Homolysis in the Reaction of Grignard Reagents. II. The Reaction of Pyridazine

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Pyridazine reacts with Grignard reagents by a homolytic mechanism as seen from the presence of *N*-alkylated dimers, dialkyl- and trialkyl-pyrroles as well as other 'radical-type' compounds in the reaction product. The non-alkylated product 1,4-dihydropyridazine was also found. The kinetics of the reaction indicate high reactivity of tertiary and secondary reagents and low reactivity of methylmagnesium bromide as expected for a homolytic reaction.

Depending on the redox properties of the substrate, Grignard reagents react either by a heterolytic, anionic, one-step mechanism or by a multistep, homolytic, radical-type mechanism. Methylmagnesium bromide, for example, probably reacts with acetone by simple nucleophilic addition. *tert*-Butylmagnesium bromide on the other hand reacts with benzophenone by a two-step mechanism, in which the first and rate-determining step is induced homolysis of the Grignard reagent with production of the magnesium diphenylketyl and the *tert*-butyl radical. Recombination and/or disproportionation of the radicals yield the products.[1]

The mechanism of the reaction of methylmagnesium bromide with benzophenone is less clear, since only trace amounts of radical intermediates or radical by-products are observed. That the mechanism in this case is homolytic (or near-homolytic) has been inferred from the linear correlation of log[rate (Ph_2CO+RMgX)] versus oxidation potential for a series of Grignard reagents.[2] The correlation of log (rate) versus C–Mg bond strength is also linear, and evidence has been obtained that the rate-determining step is concerted transfer of magnesium and of an electron, which is equivalent to homolytic fission of the carbon—magnesium bond.[3]

The distinction between the anionic and the radical mechanism is then possible either from an analysis of the product distribution, if large amounts of radical-type products are found, or from a study of the reactivities of the various Grignard reagents. In a radical-type reaction the normally nucleophilic alkyl of the Grignard reagent may add to a heteroatom such as N or O[4,5] or to the negatively polarised end of a double bond,[6] and dimerisation or disproportionation products such as benzopinacol or alkene/alkane pairs may be formed. Proof of a radical mechanism by means of the reactivity series has only been presented for a few substrates such as benzophenone,[2] azobenzene,[4] and di-t-butyl peroxide.[7] The method requires that the substrate is not too reactive and shows regular kinetics.

Pyridazines and substituted pyridazines have been shown by Letsinger to react with Grignard reagents with the formation of 4-alkylpyridazines from oxidized 1,4-dihydroalkylpyridazines, which were not isolated.[8] Reported yields were low, (17–23 %) and 'radical-type' by-products were not observed. Crossland *et al.* added Grignard reagents to substituted pyridazines.[9,10]

In the present work the reaction of pyridazine with Grignard reagents has been reinvestigated with the purpose of finding clues to the mechanism and/or improving the yields.

Results and discussion

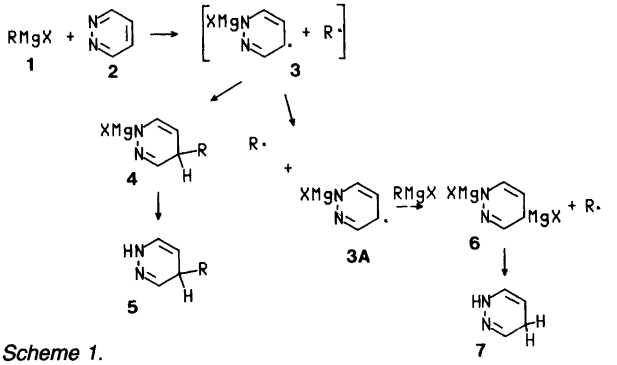
1,4-Addition of Grignard reagents to pyridazines to form 4-alkyl-1,4-dihydropyridazines takes place with all Grignard reagents, but the yields are usually low. With methylmagnesium bromide this is due to low reactivity, and most of the starting material is found unchanged after work-up, even after several days. Butyl- and isopropyl-magnesium bromide, however, also give low yields of a 1,4-addition product, even if the starting material is consumed completely. The by-products formed are high-boiling and form a tar if distillation is attempted. They also decompose with tarring on exposure to oxygen.

