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A NEW PYRIDINE SYNTHESIS AND ITS REDIRECTION TO A PYRROLE SYNTHESIS WITH CUPROUS CHLORIDE

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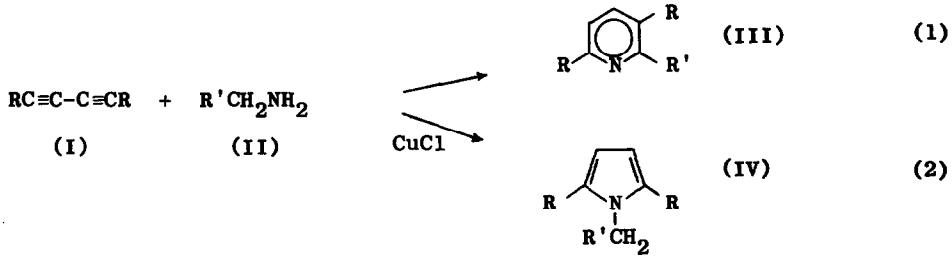
When solutions of diphenylbutadiyne (Ia) in benzylamine (IIa) (15-30% w/v) were refluxed for two to three hours under nitrogen, 2,3,6-triphenylpyridine (IIIa) was obtained in yields of 50 to 70% based on (Ia) (Eq. 1). This discovery was unexpected in that a pyrrole synthesis is based on the reaction between conjugated diynes and amines in the presence of small amounts of cuprous chloride (Eq. 2). In particular, (Ia) and (IIa) were reported to give



N-benzyl-2,5-diphenylpyrrole (IVa) in 87% yield by this route.[1] Reaction (1) is of interest in that it provides a particularly simple pyridine synthesis since conjugated acetylenes are readily prepared by the catalytic oxidative coupling of acetylenes.[2]

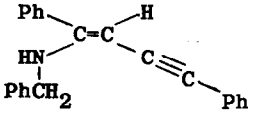
Although Eq. 2 is reported to require only 0.1 mole % catalyst, it was found that both (IIIa) and (IVa) were formed in the presence of cuprous chloride as illustrated in Table I. Absence of catalyst (experiment 4) gave only (IIIa) in 70% yield after 2 1/2 hours at 180°. A 60% yield of (IVa) was obtained in experiment 1, however, using 25 mole % catalyst after 3 hours at 150°. Thus

TABLE I

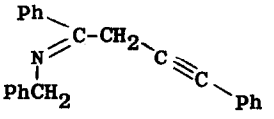
Dependence of Product on Reactant Ratio and Copper Concentration

Experiment	PhC_4Ph (m·mole)	$PhCH_2NH_2$ (m·mole)	CuCl (m·mole)	Ratio (IIIa/IVa)
1	20	20	5	0.1
2	20	20	0.2	2
3	15	92	0.2	7
4	15	92	0	>100

coordination of the reactants to cuprous chloride completely changes the nature of the cyclization. A probable reason for this becomes evident when one considers the possible function of the catalyst in the pyrrole synthesis. A redox function for the copper catalyst is unlikely since the reactions were carried out under nitrogen and the color of cupric species was absent. The ability of cuprous salts to coordinate both acetylenes and amines however would be sufficient to cause catalysis by virtue of bringing the reactants into close proximity resulting in a more favorable entropy term. A plausible intermediate in the pyrrole cyclization is (A), while either (A) or better its isomer (B) has an active benzylic CH_2 whose addition to the triple bond would lead to a dihydropyridine. Coordination of both nitrogen and acetylene to cuprous chloride should facilitate only the former process and may actually hinder the latter.



(A)



(B)

Under the conditions of the reaction, a dihydropyridine would be expected to polymerize[3] or lose hydrogen to some substrate and form (IIIa). Gel permeation chromatography revealed the presence of higher molecular weight products in the pyridine synthesis corresponding to a dimer and trimer of (IIIa). Although their structure was not determined, it was established by H^1 NMR that these reaction products were also composed of equimolar amounts of amine and acetylene when R = m $CH_3C_6H_4$ and R' = C_6H_5 or when R = C_6H_5 and

R' = p $CH_3C_6H_4$. The reaction mixture was examined for evidence of hydrogenated products of (Ia), but none were found. Hydrogenolysis of (IIa) is an alternative possibility. In a sealed tube experiment (R = Me, R' = Ph), a gas smelling strongly of ammonia was evolved on opening the tube. In experiments carried out in air, it seems likely that oxygen is the oxidant. The use of secondary amines in place of benzylamine should produce more stable dihydropyridines. When N-methylbenzylamine was reacted with (Ia), products were isolated whose NMR spectra were consistent with a mixture of the various possible dihydropyridines.

The initial step in the formation of (A) or (B) is likely to be a nucleophilic attack of amine on the acetylene. Consistent with this, addition of dimethylsulfoxide was found to enhance the rate of pyridine formation while the presence of oxygen or a free radical inhibitor, 2,6-di-t-butyl-4-cresol, had no effect. The presence of dimethylsulfoxide does lead to some oxidation of pyridines to pyridine N-oxides, however. The scope of the synthesis is presently under investigation. Preliminary results show that pyridine formation also proceeds readily for substituted aromatics, e.g., R = m $C_6H_4CH_3$, R' = p $C_6H_4CH_3$. For alkyl substituted reactants, e.g., R = methyl, R' = cyclohexyl, pyridines have as yet been isolated only in low yield.

In experiment 1, 3.03 g (Ia) were refluxed in 10 ml benzylamine. During the reaction glpc showed the gradual disappearance of (Ia) and the formation of a single high boiling product. After 2 1/2 hrs, the solution was diluted with 100 ml benzene and the excess benzylamine extracted with 100 ml 15% aqueous acetic acid followed by 100 ml 3% aqueous acetic acid, each containing 0.1 g sodium chloride. The benzene solution was then extracted four times with the following mixture: 20 ml conc. HCl, 80 ml MeOH and 10 ml H_2O. The combined HCl extracts were then neutralized with an excess of NaOH and extracted with chloroform. On evaporation, the chloroform gave 3.2 g of (IIIa) which was recrystallized from ethanol. Both (IIIa) and (IVa) gave satisfactory elemental analyses, but (IIIa) was best distinguished from (IVa) by its mass spectrum (Parent ion of (IIIa) is 307, (IVa) is 309) and by NMR. The proton

NMR of (IIIa) gave only complex absorptions in the region 8.4 to 7.0 δ, whereas (IVa) gave a vinyl absorption at 6.4 δ and a benzylic CH_2 absorption at 5.2 δ. The C_{13} NMR spectrum of (IIIa) (natural abundance) further showed the expected 17 line spectrum while (IVa) gave only the expected 11 absorptions; m.p. (IIIa) 111-112° (lit.[4] 115°), picrate 168-169° (lit. 163°).

References

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