thioethers 31 were converted into oximes by reaction with hydroxylamine hydrochloride in the presence of aqueous sodium bicarbonate. Oximes were then oxidized with aqueous NaOCl to give nitrile oxides, which cyclize spontaneously to dihydro-3H-[1,2]oxazolo[3',4',5]thiopyrano[2,3-b] quinolone 34 in 81–86% yield. The oxidation was also carried out employing chloramine-T and mercuric acetate (Scheme 9) [27].

Treatment of compound 1 with sodium iodide in acetonitrile followed by reduction with sodium borohydride to afford 2-iodoquinoline 35. Next, Pd(0)-mediated cross-coupling of the latter compound and 2-tributylstannyl acrylic acid,
prepared in 95% yield by Pd(0)-promoted hydrostannylation of propiolic acid, provided compound 36 in 61% yield. Exposure of 36 to diphenyl phosphorazidate (DPPA) afforded the acyl azide 37 in an unoptimized 31% isolated yield. Cyclocondensation of azide 37 with 1-(1-cyclohexenyl)pyrrolidine yielded camptothecin 39 via the formation of intermediate enamine 38 (Scheme 10) [20].

3.2. Addition Reaction on Aldehyde Group. Benzimidazo[2′,1′:2,3][1,3]thiazino[6,5-b]quinoline 41 was prepared by the reaction of compound 1 with 2-mercaptopbenzimidazole 40 (Scheme 11) [28].

In the same fashion, [1,2,4]triazolo[5′,1′:2,3][1,3]thiazino [6,5-b]quinolines 43 were synthesized by the reaction of compound 1 with 1,2,4-triazole-5-thiols 42 (Scheme 12) [29].
Reaction between compound 1 and acetone in the presence of piperidine and acetic acid gave 4-(2-chloroquinoline-3-yl)-4-hydroxybutan-2-one 44 accompanied with a small amount of chalcone. Reduction of β-keto alcohols 44 with sodium borohydride yielded the diastereoisomer 1,3-diols 45a,b in 64–92% yield. The intramolecular cyclization of 1,3-diols was performed in DMF containing HCl to produce (2R,4S) 46a and (2S,4S)-2,4-dimethyl-3,4-dihydro-2H-pyrano[2,3-b]quinoline 46b (Scheme 13) [30].

Mg-Al hydrotalcite catalyzes the reaction between compound 1 and nitromethane very efficiently to afford threo (1S,2R)-1-(2-chloroquinoline-3-yl)-2-nitropropane-1-ol 47a [6]. On the other hand, it was reported synthesis of 1-(2-chloroquinoline-3-yl)-2-nitroethanol 47b and 2-chloro-3-(2-nitrovinyl)quinoline 48 from reaction of 1 with nitromethane (Scheme 14) [7]. The synthesized compounds were tested in vitro for their antimycotic activity against Aspergillus fumigatus, Trichophyton mentagrophytes, Microsporum Gypseum, Epidermophyton floccosum and Candida albicans [7].

Grignard reaction of compound 1 with either MeMgI or PhMgI followed by oxidation using pyridinium chlorochromate gave 3-acetyl-2-chloroquinolines 49 [31]. Methyl thieno[2,3-b]quinoline-2-carboxylates 51 were...
prepared in 70–80% yield by reaction of ketone 49 with methyl 2-mercaptoacetate in DMF containing anhydrous K₂CO₃ followed by cyclization in methanol containing piperidine. Compounds 49 were condensed with aromatic aldehyde to give the corresponding chalcones 52. The latter compounds were cyclocondensed with hydrazine to produce pyrazoles 53 (Scheme 15) [32].

Reduction of compound 1 followed by treatment with phosphorous tribromide and salicylaldehyde yielded chromeno[4,3-b]quinoline-4-carbaldehyde 54 which was reduced by Pd-C in methanol to produce 3-(3-(hydroxymethyl)quinolin-2-yl)benzaldehyde 55 (Scheme 16) [33].

