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Review paper

REVIEW

Condensation of 1,3-diketones with cyanoacetamide: 4,6-disubstituted-3-cyano-2-pyridones

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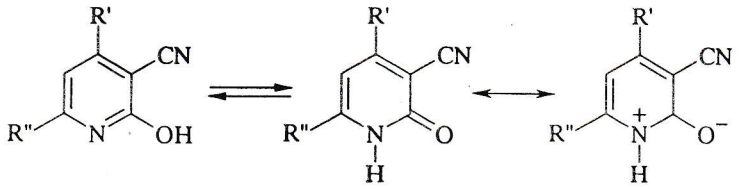
Key words: 1,3-diketones, substituted 3-cyano-2-pyridones, catalysis, enzymes, ion-exchange resins, phase-transfer catalysts, kinetics of condensation.

1. INTRODUCTION

Considering the structural characteristics of 2-pyridones in general, pyridinol-pyridone tautomerism, with the pyridone form being the dominant and also subject to resonance (Scheme 1), we believed that the group –NH–C(=O)–, similar to the protein amide bond, could give rise to physiological activity. It could be visualized that an interaction with tissues in living organisms could occur, for example, *via* hydrogen-bond formation. Therefore it was to be expected that an interaction of the eventually physiologically active pyridone will be effective through hydrogen bond formation, and the activity of the hydrogen in the –NH–C(=O)– group be highly influenced by both tautomerism and resonance. In the extensive investigations which are presented in this review it was undertaken to study the stereoselectivity and mechanism of the condensation reaction and also the structure-activity relationships in 4,6-disubstituted-3-cyano-2-pyridones, which we believed could give an insight into the physiological activity of this type of compounds, in correlation with the data of pre-clinical and clinical investigations when available.

Among the numerous reactions for the synthesis of pyridine derivatives from acyclic components, the condensation of 1,3-dioxo compounds with cy-



Scheme 1. Tautomerism and resonance in 2-pyridones.

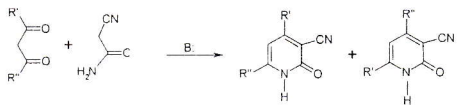
anoacetamide is fairly frequently reported in literature. The 1,3-diketones were the reagents of choice. Practically the only products obtained were 4,6-disubstituted-3-cyano-2-pyridones. These reactions proceed under mild conditions in good to excellent yields, in solvents ethanol and mixtures of ethanol and water as solvents. The reaction is subject to base catalysis and alkaline hydroxides, carbonates, alkoxides and ammonia are usually employed, but also the organic bases piperidine and diethylamine. As a rule, the reaction of symmmetrical diketones with cyanoacetamide yields one disubstituted 3-cyano-2-pyridone, while unsymmetrical diketones afford a mixture of products.[1]

The original Guareschi-Thorpe synthesis of 4,6-dimethyl-3-cyano-2-pyridone[2,3] was later extended (1929-1931) to the investigation of reaction conditions and selectivity.[5-7] Although a limited number of 1,3-diketones and catalysts were employed at this stage, there were extensive discussions relating to the possible mechanism. It was generally concluded that the more positive carbonyl reacts first, but that steric effects should be taken into consideration. Also, the investigators in that period were very much concerned as to whether the reaction is a Knoevenagel condensation or a Michael addition,[8] which is irrelevant from the point of view of electronic effects, although, as it was consequently established, the extent of enolisation of this type of dioxo compounds favours the second option.[9,10] The almost complete enolization of 1,3-diketones was further corroborated in a ^{1}H-NMR study of the intramolecular hydrogen bonding.[11]

The investigations of this reaction seem to have been abandoned for long period. Occasional papers appeared which mostly introduced the variations and improvements of the reaction conditions.[12-17] However, in the 1980's, there was a renewed interest in substituted pyridones and related compounds. The references are largely patent literature oriented towards the synthesis of new compounds.[18-21] It should be noted that at this stage, a paper also appeared dealing with a new type of catalysts, quaternery ammonium salt (TEBA) usually employed in phase-transfer catalyzed reactions.[22] The revival of the interest in the synthesis of substituted 3-cyano-2-pyridones is no doubt due to the discovery of their cardiotonic and antidiabetic activity.[18-21]

