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Trimethylsilyl Chloride/Tetramethylethylenediamine Facilitated Additions of Organocopper Reagents (RCu) to Enones

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Summary: Alkylcoppers (RCu) add readily in a conjugate fashion to enones in the presence of TMSCl and TMEDA to give high yields of trimethylsilyl enol ethers.

In 1980 Normant and co-workers[1]made the observation that TMSCl does not readily react with cuprates at low temperatures. In late 1985, Corey and Boaz[2] noted that TMSCl serves to enhance the rate of additions of cuprates to enones. These reports and the observations of Bassindale and Stout[3] on the activation of silyl halides by a variety of nucleophilic addends prompted us to investigate variations of the TMSCl/cuprate chemistry in a effort to solve a synthetic problem which we had encountered. The very recent report by Nakamura and Kuwajima and co-workers[4] on the effects of hexamethylphosphoric triamide (HMPA) and 4-dimethylaminopyridine (DMAP) in conjunction with TMSCl facilitated additions of organocopper reagents to enones prompts us to report on our observations utilizing tetramethylethylenediamine (TMEDA)[5] as a promoter in reaction of enones with *alkyl-* or *arylcoppers* in the presence of TMSCl. The choice of TMEDA was guided by idea that the ligand might serve to stabilize and solubilize the copper reagents and at the same time increase the reactivity of the silyl halide. In addition, the ready availability, low cost, and water solubility were attractive features.

In addition to rate promotion and yield enhancement, the presence of TMSCl in the reaction mixture would presumably lead directly to silyl enol ethers (Scheme 1); in many instances this could be of considerable advantage for further synthetic transformations. Alexakis and co-workers[6] have reported the interesting observation that TMSCl is effective in promoting 1,4-additions of lithium dialkylcuprates to α,β-unsaturated carbonyl compounds but that silyl enone ethers are formed in these reactions only in the presence of triethylamine or HMPA. We have also observed that TMEDA facilitates the trapping of the enolate resulting from conjugate addition. These reactions provide excellent yields of silyl enol ethers which can be isolated in a state of high purity with minimal effort.

Scheme 1

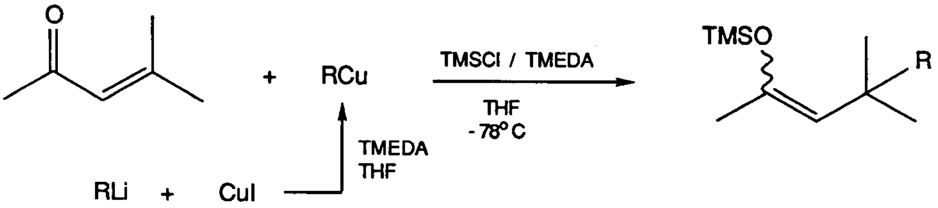
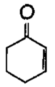
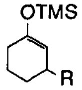
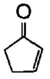
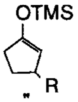
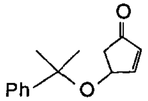
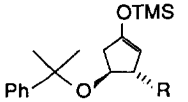
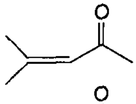
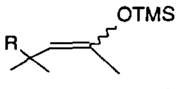
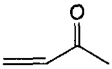
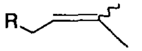


Table. TMSCl/TMEDA Facilitated Additions of RCu to Enones

Entry	Enone	RLi	Equiv TMSCl/TMEDA	Time (h)	Product	Yield (%)
1		n-Bu	2.5 /3.0	0.2		96
2	"	"	1.1 /1.2	0.2	"	94
3	"	"	1.1 / 0.2	0.2	"	93
4	"	"	--- /3.0	1.5	"	70[b]
5	"	"	2.5 / ---	3.0	"	11[b]
6	"	s-Bu	2.5 /3.0	0.3	"	97
7	"	"	1.1 /1.2	0.2	"	83
8	"	Ph	2.5 / 3.0	1.0	"	67
9	"	"	--- /3.0	3.0	"	0
10	"	Me	2.5 /3.0	1.5	"	80
11	"	"	---- /3.0	3.5	"	69[b]
12		n-Bu	2.5 / 3.0	0.25		81
13	"	"	1.1 / 1.2	0.2	"	88
14	"	"	1.1 /0.2	0.3	"	80
15	"	t-Bu	2.5 / 3.0	0.3	"	92
16	"	"	1.1 / 0.2	0.25	"	93
17	"	s-Bu	1.1 /1.2	0.25	"	93
18	"	Ph	1.1 /1.2	1.0	"	20
19	"	"	---- / 3.0	2.5	"	6[b]
20		n-Bu	2.5 /3.0	0.25		94
21	"	"	---- / 3.0	0.3		93[b][c]
22		"	2.5 / 3.0	1.0		68[d] [E:Z, 1:3.3]
23		"	2.5 / 3.0	0.2		98[d] [E:Z,1:3.2]
24	"	"	---- /3.0	0.25	"	97[b]

