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THE MONO-ALKYLDECYANATION OF TETRAFLUOROTEREPHTHALONITRILE BY REACTION WITH GRIGNARD REAGENTS

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Summary

Treatment of tetrafluoroterephthalonitrile in THF with alkyl Grignard reagents gives the corresponding 4-alkyltetrafluorobenzonitrile in about 60% yield. The scope and limitations of this transformation are reported.

Introduction

Aromatic nitriles almost invariably react with Grignard reagents to give ketimines, which are rarely isolated but which undergo hydrolysis upon work-up to give the corresponding ketones (eq. 1) [1].

$$\text{ArCN} \xrightarrow{\text{RMgX}} [\text{ArCRNH}] \rightarrow \text{ArCRO} \qquad (1)$$

In two instances [2,3] small yields of products resulting from cyano group replacement (eq. 2) have been reported.

$$\text{ArCN} \xrightarrow{\text{RMgX}} \text{ArR} \qquad (2)$$

Most surprisingly, this cyano group replacement reaction can become the major pathway for reaction of tetrafluoroterephthalonitrile (I) with certain Grignard reagents in tetrahydrofuran (THF).

Experimental

Typically, the aromatic nitrile (10 mmol) was stirred in THF (20 ml) together with the additive, if any, and the mixture was brought to the desired temperature. A THF solution of the Grignard reagent (about 1 mmol per ml) was then added dropwise. Samples of the mixture were removed at intervals and treated with aqueous

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hydrochloric acid. The organic products were extracted into methylene chloride and examined by GLC (2 m 5% LAC-2R-446 at 50 to 150°C). The results are shown in Tables 1 and 2.

Product isolation

After completion of the Grignard reaction, water was added to destroy unconsumed Grignard reagent, the THF was distilled off and the residue acidified. Volatile products were then isolated, preferably by steam distillation, but extraction into toluene followed by fractional distillation under reduced pressure can also be used.

The method provides a convenient synthesis of 4-alkyltetrafluorobenzonitriles. Isolated yields were typically 50 to 55%.

Discussion

As a starting material, I appears to offer numerous possibilities for syntheses because of the multiplicity of potential modes of nucleophilic attack. Thus, replacement of fluoride ion by alkyl in the reactions of Grignard reagents with perfluoroaromatics is well known [4], and this reaction is likely to be accelerated by the presence of activating substituent groups such as cyano. Nevertheless, on treatment of the pentafluorobenzonitrile with phenyl magnesium bromide, pentafluorobenzophenone was the only product detected [5]. In this case the customary ketone-forming reaction was markedly more rapid than any fluoride displacement reaction.

Terephthalonitrile reacts with butyl Grignard to form the expected diketone [6]. This shows that a *para*-cyano substituent is insufficient in itself to divert the reaction of an aromatic nitrile with a Grignard reagent from its usual ketone forming course. Moreover, the influence of various other powerful electron-withdrawing groups, e.g. trifluoromethyl, *para* to an aromatic cyano group was reported to increase the rate of reaction of the nitrile with Grignard reagents, and phenones were the only products detected [7].

On the basis of the above reports, treatment of I with Grignard reagents would be expected to lead mainly to phenones together with lesser quantities of products resulting from replacement of fluoride ion. However, suitable choice of reagent and reaction conditions allows the reaction to be steered along the cyano-replacement pathway (Table 1).

The cyano-replacement reaction is highly solvent dependent. With methyl magnesium bromide, by far the highest yield of 4-methyl-2,3,5,6-tetrafluorobenzonitrile (II) was observed in THF. Addition of methyl Grignard in THF to I in dimethoxymethane, 1,4-dioxane, tetrahydrothiophene, diglyme, 1,2-dimethoxyethane, anisole or diethyl ether, afforded mainly either unreacted I or involatile products. Interestingly, in diethylether, II was formed together with comparable amounts of the ketonic products, not detected in comparable THF reactions, which would usually be expected from the reaction of nitriles with Grignard reagents. Partial substitution of toluene for THF as the reaction medium almost completely suppressed the formation of II and, instead, 2,3,5,6-tetrafluorobenzonitrile (IV) was the major volatile product. These observations suggest that alkyldecyanation is favoured by a polar reaction medium.

