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"MSCL-DMF/DMAC: A VILSMEIER-HAACK TYPE REAGENT FOR THE SYNTHESIS OF 2-CHLORO-3-FORMYL QUINOLINES/ 2-CHLORO-3-ACETYL QUINOLINES"

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ABSTRACT
2-Chloro-3-formyl quinolines and 2-chloro-3-acetyl quinolines were synthesized by reaction of N, N-dimethyl formamide (DMF)-methane sulfonyl chloride (MsCl) or N, N-dimethyl acetamide (DMA) - methane sulfonyl chloride (MsCl) system with corresponding acetanilide respectively. Methane sulfonyl chloride adducts with N, N'-dimethyl formamide (DMF) and N, N'-dimethyl acetamide (DMA) were explored as an alternative to Vilsmeier –Haack (VH) type reagents for effective synthesis of 2-chloro-3-formyl quinolines and 2-chloro-3-acetyl quinolines. Reaction times and temperature reduced significantly using this adduct as compaired with N, N'-dimethyl formamide - phosphoryl chloride adduct or N, N-dimethyl acetamide - phosphoryl chloride adduct. The synthesized compounds were characterized by melting points, ^{1}H- NMR and mass spectral data.

KEYWORDS: 2-Chloro-3-formyl quinolines, 2-Chloro-3-acetyl quinolines, Methane sulfonyl chloride.

1. INTRODUCTION
The Vilsmeier Haack reagent is the most versatile reagent in organic synthesis and the Vilsmeier Haack reaction (VHR) is commonly used in organic synthesis for formylations as well as acetylations. The reactive intermediates involved in the VHR are the halomethyleniminium salts derived from the action of phosphoryl chloride on N, N-disubstituted formamides [i-iii]. The Vilsmeier Haack reaction under conventional conditions involves electrophilic substitution of an activated aromatic ring with a chloromethyleniminium salt to yield the corresponding iminium species [iv]. The cyclizations of iminium species under Vilsmeier Haack conditions is an important synthetic tool of organic chemistry, and provides a facile entry into large numbers of heterocyclic systems [v-xi]. But the Vilsmeier-Haack reaction bearing specific thermal hazards as both the Vilsmeier-Haack intermediate in N,N-dimethylformamide or in N,N-dimethylacetamide are thermally unstable and can generate high and fast temperature and pressures rises when heated[xii-xiv]. VH adducts ($POCl_3$-DMF) [xv], exhibited efficient synthetic applications in the formylation and acetylations of organic compounds since Vilsmeier and Haack used for the first time in 1927 for the direct introduction

of formyl group (-CH = O) into aromatic nucleus, by preparing phosphorus oxychloride ($POCl_3$) and DMF. Over the decades, the Vilsmeier-Haack (VH) reagent is used as an efficient, economical and mild reagent for the formylations/acetylations of aromatic and heteroaromatic substrates. Basically, DMF and oxychloride under chilled conditions in situ forms a chloromethyleniminium salt, which is used as a powerful synthetic tool to achieve several aromatic and heterocyclic compounds including quinoline derivatives. But the oxychloride such as phosphoryl chloride, thionyl chloride, phosgene or triphosgene that are used in the preparation of VH reagents are toxic in nature. In last few decades several chemists and biochemists modified the classical VH reagent using different types of oxychloride such as PCl_5/DMF [xvi], $SOCl_2$-DMF/DMA [xvii], TCTA-DMF/DMA [xviii], TCCA-DMF/DMA [xix], OPC-DMF/DMA [xx], $COCl_2$-DMF/DMA [xxi], and Triphosgene-DMF/DMA [xxii], Tf_2O-DMF [xxiii]. Although, most of the VH type adducts are reported under different reaction methodologies in last few years which are suffering drawbacks like harsh reaction condition, longer reaction time, toxic and corrosive reagents, low yields of products, required excess amounts VH adducts while MsCl-DMF/DMAc has been utilized as a mild activation reagent in Vilsmeier–Haack formylation [xxiii]. Methane sulfonyl chloride acts as an efficient catalyst for electrophilic activation of amides [xxix]. So considering all these facts, in the present work we wish to employ as MsCl-DMF/DMAc i.e. methane sulfonyl chloride-DMF/DMAc as an alternative VH type reagent for effective synthesis of 2- chloro-3-formyl quinolines or 2-chloro-3-acetyl quinolines from acetanilides under conventional reaction conditions.

