Bull. Pharm. Sci., Assiut University, Vol. 18, Part 1, June 1995, pp. 49-53

KINETIC STUDIES ON THE ALKYLATING ACTIVITY OF CERTAIN NEW CHALCONES OF ACETYLPYRIDINES

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تم تخليق بعض مركبات الشالكون المشتقة من تفاعل الاستيل بيريدين وبعض بارا مشتقات الدهيدات البنزين. وقد قيمت الفاعلية الالكيلية لهذه المركبات بالدراسة الكيناتيكية لتفاعل هذه المركبات مع ٢-مركابتوايثانول. ولوحظ أن المركبات التى تحمل مجموعات ساحبة للالكترونات فى الموقع بارا بالنسبة لقاطع البنزيلدين تظهر فاعلية أعلى من مثيلاتها التى تحمل مجموعات معطية كما وجد أن أملاح البيريدينيوم تقلل كثيرا من التفاعل.

The synthesis of a number of chalcones derived from acetylpyridines and some p-substituted benzaldehydes has been accomplished. These compounds were evaluated for their alkylating activity by kinetic studies of their reaction with 2-mercaptoethanol. Compounds with electron withdrawing groups in the p-postion of benzylidine moiety showed higher activities than compounds with electron donating groups. Quaternization of the pyridine ring decreased activity profoundly.

INTRODUCTION

It has been known that α,ß-unsaturated ketones react with thiol to give ß-ketothioethers[1-5] and this property explain the bioactivities of a number of α,ß-unsaturated ketones[6-8]. The bioactivity of α,ß-unsaturated ketones has been attributed partially to a judicious balance between their hydrophilic and hydrophobic portions[9].

Determination of the second order rate constants for the reaction of chalcones with 2-mercaptoethanol could be considered as a good method to compare between bioactivities of these chalcones[7].

In the present investigation certain new chalcones were prepared by interaction of 2 and 3 acetylpyridines with different p-substituted benzaldehydes. The prepared compounds were investigated for their alkylating activity by determination of the second order rate constant of their interaction with 2-mercaptoethanol.

EXPERIMENTAL

Melting points are uncorrected. UV spectra were recorded on Pye Unicam SP-1750 UV\VIS spectrophotometer. IR spectra (in KBr or nujol) were recorded on 740 Shimadzu, ^{1}H NMR spectra were recorded on Varian 60 MHz in $CDCl_3$ or DMSO, and TMS used as internal standard. Chemical shifts (δ) are given in ppm. Elemental analyses for C, H, N were performed at the unit of microanalysis, Assiut University and Cairo University. Analytical TLC were performed on precoated TLC plates of silica gel 60F254. The solvent system was ethyl acetate .

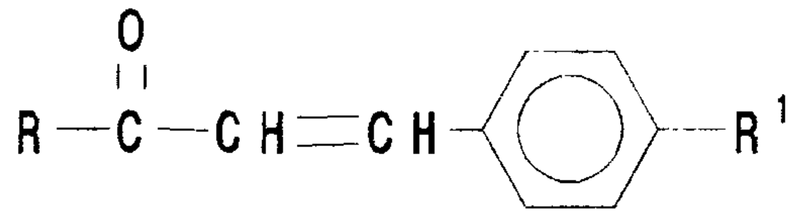
CHEMISTRY

Synthesis of benzylidene acetylpyridines (I, II)

To a cold mixture (0°C) of the acetylpyridine (25 mmol) in 60 % aqueous ethanol (20 ml) and potassium hydroxide (1.15 g, 20 mmol) in 60 % aqueous ethanol (5 ml), the appropriate aldehyde (25 mmol) was added while stirring the temperature was kept at (0°C) all over the experiment. The product prepared was filtered, washed with water, dried and crystallized from aqueous methanol. Data are shown in table (1).

Received in 14/11/1994 & Accepted in 9/7/1995

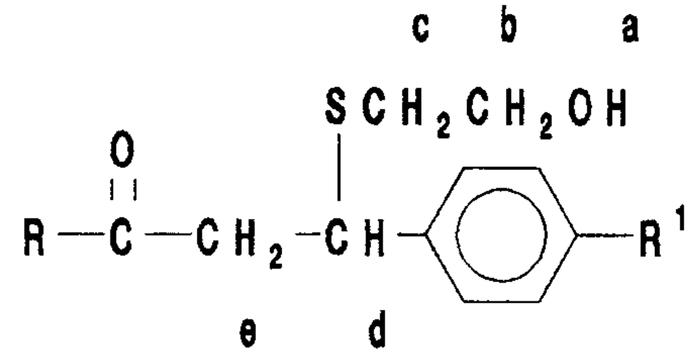
Table 1: Reaction of 2 and 3-acetylpyridines with p-substituted benzaldehyde.