Details of some of the more important synthetic procedures are given in Table I. If unsymetrical diketones were the reagents in the condensation reaction, two products were formed, and the data are given for the more abundant isomer. Although the patenting proves that the investigations were intensified, again in the period 1985–1997 papers and patents concerned with the synthesis of substituted

TABLE I. Condensation of 1,3-diketones with cyanoacetamide yielding 4,6-disubstituted 3-cyano-2-pyridones: literature data



R'	R''	Conditions	Yield (%)	Reference
Me	Me	Piperidine, *T*	87	12,13
		Piperidine, *T*		14
		Et_2NH, alc.		4
		NaOEt, alc.		5
		Na der. of cyanoacetamide, benzene, *RT*, overnight	5	
		Phos.bufer, water sol., pH 8.5-9, 25 °C, 1 d.	74	15
		K_2CO_3, water, pH 8.5-9, 25 °C		15
		Et_2NH, alc.	94-98	5
		Piperidine, alc.	60	7
		Na der. of methylenamide, benzene, *RT*, overnight		7
Et	Me	Et_2NH, alc.,50 °C, then *RT*, 1 d		4
Et	Et	Et_2NH, alc., 2 h, then *RT*, overnight	90	5
Ph	Me	Et_2NH, alc.		7
		Et_2NH, alc.,50 °C, then *RT*, 1d		5
Ph	Et	Et_2NH, alc., 50 °C, then *RT*, 1 d		4
Ph	Ph	Piperidine, alc.	40	7
		Et_2NH, alc., *RT*, overnight	55-70	5
		NaOEt, alc.,60 °C, 24h	18-20	5
p-Tolyl	Me	Et_2NH, alc., 60 °C, 10 min.	80	6
		Et_2NH, alc.		6
p-Tolyl	Ph	Et_2NH, alc., *RT*,7-10 d	34	5
n-Pr	*n*-Pr	MeOH, NaOMe, *RT*		19
3 Py	Me	EtOH, triethylamine, room *T*	39.61	23
4 Py	Me	EtOH, triethylamine, room *T*	73.24	23
Me	Me	50% NaOH, TEBA, 4 h, room temp.	95	22
Me	Ph	50% NaOH, TEBA, 4 h, room temp.	90	22
Ph	Ph	50% NaOH, TEBA, 4 h, room temp.	88	22

T-temperature, *RT*-reflux temperature, alc.-alcohol, d-day, h-hour

3-cyano-2-pyridones only occasionaly appeared.[23-26] These references deal with new compounds, either as the final products[23,24,26] or as intermediates.[26] The substantial antiviral activity of some of the synthesized compounds was established as well.[24] However, as far as we know only three compounds of structures similar to 4,6-disubstituted-3-cyano-2-pyridones are commercialized so far.[27]

2. RESULTS AND DISCUSSION

Preliminary investigations included the synthesis of known and new 4,6-dialkyl-3-cyano-2-pyridones, the study of the reaction conditions and the development of a spectrophotometric method for following the course of the reaction.[28] In the later stages, unsymmetrical, 4(6)-methyl-6(4)-substituted phenyl-3-cyano-2-pyridones were also synthesized.[29,30] The condensations were performed mostly by modified or unmodified literature procedures, and the details are given in Table II. The 1,3-diketones were reacted with cyanoacetamide, most frequently in ethanol, at reflux temperature, in the presence of a variety of basic catalysts, both organic and inorganic, piperidine being the preferred one.[28-33]

It was also attempted to use more unorthodox catalysts for this reaction, but the results of catalysis by phase transfer catalysts[34] (dilute systems) and polymer supported phase-transfer catalysts (strongly basic ion exchangers)[35] did not give spectacular results either in terms of the yield or selectivity of the reaction. The results of these experiments are also given in Table II.

