ELSEVIER

Journal of Organometallic Chemistry 624 (2001) 167–171

Journal of Organometallic Chemistry

www.elsevier.nl/locate/jorganchem

Alkylation of nitroarenes with Grignard reagents via oxidative nucleophilic substitution of hydrogen

Mieczysław Mąkosza *, Marek Surowiec

Institute of Organic Chemistry, Polish Academy of Sciences, ul. Kasprzaka 44/52, PL-01-224 Warsaw, Poland

Received 5 October 2000; accepted 6 December 2000

Dedicated to Professor Jean Normant on the occasion of his 65 birthday

Abstract

Alkylation of nitroarenes with Grignard reagents via oxidative nucleophilic substitution of hydrogen (ONSH) can be efficiently executed with potasium permanganate in liquid ammonia as an oxidative system for the σ^H adducts. The addition of RMgX to $ArNO_2$ of stoichiometry 1:1 is accompanied with a redox process apparently of stoichiometry 2:1. Because of that, real stoichiometry of the reaction between nitroarenes and Grignard reagents is ca. 1:1.5. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Grignard reagents; Nitro compounds; Alkylation; Oxydative nucleophilic substitution of hydrogen; Oxidation

1. Introduction

Direct alkylation of nitroarenes via nucleophilic replacement of hydrogen can be executed on two principal ways — vicarious nucleophilic substitution (VNS) or oxidative nucleophilic substitution (ONSH) [1,2]. Both of these reactions proceed via addition of carbon nucleophiles to a nitroarene ring *o*- or *p*- to the nitro group producing σ^H adducts, which are subsequently converted into the final products. The VNS reaction takes place when the carbon nucleophiles contain a leaving group X at the carbanion center so the σ^H adducts undergo base induced β-elimination of HX. Alternatively the σ^H adducts of C-nucleophiles can be oxidized with a variety of external oxidants to give products of ONSH. Amongst numerous observations of such processes of particular value are reactions of alkyl magnesium halides with nitroarenes followed by oxidation of the produced σ^H adducts with DDQ or $KMnO_4$ in aqueous acetone reported by Bartoli [3].

Although $KMnO_4$ is an efficient strong oxidant, its use in aqueous acetone could result in protonation of the σ^H adducts and undesired side reactions. Perhaps for this reason this procedure of oxidative alkylation does not assure high yields of the products.

Oxidation of σ^H adducts of ammonia or amide anions is very efficiently executed with $KMnO_4$ in liquid ammonia, a system introduced by van der Plas for oxidative amination of electrophilic heteroarenes [4]. We have found that $KMnO_4$ in liquid ammonia oxidizes efficiently σ^H adducts of the carbanions derived from 2-phenyl propionitrile, and other nitriles to nitroarenes giving the ONSH products, often in quantitative yields [5].

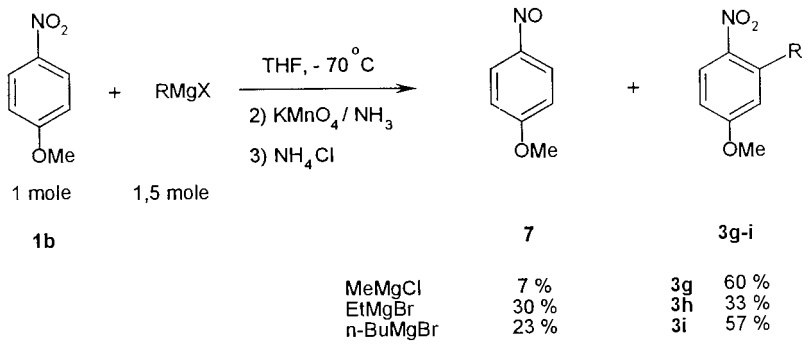
2. Results and discussion

Reported yields of oxidative alkylation of nitroarenes with RMgX and aqueous $KMnO_4$ are not always high, whereas the relatively high price of DDQ and the necessity to separate byproducts prevents its use in preparative experiments. Moreover application of $KMnO_4$ in aqueous acetone for oxidation of the σ^H adducts of MeMgCl to *p*-chloronitrobenzene and *p*-nitroanisole according to the procedure reported by Bartoli gave in our hands lower yields than these reported (33 and 34%) instead of 40 and 56% respectively [3]. In

* Corresponding author. Tel.: +48-22-631-8788; fax: +48-22-632-6681.

