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PRELIMINARY COMMUNICATION

CYCLIZATION REACTIONS OF γ-(3- AND 4-PYRIDYL)PROPYL GRIGNARD REAGENTS

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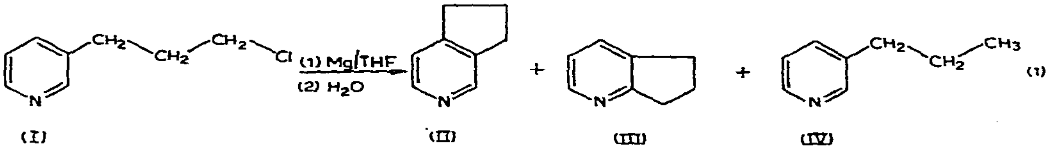
As a continuation of our research on the alkylation of aza-aromatic heterocycles by organometallic reagents [1-4], we have been particularly concerned with the competition between alkylations at C–2 and C–4 in pyridines. To this end, the intramolecular alkylations possible with γ-(3- and 4-pyridyl)propyl Grignard reagents have been examined in detail. Contemporaneous with our studies was the report that γ-methyl-γ-(4-pyridyl)butyl chloride and magnesium in tetrahydrofuran yielded a mixture of 4-isopropylpyridine (35%), γ-methyl-γ-(4-pyridyl)butane (55%) and ethylene upon hydrolysis[5]. These results were taken as evidence that fragmentation of the Grignard reagent, 4-C_5H_4N–$C(CH_3)_2CH_2CH_2MgCl$, into 4-C_5H_4N–$C(CH_3)_2MgCl$ and ethylene had occurred. Direct NMR examination of the Grignard solution verified the presence of the Grignard species and ethylene. Since our results with related Grignard reactions have a bearing on this remarkable, apparent fragmentation of a Grignard reagent, we wish to report them at this time.

The reactions of magnesium in tetrahydrofuran with γ-(3-pyridyl)propyl chloride and with γ-(4-pyridyl)propyl chloride, respectively, yielded the following products upon hydrolysis (Table 1):



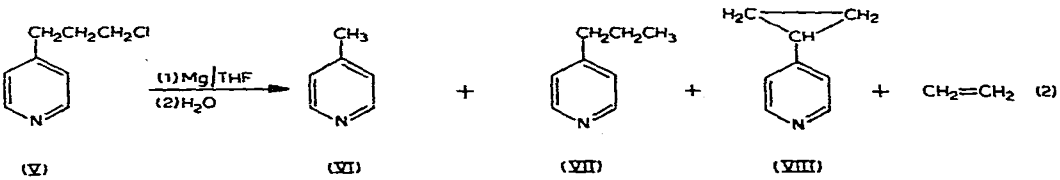


TABLE 1

REACTIONS OF γ-(3-AND 4- PYRIDYL)PROPYL CHLORIDES WITH MAGNESIUM[a]

Reaction products[b] from	
γ-(3-Pyridyl)propyl chloride	γ-(4-Pyridyl)propyl chloride
3,4-Pyrindane (II) b.p.: 52–53°/5 mm picrate: m.p. 139–140.5°[c] styphnate: m.p. 175–176.5°[c]	γ-Picoline (VI) b.p.: 140–142°/760 mm picrate: 165–167°
2,3-Pyrindane (III)[d] b.p.: 39–40°/8 mm picrate: m.p. 179–181.5°	4-Propylpyridine (VII) b.p.: 49–50°/3.4 mm picrate: m.p. 129–131°
3-Propylpyridine (IV) b.p.: 30–31°/0.7 mm picrate: m.p. 97–99°	4-Cyclopropylpyridine (VIII) b.p.: 58–60°/6.4 mm picrate: m.p. 158–160°

[a] In a typical run 0.05 mole of either chloride was allowed to react with 0.055 g-atom of magnesium turnings in a total volume of 250 ml of freshly purified tetrahydrofuran. Individual reactions required *ca.* 1–3 days at 25° for complete consumption of chloride. After usual work-up *ca.* 50–60% of the expected products was isolated by distillation (losses due to solubility of bases in H_2O–THF). Individual components were separated by spinning-band distillation or GLC analysis. [b] The NMR and IR spectra of all products were identical with those of authentic samples. The melting points of all derivatives were undepressed when these substances were admixed with authentic samples. [c] Authentic samples were kindly provided by Professor V. Prelog of E.T.H., Zurich. [d] Professor J.A. Adamcik of Texas Technological College, Lubbock, assisted us by providing a sample of 4,6-dichlorocyclopenteno-2,3-pyrindane, an intermediate for the synthesis of III.

