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The Role of Silanes on the Copper-Catalyzed Conjugate Alkylation of Enones by Organoaluminium Reagents

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Abstract: The effect of silanes as additives in the copper-catalyzed conjugate alkylation of enones by various organoaluminium reagents was investigated. TMSCl led to significant lower amounts of CuBr catalyst needed in the reaction of trimethylaluminium with enones, but was unsuccessful in the case of organoaluminium compounds of the formula Me_2AlY (Y = Cl, OR). Me_2AlOEt turned out to be a useful reagent for methylation without support of additives.

In previous papers we described the conjugate alkylation of α,β-unsaturated carbonyl compounds by triethyl- and trimethylaluminium (TMA) catalyzed by Cu^I salts[1,2] or $Ni(acac)_2$[3]. Throughout our investigations we were interested in the use of organoaluminium compounds of the general formula $R_{3-x}AlY_x$ (Y = non-transferable ligand, x = 1, 2) to optimize the alkyl ligand ratio. Furthermore the effect of silanes as additives was determined by kinetic and preparative investigations on the Cu^I-catalyzed reaction of isophorone **1** with various organoaluminium reagents under the influence of TMSCl, TMSBr and without additives. As reported previously[2], **1** is a less active enone towards this type of reaction and therefore kinetics could be followed easily.

The effect of silanes in the CuBr-catalyzed reaction of TMA with **1** was not significant under standard conditions (5 mol% of catalyst, TMA, room temperature). Using TMSCl the reaction was slightly faster than the non-supported one yielding mainly the corresponding silyl enol ether **2a**[4], as detected by GC[5] and TLC (Figure 1)[4,5]. When using TMSBr only low concentrations of **2a** were detected during the reaction[6], but a highly exothermic reaction was observed in this case going along with an acceleration of the 1,4-addition. This thermic effect seemed to be the only reason for this fast reaction, as deduced from the extremely decreased turnover rates after recooling within the first 0.5 h. Possibly, this can be explained by an interaction of silane and organoaluminium reagent to give a less active organometallic species by forming Me_4Si[7] or mixed aluminium-silicium "ate" complexes[8,9]. But it should be emphasized that the silane seemed to be compatible to the organoaluminium compounds even before adding the enone. However, yields of **2** were nearly quantitative on all three counts (Table 1, entry 1-3). The end of these reactions was indicated by the appearance of a Cu^0 precipitate formed due to a decomposition of organocopper intermediates.

When turning to lower amounts of catalyst, the use of TMSCl rose to significant importance (Figure 2)[4,5]. Using less than 1 mol% of catalyst consumption of starting material was incomplete due to the long reaction times, wherein decomposition of catalyst was observed. However, under the influence of TMSCl the reaction times significantly decreased and complete conversion was observed; **2** was isolated in high yields using 0.5 mol% (91%) and 0.1 mol% (87%) of CuBr (Table 1). Obviously, the activation of enones by TMSCl[9,10] led to similar preparative results as has been obtained under standard conditions by significantly lowered amounts of copper catalyst needed.

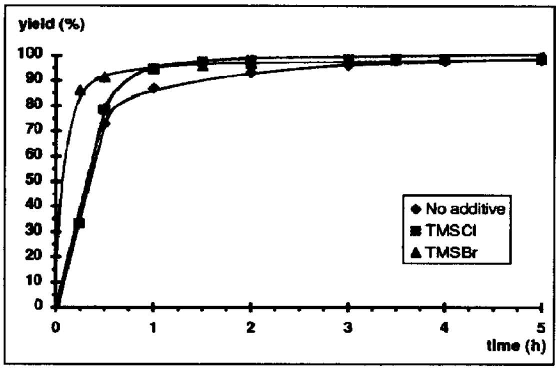


Figure 1. Kinetics Using Me_3Al/cat. CuBr as Reagent. Conditions: 5 mol% CuBr, 1.2 equiv. of silane, 10 mmol of **1**.

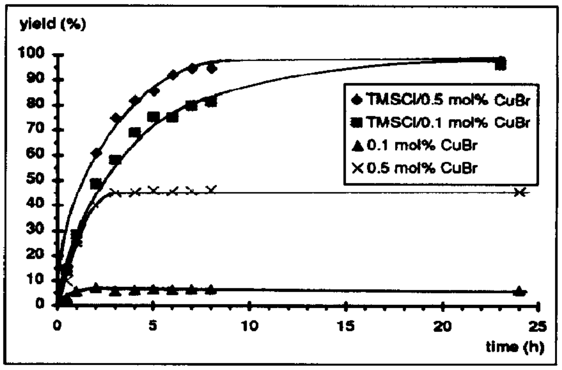


Figure 2. Kinetics Using Me_3Al/cat. CuBr as Reagent. Conditions: Cat. CuBr, 1.2 equiv. of silane, 20 mmol of **1**.

