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A highly efficient synthesis of 2-chloro -3-formyl-8-methyl quinoline: Vilsmeier-haack reagent

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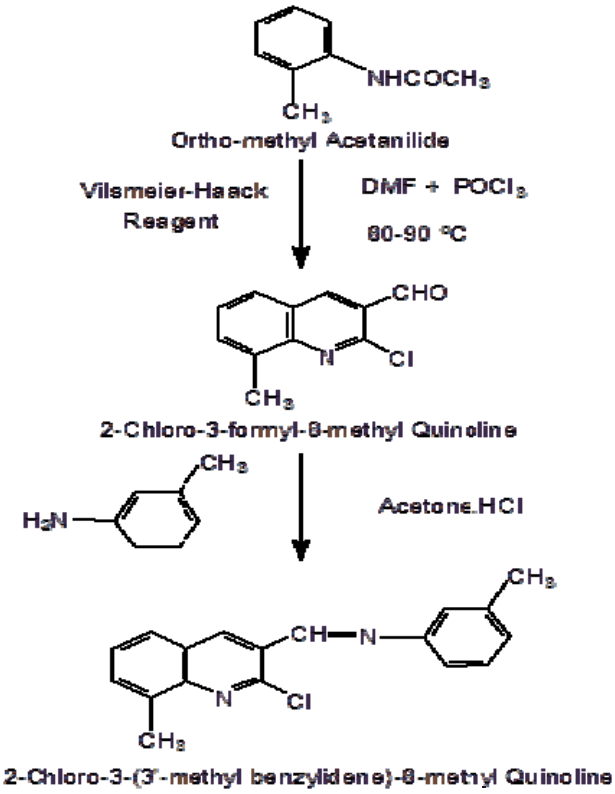
Abstract
For the synthesis of substituted i.e. 2-chloro-3-formyl-8-methyl Quinoline an highly efficient, simple and convenient method through Vilsmeier-Haack reagent has been developed in high yields, less raw material, and less time requiring for completion of reaction.
In the present research work the substituted quinoline and acetanilide are synthesized through Vilsmeier reaction has been reported to the substitution reaction by substituted acetanilide bearing electron donating group at ortho position and electron attracting group at ortho position are investigated and it is good in all case.
Further, the nucleophilic substitution reaction of the substituted quinoline is also investigated.
Similarly in quinoline the –CHO (formyl) group is subjected for further transformation of formyl group in to (4'-NO_2 nitro group, 3'N-NH-C_6H_5) 3'-CH_3 group and 3'-N-benzylidene group.

Keywords: Vilsmeier reagent, 2-chloro-3-formyl-8-methyl Quinoline, TLC, Formylation.

1. Introduction
Substituted quinolines are very simply, efficiently and conveniently synthesized in less time and high yield with less amount of raw material under mild condition with the help of Vilsmeier-Haack reagent (DMF + POCI3) and substituted acetanilide. Quinolines has been possesses a wide spectrum of biological activities.
Now a days quinoline derivatives are used for a convenient starting material of various further substituted quinoline.
Formylation of heterocyclic compounds [3] may be archived by heating heterocyclic compound with Vilsmeier reagent. i.e (DMF + POCI3) phosphorous oxy chloride and dimethyl formamide, the intermediate is hydrolysed in the presence of mildbase give 2-(ortho)-substituted heterocyclic compound [7]. This reaction is known as Vilsmeier-Haack reaction.

2. Methods and Materials
All chemicals were used of analytical grade from sigma Aldrich and S.d. Fine Chem. limited. All melting points were taken in open capillaries and are an correct.
The progress of all reaction of the synthesized compound was monitored by TLC. i.e (thin layer chromatography).
TLC was run using TLC aluminium sheets adsorbent silica gel, chloroform solvent pet-ether, ethylacetate (9:5, 0:5).Spot were visualized using solid iodine fumes, by the keeping of TLC plate in iodine chamber.

2.1 Reaction



2.2 Experimental Procedure for:-

The completion of reaction and purity of Synthesized products were monitored by silica gel TLC melting point determined by open capillary method.

