Pergamon

Tetrahedron Letters 40 (1999) 8251–8254

TETRAHEDRON
LETTERS

A convenient transformation of *N*-substituted ureas into *N*-(*t*-butoxycarbonyl)amines using a copper(II) salt–lithium *t*-butoxide system

Jun-ichi Yamaguchi,* Yuji Shusa and Takayuki Suyama *

Department of Applied Chemistry, Faculty of Engineering, Kanagawa Institute of Technology, Shimo-ogino, Atsugi-shi, Kanagawa 243-0292, Japan

Received 20 August 1999; accepted 8 September 1999

Abstract

Treatment of *N*-substituted ureas with a copper(II) reagent prepared from lithium *t*-butoxide and copper(II) halide led to give the corresponding *N*-(*t*-butoxycarbonyl)amines under mild conditions. On the contrary, no reaction of *N,N*-disubstituted ureas proceeded. Under the conditions the generation of azodicarbonyldiamide derivatives is expected. Further treatment of azodicarbonyldiamide derivatives with the copper(II) reagent also proceeded to give the corresponding *N*-(*t*-butoxycarbonyl)amines. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: azo; azo compounds; carbamates; copper; copper compounds; ureas.

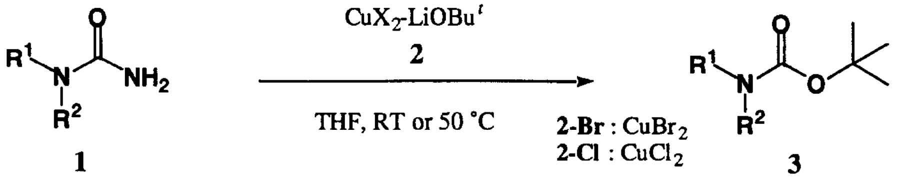
In many types of organic synthetic reactions, transformation of some functional groups into others is an important process. Since urea compounds are applied to the fields of chemicals and medicines, the preparation of these compounds is a basic task in organic synthetic chemistry.[1] In contrast, transformation of ureas into other functional groups has been hardly reported.

Previously, we showed the transformation of primary carboxamides to the corresponding *N*-(*t*-butoxycarbonyl)amines (*N*-Boc-amines) using a copper(II) bromide–lithium *t*-butoxide system.[2] This reaction is formally regarded as a type of 1,1-elimination of hydrogen from the amino group and it would promote generation of a nitrene-like species. In analogy to the above reaction, treatment of some compounds bearing a carbamoyl group at the hetero atoms with a copper(II) reagent can also generate a nitrene-like species. Among them, we were interested in the reactivity of a compound which has a nitrogen atom instead of a carbon atom at the α-position of the carbamoyl group. In this Communication, we wish to report that the treatment of *N*-substituted ureas (**1**) or azodicarbonyldiamides (**5**) with a copper(II) reagent (**2**) in tetrahydrofuran (THF) gave the corresponding *N*-Boc-amines (**3**) in high to excellent yields (Schemes 1 and 3).

---

* Corresponding authors. E-mail: yamagu@chem.kanagawa-it.ac.jp

PII: S0040-4039(99)01751-7



Scheme 1.

Table 1

Treatment of phenylurea (**1a**) with a copper(II) reagent[a]

Run	CuBr$_2$-LiOBu^t (equiv.)	Temperature	Time (min)	Yield of **3a** (%)
1	2.0	RT	30	19
2	3.0	RT	30	50
3	4.0	RT	30	90
4[b)]	4.2	50 °C	5	93
5	4.0[c)]	RT	30	46

a) A THF stock solution (0.885 mmol / ml) of *t*-butylalcohol was used except for run 4. b) Concentration is 2 ml of THF versus 0.4 mmol of **1a**. c) Copper(II) chloride was used instead of copper(II) bromide.

First, we examined treatment of phenylurea (**1a**) with several equimolar amounts of a copper(II) reagent (**2**-Br), which was prepared by copper(II) bromide and lithium *t*-butoxide. In all of the reactions, some gases were evolved instantly when **1a** was added to a THF solution of **2**. The results listed in Table 1 show that the yield of *N*-(*t*-butoxycarbonyl)aniline (**3a**) evidently depends on the reaction conditions such as the equimolar amounts (runs 1–4). Although the yield of **3a** was lower, the reaction with a copper(II) reagent (**2**-Cl) prepared from copper(II) chloride and lithium *t*-butoxide also proceeded under similar conditions (run 5).

