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CONJUGATE ADDITION REACTIONS OF ORGANOCUPRATES DERIVED FROM α- AMINOALKYL CARBANIONS

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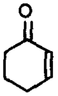
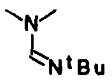
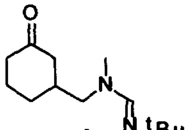
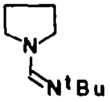
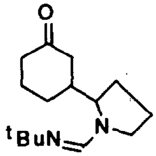
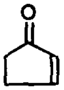
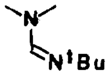
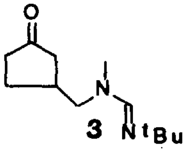
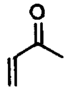
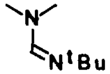
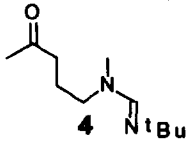
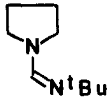
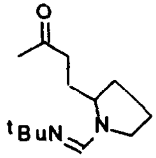
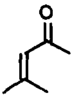
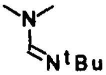
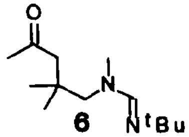
Abstract: α-Aminoalkyl carbanions derived from formamidine derivatives afford higher order cyanocuprate reagents ($R_2CuCNLi_2$) that undergo 1,4-addition reactions to α,ß-enones.

Organocopper chemistry has become a mainstay of organic synthesis and the conjugate addition reaction plays a prominent role.[1] The utilization of cuprates containing highly functionalized transferable ligands significantly expands the synthetic utility of these reagents and the use of α-heteroatom stabilized carbanions has received attention for oxygen[2] and sulfur[3] systems. To our knowledge, cuprates derived from α-nitrogen carbanions have not been utilized in conjugate addition reactions even though they have been alkylated with alkyl halides.[4] Although lithium azo carbanions are reported to undergo a 1,4-conjugate addition reaction with methyl crotonate, the reaction is extremely limited by substrate structure.[5] We now report that cuprates can be prepared from formamidine-derived carbanions and undergo conjugate addition reactions with a variety of α,ß-enones.

Initially, the tert-butyl formamidine of N,N-dimethylamine was deprotonated (tert-BuLi, THF, -78 to -25°C) and treated with several Cu(I) salts in order to assess the ability of different organocopper and cuprate reagents to transfer the α-aminoalkyl ligand to cyclohexenone in a 1,4-fashion. This screening process revealed that homocuprates (R_2CuLi), acetylenic mixed cuprates ($RC{\equiv}CCuRLi$), and amidocuprates ($R_2NCuRLi$) either failed to effect the conjugate addition reaction or afforded complex reaction mixtures. The phenylthio mixed cuprate[6a] ($PhSCuRLi$), "higher order (H.O.)" cyanocuprate[1a] ($R_2CuCNLi_2$) and the organocopper (RCu/TMEDA/TMSCl) reagent[6b] all gave good yields of the conjugate addition product[7] (Table, entries 1-5). The "(H.O.)" cyanocuprate and phenylthiocuprate reagents gave homogeneous

Table. Conjugate addition reactions of organocopper reagents derived from lithiated formamidines.

entry	substrate	formamidine	copper reagent	solvent/ additive	product	% yield[a]
1			RCuSPhLi	THF	 **1**	86[b]
2				THF/Et_2O		66
3				THF/TMSCl		49
4			RCu/TMEDA	THF/TMSCl		89[c]
5			$R_2CuCNLi_2$			85
6			$R_2CuCNLi_2$	THF/TMSCl	 **2**	79[d,e]
7			$R_2CuCNLi_2$	THF/TMSCl	 **3**	83
8			RCu/TMEDA	THF/TMSCl		38
9			$R_2CuCNLi_2$	THF/TMSCl	 **4**	98
10			$R_2CuCNLi_2$	THF/TMSCl	 **5**	71
11			$R_2CuCNLi_2$	THF/TMSCl	 **6**	61