Condensation of 1,3-diketones with cyanoacetamide was also performed using enzymes as catalysts which gave interesting results. Lipase from *Candida cylindracea* (rugosa) and hog pancreas were used at low temperatures in water. The obtained alkyl and aryl pyridones, as well as the yields are given in Table III. The reaction was also tried in different oganic solvents but pyridones were not formed, indicating that water is crucial for the action of lipase. Although the yields were low to moderate, except when a high excess of cyanoacetamide was used, the orientation in the reaction was different than when chemical catalysis was involved and the selectivity very high, so that practically only one of the two possible positional isomers were obtained.[36-40]

The 4,6-disubstituted-3-cyano-2-pyridones are either new compounds or are synthesized by new or modified methods and, as such, are protected by a Yugoslav patent application.[41]

3. SELECTIVITY OF THE REACTION

In the reaction of 5-methylhexane-2,4-dione and 5,5-dimethylhexane-2,4-dione with cyanoacetamide it was established, on the basis IR, NMR and MS spectroscopy that only one product is formed, whereas bulkier alkyl groups, isopropyl and *tert*-butyl, preferentially occupy position 4 in the pyridone nucleus.[28,42] This is not in agreement with the statement that the bulkier alkyl group is found at the 6 position, although it was stated that a mixture of isomers is usually obtained.[1] Comparison of the polar[43] and steric[44] substituent constants for the methyl and *tert*-butyl group indicates that the steric effect should be dominant. However, the observed orientation could be explained by enolization of the reacting diketone. The most favourable conformation of 1,3-diketones is the one where the carbonyl groups are as separated as possible. If bulky substituents are present, enolization occurs rather than the attainment of the less favourable conformation. It has been shown,

TABLE II. Condensation of 1,3-diketones with cyanoacetamide yielding 4,6-disubstituted 3-cyano-2-pyridones. Our work (R' and R" as given in Table I)

R'	R"	Conditions	Yield(%)	Reference
Me	Me	K_2CO_3, *T*, alc.	87	33
		K_2CO_3, 60 °C, water	78.5	34
		K_2CO_3, 60 °C, hexane	67.6	34
		K_2CO_3, 60 °C, toluene	67.6	34
		K_2CO_3, 60 °C, ethanol	32.4	34
		KOH, *T*, alc.,	69	33
		KOH, 60 °C, water,	78.5	34
		KOH, 60 °C, hexane,	59.5	34
		KOH, 60 °C, toluene,	62.2	34
		KOH, 60 °C, ethanol,	40.5	34
		NaOH, *T*, alc.	63	33
		NaOH, 60 °C, water,	73	34
		NaOH, 60 °C, hexane,	81.1	34
		Piperidine, *RT*, alc.	57	31
Me	Et	Piperidine, *RT*, alc.		28
Me	*n*-Pr	Piperidine, *RT*, alc.		36
Me	*i*-Pr	Piperidine, *RT*, alc.	52	28
		Et_2NH, *RT*, alc.		28
Me	*n*-Bu	Piperidine, *RT*, alc.		36
Me	*i*-Bu	Piperidine, *RT*, alc.	44	36
Me	*t*-Bu	Piperidine, *RT*, alc.	56	28
		Et_2NH, *RT*, alc.		28
Me	*n*-Pe	Piperidine, *RT*, alc.		36
		K_2CO_3, 60 °C, water,	62.7	34
		K_2CO_3, 60 °C, hexane,	70.6	34
		K_2CO_3, 60 °C, toluene,	35.3	34
Me	Ph	Piperidine, *RT*, alc.		30
		Ion-exchange resin, mix. of water and alc., 70 °C, 2 h		35
Me	*p*-MeOPh	Piperidine, *RT*, alc.		30
Me	*p*-NO_2Ph	Piperidine, *RT*, alc.		30
Me	*m*-NO_2Ph	Piperidine, *RT*, alc.		30
Me	*p*-ClPh	Piperidine, *RT*, alc.		30
Me	*p*-BrPh	Piperidine, *RT*, alc.		30

T-temperature, *RT*-reflux temperature, alc.-alcohol, h-hour

TABLE III. Condensation of 1,3-diketones with cyanoacetamide (CAA) yielding 4,6-disubstituted 3-cyano-2-pyridones: enzyme catalysis (R' and R" as given in Table I)

