International Journal of Chemical Studies

P-ISSN: 2349–8528
E-ISSN: 2321–4902
www.chemijournal.com
IJCS 2022; 10(1): 177-180

Received: 13-11-2021
Accepted: 26-12-2021

Anant S Tekale
Research Laboratory,
Department of Chemistry.
Shivaji Mahavidyalaya, Udgir,
Latur, Maharashtra, India

Corresponding Author:
Anant S Tekale
Research Laboratory,
Department of Chemistry.
Shivaji Mahavidyalaya, Udgir,
Latur, Maharashtra, India

Synthesis of new Quinoline derivatives using Vilsmeier-Haack reagent: And its spectral characterizations

Anant S Tekale

Abstract
To create substituted compounds, such as 2-chloro-3-formyl-8-methyl Via the Vilsmeier-Haack reagent, a very effective, straightforward, and practical technique for producing quinoline has been devised. This approach has high yields, uses less raw materials, and takes less time to complete the reaction. The substitution reaction by substituted acetanilide having an Ortho electron donating group and an ortho electron attracting group is explored in the current research effort, and it is good in all cases. Substituted quinoline and acetanilide are produced using the Vilsmeier reaction. Additional research is done on the substituted quinoline's nucleophilic substitution process. Similar to this, the -CHO (formyl) group in quinoline undergoes additional transformation into the 4'-NO2 nitro group, the 3'N-NH-C6H5 group, the 3'-CH3 group, and the 3'-N-benzylidene group.

Keywords: 2-chloro-3-formyl-8-methyl Quinoline, Synthesis and Characterization of substituted Quinoline Vilsmeier reagent, Formylation, TLC

Introduction
With the aid of the Vilsmeier-Haack reagent (DMF + POCI3) and substituted acetanilide, substituted quinolines are very easily, effectively, and conveniently synthesised in little time and high yield with less amount of raw material under mild conditions. Quinolines are known to have a variety of biological effects. Quinoline derivatives are now a practical starting point for numerous additional substituted quinolines. Heterocyclic compounds [3] can be formylated by heating them in the presence of the Vilsmeier reagent. Dimethyl formamide and phosphorous oxy chloride, or (DMF + POCI3), are the intermediates that are hydrolyzed in the presence of mild base to produce a 2-(ortho)-substituted heterocyclic molecule [7]. Vilsmeier-Haack reaction is the name of this response.

Methods and Materials
All of the chemicals used were analytical grade and came from Sigma Aldrich and S.D. Fine Chem. Ltd. The solvents were purified using accepted techniques. Each melting point was measured in an open capillary and is accurate. TLC was used to track the development of each reaction of the produced molecule (thin layer chromatography). TLC was conducted utilising TLC aluminium sheets, silica gel, petether, and chloroform as solvents (9:5, 0:5). By keeping the TLC plate in the iodine chamber, the spot was visualised using solid iodine fumes.

Experimental Procedure
The silica gel TLC melting point obtained by open capillary technique was used to monitor the reaction's completeness and the purity of the synthesised products. The Meth-Cohn *et al*. technique [1-2] was used to create the substituted Quinoline compounds.

Ortho- substituted acetanilide
In a 150 ml conical flask, combine 5 ml of Ortho-substituted aniline, 5 ml of acetic anhydride, and 5 ml of glacial acetic acid. Mix the reaction mixture well, and then use an air condenser to reflux it for 60 minutes. After the required amount of time for the reaction has passed, slowly pour the heated reaction mixture into 200 ml of ice-cold water in a beaker while stirring continuously. After cleaning with water, filter the product. Reconstitute the crude acetanilide with either diluted acetic acid or hot water.

