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GRIGNARD REAGENTS SELECTIVE ATTACK TO NITROARENIC FUNCTION IN THE PRESENCE OF OTHER ELECTROPHILIC GROUPS

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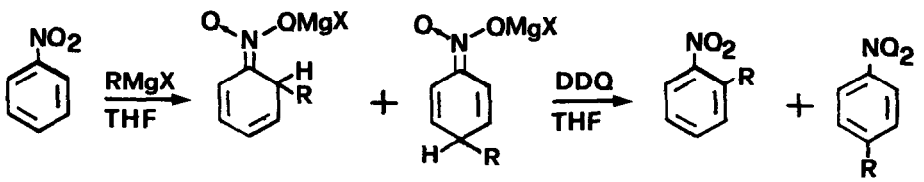
Abstract: Exclusive alkylation of the nitroarenic system takes place in competitive reactions of RMgX with nitrobenzene and various electrophiles such as ketones, esters, cyano- and iodo-derivatives and in reactions with some functionalized nitrobenzenes, only aldehydes show comparable reactivity.

Grignard reagents are undoubtedly an indispensable tool in preparative organic chemistry, when it is necessary to transfer an alkyl group to an electrophilic centre. However these reagents are considered to be insufficiently selective, owing to their high reactivity and basicity.[1] For instance they are known not to be able to distinguish among different carbonyl functions (aldehyde, ketone, ester, amide), nor to give a selective attack to the carbonyl group in the presence of nitro, cyano and iodo functions.

The recently discovered peculiar reactivity of Grignard reagents with nitroarenes has found interesting synthetic applications[2] and to date an equivalent to this reaction has not been yet reported. Since in these reactions substitution of a Grignard reagent with a less reactive but more selective organometallic compound cannot be accomplished, we turned our attention to the possibility of achieving selective alkylation, thus exploring conditions for the reaction to occur in the presence of electrophilic species highly reactive towards RMgX. In this communication we report results on competitive reactions of CH_3MgX and C_2H_5MgX with nitrobenzene and various electrophiles and with some functionalized nitrobenzenes.

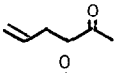


R= CH_3; C_2H_5

The addition of CH_3MgX to a 1:1 mixture of nitrobenzene and acetophenone (1 eq. each; table I, entry 5) at -70°C in THF, followed by oxidation with DDQ of the unstable nitronate

adduct intermediates[3], (according to scheme) gave 100% of unreacted ketone, 75% of o- and p-nitrotoluene and only 4% of unreacted nitrobenzene. The yields of products arising from attack to nitrobenzene as well as the amount of unreacted nitrobenzene are quite similar to those obtained in the reaction of CH_3MgX and nitrobenzene alone, under the same experimental conditions (entry 2). C_2H_5MgX (entry 6) shows an analogous behaviour. The low temperature is an essential condition for ensuring an almost complete selectivity. When the reaction was carried out at 0°C (entry 4), a significant amount of acetophenone reacted competitively with CH_3MgX, as detected by the presence of 9% of 2-phenyl-2-propanol and of traces of

Table I - Results of the Addition of Methyl- and Ethylmagnesium Halides (1 eq.) to a 1:1 Mixture (1 eq. each) of Nitrobenzene (NB) and a Competitive Electrophilic Substrate (ES) in THF.

Entry	R in RMgX	ES	T (°C)	NB unreacted (%)[a]	ES unreacted (%)	Products (%) from NB	Products (%) from ES
1	Me	none	0	4	-	69 (2:1)	-
2	Me	none	-70	4	-	74 (2:1)	-
3	Et	none	-70	5	-	72 (3:4)	-
4	Me	Ph-C(=O)-CH_3	0	12	85	60 (2:1)	10[d]
5	Me	"	-70	4	100	75 (2:1)	0
6	Et	"	-70	6	100	68 (3:4)	0
7	Me	Ph-C(=O)-H	-70	53	72	38 (2:1)	22[e]
8	Me		-70	7	97	72 (2:1)	2[f]
9	Me	Ph-C(=O)-Ph	-70	6	100	71 (2:1)	0
10	Me	Ph-C(=O)-OEt	-70	4	100	73 (2:1)	0
11	Me	Ph-C≡N	-70	5	100	72 (2:1)	0
12	Me	PhI	-70	2	100	74 (2:1)	0

[a] GLC[4] yields calculated with respect to RMgX. [b] Ratio between o- and p-alkylnitrobenzene in parenthesis. [c] Zero percent indicates no revealed peak. [d] as 9% of 2-phenyl-2-propanol and 1% of 1-phenylethanol. [e] As 1-phenylethanol. [f] As 2-methyl-5-hexen-1-ol.