R'	R"	Conditions	Yield (%)	Reference
Me	Me	lipase from *Candida cylindracea*, water, *T*, several days, eqv. mol.	19	38
		lipase from *Candida cylindracea*, water, *T*, 1 d, excess of CAA	85.5	40
			93.5	40
		lipase from hog pancreas, water, *T*, 1 d, excess of CAA	85.0	40
Me	Et	lipase from *Candida cylindracea*, water, *T*, several days, eqv. mol.	38	38
		lipase from *Candida cylindracea*, water, *T*, 1 d, excess of CAA	70.9	40
Me	*n*-Pr	lipase from *Candida cylindracea*, water, *T*, several days, eqv. mol.	26.5	38
		lipase from *Candida cylindracea*, water, *T*, 1 d, excess of CAA	77.5	40
Me	*i*-Pr	lipase from *Candida cylindracea*, water, *T*, several days, eqv. mol.	35.5	38
		lipase from *Candida cylindracea*, water, *T*, 1 d, excess of CAA	83.2	40
Me	*n*-Bu	lipase from *Candida cylindracea*, water, *T*, several days, eqv. mol.	40	38
		lipase from *Candida cylindracea*, water, *T*, 1 d, excess of CAA	69.7	40
Me	*i*-Bu	lipase from *Candida cylindracea*, water, *T*, several days, eqv. mol.	88	38
		lipase from *Candida cylindracea*, water, *T*, 1 d, excess of CAA	61.6	40
Me	*t*-Bu	lipase from *Candida cylindracea*, water, *T*, several days, eqv. mol.	14.5	38
Me	*n*-Pe	lipase from *Candida cylindracea*, water, *T*, several days, eqv. mol.	32	38
		lipase from *Candida cylindracea*, water, *T*, 1 d, excess of CAA	99.8	40
Me	Ph	lipase from *Candida cylindracea*, water, *T*, several days	9.5	37,39
Me	*p*-MeOPh	lipase from *Candida cylindracea*, water, *T*, several days, eqv. mol.	4.2	37,39
Me	*p*-NO_2Ph	lipase from *Candida cylindracea*, water, *T*, several days, eqv. mol.	9.5	37,39
Me	*m*-NO_2Ph	lipase from *Candida cylindracea*, water, *T*, several days, eqv. mol.	4.0	37,39
Me	*p*-ClPh	lipase from *Candida cylindracea*, water, *T*, several days, eqv. mol.	4.1	37,39
Me	*p*-BrPh	lipase from *Candida cylindracea*, water, *T*, several days, eqv. mol.	7.5	37,39

in an NMR study, that enolization is favoured by branching of the alkyl substituents.[11] Also, the IR spectra of 1,3-diketones in the enol form show an abnormal carbonyl absorption, which was attributed to intramolecular hydrogen bonding, the single bonded structure being stabilised by resonance, as it is represented in Scheme 2.[10] Therefore, in the investigated reaction, the position of the nucleophilic attack is determined by the relative destabilisation of the two competing carbonyls. If hyperconjugation is assumed, the methyl group is a better electron donor than the *tert*-butyl or isopropyl group, hence the observed orientation.[42]

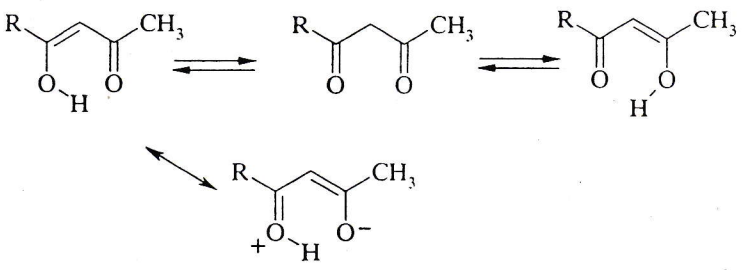
The orientation in the studied cyclization reaciton was also investigated for a series of phenyl substituted 1-methyl-3-aryl-1,3-diketones.[30] In the majority of experiments a mixture of positional isomers was obtained, which were separated by fractional crystalization and identified. However, the exact ratio, of the isomers was determined on the basis of a study of the ^{1}H-NMR spectral data of the methyl and 5H (phenyl) hydrogen chemical shifts. On the basis of the data given in Table IV, it was concluded that the reaction occurs preferentially on the carbonyl group which is more susceptible to nucleophilic attack. In the substituted aryl diketones investigated, one carbonyl group is influenced by a methyl group and the other by a phenyl or substituted phenyl group. Depending on the substitution of the phenyl nucleus, the activity of the respective groups towards nucleophilic attack will be as follows:

$$p\text{-}NO_2Ph > m\text{-}NO_2Ph > Ph > p\text{-}ClPh > p\text{-}BrPh > p\text{-}MeOPh$$

and the order of the 4:6 ratios approximately the same, although the values show the influence of other additional effects, such as the enolisation of the starting diketones, as shown in Scheme 2.

