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Cerium(III) Chloride Mediated Michael Addition of RMgX to Nitroenes: a Very Efficient Access to Complex Nitroalkanes

Giuseppe Bartoli*, Marcella Bosco and Letizia Sambri

Dipartimento di Chimica Organica "A.Mangini", v.le Risorgimento, 4, I-40136, Bologna, Italy

Enrico Marcantoni

Dipartimento di Scienze Chimiche, via S.Agostino 1, I-62032 Camerino (MC), Italy

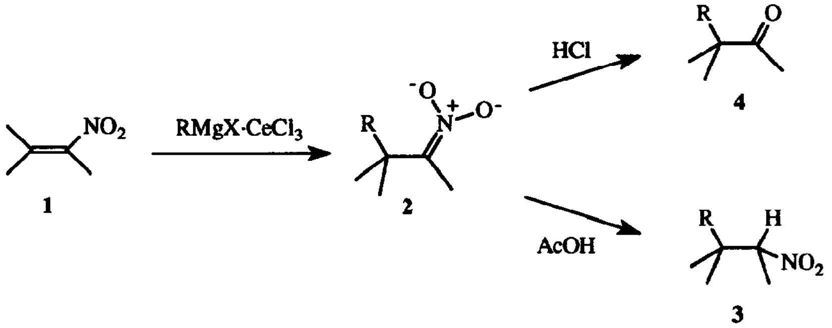
Abstract : Reactions of RMgX-$CeCl_3$ complexes with nitroenes lead to functionalized nitroalkanes in very good yields.

Nitroalkenes are exceptional Michael acceptors and this property dominates the chemistry of this class of compounds providing a general way to construct functionalized aliphatic nitrocompounds, which are versatile intermediates in organic synthesis [1]. However the reaction generally doesn't work well with not stabilized carbanions. In fact high-basicity organometallics, such as alkyl cuprates [2], Grignard reagents [3] and alkyllithium derivatives [4], can promote in several instances undesired polymerization or redox processes depending on the nature of the nitrosubstrate. For example, allyl [5] and arylmagnesium [6] halides add in satisfactory yields only to nitroenes having in β-position an aromatic substituent. Likewise, alkyllithium compounds work well only with nitroallyl pivalate [7].

Cerium(III) chloride has been recently reported to be an efficient additive to depress proton abstraction and redox processes in the reaction of RMgX with carbonylic compounds, but to give untractable mixtures in reactions with nitrocompounds [8]. We found, on the contrary, that an appropriate choice of experimental conditions allows to obtain dialkyl hydroxylamines in excellent yields [9]. Because of the easy availability of this reagent it seemed of interest to test its efficiency in the Michael addition to nitroenes. For this purpose, in this preliminary communication, we analyse the reactivity of various RMgX-$CeCl_3$ complexes towards four nitroenic compounds of different electrophilicity and stability.

However unavoidable problems connected with the decomposition of the intermediate nitronate adduct **2** (Scheme 1) must be taken into account in this reaction. A feeble acidic quenching (CH_3COOH) favours the aci-nitro tautomerization to the nitro compound **3**, while a strong acidic one (HCl) promotes the hydrolysis to the corresponding ketone **4** (Nef reaction).

The aci-nitro tautomerization suffers from steric hindrance at nitronate carbon, and then in the reaction with substrates that give secondary nitroalkanes, such as 1-nitrocyclohexene and 3-nitro-2-pentene, the formation of appreciable amounts of ketone was often observed after aqueous acetic acid quenching. We found that the optimum conditions to minimize ketone formation require the addition of glacial acetic acid to the reaction mixture at low temperature to carry out the decomposition of the nitronate-intermediate.



Scheme 1

As shown in the table, complexes $CeCl_3$-RMgX give the corresponding Michael addition products in excellent yields. In the case of *p*-OCH_3 and *p*-CH_3 substituted β-nitrostirenes (entry 1-6), conversions into the corresponding primary nitroalkanes are almost quantitative, except with a secondary hindered reagent (entry 4, 74% yield). In the case of 1-nitrocyclohexene (entry 7-10) and 3-nitro-2-pentene (entry 11-13), high conversions were again observed; however the yields in nitroalkanes are less satisfactory because of the formation of a small amount of the corresponding ketone. Neverthless in all cases yields exceed 70%.

