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AN H-1, C-13 AND N-15 NMR STUDY OF THE PAAL-KNORR CONDENSATION OF ACETONYLACETONE WITH PRIMARY AMINES

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Abstract. - The reaction of primary amines with acetonylacetone is shown by H-1, C-13 and N-15 NMR spectroscopy to proceed to the N-substituted -2, 5-dimethylpyrroles via the intermediacy of N-substituted imines. Increased steric hindrance reduces rates of imine formation and decay.

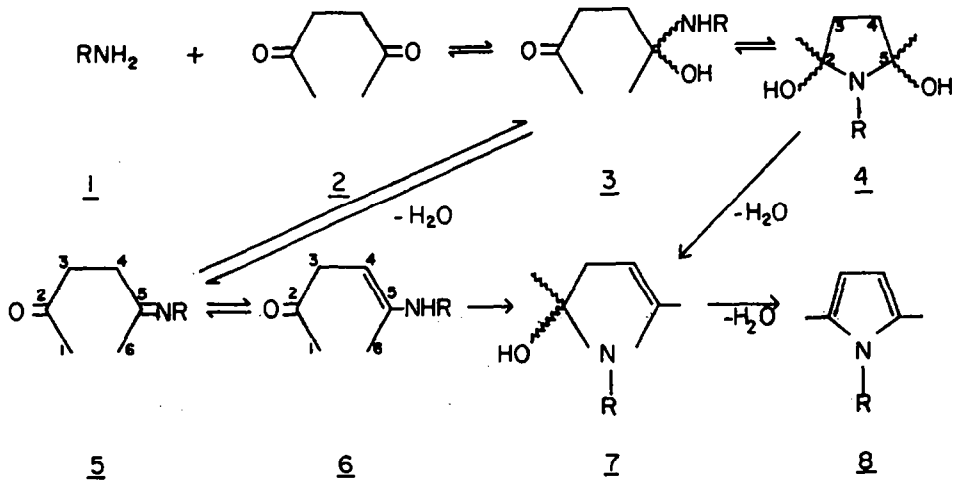
The pyrrole skeleton is widely distributed in natural products.[1a] An important synthetic and biosynthetic route to pyrroles is the reaction of a 1,4-dicarbonyl compound with a primary amine, the Paal-Knorr condensation.[1b] No mechanism for this reaction is given in the two definitive monographs on pyrrole chemistry[1,2] and the older literature concentrates largely on the preparative aspects of the reaction.[3a,b,c] As early as 1906[3d], however, imines were isolated in this reaction under preparative conditions and the suggestion made that ring-closure of the enamine 6 (Scheme 1) present in equilibrium with the imine 5 was the key step. Experimental backing for this was subsequently provided by Broadbent et al.[4] who detected the imine by IR spectroscopy but failed to detect the enamine, concluding, ".....it is probable that the reactive form of the intermediate is the isomeric enamine, which may not be directly observable since the equilibrium between the two heavily favours the hydrazone form.....".[4]

Following an extensive kinetic investigation,[5,6] one of us concluded that this reaction is indeed an addition elimination at the carbonyl carbon, consistent with the known mechanisms of the interaction of amines with aldehydes and ketones[7a], but proposed the intermediacy of the dihydroxypyrrolidine 4 on the basis of ^{1}H NMR evidence[8] (Scheme 1). A similar intermediate was recently implied by Sundberg[9] without supportive evidence. The present work was undertaken to see which intermediate(s) could be detected on the pathway 1 + 2 ----> 8 (Scheme 1).

Basis of Investigation

A variety of amines (1a - 1i) were mixed with acetonylacetone (2) in a 1:1 mole ratio in $CDCl_3$ solution and the reaction followed by ^{13}C NMR spectroscopy. In the case of 1a and 1c (Scheme 1), the reactions were also followed by ^{1}H- and ^{15}N- NMR spectroscopy and the products isolated and characterised. All peaks due to starting materials and products were identified by reference to their authentic spectra when these were available, or, if not, by analogy to similar compounds.

