Synthesis of Pyrimidines from β-Dicarbonyl Compounds and Cyanogen: a Metal-catalysed One-pot Process

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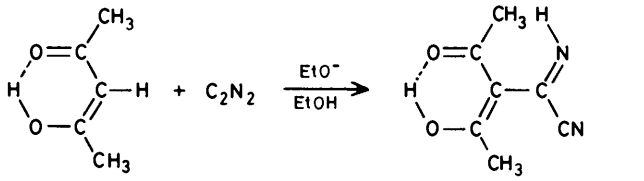
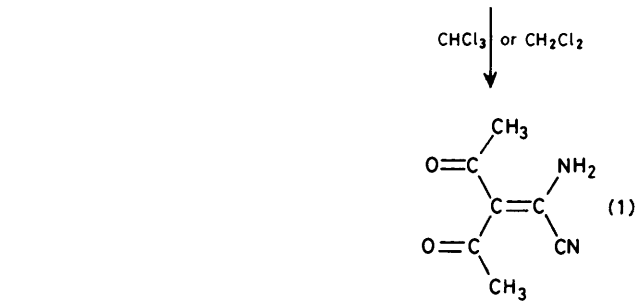
Highly functionalized pyrimidines can be prepared in good yields, by a one-pot procedure, from cyanogen and β-dicarbonyl compounds at ambient conditions in dichloroethane in the presence of catalytic amounts of $Ni(acac)_2$ or $Cu(acac)_2$. The pyrimidines obtained were fully characterized by a variety of physicochemical methods. The presence of at least one keto group in the substrate appears to be a necessary condition for the success of the synthesis, which fails, for instance, for dimethyl malonate. A kinetic study on the synthesis of 2-(1-amino-2-acetylbut-1-enonyl)-4-carboxamido-5-acetyl-6-methyl-1,3-diazine has been carried out by employing $Cu(acac)_2$ as catalyst. A crucial step in the catalytic process is an insertion reaction of C_2N_2 into the C–H methine bond of a metal-co-ordinated 3-cyanoiminomethylpentane-2,4-dionato ligand, which leads to the formation of a carbon–carbon bond. This process characterizes this new pyrimidine synthesis, in that, as a rule, previously known ring-closure reactions implied only carbon–nitrogen bond formation. The simple addition product of C_2N_2 to acetylacetone, 3-cyanoiminomethylpentane-2,4-dione, is found to play an important kinetic role and its reaction with the organometallic ring mentioned above is a second critical process for the success of the ring closure.

We have recently reported that cyanogen can be catalytically added to acetylacetone in dichloromethane under ambient conditions in the presence of various acetylacetonate complexes of divalent first row transition metals.[1] The ethoxide ion-catalysed addition of C_2N_2 to Hacac in ethanol has long been known and leads to 3-cyanoiminomethylpentane-2,4-dione,[2] hereafter referred to as Hα. This compound displays a keto–enol structure in the solid state, but in chlorinated solvents it exists essentially as a vinylogous amide [1] [equation (1)].

In contrast to this base-catalysed synthesis, the metal-catalysed addition reaction leads to a heavily functionalized pyrimidine, *i.e.* to 2-(1-amino-2-acetylbut-1-enonyl)-4-carboxamido-5-acetyl-6-methyl-1,3-diazine (hereafter referred to as PYR I) [equation (2)]. PYR I is a high melting yellow crystalline compound which has been fully characterized by the usual physicochemical methods and by a single-crystal *X*-ray structural analysis.[1]

In the light of our current studies on the co-ordination chemistry of C_2N_2 and in view of the apparent novelty of this pyrimidine synthesis we have extended the scope of the organic substrate investigated by considering a variety of β-dicarbonyl compounds. These were chosen as model substrates, thus giving reliable information on the extent of the new synthesis. Moreover, mechanistic information on the catalytic process has been also collected and discussed. We have recently published a brief account on the extent of the synthesis.[3]





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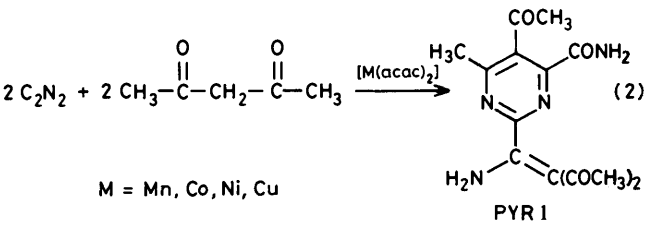
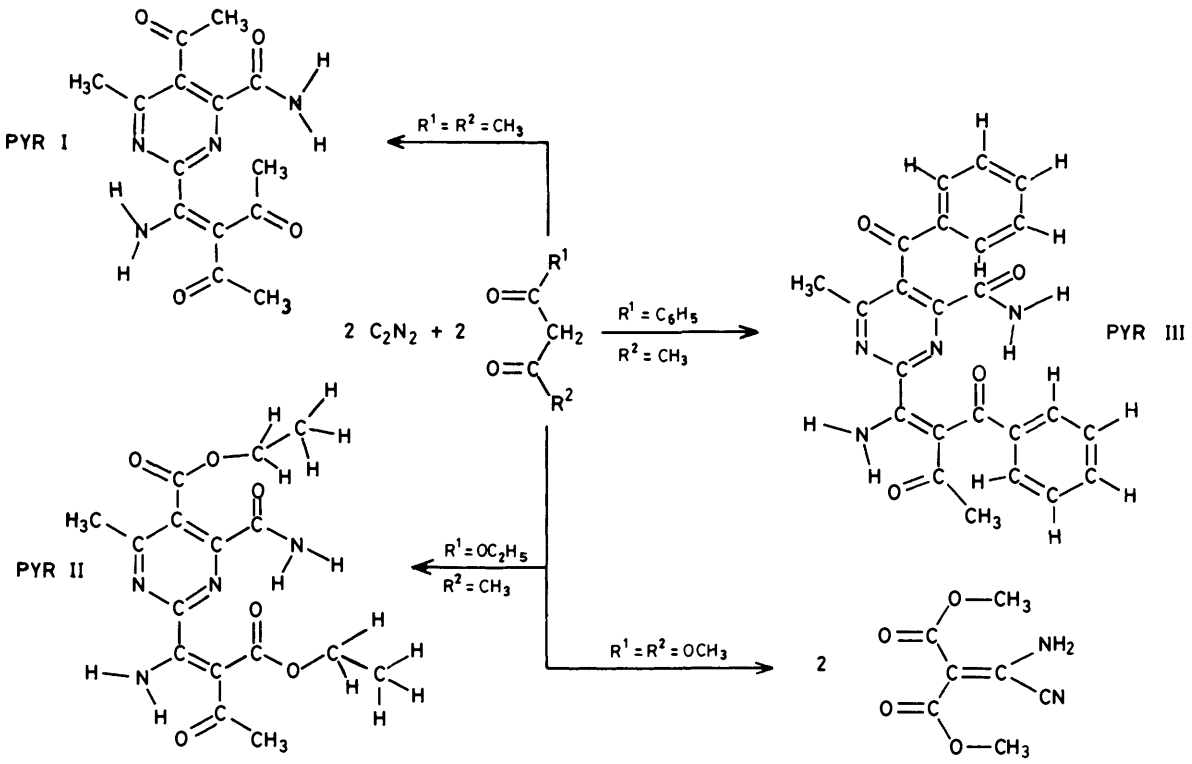


(2)

Results and Discussion

Extent of the New Pyrimidine Synthesis.—Benzoylacetone, ethyl acetoacetate, and dimethyl malonate undergo facile cyanation in dichloroethane under ambient conditions with both $Ni(acac)_2$ and $Cu(acac)_2$ as catalysts. The pattern of the products obtained is reported in Scheme 1 and the working conditions, yields, and selectivity are summarized in Tables 1 and 2.

