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A NEW PYRIDINE SYNTHESIS FROM CONJUGATED ACETYLENES AND SUBSTITUTED METHYLAMINES

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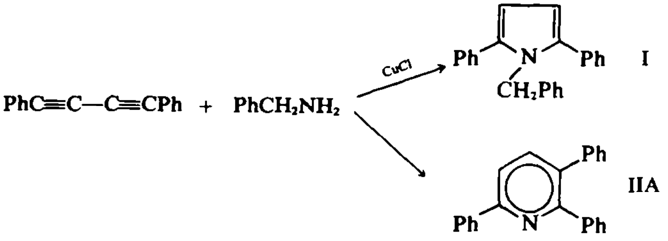
Abstract—Conjugated acetylenes $R{-}C{\equiv}C{-}C{\equiv}C{-}R$ react with substituted methylamines $R'CH_2NH_2$ at 145–180° to produce corresponding pyridines and/or the corresponding pyridine N-oxides when the reaction is carried out in the presence of air or dimethylsulfoxide. For R = Ph and R' = cyclo C_6H_{11}, n C_8H_{17} and $PhCH_2$, 2,5-diphenylpyridine was also formed, in the last case as the dominant product. For $R = PhOCH_2$ and R' = Ph, equivalent amounts of 2-phenyl-3-methyl-6-phenoxymethylpyridine and 2-phenyl-3-phenoxymethyl-6-methylpyridine were formed together with phenol. These results indicate formation of dihydropyridines and their oxidation via radical intermediates.

We have previously reported[1] that in the preparation of N-benzyl-2,5-diphenyl pyrrole I via reaction (1)[2] an unexpected by-product was 2,3,6-triphenylpyridine **IIA**. The yield of **IIA** was found to increase as the concentration of cuprous chloride was decreased.

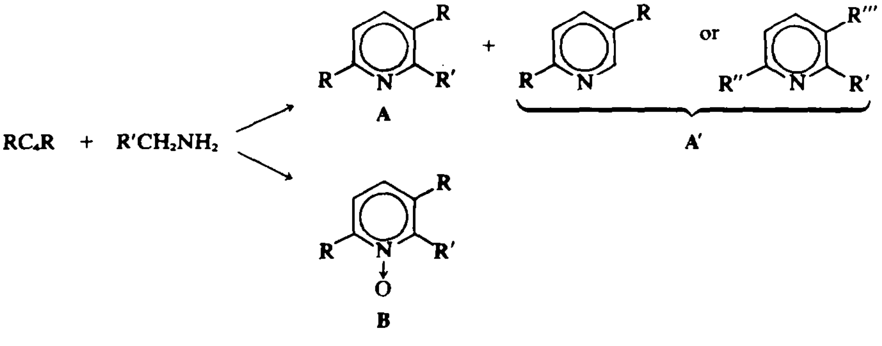


(1)

(2)

We have now investigated this new pyridine synthesis and found that in addition to the 2,3,6-trisubstituted pyridine (**A** in reaction 3), lower molecular weight pyridines **A'** may be formed depending on the nature of the substituents R & R'. Further, in the presence of air or an oxidant the 2,3,6-trisubstituted pyridine N-oxide **B** corresponding to **A** is also produced.

These results are rationalized in terms of a mechanism involving the intermediacy of dihydropyridines which can aromatize by a variety of paths including radical elimination.



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EXPERIMENTAL

Reactions were carried out using an excess of amine as previously described[1] (method a) or in the additional presence of dimethylsulfoxide (method b) as in the following example. Details of other experiments are noted in the tables.

2-*p*-*Tolyl*-3,6-*Diphenylpyridine* (IIIA)

Diphenylbutadiyne, 3 g (14·9 m mole) was heated to 145° (oil bath) under nitrogen with 5 ml dimethylsulfoxide and 10 ml 4-methylbenzylamine while stirring magnetically. The reaction was stopped after 3½ h when the conversion of diphenylbutadiyne exceeded 98%. The product mixture was diluted to 300 ml with benzene and the excess amine successively extracted with three 300 ml portions of 0·1% aqueous sodium chloride containing (a) 16 ml glacial acetic acid, (b) 5 ml acetic acid, (c) nil. On evaporation, the benzene solution gave 4·6 g of crude product which was dissolved in 50 ml hot carbon tetrachloride, filtered and cooled to give 1·8 g (38%) of 2-p-tolyl-3,6-diphenylpyridine N-oxide **III B**. The filtrate was then evaporated down and the product recrystallized from methanol to give 2·4 g (51%) of a different white crystalline solid identified as **III A**.

