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PROPOSED RADICAL PATHWAY FOR THE ADDITION OF ALLYL GRIGNARD REAGENTS TO CONJUGATED ANILS

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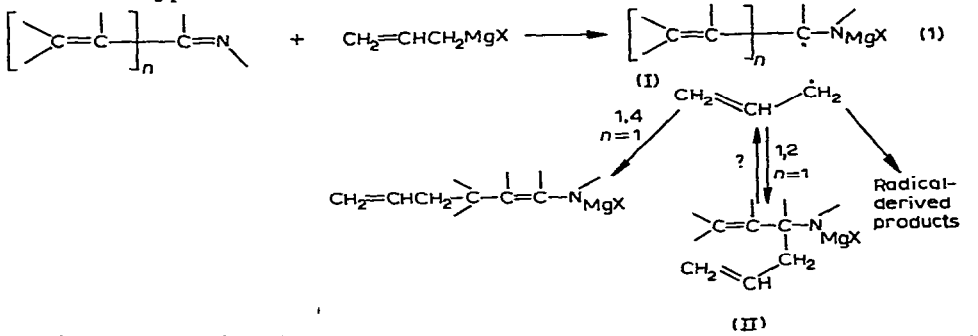
SUMMARY

The products from the individual reactions of allylmagnesium bromide with 2-styrylpyridine, with 4-styrylpyridine and with α-allylbenzhydrylaniline, respectively, were examined, in order to test the possible role of electron-transfer processes both in the addition and elimination steps of Grignard reagent–anil interactions. In contrast with the smooth 1/1 adduct of the Grignard reagent with the exocyclic double bond of 2-styrylpyridine, the corresponding reaction with 4-styrylpyridine led principally to oligomeric and/or polymeric adducts. Moreover, heating α-allylbenzhydrylaniline in benzene with an excess of the Grignard reagent led to benzhydrylaniline, suggestive of C–C bond homolysis. The results, taken together with other information on Grignard reagent–anil interactions, are consistent with a radical mechanism, possibly initiated by electron transfer.

Allylic Grignard reagents, exemplified by allylmagnesium halide, diallylmagnesium, benzylmagnesium halide and the ambidentate butenylmagnesium system, display the greatest reactivity among organomagnesium compounds in additions to C=O[1], C≡N[2], and even C=C[3] or C≡C[4] linkages. Steric factors in the substrate which often decisively prevent 1,2-addition with typical Grignard reagents are far less important with allylic Grignard reagents. Thus, acetomesitylene, $C_6H_2(CH_3)_3COCH_3$, does not add methylmagnesium halides, but rather is converted into its enolate salt[5], $C_6H_2(CH_3)_3C\overset{OMgX}{\underset{CH_2}{<}}$; on the other hand, this ketone undergoes prompt 1,2-addition[6] with either benzyl or butenyl Grignard reagents*. Again, neither methyl Grignard reagent nor phenyl Grignard reagent reacts with benzophenone anil in ether at room temperature, but allyl Grignard reagent does add rapidly and quantitatively[8]. Similarly, high reactivity and insensitivity to steric hindrance characterize the additions of allyl Grignard reagents to other anils and aza-aromatic heterocycles[9,10]

* Recently Benkeser, Young and their coworkers[7] have shown that the butenyl Grignard reagent can, however, react preferentially to yield varying proportions of different 1,2-adducts, *i.e.*: (*a*) 1-methylallyl-; (*b*) *cis*-2-butenyl- and (*c*) *trans*-2-butenyl-carbinols. As the ketonic substituents were increased in bulk, the proportion of the crotyl carbinol increased, as well as the relative amount of its *trans* isomer. For example, ethyl isopropyl ketone gave (*a*), (*b*) and (*c*) in the ratio, 95/4/1; di-tert-butyl ketone gave 0/61/39.