It can be seen from the data of Scheme 1 and Tables 1 and 2 that heavily functionalized pyrimidines can be obtained under mild conditions and with considerable yields from compounds containing at least one keto-function. Thus acetylacetone, ethyl acetate, and benzoylacetone can be cyanated and converted into pyrimidines, albeit with different kinetic efficiencies and selectivities, while dimethyl malonate is found to undergo cyanation, which is not followed by cyclodimerization to the corresponding pyrimidine.



Scheme 1. The cyanation of β-dicarbonyl compounds catalysed by $Ni(acac)_2$ in $C_2H_4Cl_2$

Table 1. Catalytic synthesis of pyrimidines from C_2N_2 and β-dicarbonyl compounds at room temperature

Catalyst (1.2×10^{-3}M)	Substrate [a] (M)	Cyanogen (M)	Time (h)	% Reaction [b] (upon the substrate)	% Reaction [c] (upon the product)	Selectivity (%)
$Ni(acac)_2$	Hacac	0.46	24	78		
	(0.30)		144	100	100	100 [d]
$Cu(acac)_2$	Hacac	0.46	24	58		
	(0.30)		144	90	90	100 [d]
$Cu(acac)_2$	Hacac	0.40	24	58		
	(0.35)		144	92		
			288	100	100	100 [e]
$Cu(acac)_2$	Heaa	0.40	24	30		
	(0.35)		144	40		
			288	45	20	44 [e]
$Cu(eaa)_2$	Heaa	0.40	24	22		
	(0.35)		144	37		
			288	42	21	50 [e]
$Ni(acac)_2$	Heaa	0.40	24	39		
	(0.35)		144	75		
			288	83	41	49 [e]
$Ni(acac)_2$	Hba	0.42	288		22	
	(0.37)					

[a] Hacac = acetylacetone, Heaa = ethyl acetoacetate, Hba = benzoylacetone. [b] *i.e.* progress of the reaction irrespective of the nature of the products. [c] *i.e.* progress of the reaction based on the isolated pyrimidine product. [d] CH_2Cl_2. [e] $C_2H_4Cl_2$.

A further preliminary observation is the fact that the figures referring to the consumption of the substrate (and formation of the products) have no thermodynamic implications and do not mean that the conversion of ethyl acetoacetate and benzoylacetone into the corresponding pyrimidines cannot reach 100% (consumption of the substrate). They simply refer to a reaction time (288 h) thought to be convenient for testing the practical extent of the new synthesis.

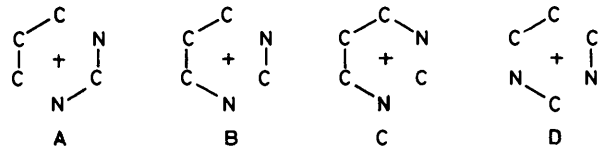
The new compounds depicted in Scheme 1 have been characterized by elemental analysis, i.r. and visible-u.v. spectrometry, n.m.r. and mass spectra, and PYR II by single-crystal *X*-ray analysis. PYR II and PYR III are both high melting crystalline compounds (as PYR I), moderately (PYR II) or scarcely (PYR III) soluble in common organic media. The cyanation product of dimethyl malonate is, in contrast, a considerably lower melting compound, much more soluble in common organic solvents. The canonical formula reported in Scheme 1 for this last compound refers to the predominant tautomeric species existing in $CDCl_3$ solution.

In purely phenomenological terms (for some mechanistic

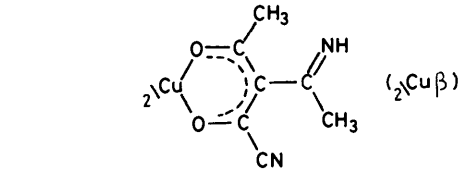
Table 2. Catalysed addition of C_2N_2 to dimethyl malonate [a] at room temperature in $C_2H_4Cl_2$

Catalyst (1.2×10^{-3}M)	Substrate (M)	Cyanogen (M)	Time (h)	% Reaction (based on substrate consumption)
$Ni(acac)_2$	0.35	0.40	24	12
			144	13
			288	18
$Cu(acac)_2$	0.35	0.40	24	0
			144	17
			288	19

[a] Hereafter referred to as Hdmm.



Scheme 2. Previously known and new synthetic procedures for the synthesis of the pyrimidine ring



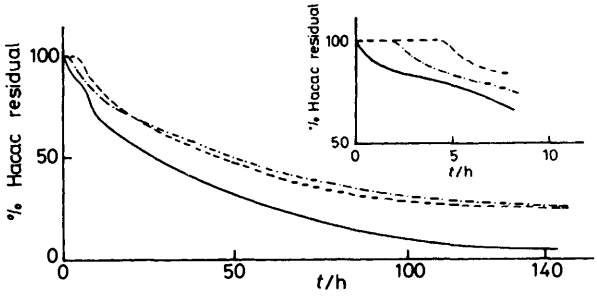


Figure 1. Plot of % residual Hacac *versus* time for different catalysts: [Hacac] 0.35M; [C_2N_2] 0.4M: —— [$Cu(acac)_2$] 1.2×10^{-3}M; — — — [$Cu\beta_2$] 1.2×10^{-3}M; — · — · — 1[$Cu(acac)_2$] + 1[$Cu\beta_2$] 1.2×10^{-3}M

implications see the next section) some general considerations can be drawn on the basis of the data of Tables 1 and 2. Dichloromethane and dichloroethane are equally convenient solvents for the synthesis of PYR I, but $Ni(acac)_2$ is a kinetically superior catalyst to $Cu(acac)_2$.

The selectivity towards the synthesis of pyrimidines drops considerably on going from Hacac to Heaa as well as the rate of cyanation of the dicarbonyl substrate, but both rate and selectivity for the synthesis of PYR II are not seriously affected by the original nature of the copper(II) catalyst, *i.e.* they are not affected whether one employs $Cu(acac)_2$ or $Cu(eaa)_2$. A clear explanation of this behaviour is given after discussion of the mechanism. On the other hand, the nature of the metal centre considerably affects the rate of cyanation of Heaa but not the selectivity towards the synthesis of PYR II. Finally, a remarkable drop in catalytic efficiency towards the pyridine synthesis is observed, with $Ni(acac)_2$ as a catalyst, on passing from purely aliphatic dicarbonyl compounds (Hacac, Heaa) to a typical alkylaryl one such as benzoylacetone.

In spite of the large number of questions raised by our data and by the limited number of unambiguous answers given by our mechanistic study, we wish to underline the remarkable originality and extent of our approach to the synthesis of the pyrimidine ring as well as its one-pot character and the quite mild experimental conditions.

The numerous syntheses of the pyrimidine ring known so far are largely summarized in Scheme 2 (procedures A—C),[4] whereas, from a synthetic point of view, our one-pot synthesis can be described, in the whole, by process D.

However, it will be shown later that the mechanism of this reaction implies: (i) preliminary C–C bond formation by C_2N_2 insertion into the C–H methine bond of the metal-acetylacetonato ring and (ii) subsequent metal-promoted cyclization of the resulting ligand with an ' external ' cyanoenaminedione moiety. In consequence the final stage of formation of the pyrimidine ring is represented by process B.