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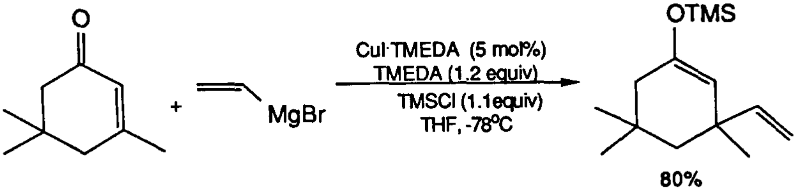
[a] All reactions were carried out for the indicated times at -78°C according to the procedure described in the text using equimolar amounts of RLi and enone. Except were indicated yields refer to isolated yields of the silyl enol ethers. [b] Yields refer to isolated yields of ketones. [c] Only one isomer detected. [d] E:Z ratio determined by 300 MHz ^{1}H NMR integration.

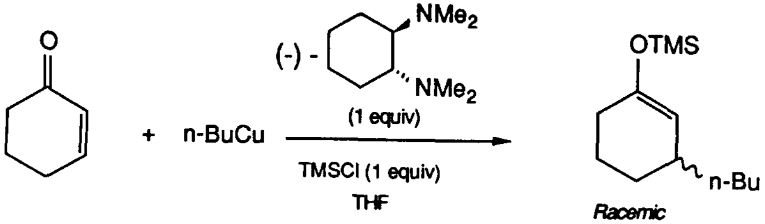
The Table summarizes our results to date. In addition to the advantages noted above, several interesting features emerge. Nakamura and Kuwajima and co-workers, in the work cited above, utilized copper(I) bromide-dimethyl sulfide complex as they found copper (I) iodide to be less effective. Our results were obtained utilizing commercial CuI directly. Our early experiments involved the use of three equivalents of TMEDA per equivalent of CuI as this lead to a homogeneous reaction medium. Subsequently we found that the less than one equivalent of TMEDA was sufficient for the rapid production of the desired silyl enol ethers in equally high yields. Our experiences in these studies lead us to the suggestion that the salt or complex formed with TMSCl and the nucleophilic addend is the effective promoter in these reactions rather than TMSCl per se. In consonance with the observations of Nakamura and Kuwajima and co-workers, we have found that THF is a superior medium to diethyl ether for these reactions.

This procedure offers a straightforward, efficient use of RCu, derived from RLi, in conjugate additions to enones utilizing only small amounts of TMEDA rather than greater than stoichiometric amounts[4] of highly toxic HMPA or the use of DMAP, which is relatively expensive. In general, high yields of the silyl enol ether or ketone may be obtained by a simple procedure after only short reaction times (*i.e.*, 10 min.) at low temperatures using commercially available, unpurified CuI. The additions of methylcopper, normally an insoluble, oligomeric and relatively unreactive substance, proceed in fair yields (entries 10 & 11) with TMEDA alone; this suggest that the ligand is functioning as a solubilizing agent. The enhanced yields and shorter reaction times with the TMEDA/TMSCl combination indicates a synergistic effect of the combination. The additions of phenylcopper (entries 8, 9, 18 & 19) resulted in lower yield. (In each of these cases the reaction involved the use of Et_2O as a co-solvent, which may be responsible for the reduced yields.) Additions of vinylcopper produced from vinyllithium[8] to enones under these conditions gave adducts in yields less then 20%. However, using vinylmagnesium bromide as a source of vinyl anion, the conjugate addition to isophorone proceeded smoothly to give the enol ether in 80% yield (eq 1). In this case, using a Grignard reagent, only a catalytic amount of CuI TMEDA complex[9] was necessary to give the reaction. Such parametric limitations to this reaction are currently under investigation.



