

REACTION OF ORGANOMETALLIC REAGENTS WITH TRIETHOXYACETONITRILE.

A NEW AND SHORT SYNTHESIS OF α -KETOESTERS.

Georges P. AXIOTIS

Laboratoire de Chimie Organique Physique, E.R.A. au CNRS n° 689, Université Claude
Bernard, LYON I, 43 boulevard du 11 Novembre 1918, VILLEURBANNE 69622 (FRANCE)

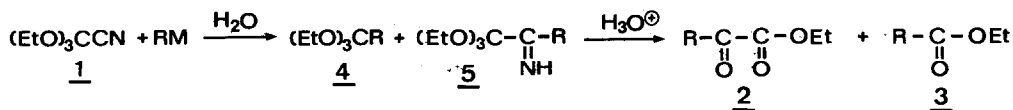
Summary : Grignard reagents react with triethoxyacetoneitrile to give esters, while organolithium reagents provide α -ketoesters in excellent yields.

The reaction of organometallic reagents with α -oxygenated nitriles was studied on several occasions¹⁻⁴ and it was pointed out that the great reactivity of these compounds, permits the synthesis of interesting intermediates in organic chemistry. In the case of α, α -dialkoxynitriles⁴, it was shown that it is possible to add one or two equivalents of organometallic reagent and to obtain after hydrolysis α -diketone monoketals or α -aminoketals in excellent yields.

These results prompted us to try to extend them to α -trialkoxycetonitriles such as triethoxyacetoneitrile 1, by using different organometallic reagents. Compound 1 corresponds to a protected form of cyanofornic acid ethyl ester and addition of an organometallic reagent RM to the cyano-function of 1 could afford the very interesting α -ketoesters 2. Moreover, such a reaction has never been reported in the litterature. It has only been reported that 1 reacts with sodium alkoxides to give the corresponding orthocarbonates after nucleophilic displacement of the cyano-function by the alkoxide⁵. This reaction seems to be the normal reaction of 1.

We expected however, that the greater nucleophilicity of organometallic reagents in comparison with alkoxides, would permit an addition reaction to 1 or at least a favorable competition rather than the substitution reaction mentioned above.

Nitrile 1 reacts with organomagnesium or lithium derivatives in ether⁶ to give, after acid hydrolysis and in 80-89 % yield, the ester 3 after substitution of the cyano-group and/or the α -ketoester 2 after addition to the cyano-function. When hydrolysis is carried in basic medium the orthoester 4 and the ketimine 5 can be isolated :



With n-butyl, s-butyl or phenyl magnesium bromide the ester 3 is predominant (70-100 %). Actually, this substitution reaction giving 3 is an illustration of a general process occurring when compounds of the form $(\text{RO})_3\text{CX}$, where X = hydrogen, alkyl, phenyl or α -ethylenic group are treated with various organometallic reagents^{5,7,8}.

With methyl, n-butyl, s-butyl or phenyllithium, the α -ketoester 2 is exclusively
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obtained according to our expectation.

The striking difference in the behavior of the two organometallics is presumably due to the steric hindrance of the nitrile 1. The well known lesser sensitivity of organolithium reagents towards steric hindrance allows the addition reaction to proceed. It has actually been reported⁹ that there is almost no reaction of organomagnesium reagents with hindered nitriles of the general form R_3CCN , where R are various alkyls, while addition proceeds easily with organolithium reagents, giving the corresponding ketones. Nitrile 1 has a comparable hindrance to nitriles R_3CCN and consequently, it is not surprising that organomagnesium reagents displace the cyano group rather than to add on it.

The synthesis of α -ketoesters 2 described here is advantageous in comparison with previously reported methods¹⁰ as it is brief, simple, starting from material easy to synthesize¹¹ and seems general while it works with alkyl, even secondary alkyl, and phenyl lithium reagents. α -ketoesters 2 are vital biochemical intermediates and important substances in the field of organic chemistry. They have been used for example, for asymmetric synthesis of α -aminoacids¹². Reported syntheses of 2 are generally difficult to realize as requiring numerous steps. They suffer from lack of generality as applying, for most of them, to particular structures and, in general, reported overall yields are not always satisfactory.

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