2. RESULTS AND DISCUSSION

As an effort to develop innovative methodology, we report herein simple and efficient methane sulfonyl chloride-DMF/DMAc adducts and acetanilide for the synthesis of 2-chloro-3-formylquinoline and 2-chloro-3-acetyl-quinoline.

Initially, 4-Chloroacetamide, MsCl and DMF, were selected as reference substrates, for optimization of reaction condition**.** Different time, temperature and equivalents of adducts were screened as summarized in **Table-1.**

As a result of optimization studies it is observed that, 3.0eq adduct is minimum requirement of reaction (**Entry-3, Table-1**) while 4.0 hour is sufficient time for the completion of reaction (**Entry-6, Table-1**) at 85°C. We also investigated reaction temperature and observed that at lower temperature yields are obtained less due to incomplete conversion of reaction while at higher temperature yield was comparable.

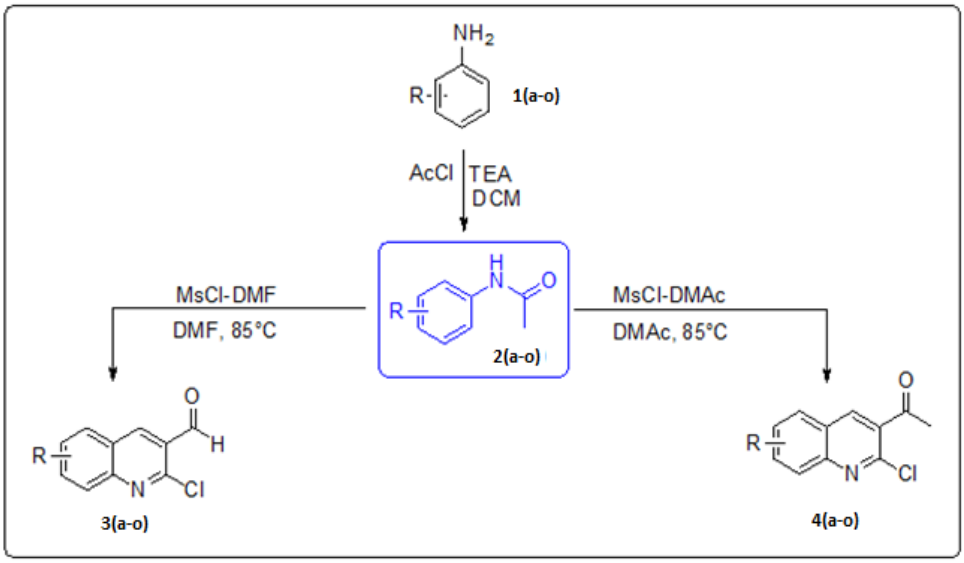
Table-1: Optimization of reaction conditions for the synthesis of 2-chloro-3-formyl quinolines and 2-chloro-3-acetyl quinolines and their reactions.

Entry	MsCl-DMF (Eq.)	Time (h)	Temperature °C	Yield (%)
1.	5.0	8	80	82
2.	4.0	8	80	85
3.	**3.0**	8	80	87
4.	1.0	8	80	43
5.	2.0	6	80	85
6.	**3.0**	**4**	**80**	**89**
7.	2.0	2	80	27
8.	2.0	4	60	76

9.	2.0	4	30	19.0

* **Reaction conditions:** 1 (1.0eq.), MsCl (3.0 eq.) and DMF (3.0 eq.) was maintained at 85°C for 4.0 hour.

Scheme-1: Synthesis of 2-chloro-3-formyl quinolines and 2-chloro-3-acetyl quinolines.



3/4	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**
R	H	6-Me	7-Me	8-Me	8-Et	6-OMe	7-OMe	8-OMe
3/4	**i**	**j**	**k**	**l**	**m**	**n**	**o**	
R	6-Br	6-Cl	7-Cl	8-Cl	6-NO_2	7-NO_2	8-NO_2	

Table-2 *Exploration of reaction conditions on a selected substrates i.e.2 (a-o) to afford products i.e.3 (a-o) & 4(a-o).*