^{1}H NMR spectroscopic examination of the crude product from the reaction between butylmagnesium bromide and pyridazine showed a doublet with a chemical shift typical of the C6-hydrogen of a 1,4-dihydropyridazine (Table 1). While this signal is normally a double doublet because of coupling with N–H and C5–H, doublet signals with the typical C6–H shift were assigned to an *N*-butylated compound since it was accompanied by a CH_2 triplet at δ 3.5. The *N*-alkylated products were particularly formed when Grignard reagents or dialkylmagnesiums were added to a large excess of pyridazine.

When the product from the reaction between dibutylmagnesium with pyridazine was distilled at 0.05 mmHg in a Kugelrohr apparatus, an *N*-alkylated dimer was isolated as

Table 1. NMR spectra of 1,4-dihydropyridazines in $CDCl_3$ at 250 MHz (chemical shifts in ppm, *J* in Hz).

Substituent	H1	H3	H4	H5	H6	Alkyl substituent
None	6.18 (s)	6.50 (m)	2.68 (ddd, *J* 4.1/3.2/0.7)	4.44 (m)	6.25 (t, *J* 2.7)	
4-CH_3	6.8 (s)	6.37 (t, *J* 2.8)	2.68 (m)	4.45 (m)	6.23 (dd, *J* 7.6/3.8)	1.10 (d, 3 H, *J* 7.2)
4-C_2H_5	6.3 (s)	6.42 (t, *J* 2.8)	2.70 (m)	4.48 (m)	6.27 (dd, *J* 7.6/3.8)	1.45 (m, 2 H) 1.18 (t, 3 H *J* 6.3)
4-$(CH_3)_2CH$	6.97 (s)	6.48 (t, *J* 2.8)	2.64 (m)	4.50 (m)	6.32 (dd, *J* 7.6/3.8)	0.93 (dd, *J* 7.0/2.5)
4-C_4H_9	6.85 (s)	6.45 (t, *J* 2.8)	2.73	4.48	6.26 (dd, *J* 7.6/3.8)	1.25–1.50 (m 6 H) 0.87–0.97 (m, 3 H)
4-*i*-C_4H_9	7.10 (s)	6.45 (t, *J* 2.8)	2.77 (m)	4.50 (m)	6.28 (dd, *J* 7.6/3.8)	1.80 (m, 1 H) 1.25 (m, 2 H), 0.90 (d, 6 H *J* 6.5)
4-*t*-C_4H_9	6,83 (s)	6.57 (br s)	2.54 (dd, *J* 3.9/4.3)	4.57 (m)	6.36 (dd, *J* 7.6/3.8)	0.91 (s, 9 H)
4-C_3H_5	7.5 (s)	6.38 (t)	2.82 (m)	4.45 (m)	6.26 (dd, *J* 4.3/3.1)	2.1–2.4 (m, 2 H) 5.6–5.9 (m 2 H), 5.0–5.2 (m 1 H)
4-$C_6H_5CH_2$	7 (s)	6.42 (t)	3.02 (m)	4.46 (m)	6.23 (dd, *J* 7.6/3.8)	7.30 (m, 5 H) 2.68 (m 2 H)
4-C_6H_5		6.50 (t, *J* 2.7)	3.96 (t, *J* 3.0)	4.61 (m)	6.36 (dd, *J* 7.6/3.8)	7.7–6.8 (m, 6 H)
5-C_4H_9	6.90 (s)	6.52 (t, *J* 3.0)	2.65 (d, *J* 3.0)	4.49 (m)	6.01 (dd, *J* 4.0/0.7)	1.25–1.45 (m, 4 H) 1.95 (t, 2 H *J* 7.0), 0.85–1.00 (m 3 H)
5-C_6H_5		6.72 (t, *J* 3.0)	3.10 (d, *J* 3.0)		6.77 (d, *J* 4.2)	7.5–7.1 [m, 6 H (incl. H1)]

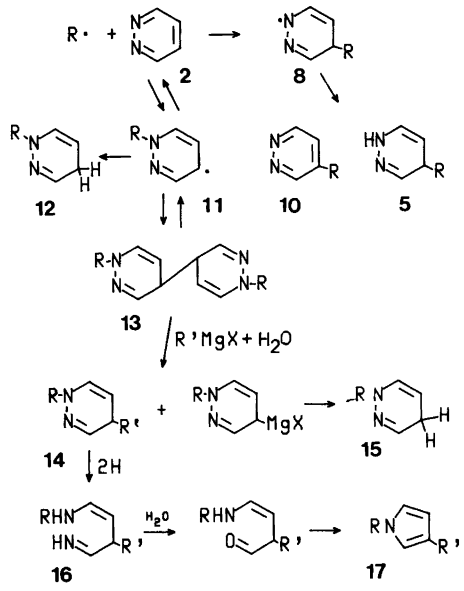


Scheme 1.

a high boiling viscous oil. The structure followed from the NMR spectrum (see the Experimental) and the determination of the molecular weight, 274, by MS. The structure is given as **13** (R = butyl) in Scheme 2.

