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# Preparation of Tertiary Amides from Carbamoyl Chlorides and Organocuprates

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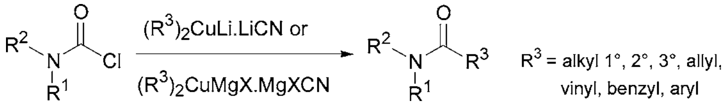
## ABSTRACT



**Reaction of carbamoyl chlorides with cyano-Gilman cuprates affords tertiary amides in good to excellent yields. The reaction is general due to the possibility of using reagents made either from organolithium or from Grignard compounds. The characterization of the main side products allowed for the suggestion of a possible mechanism.**

Despite numerous efforts to replace it, phosgene is still widely used in organic chemistry, providing the carbonyl part of many functional groups. Under basic conditions,[1] it reacts with secondary amines to afford carbamoyl chlorides, which are often used in situ because of their high reactivity toward nucleophiles. Thus, straightforward access to stable carbamates and ureas is achieved with alcohols and amines, respectively.[2] Less common are their reactions with carbanions yielding amides. Indeed, unlike acid chlorides or chloroformates, carbamoyl chlorides do not react properly with Grignard reagents without a catalyst.[3] Moreover, the coupling is limited to alkyl and aryl Grignard reagents (not vinyl). Their reactions with organolithium reagents are mainly described with aromatic carbanions.[4] Moreover, they are carried out with an excess of carbamoyl chloride. A few more reports described the Sonogashira[5] or Stille[6] type couplings with carbamoyl chlorides. Only acetylenic, aryl, or vinyl amides could be prepared by these methods. Organopotassium,[7] organozinc,[8] and organotitanium[9] were used in specific cases for this transformation. Thus, there is a need for a general method for making amides from carbamoyl chlorides. In our continuing interest in synthesizing amides and lactams from carbamoyl chlorides[3,10] we report here an efficient method using organocuprates as organometallic species. For our study we selected three carbamoyl chlorides, **1** and **2**, which are commercially available, and **3**, which is easily prepared[1c] (Figure 1).

First, we examined the reaction of **1** or **2** with the less reactive organocopper reagents ($MeCu{\cdot}LiI$, $MeCu{\cdot}MgICl$, $n\text{-}BuCu{\cdot}LiBr{\cdot}Me_2S$, $MeCu{\cdot}LiI{\cdot}2PBu_3$, $n\text{-}BuCuCNLi$).[11] The

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[11] Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135−631.

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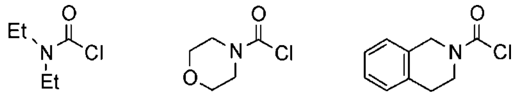


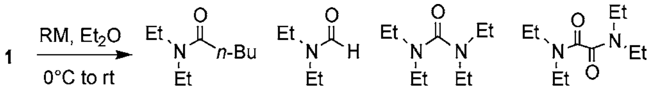
**1** **2** **3**

**Figure 1.** Selected carbamoyl chlorides.

reactions, attempted in THF or $Et_2O$, did not afford a conversion higher than 20% into the expected amides. Similar results were obtained when the organometallic reagents were used in combination with a catalyst: MeCu·LiI and 5% $PdCl_2(PPh_3)_2$,[12] *n*-BuCuCNLi and 5% $NiCl_2(PPh_3)_2$, and EtMgCl and 3% $Li_2CuCl_4$.[13]

Next, we turned our attention toward the reaction of carbamoyl chloride **1** with Gilman and cyano-Gilman cuprates (RM).[11] The results (Scheme 1) showed that the highest yield of amide **4a** was obtained using the cyanocuprate, with little or no formamide **5**, urea **6**, and oxalamide **7**. Moreover, in the reaction of the Gilman reagent, GC-MS analysis revealed also the presence of substantial amounts of 5-nonanone and octane (3−4% of each). Therefore, we selected copper(I) cyanide as the copper salt for the preparation of cuprate reagents.

**Scheme 1.** Lithiated Organocuprate Reaction with Carbamoyl Chloride **1**[a]



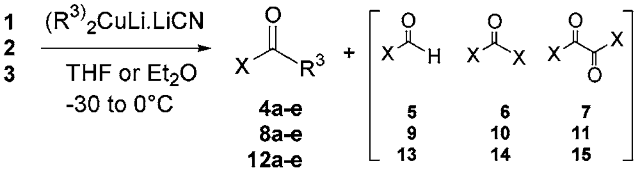
| | **4a** | **5** | **6** | **7** |
|---|---|---|---|---|
| $(n\text{-Bu})_2CuLi.LiI$ | 75 | 12 | 2 | 2 |
| $(n\text{-Bu})_2CuLi.LiCN$ | 95 | 2 | 0 | 0 |

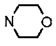
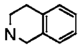
[a] Ratios in % determined by GC-MS analysis.