Next, transformations of various ureas, namely, *N*-arylureas (**1b–d**),[3] *N*-alkylureas (**1e–i**),[4] and *N,N*-disubstituted ureas (**1j** and **1k**),[5] were performed (Table 2). In most of the cases, some gases were also evolved instantly when **1** was added to a THF solution of **2**. The results listed in Table 2 show that the yield of **3** depends on a combination of the structure of **1** and the reaction conditions. Both reactions of *N*-arylureas (**1b** and **c**) with 4.2 equimolar amounts of **2**-Br gave the best results (runs 1 and 2). However, the reaction of **1d** with **2**-Br provided the corresponding *N*-Boc-amine in low (62%) yield because bromination of the aromatic ring may proceed and **2**-Cl was effective in the transformation of **1d** (Run 3). Further, **2**-Cl was also effective when *N*-alkylureas (**1e–i**) were used as starting materials except for cyclohexylurea (**1g**). In contrast, no reaction of *N,N*-disubstituted ureas (**1j** and **1k**) proceeded to give the corresponding *N*-Boc-amines (**3**) (runs 9 and 10). In addition, no evolution of gases was observed in both reactions.

A typical reaction procedure is as follows: to a THF solution of lithium *t*-butoxide (1.68 mmol), which was prepared from *t*-butylalcohol (0.16 ml, 1.68 mmol) in THF (2 ml) and a *n*-hexane solution of *n*-BuLi (1.1 ml, 1.68 mmol), was added copper(II) bromide (375 mg, 1.68 mmol) at room temperature under nitrogen, and the mixture was stirred for 15 min. Then *N*-phenylurea (54 mg, 0.4 mmol) was added to the reaction mixture. After being stirred for 30 min, the reaction was quenched by addition of 7.5% aqueous solution of ammonia. The organic materials were extracted with CH_2Cl_2, and the extract was dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by preparative TLC (*n*-hexane:EtOAc 4:1) and *N*-(*t*-butoxycarbonyl)aniline (72 mg) was isolated in 93% yield.

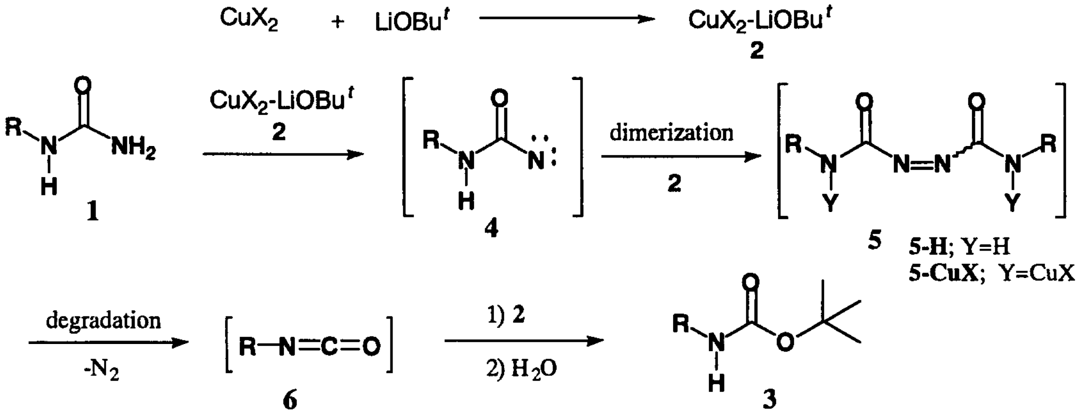
Table 2
The reaction of various ureas with a copper(II) reagent[a]

Run	R^1	R^2		CuX_2-$LiOBu^t$ (equiv.)	Temp. (°C)	Time(min)	Yield(%)[b)]
1	4-MeC_6H_4	H	**(1b)**	$CuBr_2$ (4.2)	50	5	85
2	2-ClC_6H_4	H	**(1c)**	$CuBr_2$ (4.2)	50	5	90
3	*N*-Boc-5-indolyl	H	**(1d)**	$CuCl_2$ (6.0)	50	5	83
4	$PhCH_2$	H	**(1e)**	$CuCl_2$ (6.0)	50	5	76
5	Ph(Me)CH	H	**(1f)**	$CuCl_2$ (6.0)	50	5	84
6	cyclohexyl	H	**(1g)**	$CuBr_2$ (4.2)	RT	30	80
7	$Ph(CH_2)_2$	H	**(1h)**	$CuCl_2$ (6.0)	50	5	81
8	$Ph(CH_2)_3$	H	**(1i)**	$CuCl_2$ (6.0)	50	5	80
9	Ph	Ph	**(1j)**	$CuBr_2$ (4.2)	RT	30	-
10	$PhCH_2$	$PhCH_2$	**(1k)**	$CuBr_2$ (4.2)	RT	30	-

a) All the reactions were performed by a similar procedure as described in the text, unless otherwise noted.

