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REDUCTION OF NITRONATE ADDUCTS FROM RMgX AND 1-METHOXY-4-NITRONAPHTHALENE TO OXIMES OR AMINES BY TRIVALENT PHOSPHORUS REAGENTS

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Summary: The reduction of nitronate adducts from 1-methoxy-4-nitronaphthalene and Grignard reagents (CH_3MgX, $PhCH_2CH_2MgX$, $i\text{-}C_3H_7MgX$, $c\text{-}C_6H_{11}MgX$ and $t\text{-}C_4H_9MgX$) with hexamethyl phosphorous triamide and phosphorous trichloride is reported. With the former reagent the reaction is chemio and stereoselective and only the E-oxime is recovered being the E-2-alkyl-4-methoxy-1(2H)naphthalenone oximes and the E-2-alkyl-2,3-dihydro-1,4-naphthoquinone-1-oximes obtained after quenching with NH_4Cl and HCl respectively. Oxime stereochemistry is assigned by LIS values caused by $Eu(dpm)_3$ on ^{13}C signals of 2-methyl-4-methoxy-1-(2H)naphthalenone oxime and 2-methyl-2,3-dihydro-1,4-naphthoquinone-1-oxime. Complete reduction to amines is obtained with phosphorous trichloride.

Nitronate adducts from conjugate addition of alkyl magnesium halides to nitroarenic systems have proved to be useful and versatile intermediates[1] in the synthesis of a large variety of aromatic or cyclohexadienic alkylated derivatives. Generally oxidizing[2] and electrophilic[3] reagents have been employed in these reactions, while the only example of reduction is confined to their conversion into alkyl substituted aromatic amines by means of an excess of RMgX in the presence of CuI as a catalyst[4]. On the other hand the reaction of nitronic compounds with reducing agents has generally received little attention.

On pursuing our studies on synthetic applications of the nitronate adducts, we wish to report now the results obtained in the reduction of the adduct from RMgX and 1-methoxy-4-nitronaphthalene(1) with phosphorous reagents.

Reduction with hexamethyl phosphorous triamide. Synthesis of E-2-alkyl-4-methoxy-1-(2H)naphthalenone oximes (4a-e) and E-2-alkyl-2,3-dihydro-1,4-naphthoquinone-1-oxime (5a-e).

A tetrahydrofuranic solution of the nitronate adducts (3a-e) from 1 and RMgX (2a, R=Me; 2b, R=$PhCH_2CH_2$, 2c, R=i-Pr; 2d, R=c-C_6H_{11}; 2e, R=t-Bu) freshly prepared with the procedure previously described,[5] was treated with 1.4 eq. of $P(NMe_2)_3$. The reaction, carried out for 48 hrs, was then quenched with aqueous ammonium chloride. The usual work up gave the 2-alkyl-4-methoxy-1-(2H)naphthalenone oximes (4a-e) in satisfactory yields. Table I contains yields and analytical data of oximes 4.

The alternative quenching with a methanolic solution of HCl, followed by few minutes of stirring, led to 2-alkyl-2,3-dihydro-1,4-naphthoquinone-1-oximes (5a-e). Table II contains yields and analytical data of oximes 5.

In this reaction, a little amount of 2-alkyl-1,4-naphthoquinone as by-product was also isolated. Under our experimental conditions, this by-product ranges from about 10% to 4% going from primary to secondary and tertiary substituents. The formation of naphthoquinone may be ascribed to the occurence of an hydrolysis process of the oximes 5 to 2,3-dihydro-1,4-naphthoquinones followed by oxidation by