Recent investigations have adduced a variety of evidence pointing to a radical pathway as a principal or important route in many organometallic reactions[11]. Consequently, we were prompted to examine certain reactions of allylmagnesium bromide with conjugated anils, in order to learn whether product analysis would afford any evidence pointing to free-radical intermediates. The proposed generation of radicals would ensue from an induced homolysis, analogous to the original Blicke–Powers[12] hypothesis:



Such an electron-transfer view rationalizes 1,2- and 1,4-additions by collapse of caged radicals (I) preferentially with each other[13]. Therefore, we chose to examine the individual behavior of 2-styrylpyridine and of 4-styrylpyridine toward allylmagnesium bromide, the first substrate to test a spatially feasible 1,4-addition, the second substrate to test the 1,6-separation of the reacting sites. Moreover, as a further test of the formation of (I), we have attempted to study the proposed reverse reaction (II) → (I) by heating *N*-(α-allylbenzhydryl)aniline with excess allylmagnesium bromide in benzene. By the principle of microscopic reversibility, the proposed process, (II) → (I), should shed light on the mechanism of addition suggested in eqn. (1). We now report that the allyl Grignard reaction products from both 4-styrylpyridine and *N*-(α-allylbenzhydryl)aniline are best explicable in terms of intermediate (I).

EXPERIMENTAL

All operations involved in the preparation and reactions of allylmagnesium bromide were conducted under an atmosphere of dry and oxygen-free nitrogen. The preparation of the Grignard reagent in ethyl ether was achieved in the usual manner[14] and employed the typical Grignard-grade magnesium. The desirability of using triply sublimed magnesium for this study did not seem great, since the possible role of radical processes in allyl Grignard reactions as ordinarily conducted was at issue.

The reactions solvents were chemically pure and were refluxed over and distilled from metal hydrides immediately before use. The 2- and 4-styrylpyridines were obtained from the Aldrich Chemical Company and used after verifying their purity. *N*-(α-Allylbenzhydryl)aniline was prepared and purified according to published directions[8].

Reaction of 2-styrylpyridine with allylmagnesium bromide: formation of 2-(2-phenyl-4-pentenyl)pyridine

A solution of 4.0 g (0.022 mole) of 2-styrylpyridine in 200 ml of anhydrous

ether admixed with 0.045 mole of allylmagnesium bromide in 55 ml of ether led, after 10 min, to the deposition of a brown precipitate. After the heterogeneous mixture was stirred for 4 days, the system was hydrolyzed with aqueous ammonium chloride solution. The organic extract, after drying with anhydrous calcium sulfate, revealed by GLC analysis only one product and no starting material. Removal of solvent and distillation under reduced pressure provided 3.5 g (70%) of 2-(2-phenyl-4-pentenyl) pyridine, b.p. (0.36 mm) 93–94°. (Found: C, 86.07; H, 7.72; $C_{16}H_{17}N$ calcd.: C, 86.05; H, 7.67%.) The infrared spectrum (neat) showed characteristic absorptions at 910 and 990 cm^{-1} (CH vinyl def.). The NMR spectrum (CCl_4, δ-scale) had absorptions at 2.52 (2H, mult.), 3.0 (3H, unsym. dbt.), 4.75–6.0 (3H, vinyl), 6.7–7.4 (8H) and 8.45 (1H, α, dbt.).

Reaction of 4-styrylpyridine with allylmagnesium bromide: formation of some 4-(2-phenyl-4-pentenyl)pyridine and higher molecular-weight products.

The reactants dissolved in ether were combined in the same amounts as with 2-styrylpyridine. Again a brown color developed immediately and an oily solid was gradually deposited upon the walls of the flask. After a 4-day stirring period the reacting mixture was hydrolyzed with aqueous NH_4Cl solution and the dried organic extract examined by GLC. Aside from small amounts of starting material, 4-(2-phenyl-4-pentenyl)pyridine (*cf. infra*) and a minor component having a retention time similar to this adduct, over 70% of the product was of higher molecular weight. This polymeric-like fraction came off >300° in a broad plateau, presumably because of gradual thermal degradation.