The scope of the reaction of carbamoyl chlorides **1**−**3** with cyanocuprates generated from commercially available organolithium solutions was studied next. The results are summarized in Table 1. Aryl and alkyl amides were produced in good to excellent yields with the exception of **8e** (entry 10), and better results were obtained in THF compared to $Et_2O$. With branched alkyl cuprates (*sec* and *tert*-butyl), moderate to good yields of amides were obtained considering the steric demand of the organometallic reagent (entries 3, 6−8, 13).

The side products formed beside the expected amides, i.e., formamides **5**, **9**, **13**, ureas **6**, **10**, **14**, and oxalamides **7**, **11**, **15**, were independently synthesized for unambiguous characterization and quantitation. The nature and the amount of side products deserve some comments. Formamides (5−11%) are mainly produced in $Et_2O$ when using *sec* or *tert*-butyl cuprates. A mechanism involving a copper(III) intermediate[14] followed by a $\beta$-elimination process is proposed (Scheme 2).[15] A radicalar decomposition of the same intermediate (path a) could explain the formation of oxalamides (1−14%). Ureas (2−9%) were formed probably according to path b. The reaction of **2** was also attempted with alkyl cuprates in the presence of LiCl,[16] α-methylstyrene,[17] or *p*-trifluoromethylstyrene[18] or in 2-methyltetrahydrofuran,[19] but none of these experiments improved the previous results.

**Table 1.** Amides from Carbamoyl Chlorides and Cyano-Gilman Reagents



| entry | sm[a] | X | cuprate[b] R$^3$ | amide (%)[c] | THF | $Et_2O$ |
|---|---|---|---|---|---|---|
| 1 | **1** | $NEt_2$ | *n*-Bu | **4a** | 85 | 70 |
| 2 | **1** | | *s*-Bu | **4b** | 90 | 62 |
| 3 | **1** | | *t*-Bu | **4c** | 37[f] | 33[f] |
| 4 | **1** | | Ph | **4d** | 50 | 70 |
| 5 | **1** | | Me | **4e** | 90 | 80 |
| 6 | **2** |  | *n*-Bu | **8a** | 83[e] | 38 |
| 7 | **2** | | *s*-Bu | **8b** | 50[e] | 33[d] |
| 8 | **2** | | *t*-Bu | **8c** | 62[e] | 43[d] |
| 9 | **2** | | Ph | **8d** | 64 | 70 |
| 10 | **2** | | Me | **8e** | 30 | 20 |
| 11 | **3** |  | *n*-Bu | **12a** | 75 | 70 |
| 12 | **3** | | *s*-Bu | **12b** | 75 | 70 |
| 13 | **3** | | *t*-Bu | **12c** | 85[e] | 55[f] |
| 14 | **3** | | Ph | **12d** | 84 | 83 |
| 15 | **3** | | Me | **12e** | 70 | 68 |

[a] Starting material. [b] Cyanocuprate reagents were prepared at −30 °C. Reaction time: 2 h. [c] GC yields. Ratios of formamides, ureas, and oxalamides are given in Supporting Information. [d] Also recovered was 5−10% starting material. [e] Also recovered was 10−20% starting material. [f] Also recovered was 20−40% starting material.

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(15) We proposed the involvement of copper(III) and radical intermediates to explain the formation of the reaction products. For a complete discussion, see: Bertz, S. H.; Dabbagh, G.; Mujsce, A. M. *J. Am. Chem. Soc.* **1991**, *113*, 631−636.

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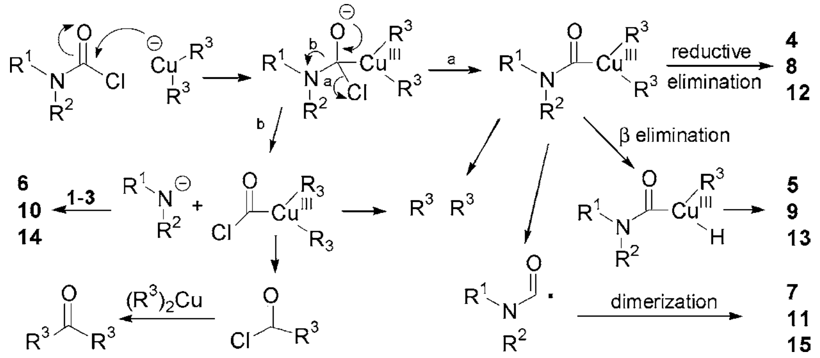
(17) This reagent was used to trap free radicals; see ref 15.

