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# REACTIONS OF SOME GRIGNARD REAGENTS WITH 2,6-DICHLOROPYRIDINE

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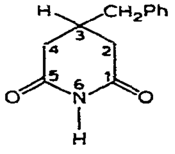
## SUMMARY

Reaction of benzylmagnesium chloride with 2,6-dichloropyridine gave 3-benzylglutarimide. Allylmagnesium chloride with 2,6-dichloropyridine, in a 1/1 molar ratio, gave 2-allyl-6-chloropyridine; and in a 2/1 molar ratio gave 2,6-diallylpyridine.

Incidental to a study concerned with polyhaloaryl organometallic compounds, we have observed an interesting reaction between 2,6-dichloropyridine and benzylmagnesium chloride. Using a 1/1 molar ratio, the reaction of benzylmagnesium chloride in ether with 2,6-dichloropyridine in THF at 0° gave a compound, m.p. 127–128.5°, containing nitrogen but no chlorine. The IR spectrum showed a band at 3400 $cm^{-1}$ ($\rangle$NH) and a broad band at 1650–1750 $cm^{-1}$ (–CO–NH–CO–), while the NMR spectrum in $CDCl_3$ showed a signal at $\delta$ 8.5 ppm which disappeared on exchange with $D_2O$. Mass spectrometry indicated the molecular weight to be 203. The spectral data thus suggested that compound (I) is 3-benzylglutarimide.



(I)

Consistent with the above formulation, compound (I), on reduction with lithium aluminum hydride gave 4-benzylpiperidine, and on boiling with concentrated hydrochloric acid gave 3-benzylglutaric acid.

The interactions of Grignard reagents with aza-aromatic heterocycles such as pyridine, quinoline and acridine have been reported[1] periodically. Previous studies in this laboratory have demonstrated that the benzyl- and allyl-Grignard reagents in their reactions with these heterocycles exhibit a high order of reactivity

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when compared to that of other Grignard reagents[2]. Alkyl Grignard reagents[3] on reaction with pyridine give small yields of mixtures of 2- and 4-alkylpyridines. But the reaction of pyridine with an alkyl halide and fresh magnesium powder has given[4] good yields of the 4-alkylpyridine, essentially free from the 2-isomer. This interesting result indicated a mechanism different from that operating in reactions of pre-formed Grignard reagents with pyridine. Of particular interest is the reaction of benzyl Grignard reagent with pyridine. Benkeser and Holton[5] showed that this reaction gives a mixture of the 2- and 4-benzylpyridines and not exclusively the 2- or 4-benzyl isomer as reported by previous workers[6,7].

Conjugate additions of Grignard reagents to aromatic systems have been well documented[8]. A conjugate addition of benzylmagnesium chloride to 2,6-dichloropyridine and subsequent hydrolysis, could give compound (I). In particular the satisfactory yield (60%) may be noted, because benzylmagnesium chloride reacted with pyridine to give the benzylpyridines in low yield[5-7] (*ca.* 9%).

Compound (I) could not be isolated when the reaction mixture was allowed to come to room temperature or when ether alone was used. Reaction of benzylmagnesium chloride with 2,6-dichloropyridine in a 2/1 molar ratio gave compound (I) in low yield.

Reaction of allylmagnesium chloride with 2,6-dichloropyridine in a 1/1 molar ratio, gave 2-allyl-6-chloropyridine (56% yield), and in a 2/1 molar ratio, gave 2,6-diallylpyridine (50% yield). It may be noted that allyl Grignard reagent on reaction with pyridine has given[2] 4-allylpyridine in 9% yield, but with 2-bromopyridine 2-allylpyridine has been obtained in 41% yield.

Recently[9], it was shown that the reaction of phenylmagnesium halides in THF or ether with 2-chloropyridine gave good yields of 2-pyridylmagnesium halides. However, we have not yet observed any halogen–metal exchange in the reaction of 2,6-dichloropyridine with phenylmagnesium bromide. 2,6-Dichloropyridine was recovered in 85% yield.

The reaction of benzylmagnesium chloride or allylmagnesium chloride with 2,6-dichloropyridine might involve a one-electron transfer in the first step. A radical intermediate would be formed having free spin at the 2- and 4-positions of the pyridine nucleus. For steric reasons, the benzyl radical may couple at the 4-position but the allyl radical can easily collapse in a cyclic fashion giving the 2-adduct. This could explain why these Grignard reagents react readily while alkyl Grignards do not. It could also explain how the presence of chlorine atoms makes these reactions facile.

## EXPERIMENTAL

All reactions were carried out under an atmosphere of dry oxygen-free nitrogen. Tetrahydrofuran was dried over sodium, followed by distillation from sodium benzophenone ketyl. IR and NMR spectra were determined employing PE-21 infrared, and A-60 NMR spectrometers, respectively. All melting points are uncorrected. Molecular weights were determined by mass spectrometry.