Scheme

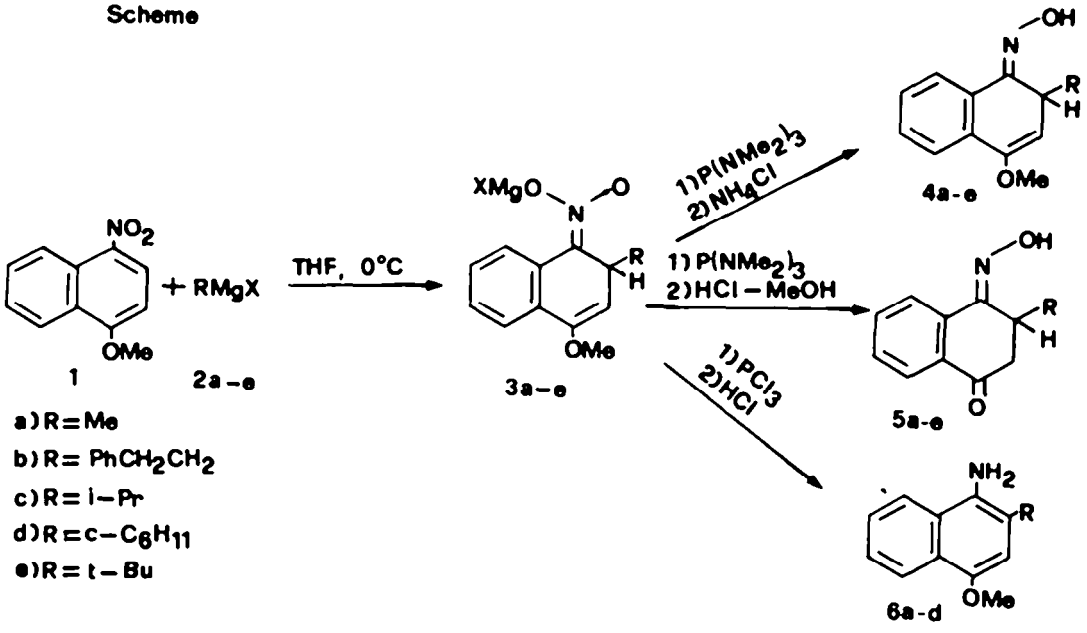


Table I - Synthesis of 2-Alkyl-4-methoxy-1-(2H)naphthalenone oximes (4a-e). Yields and Spectral Data.

Compound[a]	Yield[b] (%)	m.p. (°C)	IR (KBr) ν(cm^{-1})	^{1}H-NMR ($CDCl_3$) ppm from Me_4Si
4a	46	138-40	1665 C=N 3200 OH	1.24 (d, 3H, CH_3, $J_{CH_3\text{-}2}$ = 7 Hz), 3.75 (s, 3H, OMe), 4.0-4.3 (m, 1H, H2), 5.04 (d, 1H, H3, $J_{2,3}$ = 5.4 Hz), 7.3-7.9 (m, 4H, arom), 8.3 (s, 1H, OH).[c]
4b	42	104-7	1660 C=N 3220 OH	1.8-2.1, 2.5-2.8 (m, 4H, CH_2CH_2), 3.78 (s, 3H, OMe), 4.25 (m, 1H, H2), 5.08 (d, 1H, H3, $J_{2,3}$ = 5.6 Hz), 7.1-7.9 (m, 9H, arom), 9.1-9.5 (m, 1H, OH).[c]
4c	45	129-31	1645 C=N 3240 OH	0.74 (d, 3H, CH_3, J_{CH_3CH} = 6.8 Hz), 0.97 (d, 3H, CH_3, J_{CH_3CH} = 6.8 Hz), 2.0-2.4 (m, 1H, CH), 3.78 (s, 3H, OMe), 4.07 (t, 1H, H2), 5.08 (d, 1H, H3, $J_{2,3}$ = 5.6 Hz), 7.3-7.9 (m, 4H, arom), 8.4 (s, 1H, OH).[c]
4d	51	115-7	1650 C=N 3230 OH	0.9-1.9 (m, 11H, aliph), 3.80 (s, 3H, OMe), 4.06 (t, 1H, H2), 5.08 (d, 1H, H3, $J_{2,3}$ = 5.6 Hz), 7.3-7.9 (m, 4H, arom), 8.3 (bs, 1H, OH).[c]
4e	48	183-5	1660 C=N 3260 OH	0.86 [s, 9H, $(CH_3)_3$], 3.76 (s, 3H,OMe), 4.02 (d, 1H, H2, $J_{2,3}$ = 6.0 Hz), 5.05 (d, 1H, H3), 7.3-7.7 (m, 4H, arom), 8.75 (bs, 1H, OH).[c]

[a] All compounds gave satisfactory microanalysis. [b] Ponderal yields calculated with respect to 1-methoxy-4-nitronaphthalene. [c] Shifts vary with concentration.