The substituted Quinoline compounds were synthesized by the method of Meth-Cohn et al [1-2].

I) To Prepare ortho- substituted acetanilide

Take 5 ml of ortho-substituted aniline, 5ml of acetic anhydride and 5 ml of glacial acetic acid in a 150 ml conical flask. Shake the reaction mixture thoroughly and then reflux, it for 60 minutes using an air condenser.

After completion of requiring duration of reaction, Pour the hot reaction mixture to 200 ml of ice cold water in a beaker with constant stirring. filter the product and wash with water. Recrystllise the crude acetanilide either from boiling water or dilute acetic acid.

II) To Prepare Quinoline Derivative

(Synthesis of 2-Chloro-8-methyl-3-formyl Quinoline):

Take Dimethyl formamide (DMF) 5 ml and and is cooled to O^0C temperature in a flask equipped with a drying tube. then 18 ml of $POCl_3$ (Phosphorous oxy chloride) is added drop wise with stirring to it. Then to this solution add 4 grams of O-methyl acetanilide. After few minutes the solution of reaction mixture is refluxed for 6-8 hours using air condenser and the temperature of reaction mixture is maintained between 80-90 °C.

After completion of requiring duration, the reaction mixture is cooled and poured in 100 ml beaker containing ice-cold water and stirred about half an hour then filter precipitated quinoline and wash with water and dried, recrystallized from ethyl acetate.

III) To Prepare (substituted benzylidene) quinoline

In a clean and dry round bottom flask take recrystilized 2-chloro-3-formyl-8-methyl Quinoline about (2 mmole) and (2 mmole) of 4-Nitro aniline, add 8 ml of methanol and 4-5 drops of glycial acetic acid. Shake the reaction mixture thoroughly and then reflux it for about 1-2 hours using air condenser.

After completion of requiring duration of reaction cool and pour the reaction mixture in a ice-cold water, filter and dried, Recrystallized it. from ethyl acetate.

2.3 Characterization data of the synthesized compound

Acetanilide: Yield: 54.54 %; m.p.:114 ° C; Anal. Calcd for C8H9NO: C:71.11 %;H:6.66 %; N:10.37;O11.85 %.; IR (KBr) cm^{-1}: 3295 (N-H),1664 (CO), 1584 (C=C).

^{1}H-NMR (300 MHz, DMSO-*d6*); δ 8.72 (s, 1H, NH), 2.1 (s, 3H, CH_3), 7.2 (d, 1H, Ar-H), 7.1 (s, 1H, Ar-H), 7.0 (d, 1H, Ar-H).

^{13}C-NMR (75 MHz, DMSO-*d6*); δ 138.2 (ipso), 169.5 (CO), 24.1 (CH_3), 120.4, 128.7, 124.1.

2-Methyl Acetanilide: Yield: 52.55%; m.p.: 109-112° C; Anal. Calcd for $C_9H_{11}NO$: C: 72.11%;H: 7.38 %; N:9.39 %.; IR (KBr) cm^{-1}: 3279 (N-H),1658 (CO), 1581 (C=C),2851 (Ar-CH_3 -C-H).

^{1}H-NMR (300 MHz, DMSO-*d6*); δ 8.69 (s, 1H, NH), 2.1 (s, 3H, CH_3), 4.25 (s, 3H, Ar- CH_3), 7.2 (d, 1H, Ar-H), 7.1 (s, 1H, Ar-H), 7.0 (d, 1H, Ar-H).

^{13}C-NMR (75 MHz, DMSO-*d6*); δ137.1 (ipso), 170(CO), 21, (CH_3), 137.5(ArC-CH_3)119, 127, 122.

2-Nitro Acetanilide: Yield: 57.62%; m.p.:90-94 °C; Anal. Calcd for $C_8H_8N_2O_3$:C:53.33%;H:4.44%; N:15.55 %.O:26.66%; IR (KBr) cm^{-1}: 3298 (N-H),1680 (CO), 1585 (C=C),1514 (Ar-NO_2).

