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Transformation of Primary Carboxamides to N-(t-Butoxycarbonyl)amines Using $CuBr_2$–$LiOBu^t$

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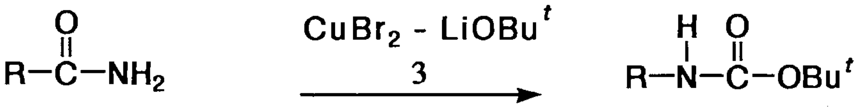
The reaction of primary carboxamides with the copper(II) reagent prepared from copper(II) bromide and lithium t-butoxide gave the corresponding N-(t-butoxycarbonyl)amines in good to high yields.

Recently we reported the oxidations of alcohols[1)] and amines[2)] with $CuBr_2$–$LiOBu^t$, in which bromo(t-butoxy)copper(II) is assumed to serve as an active species. These oxidations are formally regarded as removal of hydrogens from adjacent two atoms. The alternative mode of dehydrogenation which would be promoted by the copper(II) oxidizing agent is 1,1-elimination of hydrogens. Then we have examined such oxidations, and describe here the transformation of primary carboxamides (**1**) to N-(t-butoxycarbonyl)amines (BOC-amines) (**2**) (Eq. 1).



$$\underset{\mathbf{1}}{\mathrm{R{-}C({=}O){-}NH_2}} \xrightarrow[\mathbf{3}]{CuBr_2\text{ - }LiOBu^t} \underset{\mathbf{2}}{\mathrm{R{-}N(H){-}C({=}O){-}OBu^t}} \qquad (1)$$

When benzamide (**1a**) was treated with 2.2 equiv. of $CuBr_2$–$LiOBu^t$(**3**), the BOC-amine **2a** was produced in 36% yield (run 1). It was found that **2a** was obtained in good yields by the use of more than 3 equiv. of the oxidizing agent **3** (runs 2 and 3). On the basis of these results, we speculated that the present transformation would consist of the formation and Curtius rearrangement of nitrene intermediate **5** and the addition of bromo(t-butoxy)copper(II) (**4**) to isocyanate **6** (Eq. 2). In fact, **2a** was produced in 84% yield by the reaction of phenyl isocyanate with **3** (1.1 equiv.) in THF at room temperature, whereas the treatment with t-butanol under the similar reaction conditions gave no addition product.

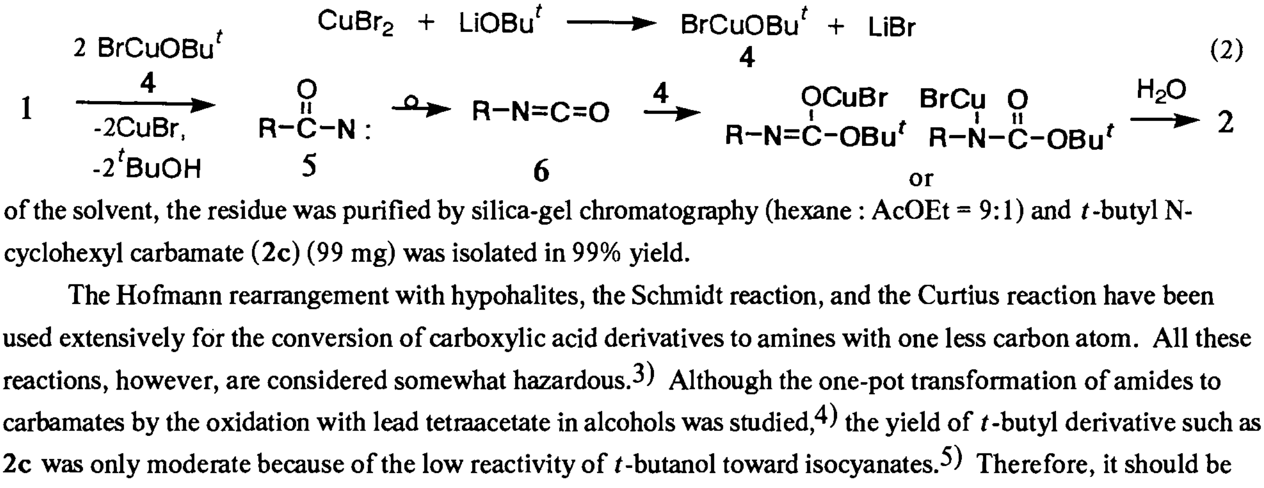
As shown in Table 1, various BOC-amines (**2**) were obtained in good to high yields by the reaction of primary carboxamides (**1**). In the case of the reaction of 3-phenylpropionamide (**1g**), however, no desired product was obtained, but the formation of insoluble materials was observed presumably due to the polymerization of 2-phenylethyl isocyanate (**6g**). In order to accelerate the addition of **4** to **6g**, the use of a large excess of **3** and higher reaction temperature was examined. Although the reaction carried out at 45 °C gave the BOC-amine **2g** in 20% yield along with t-butyl 3-phenylpropionate (**7g**) (run 10), **7g** was preferentially produced under reflux (run 11).