E-mail address: icho-s@icho.edu.pl (M. Mąkosza).

PII: S0022-328X(00)00931-1



Scheme 1.

the reaction mixture we have found 4,4′-dichloro-2,2′-dimethyl-azoxybenzene (**5c**) and 4,4′-dichloro-2-methyl-azoxybenzene (**5b**) what indicates that the σ^H adducts undergo other reactions than oxidation, thus search for simple and efficient oxidation system was justified.

Since liquid ammonia decomposes the Grignard reagents, the following procedure was elaborated for oxidation of the σ^H adducts with $KMnO_4$ in liquid ammonia: first σ^H adducts were generated via addition of RMgX to nitroarenes in THF solution at -70°C. To this solution powdered $KMnO_4$ was added and subsequently ammonia was condensed. It was sufficient to condense ca. 5 ml of ammonia for 10 ml of a THF solution to assure an efficient oxidation process. In preliminary control experiments yields of products of oxidative alkylation in liquid ammonia were consistently better than those reported by Bartoli.

An important question is the real stoichiometry of the process. For oxidative alkylation of nitroarenes with Grignard reagents Bartoli recommended the use of a twofold excess of the latter, whereas in the paper by Bentley nitroarenes and RMgX were used in ratio 1:1.5 [6].

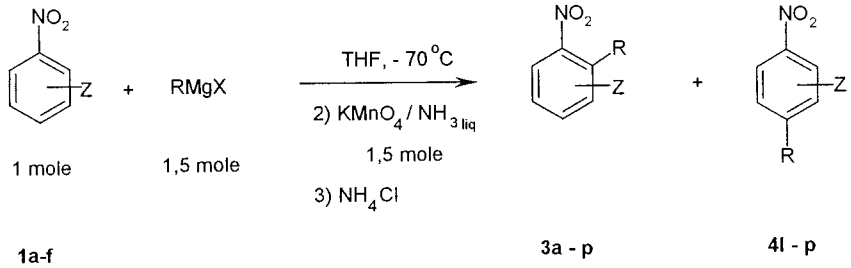
One can assume that the reaction of $ArNO_2$ with RMgX follows two competing pathways: addition to the ring producing σ^H adducts according to stoichiometry 1:1 and other processes such as addition to the NO_2 group, reduction, etc. of stoichiometry 1:2 or more. Using the standard procedure for oxidation of the σ^H adducts for the reaction of *p*-chloronitrobenzene with MeMgCl in ratio 1:1, 1:1.5, 1:2 we have obtained the oxidative methylation product in yields of 52, 70 and 72%, respectively. Since the use of an excess, even substantial, of MeMgCl does not result in decrease of yield of the methylated product formed via oxidation of the σ^H adducts, it appears that these two reactions compete at an early stage and the σ^H adducts once formed are not affected by an excess of MeMgCl. In the reaction mixture only traces of methylated azoxy-compounds produced from σ^H adducts (**5b** and **5c**) as well as significant amounts of product of reduction of the starting nitroarene-4,4′-dichloro-azoxybenzene **5a** are always present, thus the competing reaction in stoichiometry 1:2 is apparently a redox process. This supposition was supported by the reaction of 4-nitroanisole with the Grignard reagents. It is well-known that product of partial reduction of this compound — *p*-nitrosoanisole is more stable than *p*-chloronitrosobenzene. Indeed in this reaction we obtained nitrosoanisole even upon oxidation of the reaction mixture with $KMnO_4$, whereas the starting nitroanisole was not found in the reaction mixture (Scheme 1).

Next we studied how the yields of this reaction are affected by the nature of R in RMgX and also by some substituents in nitroarenes. Results of these experiments are given in Table 1 (Scheme 2). We have found that yields of products of ONSH were somewhat increased when we used Grignard reagents containing longer R. But when secondary Grignard reagents were used, yields of the oxidative alkylation products were substantially lower, perhaps because they are stronger reducting agents than the primary Grignard reagents. For this reason we have not used tertiary Grignard reagents in this reaction. Suprisingly yields of the reaction of

Table 1
Oxidative alkylation of nitroarenes with Grignard reagents and $KMnO_4$ in THF–liquid ammonia (Scheme 2)

