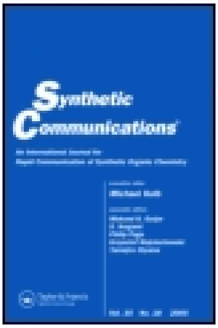

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An Alternative Procedure for the O-Trimethylsilylation of Enolates Generated by Copper-Catalyzed 1,4-Additions

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AN ALTERNATIVE PROCEDURE FOR THE O-TRIMETHYLSILYLATION OF ENOLATES GENERATED BY COPPER-CATALYZED 1,4-ADDITIONS

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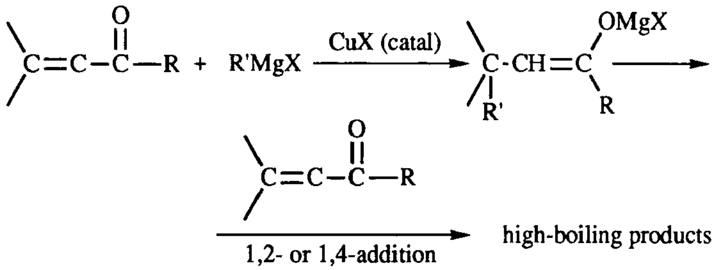
Abstract:

Anhydrous lithium bromide has been successfully used as an additive instead of hexamethylphosphoric triamide in the O-trimethylsilylation of enolates generated by copper halide-catalyzed reaction of Grignard reagents with a number of α,β-unsaturated carbonyl compounds. Some conjugate additions also proceed satisfactorily in the absence of lithium bromide.

A serious problem in copper-catalyzed conjugate additions of Grignard reagents to α,β-unsaturated aldehydes and ketones is the further reaction of the adduct with the substrate[1,2].



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Especially simple substituted carbonyl compounds such as crotonaldehyde and methyl vinyl ketone are sensitive towards this subsequent reaction. Recently[3] this problem has been solved by carrying out the conjugate addition in the presence of a certain amount of hexamethylphosphoric triamide (HMPT) and using trimethylchlorosilane to trap the initial enolate generated.

We have found that in a number of reactions the carcinogeneous HMPT can be replaced by anhydrous lithium bromide, which presumably activates Me_3SiCl by conversion into Me_3Si-Br (compare[4]). This salt also effects some solubilization of the magnesium salt produced in the reaction, thus rendering the reaction mixture better stirrable. The latter condition is also met by using Grignard reagents prepared in diethyl ether (instead of THF, in which solvent the Grignard compound crystallizes out at the low reaction temperatures). In reactions with the less sensitive substrates 2-cyclohexenone and mesityl oxide the activation of Me_3SiCl by addition of lithium bromide appeared to be not necessary.

For obtaining high yields the reactions have to be carried out at temperatures below −30°C. Upon raising the temperature, the copper halide-catalyzed reaction of the added Me_3SiCl with the Grignard compound in the reaction flask becomes increasingly important.

Procedure:

To 100 ml of dry tetrahydrofuran were added 0.2 mol of anhydrous lithium bromide (the commercial anhydrous salt was heated during 30 min at 150°C in a vacuum of <1 mm Hg) and 0.05 mol of finely powdered copper(I)bromide. A solution of 0.12 mol of *t*-butylmagnesium bromide in 100 ml of diethyl ether was added to the light-green solution while keeping the temperature of the mixture below −40°C. A mixture of 0.20 mol of trimethylchlorosilane (distilled from a small amount of *N*,*N*-diethylaniline), 0.10 mol of the freshly distilled methyl vinyl ketone and 50 ml of diethyl ether was then added dropwise over 45 min with efficient stirring, while maintaining the temperature between −40 and −50°C. After each drop the grey suspension turned yellow for a few seconds. After an additional 15 min (at −40°C) the temperature of the reaction mixture was allowed to rise to 0°C. Triethylamine (~30 ml) was added, whereupon the mixture was poured into 200 ml of a cold (0°C aqueous solution of 30 g of ammonium chloride. After vigorous shaking and separation of the layers two extractions with ether were carried out. After washing the combined aqueous layers several times with aqueous ammonium chloride (until the aqueous layer had reached pH ~7) and drying over

Table

Carbonyl compound	RMgBr R	Solvent for RMgBr	Reagents	Yield (%)	*E/Z* ratio
crotonaldehyde	Ph	THF	2eq HMPT-TMSCl	93	5.3
crotonaldehyde	Ph	THF	2eq LiBr-TMSCl	87	5.3
crotonaldehyde	Ph	Et_2O	2eq LiBr-TMSCl	76	5.3
crotonaldehyde	t-C_4H_9	THF	2eq LiBr-TMSCl	87	5.4
methyl vinyl ketone	n-C_4H_9	Et_2O	2eq LiBr-TMSCl	81	~1
methyl vinyl ketone	t-C_4H_9	Et_2O	2eq LiBr-TMSCl	80	2
methyl vinyl ketone	Ph	Et_2O	2eq LiBr-TMSCl	74	1.2
2-cyclohexenone	n-C_4H_9	Et_2O	2eq TMSCl	96	
2-cyclohexenone	t-C_4H_9	Et_2O	2eq TMSCl	91	
2-cyclohexenone	Ph	Et_2O	2eq TMSCl	94	
2-cyclohexenone	CH_3MgI	Et_2O	2eq TMSCl	91	
mesityl oxide	n-C_4H_9	Et_2O	2eq TMSCl	85	*
mesityl oxide	t-C_4H_9	Et_2O	2eq TMSCl	<10	

* Comparable amounts of *E* and *Z*

$MgSO_4$ the solvents were removed under reduced pressure and the remaining liquid carefully distilled at 10 to 15 mm Hg. The identity and purity (>96%) of the product was determined with ^1H-, ^{13}C NMR spectroscopy and with GC-analysis. The reactions with 2-cyclohexenone and mesityl oxide (see table) were carried out in the absence of lithium bromide, reactions with crotonaldehyde were performed at –60°C. Further experimental details are mentioned in the table.

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