TABLE IV. ^{1}H-NMR spectral data of 4,6-disubstituted 3-cyano-2-pyridones in CF_3COOH

R'(C-4)	R''(C-6)	5-H	Me	4:6 ratio
p-MeOPh	Me	6.93	2.70	0.01
Me	*p*-MeOPh	7.20	2.73	
p-NO_2Ph	Me	6.90	2.74	1.50
Me	*p*-NO_2Ph	7.25	2.80	
m-NO_2Ph	Me	6.90	2.74	0.88
Me	*m*-NO_2Ph	7.25	2.80	
p-ClPh	Me	6.98	2.66	0.33
Me	*p*-ClPH	7.12	2.72	
p-BrPh	Me	6.98	2.70	0.01
Me	*p*-BrPh	7.15	2.78	
Ph	Me	6.90	2.70	0.66
Me	Ph	7.15	2.74	



Scheme 2. Keto-enol tautomerism and the resonace stabilization of the enol form in 1,3-dketones.

4. KINETICS AND MECHANISM OF THE REACTION

Analytical method for the measurrement of kinetics. – An analytical method was developed for the study of the kinetics of the reaciton of 1,3-diketones and cyanoacetamide catalysed by bases. It was established that in the UV region 200–400 nm it is possible to record both the decrease of the diketone concentraiton and of the increase of the pyridone reaction product concentration, as cyanoacetamide and the piperidine catalyst do not absorb in the above region of the UV spectra. Although an excellent isosbestic point ($\lambda = ca.295$ nm) was observed, it was not possible to calculate the rate constants from the decrease in the diketone concentration, as the corresponding maxima were subject to changes in both position and intensity with changing piperidine concentration. No such interference was observed for the products, and those data were used for all kinetics calculations. Typical UV spectra recorded during the course of the reaction are presented in Fig. 1.

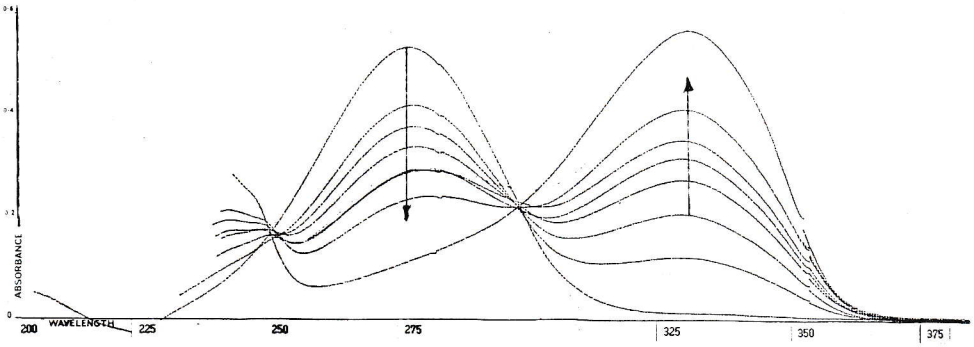


Figure 1. UV spectra for the reaction of acetylacetone with cyanoacetamide (piperidine catalyst, concentration 0.03 mol dm^3 of both reactants and catalyst).

It is usually considered that for this kind of base-catalyzed process,[45] broadly described as carbanion addition to a carbonyl function, which includes many reactions such as Claisen, Michael and Perkin condensations, there is an initial equilibrium between one of the reactants and the basic catalyst followed by the slow reaction of the formed anion with the other reagent. However, we did not find in the literature any reference to a kinetic study of the reaction of 1,3-diketones with cyanoacetamide. Therefore, we studied the rates for the piperidine-catalyzed reactions of 1,3-diketones with cyanoacetamide for pentane-2,4-dione, 5-methylhexane-2,4-dione and 5,5-dimethylhexane-2,4-dione. Preliminary investigations showed that the kinetics were complex,[31-33] and subsequent experiments were performed under a variety of experimental conditions, regarding concentration and temperature.[42] A large number of data was obtained at equimolar concentrations of reactans and catalyst, but also pseudo-first order kinetics were investigated. The reaction of the symmetrical diketone has been more extensively studied, in comparison with the other two, because of the higher reaction rate, the formation of only one isomer, and the absence of a steric factor. Activation parameters were calculated for the reactions and these results are given in Table V.