RESULTS

The reaction between diphenylbutadiyne and benzylamine was studied in the greatest detail. The acetylene and the product were monitored by GLPC. On a silicone gum column, the retention times were in the order 2,3,6-triphenylpyridine N-oxide **II B** > 2,3,6-triphenylpyridine **II A** > N-Benzyl-1,2,5-diphenylpyrrole **I**. The effect of cuprous chloride concentration has previously been discussed.[1] Its presence did not effect the rate of formation of **II A** so that (1) and (2) appear to be competing reactions in its presence. Addition of dimethylsulfoxide (DMSO) significantly increased the rate of conversion of the acetylene by reaction (2).

Thus in experiment 1 (Table 1), the conversion of acetylene was ~95% after 30 minutes, while this point was not reached in experiment 4 until 105 minutes.

Use of DMSO resulted in the formation of the pyridine N-oxide, however. Since the formation of **II A** suggested a dehydrogenation, it was hoped that the use of one equivalent of DMSO as in Expt 3 would result in a high yield of **II A** without the formation of **II B**, but this was not the case. Reaction mixtures containing no DMSO were examined for hydrogenation products of diphenylbutadiyne but none were found. The initial hydrogenation products would be cis and trans diphenylbutenyne which would be in thermal equilibrium at the reaction temperature of 180°. No significant reaction was found when trans diphenylbutenyne was heated for several hours with excess benzylamine.*

The formation of pyridine N-oxide occurred not only in the presence of DMSO but even in the presence of traces of air. When the reaction was carried out under a blanket of nitrogen using a nitrogen bypass connected to a bubbler to prevent back diffusion, no N-oxide was found. When the bubbler was disconnected however a product ratio of **II A**/**II B** = 10 was obtained in spite of the nitrogen bypass which must have allowed a very low concentration of air to diffuse back to the reaction vessel. This suggests that **II B** resulted from the oxidation of a highly reactive intermediate. The ratio of **II A**/**II B** was not significantly changed however, by carrying out the reaction in air. Thus, if **II B** is formed by the oxidation of some intermediate involved in the reaction to form **II A**, then **II A** must also be formed by other paths involving species which are not oxidized to **II B**. The yield of **II B** was increased somewhat by the presence of an oxidant (DMSO) and here too it must result from the oxidation of an intermediate since **II A** was found to be quite stable to DMSO as well as air even at 185°.

Table 1 suggests that the appearance of the N-

Table 1. Effect of dimethylsulfoxide on the reaction between benzylamine and diphenylbutadiyne

Expt.	Ratio of DMSO/acetylene (moles/mole)	Reaction conditions[a]	Yields of products[b] (%)	
			(II A)	(II B)
1	5	1 hr 185°	44	0
2	1·4	4 hr 145°	42	15
3	1·0	5 hr 145°	45	28
4	0	2-1/2 hr 185°	33	0

[a] In each case 3 g diphenylbutadiyne was reacted with 10 ml benzylamine and the reaction stopped when the acetylene conversion (monitored by GLPC) exceeded 98%.

[b] These are yields of isolated products.

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*A referee has suggested that pyridine formation results not from a disproportionation but from an oxidation by traces of oxygen contained in the nitrogen used to blanket the reaction. Our observations would be consistent with this possibility.

oxide correlates with the temperature at which the reaction is carried out. The absence of N-oxide at the higher temperature was subsequently shown to result from its reaction with benzylamine in the presence of DMSO. The effect is noticeable at the lower temperature for long reaction times (Table 2). At the highest temperature of experiment 1, the ratio of **II A**/**II B** was already 12·5 after 1½ h and increased more rapidly with time. When **II B** was heated with benzylamine in the presence of DMSO its concentration decreased at a corresponding rate. The products of this reaction were not investigated beyond establishing that **II A** was not a product.

