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Micellar effects on the kinetics and mechanism of Vilsmeier-Haack cyclisation reactions with acetanilides in nonaqueous solvents

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ABSTRACT

Vilsmeier-Haack Reaction with Acetanilides afforded formyl derivatives with DMF/$SOCl_2$. The reactions obeyed pseudo first order kinetics. There was a dramatic rate enhancement when micelle-forming surfactants such as cetyl tri methyl ammonium bromide (CTAB), sodium dodecyl sulphate (SDS) and triton-X 100 (Tx) were used as catalysts. Rate (k_ψ) versus [Surfactant or C_D] profiles was generally wavy in nature with all the surfactant systems. The results in micellar media were interpreted using Pizkiewicz's cooperativity model.

Keywords: Vilsmeier-Haack Reaction, Acetanilides, formyl derivatives

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INTRODUCTION

The chemistry of heterocycles offers challenging tasks in the development of new synthetic strategies [1]. Quinolines heterocyclic compounds [1], have been found to exhibit bactericidal, antitumor, antimalarial and anti-inflammatory [2-5] activities. Based on the nature of the N-N'-dialkyl amide Vilsmeier-Haack (VH) reagent functions as either formylating or acetylating reagent. In presence of DMF, the oxyhalides generally afford formylating agents. When DMF is replaced by DMA acetylating agent is obtained. Vilsmeier-Haack reactions with organic compounds in general and hydrocarbons with excess pi-electrons in particular undergo formylation [6-12]. This observation prompted us to take up a detailed comparative kinetic study of VH reactions with acetanilides. Dimethyl formamide (DMF) and dimethyl acetamide (DMA) are used along with $POCl_3$ and $SOCl_2$ for the preparation of VH reagents in this study. In case of non-aqueous or non-polar solvents, the micellar hydrophilic polar heads protrudes inwards while the substrate directs towards the micelle-solvent interface [13]. Continued interest in defining the analogy between micellar and enzymatic catalysis has greatly stimulated the development and utility of functional micellar reagents [14]. Many different catalytic and inhibitory effects of micelles have been reported in literature [13-15]. In present work, the catalytic activity of micelles in VH cyclisation reactions was studied.

EXPERINENTAL SECTION

Organic substrates such as acetanilides and their substituted compounds were undertaken for kinetic studies of VH reactions in ACN and DCE as described in our earlier paper and other standard literature procedures [14,15,16]. The resultant solution was neutralized by sodium hydrogen carbonate. Organic phase was extracted with DCE and dried (with $MgSO_4$,) and the solvent evaporated [16]. TLC pure formyl derivative was characterized by spectroscopic methods. When DMF is replaced by DMA in VH reagent preparation corresponding acetyl derivatives were obtained. The reactions afforded fairly good yields of end products.

RESULTS AND DISCUSSION

Under pseudo first order conditions i.e. $[Sub]_o << [VH]_o$, the plots of ln (Vt) versus time were linear with negative slope with intercept on ordinate depicting first order dependence on [Substrate] (i.e., $n_1 = 1$). (1) The First-order rate constant (k') values are presented in table (Tables 1 to 2). Indicated that k' is proportional to the first power raised to [VH Reagent] indicating first order kinetics in [VH reagent]. Slopes of these plots afforded Pseudo first order rate constant (k') values (Tables 3 to 8). (3) Rates of reaction changed significantly when the reaction medium was changed with the trend: ACN > DCE. These observations suggest a change in the nature of the reactive species on passing from high dielectric constant ACN to less polar DCE. In ACN (high dielectric media) participation of ion-pair species of VH adduct (V) and substrate was proposed in the slow step to give phosphorous oxychloromethyleniminium intermediate (B) which is supported by spectroscopic and thermodynamic data [17-22]. These intermediates species (A or B) upon hydrolysis yield the end products.

The overall order of the reaction was found to be two with a first order in presence of cationic (CTAB), anionic (SDS) and non ionic (TX) micelles. Rates were generally enhanced in micellar media. The k_Ψ–C_D profiles indicated different trends depending on nature of substrate, surfactant and organic solvent used. Menger & Portnoy's saturation kinetics and Pizkiewicz's cooperativity models were used for kinetic data interpretation. The observed k_Ψ–C_D profiles are classified into the following categories (Type A to F).