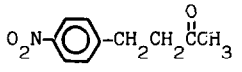
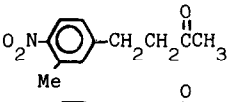
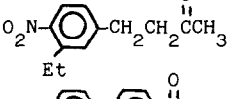
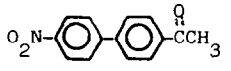
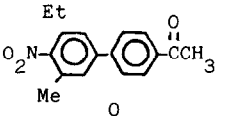
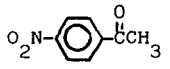
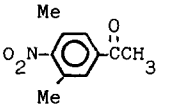
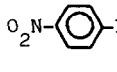
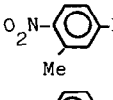
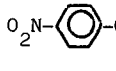
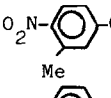
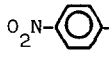
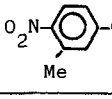
1-phenylethanol among the reaction products.

It is worth noting that the same high preferentiality for attack to nitrobenzene at -70°C is observed both with other ketones (entries 8,9) and with other electrophiles highly reactive towards Grignard reagents, such as ethyl benzoate (entry 10), benzonitrile (entry 11) and iodobenzene (entry 12).

By way of contrast, results from competitive reactions of CH_3MgX with nitrobenzene and benzaldehyde (entry 7) indicated that Grignard reagent was not so able to distinguish between nitro and carbonyl functionality, to ensure a significant selective attack to nitrobenzene even at -70°C.

It was of great interest from a synthetic point of view to verify whether the same experimental conditions as employed in the above competitive runs would be actually suitable for alkylating a nitroarenic fragment in the presence of a reactive electrophilic centre in

Table II - Results of the Alkylation of Some Functionalized Nitrobenzenes in THF at -70°C.

Entry	Substrate	R in RMgX	Product[a]	Yields (%)[b,c]
1		Me		80
2	"	Et		71
3		Me		70
4		Me		51
5		Me		74
6		Me		70
7		Me		72

[a] Products were identified by elemental MS, IR, NMR analyses or by comparison with autenthic specimens. [b] Calculated on the pure compounds after chromatographic separation on a silica gel column of the reaction mixture. [c] In all reactions the amount of unreacted material did not exceed the 5%.

the same molecular skeleton, by-passing tedious protection procedures. Data for reactions of some functionalized nitrobenzenes are reported in table II[5]. Yields in products arising from attack to nitroarenic function are quite comparable with those obtained in the blank runs (see table I, entries 2,3). In all experiments, no significant amounts of products arising from attack to other electrophilic centres were detected. It is worth noting that high selectivity is observed even when electrophilic functions are in conjugated position with respect to nitrogroup (table II, entries, 4,5,6,7).

In conclusion, the high reactivity of alkyl Grignard reagents towards mononitroarenes allows the conjugate addition of RMgX to the nitroarenic system to occur in large extent, without affecting other reactive groups, present in the same molecule such as cyano, iodo and carbonylic functions of ketones and esters, if some trivial experimental expedients are employed: i.e. low temperatures and an equimolecular amount of RMgX and substrate.

References and notes.

1. a. B. Weidmann and D. Seebach, Helv.Chim. Acta, 1980, **63**, 2451
   b. B. Weidmann and D. Seebach, Angew.Chem.Int.Ed.Engl., 1983, **22**, 31.
2. G. Bartoli, Acc.Chem.Res., 1984, **17**, 109.
3. F. Kienzle, Helv.Chim.Acta, 1978, **61**, 449.
4. Quantitative GLC analyses were carried out using the internal standard procedure, with a HP 5890 apparatus and FID-integrations, using HP 530 m column packed with phenylmethyl-silicone (OV 17) or Carbowax 20M. All compounds were identified by comparison of retention times with those of authentic samples.
5. A typical procedure follows: 4 mmol of a THF solution of Grignard reagent, titrated by the Bergbreiter's method[6] immediately before use, were added dropwise to a THF solution of 4 mmol of a nitroarene (4 mmol of nitrobenzene and 4 mmol of an electrophilic substrate in competitive runs) After 10 min., 4.4. mmol of DDQ were added, and the reaction was stirred for about 3 hours, at 0°C. The reaction mixture was then submitted to GLC analysis or chromatographic purification. It has been controlled by independent reactions that DDQ behaves as extremely chemoselective reagent in this reaction: i.e., under the above reported conditions, it quantitatively oxidizes the nitronate adduct to aromatic nitro compounds, without affecting other electrophilic functions and their reaction products.
6. D.E. Bergbreiter and E. Pendergrass, J.Org.Chem., 1981, **46**, 219.

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