All the reactions (except those involving aniline 1b and ethylamine 1i) disclose a set of peaks due to an intermediate; the relative intensities of these sets of peaks grew to a maximum value and then gradually decreased, while the product peaks formed and steadily increased in intensity. In all cases, the intermediate peaks were, for reasons discussed below, assigned to the imine 5 and not to the pyrrolidine 4. Indeed, this reaction is ideally suited for study by ^{13}C NMR and ^{15}N NMR spectroscopy because the intermediate imine 5 has characteristic sp^2 carbon and sp^2 nitrogen atoms, whereas the pyrrolidine 4 possesses no sp^2 carbons, and no sp^2 nitrogen (Scheme 1).



R = $PhCH_2$- = a
Ph- = b
Me_2CHCH_2- = c
Ph_2CHCH_2- = d
Me_3CCH_2- = e
Me_2CH- = f
PhCHMe- = g
Ph_2CH- = h
= i
Et- = j

C-13 Assignments

Two INEPT(D) pulse sequences[10] were used to confirm the C-13 assignments: a 5.1 ms predelay giving positive peaks for primary and tertiary carbons, enhanced negative peaks for secondary carbons and suppressed quarternary carbons; a 4.0 ms predelay giving positive tertiary peaks with the primaries, secondaries and quarternaries suppressed.

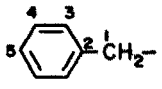
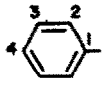
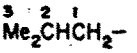
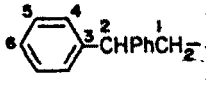
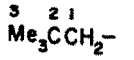
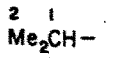
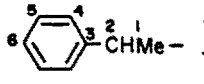
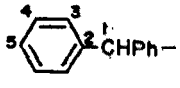
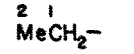
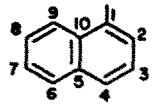
The ^{13}C NMR shifts and assignments of the N-substituent in the amines 1 (Scheme 1) are given in Table 2, and are in good agreement with the literature,[11,12] as are the assignments for acetonylacetone[12d] (C1 = 29.6 ppm; C2 = 206.9 ppm; C3 = 36.9 ppm). Peaks for the 2,5-dimethylpyrroles are given in Tables 1 and 2. The literature contains surprisingly little on the ^{13}C NMR chemical shifts and assignments of pyrroles[11,12,13,14] although a whole range of N-substituted-2,5-dimethylpyrroles have previously been synthesized and characterized.[1,2,4,6] The observed chemical shifts of the pyrrole ring carbons C(2,5), C(3,4) and the 2,5-dimethyl substituent are within the expected range[13a,14a] (Table 1). Little change occurs in the chemical shifts of the N-substituent in going from amine 1 to pyrrole 7 (Table 2).

Table 1. C-13 NMR assignments of ring and methyl carbons in N-substituted-2,5-dimethylpyrroles 8 (Scheme 1)[a]

Comp.	C(2,5)	C(3,4)	Me(2,5)
8a	127.6	105.7	12.3
8b	128.4	106.1	12.9
8c	127.3	105.5	12.8
8d	127.8	105.4	12.3
8e	127.1	106.3	13.8
8f	127.3	106.4	14.1
8g	127.8	106.5	13.8
8h	[b]	107.1	14.2
8i	128.2	105.8	12.5
8j	126.5	105.4	12.3

[a] Chemical shifts in ppm relative to TMS in $CDCl_3$. [b] Overlapping with N-phenyl carbons.

Table 2. C-13 NMR assignments[a] of the N-substituent in amine 1, intermediate 5 and pyrrole 8 (Scheme 1)

N-Substituent	Comp.	C1	C2	C3	C4	C5	C6	Literature
	1a	46.3	143.2	127.0	128.3	126.5		11
	5a	54.6	b	b	b	b		
	8a	46.5	138.7	125.6	128.6	126.9		
	1b	146.9	115.0	129.2	118.1			12[a]
	5b	c	c	c	c			
	8b	139.0	128.2	129.1	127.6			
	1c	50.0[d]	31.4[d]	20.0				12[b]
	5c	59.0	30.1	20.7				
	8c	50.8	30.1	20.7				
	1d	55.2	47.0	142.8	128.1	128.5	126.4	
	5d	56.1	52.3	b	b	b	b	
	8d	52.1	49.1	141.9	128.4	128.5	126.8	
	1e	54.5	32.2	26.9				17
	5e	62.9	32.2	27.9				
	8e	54.1	34.8	28.7				
	1f	42.7	26.0					12[d]
	5f	50.3	23.5					
	8f	47.1	22.3					
	1g	25.6	51.3	147.9	126.6	128.3	126.4	12[b]
	5g	24.9	59.0	146.4	b	b	b	
	8g	19.4	52.5	142.7	128.8	128.4	126.7	
	1h	59.7	146.0	126.8	128.4	126.6		
	5h	67.6	145.2	127.5	128.4	127.0		
	8h	62.4	140.1	127.5	128.4	127.1		
	1i	143.1[e]	109.2	126.6[f]	118.1[d]	134.6[f]	125.7	12c
	5i	g	g	g	g	g	g	
	8i	135.8	123.3	h	h	h	h	
	1j	36.9[i]	19.1[j]					16
	5j	c	c					
	8j	38.0	16.2					