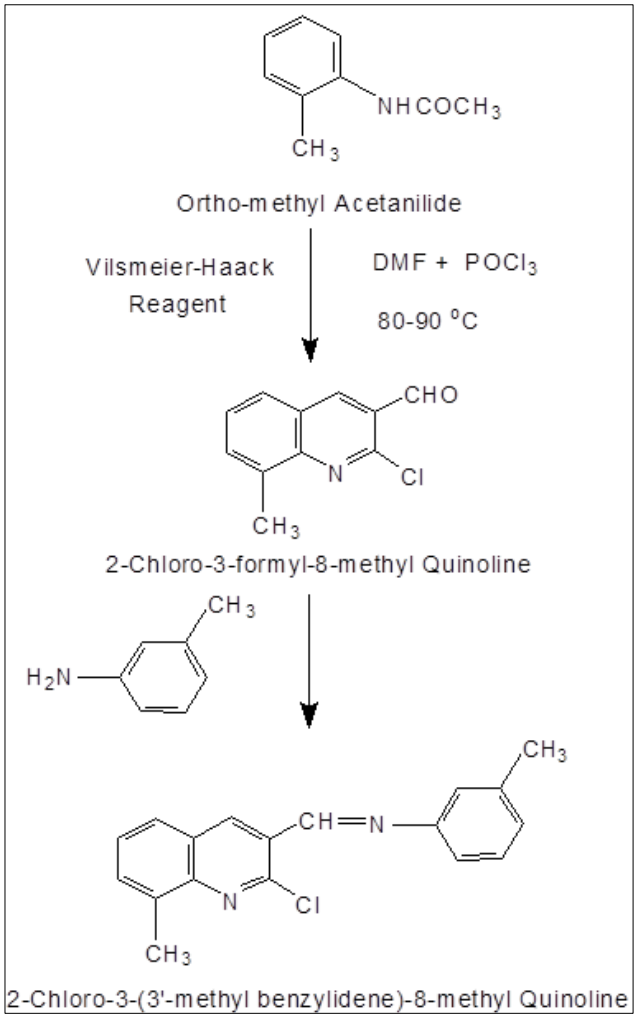
Quinoline Derivative

(Synthesis of 2-Chloro-8-methyl-3-formyl Quinoline): Take 5 ml of dimethyl formamide (DMF), cool it to 0°C, and place it in a flask with a drying tube. After that, 18 ml of POCl3 (phosphorous oxy chloride) is dropped in and stirred into the mixture. Then, add 4 grammes of ortho methyl acetanilide to this solution. After a short while, the reaction mixture's solution is refluxed using an air condenser for 6–8 hours, with the temperature of the reaction mixture being held between 80–900°C. Following the completion of the necessary time, the reaction mixture is cooled, poured into a 100 ml beaker of ice-cold water, and agitated for about 30 minutes. The quinoline is then filtered, washed with water, dried, and then recrystallized from ethyl acetate.

Substituted benzylidene Quinoline

Add 2 mmole of 4-Nitro aniline and 2 mmole of recrystallized 2- chloro-3-formyl-8-methyl quinoline to a clean, dry round bottom flask. Also add 8 ml of methanol and 4-5 drops of glacial acetic acid. The reaction mixture should be properly shaken before using an air condenser to reflux it for one to two hours. After the required amount of time has passed, cool the reaction mixture by pouring it into ice-cold water, filtering and drying it, and then recrystallizing it from ethyl acetate.

Reaction



Characterization data of the synthesized compound

Acetanilide: Yield: 54.54%; m.p.:114^0 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). 1H-NMR (300 MHz, DMSO-*d6*); δ 8.72 (s, 1H, NH), 2.1 (s, 3H, CH3), 7.2 (d, 1H, Ar-H), 7.1 (s, 1H, Ar-H), 7.0 (d, 1H, Ar- H). 13C-NMR (75 MHz, DMSO-*d6*); δ 138.2 (ipso), 169.5 (CO), 24.1 (CH3), 120.4, 128.7, 124.1.

2-Methyl Acetanilide: Yield: 52.55%; m.p.: 109-112^{0}C; Anal. Calcd for C9H11NO: C: 72.11%;H: 7.38%; N:9.39%.; IR (KBr) cm-1: 3279 (N-H),1658 (CO), 1581 (C=C),2851 (Ar- CH3 -C-H).1H-NMR (300 MHz, DMSO-*d6*); δ 8.69 (s, 1H, NH), 2.1 (s, 3H, CH3), 4.25 (s, 3H, Ar- CH3), 7.2 (d, 1H, Ar-H), 7.1 (s, 1H, Ar-H), 7.0 (d, 1H, Ar-H). 13C-NMR (75 MHz, DMSO-*d6*); δ137.1 (ipso), 170(CO), 21, (CH3), 137.5(ArC-CH3)119, 127, 122.