It is significant that carbon–carbon bond fragmentation occurred only with V. Moreover, time studies of product composition were performed on both reactions by hydrolysis of aliquots and subsequent GLC analysis. The formation of II in reaction (1) and of VI in reaction (2) occurred only in the presence of the starting chloride (I or V) and magnesium metal. Thus, in reaction (1) the complete consumption of 1 By excess magnesium at 25° led to a final ratio for II:III:IV of 20:10:70. However, removal of excess magnesium, dilution of the Grignard solution and heating gave a product ratio for II:III:IV of 20:50:30; dilution alone did not change the composition. Clearly, 2,3-pyrindane (III) is being produced by the cyclization of γ-(3-pyridyl)propyl Grignard reagent (precursor of IV). On the other hand, 3,4-pyrindane (II) is being produced only from the chloride I and magnesium metal[★].

In a similar fashion, a time study of reaction (2) showed that the ratio for VI:VII:VIII was 18:50:32 just after complete consumption of chloride V. 4-Cyclopropylpyridine (VIII) could arise rationally by the metallation of the γ-carbon in V by the RMgX formed and the expected elimination of magnesium halide from the resulting intermediate[6]. Further stirring for 12 h led to a ratio for VI:VII:VIII of 18:40:42. If the γ-(4-pyridyl)propyl Grignard reagent (IX) (a precursor of VII) were the source of γ-picoline (VI) by fragmentation, not only should the quotient of VI/VII become significantly larger but also the quotient of VI/VIII should increase. Such changes are not observed. Rather, the observed changes can best be understood by selective consumption of IX (precursor of VII) by side

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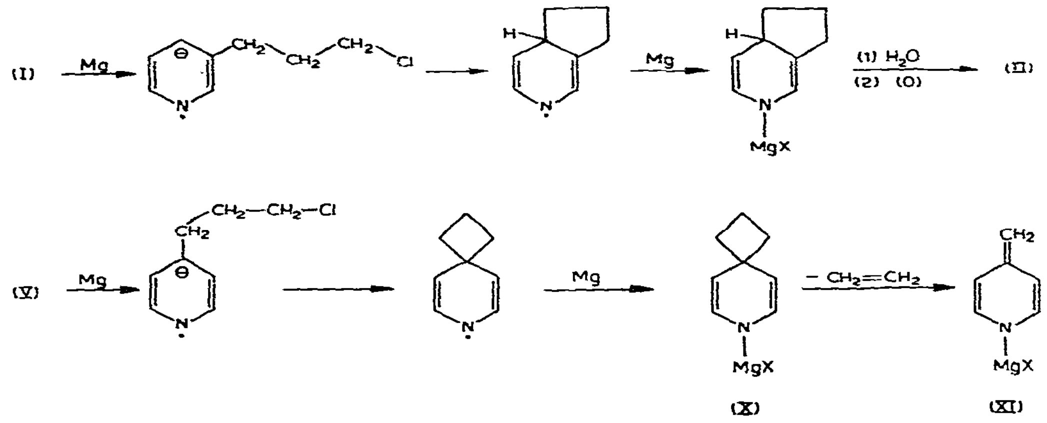
[★] Possible dihydro precursors of II and III would be expected to aromatize either by MgHX elimination or air oxidation upon work-up (*cf.* ref. 3 and 4).

reactions leading to higher boiling products. Hence, in this case we do not believe that the Grignard reagent undergoes fragmentation into γ-picolyl Grignard reagent and ethylene. In the previous report on the apparent fragmentation of $4\text{-}C_5H_5N\text{–}C(CH_3)_2CH_2CH_2MgCl$[5] it is noteworthy that the ratio of 4-isopropylpyridine and γ-methyl-γ-(4-pyridyl)butane is also independent of reaction temperature, and the published data also indicate some unreacted chloride is present.

In the light of our findings with the magnesium metal reactions of I and V, we propose a common mechanism to explain the time-independence of the relative amounts of 3,4-pyrindane (II) in reaction (1) and γ-picoline (VI) in reaction (2). While the formation of 2,3-pyrindane (III) and 4-cyclopropylpyridine (VIII) can readily be explained by ample precedents in carbanian chemistry[4,6], a different pathway seems to be operative in the formation of II and VI. The observation has been made that a mixture of alkyl halide, magnesium and pyridine leads principally to 4-alkylpyridines, whereas, preformed Grignard reagents, free of magnesium metal traces, lead exclusively to 2-alkylpyridines[7]. Further research has supported the operation of a free-radical mechanism in 4-alkylation[8]. Since we find that both starting chloride (I or V) and magnesium metal are necessary for the formation of II or VI, we suggest a radical-anion pathway:



Although a spirane derived from X has not as yet been detected, it is reasonable to suggest that it would decompose spontaneously. Structure X can be regarded as the cycloaddition adduct of an aromatic enamine salt XI and ethylene; and such adducts are often thermally labile[9].

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