Table 2. Dependence of ratio of products on reaction time for experiment 2.

Reaction time (h)	Ratio (II A)/(II B)[a]
3	2·7
4–1/2	4·2
7–1/4	5·3

[a] Ratio of GLPC areas (2 foot silicone gum, 300°).

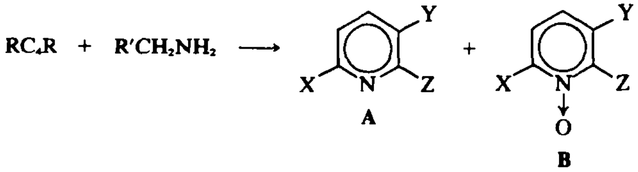
The scope of the reaction was then investigated by varying the conjugated acetylene and the amine. Reactions were carried out in both (a) the absence and (b) presence of DMSO. The N-oxides appeared as partial products when the reaction was carried out in the presence of air or DMSO. Table 3 lists the products found when R & R′ were varied for reaction (4) which is a convenient generalization of reaction (3).

Initially the expected pyridines were those corresponding to R=X=Y & R′=Z as in reaction 2. Table 3 shows that experiments 6, 7, 8 & 11 also produced other unexpected pyridines.

The introduction of methyl substituents on the phenyl groups of diphenylbutadiene or benzylamine introduced no complication (experiments 5 and 9). Reaction 2 also appears to be applicable to monosubstituted methylamines as in experiments 6, 7, and 8, however, in all three cases 2,5-diphenylpyridine was an unexpected by-product. Variation of R also produced a surprise in experiment 11 where phenol was produced in addition to a pair of isomeric pyridines of unexpected structure. In experiment 10 the expected product was formed but only slowly at high temperature.

Proton Magnetic Resonance ($CDCl_3$)

The trisubstituted pyridines gave aromatic absorptions in the range 8·4 to 7·0 δ. **IV A′** however, gave an additional quartet at 8·87 δ attributed to the proton on the 2 position of the pyridine ring ($J_{2,4}$ = 2·5 Hz, $J_{2,5}$ = 1·0 Hz). In the aliphatic region, methyl singlets were found at 2·2 and 2·4 δ **VI A**, 2·35 δ **III A**, 2·30 δ **III B**, 2·5 δ and 2·2 δ **VII A**, 2·2 δ **VIII A′** and 2·5 δ **IX A′**. Methylene singlets were observed for **VIII A′** and **IX A′** at 5·05 and 4·77 δ respectively.



(4)

Table 3. Examples of reaction 3.

Expt.	Reactants R	R′	Conditions time (min.) temp.	Product[c]	Substituents X	Y	Z	Yield[d] %
5	Ph	$pMeC_6H_4$	210/145°[b]	**III A**	Ph	Ph	$pMeC_6H_4$	51
				III B	Ph	Ph	$pMeC_6H_4$	38
6	Ph	cyclo C_6H_{11}	300/145°[a]	**IV A′**	Ph	Ph	H	23
				IV B	Ph	Ph	cyclo C_6H_{11}	10
7	Ph	nC_8H_{17}	120/180°[b]	**V A**	Ph	Ph	nC_9H_{15}	41
				IV A′	Ph	Ph	H	12
8	Ph	$PhCH_2$	580/145°[a]	**IV A′**	Ph	Ph	H	59
9	$mMeC_6H_4$	Ph	80/185°[b]	**VI A**	$mMeC_6H_4$	$mMeC_6H_4$	Ph	30
10	Me	Ph	360/185°[b]	**VII A**	Me	Me	Ph	5
11	$PhOCH_2$	Ph	60/185°[a]	**VIII A′**	$PhOCH_2$	Me	Ph	25
				IX A′	Me	$PhOCH_2$	Ph	25

[a] Absence of DMSO.
[b] Presence of DMSO.
[c] "A" Products are pyridines & "B" products are N-oxides as in reaction (4).
[d] Isolated yields.

All compounds listed in Table 3 gave the correct integrations.