To point out again the role of the used Cu^I salt we additionally checked CuCl as a catalyst (Figure 3)[4,5]. As described earlier[2a], the reaction of TMA with **1** under the catalytic influence of 5 mol% CuCl led to 10% conversion of **1** during 24 h, only; about 85% of educt were recovered. Using TMSCl as an additive the reaction rate increased considerably to give nearly 60% conversion of **1** during 8 h. After this period no further consumption of starting material was observed. This effect may be explained by a decomposition of the catalyst during long reaction times, as well. Attempts to increase the turnover rates by higher amounts of catalyst (10 mol%) failed. Due to its limited solubility in THF the amount of copper salt is of less importance if a saturation of solvent is achieved. But a higher stability of the reaction system was observed leading to higher yields of **2**. Using 5 mol% CuCl first, an additional insertion of 5 mol% of catalyst after 5 h led to similar results. The conversion was incomplete even after a third insertion of catalyst (5 mol% after 24 h) and a reaction time of 72 h. CuCl turned out to be a useless catalyst for this application, but the effect of TMSCl was shown to be very significant.

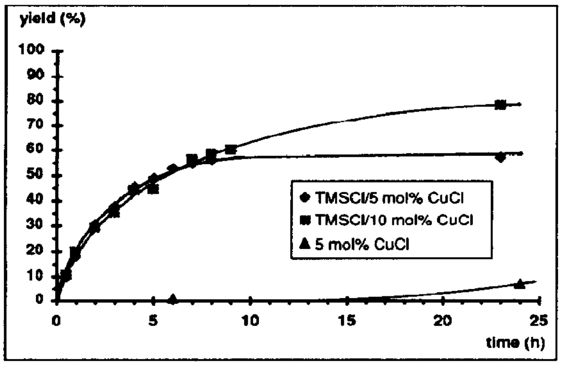


Figure 3. Kinetics Using Me_3Al/cat. CuCl as Reagent. Conditions: Cat. CuCl, 1.2 equiv. of silane, 10 mmol of **1**.

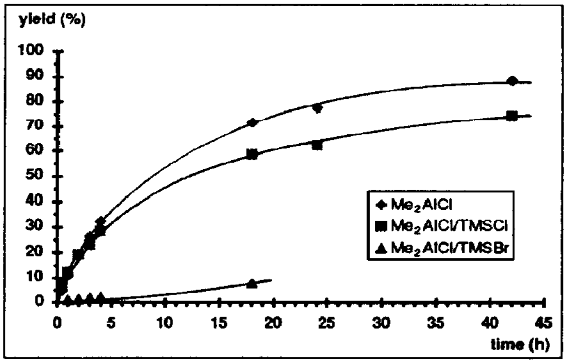


Figure 4. Kinetics Using Me_2AlCl/cat. CuBr as Reagent. Conditions: 5 mol% CuBr, 1.2 equiv. of silane, 10 mmol of **1**.

When Me_2AlCl (Figure 4)[4,5], or Me_2AlOEt respectively (Figure 5)[4,5], were used as reagents for alkylation the reaction times dramatically increased in comparison with the standard conditions. TMSCl gave an initial acceleration during the first hours *vs* the non-supported reaction and again the forming of **2a** has been detected. But concentrations of **2a** were low when using Me_2AlCl due to its strong oxophilic character; consequently the observed initial acceleration was less significant. After a period of about 3 to 5 h the reaction rates decreased in both cases and the non-supported reactions showed a faster conversion of starting material. This fact may also be explained by interactions of silane and organoaluminium reagent during the first hours of reaction as has been described for TMSBr before. For the same reason TMSBr suppressed the alkylation immediately after its insertion resulting in only up to 10% conversion during 18 h. Although the use of additives was unsuccessful in these applications both reagents gave moderate to good yields of **2** during 48 h without using additives (Table 1; entries 6, 7). The synthetic potency of Me_2AlOEt was investigated further (Table 1)[11] and good yields were obtained in the reaction with carvone **3** (93% of **4**; entry 8) and 17β-acetoxy-$\Delta^{1,2}$-3-androstenone **5** (84% of **6**; entry 10). EtOAc may be used as a solvent, but THF generally gave better results (entries 8, 9).

By using $MeAl(OEt)_2$ the observed reaction rate was very low giving only 27% of 1,4-product **2** by GC during 21 h. This type of reagent seemed to be preparatively less useful and was not further investigated.