The influence of temperature, reactant ratio and of added tetrabutylammonium

TABLE 1

REACTIONS OF I WITH VARIOUS GRIGNARD REAGENTS IN THF

Reagent	Mol. ratio Grignard/I	Temp. (°C)	Products	Yield (mol%)	Mass (m/e)
CH_3MgBr	1.6	27	p-$CH_3C_6F_4CN$	9	189
			$CH_3C_6F_3(CN)_2$	2	196
			HC_6F_4CN	3	175
CH_3CH_2MgBr	1.0	30	p-$CH_3CH_2C_6F_4CN$	30	203, 188
	2.0	30	p-$CH_3CH_2C_6F_4H$	50	178, 163
$CH_3CH_2CH_2MgBr$	2.0	−20	p-$CH_3CH_2CH_2C_6F_4CN$	78	217, 189, 188, 162
$(CH_3)_2CHMgBr$	2.0	−20	p-$(CH_3)_2CHC_6F_4CN$	52	182, 217, 202
			$[(CH_3)_2CH]_2C_6F_3CN$	5	241, 226, 184
C_6H_5MgBr	2.0	−20	$(C_6H_5)_2$, C_6H_5CN		
		20	C_6H_5OH		
$C_6H_5CH_2MgBr$	2.5	−20	p-$C_6H_5CH_2C_6F_4CN$	60	265, 91, 264
			$(C_6H_5CH_2)_2$		
$CH_2{=}CHCH_2MgBr$	2.0	−50	p-$CH_2{=}CHCH_2C_6F_4CN$	5	215, 188, 196
$CH_2{=}CHCH_2CH_2MgBr$	1.6	−20	p-$CH_2{=}CHCH_2CH_2C_6F_4CN$	60	229, 188, 41
			$CH_2CHCH_2CH_2C_6F_3(CN)_2$	9	236
cyclo-C_3H_5MgBr			Mostly unreacted I		
	2.5	−20	No volatile products detected.		
$C_6H_5CH{=}CHCH_2MgBr$	2.0	−20	$(C_6H_5CH{=}CHCH_2)_2$	80	234, 117, 115, 91

bromide on the reactions of I with methylmagnesium bromide in THF are shown in Table 2.

Temperature

The formation of IV is effectively suppressed by keeping the reaction temperature below 0°C. However, the ratio of the products II/III, where III is methyltrifluoroterephthalonitrile, is rather insensitive to temperature. Yields of II increase gradually as the reaction temperature is reduced to −20°C, probably through suppression of the formation of involatiles, but remain largely unchanged at lower temperatures.

Stoichiometry

Substantially more than 1 mol of methyl Grignard is needed per mol of I to produce II in good yield. This finding bears a superficial resemblance to the observation that only half the ethyl groups reacted on treatment of benzonitrile with ethyl magnesium bromide in THF [8]. For the benzonitrile reaction, it was proposed that the Grignard reagent existed as a dialkyl species, possibly $Et_2Mg \cdot MgBr_2$, in

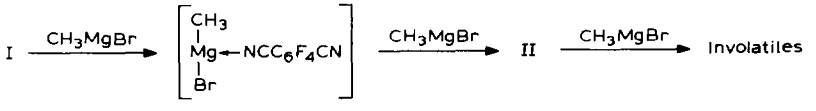
TABLE 2

RESULTS OF THE TREATMENT OF TETRAFLUOROTEREPHTHALONITRILE (I) (10 mmol) WITH METHYL MAGNESIUM BROMIDE IN THF

Mol. ratio reactants, Grignard/I	Reaction temp. (°C)	Additive (g)	Products (mol%)			
			$C_6F_4(CN)_2$	HC_6F_4CN	$CH_3C_6F_4CN$	$CH_3C_6F_4(CN)_2$
1.6	27		0	2.5	9	2
1.6	27	Bu_4NBr (1.0)	0	0	23	5
0.5	3		60	0.5	10	2.6
1.0	3		22	1.9	37	9
1.0	−20		72	0	6	1
1.2	−20		57	0	15	3
1.4	−20		50	0	27	4
1.6	−20		2	0	56	9
2.0	−20		0	0	49	9
1.6	−20		2	0	54	9
1.6	−20	Bu_4NBr (0.2)	3.5	0	67	11
1.6	−20	Bu_4NBr (0.4)	7	0	65	12
1.6	−20	Bu_4NBr (0.6)	8	0	61	12
1.6	−10		25	0	34	7
1.6	−10	Bu_4NBr (0.3)	17	0	40	10
1.6	−10	Bu_4NBr (0.6)	7	0	47	13
1.6	−10	Bu_4NBr (0.9)	24	0	42	13

which the two alkyl groups had different reactivities. The observed progress of the alkyldecyanation of I does not agree with this mechanism. At −20°C, as an equimolar quantity of methyl Grignard is gradually added to I in THF, little II is formed and I remains largely unchanged. Further addition of methyl magnesium bromide leads to rapid formation of II with a maximum yield of II resulting from 1.6 mol of Grignard. With even greater amounts of methyl magnesium bromide the yield of II falls, probably as a result of a secondary reaction between II and the Grignard reagent. Thus, treatment of II with an equimolar quantity of methyl magnesium bromide in THF at −20°C led to consumption of 30% of II within 40 min but no volatile products were detected.

