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Conjugate addition of Grignard reagents to *para*-substituted nitrobenzenes

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Abstract

Nitrobenzenes bearing masked aldehyde, ketone and ketoester functions at the 4-position undergo conjugate addition with Grignard reagents in THF at −15°C. Sequential treatment of the 4-substituted nitrobenzenes with primary or secondary alkyl magnesium halides followed by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone affords the corresponding 2-alkylated derivatives in 50–80% yields.

1. Introduction

Nitrobenzenes (**III**) bearing various substituents at the 2 and 4 positions were needed for structural elaboration through reactions at Z. The results of studies aimed at developing practicable syntheses of various **III** from commercially available compounds *p*-$ZC_6H_4NO_2$ (**I**), by use of conjugate addition of Grignard reagents [1] (Scheme 1), and at determining the dependence of the reaction upon the nature of the group R form the subject of this report.

2. Results and discussion

Bartoli reported that certain nitrobenzenes (**I**) could undergo Grignard addition in THF at −70°C even when Z contained a functional group usually reactive towards Grignard reagents [1]. We have confirmed Bartoli's findings (Table 1). With certain of the compounds **I** the conjugate addition occurred in useful yields.

Unfortunately, −70°C is unsuitable for large scale operations. Moreover, even at this low temperature, compounds **1** in which Z is CHO, COMe or CO-COOAlk, the groups most suitable for our proposed subsequent chemistry, underwent extensive side reactions (Table 1, Entries 4, 5 and 7).

However, nuclear substitution occurred selectively even at −15°C, a temperature accessible on the plant, with *inter alia* nitrobenzenes (**I**) bearing synthetically useful masked aldehyde, ketone and ketoester functions (Table 2). Alternatively, alkylation of 4-nitrophenylacetates gave products (Table 2) which could be oxidised readily to the corresponding ketoester [2]. These observations make conjugate addition of Grignard reagents to usefully functionalised nitroaromatics a practicable method for large scale synthesis.

2.1. *Stoichiometry*

The effect of reactant ratio was not studied in detail. Bartoli reported the use of compounds **I**, the Grignard reagent and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in the mole ratio 1.0 : 1.0 : 1.1. In our hands, a high extent of conversion of **I** in reasonable times was achieved most conveniently by gradual addition of up to 1.5 mol equivalents of the Grignard solution, with monitoring of the progress of the reaction by GLC (see Experimental section). When **I** had been consumed, DDQ was added in 10% mole excess over the amount of Grignard reagent used.

2.2. *Effect of the nature of the Grignard reagent*

Because a variety of products **III** were required, the influence of the nature of the Grignard reagent on the yield of the addition was examined (Table 3). Moder-

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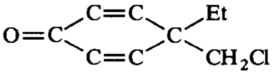
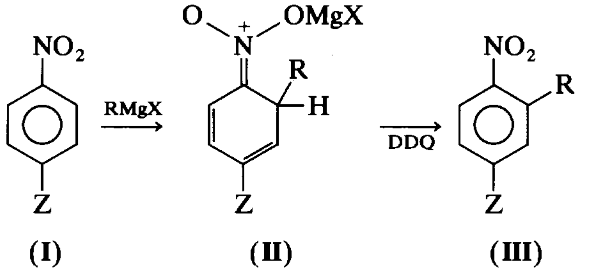
TABLE 1. Treatment of 4-substituted nitrobenzenes with *n*-alkyl magnesium halides in THF at −70°C followed by DDQ [a] at 20°C [b]

