THE REACTIONS OF COMBINED ORGANOCUPRATE-CHLOROTRIMETHYLSILANE
REAGENTS WITH CONJUGATED CARBONYL COMPOUNDS

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Summary: Organocuprates and chlorotrimethylsilane are compatible as separate species in THF or ether solution at -50 to -78°, and in combination can both accelerate and improve 1,4-addition reactions with conjugated carbonyl compounds.

Organocuprate (Gilman) reagents now play an important role in organic synthesis as a result of their unique reactivity with organic substrates. We describe herein another unusual property of these reagents, compatibility with chlorosilanes under conditions which effect many standard cuprate transformations. Chlorosilanes have frequently been used to convert enolates formed by conjugate addition of organocuprate reagents to α,β-unsaturated carbonyl compounds to the corresponding enol silyl ethers.[1] Invariably in such reactions the chlorosilane has been added to the enolate solution <u>after</u> the conjugate addition has taken place. The general success of this procedure, even when a substantial excess of cuprate reagent is present, provided a clue that the reaction of organocuprates with chlorosilanes might be fairly slow at low temperatures (e.g., -50 to -78°C). In addition, it is known that chlorotrimethylsilane (TMSCl) is remarkably stable to such powerful reagents as sodium[2] and lithium disecalkyl- and ditertalkylamides.[3]

Colorless solutions of lithium dimethylcuprate in tetrahydrofuran (THF) or ether at -78° are unchanged in appearance in the presence of chlorotrimethylsilane. Examination of the ^{1}H nmr spectrum (300 MHz) in d_8-toluene-THF[4] at -50° showed less than 0.002 ppm change in position of the cuprate CH_3 peak (at -0.287 ppm) upon addition of TMSCl. The peak due to TMSCl was unchanged at -50°; at -25° it slowly diminished and a new peak due to tetramethylsilane appeared. Conversion of TMSCl to tetramethylsilane was more rapid at 0°.

The compatibility of lithium dimethylcuprate with TMSCl was also assessed in ether and THF solution by using the analytical procedure of Bertz and Dabbagh[5] to determine lithium dimethylcuprate by reaction with benzoyl chloride to form acetophenone. Remaining lithium dimethylcuprate was determined after a 30 min exposure to 5 equiv of TMSCl at varying temperatures. In THF at -78° there was no measurable reaction (100% acetophenone), at 0° most of cuprate remained, and at 23° 67% of the original cuprate was present. The stability was somewhat poorer in ether (17% loss of cuprate at -25° occurred in 30 min). Lithium dimethylcuprate in THF was also compatible with <u>t</u>-butyldimethylsilyl triflate and triisopropylsilyl triflate at -78°. In addition, the stabilities of other organocuprates (R_2CuLi) in the presence of 5 equiv of TMSCl at -78° over a 10 min period were ascertained (using conjugate addition to benzalacetone for analysis of remaining cuprate), and it was found that <u>n</u>-butyl, <u>t</u>-butyl- and vinyl reagents were quite compatible with TMSCl in THF.

The cuprate–TMSCl reagent combination has two possible synthetic benefits besides the obvious use for the position–specific generation of silyl enol ethers: (1) to accelerate cuprate–enone reactions, and (2) to improve yields of conjugate addition products by preventing side reactions involving enolates.

As discussed in a preceding paper,[6] TMSCl accelerates cuprate–enone conjugate addition by trapping an initial d, π^*–complex and forcing conversion to β–carbon adduct. This acceleration is much more marked in THF than in ether because the normal (i.e., non–TMSCl) process is faster in ether[7] (presumably due to Li^+ or Mg^{++} assistance). The TMSCl acceleration can be used to achieve functional group selectivity as shown by simple intermolecular competition experiments with substrates 1 and 2 and a deficiency of lithium dimethyl-cuprate. At –78° with lithium dimethylcuprate in THF the acrylate ester 2 is converted to conjugate adduct faster than enone 1 by a factor of 2.5. However, in the presence of TMSCl (5 equiv of TMSCl per equiv of each substrate) the enone 1 reacts ca. 5.6 times as fast as the acrylate 2.