^{13}C *Magnetic Resonance*

The values for the pyridines synthesized are given in Table 4 together with some standard pyridines used to make assignments. The number of resolvable carbons was less than that required in the following cases: VI A (19 out of 21), III A (16 out of 17), IV A′ (12 out of 13). The values for the phenyl substituted 1 and 6 positions were readily distinguishable being furthest downfield in the range 154–157 ppm. The unsubstituted 2 position in IV A′ was also obvious at 148·4 ppm which is within the expected range of 145–150 ppm. The unsubstituted 5 position was also apparent in the substituted compounds and was in the range 117·0–120·4 ppm which compared with 115·9–122·6 ppm. in the standards. The unsubstituted 4 position and the phenyl substituted 3 position over-lapped with the range for the substituted phenyl carbons however. The values for the pyridine N-oxides were consistent with the structures assigned. ^{13}C chemical shifts relative to TMS were in the range 156–136 ppm (tertiary carbons), 131–125 ppm (phenyl & pyridine carbons) and 42–21 ppm (aliphatic carbons).

Mass Spectra

The parent ion M^+ was identified for all of the compounds described. The doubly charged parent M^{++} was also prominent. Compounds with methyl substituents on a benzene or pyridine ring also gave a large M-1 peak which in some cases was larger than the parent. In these cases, the spectra were also run at low ionizing voltages to obtain a more normal ratio for the M to M-1 peaks. Compounds VIII A′ and IX A′ showed very large peaks at (M-93) due to loss of phenoxy. In addition they sometimes showed an unusual peak at 2M-94 (456). This peak was found at 50° and an ionizing voltage of 70 eV but decreased as the temperature was raised.

Table 4. ^{13}C Chemical shifts for various pyridines[a]

Compound	Positions on the pyridine 2	3	4	5	6	Tertiary phenyl carbons	Other phenyl carbons	Aliphatic
Pyridine	150·6	124·5	136·4					
4-Phenylpyridine	150·0	120·6	147·0			137·3	126·8–128·7(3)	
3,5-Phenylpyridine	145·6	*b*	131·4			135·3 136·5	126·0–127·8(3)	
2,4,6-Triphenylpyridine	156·3	115·9	149·2			137·7 138·5	126·4–128·4(6)	
II A	154·9[c]	133·7	138·7	117·4	155·9[c]	138·3–139·7(3)	126·2–129·4(6)	
III A	154·1[c]	*b*	137·3	117·0	155·0[c]	133·1–139·5(5)	125·8–129·1(7)[d]	20·0
IV A′	148·4	*b*	135·2	120·4	156·3[c]	138·1, 139·4[d]	127·1–129·4(6)	
V A	155·5	*b*	138·7	117·6	159·5[c]	*e*	*e*	*e*
VI A	153·9[c]	*b*	138·1	117·2	155·0[c]	133·3–139·7(6)	122·8–128·9(9)[f]	20·0
VII A	155·7	*b*	139·0	121·9	158·1[c]	141·6[d]	129·4, 128·3, 128·0	24·2, 19·6
VIII A′	159·0	*b*	139·5	115·1	154·8[c]	149·2, 141·0, 139·5	129·5–120·0(6)	70·8, 19·3
IX A′	158·8	*b*	138·4	115·1	157·9[c]	140·3, 138·4[d]	129·7–121·2(6)	67·4, 23·8

[a] In CD_2Cl_2, ppm versus TMS (XL 100).
[b] This value was indistinguishable from the phenyl tertiary carbons and is included with them.
[c] The values for these 2 and 6 carbons are indistinguishable and assigned arbitrarily.
[d] One absorption not resolved.
[e] This compound was contaminated with some of the corresponding N-oxide and assignments could not be made.
[f] Two absorptions not resolved.