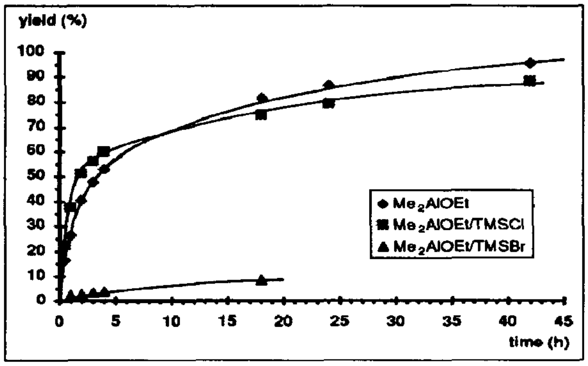
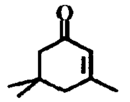


Figure 5. Kinetics Using Me_2AlOEt/cat. CuBr as Reagent. Conditions: 5 mol% CuBr, 1.2 equiv. of silane, 10 mmol of **1**.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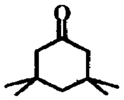
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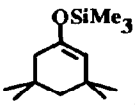

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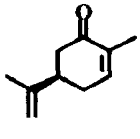
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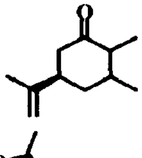
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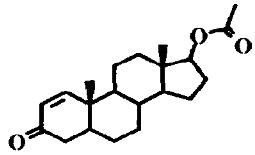
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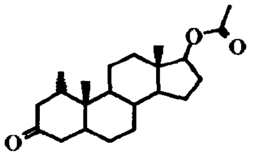
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Table 1. Alkylation of Enones by Organoaluminium Reagents.

Entry	Educt	Product	Conditions[a]	Yield[b]	Ref.
1	**1**	**2**	5 mol% CuBr, Me_3Al, THF, 5h	95%	2a
2	**1**	**2**	5 mol% CuBr, Me_3Al, TMSCl, THF, 4h	96%	2a
3	**1**	**2**	5 mol% CuBr, Me_3Al, TMSBr, THF, 5h	95%	
4	**1**	**2**	0.5 mol% CuBr, Me_3Al, TMSCl, THF, 23h	91%	
5	**1**	**2**	0.1 mol% CuBr, Me_3Al, TMSCl, THF, 23h	87%	
6	**1**	**2**	5 mol% CuBr, Me_2AlCl, THF, 48h	73%[c]	
7	**1**	**2**	5 mol% CuBr, Me_2AlOEt, THF, 48h	86%[d]	
8	**3**	**4**	5 mol% CuBr, Me_2AlOEt, THF, 18h rt, 3h 50°C	93%	
9	**3**	**4**	5 mol% CuBr, Me_2AlOEt, EtOAc, 18h rt, 6h 50°C	67%	
10	**5**	**6**	5 mol% CuBr, Me_2AlOEt, EtOAc, 16h	84%	1c

[a] Unless stated otherwise, reactions were performed at room temperature[11]. [b] Isolated yield. [c] 8% of recovered **1**. [d] 4% of recovered **1**.

To summarize the results, organoaluminium compounds of the general formula $R_{3-x}AlY_x$ (x = 0, 1) are useful reagents in the copper-catalyzed conjugate alkylation of enones. Me_2AlOEt shows a much higher preparative potential as Me_2AlCl and some more applications for reagents of the type R_2AlOR' will be worked out in proceeding papers. TMSCl as an additive did not show advantages in these cases. However, if reagents of the type R_3Al were used TMSCl led to increased reaction rates, as it was described concerning other organometallic reagents[9,10]. The role of the silane rose to great importance especially if low amounts of catalyst or catalytically less active copper salts were used. Under the influence of TMSCl the amounts of CuBr catalyst can be reduced to 0.1 mol% with good synthetic results. On the other hand, TMSBr generally seems to suppress the 1,4-addition.

References and Notes

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4 The kinetics reproduced in Figures 1 to 5 show the increase of 1,4-addition product as combined concentrations of **2** and **2a** detected by GC. The silyl enol ether **2a** will be destroyed to give product **2** during the preparative workup procedure.

5 GC: Perkin Elmer, Sigma 300; 50m CP Sil 8 CB (0.45/0.32), 60-240°C, 10°C/min, 130 kPa He.

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11 *Typical procedure:* To a stirred solution of 20 ml of THF and 1.1 ml (11.5 mmol) of TMA[12] (***Caution:*** Neat TMA is a volatile, highly pyrophoric liquid; use gastight Hamilton syringes for handling!) 0.68 ml (11.5 mmol) of EtOH was slowly added by syringe. After 0.5 h 1.52 ml (12 mmol) of TMSCl was added in one portion and stirred for an additional 5 min. Then 72 mg (0.5 mmol) of CuBr and 1.50 ml (10 mmol) of neat enone **1** was added subsequently *via* a syringe and the mixture was stirred for the given reaction time (Table 1). The reaction was quenched by careful addition of 2.0 ml of a saturated aqueous NH_4Cl solution. After recooling to room temperature the mixture was filtered through a "Duran sintered disc filter funnel (D3)" and the residue was washed three times each with 30 ml of THF. The solvent was removed from the combined filtrates under reduced pressure and the resulting crude product was purified by kugelrohr distillation. For spectral data of products **2** and **4** see ref.[2a]; for product **6** see ref.[3].

12 TMA as a commercially available solution in hexane may also be used (ref. [1,2]).

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