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UNDER SOLVENT-FREE CONDITIONS, ACETYLATION and VILSMEIER-HAACK FORMYLATION REACTIONS WITH ACETANILIDES and ANILINES

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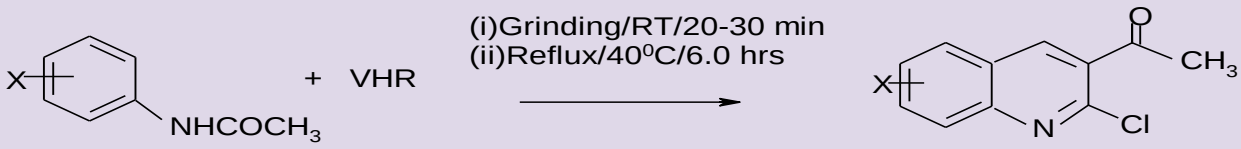
ABSTRACT

The Vilsmeier-Haack reaction with anilines and acetanilides was carried out without the use of a solvent. At room temperature, the reactants are put in a mortar and ground with a pestle for 20 to 30 minutes. Formyl derivatives were generated in surprisingly good yields when dimethyl formamide (DMF) and POCl3 were used as the VH reagent. Nevertheless, acetyl derivatives were generated when DMF was substituted for DMA in the formulation of the VH reagent. The results of solvent free reactions are better to those of solution phase reactions, with high yields and much shorter reaction times.

GRAPHICAL ABSTRACT:



Keywords: *Vilsmeier Haack Reagent, Halomethyleniminium salt, formylation, acetylation*

INTRODUCTION

One of the gentlest techniques for adding a formyl or acetyl group to different aromatic compounds is the Vilsmeier-Haack (VH) reaction [1–7]. Since its discovery in 1927[1], the Vilsmeier-Haack reagent has drawn the interest of organic chemists. It is a halomethyleniminium salt made from POCl3 and N-N'-dimethyl formamide (DMF), N-N'-dimethyl acetamide (DMA), or comparable N-N'-dialkyl amides. Di- and polyamines of the diphenylmethane derivatives are synthesised from formylated anilines [8]. Formyl phenyl aspirins are known to operate as a prodrug for formyl s, whereas formyl quinolines are known to have antibacterial properties. [10], antifungal activity [11].

In recent past enormous interest has been paid for the development of economically simple and environmentally safe methods in organic synthesis in the lines of Green Chemistry [12]. Organic reactions performed under solvent free conditions have gained much attention because of their enhanced selectivity, mild reaction conditions and associated ease of manipulation. The recent reviews and publications [13-22] in this field prove the importance of solvent free organic synthesis and highlights that this process is not only simple; but also satisfies both economical and environmental demands by replacing the toxic solvents. The use of solid acid catalysis is potentially more attractive because of the ease of removal and recycling of the catalyst and the possibility that the solid might influence the selectivity. Even though efforts were made to use operationally simple materials as catalysts, not much attention appears to have been diverted towards solvent free Vilsmeier-Haack reaction. Over the past one decade our group is also actively working on exploiting the use of a variety of eco friendly materials such as surfactants and non-conventional energy sources (such as microwave and ultra sound) to assist various organic transformations such as nitration [23] and Vilsmeier-Haack reactions [24-29]. Present investigation is one such exercise, which is aimed to explore the possibility to achieve formylation and acetylation of certain anilines and acetanilides with Vilsmeier-Haack reagents under solvent free conditions by grinding the reactants in a mortar with a pestle.

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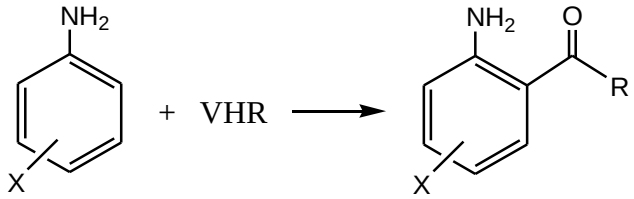
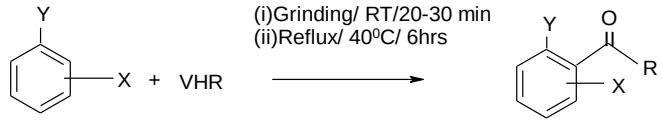
RESULTS AND DISCUSSION

When treated with DMF/SOCl2 and DMA/SOCl2, respectively, under solvent-free conditions when the reactants are ground in a mortar and pestle for about 20 to 30 minutes, aromatic compounds such as anilines and acetanilides derivatives underwent formylation and acetylation under Vilsmeier- Haack conditions in good yields. An array of substituted anilines and acetanilides are used as substrates under the current reaction conditions, as illustrated in Schemes -1 and 2, to test the universality of the reaction. Tables 4.1 and 4.2 compile the yields of key products. The products were examined using genuine samples for the purposes of IR, 1H-NMR, Mass spectra, and physical data, and they were deemed to be satisfactory.