Entry	Reactant	Product (%)	*m/e*
1	$O_2NC_6H_4COOMe$	$(4\text{-}O_2N)(3\text{-}Et)C_6H_3COOMe$ (30)	209 210 [b]
2	$O_2NC_6H_4Br$	$(4\text{-}O_2N)(3\text{-}Et)C_6H_3Br$ (50) $(4\text{-}ON)C_6H_4Br$	230(1Br) [b] 186(1Br) [b]
3	$O_2NC_6H_4CH_2Cl$	$(4\text{-}O_2N)(3\text{-}Et)C_6H_3CH_2Cl$ (45)  (15)	200(1Cl) [b] 170(1Cl) [b]
4	$O_2NC_6H_4COMe$	$(4\text{-}O_2N)(3\text{-}Me)C_6H_3COMe$ (30) $(4\text{-}O_2N)(3\text{-}Me)C_6H_3CMe_2OH$ (10)	179 195
5	$O_2NC_6H_4COCOOEt$	$(4\text{-}O_2N)C_6H_4C(Bu)(OH)COOEt$ (20) $(4\text{-}O_2N)(3\text{-}Bu)C_6H_3C(Bu)(OH)COOEt$ (35)	282 [b] 338 [b]
6	$O_2NC_6H_4CH_2CN$	$(4\text{-}O_2N)(3\text{-}Me)C_6H_3CH_2CN$ (< 20)	176
7	$O_2NC_6H_4CHO$	No volatile products detected	
8	$O_2NC_6H_4CHClCOOMe$	$(4\text{-}O_2N)(3\text{-}Me)C_6H_3CHClCOOMe$ (15)	243 (1Cl)

[a] DDQ is 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

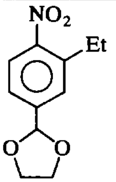
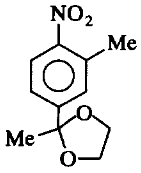
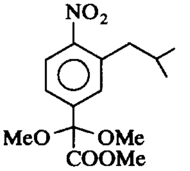
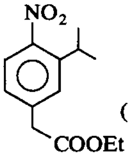
[b] Mass spectra were obtained by electron impact except those marked for which chemical ionisation was used to give $P+1$ ions.



Scheme 1

ate to good yields resulted from the use of primary and secondary alkyl Grignard reagents. With tertiary alkyl and benzyl magnesium halides the yields of the addition products were poor, and no adduct was detected from aryl, allyl or vinyl Grignard reagents.

TABLE 2. Examples of conjugate addition products (yield in %) made by Grignard addition at −15°C followed by addition of DDQ at +20°C

 (58)	 (54)
 (77)	 (69)

3. Experimental details

3.1. Materials

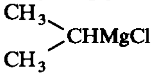
Methyl (4-nitrophenyl)chloroacetate was prepared by the method described by Makosza [3]. DDQ was obtained from Fluka, and 4-nitrophenylglyoxylic acid from Lancaster Synthesis. Solutions of Grignard reagents, the anhydrous THF and all other chemicals were purchased from Aldrich.

3.2. Preparation of masked reactants *I*

3.2.1. Protection of 4-nitrobenzaldehyde

A mixture of 4-nitrobenzaldehyde (50 g, 331 mmol), ethylene glycol (61 ml, 1.1 mol) and *p*-toluenesulphonic acid (6.6 g, 3.5 mmol) was heated under

TABLE 3. Reaction of Grignard reagents in THF at −15°C with 2(4′-nitrophenyl)-1,3-dioxolane followed by DDQ at 20°C

Entry	Grignard reagent	Conjugate addition product m/e		
		Yield (%)	Electron impact ($P-1$)	Chemical ionisation ($P+1$)
1	$MeMgCl$	48	208	210
2	$EtMgCl$	58	222	224
3	$CH_3(CH_2)_3MgCl$	50	250	
4	 $\genfrac{}{}{0pt}{}{CH_3}{CH_3}\!>\!CHMgCl$	40		238
5	$(CH_3)_3CMgCl$	15	250	252
6	$C_6H_5CH_2MgCl$	20	284	
7	C_6H_5MgCl	0		
8	$CH_2{=}CHCH_2MgCl$	0		
9	$CH_2{=}CHMgCl$	0		

reflux (Dean and Stark) in toluene (170 ml) for 21 h. Aqueous work-up gave 2(4′-nitrophenyl)-1,3-dioxolane (44.4 g, 225 mmol) (68% yield). ^{1}H NMR ($CDCl_3$): δ 4.1 (m, 4.0H), 5.9 s (1.0H), 7.6 (d, 2.0H), 8.2 (d, 2.0H). Anal. Found: C, 56.4; H, 4.8; N, 7.2. $C_9H_9NO_4$ calcd.: C, 55.4; H, 4.6; N, 7.2%.