Table 5. Elemental analyses

Compound		Calculated (%) C	H	N	Found (%) C	H	N	mp °C
I	$C_{23}H_{17}N$	89·86	5·58	4·56	89·6	5·7	4·7	111–2
II B	$C_{23}H_{17}NO$	85·42	5·30	4·33	84·7	5·3	4·4	202–3
III A	$C_{24}H_{19}N$	89·68	5·96	4·36	89·6	6·1	4·1	145–6
III B	$C_{24}H_{19}NO$	85·43	5·68	4·15	85·3	5·6	4·7	202–4
IV A′	$C_{17}H_{13}N$	88·28	5·67	6·06	88·8	5·8	6·0	171·5–2·5[a]
IV B	$C_{23}H_{23}NO$	83·85	7·04	4·25	84·0	6·8	4·3	148·5–9·0
VI A	$C_{25}H_{21}N$	89·51	6·31	4·18	89·3	6·2	4·2	80
VIII A′ and IX A′	$C_{19}H_{17}NO$	82·88	6·22	5·09	82·3	6·3	5·1	*b*

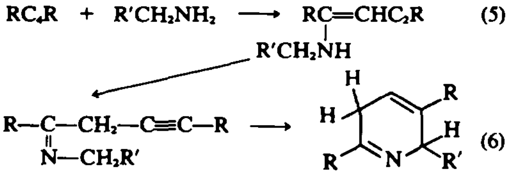
[a] Lit [3]171.
[b] Not separable.

It was attributed to a reaction in the ionizing chamber.

DISCUSSION

The results in Table 3 show that reaction 2 may be applied to other substituted methylamines and many conjugated acetylenes except probably those with simple dialkyl substitution (experiment 10). It should be remembered that product yields were considerably affected by the variable ease of isolation. The formation of unexpected pyridines in many of the experiments however, suggests that a better understanding of the mechanism of the reaction could lead to the synthesis of a wider variety of pyridines than those whose pattern of substitution corresponds to reaction 2.

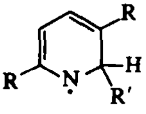
It was suggested earlier that the formation of II A could best be accounted for by the oxidation of an intermediate dihydropyridine formed by reactions 5 and 6.



$$RC_2R + R'CH_2NH_2 \longrightarrow \underset{R'CH_2NH}{RC{=}CHC_2R} \qquad (5)$$

(6)

Oxidation of the dihydropyridine would produce a variety of radicals such as **1**, **2**, **3**, **4** etc.



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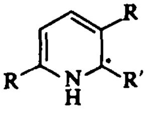

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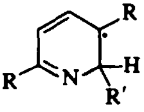

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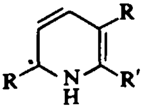
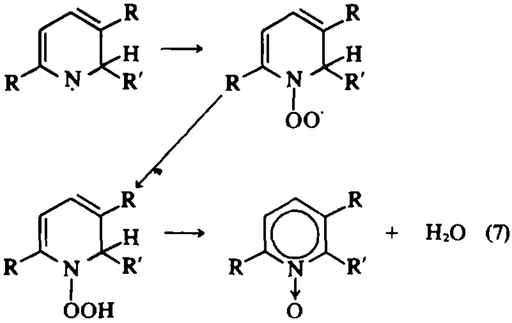
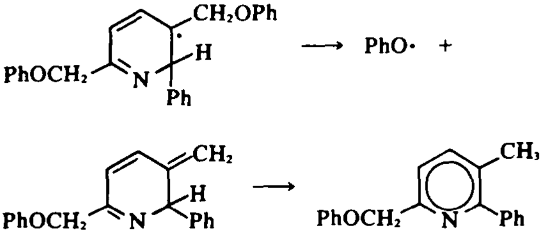


4

Disproportionation or further oxidation of these radicals would then give the normal pyridine such as II A. Some addition of oxygen might be expected as a competing reaction however (7) and would account for the formation of pyridine N-oxides.



The formation of unexpected pyridines can be accounted for by elimination of radicals from intermediates **1**–**4**. Thus when R = Ph and R' = n heptyl, cyclohexyl or benzyl, **2** can eliminate R˙ to give 2,5-diphenylpyridine. The formation of this product should therefore be enhanced by the stability of the expelled radical R'. This consideration lead to the choice of phenethylamine which gave the highest yield of 59% in experiment 8. Formation of VIII A' and IX A' can be accounted for in a similar manner by elimination of the phenoxy radical from **3** and **4** in reactions such as (8).



(8)

Clearly, aromatization to produce pyridines of specific structure can be promoted by the stability of the radicals expelled from slected substituents.

REFERENCES

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