R	Comp. No.	R^1	Yield %	M.p °C	Mol. formula	Microanalysis Calcd/Found C%	H%	N%	IR (cm^{-1})	^1H NMR (ppm)
2-Pyrid.	**Ia**	H	72	125-6	$C_{14}H_{11}NO$	80.38 79.90	5.26 4.85	6.69 6.40	1683-1644	8(m,2HC5,C6); 7.23-6.63(m,9H,2H,C3,C4; 5 aromatic H; 2H,CH=CH)
	Ib	OCH_3	70	86	$C_{15}H_{13}NO_2$	75.31 75.01	5.43 5.32	5.85 5.54	CO-CH=CH	8.7(d,1H,C6); 8.26(d,1HC4); 8.16-7.2(m,2HC3,C5); 6.93-8.16(m,6H superimposed with dd, 4 aromatic H and 2H, CH=CH); 3.86 (s, 3H OCH3)
	Ic	Cl	50	95-7	$C_{14}H_{10}ClNO$	68.99 69.21	4.10 3.90	5.74 5.63		9-8.73(m,1HC6); 8.56-8.43(m,1HC5); 8.4-8.2(m,2HC3,C4) 8.2-7.2(m,6H superimposed with dd 4 aromatic H & 2H, CH=CH)
3-Pyrid.	**IIa**	H	67	78-9	$C_{14}H_{11}NO$	80.38 80.60	5.26 5.50	6.69 6.45		
	IIb	OCH_3	70	98	$C_{15}H_{13}NO_2$	75.31 74.98	5.43 5.23	5.85 5.27		9.5(d,1HC2); 9.1(m,1HC6); 8.6-8.26(m,2HC4,C5);7.9-7.26(m-6H superimposed with dd, 4 aromatic H,2H, CH=CH); 4.2(s,3H OCH3)
	IIc	Cl	53	183-4	$C_{14}H_{10}ClNO$	68.99 68.60	4.10 3.98	5.74 5.61		
3-Pyrid Q	**IIIa**	H	58	202-4	$C_{15}H_{14}INO$	51.28 50.92	3.98 3.70	3.98 3.63		9.73(s,1HC2); 9.16(m,2H,C5,C6); 8.4(1H,C4); 8.36-7.4(m,7H, 5 aromatic H,2H CH=CH); 4.5(s,3H,$^+$N-CH3)
	IIIb	OCH_3	46	194-5	$C_{16}H_{16}INO$	50.39 50.79	4.19 4.06	3.67 3.73		9.73(s,1H,C2); 9.16(m,2H,C5,C6); 8.26(m,1H,C4); 7.93-7.13(m,6H, superimposed with dd, 4 aromatic H;2H, CH=CH); 4.5(s,3H,$^+$NCH3); 3.9(s,3H,OCH3)

Q = quaternized; ^1H NMR of comp. IIIa and IIIb were done in DMSO.

Table 2: Reaction of chalcones with 2-mercaptoethanol.



R	Comp. No.	R^1	Yield %	M.p °C	Mol. formula	Microanalysis Calcd/Found			IR (cm^{-1})	^1H NMR (ppm)
						C%	H%	N%		
2-Pyrid.	**IVa**	H	50	156	$C_{16}H_{17}NO_2S$	66.89 66.42	5.92 5.54	4.87 4.90	1710-1691 $COCH_2CH$	9-7.6(m,4HC6,C5,C4&C3); 7.56-6.76(m, 5 aromatic H); 4.5-4(m,3H,a,b,became 2H after deuteration); 3.9-3.5 (m,3H,e,d); 2.63(t,2H,c)
	IVb	OCH_3	42	semisolid	$C_{17}H_{19}NO_3S$	64.35 64.80	5.99 5.50	4.41 4.35		
	IVc	Cl	35	semisolid	$C_{16}H_{16}ClNO_2S$	59.72 59.30	4.97 5.10	4.35 4.18		
3-Pyrid.	**Va**	H	48	135-7	$C_{16}H_{17}NO_2S$	66.89 67.40	5.92 5.70	4.87 5.00		
	Vb	OCH_3	55	68-70	$C_{16}H_{19}NO_3S$	64.35 64.75	5.99 6.23	4.41 4.55		9.5(m,1H,C2); 9.06(m,1H,C6); 8.66-8(m,2H,C5,C4);7.7-7.16(dd,4 aromatic H); 4.7(t,1H,a,disappeared on deuteration); 4.4-3.76(m,8H,OCH3,b,e,d); 2.73(t,2H,c)
	Vc	Cl	30	155-156	$C_{16}H_{16}ClNO_2S$	59.72 60.15	4.97 4.70	4.35 4.38		
3-Pyrid Q	**VI**	OCH_3	65	210-212	$C_{18}H_{22}INO_3S$	47.05 47.50	4.79 4.40	3.05 3.46		9.72(s,1H,C2); 9.13(m,2H,C6,C4); 8.26(m,1H,C5); 7.9-7.2(dd, 4 aromatic H); 4.9-4.5(m,4H,a,$^+$N-CH3, became 3H after deuteration); 4.4-3.83(m,8H,OCH3,b,e,d); 2.7(t,2H,c)