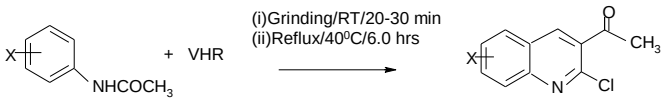
Scheme 1:



Where R = H when VHR = DMF+ POCl3; R = CH3 when VHR = DMA+ POCl3

Y= OH, NH2 and NHCOCH3; X = electron donating or electron withdrawing groups

Scheme 2:



Where R = H when VHR = DMF+SOCl2; R = CH3 when VHR = DMA+SOCl2

Y= NH2; X = electron donating or electron withdrawing groups

Observed rate enhancements followed by increase in reaction yields in micelle mediated reactions could be explained due to the fact that micelles function as micro reactors and enhance rate of the reaction. The progress of the reaction in the absence of a solvent may be attributed to the heat energy produced by the mechanical energy used to grind the reaction mixture in the mortar. The yields are far better than those of comparable solution phase processes. Under solvent-free conditions, the reaction is finished in 20 to 30 minutes, indicating that the current approach could be used for formylation/acetylation reactions on a modest scale. This technology might be viewed as a green chemistry focused synthesis of VH reactions because the reaction time of the solvent free reaction is at least six times shorter than the analogous solution phase reaction and avoids the use of hazardous solvents.

EXPERIMENTAL SECTION:

The substrates used in the present study viz., anilines and acetanilides are procured from either Aldrich or Merck. The solvents acetonitrile (ACN) and dichloro ethane (DCE) were either HPLC grade or purified according to standard literature reports.

General Procedure for preparation of Vilsmeier-Haack Reagent: The Vilsmeier Haack (VH) adduct is prepared afresh before use from POCl3 and dimethyl formamide (DMF). To a chilled (at –50C) dimethyl formamide (DMF) in dichloro ethane (DCE) or acetonitrile (ACN), calculated amount of POCl3 was slowly added drop wise and stored under cold conditions. Similar procedure is adapted for dimethyl acetamide (DMA) systems.

Generic Vilsmeier-Haack Synthesis Process in Reflux Condition: A previously cleaned round bottom flask was filled with a centimolar (0.01mol) amount of organic substrate (Anilines or Acetanilides), 0.015 moles of VH reagent, and solvent DCE. This mixture was then refluxed for approximately 6.0 hours. ACN is used as the solvent in a second run of the same experiment. The reaction mixture is treated with 5% sodium thio sulphate solution after it has finished, as shown by TLC, and then pet ether is added. To obtain a pure product, the organic layer was separated, dried over Na2SO4, and evaporated under vacuum. Column chromatography was then used to purify the mixture using chloroform:n-hexane (8:2) as the eluent. Both formylation and acetylation processes have been carried out successfully using this approach.

Generic Vilsmeier-Haack Synthesis Process in Solvent-Free Conditions: 0.015 moles of VH reagent and a centimolar (0.01mol) organic substrate (anilines or acetanilides) were combined in a previously cleaned mortar and ground for 20 to 30 minutes. The reaction mixture is treated with 5% sodium thio sulphate solution after the reaction has finished, as determined by TLC, and then pet ether is added. To obtain a pure product, the organic layer was separated, dried over Na2SO4, and evaporated under vacuum. Column chromatography was then used to purify the mixture using chloroform:n-hexane (8:2) as the eluent. Both formylation and acetylation processes have been carried out successfully using this approach. According to our table 4.3 and 4.4, isolated products were characterised using spectroscopic techniques.

CONCLUSIONS

In conclusion, under solvent-free circumstances, we successfully showed the Vilsmeier-Haack reaction with certain anilines and acetanilides. The current discovery is superior than solution phase reaction. It is carried out with easily available and inexpensive reagents. Simple work-up at ambient temperature and mild, ecologically safe circumstances allow the reaction to proceed. The present study is a considerable advancement in Vilsmeier-Haack synthesis due to the significantly shorter reaction times (approximately 12 times shorter than heat reactions) and improved reaction yields.