It should be pointed out that the formation of fairly sophisticated highly functionalized pyrimidines, such as PYR I—III, does not requires any time-consuming prefunctionalization of the reagents, which are standard chemicals; furthermore the turn-over numbers observed in our catalytic processes ranged from 300 (Hacac) to 70 (Hba) under the conditions of Table 1, but higher figures are likely to be obtained. No optimization experiments have been carried out.

Mechanism of the Synthesis of PYR I.—Among the catalytic syntheses described by us we focused our attention on the cyanation of Hacac to PYR I:

$$2\ \text{Hacac} + 2\ C_2N_2 \xrightarrow[C_2H_4Cl_2]{Cu(acac)_2} \text{PYR I}$$

The choice of Hacac as substrate was dictated by the 100% selectivity of the relevant synthesis and the choice of $Cu(acac)_2$ as catalyst was suggested by the higher molecular complexity of $Ni(acac)_2$ with respect to that of $Cu(acac)_2$. Furthermore an independent study [5a] for the $Cu(acac)_2$–Hacac–C_2N_2 system has provided useful basic information on the nature of the species in solution and their equilibria. In particular it was shown that the [acac·$C_2N_2^-$] moiety exists as 3-(cyanoiminomethyl)pentane-2,4-dionato (α^-) [equation (1)] when bonded to a proton and as 1-cyano-2-(1-iminoethyl)butane-1,3-dionato (β^-) when bonded to copper(II).

The set of experiments, the results of which will be employed for the proposal and the discussion of the mechanism, is collected in Table 3.

The analysis of the profiles of percentage residual concentration of Hacac *versus* time as a function of the various experimental conditions gave clear, qualitative information on the kinetic effect caused by acting on the kinetic variables.

The most remarkable kinetic feature exhibited by the percentage reaction *versus* time profiles is a clear and reproducible induction period which is observed when $Cu\beta_2$ and $Cu(acac)\beta$ are used as catalysts. Only with $Cu(acac)_2$ could a smooth progress of the reaction be observed (Figure 1). It is noteworthy that after this time the curves for $Cu\beta_2$ and $Cu(acac)\beta$ become roughly parallel to that given by $Cu(acac)_2$ and that only for $Cu(acac)_2$ can 100% conversion into PYR I be achieved.

The effect of the initial concentration of $Cu(acac)_2$ on the rate of the synthetic process is clearly evident in Figure 2. From this pattern, a very important catalyst concentration effect can be grasped immediately, *i.e.* a general decrease of

Table 3. Reaction conditions employed for the mechanistic study of the cyanation of Hacac in $C_2H_4Cl_2$

$[Cu(acac)_2]$/M	$[Cu\beta_2]$ [a]/M	[Hacac]/M	$[C_2N_2]$/M	[Hα]/M	Note
1.2×10^{-3}		0.35	0.40		
	1.2×10^{-3}	0.35	0.40		
0.6×10^{-3}	0.6×10^{-3}	0.35	0.40		*b*
4.0×10^{-4}		0.35	0.40		
8.0×10^{-4}		0.35	0.40		
5.7×10^{-3}		0.28	0.30		
'0.1'		0.28	0.30		*c*
'0.1'		0.28	0.60		*c*
'0.1'		0.28	0.80		*c*
1.2×10^{-3}		0.35	0.40	2×10^{-2}	
	1.2×10^{-3}	0.35	0.40	'0.2'	*d*
	1.2×10^{-3}	0.35	0.40		*e*
1.2×10^{-3}		0.70	0.35		
1.2×10^{-3}		0.35	0.70		
1.2×10^{-3}		0.15	0.40		
1.2×10^{-3}		0.70	0.40		

[a] $[Cu\beta_2]$ = bis-[1-cyano-2-(1-iminoethyl)butane-1,3-dionato]copper(II).[5] [b] In these conditions the predominant species is the mixed complex Cu(acac)β. [c] The symbol '0.1' indicates the analytical concentration of $Cu(acac)_2$ (*i.e.* including dissolved and undissolved catalyst). [d] Analytical concentration. [e] Addition of C_2N_2 was carried out after equilibration (1 h) of the solution obtained from $Cu\beta_2$ and Hacac.

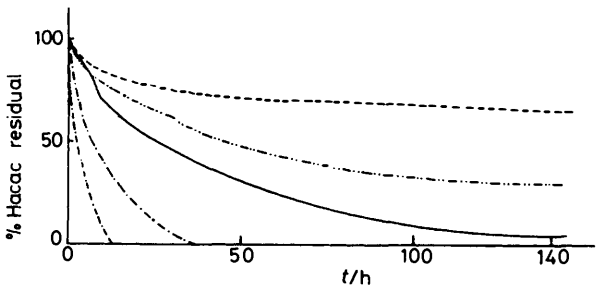


Figure 2. Plot of % residual Hacac *versus* time for different $Cu(acac)_2$ concentrations: [Hacac] 0.35M; $[C_2N_2]$ 0.40M: $[Cu(acac)_2]$, ——— 4×10^{-4}M; — · · — 8×10^{-4}M; —— 1.2×10^{-3}M, — · — · — 5.7×10^{-3}M: [Hacac] 0.28M; $[C_2N_2]$ 0.30M: $[Cu(acac)_2]$, — · — · 5.7×10^{-3}M; — — · · '0.1' M (analytical concentration)

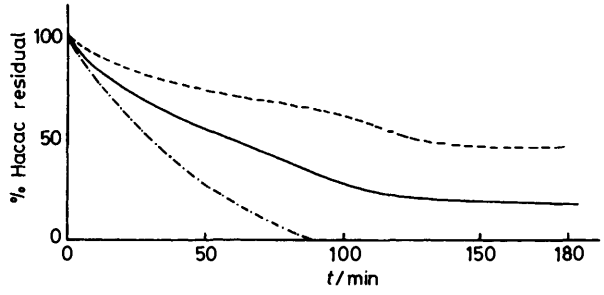


Figure 3. Plot of % residual Hacac *versus* time at various C_2N_2 concentrations: $[Cu(acac)_2]$ '0.1' M; [Hacac] 0.28M: $[C_2N_2]$ - - - - 0.30M; ——— 0.60M; — · — · 0.80M

catalytic efficiency with the Cu^{II} concentration (the selectivity remains 100% !).

A roughly linear dependence of the $t_{\frac{1}{2}}$ values of the catalytic process upon the cyanogen concentration has been observed both at 1.2×10^{-3}M ([Hacac] 0.35M, $[C_2N_2]$ 0.4M, $t_{\frac{1}{2}} \simeq 23$ h; [Hacac] 0.35M, $[C_2N_2]$ 0.7M, $t_{\frac{1}{2}} \simeq 13$ h) and 0.1M analytical catalyst concentration (Figure 3). Under these last conditions we have also examined the qualitative composition of the species dissolved in the reacting solution (see Experimental section). We have found that for 0.3M-C_2N_2 the only reaction product observed in solution is PYR I coexisting with

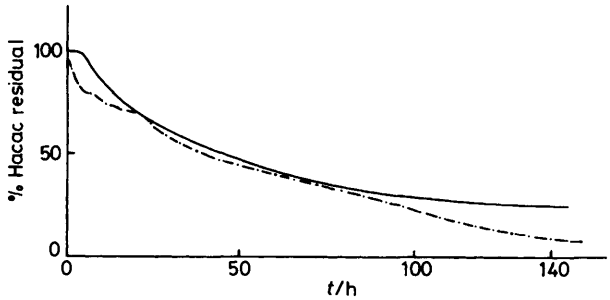


Figure 4. Effect of added Hα on the % residual Hacac *versus* time plot: $[Cu\beta_2]$ 1.2×10^{-3}M; [Hacac] 0.35M; $[C_2N_2]$ 0.4M: [Hα] —— 0.00M, — · — · '0.2' M (analytical concentration)

Hacac and $Cu(acac)_2$. For 0.8M-C_2N_2 a quite evident accumulation of Hα can be observed for a few minutes coexisting with β^--containing copper(II) species. But, after *ca.* 50 min, which corresponds to complete dissolution of suspended $Cu(acac)_2$, PYR I is the only organic product present. Remarkably, roughly the same time was required [5a] to solubilize $Cu(acac)_2$ in the cyanation reaction (in the absence of Hacac !) with the same concentration of copper complex and cyanogen as in the catalytic experiment.