Table II - Synthesis of 2-Alkyl-2,3-dihydro-1,4-naphthoquinone-1-oximes (5a-e). Yields and Spectral Data.

Compound[a]	Yield[b] (%)	m.p. (°C)	IR (KBr) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$) ppm from Me_4Si
5a	44	154-6	1690 C=O 3240 OH	1.21 (d, 3H, CH_3, J_{CH_3-2} = 7.2 Hz), 2.56-3.13 (m, 2H, H3, J_{3a-2} = 2.2 Hz, J_{3b-2} = 5.8 Hz, J_{3a-3b} = 16 Hz), 3.80-4.50 (m, 1H, H2), 7.4-8.2 (m, 4H, arom), 8.58 (bs, 1H, OH).[c]
5b	40	135-7	1680 C=O 3320 OH	1.5-2.1 and 2.4-3.0 (m, 6H, CH_2CH_2 and H3), 3.8-4.3 (m, 1H, H2), 6.8-8.2 (m, 9H, arom), 8.50 (bs, 1H, OH).[c]
5c	60	131-3	1700 C=O 3250 OH	0.90 (d, 3H, CH_3, J_{CH_3CH} = 6.6 Hz), 1.00 (d, 3H, CH_3, J_{CH_3CH} = 6.6 Hz), 1.61 (m, 1H, CH), 2.67-3.15 (m, 2H, H2, J_{3b-2} = 5.2 Hz, J_{3a-2} = 2.8 Hz, J_{3a-3b} = 16.6 Hz), 3.6-3.9 (m, 1H, H2), 7.4-8.1 (m, 4H, arom), 8.24 (bs, 1H, OH).[c]
5d	56	160-2	1660 C=O 3230 OH	0.7-2.1 (m, 11H, aliph), 2.64-3.18 (m, 2H, H3, J_{3b-2} = 5.4 Hz, J_{3a-2} = 2.2 Hz, J_{3a-3b} = 16.4 Hz), 3.6-4.0 (m, 1H, H2), 7.4-8.2 (m, 4H, arom), 8.48 (bs, 1H, OH).[c]
5e	57	152-5	1670 C=O 3280 OH	0.88 [s, 9H, $(CH_3)_3$], 2.6-3.2 (m, 2H, H3, J_{3b-2} = 6.6, J_{3a-2} = 20 Hz, J_{3a-3b} = 17.6 Hz), 7.34-8.13 (m, 4H, arom), 8.46 (m, 1H, OH).[c]

[a] All compounds gave satisfactory microanalysis. [b] Ponderal yields calculated with respect to 1-methoxy-4-nitronaphthalene. [c] Shifts vary with concentration.

air moisture during the work-up of the reaction.

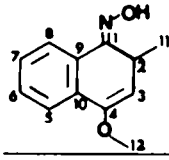
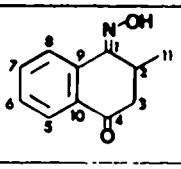
Longer reaction times increase the amount of naphthoquinone to the detriment of the oxime. Moreover the more sterically hindered the compounds 5 are, the slower the process is.

Both the reactions leading to oximes 4a-e and 5a-e result to be chemio and stereoselective. In fact under the employed conditions, further reduction of oximes to naphthyl amines does not occur and, between the two possible oximes, only the E-isomer is obtained, indicating that the reduction stage of the reaction involves the less hindered oxygen atom of the nitronic function: i.e. the oxigen anti to the C-2, even when the alkyl fragment bonded to this carbon is the moderate in size methyl group.

Configurational assignement

Recently it has been reported[6] that addition of $Eu(dpm)_3$ to oximes shifts upfield the ^{13}C signals of the carbon anti to the lone pair of the nitrogen and downfield the ones of the other nuclei near to the nitrogen atom. This behaviour provides an unambiguous method for configurational assignement to oximes even in cases where only one isomer is available. With this in mind the lanthanide induced shifts

Table III - Significant ^{13}C Chemical Shifts and LIS Values[a] by $Eu(dpm)_3$ of 2-Methyl-4-methoxy-1-(2H)naphthalenone oxime (4a) and 2-Methyl-2,3-dihydro-1,4-naphthoquinone-1-oxime (5a).