The reaction product was chromatographed on an alumina column, with petroleum ether/benzene eluting mixtures. The first fractions consisted principally of that volatile product component seen in GLC analysis. This product seems to be 4-(2-phenyl-4-pentenyl)pyridine based upon the following NMR data (CCl_4, δ-scale): 2.45 (*ca.* 2H, mult.), 2.9 (3H, apparent sing. with sh.), 4.85–6.1 (3H, vinyl), 6.9–7.3 (6.8H) and 8.45 (2H, α, mult.). However, the excessive absorption in the aryl region and additional peaks centered at 2.0 (*ca.* 2H), 1.3 and 0.9 (*ca.* 2H) must be ascribed to impurities. A product exhibiting identical NMR characteristics could be distilled in small amounts out of the crude reaction product (b.p. 150–160° at 5 mm).

The NMR spectra of later column chromatographic fractions had negligible absorption in the vinyl region (4.0–6.5 ppm), but pronounced absorptions in the aliphatic region (0.8–2.2 ppm). Since these fractions were acid-soluble, such aliphatic absorptions were not due to hydrocarbon impurities. A typical chromatographic fraction had the following NMR characteristics: 0.75 (1H, doublet), 1.14 (3H, triplet), 2.1 (3H, mult.), 3.1 (2H, mult.), 3.6 (1H, mult.), 6.4–7.1 (10H, sharp sing. at 6.82 and 7.02) and 8.2 (2.5H). The crude product from an 8-day run of 4-styrylpyridine and allyl Grignard reagent displayed an NMR spectrum very similar to that of the foregoing chromatographic fraction. No absorptions due to 4-styrylpyridine or 4-(2-phenyl-4-pentenyl)pyridine were discernible. On the other hand, the NMR spectrum on the crude product of a one-day run showed the presence of small amounts of 4-styrylpyridine and 4-(2-phenyl-4-pentenyl)pyridine, even though the aliphatic absorptions at 0.8–2.2 ppm were already very prominent.

Mass spectral analysis of the crude, acid-soluble reaction product from a 1-day run displayed the following prominent peaks (70 eV, 150° inlet): highest observed

mass, 669, 446, 445, 404, 403, 363, 362, 311, 269, 223, 182, 181, and 180. The peaks at 223, 446, and 669 accord with multiples of the 4-(2-phenyl-4-pentenyl)pyridine unit volatile enough to be detected by the spectrometer. The other prominent peaks can by accounted for by the anticipated facile loss of allyl, benzyl, allylic hydrogen and related fragments from the oligomers or polymers.

Reaction of N-(α-allylbenzhydryl)aniline with allylmagnesium bromide

A solution of 6.58 g (0.022 mole) of *N*-(α-allylbenzhydryl)aniline in 100 ml of anhydrous ether was admixed with 0.075 mole of allylmagnesium bromide in 75 ml of ether. After the initial exothermic reaction the mixture was stirred at room temperature for 36 h. The ether was evaporated under nitrogen and 100 ml of dry benzene added. The brown mixture was stirred under reflux for 6 days. (After *ca.* 30 min a greenish tinge was noticed). GLC of the dried organic extract of the hydrolyzed product revealed the presence of three major products and seven minor products. The principal product was *N*-benzhydrylaniline (isolated by column chromatography); aniline and benzophenone anil also were significant products. By GLC retention times the absence of benzophenone, *sym*-tetraphenylethane, 1,1-diphenyl-1-butene, 1,1-diphenyl-1,3-butadiene, diphenylmethane and significant amounts of 1,1-diphenyl-1,6-heptadiene was assured. A significant component having a retention time similar to, but not identical with, that of 1-phenylnaphthalene, may be a cyclization product resulting from any 1,1-diphenylbutadiene formed during the reaction*.