^{1}H-NMR (300 MHz, DMSO-*d6*); δ 8.73 (s, 1H, NH), 2.2 (s, 3H, CH_3), 7.2 (d, 1H, Ar-H), 7.0 (s, 1H, Ar-H), 6.9 (d, 1H, Ar-H).

^{13}C-NMR (75 MHz, DMSO-*d6*); δ 136.9 (ipso), 169 (CO), 24.2 (CH_3),148.3(ArC-NO_2),121,127,123.

4-Chloro Acetanilide: Yield: 53.11%; m.p.: 176-178° C; Anal. Calcd for C_8H_8NOCI: C:56.80%H:4.73 %; N:8.28 %.O:9.46%; CI:20.71%;

IR (KBr) cm^{-1}: 3292 (N-H), 1665 (CO), 1585 (C=C), 759 (C-CI).

^{1}H-NMR (300 MHz, DMSO-*d6*); δ 8.70 (s, 1H, NH), 2.1 (s, 3H, CH_3), 3.6 (HC-CI), 7.2 (d, 1H, Ar-H), 7.1 (s, 1H, Ar-H), 7.0 (d, 1H, Ar-H).

^{13}C-NMR (75 MHz, DMSO-*d6*); δ 138 (ipso), 169 (CO), 23.9 (CH_3),156 (Ar-CI),131,126,120.

2-Chloro-3-formyl Quinoline: Yield: 62.82%; m.p.:143 ° C; Anal. Calcd for$C_{10}H_6NOCI$: C: 62.82%H:3. 14 %; N:7.32 %.O:8.37%; CI:18.32%;

($CDCI_3$) ; δ ^{1}H NMR : 10.5 (s,1H,CHO),8.8 (s,1H,H-4),8.1(m,1H,H-6),7.7(m,1H,H-7).

^{13}C-NMR ($CDCI_3$); δ 189.12.

MS m/z: 193(M^{++}+2), 191(M^{++}), 190,162,155,127.

2-Chloro-3-formyl-8-Methyl Quinoline: Yield: 63%; m.p.:138 ° C; Anal. Calcd for $C_{11}H_8NOCI$: C: 64.39%H: 3.90 %; N: 6.82 %.O:7.80%; CI: 17.07%;

($CDCI_3$) ; δ ^{1}H NMR : 10.4 (s, 1H,CHO),8.7 (s,1H,H-4), 8.1-7.4 (m,3H,H-5,H-6 andH-7), 2.8 (s,3H, CH_3).

^{13}C-NMR ($CDCI_3$); δ 189.51.

2,6-Dichloro-3-formyl Quinoline: Yield:69 %; m.p.:138 ° C; Anal. Calcd for$C_{10}H_5NOCI_2$: C:53.33% H:2.22 %; N:6.22 %.O:7.11%; CI:31.11%;

($CDCl_3$) ; δ ^{1}H NMR : 10.8 (s,1H,CHO),8.6 (s,1H,H-4),8.1 (m,1H,H-8),7.7 (m,1H, H-5).
^{13}C-NMR ($CDCl_3$); δ 189.49.
IR (KBr) cm^{-1}: 3050, 1693, 1628, 1379, 1038.

2-Chloro-3-formyl-8-Nitro Quinoline: Yield: 65 %; m.p.:124 º C; Anal. Calcd for$C_{10}H_5N_2O_3CI$: C: 50.84%H: 2.11 %; N:11.86 %.O:20.33%; CI:14.83%;
($CDCl_3$) ; δ ^{1}H NMR : 10.5 (s,1H,CHO),8.9 (s,1H,H-4), 7.7 (m,1H, H-5), 8.1 (m,1H,H-6,H-7).
^{13}C-NMR ($CDCl_3$); δ 189.31

2-Chloro-3-(3'-methyl benzylidene)-8-Methyl Quinoline: Yield:57 %; m.p.:197 º C; Anal. Calcd for $C_{18}H_{15}N_2CI$: C:73.46 %H:5.10 %; N:9.52 %; CI:11.90%;
IR (KBr) cm^{-1}: 2925 (-CH_3), 1333 (C-N), 1622 (C=N) imine,776 (C-CI),1588 (C=C) Aromatic.
($CDCl_3$); δ ^{1}H NMR: 7.2-7.6 (8Hm Ar-H),8.9 (1H,sCH=N),2.5 (6H,s,- CH_3).