4-Chloro Acetanilide: Yield: 53.11%; m.p.: 176-178^{0}C; Anal. Calcd for C8H8NOCI: 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 (CCI).1H-NMR (300 MHz, DMSO-*d6*); δ 8.70 (s, 1H, NH), 2.1 (s, 3H, CH3), 3.6 (HC-CI), 7.2 (d, 1H, Ar-H), 7.1 (s, 1H, Ar-H), 7.0 (d, 1H, Ar-H). 13C-NMR (75 MHz, DMSO-*d6*); δ 138 (ipso), 169 (CO), 23.9 (CH3),156 (Ar-CI),131,126,120.

2-Nitro Acetanilide: Yield: 57.62%; m.p.:90-94 °C; Anal. Calcd for C8H8N2O3: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-NO2).1H-NMR (300 MHz, DMSO-*d6*); δ 8.73 (s, 1H, NH), 2.2 (s, 3H, CH3), 7.2 (d, 1H, Ar-H), 7.0 (s, 1H, Ar-H), 6.9 (d, 1H, Ar- H). 13C-NMR (75 MHz, DMSO-*d6*); δ 136.9 (ipso), 169 (CO), 24.2 (CH3),148.3(ArC-NO2),121,127,123.

2-Chloro-3-formyl Quinoline: Yield: 62.82%; m.p.:143 °C; Anal. Calcd forC10H6NOCI: C: 62.82%H:3. 14%; N:7.32%.O:8.37%; CI:18.32%; (CDCI3); δ 1H NMR: 10.5 (s,1H,CHO),8.8 (s,1H,H- 4),8.1(m,1H,H-6),7.7(m,1H,H-7). 13C-NMR (CDCI3); 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 C11H8NOCI: C: 64.39% H: 3.90%; N: 6.82%. O:7.80%; CI: 17.07%; (CDCI3); δ 1H 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, CH3).13C-NMR (CDCI3); δ 189.51.

2-Chloro-3-formyl-8-Nitro Quinoline: Yield: 65%; m.p.:124^{0}C; Anal. Calcd forC10H5N2O3CI: C: 50.84%H: 2.11%; N:11.86%.O:20.33%; CI:14.83%; (CDCI3); δ 1H 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). 13C-NMR (CDCI3); δ 189.31.

2,6-Dichloro-3-formyl Quinoline: Yield:69%; m.p.:138 °C; Anal. Calcd forC10H5NOCI2: C:53.33% H:2.22%; N:6.22%. O:7.11%; CI:31.11%; (CDCI3); δ 1H NMR: 10.8 (s,1H,CHO),8.6 (s,1H,H-4),8.1 (m,1H,H-8),7.7 (m,1H, H-5).13C-NMR (CDCI3); δ 189.49.IR (KBr) cm-1: 3050, 1693, 1628, 1379, 1038.

2-Chloro-3-(3'-methyl benzylidene)-8-Methyl Quinoline: Yield:57%; m.p.:197^0 C; Anal. Calcd for C18H15N2CI:C:73.46%H:5.10%; N:9.52%; CI:11.90%; IR (KBr) cm-1: 2925 (-CH3), 1333 (C-N), 1622 (C=N) imine, 776 (C-CI),1588 (C=C) Aromatic. (CDCI3); δ 1H NMR: 7.2-7.6 (8Hm Ar-H),8.9 (1H,sCH=N),2.5 (6H,s,- CH3).

2-Chloro-3-(benzylidene)-8-Methyl Quinoline: Yield:65%; m.p.:181^0 C; Anal. Calcd for C17H13N2CI: C: 72.85%H:4.64%; N:10%; CI:12.5%; IR (KBr) cm-1: 2922 (-CH3), 1323 (C-N), 1628 (C=N) imine, 770 (C-CI), 1585 (C=C) Aromatic.(CDCI3); δ 1H NMR: 7.1-7.68 (9Hm Ar-H), 8.8 (1Hs, CH=N),2.43 (3H,s,- CH3).