[a] Chemical shifts in ppm relative to TMS in $DCCl_3$. [b] Overlapping with product. [c] No intermediate detected at 22 °C or -15 °C. [d] 0.4 ppm upfield of literature. [e] 0.9 ppm downfield of literature. [f] 0.3 ppm downfield of literature. [g] C_1-C_{10} are overlapping with starting material. [h] C_3-C_{10} are overlapping. [i] 1.0 ppm downfield of literature; [j] 1.4 ppm downfield of literature; literature values are of neat liquid.

Table 3. C-13 NMR assignments of N-substituted imines 5 (Scheme 1)[a] (other than those of N-substituent)

Comp.	C1	C2	C3	C4	C5	C6
5a	b	b	38.5	35.5	b	18.8
5b	c	c	c	c	c	c
5c	29.9	207.8	38.7	35.6	166.6	18.0
5d	30.0	206.8	38.4	35.3	167.7	18.3
5e	30.0	206.9	38.3	35.4	165.8	18.0
5f	30.3	207.9	39.0	35.7	164.1	17.2
5g	30.2	208.0	38.7	35.7	165.7	17.9
5h	30.1	207.9	38.5	35.8	167.7	18.6
5i	30.2	208.0	38.4	36.0	166.0	20.3
5j	c	c	c	c	c	c

[a] Chemical shifts in ppm relative to TMS in $CDCl_3$. [b] Imine concentration too low to be observed. [c] No intermediate observed at 22 °C or -15 °C.

The ^{13}C NMR assignments of the intermediates are given in Tables 2 and 3. The N-substituent chemical shifts are essentially the same as those in the amine 1 (Table 2) with the singular exception of C1, which in each case is in the pyrrole *ca.* 5-10 ppm downfield from the corresponding amine, reflecting the change in hybridisation at the nitrogen; i.e. sp^3 (amine) ---> sp^2 (imine). In confirmation, the characteristic C=NR of the imine 5 carbon is seen in the range 164.1-167.7 ppm (Table 3), (expected: 160-170 ppm).[14b] The two methylenes C3 and C4, (Scheme 1) always straddle the shift of the methylene in acetonylacetone. No peaks for enamine 6 (Scheme 1) sp^2 carbons, C4 and C5 (expected in the region 100-150 ppm),[13c] nor for the sp^3 pyrrolidine 4 carbon C2 (70-140 ppm),[13b] were ever observed.

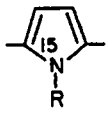
N-15 Assignments

Table 4 gives the ^{15}N-resonances in the reactions of *neo*-pentylamine (1e) and *iso*-butylamine (1c) with acetonylacetone 2. Both amines resonate upfield (expected in the region -300 to -400 ppm),[15a] characteristic of a pure sp^3-nitrogen. In contrast, the pyrrole nitrogens are *ca.* 150 ppm downfield from the amines (-150 to -250 ppm)[15a] because of the partial double bond character of the C-N bond. The isolated peaks at -67.4 ppm and -70.5 ppm are characteristic of the precisely sp^2-hybridised nitrogen (-30 to -80 ppm)[15a] in imines (the sp^3-N of diol 4 is expected at ca -300 to -400 ppm[15a]). This confirms the C-13 assignments.

