

The Synthesis of 6-substituted-2-chloroquinoline-3-carbaldehyde using Vilsmeier-Haack Reaction

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Abstract: The use of formylation reaction as synthetic strategy to form versatile carboxaldehyde intermediates is still of interest, due to both their intrinsic pharmacological properties and chemical reactivity. Formylation reactions have been described for many heterocyclic derivatives, via the intermediate carboxaldehydes, which is mainly formed using Vilsmeier-Haack reaction. Despite this versatile importance of Vilsmeier-Haack reagent and in continuation of our interest in quinoline nucleus, the synthesis of a series of 6-substituted-2-chloroquinoline-3-carbaldehydes (3a-h) was carried out. All the compounds were characterized by IR, ¹H NMR spectroscopic studies. The characteristic two peaks of aldehyde in IR and the ¹H NMR signals at δ value 9-11 indicates the formation of quinoline-3-carbaldehyde from the corresponding oximes.

Keywords: Aromatic aldehydes, Vilsmeier-Haack reagent, dimethylformamide, acid chloride, acetophenone oximes, spectral data

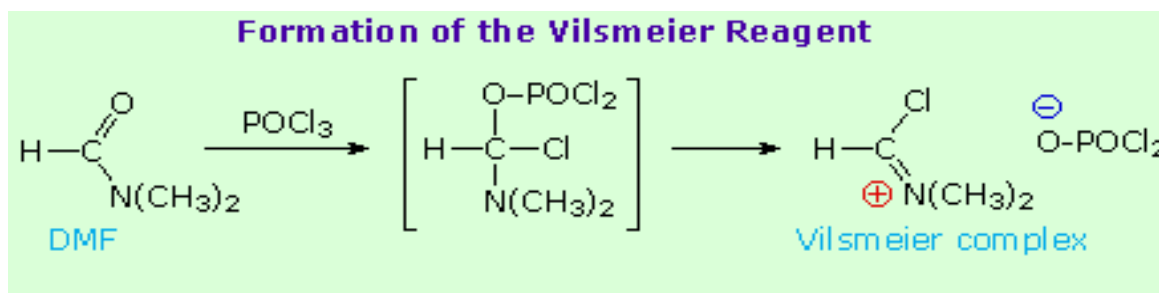
1. Introduction

The Vilsmeier-Haack reaction is an important method for the synthesis of various aromatic aldehydes and α - β -unsaturated aldehydes [1]. In addition to this the reactions of carbonyl compounds and its derivatives with Vilsmeier reagent are highly versatile and often lead to products of high synthetic potential [2-5]. The reagent is also used in a variety of cyclization and cycloaromatization reactions. The application of the Vilsmeier-Haack (VH) reagent (POCl₃/DMF) for the formylation of a variety of both aromatic and heteroaromatic substrates is well documented [6]. The conventional Vilsmeier-Haack reaction involves the reaction of the electron rich aromatic compounds or alkenes with the iminium salts obtained from formamides (DMF or N-methyl formanilide) and acid chlorides (POCl₃). The initial step is an iminoalkylation, which is essentially an electrophilic substitution [7-8].

The reaction leads to the formation of an aldehyde on alkaline hydrolysis as illustrated in fig 1. Besides this, the reagent has also been extensively used for effecting various chemical transformations with other classes of compounds [9-11]. There is a growing interest in formylation as an interesting strategy to form intermediate carboxaldehydes, due to their intrinsic pharmacological properties and chemical reactivity [13].

Other than DMF and N-methyl formanilide, formamides such as benzyl methyl formamide, N-formyl piperidine and N-formyl morpholine are also employed in the Vilsmeier-Haack reaction. Thionyl chloride, phosgene and oxalyl chloride etc. are the acid chlorides used in addition to the most popular POCl₃ [15]. While, DMF is used as the solvent in most occasions, other solvents such as dichloromethane, chloroform etc. may also be used. Therefore, the Vilsmeier-Haack reagent is considered as an efficient, economical and mild reagent for the formylation of reactive aromatic and heteroaromatic substrates [16-18]. It is now used as a powerful synthetic tool for the construction of many heterocyclic compounds [19-20].