The observed accumulation of Hα and its successive complete disappearance clearly indicate that this species is an important reaction intermediate in the overall catalytic process; this was not unexpected as Hα is the only product in the cyanation of Hacac with $Zn(acac)_2$ catalyst.[5b]

The effect of added Hα on the reaction rate is shown in Figure 4, from which it is seen that the essential effect of this species is the complete elimination of the induction time. It is seen, at the same time, that for a Hα analytical concentration of 0.2M, the synthesis of PYR I is achieved *at the expense of all free Hα with no Hacac consumption* in the very early stage of the catalytic process.

Another effective way for removing the induction time typically observed with $Cu\beta_2$ as a catalyst can be achieved by adding $Cu\beta_2$ to a solution of Hacac and letting the system stand for a convenient time before the addition of the required amount of C_2N_2. Figure 5 illustrates this effect as well as the identity of the behaviour of $Cu(acac)_2$ in the presence of free Hα with that of $Cu\beta_2$ as catalyst.

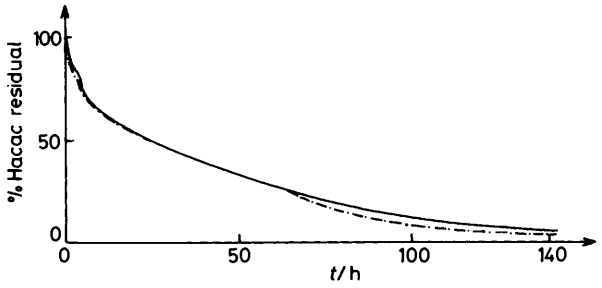


Figure 5. Removal of the induction time in the % residual Hacac *versus* time plot for $Cu\beta_2$ as catalyst by pre-equilibration with Hacac. Comparison with $Cu(acac)_2$ in the presence of Hα: —— [$Cu(acac)_2$] 1.2×10^{-3}M, [Hacac] 0.35M, [C_2N_2] 0.40M, [Hα] 2×10^{-2}M; ——— [$Cu\beta_2$] 1.2×10^{-3}M pre-equilibrated with [Hacac] 0.35M, [C_2N_2] 0.40M

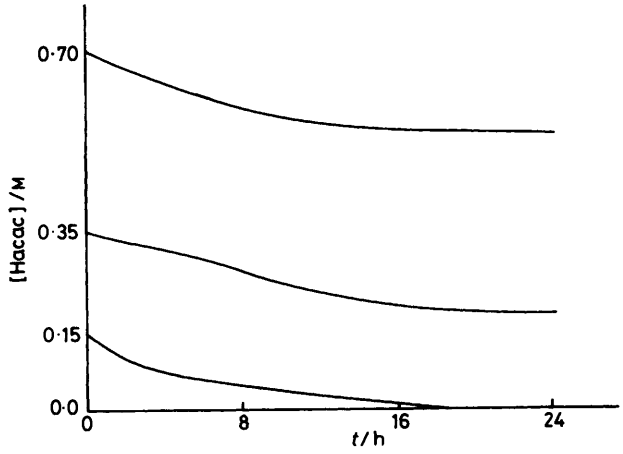


Figure 6. Plots of [Hacac] *versus* time different $[Hacac]_0$: [$Cu(acac)_2$] 1.2×10^{-3}M, [C_2N_2] 0.40M

The last important kinetic observation is the small role played by the concentration of Hacac on the overall reaction rate. Comparison of the plots in Figure 6 shows that the rate of Hacac consumption is practically independent of its concentration.

A further result pertinent to the proposal of the catalytic mechanism concerns the interaction of $Cu\beta_2$ with Hα and Hacac. When $Cu\beta_2$ (1.2×10^{-2}M) interacts with Hα (3×10^{-2}M), a colour change from green to yellow occurs in 10 min, no precipitation of any species occurs, but the i.r. spectrum of the solution reveals the formation of small amounts of PYR I ($< 10^{-3}$M). This situation is stable for 12 h, but when Hacac up to 0.35M is added, precipitation of PYR I is observed after 30 min. After 48 h the yield in PYR I is 25% (based on the metal-co-ordinated β^- and added Hα).

Before discussing the problem of the mechanism of the catalytic action of $Cu(acac)_2$ for the pyrimidine synthesis, it is necessary to clarify that the proposed mechanism is based on the interaction of *species which are clearly identified as predominant* in solution, *i.e.* $Cu(acac)_2$, Cu(acac)β, Hacac, Hα, C_2N_2.[5a] In this respect the proposals based on an Mα–Hβ[1] or Mα–Hα [5b] interaction seem less likely for the $Cu(acac)_2$ catalyst, as it involves species for which no definite evidence of accumulation in solution is available.[5b]

Most of the results here and elsewhere [5a] described can be mechanistically accounted for on the basis of the catalytic cycle in Scheme 3. The sequence of the elementary acts implies: (1) metal-assisted C_2N_2 attack at one organometallic ring with formation of the co-ordinated 3-cyanoiminomethylpentane-2,4-dionato ligand (α) which isomerizes to β. This electrophilic attack by cyanogen appears to be particularly important in that it represents the first crucial step (C–C bond formation !) in the building up of the pyrimidine ring. (2) There is subsequent replacement of co-ordinated β by acac and rearrangement of the liberated Hβ to Hα. (3) There is a further C_2N_2 attack on the resulting $Cu(acac)_2$ as in stage (1). (4) End-on co-ordination to the metal in Cu(acac)β of a free Hα through the nitrogen lone pair of the C≡N group takes place. This event, which should occur *via* the same ring-opening mechanism proposed in the addition of C_2N_2 to Cu(acac)β,[5a] leads to electrophilic activation of the C≡N group, so favouring its interaction with the imino and carbonyl residues of the co-ordinated β ligand, to give a Hα–β molecular adduct. (5) Substitution with protonation by Hacac of this adduct occurs to give PYR I in solution with renewal of $Cu(acac)_2$ and consequent closing up of the catalytic cycle.

This simplified cycle is based on the fundamental observation that Hα does not undergo cyclodimerization in the absence of catalysts such as $Ni(acac)_2$ or $Cu(acac)_2$ so that at least one acac·$C_2N_2^-$ unit has to be metal-bonded; furthermore, it is qualitatively consistent with the observed influence of the concentration of the various kinetically important species.

According to the proposed mechanism the crucial catalytic step is represented by the attack of free Hα on Cu(acac)β, so that all steps which increase the concentrations of these species in solution should be expected to be catalytically productive.

The effect of increasing concentration of $Cu(acac)_2$ (Figure 2) is evident, as it increases the overall concentration of the catalytically relevant metal centres.