(18) This reagent was used to accelerate reductive elimination and to avoid $\beta$-elimination; see: Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 174−175 and references therein.

(19) Formamides were mainly produced in $Et_2O$. We tried 2-Me-THF as a better coordinating solvent than THF to completely suppress $\beta$-elimination and eventually to improve the overall yield (entries 7 and 8).

**Scheme 2.** Proposed Mechanism



Due to their unique reactivity,[20] magnesiocuprates appeared as a viable alternative to lithiated cuprates because of the diversity of commercially available organomagnesium products or the easiness of their preparation.[21] Reactions of carbamoyl chloride **2** with cyano-Gilman magnesiocuprates were carried out in $Et_2O$ or THF at room temperature over 15 h, and the most representative results are summarized in Table 2. $Et_2O$ proved to be a better solvent than THF (entries 1−2 and 6−7), affording amides **8a** and **8f** in good yields. Urea **10**, the only byproduct, was formed in an amount not exceeding 10% (data not shown in Table 2). All types of carbon residues were coupled efficiently with carbamoyl chloride **2**: primary, secondary, and tertiary alkyl, phenyl, benzyl, allyl, and vinyl. In the latter case, the reaction was slow and only 50% conversion was observed after 15 h at room temperature (entry 10), but we did not detect any 1,4-addition product. The reactions were slower but cleaner compared to our previous experiments with lithiocuprates. The structure of the cyanocuprate reagents could explain such differences. Whereas the lithiocuprates generated from copper cyanide can be described as diorganocuprates with a dilithium cyanide countercation,[22] their magnesium counterparts appear as monoalkyl-cyanocuprate magnesium complexes with the cyanide still bound to the copper.[23] The second equivalent of organomagnesium remaining in the solution could account for the formation of urea **10**.[3] Since monoorganocyanocuprates are unable to react with carbamoyl chlorides,[24] we cannot preclude the existence of the diorganocuprate complex in small amounts, which may be the reactive species.

**Table 2.** Reaction of 2 with Cyano-Gilman Magnesiocuprates

| entry | 2 RMgX + CuCN[a] | amide | yield[b] |
|---|---|---|---|
| 1 | *n*-BuMgBr | **8a** | 79 |
| 2 | *n*-BuMgBr[c] | **8a** | d |
| 3 | *s*-BuMgBr | **8b** | 75 |
| 4 | *t*-BuMgCl | **8c** | 56 |
| 5 | PhMgBr | **8d** | 70 |
| 6 | *c*-HexMgCl | **8f** | 62 |
| 7 | *c*-HexMgCl[c] | **8f** | 51 |
| 8 | allyl-MgBr | **8g** | 51 |
| 9 | BnMgCl | **8h** | 69 |
| 10 | $Me_2C{=}CHMgBr$ | **8i** | 45[e] |

[a] Cyanocuprate reagents (1.05 equiv compared to **2**) were prepared in $Et_2O$ at −30 °C. [b] Isolated yield. [c] Reactions carried out in THF. [d] Less than 50% conversion. [e] Also recovered was 50% unreacted carbamoyl chloride **2**.

Finally, we used milder organometallic reagents compatible with a wide range of functional groups. The reactions of **2** with mixed copper−zinc reagents[25] (RZn(Cu)X or RCu(CN)ZnX·2LiCl) and diorganozinc reagents ($R_2Zn$) did not provide amide **8** (even with catalytic $Pd(PPh_3)_4$), whereas contrasting results were obtained with monoorganozinc reagents ($R^3ZnX$).[26]

In conclusion, we have disclosed an efficient method for the synthesis of tertiary amides. It involved the coupling reaction of carbamoyl chlorides with alkyl (including branched alkyl), aryl, vinyl, allyl, and benzyl cyanocuprates. The nature of the solvent was crucial to minimize the side reactions. As precursors of cyanocuprates, organolithium and, more advantageously, Grignard reagents were used. This reliable methodology provides a viable alternative to carbon monoxide and a new use for phosgene, or its substitutes, as a carbonylating reagent to synthesize tertiary amides, mostly when corresponding acids are not easily available. Due to the peculiar reactivity of organocopper reagents,[25] work is now in progress to extend the scope of the reaction to functionalized substrates or reagents.

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(24) We assume that RCuCNMgX reagents have a similar or lower reactivity towards **2** than their lithiated counterparts.

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(26) In refluxing toluene, low conversion occurred with *n*-BuZnCl and 72% yield of **8d** was isolated with PhZnCl, where both reactions were carried out with 5% $Pd(PPh_3)_4$.

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**Supporting Information Available:** Experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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