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Acylation of α-Aminoalkyl- Copper and Cuprate Reagents with Acid Chlorides: Improved Yields with Soluble Copper (I) Salts

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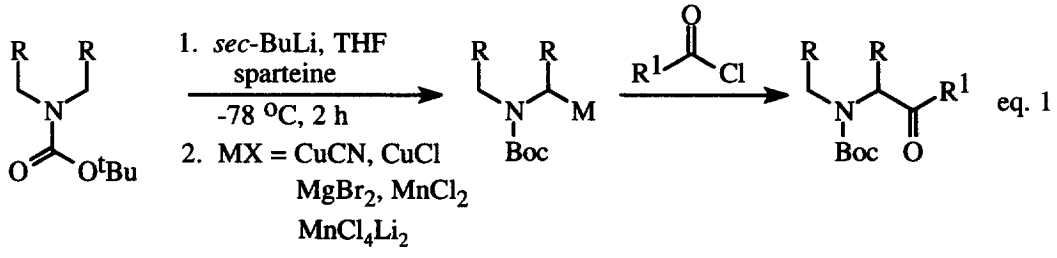
Abstract: α-Aminoalkylcopper reagents prepared from soluble CuX·2LiCl give modest to good yields of α-aminoketones upon reaction with acid chlorides. Higher yields are generally obtained with CuCl·2LiCl than with CuCN·2LiCl. Improved yields can be obtained by utilization of cuprate reagents prepared from CuCN·2LiCl and 2.0 equivalents of α-lithiocarbamates. © 1997, Elsevier Science Ltd. All rights reserved.

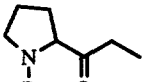
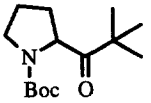
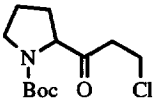
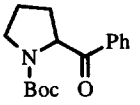
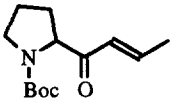
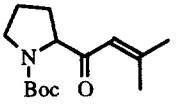
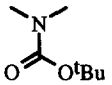
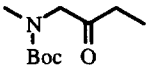
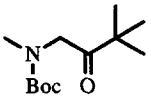
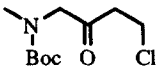
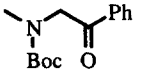
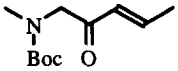
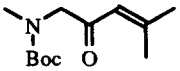
Although a variety of electrophiles acylate organometallic compounds, the reaction is sensitive to the particular organometallic reagent and electrophile being employed. Difficulties often arise and solutions generally involve matching the thermal stability and reactivity of the organometallic reagent with an electrophile of appropriate reactivity. Organolithium and Grignard reagents have been acylated with amides[1], esters[2], and acid chlorides[3] while stoichiometric or catalytic organocopper and cuprate[4a] reagents are generally acylated with acid chlorides[4b-c], thiol esters[4d], and selenoesters[4e]. Recently, organomanganese compounds have begun to rival organocopper and cuprate reagents in acylation reactions.[5] In an effort to expand the chemistry of α-aminoalkylcuprates[6], we sought to effect acylation of these reagents. Surprisingly, the direct acylation of α-aminoalkylcuprates proved problematic and several α-metallated reagents were examined. We now report that α-aminoalkyl- organocopper and cuprate reagents prepared from soluble Cu(X)·2LiCl in THF afford good to excellent yields of α-aminoketones.

The *tert*-butyl carbamates of pyrrolidine (**1**) and *N,N*-dimethylamine (**2**) were deprotonated with *sec*-BuLi (THF, -78 °C, 1 h) in the presence of sparteine and then treated with metal halides to form the various organometallic reagents (eq. 1). In preliminary experiments, α-aminoalkylcuprates prepared from the 2-lithio derivative of **1** and CuCN in THF reacted with propionyl chloride to afford α-aminoketone **3** in low [25-30 %, with RCuCNLi] to moderate [57%, 2RLi + CuCN] yields.[7] Utilization of benzoyl chloride with the latter reagent gave slightly higher yields (65-75%) and both of the reagents gave low yields when prepared from Boc-protected



eq. 1

Table. Acylation of α-aminoalkyl copper and cuprate reagents.