Entry	Z	RMgX	Product of ONSH	yields %	
1	4-Cl (**1a**)	MeMgCl	**3a**	70	(77)[a]
2		EtMgBr	**3b**	63	-
3		*n*-PrMgBr	**3c**	75	-
4		*n*-BuMgBr	**3d**	75	(84)[a]
5		*n*-DecylMgBr	**3e**	70	-
6		CyclohexylMgCl	**3f**	35	-
7	4-OMe (**1b**)	MeMgCl	**3g**	60	(63)[a]
8		EtMgBr	**3h**	33	-
9		*n*-BuMgBr	**3i**	57	(61)[a]
10		*i*-PrMgBr	**3j**	35	-
11	4 - CH(O)(O) (**1c**)	MeMgCl	**3k**	49	-[i]
12	H (**1d**)	MeMgCl	**3l, 4l**	40, 20	(43, 20[a]
13		*i*-PrMgBr	**3m, 4m.**	20, 32	-
14		*n*-BuMgCl	**3n, 4n**	33, 38	-
15	2-Cl (**1e**)	*n*-BuMgCl	**3o, 4o**	12, 40	-
16	(**1f**)[b]	*n*-BuMgCl	**3p, 4p**	35, 31	-

[a] Grignard reagents were complexed with TMEDA before the reaction with $ArNO_2$.
[b] **1f** 1-nitronaphtalene



Scheme 2.

EtMgBr with nitroarenes were lower than those of other primary reagents.

It is well known that the reaction pattern of the Grignard reagents is strongly affected by the degree of covalent bonding C–Mg, association in solution, etc. which can be changed using solvents of various solvating power or additives, such as DABCO, associating with metal cations [7]. We have made some experiments using DABCO, TMEDA and HMPT as additives to the solution of the Grignard reagents before the reaction with nitroarenes. It seems that only *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) exerts moderate effect on the reaction course (Table 1). When other agents such as DABCO or HMPTA were used we have not observed increase of yields of the ONSH products. Addition of TMEDA to the Grignard reagents results in precipitation of a partially insoluble complex.

In conclusion we have elaborated an efficient and simple procedure for oxidative alkylation of nitroarenes with the Grignard reagents and $KMnO_4$ in liquid ammonia as oxidant of the intermediate σ^H adducts.

3. Experimental

Melting points were uncorrected. ^{1}H-NMR spectra were recorded with a Varian Gemini 200 (200 MHz) instrument. Chemical shifts are reported in ppm relative to Me_4Si as internal standard; coupling constants *J* are in Hz. For column chromatography silica gel 230–400 mesh, Merck was used. THF was distilled over potassium benzophenon ketyl before reaction. Starting nitroarenes **1a**, **b**, **d** were commercial products. 2-(4′-nitrophenyl)-1,3-dioxolane was prepared according procedure reported by Bentley [5].

Satisfactory combustion analyses within ± 0.4 were obtained for all compounds **3a**–**3k, 3n**–**3p**, **4n**–**4p** and **5c**.

3.1. General procedure for the reaction of nitroarenes with the Grignard reagents

To a stirred solution of nitroarene (2 mmol) in THF (20 ml) cooled to -70°C under argon a solution of alkylmagnesium halide in THF (3 mmol) was added dropwise during ca. 2.5 min. After 5 min powdered $KMnO_4$ (474 mg, 3 mmol) was added and subsequently liquid NH_3 (ca. 10 ml, -70°C) condensed in the mixture. The reaction mixture was stirred for 15 min, NH_4Cl (318 mg, 6 mmol) was added and the cooling bath was removed. To the mixture was added a saturated solution of oxalic acid in aq. HCl (20 ml, 10%) and the mixture was extracted with CH_2Cl_2 (4 × 10 ml). The combined organic layers were dried over $MgSO_4$ and filtered through silica gel. After evaporation of the solvent the products were purifed by column chromatography on silica gel using hexane as an eluent.

3.1.1. 2-Methyl-4-chloronitrobenzene (**3a**)

Orange oil (lit. [3] oil). ^{1}H-NMR (200 MHz, $CDCl_3$) $\delta = 7.96$ (1H, d, $J = 7.81$), 7.26–7.37 (2H, m), 2.61 (3H, s).

3.1.2. 2-Ethyl-4-chloronitrobenzene (**3b**)

Orange oil (lit. [8] oil). ^{1}H-NMR (200 MHz, $CDCl_3$) $\delta = 7.87$ (1H, d, $J = 8.61$), 7.25-7.38 (2H, m), 2.92 (2H, q, $J = 7.51$), 1.30 (3H, t, $J = 7.49$).