2-Chloro-3-(4'-nitro benzylidene)-8-Methyl Quinoline: Yield: 57%; m.p.:140 °C; Anal. Calcd for C17H12N3O2CI: C:62.76%H: 3.69%; N: 12.92%.O:9.84%; CI: 10.76%; IR (KBr) cm-1: 2930 (-CH3), 1342 (C-N), 1635 (C=N) imine,775 (C-CI), 1580 (C=C) Aromatic 1525 (N=O). (CDCI3); δ 1H NMR: 7.1-7.63 (8Hm Ar-H), 8.3 (1Hs, CH=N),2.48 (3H,s,- CH3).

2-Chloro-3-(benzylidenehydrazido)-8-Methyl Quinoline: Yield:62%; m.p.:207 °C; Anal. Calcd for C17H14N3CI: C:69.17% H: 4.74%; N: 14.23%; CI: 11.86%; IR (KBr) cm-1: 2932 (-CH3), 1340 (C-N), 1637 (C=N) imine, 777 (C-CI), 1582 (C=C) Aromatic. (CDCI3); δ 1H NMR: 7.1-7.8 (9Hm Ar-H), 8.73 (1Hs, CH=N), 2.44 (3H, s,- CH3),3.7 (=N-NH-).

Table 1: Physical data of synthesized compounds

Sr. No.	Molecular formula of Compound	M.P. in °C	Yield in GM	% Yield in GM	Molecular Weight.	Elemental analysis in%				
						C	H	N	O	CI
1	C_8H_9NO	114 °C	3.90	54.54	135.16	71.11	6.66	10.37	11.85	_
2	$C_9H_{11}NO$	109-112 °C	3.60	52.55	149	72.48	7.38	9.39	10.73	_
3	$C_8H_8N_2O_2$	90-94 °C	3.40	57.62	164	58.53	4.87	17.07	19.51	_
4	C_8H_8NOCI	176-178 °C	3.50	53.11	169	56.80	4.73	8.28	9.46	20.71
5	$C_{10}H_6NOCI$	143 °C	6	62.82	191	62.82	3.41	7.32	8.37	18.32
6	$C_{11}H_8NOCI$	138 °C	3.46	63	205	64.39	3.90	6.82	7.80	17.07
7	$C_{10}H_5N_2O_3CI$	124 °C	3.40	65	236	50.84	2.11	11.86	20.33	14.83
8	$C_{10}H_5NOCI_2$	138 °C	3.93	69	225	53.33	2.22	6.22	7.11	31.11
9	$C_{18}H_{15}N_2CI$	197 °C	1.67	57	294	73.46	5.10	9.52	_	11.90
10	$C_{17}H_{12}N_3O_2CI$	140 °C	1.86	57	325	62.76	3.69	12.92	9.84	10.76
11	$C_{17}H_{14}N_3CI$	207 °C	1.82	62	295	69.15	4.74	14.23	_	11.86
12	$C_{17}H_{13}N_2CI$	181 °C	1.82	65	280	72.85	4.64	10	_	12.5

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

Sr. No.	Molecular Formula		Rf Value	Time Period at 80-90 °C
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

Results and Discussion

Vilsmeier-Haack reagent has been utilised to successfully synthesis a variety of biologically active heterocycles (table 1) in higher yield. Based on the product yield, the current investigation on formylation (aromatic electrophilic substitution) was determined to have better support. Vilsmeier-Haack reagent produced the substituted quinolines and their derivatives in good yields (60-80%). It was made by employing an air condenser to reflux 2-chloro-3-formyl quinoline and aromatic aniline as a replacement for two to three hours.

Through a two-step process, the necessary substituted 2-chloro-3-formyl quinoline was created. As a result, the precursor to substituted acetanilide is created by reacting (different) substituted anilines with acetic anhydride in the presence of acetic acid, and the reaction mixture then refluxes for 60 minutes at 80 to 90 °C on an air condenser. The following step was the Vilsmeier cyclization of acetanilide, which involved adding POCI3 (phosphoryl chloride) to the substrate (acetanilide) in DMF (N,N-dimethyl form amide) at 0-5 °C and then refluxing the reaction mixture for around 4 hours at 80-90 °C to produce 2-chloro-3-formyl quinoline.