The effect of C_2N_2 concentration (Figure 3) is quite reasonable in that it determines the rate of production of the mixed Cu^{II} complex by attack on $Cu(acac)_2$ according to reaction (3).[5a] The resulting mixed complex gives different products as a consequence of its reaction with Hacac, Hα, or C_2N_2.

$$(acac)Cu(acac) + C_2N_2 \longrightarrow (acac)Cu\beta \quad (3)$$

$$(acac)Cu\beta + Hacac \rightleftharpoons (acac)Cu(acac) + H\alpha \quad (4)$$

$$(acac)Cu\beta + H\alpha \rightleftharpoons (acac)Cu\beta \cdot H\alpha \quad (5)$$

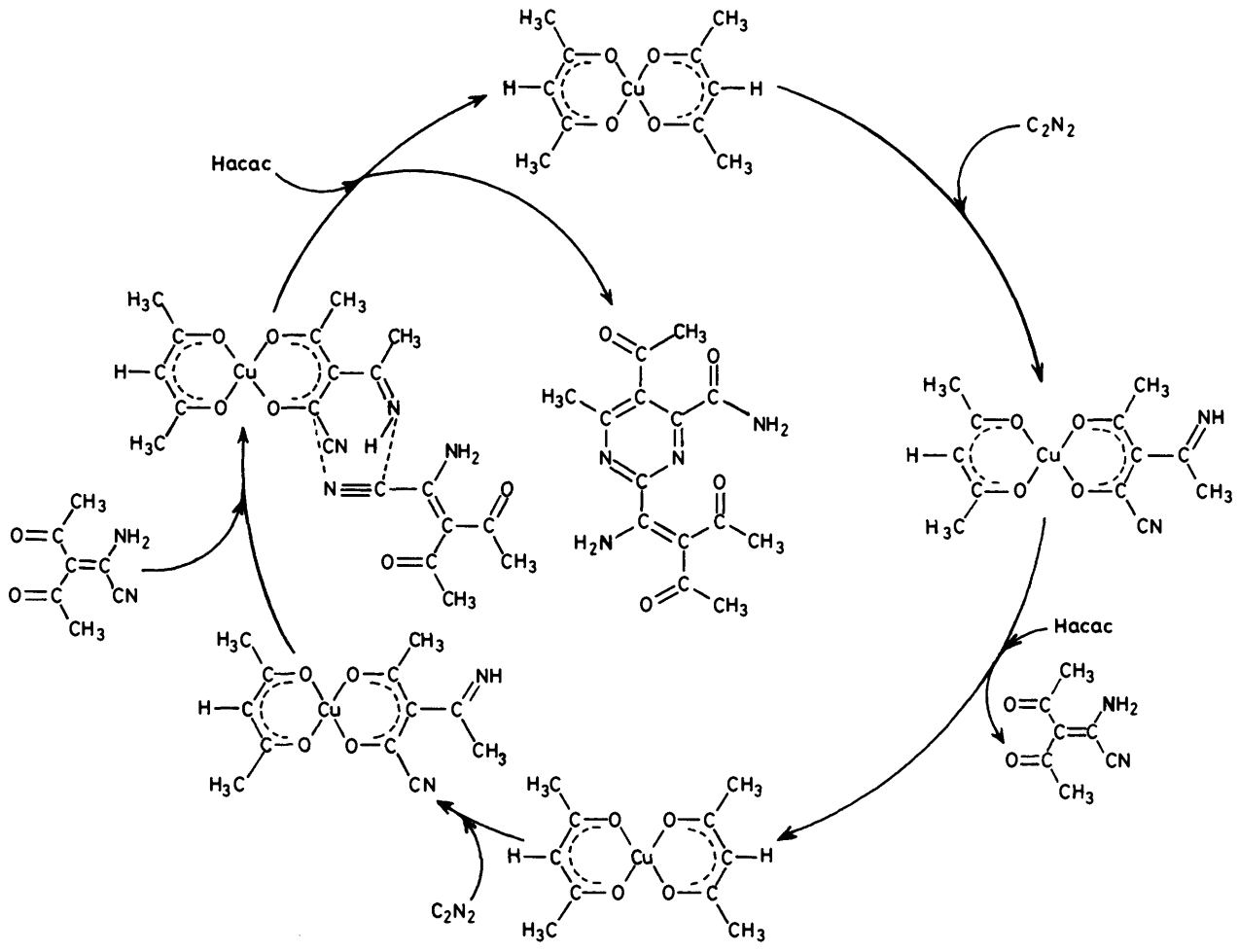
$$(acac)Cu\beta + C_2N_2 \longrightarrow \beta Cu\beta \quad (6)$$

Reactions (4) and (5) are important in that (4) gives Hα in solution and (5) represents the fundamental chemical event for the cyclization of one molecule of Hα with a β anion. Reaction (6) is also productive in the catalytic cycle, because $Cu\beta_2$ is expected to react with $Cu(acac)_2$ to give the thermodynamically more favoured mixed complex as in reaction (7). Furthermore $Cu\beta_2$ can also react with Hacac thus releasing Hα in solution [reaction (8)].[5a]

$$Cu\beta_2 + Cu(acac)_2 \rightleftharpoons 2Cu(acac)\beta \quad (7)$$

$$Cu\beta_2 + Hacac \rightleftharpoons Cu(acac)\beta + H\alpha \quad (8)$$

On the basis of the fact that all the above substitution equilibria are fast with respect to the rate of catalysis,[5a,6] we can safely state that we are not dealing with a catalyst, but rather with a *catalytic system* which, in principle, should be to some extent insensitive to the type of the starting β-diketonate complex. This means that the profile of Hacac consumption should be independent of the use of $Cu\beta_2$ or $Cu(acac)_2$ as catalysts, if the same concentrations of Hacac, C_2N_2, and Hα are employed, and fully explains the finding that $Cu(eaa)_2$ and $Cu(acac)_2$ are equally catalytically effective



Scheme 3. Proposed simplified catalytic cycle for the synthesis of PYR I

for the cyanation of ethyl acetoacetate (Table 1). It should be pointed out that this expectation is rigorously verified for $Cu\beta_2$ if it is allowed to balance with Hacac [equations (8) and (4)] before C_2N_2 addition (Figure 5), while it is not so if C_2N_2 and Hacac are added to a solution containing $Cu\beta_2$.

The importance of the concentration of Hα, is, on the other hand, stressed by its strong effect on the induction time, which completely disappears for [Hα] '0.2'M (see legend of Table 3). Clearly Hα reacts with Cu(acac)β [equation (5)] giving the molecular adduct (acac)Cuβ·Hα, which, reacting in its turn with Hacac, restores $Cu(acac)_2$ according to reaction (9). In fact Hα is rapidly consumed to give PYR I and

$$(acac)Cu\beta\cdot H\alpha + Hacac \rightleftharpoons Cu(acac)_2 + PYR\ I \quad (9)$$

the profiles of Hacac consumption become strictly similar to the cases where $Cu(acac)_2$ is the starting catalyst (Figure 4).

The very small effect on the reaction rate caused by increasing Hacac concentrations is also consistent with the proposed mechanism in that the exchange reaction (4) is always faster [5a] than the overall rate of PYR I formation and that this should be true also for reaction (9).

The equilibria described so far justify our assumption that the crucial step in the catalytic process is the reaction between Hα and Cu(acac)β and not reaction (10) which is quite possible in principle. Reaction (10) should in fact make a small contribution to the synthesis of PYR I, because of the very low $Cu\beta_2$ concentration in the catalytic conditions (high Hacac concentration). The concentration of Cu(acac)β is on the other hand less affected by Hacac as the consequence of equation (7).

$$\beta Cu\beta + H\alpha \longrightarrow \beta Cu\beta\cdot H\alpha \quad (10)$$

It is quite apparent that the reaction rate for catalytic C_2N_2 addition to Hacac to give PYR I results from a complicated balance of a variety of important elementary steps. This circumstance explains why we encountered such severe problems in treating mathematically the experimental kinetic law, but we think that at least a fundamental statement should be possible. In view of the relative rates of the various elementary steps found to be important in the overall process, the rate of formation of PYR I is practically coincident with that of cyanation of $Cu(acac)_2$.