A typical experimental procedure is as follows: To a THF (4 ml) solution of lithium t-butoxide (2.1 mmol) was added copper(II) bromide (491 mg, 2.1 mmol) at room temperature under argon, and the mixture was stirred for 15 min. Then a THF (2 ml) solution of cyclohexanecarboxamide (64 mg, 0.5 mmol) was added to the reaction mixture. After being stirred for 4 h, the reaction was quenched by addition of 3.5% aqueous solution of NH_3. The organic materials were extracted with CH_2Cl_2, and the extract was dried over Na_2SO_4. After removal

Table 1. The preparation of N-(*t*-butoxycarbonyl)amines (BOC-amines) (**2**)[a]

Run	R	$CuBr_2$-$LiOBu^t$ (**3**) equiv.	Temp ℃	Time h	Product (Yield / %)[b]
1	Phenyl	2.2	room temperature	3	**2a** (36)
2	Phenyl	3.3	room temperature	3	**2a** (69)
3	Phenyl	4.2	room temperature	6	**2a** (77)
4	Benzyl	4.2	room temperature	3	**2b** (72)
5	Cyclohexyl	4.2	room temperature	4	**2c** (99)
6	1-Ethylpentyl	4.2	room temperature	3	**2d** (93)[c]
7	1-Adamantyl	4.2	room temperature	5	**2e** (75)
8	*t*-Butyl	4.2	room temperature	5	**2f** (84)[d]
9	2-Phenylethyl	4.2	room temperature	2	-
10	2-Phenylethyl	10	45	5	**2g** (20), **7g** (52)[e]
11	2-Phenylethyl	10	reflux	2	**7g** (80)[e]

a) All reactions were performed with a similar procedure as described in the text, unless otherwise noted. b) The structures of these compounds were identified by the comparison of their spectral data and the mixed examination with the authentic samples prepared by the *t*-butoxycarbonylation of the corresponding amines.[6] c) The structure of **2d** was supported by IR and NMR spectra. d) Isolated by distillation. e) The structure of **7g** was supported by IR and NMR spectra and elemental analysis.



(2)

of the solvent, the residue was purified by silica-gel chromatography (hexane : AcOEt = 9:1) and *t*-butyl N-cyclohexyl carbamate (**2c**) (99 mg) was isolated in 99% yield.

The Hofmann rearrangement with hypohalites, the Schmidt reaction, and the Curtius reaction have been used extensively for the conversion of carboxylic acid derivatives to amines with one less carbon atom. All these reactions, however, are considered somewhat hazardous.[3] Although the one-pot transformation of amides to carbamates by the oxidation with lead tetraacetate in alcohols was studied,[4] the yield of *t*-butyl derivative such as **2c** was only moderate because of the low reactivity of *t*-butanol toward isocyanates.[5] Therefore, it should be noted that the present reaction provides a useful and less hazardous method for the transformation of primary carboxamides to the protected amines.

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References

1) J. Yamaguchi, S. Yamamoto, and T. Takeda, *Chem. Lett.*, **1992**, 1185.
2) J. Yamaguchi and T. Takeda, *Chem. Lett.*, **1992**, 1933.
3) S. R. Sandler and W. Karo, "Organic Functional Group Preparations," 2nd ed, Academic Press, New York (1983), vol. 1, p. 368. For the less hazardous method, see T. Shioiri, K. Ninomiya, and S. Yamada, *J. Am. Chem. Soc.*, **94**, 6203 (1972); S. Yamada, K. Ninomiya, and T. Shioiri, *Tetrahedron Lett.*, **1973**, 2343.
4) B. Acott, A. L. J. Beckwith, and A. Hassanali, *Aust. J. Chem.*, **21**, 197 (1968).
5) T. Mukaiyama, S. Motoki, and Y. Hamada, *Bull. Chem. Soc. Jpn.*, **26**, 49 (1953).
6) O. Keller, W. E. Keller, G. V. Look, and G. Wersin, *Org. Synth.*, Coll. Vol. VII, 70 (1990).

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