Several lines of evidence argue that these TMSCl effects are not due to prior complexation of TMSCl with the carbonyl oxygen of the educt. The ^{1}H nmr spectra of 3 shows no evidence of change of chemical shifts

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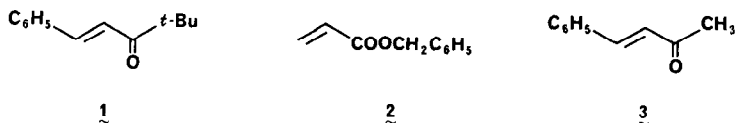
in the presence of increasing amounts of TMSCl. There is only a minor (factor of 3.2) increase in relative rates of reaction of enones 3 and 1 with lithium dimethylcuprate in THF at –78° with increasing concentration of TMSCl. A much greater increase (at least 10^2) would be expected for prior complexation of TMSCl with the enone oxygen. A third argument against prior complexation is the result obtained in the competition between enone 1 and acrylate 2. The carbonyl group of 2 would appear to be more basic toward TMSCl than that of 1. Finally, we have found that organocuprate reactions which cannot involve d, π^*–complexes, such as nucleophilic displacement of epoxides or cyclopropane 1,1–diesters, are not accelerated by TMSCl.

We had hoped that TMSCl acceleration might be used to facilitate 1,4–addition to β–disubstituted enones and thereby improve the capability of the cuprate–enone reaction for the attachment of angular carbon in poly-cyclic systems. The reaction of bicyclic enone 4 with lithium dimethylcuprate and TMSCl in THF at –78° was in fact very fast. However, 1,2–addition predominated over 1,4–addition by ca. 2 to 1. On the other hand in

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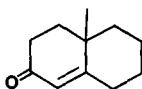
<u>situ</u> TMSCl did improve the 1,4-selectivity of the reaction of lithium diallylcuprate (in THF) with 2-cyclohexen-one. As previously reported, we found that this reaction was exceedingly sensitive to impurities in the Cu(I) salt used to generate the cuprate reagent.[7] Using commercial Cu(I) salts, 1,4-addition is accompanied by much 1,2-addition. Even with carefully purified CuI[8] a mixture of 1,4- and 1,2-adducts (ratio 82 : 18) was obtained from the reaction of lithium diallylcuprate and 2-cyclohexenone at −78° in THF. However, in the presence of 5 equiv of TMSCl and using CuI from the same batch only 1,4-adduct was obtained (87% isolated yield, <2% 1,2-adduct by tlc analysis) from this reaction.[9]

The conjugate addition reaction of organocopper reagents with α,β-unsaturated aldehydes is often complicated by the occurrence of competing 1,2-addition[10a,b,c] and also by the condensation of intermediate enolate with enal.[10] Furthermore, product losses occur during workup of the reaction mixture due to condensation reactions. For this reason the addition of hexamethylphosphoric triamide and TMSCl to the reaction mixture and subsequent hydrolytic desilylation of the resulting enol silyl ether have been employed.[10a,b,c] It has been reported[10a] that cinnamaldehyde and lithium dimethylcuprate give a 74% isolated yield of conjugate adduct by this last procedure. We found that the inclusion of TMSCl in the reaction mixture with the cuprate prior to the addition of cinnamaldehyde permitted the use of a less reactive reagent (lithium methylcyanocuprate, 1.5 equiv, THF, −78°) due to TMSCl acceleration and resulted in a 98% yield of 1,4-conjugate adduct after hydrolysis of the silyl enol ether in the same flask.

The reaction of lithium dimethylcuprate (ether, −78°) with dienone 5 gave the 1,6-adduct 6 in only 46% yield along with more polar condensation products. Addition of dienone 5 to a mixture of lithium dimethyl-cuprate and TMSCl (THF, −78°) led to a 98% yield of the TMS enol ether of 6.

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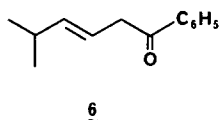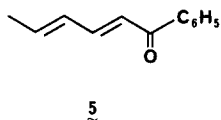
The results reported herein depend on the compatibility of strongly nucleophilic organocuprates and the powerful electrophile TMSCl. The question of why these reagents can coexist together in solution is still open. It is possible that the Cu (III)−Si bond which would result from coupling is quite weak compared to the Si−Cl bond, making for a relatively low rate of displacement by copper on silicon. Whatever the reason, the compatibility of organocuprates and chlorosilanes offers new opportunities in organometallic reactions.[11]

References and Notes

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(Received in USA 30 August 1985)