Heterocyclic moieties, mainly Quinoline nucleus, particularly the 2-chloroquinoline-3-carbaldehydes have been in the focus of interest of medicinal chemists in the past decades because of the outstanding pharmacological properties such as antimicrobial [21-23], antimalarial [24, 25], anti-inflammatory [26-29] and anti-parasitic activity [30]. The importance of Vilsmeier-Haack reaction in the field of chemistry and role of 2-chloroquinoline-3-carbaldehydes in pharmacology, prompted us to synthesize a series of 6-substituted-2-chloroquinoline-3-carbaldehydes, which can be employed further either to fuse with various other heterocyclic moieties or some to design some new derivatives of quinolines as well.



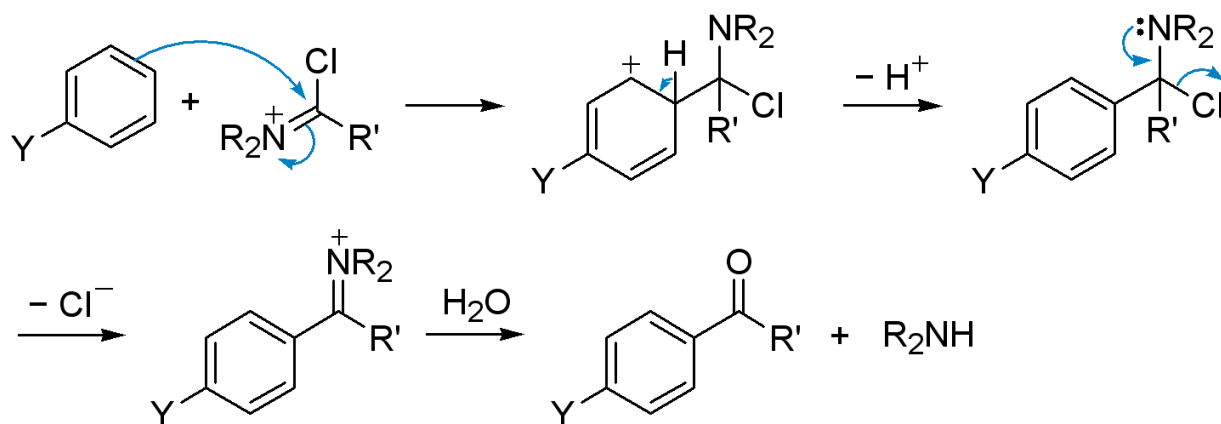
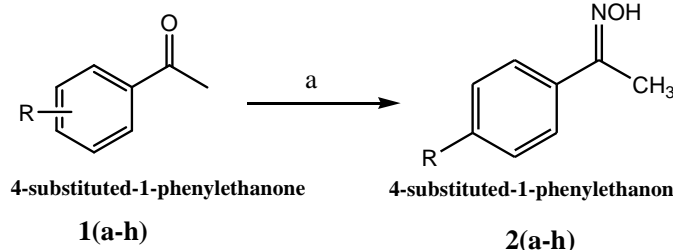


Figure 1: Formation of Vilsmeier Reagent in-situ and its application to generate aromatic aldehyde

2. Synthesis

The synthetic scheme for the synthesis of 6-substituted-2-chloroquinoline-4-carbaldehydes (**3a-h**), start with the substituted acetophenone (**1a-h**), available commercially. Then these acetophenones were reacted with hydroxylamine hydrochloride in the presence of sodium acetate as catalyst to yield 4-Substituted-1-phenylethanone oximes (**2a-h**) as shown in scheme 1. After that these 4-substituted-1-phenylethanone oximes were subjected to Vilsmeier-Haack reaction in the presence of POCl₃/DMF, to yield the final compounds (**3a-h**).



Scheme 1: Synthesis of 6-substituted-2-chloroquinoline-4-carbaldehyde using reaction conditions; a- NH₂OH.HCl, CH₃COONa, refluxing (45°C, 3-6hrs), b-DMF, POCl₃, stirring at 50-60°C for 16 hrs under anhydrous conditions.

3. Experimental

The chemicals used for experimental work were commercially procured from various chemical units - E. Merck India Ltd., CDH, S.D Fine Chem. Ltd. and were of L.R. grade and purified by standard procedure before their use. MR-VIS Visual melting point apparatus (LAB India) was used to record the melting points of the synthesized compounds using slide methods and are uncorrected. The Colour of the compounds was detected by visualizing them in direct sunlight. The IR spectra were recorded on Hitachi 150-200 spectrophotometer using KBr. ¹H-NMR spectra were recorded on Bruker spectropsin DPX-300 MHz in CDCl₃ or DMSO-*d*₆ using [(CH₃)₄Si] (TMS) as an internal standard and chemical shift (δ) values are reported in parts per million (ppm).

