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Cerium(III) Chloride Mediated Addition of Grignard Reagents to Nitroalkanes: Synthesis of *N,N*-Disubstituted Hydroxylamines

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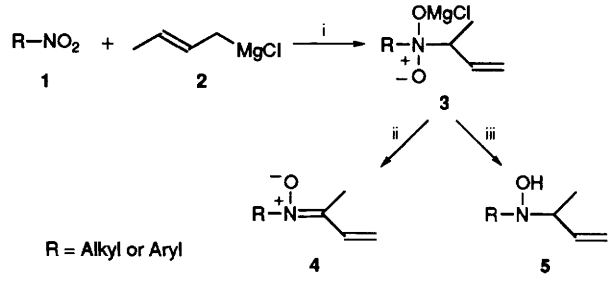
Reaction of nitroalkanes with Grignard reagents, in the presence of anhydrous $CeCl_3$ in tetrahydrofuran at −78 °C, affords *N,N*-disubstituted hydroxylamines in fair to good yields, depending on the nature of the reagent used.

The course of the reaction of nitroalkanes with Grignard reagents strongly depends on the nature of the carbanionic framework. Recently, we reported that the reaction between aliphatic nitro compounds and allylic or benzylic Grignard reagents can provide a good approach to the synthesis of nitrones.[1] The success of this procedure has been ascribed to the low basicity of carbanions possessing π character. These nucleophiles selectively attack the electrophilic nitrogen atom, leading to an unstable tetrahedral intermediate that, upon acidic quenching, can be converted to the parent nitrone or can be reduced to the corresponding hydroxylamine (Scheme 1).[2] Every attempt to reiterate the same reaction with the more basic alkyl or aryl organomagnesium reagents, regularly led to frustrating results since proton transfer and/or redox processes occur predominantly.[1,3]

The elaboration of a procedure to extend the reaction of nitroalkanes towards alkyl or aryl moieties would be of considerable interest since *N,N*-disubstituted hydroxylamines are difficult to synthetize by common methods.[4] In this context, organocerium reagents have captured our attention because they are known to possess a rather low basicity that enables them to be used with readily enolizable substrates.[5]

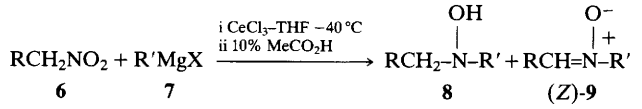
We report here that the use of organocerium reagents provides a considerable suppression of proton transfer and redox processes in the reaction with nitroalkanes, allowing the formation of *N,N*-disubstituted hydroxylamines in good yields (Table 1).† Rather surprisingly, nitro compounds are reported to react with organocerium reagents at −78 °C giving many products.[6] Since no further details are given for this reaction, we presume that the success of our reaction could be ascribed to the different experimental procedure followed. The organocerium reagents employed can be generated *in situ*, by addition of the corresponding Grignard reagent to a suspension of dry $CeCl_3$ and the nitroalkane at −40 °C (method A), or preformed before the addition of the



1 2 3 4 5

Scheme 1 *Reagents and conditions*: i, THF, −70 °C; ii, aq. NH_4Cl; iii, H^-, Pd/C, 20 °C

Table 1 Products and yields of the reaction between Grignard reagents and nitro compounds in THF at −40 °C in the presence of $CeCl_3$, followed by acidic quenching



6 7 8 (*Z*)-9

Entry	RCH_2NO_2	R'	Yield (%) 8	(*Z*)-9
a	1-Nitrobutane	1-Propyl	90	—
b	1-Nitrohexane	Methyl	92	—
c	1-Nitrohexane	1-Propyl	81	—
d	1-Nitrohexane	Phenyl	86	—
e	1-Nitrocyclohexane	1-Propyl	82	—
f	1-Phenylnitromethane	1-Propyl	92	—
g	1-Nitrohexane	2-Propyl	67	8
h	1-Nitrononane	2-Propyl	65	10
i	1-Nitrohexane	2-Pentyl	58	16