(1)

The possibility that a homochiral 1,2-diamine would be useful in effecting asymmetric syntheses was investigated. When TMEDA was replaced by (-)-(*R*,*R*)-*N*,*N*,*N'*,*N'*-tetramethylcyclohexane-1,2-diamine[7] reaction of *n*-BuCu with cyclohexenone an optically inactive product was obtained (eq 2).



(2)

Although the behavior of the reaction with organocopper reagents closely parallels that of the organocuprates the exact mechanistic details remain for additional studies. At this juncture it appears that TMSCl in the absence of a nucleophilic addend (amine, phosphine, HMPA, etc.) is not effective for the production of TMS enol ethers. TMEDA alone may provide some assistance in the addition of RCu to enones and furthermore may facilitate the transmetalation reaction. TMEDA and TMSCl is an effective combination, facilitating the conjugate addition of RCu to enones and the subsequent trapping of the enolate at the TMS enol ether.

Experimental Procedure: To a clean dry, two-necked 25-mL flask equipped with a magnetic stirrer and an addition funnel was added Cu(I) iodide (0.40 g, 2.1 mmol) and TMEDA (see Table). The apparatus was then flushed with argon and 4 mL of THF was added. After the contents were stirred at room temperature for several minutes the flask was cooled to -78°C and the akyllithium reagent (2.0 mmol) was added followed by stirring at -78°C for 20 min. The trimethylsilyl chloride was added neat followed by the enone (2.0 mmol), as a solution in 2 mL of THF, was then added dropwise with stirring. After the indicated time the cold reaction mixture was poured into a separatory funnel containing a mixture of 75 mL of ice cold 0.1 N HCl and 100 mL of pentane and the contents were shaken briefly. The pentane solution was separated, washed with 25 mL of cold, saturated aqueous $NaHCO_3$ and dried over anhydrous Na_2SO_4. Further purification could be achieved by dissolution of the concentrated pentane extract in 25 mL of DMSO followed by extraction with four 25-mL portions of pentane. The combined pentane extracts are the washed with two 50-mL portions of saturated aqueous $NaHCO_3$ and dried over Na_2SO_4. Concentration of the resulting pentane extract gave the TMS enol ether in a high state of purity.

Alternatively, the ketone was be isolated by pouring 10 mL of saturated aqueous NH_4Cl into the cold reaction mixture and allowing the resulting mixture to warm with stirring to room temperature. The mixture was diluted with 30 mL of ether, washed with 0.5 N HCl, saturated aqueous $NaHCO_3$ and dried over anhydrous $MgSO_4$. The ether solution was concentrated and the residue was purified by column chromatography on silica gel using 5:1 pentane/Et_2O.

Acknowledgment. This work was supported by a grant from the National Science Foundation.

References and Notes

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2) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, 6015, 6019.
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5) TMEDA is reported to exert a slight influence on the stereochemistry of additions of polymeric n-BuCu to methyl butynoate (Anderson, R. J.; Corbin, V. L.; Cotterrell, G.; Cox, G. R.; Henrick, C. A.; Schaub, F.; Siddall, J. B. *J. Amer. Chem. Soc.* **1975**, *97*, 1197.
6) Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, 1047.
7) Purchased from Strem Chemical Company.
8) House, H. O.; Umen, M. J. *J. Org. Chem.* **1973**, *38*, 3893, Seyferth, D.; Weiner, M. A. *J. Amer. Chem. Soc.* **1961**, *83*, 3583.
9) Prepared by treatment of purified CuI with 3 equiv of TMEDA, dissolution in THF and precipitation with hexane as a white crystalline solid (61%): mp 214°C d. Elemental analysis (Calc'd. for $C_6H_{16}CuIN_2$ C, 23.50; H, 5.26; N, 9.13. Found. C, 23.58; H, 5.33; N, 8.89) suggests a 1:1 complex.

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