3.2.2. *Protection of 4-nitroacetophenone*

This was carried out as described for the aldehyde. A 69% yield of 2-methyl-2-(4′-nitrophenyl)-1,3-dioxolane was obtained. ^{1}H NMR ($CDCl_3$): δ 1.6 (s, 3.0H); 3.7 (m, 2.0H), 4.0 (m, 2.0H), 7.7 (d, 2.0H), 8.2 (d, 2.0H) Anal. Found: C, 56.4; H, 5.4; N, 6.8. $C_{10}H_{11}NO_4$ calcd.: C, 57.4; H, 5.3; N, 6.7%.

3.2.3. *Preparation of methyl 4-nitrobenzoylformate dimethylketal*

A solution of 4-nitrophenylglyoxylic acid (2.27 g, 11.6 mmol) in dry methanol (100 ml) containing triethyl orthoformate (10.6 g, 100 mmol) was saturated with gaseous hydrogen chloride. The solution was kept at room temperature for three days and volatile materials were taken off under reduced pressure to leave a residue containing the methyl ester along with some ketal. The residue was dissolved in dry methanol containing triethyl orthoformate (5 g, 50 mmol) and the solution saturated with hydrogen chloride. The mixture was kept for two days at room temperature and the solvent removed to leave a solid (2.9 g, 11.4 mmol) (98% yield). ^{1}H NMR ($CDCl_3$): δ 3.3 (s, 6.0H), 3.8 (s, 2.9H), 7.8 (d, 1.9H), 8.3 (d, 2.1H).

3.2.4. *Grignard additions*

The method is adequately illustrated by a single example. To a stirred solution of methyl 4-nitrobenzoylformate dimethylketal (2.0 g, 7.8 mmol) in anhydrous THF (100 ml) at -15°C 2 M isobutylmagnesium chloride in ether (3 ml, 6 mmol) was added dropwise. After 30 min a small sample was withdrawn, shaken with a mixture of water and dichloromethane, and the organic layer examined by GLC on CPSIL 5CB at 110°C to 250°C. Much unreacted ketal remained, but a new species of longer retention time had begun to form. (This may have been the alkyl nitroso compound [4].) A further quantity of the Grignard solution (3 ml) was added and, after a further 1 h, GLC showed that all the starting ketal had been consumed and that there was a single volatile product. DDQ (3.0 g, 13.2 mmol) was added to the mixture which was then stirred overnight without cooling. Water (300 ml) was added and the mixture was extracted with dichloromethane (3 × 150 ml). The combined extracts were washed, dried ($MgSO_4$) and evaporated at reduced pressure to leave a residue, which was subjected to column chromatography on silica with dichloromethane as eluent. This yielded a fraction (1.96 g, 6.0 mmol) (77% yield) consisting of essentially pure alkylated product (Table 2). ^{1}H NMR ($CDCl_3$): δ 0.9 (d, 6.2H), 1.9 (m, 1.0H), 2.8 (d, 1.8H), 3.3 (s, 6.2H), 3.75 (s, 3.1H), 7.2 (m, 1.8H), 7.6 (d, 1.8H), 7.9 (d, 1.0H).

References

1 G. Bartoli, M. Bosco and R. Dalpozzo, *Tetrahedron Lett.*, *26* (1985) 115.
2 W. Polaczkowa, T. Jaworski and J. Wolinski, *Roczniki Chem.*, *27* (1953) 468.
3 M. Makosza, K. Sienkiewicz and K. Wojciechowski, *Synthesis* (1990) 850.
4 G. Bartoli, *Acc. Chem. Res.*, *17* (1984) 109.