Reaction of 4-amino-5-aryl-4H-1,2,4-triazole-3-thiols 56 with 1 was carried out without solvent using inorganic solid supports (e.g., silica or alumina) either in microwave irradiation [1, 2] or in DMF containing potassium carbonate [5] to give the triazolothiadiazole 57. The synthesized quinoline derivatives have been assessed for their anti-inflammatory, antibacterial, and antifungal activities (Scheme 17) [5].

3.3. Oxidation of Aldehyde Group. Oxidation of compound 1 with alkaline silver nitrate in ethanol gave the corresponding acid 53 in 73–75% yields. 2-Chloroquinoline-3-carboxylic acids 58 reacted with either o-phenylenediamine or 4,5-dichloro o-phenylenediamine in xylene to afford quinob[2,3-b][1,5]benzodiazepine-12-ones 54 in 39–72% yield. In contrast the reaction of those acids 58 with 4,5-dimethyl o-phenylenediamine yielded benzimidazoles 60 in 60–70% yield (Scheme 18) [34].

3.4. Condensation Reactions

3.4.1. Reactions with Active Methylene Compounds. Compound 1 was condensed with either acetylacetone or ethyl
cyanoacetate to give compounds 61 and 62, respectively [35]. Methyl thieno[2,3-b]quinoline-2-carboxylates 63 were prepared in 70–80% yield by cyclocondensation of compound 1 with methyl 2-mercaptoproacetate in DMF containing anhydrous K$_2$CO$_3$ (Scheme 19) [32].

Chalcones 65 were synthesized from reaction between compound 1 and aromatic or heterocycle aldehydes 64. The synthesized chalcones were evaluated for their anti-inflammatory activity (Scheme 20) [8].

Cyclization of chalcones 65 with hydrazine, phenylhydrazine, or thiourea to yield pyrazolylquinolines 61 and quinolinylpyrimidine-2-thione 62, respectively, was reported. The anti-inflammatory activity of the prepared compounds was studied (Scheme 21) [9].
Treatment of compound 1 with acetic anhydride and sodium acetate afforded the corresponding 2-oxopyrano[2,3-b]quinolines 72. Compounds were subjected to ammonia to yield the corresponding naphthyridines 73. The synthesized compounds were tested for their antimalarial, diuretic, clastogenic, and antimicrobial properties (Scheme 22) [10].

Cyclization of chloro(cyanovinyl)quinolines 74, prepared from condensation of 1 with 2-(4-chlorophenyl)acetonitrile, with secondary amines (e.g., piperidine, morpholine, and 4-methyl-1-piperazine), gave substituted benzonaphthyridines 75 in 34–98% yield (Scheme 23) [36].

3.4.2. Reactions with Hydrazine, Hydroxylamine, Hydrazides, (Thio)Semicarbazide, and (Thio)Urea. Quinolino[3,2-f]-1,2,4-triazolo[3,4-b]1,2,4-thiadiazepines 76 were prepared...
by cyclocondensation of 1 with 4-amino-5-aryl-4H-1,2,4-triazole-3-thiols 56 in DMF (Scheme 24) [37].

Reactivity of compound 1 with phenyl hydrazine yielded 1-phenyl-1H-pyrazolo[3,4-b]quinoline 77 [7, 17, 38], whereas interaction with hydroxylamine hydrochloride afforded isoazol[5,4-b]quinolines 78. Compounds 1 reacted with o-phenylenediamine and ethylenediamine in a 2:1 molar ratio to afford N,N'-bis-(2-chloroquinoline-3-yl-methylene)-o-phenylenediamines 79a and N,N'-bis-(2-chloroquinoline-3-yl-methylene)-ethylenediamines 79b, respectively. Pyrimido[4,5-b]quinolin-2-ol 80a and pyrimido[4,5-b]quinoline-2-thiol 80b were synthesized from reaction of compound 1 with urea and thiourea, respectively (Scheme 25) [17].