Only quinolines with methyl groups replaced need to be heated for 4–10 hours. Melting point, IR, and 1H NMR spectra were used to confirm the structure of every produced molecule. Moreover, Thin Layer Chromatography is used to keep track of all responses. When we examined the reaction mixture's development, we discovered that Rf values ranged from 0 to 1. The value of the movement of material along the TLC plate is calculated using the Rf value.

The distance covered by the substrate (material) spotted on the TLC plate divided by the solvent's transit distance yields the Rf value, which is always between 0 and 1. Utilizing a silica gel plate and ethyl acetate as the development solvent, and after viewing, we discovered that the less polar component has travelled further and the more polar compound has travelled less far, is one way to sum up a TLC analysis. This table displays the Rf values for all synthesised products.

Conclusion

With Vilsmeier reagent, several heterocyclic compounds have been produced quickly, easily, and without harming the environment. i.e., dimethyl formamide and phosphorous oxy chloride (DMF + POCI3). Heterocycles made through synthesis have a high yield. TLC, Melting Point was used to categorise all synthetic substances. It has been established a practical and effective method for producing substituted quinoline and its derivatives with high yield. The multi-component Vilsmeier-Haack reaction's synthetic range is successfully expanded by the reaction/method. Also, the current method is easily adaptable to the large-scale synthesis and production of the substituted quinolines, the physical information, including the elemental composition, melting temperature, yield, yield percentage, and molecular weight, was displayed in table no. 1. And table no. 2 shows the Rf value and reaction time period.

Acknowledgement
The writers appreciate UGC. UGC Western Regional Office in Pune provided financial support for this endeavour. Also, the authors appreciate the facilities provided in the department by the head of the chemistry department and the principal of Shivaji College, Udgir.

References

1. Meth-cohn O, Narine B. Versatile new synthesis of quinolines, thienopyridines and related fused pyridines. (Tetrahedron lett.). 1978;19:2045-2048.
2. Meth-cohn O, Narine B, Tarnowski B. A Versatile new synthesis of quinolines and related fused pyridines. The synthesis of 2-chloroquinoline-3- carbaldehydes. J Chem. Soc; Perkins Trans-1. 1981, 1520-1530.
3. Ambika Srivastava, Singh KM. Indian journal of chemistry. 2005;44B:1868-1875.
4. Bandgar BP, Makane SS synlett; c2003. p. 262.
5. Venugopal M, perumal PT, Rajaduraj S. Tetrahedron let. 1974, 913.
6. Judit Toth, GaborBlasko, AndrasDancso: synthetic communication. 2006;3653581-3589. (Taylor and Francis).
7. Yogeshmurti, Sujeet K, Gupta, Pathak. Derpharma chemical. 2010;2(4):271-277.
8. Sekar M, prasad RKJ. J Chem, Technol, Biotechnol; c1998. p. 32-52.
9. Sheeja Devi K, *et al.* Asian. J of pharmaceutical and medicinal chemistry. 2013;1(1):39-47.
10. Bakr F, Abdel-Wahab, Rizk E. khidre. –ARKIVOC. 2012;(i):211-276.
11. Bakr F, Abdel-Wahab, khidre. (Review article) (Hindwai) Journal of chemistry. 2013. ID851297:13.
12. Hemant Badwik, Vanktraman S, Deepa Thakur. (A Jr c) Asian journal research chem. 2011;4(6).
13. Jaya Kumar Swamy BHM, Praveen Y. Pramod; Journal of pharmacy research. 2012;5(5):2735-2737.
14. Ameya A Chavan, Nandini R Pai. Molecules. 2007;12:2467-2477.
15. Rajput AP, Girase P. (review article) International journal of pharma- ceutical, chemical and biological sciences. (IJPCBS). 2012;3(1):25-43.
16. Badgujar DM, Talawar MB, Asthana SN, Maulikar PP./ J of scientific and industrial research; c2008. p. 67.