2-Chloro-3-(4'-nitro benzylidene)-8-Methyl Quinoline: Yield: 57%; m.p.:140 º C; Anal. Calcd for $C_{17}H_{12}N_3O_2CI$: C: 62.76%H: 3.69 %; N: 12.92 %.O:9.84%; CI: 10.76%;
IR (KBr) cm^{-1}: 2930 (-CH_3), 1342 (C-N), 1635 (C=N) imine, 775 (C-CI), 1580 (C=C) Aromatic 1525 (N=O).
($CDCl_3$); δ ^{1}H NMR: 7.1-7.63 (8Hm Ar-H), 8.3 (1Hs, CH=N), 2.48 (3H,s,- CH_3).

2-Chloro-3-(benzylidene)-8-Methyl Quinoline: Yield:65 %; m.p.:181 º C; Anal. Calcd for $C_{17}H_{13}N_2CI$: C: 72.85%H:4.64 %; N:10 %; CI:12.5%;
IR (KBr) cm^{-1}: 2922 (-CH_3), 1323 (C-N), 1628 (C=N) imine, 770 (C-CI), 1585 (C=C) Aromatic.
($CDCl_3$); δ ^{1}H NMR: 7.1-7.68 (9Hm Ar-H), 8.8 (1Hs, CH=N),2.43 (3H,s,- CH_3).

2-Chloro-3-(benzylidenehydrazido)-8-Methyl Quinoline: Yield:62 %; m.p.:207 º C; Anal. Calcd for $C_{17}H_{14}N_3CI$: C: 69.17% H: 4.74 %; N: 14.23%; CI: 11.86%;
IR (KBr) cm^{-1}: 2932 (-CH_3), 1340 (C-N), 1637 (C=N) imine, 777 (C-CI), 1582 (C=C) Aromatic.
($CDCl_3$); δ ^{1}H NMR: 7.1-7.8 (9Hm Ar-H), 8.73 (1Hs, CH=N), 2.44 (3H, s,- CH_3),3.7 (=N-NH-).

3. Results and Discussion

Different biological active heterocycles (table 1) have been successfully synthesized in higher yield using Vilsmeier-Haack reagent. In the present study on Formylation (Aromatic Electrophilic Substitution) was found to be better support on basis of the yield of the product.

The substituted quinolines and it's derivatives was synthesized by Vilsmeier-Haack reagent in good yield (60-80%).It was prepared by refluxing 2-chloro-3-formyl quinoline and substituted aromatic aniline for 2-3 hours using air condenser.
The required substituted 2-chloro-3-formyl quinoline was prepared by two stage procedure. Thus, in that first the starting material which is substituted acetanilide is prepared by the reaction between (various) substituted aniline and acetic anhydride in presence of acetic acid, then this reaction mixture reflux for about 60 minutes at 80-90 ºC on air condenser.
Then next stage consisting the Vilsmeier cyclisation of acetanilide, in which $POCl_3$ (phosphoryl chloride) adding to the substrate (acetanilide) in DMF (N,N-dimethyl formamide) at 0-5ºC then reaction mixture refluxed for about 4 hours at80-90ºC to get 2-chloro-3-formyl quinoline .Only methyl group substituted quinolines requires 4-10 hours heating.
The structure of all synthesized compounds were confirmed by IR,^{1}H NMR spectra and melting point. And all the reactions are monitored by Thin Layer Chromatography. In which we checked the progress of reaction mixture and we found that Rf values in between 0-1.
The Rf value is used to determine the value of the movement of material along the TLC plate. The Rf value is equal to the distance travelled by the substrate (material) spoted on TLC plate divided by the distance travelled by solvent, it's value is always between zero and one. A TLC analysis might be summarized something like, Using silica gel plate and ethyl acetate as the development solvent and after visualization we observed that the less polar compound has travelled further and more polar compound has travelled less far.
The following table showing Rf value of all synthesized products.