^1H Assignments

Table 5 gives the ^1H-chemical shifts and assignments of the amines 1c and 1e (Scheme 1). The diketone 2 chemical shifts are 2.65 ppm (CH_2) and 2.12 ppm (CH_3); all peaks are in good agreement with the literature.[20] The ^1H-chemical shifts and assignments of the N-substituents of the pyrroles 8c and 8e are given in Table 5. For the H(3,4), (8c) and (8e) show peaks at 5.68 ppm (s) and 5.72 ppm (s), respectively. For the 2,5-Me groups, peaks for 8c and 8e are found at 2.15 ppm (s) and 2.18 ppm (s), respectively. The values for 8c are in broad agreement with those previously assigned by one of us.[8] The N-substituent methylene peaks (H-1; Table 5) undergo a downfield shift (1.0 - 1.2 ppm) in going from amine 1 to pyrrole 8, due to the diatropic ring current of the latter;[7b] the other N-substituent peaks are relatively unaffected (Table 5).

Table 4. ^{15}N-NMR assignments of the Paal-Knorr reaction (Scheme 1)[a]

R	$R^{15}NH_2$	^{15}N of imine	
Me_3CCH_2	-366.2[b]	-67.4	-223.1
Me_2CHCH_2	-361.6[c]	-70.5	-223.9

[a] Chemical shifts in ppm upfield of CH_3NO_2 in d_6-dmso. [b] Literature[14b]: -368.7 ppm in methanol; -367.6 ppm in cyclohexane. [c] 0.4 ppm downfield of literature[14b]; literature values are of neat liquid.

Table 5. H-1 NMR assignments[a] of N-substituent in amine 1, intermediate 5 and pyrrole 8 in the Paal-Knorr reaction (Scheme 1).

Comp.	$N\text{-}CH_2CHMe_2$			Comp.	$N\text{-}CH_2CMe_3$	
	H-1	H-2	H-3		H-1	H-3
(1c)	2.49(d; $^3J_{1,2}$=6 Hz)	1.57[b]	0.90 (d; $^3J_{3,2}$=9 Hz)	(1e)	2.39 (s)	0.85 (s)
(5c)	2.97(d; $^3J_{1,2}$=6 Hz)	c	0.89 (d; $^3J_{3,2}$=9 Hz)	(5e)	2.87 (s)	0.89 (s)
(8c)	3.30(d; $^3J_{1,2}$=9 Hz)	1.96[b]	0.87 (d; $^3J_{3,2}$=6 Hz)	(8e)	3.55 (s)	0.96 (s)

[a] Chemical shifts in ppm relative to TMS in $CDCl_3$. [b] Binomial nonet ($^3J_{2,1}$=$^3J_{2,3}$=7Hz). [c] Overlapping with starting material.

The ^{1}H-chemical shifts and assignments of the intermediate 5 are given, for the N-substituent, in Table 5. Additionally, 5c and 5e each show two methyl peaks at 2.15 ppm (s) (MeC=O) and 1.77 ppm (s) (MeC=N), and at 2.14 ppm (s) (MeC=O), and 1.76 ppm (s) (MeC=N), respectively. Thus, with the exception of the methylenes H-3 and H-4 which are overlapping, all the proton resonances are well resolved. Little change occurs in the ^{1}H-chemical shifts of the N-substituent in going from amine 1 to imine 5 (Table 5), with the exception of the N-methylenes (H-1; Table 5) which are *ca.* 0.5 ppm downfield in the latter, reflecting the change in hybridisation at the nitrogen. The doublet at 2.96 - 2.98 ppm, assigned previously to the N-methylene protons in the pyrrolidine 4[8] is now assigned to the same protons in the imine 5 (Table 5). Further confirmation is provided by the characteristic methyl singlets H-1 and H-6 (see above), which resonate in the expected regions.[16b] The ^{1}H-analysis therefore confirms the ^{13}C- and ^{15}N- results.

Discussion

Reasonable mechanistic pathways for the transformation of diketone and amine into the pyrrole are set out in Scheme 1. As the imine is the only intermediate observed, and as the imine can be observed in the presence of both starting materials and products, it follows that there are two rate-determining steps in the reaction sequence, one *preceding* imine formation and the other *succeeding* it. The first slow step must be the *intermolecular* nucleophilic attack 1 + 2 --> 3. This is consistent with Jencks' observation[18] that carbinolamines 3 readily eliminate water to give the thermodynamically more stable imines 5, and the observation made by one of us[6a] that in acidic media carbinolamine 3 formation is exclusively rate-determining.