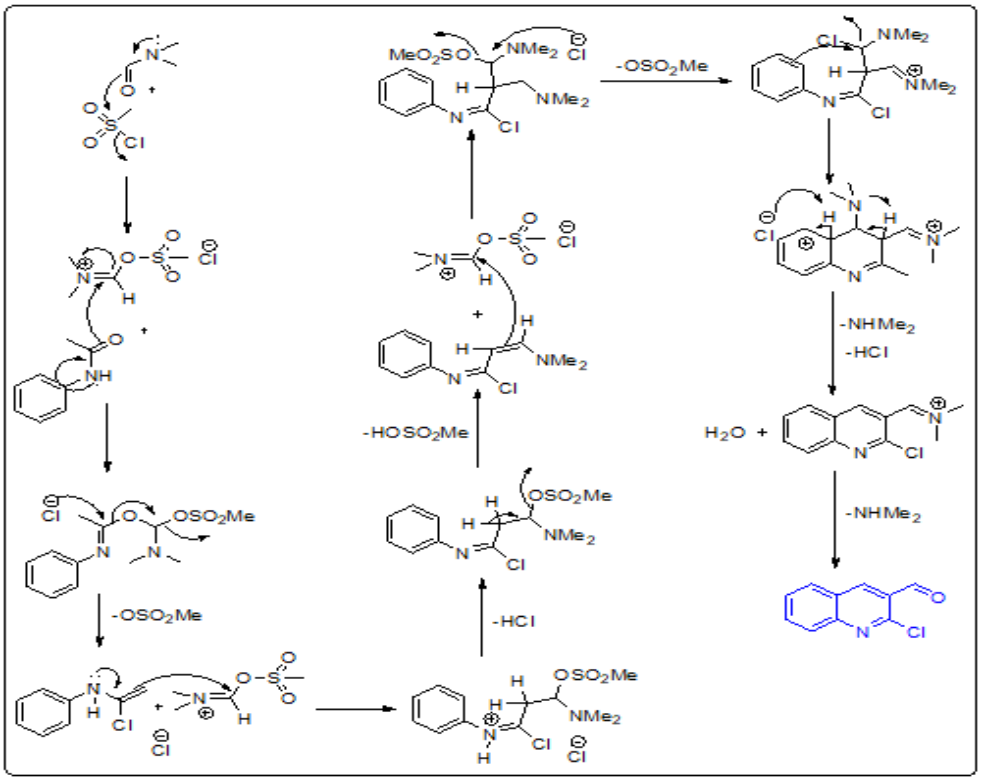
Comp.	R	Yield (%)		Melting points, °C		Comp.	R	Yield (%)		Melting points, °C	
		Obs.	[Ref.]	Obs.	Reported [Ref.]			Obs.	[Ref.]	Obs.	Reported [Ref.]
3a	H	88	96, [xxxi]	147.2	146-149, [xxv]	4a	H	80	88, [xxxii]	71.2	74-76, [xxvi]
3b	6-Me	82	96, [xxxi]	121.3	123, [xxv]	4b	6-Me	73	90, [xxxii]	74.8	72–74, [xxvii]
3c	7-Me	81	86, [xxxiii]	150.1	146, [xxv]	4c	7-Me	71	77, [xxxiv]	73.9	74–76, [xxvii]
3d	8-Me	81	87, [xxxv]	136.3	137, [xxv]	4d	8-Me	82	79, [xxxvi]	88.7	84–86, [xxvii]
3e	8-Et	79	72, [xxxvii]	92.8-95	98, [xxv]	4e	8-Et	78	88, [xxxii]	79.3	79-81, [xxvi]

3f	6-OMe	84	92, [xxxi]	148.2	146, [xxv]	4f	6-OMe	81	88, [xxxii]	75.2	82–84, [xxvii]
3g	7-OMe	84	92, [xxxviii]	191-193	196, [xxv]	4g	7-OMe	72	71, [xxxiv]	119.8	119-120, [xxvii]
3h	8-OMe	80	69, [xxxix]	193.4	190, [xxv]	4h	8-OMe	79	73, [xl]	93.6	93-95, [xxvii]
3i	6-Br	82	90, [xxxi]	187.9	188, [xxv]	4i	6-Br	83	88, [xxxii]	84.9	122, [xxvi]
3j	6-Cl	65	83, [xli]	161.8	160, [xxv]	4j	6-Cl	51	90, [xxxii]	136.7	139-140, [xxvi]
3k	7-Cl	63	85, [xlii]	153.7	191, [xxv]	4k	7-Cl	51	90, [xxxii]	136.7	135-138, [xxvi]
3l	8-Cl	82	92, [xliii]	182.9	181 , [xxviii]	4l	8-Cl	83	91, [xliv]	84.9	82, [xxvi]
3m	6-NO_2	65	69, [xlv]	151.8	151 , [xxviii]	4m	6-NO_2	51	78, [xxxii]	136.7	130, [xxvi]
3n	7-NO_2	69	74, [xxxix]	160.3	162, [xxviii]	4n	7-NO_2	49	74, [xxxii]	138.5	135-137, [xxvi]
3o	8-NO_2	63	65, [xlvi]	153.7	155, [xxviii]	4o	8-NO_2	56	78, [xxxii]	129.6	128-131, [xxvi]