TABLE V. Activation parameters for the reaction of acetylacetone with cyanoacetamide at three different temperatures

T °C	Rate constants s^{-1}	$E^{\neq}$ kJ mol^{-1}	log A	$\Delta S^{\neq}$(60 °C) J K^{-1} mol^{-1}
50	0.34			−142.3
60	0.55	41.5	6.27	
70	0.94			

[a]Values of $E^{\neq}$ and $\Delta S^{\neq}$ are accurate to within 10 kJ mol^{-1} and 1.0 J K^{-1} mol^{-1}, respectively.

It has been established that both reactants, as well as the catalyst affect the rate of the reaction. Also, it is known that this reaction proceeds at low concentrations of reactive species, considering that cyanoacetamide is a weak acid and the diketone is enolised and subject to self condensation,[1] which leads to a highly complex kinetic behaviour. The steady state approximation has been suggested as a solution for these kinds of kinetic problems.[44,46] This approach yielded a relationship which indicated that the rate constant is evidently a composite one, and it is, theoretically, to be excepted that the reaction should conform to the third-order rate law.

$$\text{rate} = (k_1/k_{-1})k_2\,[\text{CAA}]\,[\text{AA}]\,[\text{PIP}] = k_{\text{obs}}\,[\text{CAA}]\,[\text{AA}][\text{PIP}]$$

However, rate data for four equimolar concentrations of the reactants and catalyst, presented in Table V for acetylacetone, fitted the second-order rate equation very well, with correlation coefficients in the range 0.997–0.999. This could have been expected because the catalyst concentration is essentially constant, as piperidine is recovered in the fast step which follows the formation of the active intermediate. Therefore, we felt it justified to interpreted the data from experiments at equimolar concentrations by the second order rate law.

Bearing in mind the concept of the steady state approximation, comparison of the rate constants obtained at equimolar concentrations with those obtained with an excess of either reactant or the catalyst, it was established that the observed rate constant is a composite one which encompases the equilibrium constant of the first step of the reaction (Scheme 3), the rate constant of the second, rate determing step and the concentration of acetylacetone

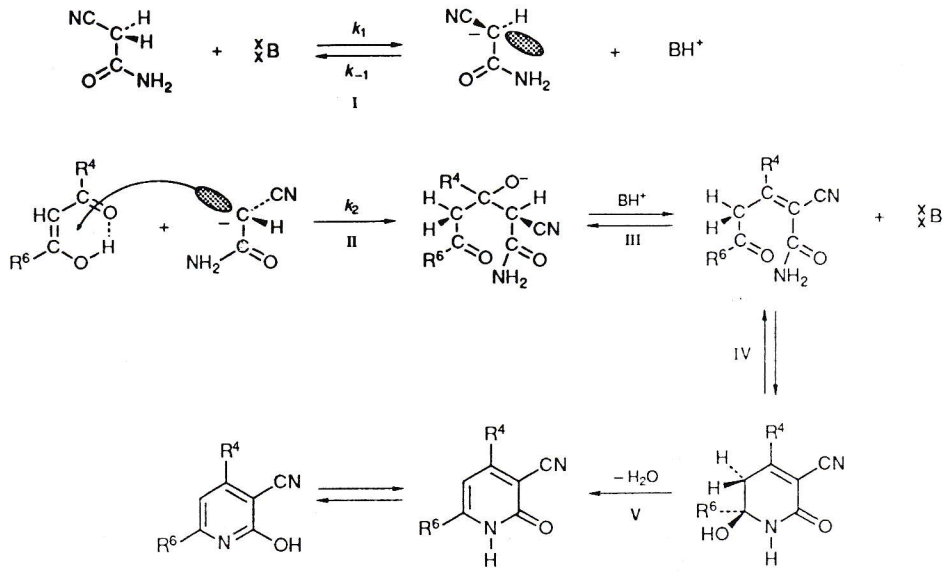
$$k_{obs}=k_2k\,[AA]$$

which is the reagent which takes part in the slow step of the reaction.