Significant Carbons	 **4a**		 **5a**	
	^{13}C shifts (ppm from Me_4Si)	LIS values (ppm)	^{13}C shifts (ppm from Me_4Si)	LIS values (ppm)
C-2	29.43	-3.6	27.99	-0.1
C-3	100.82	1.0	44.18	0.9
C-8	124.19	10.1	124.88	1.9
C-9	132.01	2.4	132.20	0.9
C-10	128.42	0.6	130.28	0.4
C-11	19.00	4.0	18.04	0.7
C-12	55.05	0.1	-	-

[a] Negative values indicate upfield shifts.

(LIS) caused by $Eu(dpm)_3$ on the oximes 4a and 5a were determined (see table III).

The upfield shift of C-2 carbon and the downfield ones of the C-8, C-9 and C-11 nuclei are consistent in both compounds, with the E-isomer configuration.

Moreover the very small LIS values, showed by C-3, C-10 and C-12 in compound 4a and by C-3 and C-10 in compound 5a, indicate a negligible complexation of $Eu(dpm)_3$ to the oxygen of the methoxy and of the carbonilic function respectively.

In addition the E-configuration of the oximes 4b-e and 5b-e can be reliably deduced from the inspection of the H-2 chemical shift values which are very similar to those of the oximes 4a and 5a respectively along the whole series both for 4 and 5 derivatives.[7]

Reduction with phosphorous trichloride. Synthesis of 2-alkyl-4-methoxy-1-naphthylamines (6a-d).

The treatment of nitronate adducts 3a-d with 1.4 eq. of PCl_3 followed by quenching with HCl 18% and usual work-up gave the 3-alkyl-3,4-dihydro-4-nitro-1-(2H)naphthalenones, the 2-alkyl-4-methoxy-1-naphthylamines (6a-d) and little amounts of oximes 5a-d. The first compounds arose from the aci-nitro tautomerism and from hydrolysis of the vinyl ether function in the acidic reaction medium of the nitronate adducts which were not reduced by the phosphorous reagent.

When 2 eq. of the reducing agent were used, the complete reduction of compounds 3a-d to amines 6a-d was obtained in high yields. Table IV contains yields and analytical data for compounds 6a-d.

In the case of nitronate 3e only the oxime 5e is always recovered, probably because the great bulkiness of the t-butyl prevents PCl_3 from reducing the sterically hindered oxygen of the nitronic function.

In conclusion, although under the same experimental conditions, phosphorous trichloride is not chemioselective with respect to hexamethyl phosphorous triamide, it has the advantage of being a more efficient reducing agent, allowing the amines to be obtained in much

Table IV - Synthesis of 2-Alkyl-4-methoxy-1-naphthylamine (6a-d) Yields and Spectral Data.

Compound[a]	Yield[b] (%)	m.p.	IR(CCl_4) ν_{NH_2} (cm^{-1})	^{1}H-NMR ($CDCl_3$) ppm from Me_4Si
6a	65	oil	3410 3480	2.37 (s, 3H, CH_3), 3.7 (s, 2H, NH_2),[c] 3.96 (s, 3H, OMe), 6.64 (s, 1H, H3), 7.3-8.2 (m, 4H, arom).
6b	55	oil	3360 3480	2.3-3.4 (m, 4H, CH_2CH_2), 3.8 (s, 3H, OMe), 3.9 (s, 2H, NH_2),[c] 6.9 (s, 1H, H3), 7.8-8.1 (m, 9H, arom).
6c	60	oil	3390 3470	1.35 (d, 6H, CH_3, J_{CH_3CH} = 6.8 Hz), 3.23 (ept, 1H, CH), 3.98 (s, OMe, 3H), 4.1 (s, 2H, NH_2),[c] 6.75 (s, 1H, H3), 7.3-8.3 (m, 4H, arom).
6d	70	oil	3360 3480	1.0-2.2 (m, 11H, aliph), 2.7 (s, 2H, NH_2),[c] 3.9 (s, 3H, OMe), 6.7 (s, 1H, H3), 7.2-8.3 (m, 4H, arom).