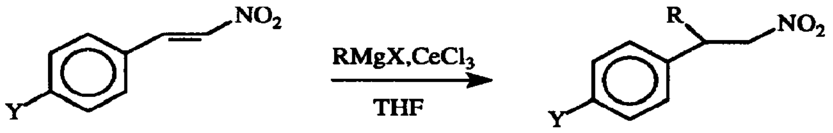
A typical procedure follows. The organocerium reagent was generated by addition of the corresponding Grignard compound (3.48 mmol) to a suspension of anydrous $CeCl_3$ (3.48 mmol) in THF (15 ml), at -78°C in the case of allyl and benzyl Grignard, and at 0 °C for the other reagents, under N_2 and vigorous stirring for 1.5 h. A solution of nitroene (1.74 mmol) in THF (5 ml) was added dropwise to this suspension at -40°C; after 10 min the reaction was quenched with glacial AcOH (10 eq, 17.4 mmol) and left to stir under N_2 for 5 min; then it was diluted with water and extracted with hexane. Usual work up gave pure nitroalkane[10].

Two other methods of high efficiency for introducing functionalized alkyl chains into the β-position of a nitroene substrate are known in literature, which utilize alanes[11] and copper-zinc reagents[12] as alkylating reagents respectively. Alanes are difficultly available and have more restricted applicability than cerium reagents. In addition, mixed alanes can show poor selectivity for preferential transfer of one alkyl group.

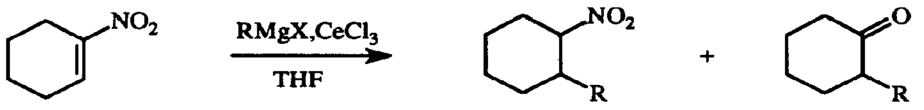
The copper-zinc reagents method, reported by Knochel[12], can be considered complementary to the present method. In fact, although it uses very complicated reagents and requires long reaction times, it allows to introduce alkyl chains containing functionalities such as -CN, -Cl, -COOR, which aren't compatible with a method based on the Grignard compounds as organometallic starting material.

With regard to the method here reported, we wish to outline the role of cerium in the reaction. In our opinion[13], polymerization phenomena, observed in reaction with RMgX alone, are promoted by radical species (nitroene radical anion and alkyl radical) formed through a single electron transfer process from RMgX to the

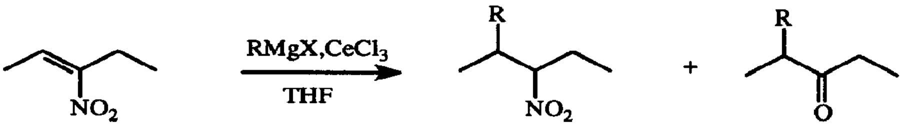
Table: Michael Addition of $CeCl_3$-RMgX Complexes to Nitroenes



entry	Y	R-	yield in nitro compound(%)[a]
1	CH_3	CH_3	93
2	CH_3	n-Bu	90
3	CH_3	allyl	>97
4	OCH_3	i-Pr	74
5	OCH_3	$PhCH_2CH_2$	89
6	OCH_3	$PhCH_2$	97



entry	R-	yield in nitro compound[b] (%)	yield in ketone (%)
7	$PhCH_2CH_2$	93 (3:1)[c]	3
8	CH_3	78 (3:1)[c]	6
9	n-Bu	77 (3:1)[c]	7
10	allyl	80 (6:1)[c]	7



entry	R-	yield in nitro compound[b] (%)	yield in ketone (%)
11	n-Bu	76 (3:1)[d]	7
12	allyl	70 (5:1)[d]	8
13	$PhCH_2$	71 (5:1)[d]	14

a) yields in pure isolated products; b) global yield of the isolated mixture of the two formed diastereoisomers c) diastereoisomeric ratio determined by ^1H NMR data and confirmed by GC-MS analysis, d) diastereoisomeric ratio determined by GC-MS analysis. ^1H NMR data weren't suitable to distinguish the two diastereoisomers.

strong electron acceptor nitro substrate. Thus cerium(III) chloride, lowering the electron donating power of RMgX, depresses these undesired side processes.

In conclusion, a simple and practical method to obtain functionalized nitroalkanes is now available.

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