A run similar to the foregoing was carried out but the reaction mixture was hydrolyzed with deuterium oxide (99.8%). The benzhydrylaniline isolated was shown by NMR analysis to contain no C–D bonds.

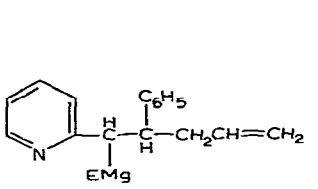
RESULTS AND DISCUSSION

The test of the competition between 1,2-addition to conjugated anils and various types of 1,4-, 1,6- or 1,*n*-addition is amenable to study with the 2- and 4-styrylpyridines, since the pyridine ring itself is only slowly attacked, even by allyl Grignard reagents[9]. Hence, conjugate addition involving the exocyclic styryl group was anticipated. The smooth 1,4-addition observed with 2-styrylpyridine, leading to 2-(2-phenyl-4-pentenyl)pyridine upon hydrolysis, confirms the validity of this assumption. Attempted addition of the allyl Grignard reagent to 4-styrylpyridine, however, proceeded less readily and only small amounts of 4-(2-phenyl-4-pentenyl)pyridine were realized upon hydrolytic work-up. The preponderance of product consisted of higher molecular weight oligomers and polymers, apparently made up of repeating units derived from 4-(2-phenyl-4-pentenyl)pyridine. This conclusion is based upon the GLC behavior indicative of high molecular weight products, the mass spectral observation of fragments attributable to such oligomers, and the NMR data of such products revealing a high proportion of aliphatic C–H and little or no vinylic C–H bonds.

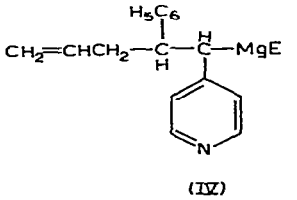
The difference in behavior between 2-styrylpyridine and 4-styrylpyridine cannot readily be explained in terms of some great divergence in reactivity between

* The GLC analysis of *N*-(α-allylbenzhydryl)aniline itself on silicone oil-on-firebrick gives a small parent peak but prominent peaks for aniline and 1,1-diphenyl-1,3-butadiene.

the allyl Grignard adducts (III) and (IV). If the initially formed (IV) were to effect the formation of polymer, one would expect that it would attack unreacted 4-styrylpyridine preferentially, leading essentially to poly-4-styrylpyridine*. But the NMR data demand polymeric products in which the allyl group has been converted into aliphatic linkages. Also, since the adduct (III) showed no tendency to polymerize during 4 days, it is unlikely and unprecedented that the polymeric products be ascribed to the polymerization of (IV) itself during the 1- to 4-days reaction period. Hence, another explanation must be sought for the prevalence of intermolecular reactions leading to oligomers and/or polymers of (IV).



(III)



(IV)

Also bearing on this unusual behavior of 4-styrylpyridine is the outcome of heating *N*-(α-allylbenzhydryl)aniline with an excess of allyl Grignard reagent. The principal products identified were *N*-benzhydrylaniline, benzophenone anil and aniline (the last thought to have resulted from the thermal elimination of C_6H_5NH-MgE from the starting material). It is highly improbable that the benzophenone anil was present as such in the original reaction system, since if it were formed, it would have reacted promptly with the excess of allyl Grignard reagent employed. Finally, the *N*-benzhydrylaniline, undeuterated at the α-carbon atom upon deuterolytic work-up, seems unlikely to have arisen from the allyl Grignard reagent via hydride reduction, since allylic and benzylic Grignard compounds are not reported to reduce carbonyl or azomethine linkages in this manner[16].

