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Beryllium Dichloride : Efficient promoter for the Addition of Organolithiums and Organomagnesiums to Cyclohexen-2-one

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Abstract: Organoberyllium compounds, generated by transmetallation from Grignard and organolithium reagents react with 2-cyclohexenone to give predominantly the adducts resulting from conjugated addition. The chemoselectivity of this reaction was found to be highly dependent upon the nature of organic moiety and of the conditions used.

Control of the site of attack of organometallics onto enones has been the subject of intensive work from the early age of organic chemistry. This has been achieved by the use of the proper counter ion, solvent or/and conditions. Organolithiums[1] proved to be by far the most popular reagents to promote the introduction of an organic moiety on the carbonyl carbon of enones, whereas organocoppers[2] predominantly add on their C,C double bond.

Nevertheless, in some cases organocopper cannot be produced or do not react as expected and therefore it still remains a need for new reagents able to replace them.[3] We now report our preliminary results concerning the reactivity of Grignard and organolithium reagents, in the presence of beryllium chloride, with cyclohexenone. Under the conditions we used, organoberylliums are intermediary produced. Although these reagents have already been prepared, distilled and characterized,[4] they do not enjoy the popularity of organomagnesiums and organolithiums whose metal is the close neighbor of beryllium in the periodic table.

This is probably due to the fact that, unlike magnesium and lithium, beryllium does not react with alkyl halides[5] and also because beryllium derivatives are suspected to be toxic.[6] The most usual synthesis of organoberylliums is the transmetallation between Grignards[7] or organolithium[8] compounds and beryllium halides (Scheme) but the removal of the co-produced salts and purification of diorganoberylliums from the reaction mixture is often cumbersome.

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The reactivity of organoberylliums towards enones remains unexplored to our knowledge since only one isolated example of the conjugate addition of diphenylberyllium on chalcone has been reported.[9]

We first found that salt free dibutylberyllium, prepared[8] by transmetallation of *n*-butyllithium (in hexane) with beryllium chloride (0.5 eq., THF, 20°C, 1.5 h) and isolated by distillation, reacts with 2-cyclohexenone **1** to produce **2** in reasonably good yield (Scheme, Table 1, entries a, b).

Interestingly, addition across the C,C double bond of **1** leading to **3** is achieved if distillation is omitted and if **1** is directly added to the mixture resulting from the reaction of *n*-butyllithium with beryllium chloride. Almost exclusive conjugate addition is observed in THF especially if the reaction is carried out at 0°C instead of 20°C (Scheme, Table 1, entries c, d).

However, conjugate addition does not take place when (i) the reaction is performed in ether instead of THF (Table 1, entry e), (ii) the reaction is carried out in THF with a mixture of distilled dibutylberyllium[8] and LiCl (2 eq., Table 1, entry f), contrary to what we would have expected on the basis of the results reported above or, (iii) the reaction is performed in THF with butylberyllium chloride (from 1 eq each of BuLi and $BeCl_2$) instead of dibutylberyllium (Table 1, compare entry g to d) (iv) butyllithium is added to the enone pre-complexed with one equivalent of beryllium dichloride.

Scheme

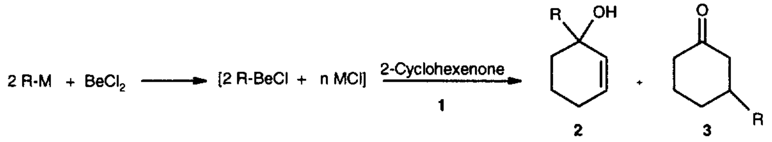

Table 1

Entry	Reagent	Conditions	Yield in **2**+**3**[a] (Recovered **1**)	**2**/**3** ratio
a	$(Bu)_2Be$ [b]	Ether, 20°C	85	82 / 18
b	$(Bu)_2Be$ [b]	THF, 20°C	54	99 / 1
c	2 BuLi + $BeCl_2$	THF, 20°C	78	3 / 97
d	2 BuLi + $BeCl_2$	THF, 0°C	71[c]	0 / 100
e	2 BuLi + $BeCl_2$	Ether, 0°C	51[d]	100 / 0
f	Bu_2Be + 2 LiCl	THF, 20°C	40	99 / 1
g	BuLi + $BeCl_2$	THF, 0°C	0 (55)	-
h	2 BuMgCl, 2 $BeCl_2$	THF, 0°C	58	12 / 88
i	2 BuMgBr, 2 $BeCl_2$	THF, 0°C	79	6 / 94
j	2 BuMgCl, 2 $BeCl_2$	THF, 0°C, 1.2 Me_3SiCl[e]	85	1 / 99