** [Ref.]: References*

To further extend the scope of MsCl-DMF adduct, synthesis of substituted acetanilide used to synthesize a range of substituted 2-chloro-3-formyl quinolines under optimized reaction conditions. The same optimized reaction condition explored for the synthesis of 2-chloro-3-acetyl quinolines using MsCl-DMA adduct along with substituted acetanilide. The detailed results were summarized in **Table -2.**

3. Plausible Mechanism: Plausible mechanism represented as follows,



4. EXPERIMENTAL SECTION

All chemicals and reagents were purchased from commercial resources like Avra, Spectrochem and Finar and utilized directly without purification. Reaction progress was monitored on TLC plate of silica-gel and visualized under UV light. Melting points were obtained by using Lab-India MR. Vis+ apparatus. The ^{1}H-NMR spectra were determined using Bruker 300/400 MHz instrument using TMS as the internal standard. Isolated compounds were purified using re-crystallization technique.

4.1 General procedure for the preparation of substituted Acetanilide [2(a-r)].

To a well equipped RBF, substituted aniline (1.0eq) and triethylamine (2.0eq) charged with dichloromethane (10.0 rel volume) and stirred well. To the above mass, acetyl chloride (1.1eq) was added slowly at ambient temperature and stirred till completion of reaction at ambient temperature. After completion of reaction, reaction mass diluted with water, basified with sodium bicarbonate water solution. Layers were separated and dichloromethane layer concentrated to get desired acetanilide. All the synthesized products are reported in literature and were identified by comparison of their observed melting points and ^{1}H-NMR values with reported values.

4.2 General procedure for the preparation of substituted 2-chloro-3-formyl-quinolines 3(a-r).

A mixture of MsCl (3.0eq) and DMF (3.0eq) was stirred at (20-25) °C for 1.0h.

Substituted acetanilide (1.0eq) was charged at (20-25) °C and stirred for 30 min. Reaction mass heated to 85°C and maintained for 4h. Progress of the reaction monitored by TLC. After complete conversion of substituted acetanilide to desired product, reaction mass quenched by ice cold water, basified with $NaHCO_3$ Aq. solution and extracted with dichloromethane.

Organic layer dried over sodium sulfate and concentrated under vacuum to obtain crude product. The isolated crude product was re-crystallized from MTBE to afford a pure solid of substituted 2-chloro-3- formyl-quinolines in good to excellent yield. All the synthesized products are identified by comparison of their observed melting points and ^{1}H-NMR values with reported values.

Same process used for the preparation of remaining molecules.

Spectral data of some selected compounds:

3a: (^{1}H-NMR, 300 MHz, $CDCl_3$): δ= 10.5 (s, 1H), 8.8(s, 1H), 8.1(m, 2H), 7.9(m, 1H), 7.7(m, 1H).

3b: (^{1}H-NMR, 300 MHz, $CDCl_3$): δ= 10.6 (s, 1H), 8.5(s, 1H), 8.0(m, 1H), 7.75(m, 1H), 7.65(m, 1H), 2.6(s, 3H).

3c: (^{1}H-NMR, 300 MHz, $CDCl_3$): δ= 10.4 (s, 1H), 8.9(s, 1H), 7.9(m, 1H), 7.85(m, 1H), 7.7(m, 1H), 2.6(s, 3H).

3d: (^{1}H-NMR, 300 MHz, $CDCl_3$): δ= 10.4 (s, 1H), 8.7(s, 1H), 8.1-7.4(m, 3H), 2.8(s, 3H).

3e: (^{1}H-NMR, 300 MHz, $CDCl_3$): δ= 10.6 (s, 1H), 9.0(s, 1H), 8.3-7.3(m, 3H), 3.4(q, 2H), 1.5(t, 3H).