The explanation most compatible with the behavior of *N*-(α-allylbenzhydryl)-aniline is that its magnesium salt (V) underwent a thermal dissociation to yield (VI), similar to that proposed in (I), and that radical disproportionation and hydrogen uptake then ensued (*cf.* ref. 17 for analogous cleavages in oxygen systems):

$$2\,(C_6H_5)_2\dot{C}-N(MgE)C_6H_5 \xrightarrow[\Delta]{-C_3H_5^{\cdot}} 2\,(C_6H_5)_2\dot{C}-N(MgE)C_6H_5 \xrightarrow{C_6H_5NHMgE}$$

(V), E = C_3H_5, Br or NNR (VI)

$$\rightarrow (C_6H_5)_2CH-N(MgE)C_6H_5 + (C_6H_5)_2C\left(N(MgE)C_6H_5\right)_2$$

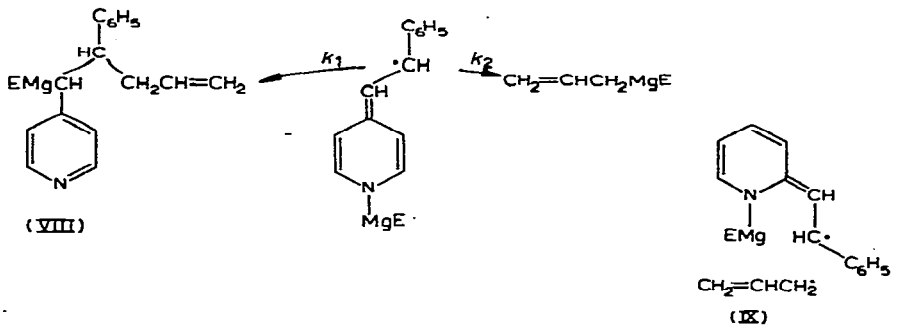
(VII)

The presumed intermediate (VI) might alternatively have gained its α-hydrogen by

* Natta and coworkers[15] have been able to polymerize either 2-vinylpyridine or 4-vinylpyridine by employing diethylmagnesium, diphenylmagnesium or phenylmagnesium bromide in tolene solution at 45°.

abstraction from the solvent or the reagents. The α,α-dianilino salt (VII) would be labile during hydrolysis, reverting to aniline and benzophenone anil.

The anomalous behavior of 4-styrylpyridine toward the allyl Grignard reagent, accordingly, also can be understood in terms of the Blicke–Powers electron-transfer hypothesis. The spatial separation of the nitrogen center and the carbon attacked [structure (I), $n=2$] may hinder simple collapse of the caged radicals and thus permit an intermolecular radical attack involving the allyl group (either of allyl Grignard reagent or of expected monomer) to complete (VIII):



As normal addition (k_2) goes on, the process leading to oligomers or polymer (k_1) would increase in prominence. With 2-styrylpyridine, on the other hand, the spatial proximity of the caged radical fragments (IX) would favor 1,4-collapse.

In accord with these views, the reactivity series of aza-aromatic heterocycles toward Grignard reagents, namely pyridine ≪ quinoline ~ isoquinoline < phenanthridine ~ acridine[9], can be accommodated to the Blicke–Powers model (I), since the radical-anions of these systems would be successively more stable, and hence more readily formed, in the same order[18]. Collapse of the caged radicals in (I), furthermore, would be less sensitive to steric hindrance. Hence, 1,2-addition of allyl and benzyl Grignard reagents would be more facile than with ordinary Grignard reagents less able to transfer electrons. Indeed, the addition of crotyl Grignard to acetomesitylene to give the (α-methylallyl)carbinol could be viewed as the preferential collapse of the substituted allyl radical at the site of higher spin density, its secondary carbon atom. Finally, the generally superior reactivity of allylic, benzylic, tert-alkyl and sec-alkyl Grignard reagents in various additions to A≡B linkages[1-4] (A, B = C, O, N, S) may reside in their ability to pursue an electron transfer pathway [*cf.* (I)]; just these organic groups would be expected to form the more stable radicals as required by the Blicke–Powers hypothesis:

$$RMgE \xrightarrow{-e^-} R^{\bullet} + MgE^{\oplus}$$

$$A{=}B \xrightarrow{+e^-} \dot{A}{-}B^{\ominus}$$

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