Progress of the chemical reaction and the purity of the synthesized compound was checked on silica gel G coated thin-layer chromatography plates in either of the following solvent systems; Toluene: Ethyl acetate: Formic acid (5:4:1, v/v/v) or Petroleum ether: Toluene: Ethyl acetate (5:4:1, v/v/v) or Ethyl acetate: Hexane (3:7, v/v). The visualization of spots on TLC was carried out in iodine chamber and UV cabinet at long wavelength under UV lamp.

General procedure for the Synthesis of 4-substituted-1-phenylethanone oximes (2a-f)

4-Substituted-1-phenylethanone oximes were synthesized by reacting different substituted acetophenones (0.1mol), with hydroxylamine hydrochloride in the presence of sodium acetate (0.12 mol). To the solution of acetophenone in ethanol, hydroxylamine hydrochloride was added. To the above mixture, sodium acetate (which act as a catalyst) and sufficient amount of water was added so that sodium acetate get dissolved. The above mixture was refluxed for 3 to 6 hours. The completion of reaction was checked from time to time using TLC. After completion of reaction, the mixture was cooled, product get precipitated out. Precipitated product was filtered and melting point of the compound was determined.

Acetophenone oximes; 2a- Yield 84.87%, M.P. 55-59°C, Off-white colour, *R_f* -0.76, IR(KBr) cm⁻¹: (OH) 3364(broad), (C=N) 1672, ¹H NMR(400 MHz, CDCl₃) δ 3.833(s, 1H, OH), 7.18-7.26(m, 3H, ArH), 7.42(d, 2H, ArH), 3.02-3.03(t, 3H, CH₃)

1-(4-hydroxyphenyl)ethanone oxime; 2b- Yield 88.7%; M.P. 96-98°C, white colour, *R_f* - 0.78, IR(KBr) cm⁻¹ (OH) 3300 (broad), (OH) 3225 (broad), (C=N) 1643, ¹H NMR (400 MHz, CDCl₃) δ 3.13(s, 1H, OH), 5.402(s, 1H, OH), 7.32-7.37(m, 2H, ArH), 7.62-7.64(m, 2H, ArH), 2.16(s, 3H, CH₃)

1-(4-methoxyphenyl)ethanone oxime; 2c- Yield 85.8%; M.P. 104-106°C, pale white colour, *R_f* - 0.81, IR(KBr) cm⁻¹ (OH) 3426 (broad), (C=N) 1648, ¹H NMR (400 MHz, CDCl₃) δ 2.42(s, 1H, OH), 4.402(s, 3H, OCH₃), 7.63(d, 2H, ArH), 6.72-6.74(m, 2H, ArH), 2.38(s, 3H, CH₃).

1-(4-chlorophenyl)ethanone oxime; 2d-Yield 92.7%, M.P. 112-115°C, white colour, R_f -0.56, IR(KBr) cm^{-1} (OH) 3245(broad), (C=N) 1665, ^1H NMR (400 MHz, CDCl_3) δ 3.833 (s, 1H, OH), 7.21 (d, 2H, ArH), 7.85 (d, 2H, ArH), 2.82 (s, 3H, CH_3)

1-(4-fluorophenyl)ethanone oxime; 2e-Yield 85%, M.P. 102-106 °C, white colour, R_f -0.52, IR(KBr) cm^{-1} (OH) 3341(broad), (C=N) 1662, ^1H NMR (400 MHz, CDCl_3) δ 4.57 (s, 1H, OH), 7.67 (d, 2H, ArH), 7.37 (d, 2H, ArH), 2.34 (s, 3H, CH_3)

1-(4-nitrophenyl)ethanone oxime; 2f-Yield 95%, M.P. 148-150°C, yellow colour, R_f - 0.428 IR(KBr) cm^{-1} (OH) 3200(broad) (C=N) 1643, ^1H NMR (400 MHz, CDCl_3) δ 3.04 (s, 1H, OH), 8.21(d, 2H, ArH), 7.92(d, 2H, ArH), 1.99 (s, 3H, CH_3)

General procedure for the synthesis of substituted-2-chloroquinoline-3-carbaldehydes (3a-f)

To dimethylformaldehyde (0.15 mol) cooled to 0°C, freshly distilled phosphorus oxychloride (0.35 mol) was added dropwise under stirring, then the respective oxime (0.05 mol) was added portion-wise. The reaction mixture was heated at 60°C for 16 h. It was then poured into ice cooled water (300ml) and stirred at below 10°C for 30 min. The 2-chloroquinoline-3-carbaldehyde was filtered and recrystallized from ethyl acetate.