Preparation of pyrazolo[3,4-b]quinolines 83 as antiviral agents was reported by treatment of compound 1 with hydroxylamine in EtOH to give oxime 81. Stirring a solution of 81 and SOCl₂ in DMF at 0°C yielded nitrile 82 which was refluxed with hydrazine in EtOH to give target compounds, which showed MIC of 1.5 μg/mL against herpes simplex virus type 2 and vasodilator activity with an EC50 of 31 Mm (Scheme 26) [11].

Wright and EP reported convenient synthesis of 3-((1H-tetrazol-5-yl)quinolin-2(1H)-one 85 from the reaction of 1 with a mixture of formic acid, hydroxylamine hydrochloride, and sodium formate at reflux temperature to give 3-cyano-2(1H)-quinolinone 84 followed by treatment of the latter compound with sodium azide and ammonium chloride [21]. On the other hand 4-(1H-tetrazol-5-yl)tetrazolo[1,5-a]quinoline 86 was synthesized by the same author from treating 2-chloroquinoline-3-carbonitrile 82 with sodium azide and ammonium chloride at reflux temperature (Scheme 27) [39].

2-Chloro-3-cyanoquinoline 82, which was prepared from compound 1, [40] reacted with hydroxylamine to give amidoxime 87 which on ring closure in DMF containing potassium carbonate yielded isoazoloquinoline 88 in 32% yield. Reaction of 82 with thiourea furnished 89 which were subjected to ring closure by reacting with chloroacetonitrile in DMF in the presence of potassium carbonate to yield 90 (Scheme 28) [33].

Benzo[b]quinolinol[3,2-f][1,4]thiazepines 91a [41], and benzo[b]quinolinol[3,2-f][1,4]oxazepines 91b [42] were synthesized from reaction of compound 1 with 2-aminothiophenol and 2-aminophenol, respectively. On the other hand, quinobenzodiazepine 92, dipyridoquinobenzodiazepine 93, and benzimidazolyl quinoline 94 were prepared from reaction of compound 1 with o-phenylenediamine via oxidation intermediate benzimidazole quinolone to benzimidazolyl quinoline with simultaneous reduction of quinobenzodiazepine 92 to dipyridoquinobenzodiazepine 93 (Scheme 29) [43].

3-Amino-2H-chromen-2-one 95 reacted with compound 1 to give compound 96. Cyclodehydrochlorination of 96 gave benzopyrano[3,4-d] benzonaphthyridines 97 in 50–60% yield (Scheme 30) [44].

Quinolinecarbaldehyde hydrazones 99 were prepared either by condensation of compound 1 with substituted hydrazinecarbothioamides or by addition of hydrazones 98 to phenylethylamine. Cyclocondensation of 2-((2-chloroquinoline-3-yl)methylene)-N-arylhydrazincarbbothioamide 99 with substituted phenacyl bromide gave thiazoles 100. Compounds 99 and 100 were tested against Gram-positive and Gram-negative bacteria (Scheme 31) [4].
Scheme 25

Scheme 26

Scheme 27
Scheme 28

(i) NH₂OH·HCl
MeCO₂Na
(ii) SOCl₂, C₆H₆
(iii) K₂CO₃, DMF

Scheme 29

R = H, Me, Cl, OMe; X = S, O

Scheme 30

R₁, R₂ = H, H, OMe; Br, H, Br, OMe; Br, Br; Cl, H

Scheme 31

R₁ = H, 7-Me, 8-Me; R₂ = H, MeC₆H₄, cyclohexyl, allyl, Bu, PhCH₂, ClC₆H₄, Ph; R₃ = Ph, 4-MeC₆H₄, 4-BrC₆H₄
4. Conclusions

2-Chloroquinoline-3-carbaldehydes are easily available and have high chemical reactivity due to the presence of two active moieties chloro- and aldehyde functions. This survey attempts to summarize the synthetic methods and reactions of 2-chloroquinoline-3-carbaldehydes from 1979 to 1999.

References


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