entry	carbamate[a]	acid chloride	CuX·2LiCl	(eq)[b]	product	no.	% yield[c]
1		CH_3CH_2COCl	CuCN	0.5			100 (91)[d]
2			CuCN	1.0		**3**	55
3			CuCl	1.0			70
	1						
4		Me_3CCOCl	CuCl	1.0		**4**	88
5		$ClCH_2CH_2COCl$	CuCl	1.0		**5**	62
6		PhCOCl	CuCN	0.5		**6**	100
7			CuCl	0.5			89-93
8			CuCl	1.0			62-65
9		$MeCH{=}CHCOCl$	CuCl	0.5		**7**	84
10			CuCl	1.0			60
11		$Me_2C{=}CHCOCl$	CuCN	0.5		**8**	99
12			CuCl	1.0			50-57
13		CH_3CH_2COCl	CuCN	0.5		**9**	98
14			CuCN	1.0			55
15			CuCl	1.0			85
	2						
16		Me_3CCOCl	CuCl	1.0		**10**	96
17		$ClCH_2CH_2COCl$	CuCl	1.0		**11**	63
18		PhCOCl	CuCN	0.5		**12**	100
19			CuCl	1.0			73
20		$MeCH{=}CHCOCl$	CuCl	1.0		**13**	55
21		$Me_2C{=}CHCOCl$	CuCl	1.0		**14**	46-53

[a] The carbamate was deprotonated with *sec*-BuLi in THF and added to the Cu(I) salt. Sparteine was used to facilitate deprotonation. [b] Equivalents of Cu(I) relative to RLi. [c] Yields are based upon purified isolated products unless otherwise noted. [d] TMEDA was used to facilitate deprotonation.

N,*N*-dimethylamine (40% and 25%, respectively). The acylation proved capricious under these reaction conditions and widely variable yields were obtained from experiment to experiment. In an effort to develop a general procedure for the acylation of α-metallated carbamates several organometallic reagents were examined. Although reaction of the Grignard reagent derived from **1** (i. *sec* -BuLi, sparteine, THF, -78 °C. ii. $MgBr_2$, 0-5 °C, 45 min.) with 2-pyridyl propionate failed at room temperature, a 48% yield of 2-(1-oxopropyl)pyrrolidine (**3**) could be obtained upon heating at reflux for 2 hrs. This result points to the significantly greater thermal stability of the 2-magnesio derivative of **1** which is in marked contrast to the thermal lability of the lithium analog. Utilization of the Grignard reagent in the presence of two equivalents of lithium hexamethyldisilazide (LHMDS)[2a] gave only trace amounts of **3** and the utilization of *N*-methyl-*N*-methoxyamides[1b] also proved unsuccessful.

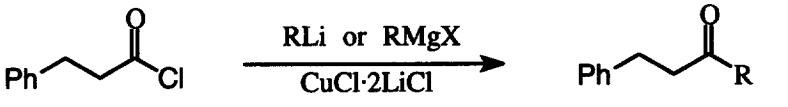
Organomanganese compounds were prepared by deprotonation of Boc-protected pyrrolidine (*sec* -BuLi, sparteine, THF, -78 °C) followed by treatment with anhydrous $MnCl_2$ or $MnCl_4Li_2$ (-78 °C and then 0 °C, 30 min.) and briefly examined. Reaction of the pyrrolidine reagent, RMnCl, with propionyl chloride gave low yields (16-24%) of α-aminoketone **3** when prepared from insoluble $MnCl_2$ or employed in the absence of catalytic amounts of CuCl. The organomanganese reagent prepared from RLi and THF soluble $MnCl_4Li_2$ reacted with propionyl chloride to give **3** in variable yields depending upon the temperature of initial RLi / $MnCl_4Li_2$ mixing (42% for 0 °C; 68% for -78 °C). The optimal conditions (75% yield with sparteine, 51% without) involved addition of $MnCl_4Li_2$ to RLi at -78 °C, aging the solution at 0 °C for 0.5 h, and then addition of propionyl chloride at -50 °C followed by slow warming to room temperature. Although these studies did not produce a high yield generally reliable procedure for the acylation of α-aminoalkylmanganese compounds, they did point to the importance of temperature effects, CuCl as a co-catalyst, and soluble forms of the metal salt precursors.