Crystal Structure of PYR II.—The crystal structure demonstrates that the compound obtained is 2-(1-amino-2-ethoxycarbonyl-2-acetyl)vinyl-4-carboxamido-5-ethoxycarbonyl-6-methyl-1,3-diazine, analogous to the pyrimidine compound obtained from Hacac [1] (Figure 7).

The common parts of two structures are very similar, despite the substitution of two methyl with two ethoxy groups. The bond distances (Table 4) and valence angles compare very well with those found in the structure of PYR I: all values are in reasonable agreement with those expected for the N(2)–C(7)–N(3) angle (125.0 and 129° in PYR I and PYR II,

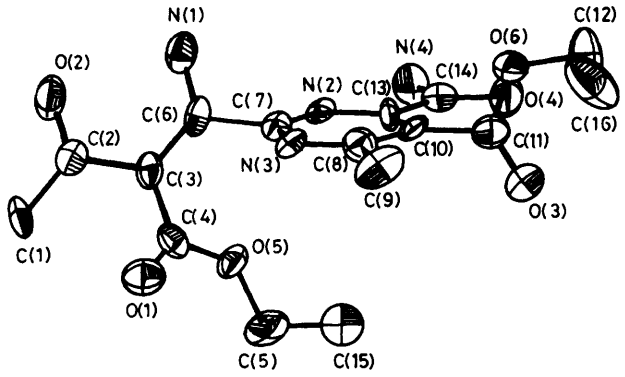


Figure 7.

Table 4. Bond lengths (Å) and angles (°) of PYR II

C(2)–O(2)	1.24(1)	C(14)–O(4)	1.24(1)
C(1)–C(2)	1.49(2)	C(14)–N(4)	1.32(1)
C(2)–C(3)	1.46(1)	C(14)–C(13)	1.51(2)
C(3)–C(4)	1.47(2)	C(11)–O(3)	1.19(1)
C(4)–O(5)	1.31(1)	C(11)–C(10)	1.51(2)
C(4)–O(1)	1.22(1)	C(11)–O(6)	1.32(1)
O(5)–C(5)	1.42(1)	O(6)–C(12)	1.48(1)
C(5)–C′(15)	1.45(3)	C(12)–C(16)	1.49(2)
C(5)–C″(15)	1.43(3)	C(9)–C(8)	1.52(2)
C(3)–C(6)	1.39(2)		
C(6)–N(1)	1.34(1)		
C(6)–C(7)	1.53(1)		
N(2)–C(7)	1.31(1)		
C(7)–N(3)	1.32(1)		
N(3)–C(8)	1.35(1)		
C(8)–C(10)	1.38(2)		
C(10)–C(13)	1.37(2)		
C(13)–N(2)	1.35(1)		
C(1)–C(2)–O(2)	120(1)	C(11)–C(10)–C(8)	120(1)
C(1)–C(2)–C(3)	119(1)	C(11)–C(10)–C(13)	122(1)
O(2)–C(2)–C(3)	121(1)	C(8)–C(10)–C(13)	118(1)
O(1)–C(4)–O(5)	123(1)	C(14)–C(13)–C(10)	123(1)
O(1)–C(4)–C(3)	123(1)	C(14)–C(13)–N(2)	115(1)
C(3)–C(4)–O(5)	114(1)	C(10)–C(13)–N(2)	122(1)
C(2)–C(3)–C(4)	121(1)	C(13)–N(2)–C(7)	115(1)
C(2)–C(3)–C(6)	119(1)	C(7)–N(3)–C(8)	115(1)
C(4)–C(3)–C(6)	121(1)	C(11)–O(6)–C(12)	118(1)
C(3)–C(6)–N(1)	127(1)	O(6)–O(12)–C(16)	106(1)
C(3)–C(6)–C(7)	120(1)	C(4)–O(5)–C(5)	118(1)
N(1)–C(6)–C(7)	113(1)	O(5)–C(5)–C′(15)	111(2)
O(4)–C(14)–N(4)	123(1)	O(5)–C(5)–C″(15)	120(2)
O(4)–C(14)–C(13)	120(1)		
N(4)–C(14)–C(13)	117(1)		
O(6)–C(11)–O(3)	127(1)		
O(6)–C(11)–C(10)	109(1)		
O(3)–C(11)–C(10)	123(1)		
C(6)–C(7)–N(2)	116(1)		
C(6)–C(7)–N(3)	115(1)		
N(2)–C(7)–N(3)	129(1)		
C(9)–C(8)–N(3)	117(1)		
C(9)–C(8)–C(10)	123(1)		
N(3)–C(8)–C(10)	121(1)		

respectively), which is quite high in both structures, suggesting that the planarity of the ring imposes abnormal values on N(2), N(3), and C(7) angles.

The geometry of the substituent groups is similar in the two structures, as shown by the angles between the mean planes and the deviations of the atoms from the planes (Table 5). The N(4)–C(4)–O(4) group is coplanar with the pyridine ring,

Table 5. Least-squares planes equations with deviations (10^{-3} Å) of the atoms from the plane. The equations of the plane are in the form $Px_0 + Qy_0 + Rz_0 = S$ in orthogonal space, with x_0 parallel to a, z_0 perpendicular to a in the ac plane, and y_0 perpendicular to ac. An asterisk denotes an atom not used in the plane calculation

Plane A: $P = 0.2517$, $Q = 0.9673$, $R = 0.0318$, $S = 3.5379$

N(2)	−7	C(6) *	181
N(3)	−5	C(9) *	−68
C(7)	12	C(11) *	20
C(8)	−7	C(14) *	−52
C(10)	10	O(4) *	−33
C(13)	−4	N(4) *	−63

Plane B: $P = 0.2277$, $Q = 0.9733$, $R = 0.0288$, $S = 3.5372$

C(13)	4	N(4)	4
C(14)	−12	O(4)	5

Plane C: $P = 0.9444$, $Q = -0.1827$, $R = 0.2734$, $S = 1.0860$

C(10)	5	O(3)	8
C(11)	−19	O(6)	6
C(12) *	−66		

Plane D: $P = 0.9306$, $Q = 0.3362$, $R = 0.1449$, $S = 2.5704$

C(6)	−1	N(1)	−2
C(7)	4	C(3)	2
C(2) *	159	O(2) *	259
C(1) *	46	C(4) *	−98

Dihedral angles (°) between planes

Plane A—Plane B	1
Plane A—Plane C	86
Plane A—Plane D	56
Plane C—Plane D	31

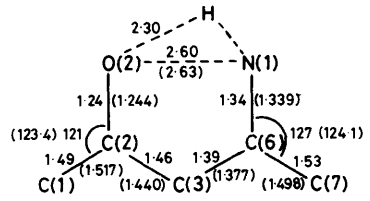


Figure 8.

but the C(13)–C(14) distance (1.51 Å), in agreement with a C_{sp^2}–C_{sp^2} value, does not suggest that the resonance extends from the ring to the substituent. The same conclusion arises by an inspection of the angles between the C(10)C(11)O(3)O(6) and C(7)C(6)N(1)C(3)C(2) planes and the pyrimidine ring, along with the C(10)–C(11) and C(6)–C(7) distances. On the other hand, the approximate planarity in the C(7)C(6)C(3)N(1)C(2)-C(1)O(2) region, along with the bond distances, suggests the resonance would extend from N(1) to O(2) through C(6), C(3), C(2), and C(1). A strong intramolecular hydrogen bond as observed for PYR I is also present in this part of the molecule and a comparison of the geometry with that found in PYR I, is presented in Figure 8. The N · · · O distance, significantly shorter than frequently observed values, can be justified only by the molecular geometry. Other intramolecular hydrogen bonds or hydrogen interactions are also a feature of the crystal: a list of the shortest contacts is reported in Table 6.