3.1.3. 2-n-Propyl-4-chloronitrobenzene (**3c**)

Orange oil. ^{1}H-NMR (200 MHz, $CDCl_3$) $\delta = 7.86$ (1H, d, $J = 8.24$), 7.25–7.60 (2H, m), 2.86 (2H, t, $J = 7.69$), 1.55–1.79 (2H, m), 1.00 (3H, t, $J = 7.36$).

3.1.4. 2-n-Butyl-4-chloronitrobenzene (**3d**)

Orange oil. ^{1}H-NMR (200 MHz, $CDCl_3$) $\delta = 7.86$ (1H, d, $J = 8.93$), 7.25–7.38 (2H, m), 2.88 (2H, t, $J = 8.12$), 1.55–1.72 (2H, m), 1.35–1.50 (2H, m), 0.95 (3H, t, $J = 7.19$).

3.1.5. 2-n-Decyl-4-chloronitrobenzene (**3e**)

Yellow crystals, m.p. 29–31°C (EtOH). ^{1}H-NMR (200 MHz, $CDCl_3$) $\delta = 7.86$ (1H, d, $J = 8.43$), 7.26–7.35 (2H, m), 2.87 (2H, t, $J = 7.86$), 1.54–1.75 (2H, m), 1.16–1.53 (14H, m), 0.88 (3H, t, $J = 6.49$).

3.1.6. 2-Cyclohexyl-4-chloronitrobenzene (**3f**)

Yellow oil. ^{1}H-NMR (200 MHz, $CDCl_3$) $\delta = 7.68$ (1H, d, $J = 8.62$), 7.42 (1H, d, $J = 2.18$), 7.23–7.31 (1H, m), 2.90–3.14 (1H, m.), 1.05–1.95 (10H, m).

*3.1.7. 2-Methyl-4-methoxynitrobenzene (**3g**)*

Colorless crystals, m.p. 43–44°C (EtOH), (lit. [3] 50–53°C). ^{1}H-NMR (200 MHz, $CDCl_3$) $\delta = 8.09$ (1H, d, $J = 9.40$), 6.75–6.85 (2H, m), 3.88 (3H, s), 2.64 (3H, s).

*3.1.8. 2-Ethyl-4-methoxynitrobenzene (**3h**)*

Yellow oil. ^{1}H-NMR (200 MHz, $CDCl_3$) $\delta = 8.03$ (d, 1H, $J = 9.57$), 6.75–6.83 (m, 2H), 3.89 (s, 3H), 2.97 (q, 2H, $J = 7.40$), 1.29, (t, 3H, $J = 7.46$).

*3.1.9. 2-n-Butyl-4-methoxynitrobenzene (**3i**)*

Orange oil (lit. [3] oil). ^{1}H-NMR (200 MHz, $CDCl_3$) $\delta = 8.01$ (1H, d, $J = 9.55$), 6.83–6.75 (2H, m), 3.88 (3H, s), 2.93 (2H, t, $J = 7.75$), 1.53–1.75 (2H, m), 1.30–1.50 (2H, m), 0.95 (3H, t, $J = 7.19$).

*3.1.10. 2-i-Propyl-4-methoxynitrobenzene (**3j**)*

Orange oil. ^{1}H-NMR (200 MHz, $CDCl_3$) $\delta = 7.87$ (1H, d, $J = 9.05$), 6.92 (1H, d, $J = 2.73$), 6.77 (1H, dd, $J = 9.02$, $J = 2.76$), 3.88 (3H, s), 3.50–3.80 (1H, m), 1.29 (6H, d, $J = 6.81$).

*3.1.11. 2-(2-Methyl-4-nitrophenyl)-1,3-dioxolane (**3k**)*

Orange oil (lit. [6] oil). ^{1}H-NMR (200 MHz, $CDCl_3$) $\delta = 7.98$ (1H, d, $J = 8.98$), 7.45–7.49 (2H, m), 5.83 (1H, s), 4.04–4.14 (4H, m), 2.61 (3H, s).

2-Methyl-nitrobenzene (**3l**), 4-methyl-nitrobenzene (**4l**), 2-*i*-propyl-nitrobenzene (**3m**), 4-*i*-propyl-nitrobenzene (4m) were identical to commercial samples.