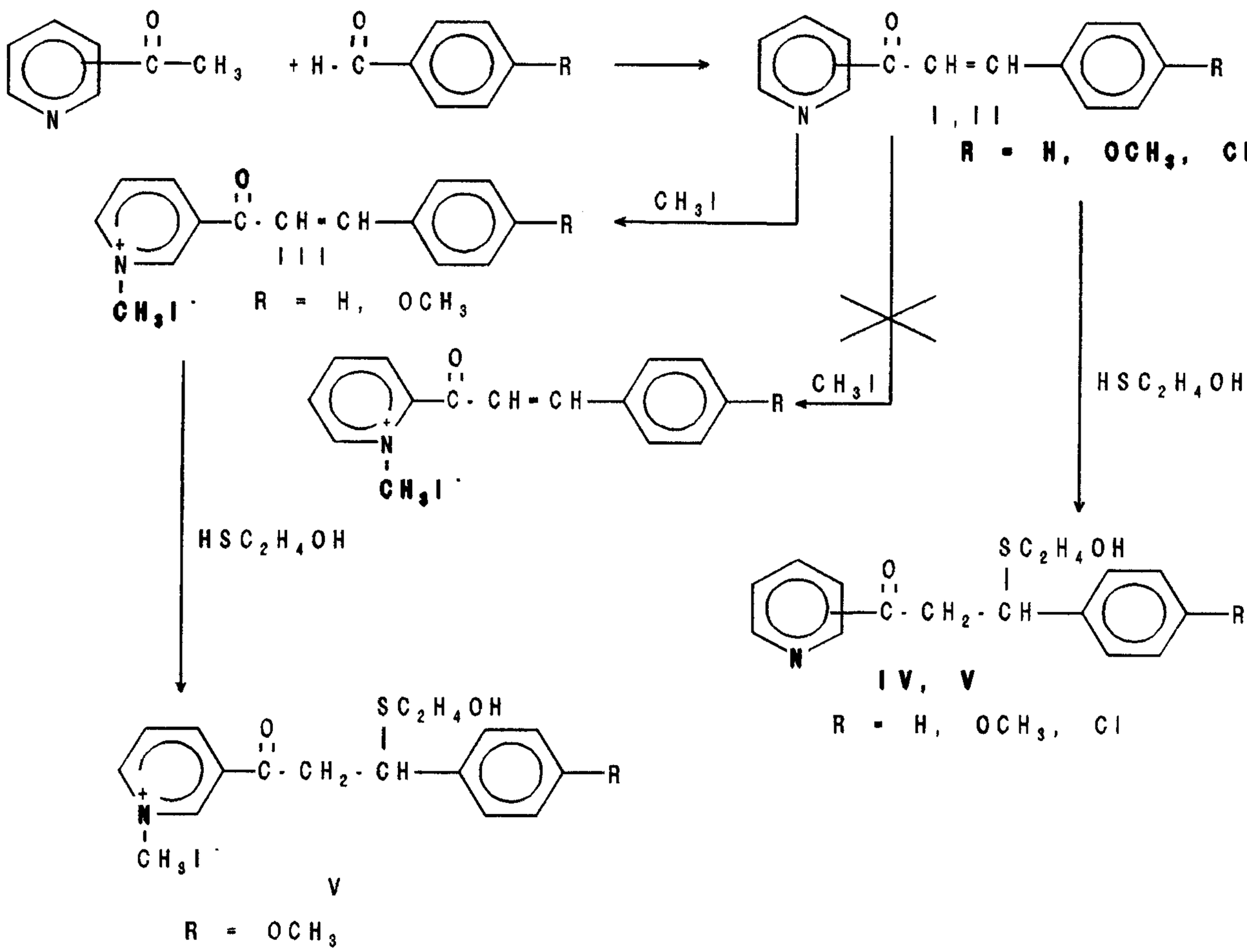
^1H NMR of comp. VI in DMSO.
TLC of comp. IVb and IVc were single spot in ethyl acetate.