Some disorder is present in the crystal in the region around C(15): two positions, in fact, can be clearly seen for the methyl group, both with an occupancy factor of *ca.* 0.5, easily explained by a rotation around the O(5)–C(5) bond. Owing to the disorder, bond distances and angles in this area [particularly the C(5)–C(15)′ and –C(15)″ bond distances and the valence angles around the C(5)] present unreliable values.

Table 6. Some shortest polar contacts in the crystal. The primed atoms belong to a symmetry-related molecule (values in Å)

N(4) · · · O(1)′	2.85
H(N4) · · · O(1)′	2.18
N(1) · · · O(2)′	3.10
N(1) · · · O(4)′	2.99
N(4) · · · O(6)′	3.24

Conclusions.—We have discovered a new one-pot synthesis of fairly sophisticated pyrimidines. The role of the metal ion is of paramount importance in making possible not only the addition of C_2N_2 to Hacac, but the subsequent cyclodimerization reaction 2 Hα ⟶ PYR I, which is the real novelty in this aspect of cyanogen chemistry. The base-catalysed addition of C_2N_2 to Hacac [2] owes its success to the circumstance that the base $acac^-$ undergoes easy C_2N_2 insertion into the C–H methine bond to give an anionic species which can be easily protonated by excess of Hacac to give the barely soluble (in ethanol at 0 °C) 3-cyanoiminomethylacetylacetone. This new metal-catalysed reaction is, in fact, a combination of cyanogen addition with a subsequent cyclodimerization process of Hα.

In our opinion, this overall reaction represents a typical example of the capabilities of metal centres in offering convenient pathways for thermodynamically possible, albeit kinetically ' impossible ', organic syntheses.

Experimental

General.—M.p.s were taken with a Kofler hot-stage apparatus and are uncorrected. I.r. spectra were measured with a Perkin-Elmer model 397 spectrophotometer. N.m.r. spectra were measured with either a Varian T60 or a Bruker WP 60 spectrometer using Me_4Si as internal standard. U.v.–visible spectra were obtained with a Perkin-Elmer 576 apparatus. Gas chromatographic measurements were performed on an f.i.d.-equipped Perkin-Elmer model 900 instrument and columns (2 m × 2 mm) filled with OV17 over Chromosorb W (10%) were employed. For the quantitative measurements n-hexadecane was used as internal standard and accurate straight lines were obtained for Hacac, Heaa, and Hdmm. Peak areas were measured by a polar planimeter. The solutions of C_2N_2 were prepared and standardized as described elsewhere.[7] The catalytic runs were carried out at 20 ± 0.1 °C.

Materials.—Solvents were reagent grade chemicals and were used as received as were the β-dicarbonyl compounds. C_2N_2 was a Matheson chemical, $Ni(acac)_2$ was a Schuchardt product and was used as received. $Cu(acac)_2$ and $Cu(eaa)_2$ were prepared and purified by published methods.[8]

General Procedure for the Catalytic Cyanation Reactions.—The reactions were carried out in one-neck, round-bottom Pyrex cylindrical vessels (*ca.* 50 ml) equipped with a Teflon-coated magnetic bar. The closure was achieved by a special glass stopcock, in which the ' male ' junction had been carefully ground to such an extent to enable a perfect adherence with the ' female ' junction of the reaction vessel without the need for silicon grease. The upper part of the stopcock bore, instead of the familiar glass tube, was a ' female ' junction in which a rubber cup was tightly inserted. This ' closing up ' system made possible perfect sealing of the solution (no loss of C_2N_2 for at least two weeks at 20 °C) when the stopcock is set in the closed position and enables the transfer of aliquot portions of solutions at any time by means of a hypodermic syringe, equipped with a conveniently long needle, when the stopcock is in the open position.

The reagents (9—20 mmol) were introduced in the order: solution of C_2N_2, substrate, n-hexadecane, pure solvent (if required). The total volume was typically 30 ml for the liquid substrate. After 5 min of moderate stirring the reference solution used for the accurate evaluation of the initial substrate concentration was transferred by a syringe into a cold vessel and then analysed by g.l.c.

In the case of Hba and Hdbm, in which no evaluation of the substrate consumption was made, the success and yield of the synthesis were evaluated by the amount of product spontaneously precipitated and by the analysis of the final solution. Also in the case of Hacac and Heaa the pyrimidinic products are scarcely soluble and the g.l.c. analysis of the solution required accurate filtration of the portions of the suspensions sucked off at various times, which was made possible by a Millipore stainless steel apparatus. For Hdmm no filtration was necessary. The product was obtained by evaporating the final solution at reduced pressure and triturating the yellow residue with diethyl ether, which produced a white microcrystalline precipitate.

Cyanation of Acetylacetone [*Catalyst* $Ni(acac)_2$ *or* $Cu(acac)_2$].—The initially yellow-orange (Ni^{II}) or green (Cu^{II}) solution turns gradually red and precipitation of yellow crystals begins within a few hours. If the solution is subjected to moderate stirring, PYR I precipitates in the form of a fine yellow powder. Mass recovery tests indicated that, in $C_2H_4Cl_2$, the fraction of product, which can be obtained by evaporating the final mother liquor, is appreciably contaminated by an impurity, which is probably responsible for the red colour observed to develop in the solution during the process. Owing to the low solubility of PYR I, however, this circumstance produces an uncertainty of perhaps 1% in the total mass balance. In CH_2Cl_2 the final solution is golden yellow and the above contamination is apparently avoided. The choice of $C_2H_4Cl_2$ is due to a variety of practical reasons. In some kinetic runs it was interesting to record the i.r. spectrum of the solutions to be analysed by g.l.c. and this was done both by means of 1 mm semi-permanent NaCl i.r. cells and/or by recording i.r. spectra in Nujol of the solid obtained by rapid evaporation of aliquot portions (*ca.* 1 ml) of the filtered reacting solution directly on a mortar under a well ventilated hood.

The physicochemical properties of PYR I have been reported elsewhere together with its *X*-ray structure.[1]

Cyanation of Ethyl Acetoacetate [*Catalyst* $Ni(acac)_2$ *or* $Cu(acac)_2$].—The general pattern observed in the PYR I synthesis was followed for PYR II. Ethyl acetoacetate (10 g) was added to a 0.9M solution of C_2N_2 in dichloroethane (150 ml). $Ni(acac)_2$ (39 mg) was then added and the solution was stirred for a few minutes. The mixture was left for 14 days at room temperature and then filtered under air. PYR II appeared as a microcrystalline reddish yellow product (7.8 g). The crude material was dissolved in boiling dichloroethane (*ca.* 300 ml) and, after filtration, cooling to room temperature, and solvent removal to leave a residue of 30 ml, well crystallized product (5 g) was obtained which was still slightly reddish yellow (the very pure compound is almost white).

The dark red mother liquor obtained upon filtration of the crude product was brought to dryness at room temperature and then treated with diethyl ether (300 ml) with vigorous stirring. The reddish yellow solid residue was filtered off and dissolved in boiling dichloroethane. Cooling to −30 °C afforded further PYR II (1.5 g). The total impure PYR II (6.5 g) was dissolved in boiling dichloroethane and final cooling down to −30 °C afforded pure PYR II (4.0 g), m.p.