3f: (^{1}H-NMR, 300 MHz, $CDCl_3$) : δ= 10.6 (s, 1H), 9.0(s, 1H), 8.1(d, 1H), 7.6(s, 1H), 7.6(m, 1H), 4.0(s, 3H).

3g: (^{1}H-NMR, 300 MHz, $CDCl_3$): δ= 10.5 (s, 1H), 8.6(s, 1H), 7.78(m, 1H), 7.5(s, 1H), 7.3(m, 1H), 4.0(s, 3H).

3h: (^{1}H-NMR, 300 MHz, $CDCl_3$): δ= 10.5 (s, 1H), 8.9(s, 1H), 8.0-7.74(m, 1H), 7.5(s, 1H), 7.3(m, 1H), 3.9(s, 3H).

3i: (^{1}H-NMR, 300 MHz, $CDCl_3$): δ= 10.8 (s, 1H), 8.8(s, 1H), 8.4(m, 1H), 7.6(m, 1H), 7.6 (s, 1H).

3j: (^{1}H-NMR, 300 MHz, $CDCl_3$): δ= 10.8 (s, 1H), 8.6(s, 1H), 8.1(m, 1H), 7.7(m, 1H), 7.6 (s, 1H).

3k: (^{1}H-NMR, 300 MHz, $CDCl_3$): δ= 10.7 (s, 1H), 8.5(s, 1H), 7.7(m, 1H), 7.5(s, 1H), 7.2 (m, 1H).

4.3 General procedure for the preparation of substituted 2-chloro-3-acetyl-quinolines 6(a-r)

A mixture of MsCl (3.0eq) and DMAc (3.0eq) was stirred at (20-25) °C for 1.0h.

Substituted acetanilide (1.0eq) was charged at (20-25) °C and stirred for 30 min. Reaction mass heated to 85°C and maintained for 4h. Progress of the reaction monitored by TLC. After complete conversion of substituted acetanilide to desired product, reaction mass quenched by ice cold water, basified with $NaHCO_3$ Aq. solution and extracted with dichloromethane. Organic layer dried over sodium sulfate and concentrated under vacuum to obtain crude product. The isolated crude product was re-crystallized from MTBE to afford a pure solid of substituted 2-chloro-3- acetyl-quinolines in good to excellent yield. All the synthesized products are identified by comparison of their observed melting points and ^{1}H-NMR values with reported values.

Same process used for the preparation of remaining molecules.

Spectral data of some selected compounds:

6b: 1H-NMR (300 MHz, CDCl3): δ= 8.29 (s, 1H), 7.92 (d, 1H), 7.68 (m, 2H), 2.75 (s, 3H), 2.51 (s, 3H).

6c: 1H-NMR (300 MHz, CDCl3): δ= 8.36 (s, 1H), 7.81 (s, 1H), 7.77 (d, 1H), 7.44 (d, 1H), 2.76 (s, 3H); 2.57 (s, 3H).

6f: 1H-NMR (300 MHz, CDCl3): δ= 8.26 (s, 1H), 7.92 (d, 1H), 7.45 (dd, 1H), 7.10 (d, 1H), 3.93 (s, 3H), 2.77 (s, 3H).

6i: 1H-NMR (300 MHz, CDCl3): δ= 2.1 (s, 3H) 7.0– 7.4 (m, 4H).

6l: 1H-NMR (300 MHz, CDCl3): δ= 2.2 (s, 3H), 7.0 –8.4 (m, 4H).
6m: 1H-NMR (300 MHz, CDCl3): δ= 2.3 (s, 3H), 7.0 – 7.4 (m, 4H).

5. CONCLUSION

In summary, in the present work we have employed an efficient and mild MsCl-DMF and MsCl-DMAc adduct first time as an efficient VH type reagent for effective synthesis of 2-chloro-3-formyl quinolines and 2-chloro-3-acetyl quinolines from acetanilides. Methane sulfonyl chloride used for the preparation of VH type reagent is readily available. The reactions afforded very good to excellent yields of under conventional conditions at 85°C. Depending on the structure of acetanilide, reaction times recorded under conventional conditions reduced from (8 to 12) hours to 4.0 hours. All synthesized compounds were characterized by their Melting points, ^{1}H-NMR.

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