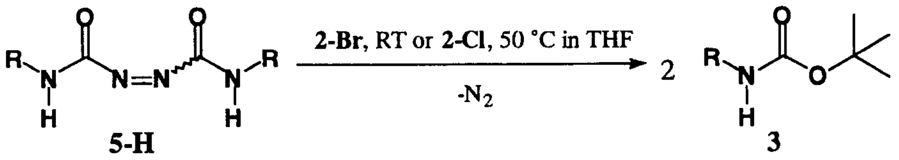
b) Isolated yield of **3**. The structures of these compounds were supported by ^1H and ^{13}C NMR, and IR spectra.

From the above results, it is assumed that the present reaction would proceed through the initial formation of azodicarbonyldiamide derivative (**5**-H or -CuX) by the dimerization of a nitrene-like species (**4**). The azodicarbonyldiamide derivative (**5**-CuX), in turn, gives the corresponding isocyanate (**6**) by its degradation. Diels and Paquin reported that pyrolysis of azodicarbonyldiethyldiamide disilver salt, which was prepared by treatment of azodicarbonyldiethyldiamide with silver nitrate, generated ethylisocyanate giving 4-ethyl-1-phenylsemicarbazide with phenylhydrazine.[6] Since it is reported that an isocyanate smoothly reacts with a copper(II) reagent to give the corresponding *N*-Boc-amine (**3**) under similar conditons,[2] an addition of the copper(II) reagent to isocyanate (**6**) will effect the reaction (Scheme 2).



Scheme 2.

As illustrated in the above reaction mechanism, generation of an azodicarbonyldiamide derivative (**5**-H or -CuX) was proposed as an active intermediate. It is interesting to note that compounds (**5**-H) can react with copper(II) reagent (**2**) to give **3**. Some desired azodicarbonyldiamide derivatives were prepared by the reaction of diethyl azodicarbonate with amines in a similar manner to that reported by Smissman and Makriyannis.[7] It was clarified that treatment of **5**-H with copper(II) reagent (**2**) also gave **3** in high to excellent yields (Scheme 3, Table 3).[8] By using two different conditions, namely, treatment of **5**-H with copper(II) chloride reagent at elevated temperature and copper(II) bromide reagent at room temperature, **3** were obtained in high yields, respectively.



Scheme 3.

Table 3
The reaction of azodicarbonyldiamides (**5**-H) with a copper(II) reagent[a]

Run	R	CuX_2-$LiOBu^t$ (equiv.)	Temp. (°C)	Time(min)	Yield(%)[b]
1	$Ph(CH_2)_2$ (**5-Ha**)	$CuBr_2$ (6.0)	RT	30	97
2		$CuCl_2$ (6.0)	50	10	92
3	cyclohexyl (**5-Hb**)	$CuBr_2$ (6.0)	RT	20	97
4		$CuCl_2$ (6.0)	50	5	78

a) All the reactions were performed by a similar procedure as described in the text, unless otherwise noted.
b) Isolated yield of **3**.

In conclusion, we have found a new and convenient transformation of *N*-substituted ureas into *N*-Boc-amines under mild conditions. Further study is now in progress.

References

1. Katritzky, A. R.; Pleynet, D. P. M.; Yang, B. *J. Org. Chem.* **1997**, *62*, 4155; and references cited therein.
2. Yamaguchi, J.; Hoshi, K.; Takeda, T. *Chem. Lett.* **1993**, 1273.
3. Kurzer, F. *Org. Synth.* **1963**, 49.
4. Kurzer, F. *Org. Synth.* **1963**, 53.
5. Durant, G. J. *Chem. Ind.* **1965**, 1428.
6. Diels, O.; Paquin, M. *Chem. Ber.* **1913**, *46*, 2000.
7. Smissman, E. E.; Makriyannis, A. *J. Org. Chem.* **1973**, *38*, 1652. **5**-Ha: mp 148–149°C (decomp., EtOH). **5**-Hb: mp 203–204°C (decomp., EtOH).
8. A typical experimental is as follows: to a THF solution (3.2 ml) of lithium *t*-butoxide (1.5 mmol) was added copper(II) bromide (335 mg, 1.50 mmol) at room temperature under nitrogen. The mixture was stirred for 15 min, and then azodicarbonyldiphenethylamide (**5**-Ha, 81 mg, 0.25 mmol) was added to the reaction mixture. After being stirred for 30 min, the reaction was quenched by addition of 15% aqueous solution of ammonia. The organic materials were extracted with CH_2Cl_2, and the extract was dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by preparative TLC (*n*-hexane:EtOAc 4:1) and *N*-(*t*-butoxycarbonyl)phenethylamine (108 mg) was isolated in 97% yield.