Type A: Sigmoid type k_ψ Vs C_D profiles are considered as Type-A curves.
Type B: The k_ψ Vs C_D profiles which were hill (bell) passing through rate maximum k_ψ are classified as Type – B curves.
Type C: In this type k_ψ Vs C_D profiles $k\psi$ decreases to a minimum at higher concentration of surfactant.
Type D: Type –D k_ψ Vs C_D profiles are wavery type
Type E: This type of k_ψ Vs C_D profiles are valley or well type curves in contrast to hill type curves.
Type F: The plots of k_ψ Vs C_D indicated a continuous increase of k_ψ Vs C_D without any limiting rate maximum.

The plots yielded straight lines with positive slope.

FORMYLATION

S.No.	Substrate	ACN			DCE		
		CTAB	Tx	SDS	CTAB	Tx	SDS
1.	Acetanilide	E	E	E	E	A	E
2.	p-Bromoacetanilide	E	E	E	B	A	C
3.	p-Nitroacetanilide	D	D	E	D	B	C
4.	p-Hydroxyacetanilide	B	E	D	D	E	D
5.	p-Methylacetanilide	E	E	E	D	F	D

ACETYLATION

S.No.	Substrate	ACN			DCE		
		CTAB	Tx	SDS	CTAB	Tx	SDS
1.	Acetanilide	D	A	D	D	B	D
2.	p-Bromoacetanilide	B	D	F	D	E	D
3.	p-Nitroacetanilide	D	D	B	F	E	F
4.	p-Hydroxyacetanilide	E	C	F	D	D	C
5.	p-Methylacetanilide	E	C	C	E	E	C

TABLE 1: Micellar catalyzed vilsmeier haack formylation reactions with organic compounds

VHR = $(DMF + SOCl_2)$ SOLVENT – (A): ACN & (B): DCE

S.No.	Substrate	Product	Solvent	Th. Reactions		CTAB		Tx		SDS	
				R.T (Hrs)	% Yield	R.T (Hrs)	% Yield	R.T (Hrs)	% Yield	R.T (Hrs)	% Yield
1.	Acetanilide	2-chloro-3-formyl quinoline	A	6	44	1.5	42	1.5	80	1.5	40
2.	4-bromoacetanilide	6-Bromo-2-chloro-3-formyl quinoline	A	6	45	1.5	55	1.5	82	1.5	52
3.	4-nitroacetanilide	6-nitro-2-chloro-3-formyl quinoline	A	6	46	1.5	48	1.5	84	1.5	50
4.	4-methylacetanilide	6-methyl-2-chloro-3-formyl quinoline	A	6	44	1.5	46	1.5	79	1.5	49
5.	4-ydroxyacetanilide	6-hydroxy-2-chloro-3-formyl quinoline	A	6	43	1.5	52	1.5	80	1.5	50
6.	Acetanilide	2-chloro-3-formyl quinoline	B	6	46	1.5	48	1.5	84	1.5	44
7.	4-bromoacetanilide	6-Bromo-2-chloro-3-formyl quinoline	B	6	50	1.5	40	1.5	88	1.5	45
8.	4-nitroacetanilide	6-nitro-2-chloro-3-formyl quinoline	B	6	42	1.5	46	1.5	86	1.5	46
9.	4-methylacetanilide	6-methyl-2-chloro-3-formyl quinoline	B	6	46	1.5	47	1.5	87	1.5	44
10.	4-hydroxyacetanilide	6-hydroxy-2-chloro-3-formyl quinoline	B	6	49	1.5	48	1.5	88	1.5	43

Table 2: Micellar Catalyzed Vilsmeier Haack Acetylation Reactions with Organic Compounds

VHR = (DMA + $SOCl_2$) **SOLVENT – (A): ACN & (B): DCE**

S.No.	Substrate	Product	Solvent	Th. Reactions		CTAB		Tx		SDS	
				R.T (Hrs)	% Yield	R.T (Hrs)	% Yield	R.T (Hrs)	% Yield	R.T (Hrs)	% Yield
1.	Acetanilide	2-chloro-3-acetyl quinoline	A	6	68	1.5	48	1.5	90	1.5	90
2.	4-bromoacetanilide	6-Bromo-2-chloro-3- acetyl quinoline	A	6	65	1.5	86	1.5	90	1.5	84
3.	4-nitroacetanilide	6-nitro-2-chloro-3- acetyl quinoline	A	6	62	1.5	88	1.5	82	1.5	80
4.	4-methylacetanilide	6-methyl-2-chloro-3- acetyl quinoline	A	6	50	1.5	88	1.5	90	1.5	86
5.	4-hydroxyacetanilide	6-hydroxy-2-chloro-3- acetyl quinoline	A	6	58	1.5	84	1.5	80	1.5	88
6.	Acetanilide	2-chloro-3- acetyl quinoline	B	6	42	1.5	44	1.5	80	1.5	40
7.	4-bromoacetanilide	6-Bromo-2-chloro-3- acetyl quinoline	B	6	55	1.5	45	1.5	82	1.5	52
8.	4-nitroacetanilide	6-nitro-2-chloro-3- acetyl quinoline	B	6	48	1.5	46	1.5	84	1.5	50
9.	4-methylacetanilide	6-methyl-2-chloro-3- acetyl quinoline	B	6	46	1.5	44	1.5	79	1.5	49
10.	4-hydroxyacetanilide	6-hydroxy-2-chloro-3- acetyl quinoline	B	6	52	1.5	43	1.5	80	1.5	51