Table 2: Molecular formula, Retention factor and Time period at 80-90 ºC of Synthesized compound:-

Sr. No.	Molecular Formula		Rf Value	Time Period at 80-90ºC
1	1-a	C_8H_9NO	0.63	60 min
2	1-b	$C_9H_{11}NO$	0.67	60 min
3	1-c	$C_8H_8N_2O_3$	0.68	10-15 min
4	1-d	C_8H_8NOCI	0.71	60 min
5	2-a	$C_{10}H_6NOCI$	0.63	4 hours
6	2-b	$C_{11}H_8NOCI$	0.65	6-8 hours
7	2-c	$C_{10}H_5N_2O_3CI$	0.70	4 hours
8	2-d	$C_{10}H_5NOCI_2$	0.74	4 hours
9	3-a	$C_{18}H_{15}N_2CI$	0.72	1-2 hours
10	3-b	$C_{17}H_{12}N_3O_2CI$	0.69	1-2 hours
11	3-c	$C_{17}H_{14}N_3CI$	0.68	1-2 hours
12	3-d	$C_{17}H_{13}N_2CI$	0.71	1-2 hours

Table 1: Physical data of synthesized compounds

Sr. No.	Molecular formula of Compound	M.P. in ºC	Yield in GM	% Yield in GM	Molecular Weight.	Elemental analysis in %				
						C	H	N	O	Cl
1	C_8H_9NO	114ºC	3.90	54.54	135.16	71.11	6.66	10.37	11.85	-
2	$C_9H_{11}NO$	109-112ºC	3.60	52.55	149	72.48	7.38	9.39	10.73	-
3	$C_8H_8N_2O_3$	90-94ºC	3.40	57.62	180	53.33	4.44	15.55	26.66	-
4	C_8H_8NOCI	176-178ºC	3.50	53.11	169	56.80	4.73	8.28	9.46	20.71
5	$C_{10}H_6NOCI$	143ºC	6	62.82	191	62.82	3.41	7.32	8.37	18.32
6	$C_{11}H_8NOCI$	138ºC	3.46	63	205	64.39	3.90	6.82	7.80	17.07
7	$C_{10}H_5N_2O_3CI$	124ºC	3.40	65	236	50.84	2.11	11.86	20.33	14.83
8	$C_{10}H_5NOCI_2$	138ºC	3.93	69	225	53.33	2.22	6.22	7.11	31.11
9	$C_{18}H_{15}N_2CI$	197ºC	1.67	57	294	73.46	5.10	9.52	_	11.90
10	$C_{17}H_{12}N_3O_2CI$	140ºC	1.86	57	325	62.76	3.69	12.92	9.84	10.76
11	$C_{17}H_{14}N_3CI$	207ºC	1.82	62	295	69.15	4.74	14.23	_	11.86
12	$C_{17}H_{13}N_2CI$	181ºC	1.82	65	280	72.85	4.64	10	_	12.5

4. Conclusion

Different heterocyclic compounds have been synthesized by simple, rapid and environmentally benign method using Vilsmeier reagent. i.e (DMF + POCI3) phosphorous oxy chloride and dimethyl formamide. Synthesized heterocycles possess good yield. All synthesized compounds were characterized by TLC, Melting Point.

A efficient and convenient method for the preparation of substituted quinoline and it's derivaties with good yield has been developed.

The reaction / method successfully expands the synthetic scope of the multi-component Vilsmeier-Haack reaction.

Further, the present procedure may be readily used to large scale synthesis and generation of the substituted quinolines, The physical data, such as molecular formula, molecular weight, melting point, Yield, % Yield and elemental analysis were shown in table no.1. And Rf value and time period of reaction are shown in table No.2

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