### *Reaction of benzylmagnesium chloride with 2,6-dichloropyridine (1/1 molar ratio)*

Benzylmagnesium chloride (0.1 mole) in ether was added dropwise to a solution of 2,6-dichloropyridine (14.06 g, 0.096 mole) in THF (50 ml) cooled to 0°.

After 30 min, Color Test I[10] was negative. Chlorotrimethylsilane (14 ml) in ether (50 ml) was added to trap any organometallic species present, and the solution stirred for 2 h. Hydrolysis with ammonium chloride solution (100 ml) and work-up afforded a solid, which, on extraction with petroleum ether (b.p. 60–80°) gave 0.9 g of 2,6-dichloropyridine, m.p. 76–78°. The residue, on crystallization from methanol, gave 11.0 g of a crystalline solid, m.p. 127–128.5°. The IR, NMR and mass spectra indicated it to be 3-benzylglutarimide, structure (I). The yield based on 2,6-dichloropyridine consumed was 60%. (Found: C, 71.20; H, 6.46; N, 7.02; mol.wt., 203. $C_{12}H_{13}NO_2$ calcd.: C, 70.96; H, 6.45; N, 6.9%; mol.wt., 203.2.)

The hydrolysate after the reaction with chlorotrimethylsilane, showed no 2-chloropyridine which may have been formed by hydrolysis[11] of any 2-chloro-6-trimethylsilylpyridine.

### *Hydrolysis of compound (I) with concentrated hydrochloric acid*

Compound (I) (2.0 g) and concentrated hydrochloric acid (20 ml) were refluxed for 4 h. The mixture was poured into ice-cold water and extracted with ether. Subsequent work-up gave a colorless oil, which on crystallization from ether/hexane, gave 0.5 g of 3-benzylglutaric acid, m.p. 104–106° (lit.[12,13] m.p. 102° and 99–101°); mol.wt. found 222; calcd. 222.

### *Reduction of compound (I) with lithium aluminum hydride*

Lithium aluminum hydride (0.05 mole) in ether was added with stirring to 2.7 g of compound (I) dissolved in THF (50 ml). The solution was stirred for 4 h. Hydrolysis with dilute sodium hydroxide and subsequent work-up gave 1.5 g of an amine. Distillation under reduced pressure gave 1.0 g of 4-benzylpiperidine, b.p. 150°/17 mm, (lit.[7] b.p. 150–152°/17 mm); m.p. of its hydrochloride 170° (lit.[7] m.p. 169°).

### *Reaction of benzylmagnesium chloride with 2,6-dichloropyridine (2/1 molar ratio)*

Benzylmagnesium chloride (0.2 mole) in ether was added dropwise to a solution of 2,6-dichloropyridine (14.06 g, 0.096 mole) in THF (50 ml) cooled to 0°. After 30 min Color Test I was negative. The solution was stirred for 2 h. Hydrolysis with saturated aqueous ammonium chloride solution (100 ml) and subsequent work-up gave 8.0 g of a complex mixture from which 1.5 g of compound (I), m.p. 125–127° was isolated.

### *Reaction of allylmagnesium chloride with 2,6-dichloropyridine (1/1 molar ratio)*

Allylmagnesium chloride (0.1 mole) in ether (prepared by a published procedure[14]) was slowly added to a solution of 2,6-dichloropyridine (14.7 g, 0.1 mole) in THF (50 ml) at 0°, and the reaction mixture was stirred for 1 h. Color Test I was negative. Hydrolysis with saturated aqueous ammonium chloride and work-up gave a brown liquid. This was treated with dilute hydrochloric acid. The acid-insoluble material (1.6 g) was 2,6-dichloropyridine. The hydrochloric acid layer was made alkaline and extracted with ether to obtain, after the customary work-up, a liquid (6.2 g, 54%), b.p. 110–114°/27 mm, $d_4^{20}$ 1.110, $n_D^{20}$ 1.5338. (Found: N, 9.39; Cl, 23.21; mol.wt., 154. $C_8H_8ClN$ calcd.: N, 9.12; Cl, 23.1%; mol.wt., 153.5.) $MR_D$ obsd. 43.1; $MR_D$ calcd. 43.2. The identity of this compound as 2-allyl-6-chloropyridine was established on the basis of its NMR spectrum in $CDCl_3$, which showed a complex pattern characteristic of an allyl group[15] and three aromatic protons in the region $\delta$ 6.95–7.7 ppm. Some polymeric material was also obtained in this reaction.

*Reaction of allylmagnesium chloride with 2,6-dichloropyridine (2/1 molar ratio)*

Allylmagnesium chloride (0.16 mole) in ether was slowly added to 2,6-dichloropyridine (11.8 g, 0.08 mole) in THF (50 ml) at 0°. After stirring for $\frac{1}{2}$ h, Color Test I was negative. The customary work-up gave a liquid (11.5 g) which on distillation afforded 2,6-diallyl pyridine (6.5 g, 50%), b.p. 110°/25 mm, $n_D^{20}$ 1.5200, (lit.[16] b.p. 103°/15 mm, $n_D^{20}$ 1.5201). This reaction also gave some polymeric material.

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