LIST OF ABBREVIATIONS: Vilsmeier Haack (VH); dimethyl formamide (DMF); dimethyl acetamide (DMA), dichloro ethane (DCE); acetonitrile (ACN)

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Table 1: Micellar Catalyzed Vilsmeier Haack Formylation Reactions with Organic Compounds

S.No.	SUBSTRATE	SUBSTRATE	Th. reaction		SDS		CTAB		Tx	
			R.T. (Hrs)	% (Yield)	R.T. (Hrs)	% (Yield)	R.T. (Hrs)	% (Yield)	R.T. (Hrs)	% (Yield)
1.	Aniline	4-amino benzaldehyde	6	42	1.5	40	1.5	30	1.5	88
2.	2-methylaniline	4-amino-3-methyl benzaldehyde	6	40	1.5	48	1.5	30	1.5	72
3.	3-methyl aniline	4-amino-2-methyl benzaldehyde	6	40	1.5	40	1.5	30	1.5	76
4.	4-nitro aniline	2-amino-5-nitro benzaldehyde	6	35	1.5	45	1.5	30	1.5	84
5.	3-chloroaniline	2-chloro-4-amino benyaldehyde	6	30	1.5	50	1.5	30	1.5	81

Table 2: Micellar Catalyzed Vilsmeier Haack Formylation

Reactions with Organic Compounds

VHR = (DMF + POCl3) SOLVENT – DCE

S.No.	SUBSTRATE	SUBSTRATE	Th. reaction		SDS		CTAB		Tx	
			R.T. (Hrs)	% (Yield)	R.T. (Hrs)	% (Yield)	R.T. (Hrs)	% (Yield)	R.T. (Hrs)	% (Yield)
1.	Aniline	4-amino benzaldehyde	6	37	1.5	27	1.5	76	1.5	82
2.	2-methylaniline	4-amino-3-methyl benzaldehyde	6	45	1.5	41	1.5	67	1.5	65
3.	3-methyl aniline	4-amino-2-methyl benzaldehyde	6	66	1.5	42	1.5	80	1.5	56
4.	4-nitro aniline	2-amino-5-nitro benzaldehyde	6	66	1.5	40	1.5	52	1.5	58
5.	3-chloroaniline	2-chloro-4-amino benyaldehyde	6	55	1.5	47	1.5	75	1.5	68

Table 3: Micellar Catalyzed Vilsmeier Haack Acetylation Reactions with Organic Compounds

VHR = (DMA + POCl3) SOLVENT – ACN

S.No.	SUBSTRATE	SUBSTRATE	Th. reaction		SDS		CTAB		Tx	
			R.T. (Hrs)	% (Yield)	R.T. (Hrs)	% (Yield)	R.T. (Hrs)	% (Yield)	R.T. (Hrs)	% (Yield)
1.	Aniline	4-amino acetophenone	6	42	1.5	45	1.5	60	1.5	50
2.	2-methylaniline	4-amino-3-methyl acetophenone	6	40	1.5	45	1.5	50	1.5	45
3.	3-methyl aniline	4-amino-2-methyl acetophenone	6	40	1.5	60	1.5	70	1.5	45
4.	4-nitro aniline	2-amino-5-nitro acetophenone	6	35	1.5	45	1.5	50	1.5	40
5.	3-chloroaniline	2-chloro-4-amino acetophenone	6	30	1.5	50	1.5	35	1.5	35

Table 4: Micellar Catalyzed Vilsmeier Haack Acetylation Reactions with Organic Compounds

VHR = (DMA + $POCl_3$) SOLVENT – DCE

S.No.	SUBSTRATE	SUBSTRATE	Th. reaction		SDS		CTAB		Tx	
			R.T. (Hrs)	% (Yield)	R.T. (Hrs)	% (Yield)	R.T. (Hrs)	% (Yield)	R.T. (Hrs)	% (Yield)
1.	Aniline	4-amino acetophenone	6	39	1.5	35	1.5	76	1.5	82
2.	2-methylaniline	4-amino-3-methyl acetophenone	6	43	1.5	40	1.5	67	1.5	65
3.	3-methyl aniline	4-amino-2-methyl acetophenone	6	64	1.5	43	1.5	80	1.5	56
4.	4-nitro aniline	2-amino-5-nitro acetophenone	6	63	1.5	41	1.5	62	1.5	58
5.	3-chloroaniline	2-chloro-4-amino acetophenone	6	53	1.5	49	1.5	75	1.5	68