The formation of **13** from pyridazine requires a radical mechanism and Schemes 1 and 2 show a possible path. Pyridazine induces homolysis of the Grignard reagent to yield the pair of radicals (**3**) in the solvent cage, Scheme 1. Most of the pairs recombine to form the 1,4-adduct **4** which is protonated to 4-alkyl-1,4-dihydropyridazine (**5**). The magnesium dihydropyridazinyl radical (**3**) may be capable of accepting another MgX from a Grignard reagent to form **6** and R· (chain reaction?), since 1,4-dihydropyridazine (**7**) is also found after work-up. The escaped alkyl radicals attack a neutral molecule of pyridazine at nitrogen to form **11** (Scheme 2), which dimerises to form **13**. Both possible diasteromers were apparently formed as seen from NMR spectroscopy (2 doublets of unequal size); but in some experiments one isomer dominated completely. A 4,4'-dimer of 1,4-dihydropyridazine has been reported formed by reduction of pyridazine with a samarium complex.[11]

While **13** (R = butyl) distils slowly below the b.p. at 105 °C and 0.05 mmHg, it decomposes immediately at



Scheme 2.

Table 2.

[C_4H_9MgCl]/M	[pyridazine]/M	[RMgX]/[pyridazine]	Conversion (%)
0.3	0.08	4.3	30
0.5	0.08	6.3	15
0.8	0.08	10	< 5
0.05	0.05	1	86
0.05	0.25	0.2	100

220 °C in the injector of the gas chromatograph. At this temperature homolytic dissociation of **13** to **11** takes place. Disproportionation of **8** then produces **5** and **10**, while **12** is formed from undissociated **11**, Scheme 2.

Grignard reagents also attack **13** in a little understood reaction which apparently takes place during the reaction of the excess Grignard reagent with water. When **13** (R = butyl) was dissolved in etheral isopropylmagnesium bromide, heat was evolved and a precipitate was formed, which soon disappeared. NMR spectroscopy, however, showed that the product was unchanged except for a downfield shift of the CH_2N protons. Apparently a complex was formed with $MgBr_2$ or RMgBr. Addition of water gave a reaction mixture, in which 1-butyl-3-isopropylpyrrole and some 1-butyl-3,4-diisopropylpyrrole were present as seen by GLC–MS and NMR. The formation of these products requires several steps (Scheme 2) including homolysis and alkylation to **14** and **15**, reduction of N–N in **14** to form **16**, hydrolysis of the imino compound followed by ring closure and elimination. An analogous series of reactions was observed after electrolytic reduction of 4-methylcinnoline with the production of skatole[12a] and of a 1,4-dihydropyridazine.[12b] The production of trialkylpyrrole requires an additional (radical?) alkylation. 1,3-Dibutylpyrrole was produced analogously from **13** (R = butyl) and butylmagnesium bromide or simply from pyridazine and a sufficiently large excess of the Grignard reagent.

From the product distribution described above it seems obvious that the mechanism for the reaction of pyridazine with Grignard reagents is of the radical type. This conclusion is supported by kinetic experiments performed in order to find the relative reactivity of the various Grignard reagents.

These results were, however, obtained only by semiquantiative procedures, since it was impossible to obtain regular kinetics for the reaction of pyridazine with Grignard reagents because of the formation of complexes. Thus, if the Grignard reagent was added to an excess of pyridazine, the reaction as measured thermographically was fast and complete. When pyridazine was added to excess Grignard reagent, however, an insoluble complex was formed in an instantaneous reaction, and further reaction of the complex was extremely slow.

Since the normal measurements using pseudo-first-order conditions were therefore useless, kinetic experiments were performed by simply mixing equal volumes of reagent and substrate in a syringe and quenching the reaction after 10 s by expelling the mixture very rapidly into a chilled mixture (−50 °C) of methanol and ether. In this way the results shown in Table 2 were obtained from NMR analysis.