TABLE 3: Effect of variation of [ctab] on the rate of VH formylation reactions:
[VHR] = 0.100 mol dm^{-3} ; 10^3 [S] = 4.00 mol dm^{-3} ; Solvent = ACN ; Temp = 323 K.

Substrate	pseudo first rate constant k' (hr^{-1})													
	(A) [CTAB] (mM) in ACN							(B) [CTAB] (mM) in DCE						
	0.0	0.25	0.5	1.25	2.5	3.75	5.0	0.0	0.25	0.5	1.25	2.5	3.75	5.0
Acetanilide	0.233	0.172	0.206	0.178	0.199	0.153	0.152	0.278	0.220	0.160	0.185	0.180	0.164	0.188
4-bromoacetanilide	0.231	0.199	0.208	0.221	0.238	0.176	0.162	0.189	0.205	0.217	0.173	0.189	0.179	0.210
4-nitroacetanilide	0.154	0.159	0.123	0.141	0.140	0.096	0.078	0.241	0.229	0.211	0.232	0.198	0.214	0.150
4-methylacetanilide	0.189	0.170	0.205	0.177	0.194	0.157	0.151	0.107	0.136	0.103	0.094	0.100	0.109	0.110
4-hydroxyacetanilide	0.199	0.190	0.204	0.148	0.176	0.152	0.191	0.100	0.118	00098	0.139	0.135	0.176	0.116

Table 4: Effect of variation of [TX] on the rate of VH formylation reactions
[VHR] = 0.100 mol dm^{-3}; 10^3 [S] = 4.00 mol dm^{-3} ; Solvent = ACN ; Temp = 323 K.

Substrate	pseudo first rate constant k' (hr^{-1})													
	(A) [Tx] (mM) in ACN							(B) [Tx] (mM) in DCE						
	0.0	0.25	0.5	1.25	2.5	3.75	5.0	0.0	0.25	0.5	1.25	2.5	3.75	5.0
Acetanilide	0.166	0.121	0.132	0.135	0.076	0.080	0.087	0.136	0.118	0.129	0.132	0.144	0.150	0.168
4-bromoacetanilide	0.203	0.183	0.120	0.169	0.164	0.138/	0.184	0.136	0.118	0.129	0.132	0.144	0.150	0.168
4-nitroacetanilide	0.204	0.200	0.204	0.142	0.143	0.134	0.169	0.126	0.168	0.226	0.161	0.095	0.105	0.092
4-methylacetanilide	0.140	0.119	0.132	0.134	0.079	0.075	0.085	0.098	0.078	0.077	0.097	0.088	0.103	0.126
4-hydroxyacetanilide	0.215	0.192	0.221	0.136	0.170	0.145	0.180	0.101	0.133	0.140	0.102	0.122	0.238	0.254

Table 5: Effect of variation of [SDS] on the rate of VH formylation reactions:
[VHR] = 0.100 mol dm^{-3} ; 10^3 [S] = 4.00 mol dm^{-3} ; Solvent = ACN ; Temp = 323 K.

Substrate	pseudo first rate constant k' (hr^{-1})													
	(A) [SDS] (mM) in ACN							(B) [SDS] (mM) in DCE						
	0.0	0.25	0.5	1.25	2.5	3.75	5.0	0.0	0.25	0.5	1.25	2.5	3.75	5.0
Acetanilide	0.097	0.055	0.061	0.069	0.035	0.020	0.010	0.257	0.226	0.166	0.185	0.177	0.164	0.183
4-bromoacetanilide	0.156	0.116	0.060	0.38	0.075	0.048	0.084	0.121	0.127	0.103	0.076	0.078	0.091	0.095
4-nitroacetanilide	0.161	0.110	0.059	0.043	0.077	0.048	0.060	0.133	0.131	0.111	0.093	0.051	0.070	0.055
4-methylacetanilide	0.235	0.273	0.196	0.233	0.218	0.172	0.166	0.081	0.112	0.082	0.084	0.101	0.084	0.061
4-hydroxyacetanilide	0.164	0.138	0.062	0.038	0.077	0.051	0.062	0.102	0.138	0.115	0.034	0.147	0.080	0.101

Table 6: Effect of variation of [CTAB] on the rate of VH acetylation reactions:
[VHR] = 0.100 mol dm^{-3} ; 10^3 [S] = 4.00 mol dm^{-3} ; Solvent = ACN ; Temp = 323 K.