Re-examination of the cuprate reagents under stringently controlled conditions revealed a probable source of the variability in chemical yield. Generation of the pyrrolidine derived cuprate (2 RLi + 0.5 equiv CuCN) at -55 °C followed by addition of propionyl chloride at this temperature and, after 15 min, rapid warming to 0 °C gave **3** in 80% yield. This result suggested a sensitive kinetic balance between cuprate decomposition and the acylation reaction and in conjunction with the organomanganese results prompted an examination of soluble sources of Cu(I) salts. Treatment of the 2-lithio derivative of **1** (2.0 equiv) with CuCN·LiCl in THF followed by propionyl chloride afforded **3** in 92% while use of CuCN·2LiCl under identical conditions gave **3** in quantitative yield (Table, entry 1). TMEDA or sparteine, used to facilitate deprotonation, gave similar results.[6b] High yields of α-aminoketones were obtained upon reaction of the pyrrolidine or *N*,*N*-dimethylamine derived cuprates with either propionyl chloride or benzoyl chloride (entries 1,6, 13, & 18). Cuprate reagents derived from **1** gave slightly higher yields when prepared from CuCN·2LiCl rather than from CuCl·2LiCl (entries 6-7).

Since these conditions inefficiently use only one of the two α-aminoalkyl ligands, the use of mixed cyanocuprate or alkylcopper reagents was examined. Cyanocuprate reagents, RCuCNLi, uniformly gave lower yields than alkylcopper reagents prepared from RLi + CuCl·2LiCl (entries 2, 14 *vs* 3, 15) in THF. The homogeneous α-aminoalkylcopper reagents prepared from THF soluble CuCl·2LiCl gave modest to good yields of α-aminoketones with saturated acid chlorides (entries 3-5, 15-16), aroyl chlorides (entries 8 & 19), and unsaturated acid chlorides (entries 10, 12 and 20-21). Mixed cuprates prepared from α-aminoalkyllithium reagents and CuN^iPr_2, $CuPPh_2$, CuSPh or (2-thienyl)CuCNLi proved ineffective in the acylation reaction.

The utilization of THF soluble CuCl·2LiCl is also useful in the preparation of simple alkylcopper reagents which react with acid chlorides to afford ketones in high yields (eq. 2). These alkylcopper reagents can be

prepared from either organolithium or Grignard reagents and afford higher yields of ketones then existing organocuprate procedures[4] and appear to be operationally simpler than the organomanganese[5] procedures. The Grignard derived alkylcopper reagents give uniformly high yields comparable to the corresponding homo mixed cuprates, $R(CH_3)CuMgX$[4b], which always give small amounts of methyl ketones. Additionally, *sec*-BuMgBr was prepared from *sec*-BuLi and $MgBr_2$ illustrating the viability of this transmetallation sequence.



eq. 2

R	% yield Li	Mg
n-Bu	90	96
tert-Bu	72	
sec-Bu	82	89
Ph	39	87

In summary, α-aminoalkylcopper reagents prepared from THF soluble CuCN·2LiCl react with acid chlorides to give modest to excellent yields of α-aminoketones while near quantitative yields can be obtained by use of cuprates prepared from 2 RLi + CuCN·2LiCl. Although the latter reagents transfer only one α-aminoalkyl ligand, the unused ligand can be easily recovered by chromatography. Alkylchloroformates gave low yields of α-aminoesters and this extension of the methodology is under investigation. The alkylcopper procedure also offers a simple, efficient, and high yield route to simple ketones from acid chlorides and organolithium or Grignard reagents.

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