The lower rates with increasing concentration of Grignard reagents are explained by the formation of complexes. Pyridazine coordinates preferentially with magnesium bromide, which is then removed from the Schlenk equilibrium:

$$2\ RMgBr \rightleftharpoons R_2Mg + MgBr_2$$

This leaves the highly reactive dialkylmagnesium in the liquid, where it reacts with any free pyridazine left in the solution.

Low yields in the alkylation of pyridazine with Grignard reagents may then be due to the lack of reactivity of the complex between $MgBr_2$ and the substrate. The use of highly reactive, halide-free dialkylmagnesium does not, however, improve the yield of 1,4-addition product, since *N*-alkylated side products are formed. The yield obtained by Letsinger (23 %) in the reaction with butylmagnesium bromide is typical and difficult to exceed. In small-scale experiments the use of a 100 % excess of Grignard reagent in an ether/THF solvent and a reaction time of 20 h afforded yields of up to 56 %.

A series of Grignard reagents was mixed with pyridazine using a standard procedure, which included inverse addition of pyridazine in ether to a small excess of Grignard reagent and a reaction time of 3 min. The crude yields were taken as an indication of the relative reactivity of the Grignard reagents and the results are given in Table 3.

Table 3. Product distribution in the reaction of RMgBr with pyridazine in diethyl ether using a standard procedure (see the Experimental).

R	Total yield (%)	Dihydropyridazine		Pyrrole	
		4-Alkyl	3-Alkyl	1-Alkyl	1,3-Dialkyl
CH_3	9	8	1	0	0
C_2H_5	40	26	1	11	2
$(CH_3)_2CH$	48	31		15	2
C_4H_9	39	30	2	6	1
i-C_4H_9	31	22		8	1
t-C_4H_9	50	50	0	0	0
C_3H_5	70	14	56		
$C_6H_5CH_2$	43	43	?	0	0
C_6H_5	50	50	?	0	0

The results indicate a reactivity series allyl > t-butyl > phenyl > isopropyl > benzyl > ethyl > butyl > isobutyl > methyl. Except for phenyl, the series is identical with the reactivity series observed with benzophenone.

Experimental

250 MHz NMR spectra in $CDCl_3$ were obtained on a Bruker AC 250. GC–MS was performed on a VG Trio-2 mass spectrometer. Grignard reagents were prepared from sublimed magensium. The pyridazine used was a generous gift from N. Clauson-Kaas, Inc, Farum, Denmark.

4-Alkyl-1,4-dihydropyridazine (**5**). *Standard procedure.* Pyridazine (0.8 g, 10 mmol) was dissolved in 10 ml of ether in a 50 ml evacuated flask fitted with a rubber stopper. A 1 M solution of alkylmagnesium bromide in ether (12 ml) was added with stirring from a syringe through the stopper. After 3 min water was added similarly letting the gas escape through the needle. Magnesium salts (and magnesium bromide-complexed pyridazine) separated as a paste. The clear ether phase was transferred to an evacuated flask. The ether was removed by means of an aspirator at 40–50 °C. The remaining oil was analysed by NMR spectroscopy and GLC–MS (Table 3). All 4-alkyl-1,4-dihydropyridazines (**5**) had very similar NMR spectra except for signals pertaining to the alkyl group (Table 1).

5-Alkyl-1,4-dihydropyridazine. Heating of 4-alkyl-1,4-dihydropyridazine at 120 °C caused rearrangement to give 5-alkyl-1,4-dihydropyridazine. In this way was produced 5-butyl- and 5-phenyl-1,4-dihydropyridazine; the latter was crystalline, m.p. 168–170 °C. They were identified by NMR spectroscopy, see Table 1. Since thermic rearrangement occurred readily in the injector of the gas chromatograph, the use of GC–MS showed up to four peaks containing isomeric 4-alkyldihydropyridazines.

1,1'-*Dibutyl*-1,1',4,4'-*tetrahydro*-4,4'-*bipyridazine* (**13**) *and 1,4-dihydropyridazine* (**7**). To 4 g of pyridazine dissolved in 10 ml of ether were added slowly with stirring 25 mM of dibutylmagnesium in 40 ml of ether. Water was added drop by drop with stirring from a syringe, allowing the gas to escape through the needle. The magnesium salts were precipitated and the ether evaporated avoiding exposure to air. The resulting oil was distilled at 15 mmHg collecting the fraction boiling at 40–55 °C, which was crude 1,4-dihydropyridazine. The NMR spectrum was the general one (Table 1), except that the C4-hydrogen at δ 2.7 was a ddd integrating to 2 H.