207—208 °C, δ ($CDCl_3$) 0.98, 1.10, 1.22 (t) and 1.28, 1.46, 1.52 (t) (ethoxide CH_3), 2.34 and 2.67 (s) (CH_3 of acetyl groups or ring-bonded CH_3), 3.92, 4.03, 4.15, 4.27 (q) and 4.33, 4.44, 4.56, 4.68 (q) (ethoxide CH_2), and 7.25 and 7.65 (s) (NH_2 amide or vinylogous amide), δ (DMSO) 0.75, 0.87, 1.00 (t) and 1.25, 1.36, 1.49 (t) (ethoxide CH_3), 2.34 (s) (CH_3 of acetyl group or ring-bonded CH_3), ill defined q from 3.68 to 3.81 and 4.24, 4.36, 4.48, 4.60 (q) (ethoxide CH_2), 8.02 and 8.44 (s) and 8.95 and 10.74 (s) (NH_2 amide or vinylogous amide: two coexisting forms?), $\nu_{max.}$ (Nujol) 3 485, 3 450, (N–H), 3 345, 3 245, (N–H), 1 740 (C=O), 1 705 (C=O), 1 680 (C=O), and 1 610 cm^{-1} (C=C and NH_2), $\lambda_{max.}$ ($C_2H_4Cl_2$) 242 (ε 10 650 l mol^{-1} cm^{-1}) and 357 nm (6 600), *m/e*, 364 (M^+, 29%), 349 (100), 303 (21), 235 (30), 179 (92), 95 (56), and 68 (16%) (Found: C, 52.0; H, 5.3; N, 15.2. Calc. for $C_{16}H_{20}N_4O_6$: C, 52.7; H, 5.5; N, 15.4%). The dark red ethereal solution mentioned above gave, upon solvent removal, a red oil (1.04 g) which was not investigated.

Cyanation of Benzoylacetone [*Catalyst* $Ni(acac)_2$].—The initial clear golden yellow solution turned gradually to a yellow suspension in which the product appeared as a voluminous yellow solid which was filtered off and washed with pure solvent (*ca.* 30 ml $mmol^{-1}$). The elemental analysis of the crude compound was not quite satisfactory and recrystallization from hot $C_2H_4Cl_2$ was necessary. Typical yields were *ca.* 25% after *ca.* 300 h. The compound was scarcely soluble in the common organic solvents. It is appreciably soluble in dimethyl sulphoxide, m.p. 321—322 °C, δ (DMSO) 2.05 and 2.20 (s) (CH_3 of acetyl group or ring-bonded CH_3), 7.50 (complex m) (ArH), and 8.09 and 8.57 (s) (NH_2 amide or vinylogous amide), $\nu_{max.}$ (Nujol) 3 490, 3 330 (N–H), 3 230, 3 190 (N–H, two almost reciprocally merged broad bands), 1 705 (C=O), 1 673 (C=O), 1 660 (C=O), and 1 620 cm^{-1} (composite band, C=C, NH_2), $\lambda_{max.}$ ($C_2H_4Cl_2$) 248 (ε 41 560 l mol^{-1} cm^{-1}) and 371 nm (10 000), *m/e* 428 (M^+, 81%), 413 (26), 351 (11), 105 (100), 77 (12), and 58 (74) (Found: C, 67.3; H, 4.7; N, 13.1. Calc. for $C_{24}H_{20}N_4O_4$: C, 67.3; H, 4.7; N, 13.1%).

Cyanation of Dimethyl Malonate [*Catalyst* $Ni(acac)_2$].—The initially clear golden solution turned gradually to a slightly turbid off-white one. The product was obtained as a white powder by solvent evaporation and recrystallization from CH_2Cl_2–n-hexane. Typical yields were 15—20% after *ca.* 300 h. The compound was soluble in chlorinated solvents, m.p. 141—142 °C, δ ($CDCl_3$) 2.26 and 2.60 (s) (non-equivalent CH_3 groups) and 7.94 (s) (NH_2), $\nu_{max.}$ (Nujol) 3 380, 3 200 (N–H, broad bands), 1 700 (C=O), and 1 600 cm^{-1} (composite band, C=C and NH_2), $\lambda_{max.}$ ($C_2H_4Cl_2$) 304 (ε 10.000 l mol^{-1} cm^{-1}), *m/e* 184 (M^+, 53%), 153 (100), 126 (46), 121 (31), 94 (25), 69 (44), 59 (46), and 53 (32) (Found: C, 45.5; H, 4.3; N, 15.25. Calc. for $C_7H_8N_2O_4$: C, 45.6; H, 4.4; N, 15.25%).

Preparation of $Cu(acac{\cdot}C_2N_2)_2$ = ($Cu\beta_2$).—The details have been already published but we report here a little different procedure, which improves the yield to 98%. $Cu(acac)_2$ (1.65 g) was suspended in $C_2H_4Cl_2$ (60 cm^3) containing C_2N_2 (0.32M). The suspension was stirred vigorously for 24 h at room temperature. The pale green microcrystalline product was obtained upon filtration on a Gooch filter and washed with pure solvent (300 cm^3) (yield 1.95 g). The product can be recrystallized from hot $C_2H_4Cl_2$.

X-Ray Single-crystal Analysis of PYR II.—Crystals were obtained from very slow evaporation of solutions of **PYR II** in acetone or dichloroethane.

Crystal data. $C_{16}H_{20}N_4O_6$, *M* 364.36, monoclinic, $P2_1/n$, $a = 13.334(7)$, $b = 10.576(6)$, $c = 12.679(6)$ Å, $\beta = 90.5(1)°$, $D_c = 1.35$ g cm^{-3}, $Z = 4$, $F(000) = 808$ e, λ (Mo-K_α) = 0.7107 Å.

Solution and refinement of the structure. Intensity data were collected from a crystal of approximate dimensions 0.1 × 0.1 × 0.1 mm on a Philips PW 1100 four-circle diffractometer using the θ–2θ scan mode (scan width = 1.20°; scan speed = 0.03° s^{-1}). A total of 3 174 independent reflections were scanned ($2 \leqslant \theta \leqslant 25°$) using a graphite-monochromatized Mo-K_α radiation. Only 1 289 reflections [$I \geqslant 2\sigma(I)$] were considered observed and used in the calculations. Intensities were corrected for Lorentz and polarization effects and an empirical absorption correction was applied.[9] The structure was solved by direct methods [10] and refined by the full-matrix least-squares method with anisotropic thermal parameters for all non-hydrogen atoms, except C(15); from the Fourier maps, two peaks were in fact clearly visible around the position of C(15); two carbon atoms were consequently introduced in the refinement with an occupancy factor of 0.5, and the temperature and occupancy factors were refined in turns. Nearly all the hydrogen atoms were located from a Fourier difference map and introduced in the refinement, but refined in a separate cycle. The weighting scheme used was $w = 3.7|\sigma^2(F_o) + 0.001\,(F_o)^2|^{-1}$, except in the last cycle of refinement, when unit weight was used. The final *R* factor was 0.107; the high value can be attributed principally to the disorder in the region near the atoms C(5) and C(15) and to the very small dimensions of the crystals employed.

The scattering factors were taken from ref. 11. Atomic positional and thermal parameters are given in Supplementary Publication No. SUP 23879 (17pp.).*

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* For details of Supplementary Publications see Instructions for Authors in *J. Chem. Soc., Perkin Trans. 2*, 1984, Issue 1.