Substrate	pseudo first rate constant k' (hr^{-1})													
	(A) [CTAB] (mM) in ACN							(B) [CTAB] (mM) in DCE						
	0.0	0.25	0.5	1.25	2.5	3.75	5.0	0.0	0.25	0.5	1.25	2.5	3.75	5.0
Acetanilide	0.100	0.117	0.098	0.138	0.132	0.176	0.116	0.100	0.118	0.100	0.141	0.135	0.177	0.116
4-bromoacetanilide	0.167	0.166	0.171	0.177	0.167	0.164	0.163	0.127	0.132	0.138	0.128	0.132	0.130	0.135
4-nitroacetanilide	0.153	0.165	0.159	0.151	0.157	0.146	0.148	0.121	0.125	0.127	0.129	0.128	0.128	0.126
4-methylacetanilide	0.126	0.117	0.127	0.122	0.106	0.109	0.106	0.195	0.205	0.200	0.229	0.184	0.231	0.149
4-hydroxyacetanilide	0.146	0.133	0.150	0.164	0.174	0.199	0.162	0.232	0.228	0.207	0.230	0.217	0.166	0.152

Table 7: Effect of variation of [TX] on the rate of VH acetylation reactions
[VHR] = 0.100 mol dm-3 ; 103 [S] = 4.00 mol dm-3 ; Solvent = ACN ; Temp = 323 K.

Substrate	pseudo first rate constant k' (hr^{-1})													
	(A) [Tx] (mM) in ACN							(B) [Tx] (mM) in DCE						
	0.0	0.25	0.5	1.25	2.5	3.75	5.0	0.0	0.25	0.5	1.25	2.5	3.75	5.0
Acetanilide	0.101	0.133	0.134	0.103	0.121	0.238	0.382	0.101	0.133	0.138	0.103	0.122	0.237	0.382
4-bromoacetanilide	0.162	0.169	0.164	0.176	0.161	0.159	0.153	0.133	0.138	0.124	0.137	0.130	0.132	0.144
4-nitroacetanilide	0.163	0.166	0.175	0.163	0.158	0.168	0.168	0.124	0.122	0.124	0.123	0.126	0.129	0.127
4-methylacetanilide	0.143	0.131	0.122	0.120	0.120	0.122	0.118	0.195	0.205	0.200	0.229	0.184	0.231	0.149
4-hydroxyacetanilide	0.144	0.134	0.128	0.127	0.125	0.129	0.129	0.203	0.188	0.218	0.150	0.179	0.163	0.191

Table 8: Effect of variation of [SDS] on the rate of VH acetylation reactions:
[VHR] = 0.100 mol dm^{-3} ; 10^3 [S] = 4.00 mol dm^{-3} ; Solvent = ACN ; Temp = 323 K.

Substrate	pseudo first rate constant k' (hr^{-1})													
	(A) [SDS] (mM) in ACN							(B) [SDS] (mM) in DCE						
	0.0	0.25	0.5	1.25	2.5	3.75	5.0	0.0	0.25	0.5	1.25	2.5	3.75	5.0
Acetanilide	0.103	0.133	0.116	0.035	0.147	0.082	0.101	0.103	0.135	0.113	0035	0.147	0.073	0.101
4-bromoacetanilide	0.145	0.162	0.167	0.158	0.162	0.166	0.173	0.139	0.142	0.156	0.154	0.142	0.129	0.134
4-nitroacetanilide	0.165	0.175	0.174	0.159	0.187	0.153	0.153	0.127	0.130	0.132	0.134	0.135	0.147	0.141
4-methylacetanilide	0.188	0.195	0.193	0.197	0.195	0.192	0.179	0.155	0.171	0.132	0.134	0.074	0.076	0.089
4-hydroxyacetanilide	0.127	0.126	0.129	0.129	0.130	0.129	0.129	0.193	0.161	0.061	0.037	0.073.	0.050	0.094

CONCLUSION

The results of present study clearly indicate direct cyclisation followed by formylation can be achieved successfully using appropriate VH reagent. Addition of CTAB, SDS and / or Tx100 indicated dramatic rate enhancements, which are sluggish under classical conditions.

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