Table 5: Micellar Catalyzed Vilsmeier Haack Formylation Reactions with Organic Compounds
VHR = (DMF + POCl3) SOLVENT – (A) DCE & (B): ACN

S. No.	SUBSTRATE	SUBSTRATE	SOL	Th. reaction		SDS		CTAB		Tx	
			VENT	R.T. (Hrs)	% (Yield)	R.T. (Hrs)	% (Yield)	R.T. (Hrs)	% (Yield)	R.T. (Hrs)	% (Yield)
1.	Acetanilide	2-chloro-3-formylquinoline	A	6	22	1.5	25	1.5	60	1.5	90
2.	4-bromoacetanilide	6-bromo-2-chloro-3-formylquinoline	A	6	30	1.5	35	1.5	60	1.5	84
3.	4-nitroacetanilide	6-nitro-2-chloro-3-formylquinoline	A	6	31	1.5	30	1.5	46	1.5	80
4.	4-methylacetanilide	6-methyl-2-chloro-3-formylquinoline	A	6	23	1.5	30	1.5	45	1.5	86
5.	4-hydroxyacetanilide	6-hydroxy-2-chloro-3-formylquinoline	A	6	23	1.5	30	1.5	46	1.5	88
6.	Acetanilide	2-chloro-3-acetylquinoline	B	6	68	1.5	40	1.5	30	1.5	80
7.	4-bromoacetanilide	6-bromo-2-chloro-3-acetylquinoline	B	6	65	1.5	45	1.5	30	1.5	80
8.	4-nitroacetanilide	6-nitro-2-chloro-3-acetylquinoline	B	6	62	1.5	32	1.5	30	1.5	88
9.	4-methylacetanilide	6-methyl-2-chloro-3-acetylquinoline	B	6	50	1.5	30	1.5	30	1.5	88
10.	4-hydroxyacetanilide	6-hydroxy-2-chloro-3-acetylquinoline	B	6	58	1.5	28	1.5	30	1.5	88

Table 6: Micellar Catalyzed Vilsmeier Haack Acetylation Reactions with Organic Compounds
VHR = (DMA + POCl3) SOLVENT – (A): DCE & (B) CAN

Table 6: Micellar Catalyzed Vilsmeier Haack Acetylation Reactions with Organic Compounds
VHR = (DMA + POCl3)SOLVENT – (A): DCE & (B) CAN

S.No.	SUBSTRATE	SUBSTRATE	SOLVENT	Th. reaction		SDS		CTAB		Tx	
				R.T. (Hrs)	% (Yield)	R.T. (Hrs)	% (Yield)	R.T. (Hrs)	% (Yield)	R.T. (Hrs)	% (Yield)
1.	Acetanilide	2-chloro-3-formylquinoline	A	6	68	1.5	48	1.5	90	1.5	90
2.	4-bromoacetanilide	6-bromo-2-chloro-3-formylquinoline	A	6	65	1.5	86	1.5	90	1.5	84
3.	4-nitroacetanilide	6-nitro-2-chloro-3-formylquinoline	A	6	62	1.5	88	1.5	82	1.5	80
4.	4-methylacetanilide	6-methyl-2-chloro-3-formylquinoline	A	6	50	1.5	88	1.5	90	1.5	86
5.	4-hydroxyacetanilide	6-hydroxy-2-chloro-3-formylquinoline	A	6	58	1.5	84	1.5	80	1.5	88
6.	Acetanilide	2-chloro-3-acetylquinoline	B	6	68	1.5	91	1.5	90	1.5	90
7.	4-bromoacetanilide	6-bromo-2-chloro-3-acetylquinoline	B	6	65	1.5	88	1.5	90	1.5	86
8.	4-nitroacetanilide	6-nitro-2-chloro-3-acetylquinoline	B	6	72	1.5	86	1.5	82	1.5	86
9.	4-methylacetanilide	6-methyl-2-chloro-3-acetylquinoline	B	6	75	1.5	84	1.5	90	1.5	82
10.	4-hydroxyacetanilide	6-hydroxy-2-chloro-3-acetylquinoline	B	6	78	1.5	89	1.5	80	1.5	88

Table 7: Vilsmeier Haack Formylation and Acetylation Reactions with organic substrates ($DMF+POCl_3$) in Solvent Free

Conditions:

S.No.	SUBSTRATE	PRODUCT	Formylation		Acetylation	
			R.T (Hrs)	% Yield	R.T (Hrs)	% Yield
1.	Aniline	4-aminobenzaldehyde	30	82	30	88
2.	2-methylaniline	4-amino-3-methylbenzaldehyde	30	76	30	72
3.	3-methylaniline	4-amino-2-methylbenzaldehyde	30	80	30	76
4.	4-nitroaniline	2-amino-5-nitrobenzaldehyde	30	78	30	84
5.	3-chloroaniline	2-chloro-4-aminobenzaldehyde	30	80	30	81
6.	acetanilide	2-chloro-3-formylquinoline	30	80	30	80
7.	4-bromoacetanilide	6-bromo-2-chloro-3-formylquinoline	30	82	30	80
8.	4-nitroacetanilide	6-nitro-2-chloro-3-formylquinoline	30	82	30	88
9.	4-methylacetanilide	6-bromo-2-chloro-3-formylquinoline	30	85	30	88
10.	4-hydroxyacetanilide	6-bromo-2-chloro-3-formylquinoline	30	84	30	88

TABLE 8: Spectroscopic Analysis of the products obtained from Vilsmeier Haack Formylation Reactions:

S.No	Substrate	Product	M+	IR(cm^{-1})	NMR Values in δ
1.	Aniline	4-amino-benzaldehyde	121	1690 (C=O)	6.75 (d,2H,Ar), 7.59(d,2H, Ar), 9.78(s,1H,CHO), 6.51 (s,2H,NH_2)
2.	Acetanilide	2-chloro-3-formylquinoline	191	1670 (C=O) 1590 (C=N)	7.43(t,1H,Ar), 7.56(t,1H,Ar), 7.86(d,1H,Ar), 8.10(d,1H,Ar), 8.78(s,1H,Ar), 9.83(s,1H,CHO)
3.	4-bromo-acetanilide	6-bromo-2-chloro-3-formylquinoline	259	1670 (C=O) 1590 (C=N)	7.83(d,1H,Ar), 7.89(s,1H,Ar), 7.98(d,1H,Ar), 8.80(s,1H,Ar), 9.23(s,1H,CHO)
4.	4-nitro-acetanilide	2-chloro-3-formyl-6-nitroquinoline	236	1670 (C=O) 1590 (C=N)	8.33(d,1H,Ar), 8.39(d,1H,Ar), 8.78(s,1H,Ar), 8.99(s,1H,Ar), 9.63(s,1H,CHO)
5.	4-methyl-acetanilide	3-formyl-2-chloro-6-methylquinoline	205	1670 (C=O) 1590 (C=N)	2.23(s,3H,CH_3), 7.39(m,2H,Ar), 8.08(d,1H,Ar), 8.79(s,1H,Ar), 9.63(s,1H,CHO)

TABLE 9: Spectroscopic Analysis of the products obtained from Vilsmeier Haack Acetylation Reactions:

S.No	Substrate	Product	M^+	IR(cm^{-1})	NMR Values in δ
1.	Aniline	4-amino-acetophenone	135	1690 (C=O)	6.65 (s,2H,NH_2), 2.65(s,3H, CH_3), 6.76(d,2H, Ar), 7.89(d,2H, Ar)
2.	Acetanilide	2-chloro-3-acetylquinoline	205	1670 (C=O) 1590 (C=N)	2.65 (s,3H,CH_3), 7.44(t,1H, Ar), 7.67(t,1H, Ar), 7.89(d,1H, Ar), 8.02(d,1H, Ar), 8.82(s,1H, Ar)
3.	4-bromo-acetanilide	6-bromo-2-chloro-3-acetylquinoline	283	1670 (C=O) 1590 (C=N)	2.65 (s,3H,CH_3), 7.85(d,1H, Ar), 8.07(d,1H, Ar), 8.12(d,1H, Ar), 8.92(s,1H, Ar)
4.	4-Nitro-acetanilide	2-Chloro-3-acetyl-6-nitro quinoline	250	1670 (C=O) 1590 (C=N)	2.65 (s,3H,CH_3), 8.18(d,1H, Ar), 8.47(d,1H, Ar), 8.82(s,1H, Ar), 9.12(s,1H, Ar)
5.	4-Methyl-acetanilide	3-acetyl-2-chloro-6-methyl quinoline	123	1670 (C=O) 1590 (C=N)	2.38 (s,3H,CH_3) 2.65 (s,3H,CH_3), 7.65(d,1H, Ar), 7.85(d,1H, Ar), 8.02(d,1H, Ar), 9.02(s,1H, Ar))

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