† *Selected spectroscopic data* for new hydroxylamines **8** prepared: **8c**: b.p. 75 °C at 5 mmHg; ν_{max}/cm^{-1} 3250 (OH); ^1H NMR (300 MHz) δ 0.90 (t, 6H, *J* 7.3 Hz), 1.20–1.40 (m, 6H), 1.50–1.70 (m, 4H), 2.60–2.75 (m, 4H), 6.40 (br, s, 1H); *m/z* (EI) 159 (M^+), 130, 88, 72, 57, 43. **8d**: b.p. 71 °C at 0.35 mmHg; ν_{max}/cm^{-1} 3300, δ_H 0.85 (t, 3H, *J* 7.3 Hz), 1.15–1.45 (m, 8H), 2.80 (t, 2H, *J* 6.9 Hz), 6.90 (br, s, 1H), 7.10–7.50 (m, 5H); *m/z* 193 (M^+), 176, 164, 88, 77, 65, 51. **8f**: b.p. 65 °C at 0.15 mmHg; ν_{max}/cm^{-1} 3280; δ_H 0.90 (t, 3H, *J* 7.3 Hz), 1.50–1.60 (m, 2H), 2.65 (t, 2H, *J* 6.8 Hz), 3.75 (s, 2H), 6.80 (br, s, 1H), 7.20–7.35 (m, 5H); *m/z* 165 (M^+), 136, 91, 77, 65, 51. **8g**: b.p. 68 °C at 5 mmHg; ν_{max}/cm^{-1} 3300; δ_H 0.95 (t, 3H, *J* 7.2 Hz), 1.10 (d, 6H, *J* 6 Hz), 1.20–1.50 (m, 8H), 2.65 (t, 2H, *J* 70 Hz), 2.95 (sep, 1H, *J* 6.8 Hz), 6.50 (br, s, 1H); *m/z* 159 (M^+), 142, 130, 88, 71, 57, 43. **8h**: b.p. 83 °C at 8 mmHg; ν_{max}/cm^{-1} 3300; δ_H 0.90 (t, 3H, *J* 7.2 Hz), 1.10 (d, 6H, *J* 6.8 Hz), 1.30–1.70 (m, 14H), 2.65 (t, 2H, *J* 7.0 Hz), 2.95 (sep, 1H, *J* 6.8 Hz), 6.04 (br, s, 1H); *m/z* 201 (M^+), 186, 172, 113, 88, 71, 57, 43. **8i**: b.p. 57 °C at 1.5 mmHg; ν_{max}/cm^{-1} 3250; δ_H 0.90–0.95 (m, 6H), 1.00 (d, 3H, *J* 7.0 Hz), 1.15–1.60 (m, 12H), 2.65 (t, 2H, *J* 6.8 Hz), 2.95–3.15 (m, 1H), 6.20 (br, s, 1H); *m/z* 187 (M^+), 172, 144, 116, 77, 60.

nitroalkane at −78 °C (method B).‡ The yields obtained with the two different approaches are comparable and are excellent when primary Grignard reagents are used. With secondary organomagnesium reagents the formation of the hydroxylamine is always coupled with a certain amount of the corresponding nitrone that has been isolated in the *Z* configuration as already observed.[1] The $CeCl_3$–RMgX couple must be used in 1.5 and 2 equiv. excess, respectively, in order to ensure better results. A large excess of reagents as well as more elevated temperatures have been proved to have a deleterious effect on the reliability of the reaction. The formation of an *N*-tetrahedral intermediate, as described for the reaction of allyl and benzyl Grignard reagents, followed by its reduction by the $CeCl_3$–RMgX species to the corresponding *N,N*-disubstituted hydroxylamine, seems to be the most probable pathway for this process. However, at present, we cannot exclude the formation of other kinds of intermediates, as for instance nitroso compounds, that would also give *N,N*-disubstituted hydroxylamines by reaction with organometallic reagents.

Further investigations on the mechanism and synthetic potentialities of this procedure are currently in progress in our laboratory.

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‡ *Typical experimental procedures are as follows*: method A: nitro compound (5 mmol), dissolved in dry tetrahydrofuran (THF) (10 ml), is added to a stirred suspension of dry cerium chloride[5a] (7.5 mmol) in dry THF (20 ml) at room temp. The mixture is stirred for 1 h and then cooled to −40 °C and the Grignard reagent (10 mmol) dissolved in dry THF (15 ml) is added dropwise. After 30 min stirring at −40 °C, the reaction mixture is quenched by addition of 10% aqueous acetic acid (40 ml) and allowed to warm to room temp. Usual work-up gives the crude product which is purified by column chromatography (hexane–ethyl acetate 6:4).

Method B: Grignard reagent (10 mmol), dissolved in dry THF (15 ml), is added to a stirred suspension of dry cerium chloride[5a] (7.5 mmol) in dry THF (20 ml) at 0 °C. After 1 h stirring at 0 °C, the mixture is cooled to −78 °C and the nitro compound (5 mmol) dissolved in dry THF (10 ml) is added dropwise. After 30 min stirring at −78 °C the reaction mixture is quenched as described in method A.

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