*3.1.12. 2-n-Butyl-nitrobenzene (**3n**)*

Yellow oil (lit. [11] oil). ^{1}H-NMR (200 MHz, $CDCl_3$) $\delta = 7.90$–7.83 (1H, m), 7.55–7.45 (1H, m), 7.38–7.26 (2H, m), 2.88 (2H, t, $J = 7.82$), 1.72–1.52 (2H, m), 1.49–1.25 (2H, m), 0.94 (3H, t, $J = 7.15$).

*3.1.13. 4-n-Butyl-nitrobenzene (**4n**)*

Yellow oil (lit. [11] oil). ^{1}H-NMR (200 MHz, $CDCl_3$) $\delta = 8.14$ (2H, m), 7.33 (2H, m), 2.72 (2H, t, $J = 7.69$), 1.72-1.52 (2H, m), 1.49–1.25 (2H, m), 0.94 (3H, t, $J = 7.22$).

*3.1.14. 2-n-Butyl-6-chloro-nitrobenzene (**3o**)*

Yellow oil. ^{1}H-NMR (200 MHz, $CDCl_3$) $\delta = 7.37$–7.32 (2H, m), 7.28–7.20 (1H, m), 2.58 (2H, t, $J = 7.74$), 1.68–1.51 (2H, m), 1.46–1.23 (2H, m), 0.92 (3H, t, $J = 7.21$).

*3.1.15. 4-n-Butyl-2-chloro-nitrobenzene (**4o**)*

Yellow oil. ^{1}H-NMR (200 MHz, $CDCl_3$) $\delta = 7.83$ (1H, d, $J = 8.31$), 7.35 (1H, d, $J = 1.75$), 7.21 (1H, dd, $J = 8.33$, $J = 1.80$), 2.67 (2H, t, $J = 7.61$), 1.71–1.54 (2H, m), 1.46–1.23 (2H, m), 0.94 (3H, t, $J = 7.22$).

*3.1.16. 2-n-Butyl-1-nitronaphtalene (**3p**)*

Yellow oil. ^{1}H-NMR (200 MHz, $CDCl_3$) $\delta = 7.91$–7.83 (2H, m), 7.72–7.48 (3H, m), 7.75 (1H, d, $J = 8.54$), 2.73 (2H, t, $J = 7.80$), 1.77–1.60 (2H, m), 1.49–1.29 (2H, m), 0.93 (3H, t, $J = 7.25$).

*3.1.17. 4-n-Butyl-1-nitronaphtalene (**4p**)*

Yellow oil (lit. [12] oil). ^{1}H-NMR (200 MHz, $CDCl_3$) $\delta = 8.62$–8.56 (1H, m), 8.18–8.10 (2H, m), 7.75–7.58 (2H, m), 7.37 (1H, d, $J = 7.88$), 3.13 (2H, t, $J = 7.70$), 1.85–1.65 (2H, m), 1.59–1.35 (2H, m), 0.98 (3H, t, $J = 7.24$).

*3.1.18. 4,4′-Dichloro azoxybenzene (**5a**)*

Orange crystals, m.p. 151–152°C ($CHCl_3$), (lit. [10]). MS(EI) m/z (relative intensity): 266 ([M^+], 55), 250 (3), 237 (3), 125 (48), 111 (base). HRMS (EI): Calc. for $C_{12}H_8ON_2^{35}Cl_2$ [M^+]: 266.00137; Found: 266.00049. ^{1}H-NMR (200 MHz, $CDCl_3$) $\delta = 8.25$ (d, 2H, $J = 9.17$), 8.16 (d, 2H, $J = 9.12$), 7.48 (d, 2H, $J = 6.65$), 7.44 (d, 2H, $J = 6.65$).

*3.1.19. 4,4′-Dichloro-2-methyl-azoxybenzene (**5b**)*

Orange crystals, m.p. 146–147°C (EtOH). MS(EI) m/z (relative intensity): 280 ([M^+], 38), 265 (89), 245 (9), 228 (13), 111 (base). HRMS (EI): Calc. for $C_{13}H_{10}ON_2^{35}Cl_2$ [M^+]: 280.01702; Found: 280.01664.