(a) Unless otherwise stated the yields and ratios have been determined by GC, using dodecane as internal standard (b) Refers to distilled $(Bu)_2Be$ (c) Yield of isolated product (d) 9 % of cyclohex-2-en-1-ol were produced. (e) Premixed with the enone.

Related results have been obtained, although the regioselectivity was slightly lower, when butylmagnesium halides were used in place of butyllithium (Table 1, entries h, i). We nevertheless substantially increased the regioselectivity by carrying out the reaction in the presence of a stoichiometric amount of chlorotrimethylsilane (Table 1, entry j).

We then extended it to the cases of differently substituted organomagnesium compounds bearing a methyl-, *sec*-alkyl-, *ter*-alkyl-, benzyl-, allyl-, aryl- or a vinyl-group in order to delineate the scope of this new reaction (Scheme, Table 2) and performed it with trimethylsilyl chloride, whose use proved to be highly beneficial for the conjugate addition of the butyl group.

Among the series of compounds possessing an Sp3 carbanionic center, methyl magnesium bromide proved to have the lowest tendency to add in a conjugate mode to 2-cyclohexone and none of the different conditions we tested improved it (Table 2, entry a). Otherwise, increasing the substitution on the carbanionic center, increased the tendency of the organic moiety to add in a conjugate manner (Table 2, entries b, c). Although the benzylic derivative added to the C,C double bond almost exclusively (Table 2, entry d) the allylic compound, which also bears a well stabilized carbanionic center, regioselectively added on the carbonyl carbon of 2-cyclohexenone (Table 2, entry e).[10]

Table 2

Entry	Reagent	Conditions	Yield in **2**+**3**[a]	**2**/**3** ratio
a	2 MeMgBr + $BeCl_2$	THF, 0°C	51	60/40
b	2 *i*-BuMgBr + $BeCl_2$	THF, 0°C, Me_3SiCl	68	6/94
c	2 *t*-BuMgCl + $BeCl_2$	THF, -78°C, Me_3SiCl	95	1/99
d	2 $PhCH_2MgCl$ + $BeCl_2$	THF, 0°C, Me_3SiCl	85	5/95
e	2 AllylMgCl + $BeCl_2$	THF, 0°C, Me_3SiCl	95	100/0
f	2 PhMgCl + $BeCl_2$	THF, 0°C, Me_3SiCl	58	0/100
g	2 VinylMgBr + $BeCl_2$	THF, 0°C, Me_3SiCl	55	33/67

(a) Refers to yield in isolated pure products.

Finally, phenylmagnesium chloride and vinylmagnesium bromide react sluggishly and provide the corresponding 3-substituted cyclohexanone as the sole or the major product (Table 2, entry f,g).

TMSCl we thoroughly used with organoberyliums does not seem to affect their reactivity but favors their conjugate addition as it has already been described for organocuprates.[11] The origin of this effect is still a matter of dicussions.[12]

The dependence of the regioselectivity of the addition on both the nature of the group added and the nature of the salts present in the reaction mixture is hard to explain since very little is known about the structure of organoberyllium reagents prepared by transmetallation. However, the state of aggregation of isolated organoberyllium compounds is known to be dependent on the nature of the alkyl group : dimethylberyllium is polymeric[13], probably as diphenylberyllium[14] whereas di-*tert*-

butylberyllium is monomeric.[15] These different states of aggregation are probably also operative in the transmetallated compounds since we found that the two former organometallics reacted sluggishly while di-*tert*-butylberyllium was very reactive, even at -78°C.

In conclusion, we have shown that organoberyllium compounds generated by transmetallation undergo efficient 1,4-addition on 2-cyclohexenone. Further work is in progress in our Laboratory to get some insights into the mechanism of this addition.

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