2-chloroquinoline-3-carbaldehyde; 3a- Yield 72%; M.P. 142-146 °C, R_f 0.42; IR (KBr) cm^{-1} 1690 (C=O), 1450-1600 (Aromatic), 2738, 2820(aldehyde)-; ^1H NMR (300 MHz, CDCl_3) δ 7.74 (t, H-7, Ar-H), 7.99 (t, H-6, Ar-H), 8.03 (d, H-5, Ar-H), 8.12 (d, H-8, Ar-H), 8.79 (s, H-4, Ar-H), 10.59 (s, 1H, CHO).

2-chloro-6-hydroxyquinoline-3-carbaldehyde; 3b- Yield 66 %; M.P. 125 °C, R_f 0.62; IR (KBr) cm^{-1} 1713 (C=O), 2720, 2878(aldehyde), 1450-1600 (Aromatic); ^1H NMR (300 MHz, CDCl_3) δ 4.58 (s, 1H, OH), 7.28 (s, H-5, Ar-H), 7.75 (d, H-7, Ar-H), 8.01 (d, H-8, Ar-H), 8.68 (s, H-4, Ar-H), 10.57 (s, 1H, CHO).

2-chloro-6-methoxyquinoline-3-carbaldehyde; 3c- Yield 62 %; M.P. 146 °C, R_f 0.53; IR (KBr) cm^{-1} 1636 (C=O), 1474-1600 (Aromatic), 2731, 2677(aldehyde); ^1H NMR (300 MHz, DMSO) δ 3.40 (s, 3H, CH_3), 6.74 (s, H-5, Ar-H), 7.62-7.64 (m, H-4, Ar-H), 7.34-7.37 (m, 2H, H-8 and H-7, Ar-H), 11.13 (s, 1H, CHO).

2,6-dichloroquinoline-3-carbaldehyde; 3d- Yield 68%; M.P. 191-192 °C; R_f 0.36; IR (KBr) cm^{-1} 1697 (C=O), 1450-1600 (Aromatic), 2792, 2856(aldehyde); ^1H NMR (300 MHz, CDCl_3) δ 7.23 (s, H-5, Ar-H), 7.6 (d, H-8, Ar-H), 8.06 (dd, H-7, Ar-H), 8.69 (s, H-4, Ar-H), 10.58 (s, 1H, CHO).

2-chloro-6-fluoroquinoline-3-carbaldehyde; 3e- Yield 56.24%; M.P. 184-188 °C; R_f 0.36; IR (KBr) cm^{-1} 1682 (C=O), 1450-1600 (Aromatic), 2729, 2842(aldehyde); ^1H

NMR (300 MHz, CDCl_3) δ 7.23 (s, H-5, Ar-H), 8.32 (d, H-8, Ar-H), 7.56 (dd, H-7, Ar-H), 8.68 (s, H-4, Ar-H), 10.57 (s, 1H, CHO).

2-chloro-6-nitroquinoline-3-carbaldehyde; 3f- Yield 72.11 %; M.P. 174 °C; R_f 0.35; IR (KBr) cm^{-1} 1705 (C=O), 1450-1600 (Aromatic), 2795, 2835(aldehyde). ^1H NMR (300 MHz, CDCl_3) δ 7.21 (s, H-5, Ar-H), 7.83 (d, H-8, Ar-H), 8.12 (dd, H-7, Ar-H), 8.73 (s, H-4, Ar-H), 10.61 (s, 1H, CHO).

4. Conclusion

A series of 6-substituted-2-chloroquinoline-3-carbaldehyde were synthesized successfully using the Vilsmeier-Haack reaction. The structures of synthesized derivatives were confirmed by spectral characterization. The study finds that this is an effective method to synthesize aromatics aldehydes based on heterocyclic compounds. Overall, this reaction is a very useful formylation method and has wide applications in the organic synthesis.

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