The sequence (shown in eq. 3) is suggested, in which the first mol of Grignard coordinates with I and renders it vulnerable to attack by a second mol of Grignard.



$$\mathrm{I} \xrightarrow{CH_3MgBr} \left[\begin{array}{l} CH_3 \\ | \\ Mg \leftarrow NCC_6F_4CN \\ | \\ Br \end{array}\right] \xrightarrow{CH_3MgBr} \mathrm{II} \xrightarrow{CH_3MgBr} \text{Involatiles} \qquad (3)$$

Influence of additives

Compound IV, which was formed in significant amounts in THF only above 0°C, presumably arises by hydrolysis of $BrMgC_6F_4CN$ upon work-up of the reaction mixtures. In an effort to convert this presumed intermediate into II, I was treated with methyl magnesium bromide in the presence of excess methyl bromide but I remained unchanged. The intense dark blue colour, observed during all successful alkyldecyanations, was not formed when excess methyl bromide was present. The intense colour may indicate that charge transfer species or radical anions are involved in the alkyldecyanation. Suppression of both reaction and colour formation by methyl bromide might, therefore, have arisen by quenching of radical anions by methyl bromide through dissociative electron capture.

Because alkyldecyanation was favoured by high solvent polarity, the possibility of increasing the polarity of THF by the addition of soluble electrolytes was considered. Quaternary ammonium salts were of particular interest since they are reported [9] to stabilise transient dipoles in non-polar solvents. It has been suggested that the electrostatic field of the quaternary ammonium cation can bring about enhanced charge separation and so facilitate transfer interactions (which may play an essential role in the alkyldecyanation). The influence of a variety of quaternary ammonium and phosphonium salts on the reaction of I with methyl magnesium bromide was investigated, but none enhanced the yield of II more than did tetrabutylammonium bromide. The influence of this additive was most marked at the higher reaction temperatures studied, but even at −20°C there was a significant effect (Table 2). This effect increased to a plateau value as the loading of tetrabutylammonium bromide increased to about 1% of the total reaction medium.

Scope of the cyano-replacement reaction

In the reaction of methyl magnesium halides with I in THF, the chloride, bromide and iodide all gave the same yield of II. In contrast, the reaction is markedly dependent on the nature of the Grignard reagents organic radical (Table 1). Ethyl, propyl and isopropyl magnesium bromides reacted much as did methyl Grignard, giving the corresponding 4-alkyltetrafluorobenzonitriles in fair yields. With cyclopropyl magnesium bromide, I was largely unchanged and no new volatile components were detected. Allyl, cinnamyl and phenyl magnesium bromides each consumed I at −20°C but the products were largely involatile. A little 4-allyltetrafluorobenzonitrile was formed at −50°C.

This pattern of reactivity follows the stability of the organic anions from which the Grignard reagents may be thought to derive. Thus, the pK_a value of simple alkanes are typically 50 while those for cyclopropane and benzene are 46 and 43 respectively [10]. Thus, the highly basic insipient carbanions of alkyl Grignards replace cyanide in I much more readily than do their less basic counterparts in which the anionic charge can be de-localised. As an exception to this interpretation, benzyldecyanation occurs in good yield despite the low basicity of the benzyl anion (the pK_a of toluene is 41).

Alkyldecyanation is probably not widely applicable even amongst highly electron deficient aromatic nitriles. Thus, 4-cyanotetrafluoropyridine reacted with methyl magnesium bromide at −20°C to give 4-methyltetrafluoropyridine in only 7% yield. Small quantities of 2,3,5,6-tetrafluoropyridine, 4-acetyltetrafluoropyridine and methyl-4-cyanotrifluoropyridine were also detected together with much involatile material. Moreover, similar treatment of 3,4,5,6-tetrafluorophthalonitrile gave methyltrifluorophthalonitrile (23% yield) as the major volatile product; no methyltetrafluorobenzonitrile was detected and most of the starting material (65%) was converted into involatile products.

The replacement by methyl of a cyano group from I but of a fluorine atom from its *ortho*-isomer agrees with the observation that the activating influence of an electron-withdrawing group is often directed more strongly towards the *para*- rather than the *ortho*-position [11]. The need for an activating group *para* to the nitrile group to be replaced explains why the alkyldecyanation of I stops when one nitrile group has been replaced; dialkyltetrafluorobenzenes were not formed in significant quantities.

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