*3.1.20. 4,4′-Dichloro-2,2′-dimethyl-azoxybenzene (**5c**)*

Orange crystals, m.p. 99°C (MeOH). ^{1}H-NMR (200 MHz, $CDCl_3$) $\delta = 8.25$ (d, 1H, $J = 8.55$), 7.63 (d, 1H, $J = 8.76$), 7.22–7.34 (m, 4H), 2.49 (s, 3H), 2.36 (s, 3H).

*3.1.21. 4-Methoxynitrosobenzene (**4**)*

Green oil (lit. [9], m.p. 20–22°C). ^{1}H-NMR (200 MHz, $CDCl_3$) $\delta = 7.93$ (2H, d, $J = 8.80$), 7.03 (2H, d, $J = 9.10$), 3.95 (3H, s). MS(EI) m/z (relative intensity) 137 ([M^+], base), 123 (6), 107 (43), 92 (78), 77 (81).

3.2. General procedure for the reaction of nitroarenes with Grignard reagents complexed with TMEDA

To a stirred solution of alkylmagnesium halide (3 mmol) in THF (20 ml) was added dropwise during ca. 2.5 min TMEDA (6 mmol) and stirring was continued for 15 min. The suspension was cooled to -70°C under argon and a solution of nitroarene (2 mmol) in THF (2 ml) was added dropwise during ca. 3 min. After 5 min powdered $KMnO_4$ (474 mg, 3 mmol) was added and subsequently liquid NH_3 (ca. 10 ml, -70°C) condensed in the mixture. The reaction mixture was stirred for 15 min and NH_4Cl was added (318 mg, 6 mmol) and cooling bath removed. The work-up was as in the general procedure for reaction of nitroarenes with Grignard reagents.

Acknowledgements

The authors thank the State Committee for Scientific Research for financial support of this work (grant no. PBZ 6.01).

References

[1] (a) M. Mąkosza, J. Winiarski, Acc. Chem. Res. 20 (1987) 282. (b) M. Mąkosza, K. Wojciechowski, Liebigs Annalen Receuil (1997) 1805. (c) M. Mąkosza, Russ. Chem. Bull. 45 (1996) 491. (d) M. Mąkosza, K. Staliński, Polish J. Chem. 73 (1999) 151.
[2] (a) F. Terrier, Nucleophilic Aromatic Displacement, Verlag Chemie, Weinheim, 1991. (b) O.N. Chupakhin, V.N. Charushin, H.C. van der Plas, Nucleophilic Aromatic Substitution of Hydrogen, Academic Press, San Diego, 1994.
[3] (a) G. Bartoli, Acc. Chem. Res. 17 (1984) 109. (b) G. Bartoli, M. Bosco, J. Org. Chem. 45 (1980) 522. (c) G. Bartoli, M. Bosco, J. Org. Chem. 47 (1982) 5227.
[4] (a) A. Counotte-Potman, H.C. van der Plas, J. Heterocyclic Chem. 18 (1981) 123. (b) H.C. van der Plas, M. Woźniak, Croatica Chemica Acta 59 (1986) 33.
[5] (a) M. Mąkosza, K. Staliński, Chem. Eur. J. 3 (1997) 2025. (b) M. Mąkosza, K. Staliński, Tetrahedron 54 (1998) 8797. (c) M. Mąkosza, K. Staliński, Synthesis 11 (1998) 1631.
[6] J.S. Bentley, D.J. Milner, J. Organomet. Chem. 447 (1993) 1.
[7] (a) C. Chevrot, K. Kham, J. Perichon, J.F. Fauvarque, J. Organomet. Chem. 161 (1978) 139. (b) J. Ducom, B. Denise, J. Organomet. Chem. 26 (1971) 305. (c) H.L. Lewis, T.I. Brown, J. Am. Chem. Soc. 92 (1970) 4664. (d) D.J. Peterson, J. Org. Chem. 32 (1967) 1717.
[8] K. Altau, J.G. Beasley, H.J. Pine, R.H. Crawford, J. Chem. Eng. Data 8 (1963) 122.
[9] C.A. Leigh, M.B. Geiger, J. Am. Chem. Soc. 54 (1932) 3064.
[10] G.A. Olah, K. Dunne, D.P. Kelly, Y.K. Mo, J. Am. Chem. Soc. 94 (1972) 7438.
[11] P. Laszlo, J. Vandormael, Chem. Lett. (1988) 1843.
[12] A.W. Dąbrowski, A.P. Gierientiew, A.M. Jurkiewicz, Zh. Obsch. Khim. 27 (1957) 421.