Table 3: Rate constant $K_{obs.}$ and K_2 for the reaction of chalcones with 2-mercaptoethanol*.

Compd. No.	λ_{max}	$K_{obs.}$ m^{-1} conc. of thiol x 10^{-4}				$K_2 . 10^2$ mol^{-1} min^{-1}
		4.4	6.6	8.8	11	
Ia	320	-0.0219	-0.0238	-0.0338	-0.0393	0.0029
Ib	352	-0.0135	-0.0173	NA	-0.0187	0.0007
Ic	328	-0.0301	-0.0437	-0.0609	-0.0798	0.0075
IIa	314	-0.0466	-0.0642	-0.0662	-0.0840	0.0051
IIb	346	NA	-0.0266	-0.0379	-0.0464	0.0044
IIc	328	-0.0341	NA	-0.0633	-0.0704	0.0056
IIIb	348	-0.0033	-0.0044	-0.0060	-0.0076	0.0001

* Concentration of chalcones 0.093 x 10^{-4}.
NA means not available.

Scheme (I)



Synthesis of benzylidine-N-methylacetyl-pyridinium iodide (III a,b)

To a solution of chalcone (II, 0.1 mol) in methanol (25 ml), a solution of methyl iodide (0.13 mol) in methanol (20 ml) was added. The reaction mixture was refluxed for 5-6 hr., the solvent was distilled off, and the residue was crystallized from methanol. Yields and physical constants are shown in table 1. Trials for quaternization of chalcone I were unsuccessful.

Synthesis of 2-hydroxyethylthiobenzyl acetyl-pyridine (IV,V, VI)

To a solution of the appropriate chalcone (2.8 mmol) in benzene (10 ml), solution of 2-mercaptoethanol (3.3 mmol) and three drops of piperidine were added. The mixture was left at room temperature (25°C) while stirring for 3 hr. or until the peak of UV characterised for the chalcone disappears. The solvent was removed by vacuum distillation and the residue was identified by TLC, M.p, IR and UV. Table (2).

Kinetic studies of the prepared chalcones

Reagents

Stock thiol : (0. 11 mmol in 10 ml benzene)
Stock chalcone : (0.093 mmol in 10 ml benzene)
Stock piperidine: (0.2 ml in 25 ml benzene)

Method

To a solution of the appropriate chalcone (0.2 ml of stock solution), 2-mercaptoethanol (2.8, 4.2, 5.6 and 7 ml of stock thiol solution) and piperidine (1ml of stock piperidine solution) were added, the volume was adjusted to 10 ml with benzene and the mixture was mixed. The absorbance was measured every 5 minutes at the coresponding λ_{max}. The total time of experiment varied according to the t½ of the compound investigated but in each case it was about 3-5 times t½ of the disappearance of chalcone. Results are listed in table (3).

RESULTS AND DISCUSSION

The unsaturated ketones were prepared by Claisen-Schmidt reaction[10] in yields of 46-72 % approximately. The reaction of chalcone with thiol at room temperature (25°C) in presence of piperidine as catalyst gave thioether compounds in yields of 30-55% approximately.

All kinetic measurements were carried out under pseudo first-order conditions where the thiol concentration is present in large excess over chalcone concentration (4-10 times molar concentration).

The course of the reaction was followed spectrophotometrically by recording the decrease in the absorbance at the corresponding λ_{max} at 314, 318, 328 and 346 nm characterised for chalcone. It was proved that there is no interference from other reagents at this wave length. Kinetic determination were obtained out by plotting ln absorbance values vs time which is linear relationship. The value of the observed first-order rate constant $K_{obs.}$ were determined at different concentrations of the thiol.

Plotting concentration of the thiol aganist the corresponding $K_{obs.}$ gave the second order rate constant as the slope of the curve. The structure of the prepared compounds were confirmed by microanalysis, IR, UV and ^1H NMR.

The results showed that compounds carrying Cl substituent in p- position of benzylidine moiety showed higher rate constants than compounds with OCH_3 group. Quaternization of the pyridine ring decreased activity profoundly.

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