The subsequent mechanistic pathway could be (a) 5 --> 3 --> 4 --> 7 --> 8 *or* (b) 5 --> 6 --> 7 --> 8. As intermediate 7 is not detected, step 7 --> 8 must in either case be fast as is expected because of the aromaticity of 8.[7b] If pathway (a) applies, the absence of the detectable concentrations of 4 implies either (i) that $k_{(4\text{-->}7)} >> k_{(3\text{-->}4)}$ or (ii) that $k_{(4\text{-->}3)} >> k_{(3\text{-->}4)}$. Neither (i) nor (ii) appears likely as in several cases where cyclic diols have been demonstrated[21,22,23] to lie on the reaction pathway in heterocyclic ring closures elimination from the diols is slower than diol formation. Hence we believe the second slow step to be the *intramolecular* nucleophilic attack (6 ---> 7). Our failure (and that of Broadbent's[4]) to detect the enamine 6 is consistent with the fact that the equilibrium 5 ---> 6 lies almost entirely to the left[7c,19] (implying a low, steady-state concentration of the enamine 6).

Table 6 gives the approximate half-lives (obtained from ^{13}C NMR peak heights) for the formation ($t_{1/2}$) and subsequent reaction ($t'_{1/2}$) of the imine (5). The data show clearly that steric hindrance in the N-substituent has a rate reducing effect on both *formation* and *disappearance* of imine 5. The observation [6a] that as the pH of the medium is raised, the rate-determining step changes, with a concomitant decrease in the order of the reaction (from 2 in acidic media to 1 in alkaline media, with a fractional order pertaining at intermediate pHs), is also consistent with our scheme.

Table 6. Approximate half-lives for the formation ($t_{1/2}$), and reaction ($t'_{1/2}$), of the intermediate 5 in the Paal-Knorr reaction (Scheme 1) at 22 °C.

R		$t_{1/2}$(hrs) (1 → 5)	$t'_{1/2}$(hrs) (5 → 8)	R		$t_{1/2}$(hrs) (1 → 5)	$t'_{1/2}$(hrs) (5 → 8)
$PhCH_2$-	(5a)	<0.05[a]	0.2-0.5[a]	Me_2CH-	(5f)	12 - 15	20 - 50
Ph-	(5b)	b	2 - 3	PhCH(Me)-	(5g)	12 - 13	20 - 30
Me_2CHCH_2-	(5c)	0.2-0.5	1 - 2	Ph_2CH-	(5h)	0.1- 0.4	0.5- 2
Ph_2CHCH_2-	(5d)	0.1-0.4	0.5-2	1-naphthyl-	(5i)	10 - 15	70 - 90
Me_3CCH_2-	(5e)	1-2	10 - 15	Et-	(5j)	b	<0.05[a]

[a] Half life at -29 °C. [b] Intermediate not seen.

Experimental

All reagents were obtained from Aldrich and used without further purification.

^{13}C-Spectra were recorded at 22 °C on a JEOL FX-100 spectrometer at 25.1 MHz. TMS in $CDCl_3$ (25% V/V) was the internal reference. The spectral window was 6002 Hz with 8K data giving a digital resolution > 1.5 Hz per point. A pw of 19 micro s (90°) with 1s pd and 0.68s aquisition time was used; accumulations varied from 500 to 2000 giving a typical signal:noise ratio > 10^3:1.

^{15}N-Spectra were recorded at natural abundance at 22 °C on a Nicolet NT 300 at 30.4 MHz with a 24 micro s (65.5 °) pw, 0.82s aquisition time and 6s pd in d_6-dmso as solvent and internal lock; CH_3NO_2 was the external standard. The sweep width of 20kHz with 32K data points gave a digital resolution of 1.2 Hz per point. Typically, 10^4 accumulations were taken for each spectrum giving a signal:noise ratio of ca. 10:1.

^1H-Spectra were recorded at 22 °C on a Nicolet NT 300 at 300.1 MHz using a 5 micro s (45°) pw with a 1s pd in $CDCl_3$ as solvent and internal lock. The spectral window was 3000 Hz with 32K data and an aquisition time of 5.65s giving a digital resolution of 0.18 Hz per point. Accumulations varied from 50-100, giving a typical signal:noise ratio > 10^3:1.

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