In an identical experiment the residual oil was distilled at 0.06 mmHg in a Kugelrohr apparatus (Buchii AG). The least volatile fraction evaporated slowly at 105 °C and was collected as crude **13** (R = butyl). NMR: δ 6.43 (s, 1 H), 6.19 (d, 1 H, *J* 7.6 Hz), 6.43 (m, 1 H), 3.31 (d, 1 H, *J* 7.1, N-CH_2), 2.90 (m, 1 H), 1.58 (m, 2 H), 1.33 (m, 4 H), 0.92 (d, *J* 7.5 Hz). MS: 274 (2, *M*), 218 (2, $M-C_4H_8$), 202 (4), 191 (12), 95 (13), 81 (100).

1-Butyl-3-isopropylpyrrole (**17**). Crude **13** (R = butyl) (100 mg) was dissolved in ether and added to 3 ml of 1 M ethereal isopropylmagnesium bromide. After 2 min water was added from a syringe as above and the ether evaporated. The remaining oil was chromatographed by preparative TLC, eluating with pentane. A fraction with R_f = 0.33 contained 3 components, which were identified by GLC–MS and NMR spectroscopy. GLC was performed on a wide-bore silicone capillary column at 100 °C + 5 °C min^{-1}. Identified were *1-butyl-3-isopropylpyrrole,* retention time 13 min. NMR: δ 6.54 (m, 1 H), 6.41 (m, 1 H), 5.97 (m, 1 H), 3.87 (q, 2 H), 2.82 (hept., 1 H), 1.20 (d, 6 H *J* 5.5 Hz), 1.3–0.8 (m, 7 H). MS: 165 (40, *M*), 150 (100, $M-CH_3$), 123 (10), 108 (25), 106 (11), 94 (73), 81 (18), 80 (37). *1.3-Dibutylpyrrole* (trace), retention time 16.5 min. NMR: δ 6.54 (m, 1 H), 6.42 (m, 1 H), 5.96 (m, 1 H), 3.79 (t, 2 H, *J* 7.2 Hz), 2.44 (t, 2 H, *J* 7.7 Hz), 1.8–1.2 (m, 8 H), 0.97–0.87 (m, 6 H). MS: 179 (35, *M*), 137 (45, $M-C_3H_6$), 136 (100, $M-C_3H_7$), 94 (27), 80 (45). *1-butyl-3,4-diisopropylpyrrole,* retention time 17.7 min. MS 207 (97, *M*), 192 (89, $M-CH_3$), 165 (52), 164 (100), 150 (50), 122 (16).

1.3-Diisopropylpyrrole. To 4 g of pyridazine in 20 ml of ether was added a mixture of 50 ml of 1 M ethereal isopropylmagnesium bromide and 50 ml of 1,4-dioxane. After 2 min, a further 50 ml of the Grignard reagent were added. After 10 min water was added dropwise until a clear organic phase was obtained. The solvents were removed *in vacuo* on a rotary evaporator and the oil was dissolved in ether. This solution was extracted with 0.1 M hydrochloric acid to remove all basic components. Evaporation of the dried ether and distillation afforded 0.6 g of 1,3-diisopropylpyrrole, b.p. 80 °C at 15 mmHg. NMR: δ 6.63 (m, 1 H), 6.49 (m, 1 H), 6.02 (m, 1 H), 4.16 (hept., 1 H, *J* 6.7 Hz), 2.82 (hept., 1 H, *J* 6.7 Hz), 1.42 (d, 6 H, *J* 6.7 Hz), 1.21 (d, H, *J* 6.7 Hz). MS 151 (38, *M*), 136 (100, $M - CH_3$), 94 (67).

Pyrolysis of N,N'-*dibutyl*-1,1',4,4'-*tetrahydro*-4,4'-*bipyridazine.* Injection of 1 μg of **13** on a GC–MS system gave four peaks which were idenfified as (a) *pyridazine* (**2**), retention time 5.5 min; (b) N-*butyl-1,4-dihydropyridazine* (**12**), retention time 12.1 min. MS 138 (2, *M*), 124 (12), 81 (100), 54 (14); (c) *4-butyl-1,4-dihydropyridazine* (**5**), retention time 14 min. MS 138 (21, *M*), 137 (33), 95 (100), 81 (24); (d) *4-butylpyridazine* (**10**), retention time 16.3 min. MS 136 (94, *M*), 94 (32), 81 (16), 77 (39), 66 (23), 65 (100), 41 (17), 39 (26).

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