The activation parameters given in Table V also support the proposition of a slow second step as the activation energy and particularly high negative value of the entropy change indicate the requirements for a specific orientation in the transition state, which is only possible to visualize in the second step.

The rate data for the condensation reaction of 5-methylhexane-2,4-dione and 5,5-dimethylhexane-2,4-dione do not show entirely the same kinetic pattern as those for the acetylacetone condensation. The determined second-order rate constants show that the reactions are much slower, by almost one order of magnitude. This is logical, considering the orientation of the reaction already discussed and the steric hindrance.

The mechanism of the reaction appears to be fairly straightforward, although the literature data indicate that both polar and steric effects influence the structure of the reaction products, *i.e.*, the ratio of the isomers.[8,30] It has also been established[42] that the kinetic pattern is fairly complex, which is particularly true for the effect of catalyst. If the catalyst and the cyanoacetamide concentration are critical for the formation of



Scheme 3. Mehanism of the condensation of 1,3-diketones with cyanoacetamide yielding 4,6-disubstituted 3-cyano-2-pyridones.

the active carbanion nucleophile, the polar and steric effect inherent to the diketone molecule determine the stability of the transition state and the intermediate addition complex. Several points should be taken into account in solving this complex situation. The reactions of all three investigated diketones conform strictly to the second-order rate law. No side or parallel reactions were observed and the reactions proceed to relatively high yields under fairly mild conditions. Furthermore, it has been reported that the reactions proceed with low concentrations of the reacting molecules.[8] The 1,3-diketone is a stronger acid than the cyanoacetamide and, in base catalysis, only a low concentration of the ionised species is present. However, the carbonyl groups of the diketone are more polarised than the amide function of the cyanoacetamide and the diketone is the acceptor of the nucleophilic attack. It is most probable that self-condensation of the diketone also occurs but this is a reversible reaction, while the formation of the active intermediate is probably irreversible.

From the presented evidence, it is reasonable to postulate that the reactions proceed as presented in Scheme 3.[42] The initial fast equilibrium (step I), yielding the carbanion nucleophile, is probably well shifted to the left ($k_1 << k_{-1}$) is followed by the slow attack of the nucleophile at the delocalised diketone structure (step II), and the dominating component k_2 of the composite overall rate constant is a measure of the rate of the slow step of the reaction. The proposal of the slow step is further corroborated by the high negative value of $\Delta S^{\neq}$, which indicates the requirements for a particular orientation of the reacting molecules in the transition state. Therefore, the evidence for the rate determing step is both kinetic and stereochemical. The pre-equilibrium is fast, but shifted to the left. There is always enough of the highly reactive cyanoacetamide anion, but the steric requirements slow down the reaction and, hence, the slow step. The subsequent protonation-dehydration and cyclisation steps (III and IV) are probably fast equilibria shifted strongly to the right and the last step (V), finally yielding the stable delocalised pyridone structure, is undoubtedly irreversible.

5. ENZYME CATALYZED REACTIONS

As has already been mentioned, in enzymatic catalysis, when alkyl diketones are concerned, the bulkier group is almost exclusively in the 4-positon, the only exception being the *n*-butyl and *n*-pentyl derivatives, where considerable amounts of the other isomer have been detected.[48] Investigation of the enzyme catalyzed reaction of aryl diketones shows that, in most cases, only the isomer with the phenyl or substituted phenyl group in position-6 is formed, with the exception of the *p*-NO_2Ph group when more C-4 isomer appeared to be formed.[39]

The study of the kinetics of the enzyme catalyzed reaction showed that the behaviour of the lipases used as catalysts in the synthesis of 4,6-disubstituted-3-cyano-2-pyridones was even more complex than when chemical catalyst were used.[40]