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[a] Yields are estimated by NMR analysis (conversion of mole ratios to weight percents and hence yields) of the crude reaction mixture, containing starting formamidines, silyl residue, and/or TMEDA, unless otherwise noted. [b] Chromatography gave 62% yield. [c] Mixture of ketone and silyl enol ether. [d] Deprotected as mixture of N-formyl amine and free amine by preparative TLC in 66% yield (>90% purity). [e] A 1: 1 mixture of diastereomers.

cuprate solutions in THF; poor results were obtained with these reagents when non-homogeneous reaction mixtures were observed. The phenylthiocuprate gave comparable yields of product in THF or THF/Et_2O mixed solvents and in the presence or absence of chlorotrimethylsilane (TMSCl), although the TMSCl reaction was not as clean. The organocopper reagent (which gave heterogeneous mixtures) required the addition of TMEDA which proved difficult to remove from the basic formamidine containing products which undergo varying degrees of decomposition upon silica gel chromatography. The highest yields and cleanest reactions were obtained with the "(H.O.)" cyanocuprates although these reagents inefficiently use one equivalent of the aminoalkyl ligand which must be removed in a purification process.

As is typical of organocopper chemistry, the reaction is sensitive to a number of reaction parameters such as substrate structure, solvent, and cuprate reagent. Although the phenylthiocuprate and alkyl copper/TMEDA-TMSCl reagent gave good yields with cyclohexenone these reagents appear not to work as well with other substrates and/or formamidines. The "(H.O.)" cyano cuprates ($R_2CuCNLi_2$) derived from the formamidines of N,N-dimethylamine and pyrrolidine gave the most consistent results affording good yields with the sterically unhindered enones cyclohexenone, cyclopentenone and methyl vinyl ketone (Table, entries 5-10).[7] These cuprates appear to have a reactivity comparable to lithium dimethylcuprate and do not add to substrates with modest steric hinderance (e.g. 3-methylcyclopentenone) although addition to mesityl oxide (entry 11)[7] has been achieved.

Although the formamidine group permits facile generation of the organolithium reagent from which the cuprate can be prepared, it poses considerable difficulty for the purification and subsequent manipulation of the conjugate addition product. The excess starting _tert_-butylformamidines can be removed, in part, by concentration in vacuo although considerable (5-30%) material remains in the final sample. Removal of the _tert_-butylformamidine protecting group has also proved problematic. The usual reagents for formamidine deprotection (e.g. KOH, H_2NNH_2, or reducing agents) are incompatible with the ketone functionality. Formamidine hydrolysis can be achieved with a MeOH/H_2O solution but mixtures of free amines and N-formyl derivatives are obtained. The isolated yields of N-formyl compounds[7] are substrate dependent with substantial decomposition occurring for the conjugate addition products obtained from methyl vinyl ketone and 2-

cyclopentenone. An analytically pure sample of 3-(N-formyl-N-methylaminomethyl)cyclohexanone was obtained by hydrolysis and subsequent Kugelrohr distillation in 46% yield based upon the enone.

In summary, α-aminoalkylcuprates have been prepared and found to undergo conjugate addition reactions to sterically unhindered ketones and this represents the first reported conjugate addition reactions of α-aminoalkyl cuprates. Manipulation of the nitrogen functionalities subsequent to the conjugate addition reaction remains a problem and carbamates[8a], oxazolines[4a] and "second generation" formamidines[8b] are currently under investigation as alternative dipole stablizing groups. These groups would provide more stable N-protected amino ketones that may be easier to manipulate in subsequent reactions.

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7. All new compounds were characterized by spectroscopic analysis (IR, ^1H and ^{13}C NMR and MS). Chromatographic purification gave relatively clean samples (> 90% pure) of **1-2** and **4**. Formamidines **1-3** and **4** were hyrolyzed to the N-formyl derivatives which gave complicated ^1H and ^{13}C NMR spectra due to N-formyl rotomers.
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