[a] All compounds gave satisfactory microanalysis. [b] Ponderal yields calculated with respect to 1-methoxy-4-nitronaphthalene. [c] Shifts vary with concentration.

shorter times.

Experimental Section

M.p.s are uncorrected and were determined with a Büchi apparatus.

^{1}H-NMR spectra were recorded at 100 MHz and ^{13}C-NMR ones at 25.16 MHz with a Varian XL-100 instrument in the FT mode. ^{13}C assignements were made with the aid of the off-resonance technique. Proton shifts are given in p.p.m. from Me_4Si in $CDCl_3$. ^{13}C shifts are given in p.p.m. from Me_4Si in CD_2Cl_2. IR spectra were recorded with a Perkin Elmer 257 spectrophotometer.

THF, dried over sodium and distilled, was redistilled from $LiAlH_4$ immediately before use. 4-Methoxy-1-nitronaphthalene (1) was a commercial product. All Grignard reagents solutions were prepared with the standard procedure and titrated using the Bergbreiter's method.[8] Commercial hexamethyl phosphorous triamide and phosphorous trichloride were distilled before use.

Preparation of nitronate adducts (3a-e) - General procedure.

A solution of 0.0065 mol of alkylmagnesium halide in THF was added dropwise to a stirred solution of 0.005 mol of 1 in 10 ml of the same solvent at 0°C during 5 minutes, flushing nitrogen.

Synthesis of 2-alkyl-4-methoxy-1-(2H)naphthalenone oxime (4a-e).

To a ice cooled solution of the nitronate adduct were added 0.01 mol of $P(NMe_2)_3$.

The reaction was stirred for 48 hours at room temperature and then poured into a saturated solution of aqueous NH_4Cl, immediately followed by extraction with CH_2Cl_2. The organic layer dried with Na_2SO_4, was evaporated under reduced pressure. The oximes were purified by chromatographic separation on a silica gel column [light petroleum (bp 40-60°)-ethyl ether 80:20 as eluant]. Yields and analytical data are reported in Table I.

Synthesis of 2-alkyl-2,3 dihydro-1,4-naphthoquinone-1-oxime (5a-e).

To a ice cooled solution of 3a-e were added 0.01 mol of $P(NMe_2)_3$. The reaction was stirred for 48 hours at room temperature and then poured into 20 ml of a 1:1 solution of CH_3OH and HCl conc. After 5 minutes the mixture was extracted with CH_2Cl_2, dried and evaporated under reduced pressure. The oximes 5a-e were separated from the by-product naphthoquinone by submitting the crude of the reaction to a chromatographic purification on a silica gel column using hexane - ethyl ether 80:20 as eluant. Yields and analytical data of compounds 5a-e are reported in table II.

Structural assignements of compounds 4a and 5a.

The LIS values reported in table III were obtained from spectra run adding to 2.0 ml of a saturated solution of the oximes 4a and 5a in CD_2Cl_2, 0.05, 0.1 and 0.2 molar ratios of $Eu(dpm)_3$ with respect to the oximes.

Synthesis of 2-alkyl-4-methoxy-1-naphthylamines (6a-d).

To a freshly prepared ice cooled solution of 3a-e t-Butanol (0.02 mol) was added and then a solution of 0.01 mol of PCl_3 in 15 ml of THF. The reaction was stirred for about 3 hours at room temperature before quenching with 10 ml of HCl 18%. After 20 minutes the solution was neutralized with a saturated solution of $NaHCO_3$, extracted with CH_2Cl_2, dried and evaporated under reduced pressure. The amines were isolated by chromatographic separation on a silica gel column using benzene-ethyl acetate 90:10 as eluant. Yields and analytical data of compounds 6a-d are reported in table IV.

With this procedure the 2-t-butyl-4-methoxy-1-naphthylamine is not obtained from the nitronate adduct 3e but the oxime 5e is only recovered in about 50% yield.

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