We believed we would have to deal with Henry-Michaelis-Menten kinetics in this reaction.[47] However, the obtained results, which present the relationship of the

initial reaction rate *vs*. the initial substrate concentraiton, indicated by the sigmoidal shape of velocity curves, that this is an example of allosteric enzymes kinetics and possibly the phenomenon called "cooperative binding" or "positive cooperativity" is operative.[48,49]

6. STRUCUTRE-ACTIVITY RELATIONSHIPS

The substituent effects were investigated in the series of 4 and 6 methyl alkyl as well as of methyl-substituted phenyl 3-cyano-2-pyridones. The original idea was to study the effect of substituents in positions 4 and 6 of the pyridone nucleus on the –CN, C=O and NH groups, which we believed could be the site of physiological activity. The spectral characteristics of these series were recorded, and the obtained ^{1}H-NMR chemical shifts, IR and UV frequences were correlated with a number of electronic and steric parameters, usually employed for the study of linear free energy relatinships.[50]

The best correlations were obtained between the IR frequences of the cyanide and carbonyl groups in the 2-pyridine nucleus and the Hammett σ constants. It was difficult to obtain the NMR spectra of a number of synthesized compounds due to the insolubility of the model substances in sovlents most convenient for the study of the chemical shifts of the –NH group hydrogen and carbonyl carbon. This data would, however, be most interesting for the evaluation of the hydrogen bond interacitons with protein receptors and eventual physiological activity.

A number of 4-alkyl-6-methyl-2-pyridone-3-carboxylic acids were synthesized from the corresponding 3-cyano-2-pyridones.[51-53] The intention was to use the carboxylic group of these model substances as a probe to study the substituent effects through its reactivity with diazodiphenyl methane.[51,52] Kinetic data from the reaction of various heteroaromatic carboxylic acids have previously been used for the investigation of structure activity relationships in pyridine and diazine systems.[54] This investigation was also difficult because of insolubility in solvents suitable for this reaction and also because of the low reaction rates.[51] However very good correlations were obtained between the IR frequences of the carboxylic group carbon and the pyridone carbonyl.[51]

7. FURTHER INVESTIGATIONS

Synthesis of new compounds and the development of new methods, particularly for the enzyme catalysed reactions, probably using different starting materials are visualized for the futher investigations.

Continuation of the study of substituent effects, particularly of the ^{1}H-NMR chemical shifts of the –NH group hydrogen and the ^{13}C-NMR chemical shift of the pyridine carbonyl will be attempted. A study of the correlations of the data from the UV spectra is also planed.

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SUMMARY

A number of 4,6-disubstituted-3-cyano-2-pyridones were synthesized by the condensation of symmetrical and unsymmetrical 1,3-diketones with cyanoacetamide. Inorganic and organic catalysts were employed, including ion-exchange resins, phase-transfer catalysts and enzymes, under a variety of reaction conditions. An analytical method had been developed for the study of the kinetics of the reaction of alkyl diketones. Together with the evidence of the selectivity, the kinetics data were used to postulate the most probable mechanism of the reaction. As the synthetized compounds are potentially physiologically active, the study of structure-activity relationships have been performed on the basis of spectroscopic data.

И З В О Д

КОНДЕНЗАЦИЈА 1,3-ДИКЕТОНА СА ЦИЈАНОАЦЕТАМИДОМ: 4,6-ДИСУПСТИТУИСАНИ 3-ЦИЈАНО-2-ПИРИДОНИ

МИЛИЦА МИШИЋ-ВУКОВИЋ, ДУШАН МИЈИН, МИРЈАНА РАДОЈКОВИЋ-ВЕЛИЧКОВИЋ, НАТАША ВАЛЕНТИЋ и ВЕРА КРСТИЋ

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Различити 4,6-дисупституисани-3-цијано-2-пиридони су синтетизовани кондензацијом симетричних и асиметричних 1,3-дикетона са цијаноацетамидом. При томе су коришћени неоргански и органски катализатори, укључујући јоноизмењивачке смоле и ензиме, под различитим реакционим условима. Развијена је аналитичка метода ради испитивања кинетике реакције кондензација алкил дикетона са цијаноацетамидом, и предложен је највероватнији механизам реакције. Испитан је утицај супституената на пиридоновом језгру на –CN, C=O и NH групе користећи спектроскопске методе.

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