

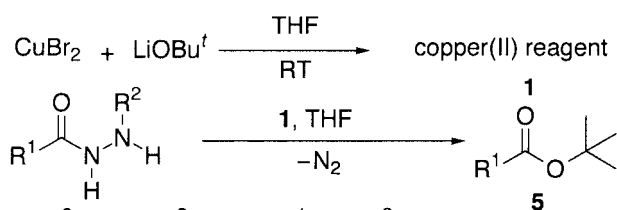
An Oxidative Transformation of *N'*-Phenylhydrazide to *t*-Butyl Ester Using a Copper(II) Halide–Lithium *t*-Butoxide System

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Reactions of hydrazides or *N'*-phenylhydrazides with a copper(II) reagent prepared from copper(II) bromide and lithium *t*-butoxide smoothly proceeded to give the corresponding *t*-butyl ester in high yield.

Previously we reported that a copper(II) reagent (**1**), which was prepared from copper(II) bromide and lithium *t*-butoxide, can be used for oxidative transformation of some functional groups containing a nitrogen atom. In a reaction of primary carboxamide¹ or *N*-substituted urea² with **1**, isocyanate is apparently generated as an intermediate. Analogously, it was assumed that treatment of hydrazide with **1** would generate an acyl cation-like species which, in turn, could react with a nucleophile. Now we wish to report that treatment of hydrazides (**2**) or *N'*-phenylhydrazide (**3**) gave the corresponding *t*-butyl esters (**5**) under mild conditions (Scheme 1).



2; R²=H: **3**; R²=Ph: **4**; R¹=Ph, R²=Me
a: R¹=Ph; **b**: R¹=4-MeC₆H₄; **c**: R¹=PhCH₂; **d**: R¹=Ph(CH₂)₃; **e**: R¹=cinnamyl; **f**: R¹=*o*-C₆H₁₁; **g**: R¹=PhCO-NHCH(CH₂Ph)-; **h**: R¹=Boc-NHCH(CH₂Ph)-; **i**: R¹=Z-NHCH(CH₂Ph)-; **j**: R¹=Z-NHMe₂-.

Boc=*t*-butoxycarbonyl; Z=benzyloxycarbonyl.

Scheme 1.

Among alkyl esters, the *t*-butyl group is an important protecting group of carboxylic acid. Although many methods for the preparation of the *t*-butyl ester are reported,³ development of new methodology is still required.

Concerning treatment of hydrazide **2** with some oxidants, the first investigation was reported by Curtius who oxidized **2** with iodine to the corresponding diacylhydrazines **6**.⁴ Several oxidizing agents, such as chlorine,⁵ iodobenzene diacetate,⁶ NaIO₄,⁷ Ag₂O,⁷ K₃[Fe(CN)₆],⁷ and sodium metaperiodate,⁸ are available for the oxidation of hydrazides. However, oxidation of hydrazide bearing some substituents on the nitrogen atom has hardly been reported.

Hydrazides **2** were easily prepared by a reaction of methyl ester with hydrazine hydrate.⁹ *N'*-Phenylhydrazides **3** were prepared by treatment of acyl chloride with phenylhydrazine in the

presence of triethylamine or by reaction of carboxylic acid with phenylhydrazine with the aid of 1,3-dialkylcarbodiimide as a condensing agent.

The first examination in the present study was treatment of benzhydrazide **2a** with 4.2 molar amounts of **1** at room temperature (Table 1, Run 1). It was found that the reaction proceeded with evolution of nitrogen to give *t*-butyl benzoate **5a** with a small amount of *N,N'*-dibenzoylhydrazine **6a**. When the amount of **1** was increased, the yield of **5a** increased (Run 2). A reaction of *N'*-phenylbenzhydrazide **3a** was also performed under similar conditions producing *t*-butyl ester **5** as the main product, and a small amount of *N,N'*-diphenylbenzhydrazide was isolated as a by-product, which was confirmed by ¹H and ¹³C NMR, and mass spectra (Run 3).¹⁰ This fact strongly indicated that not only an acyl cation-like species but also a phenyl cation-like species may be generated, followed by a reaction with the starting material **3a** to give a by-product under the reaction conditions. From the above hypothesis, it was expected that the yield of *t*-butyl benzoate **5a** would be increased using *N'*-methyl derivative (**4**) instead of **3a**.¹¹ However, although there was no formation of *N,N'*-dimethylbenzhydrazide, the yield of **5a** was reduced (Run 5).

Table 1. The transformation of benzhydrazide **2a**, *N'*-phenylbenzhydrazide **3a**, or *N'*-methylbenzhydrazide **4** to *t*-butyl benzoate **5a**^a

Run	Substrate	1 /equiv	Time /min	Yield /%
1	2a	4.2	20	50 ^b
2		6.2	20	88
3	3a	4.0	20	70 ^c
4		6.0	20	59
5	4	4.0	60	28

^aAll reactions were carried out at room temperature. ^b*N,N'*-Dibenzoylhydrazine **6a** was detected by IR spectrum. ^c*N,N'*-Diphenylbenzhydrazide was obtained in 12% yield.

As shown in Table 2, various kinds of hydrazides **2** or *N'*-phenyl derivatives **3** were converted to the corresponding *t*-butyl ester **5** under similar conditions. It was found that the reactions of **3** gave better result than that using **2** (Runs 1–7). In all reactions using **3** as a substrate, a small amount of *N,N'*-diphenylhydrazide must have been formed. Unfortunately, it was difficult to purify it from the reaction mixture except in Run 3. In the case of *N'*-phenylhydrazide derived from bulky carboxylic acid, the desired product was also obtained in high yield (Run 13).

A typical reaction procedure is as follows: to a THF (3 mL) solution of lithium *t*-butoxide (3.1 mL, THF solution, 1 mol dm⁻³) was added copper(II) bromide (692 mg, 3.1 mmol) at room temperature under nitrogen, and the mixture was stirred for 15

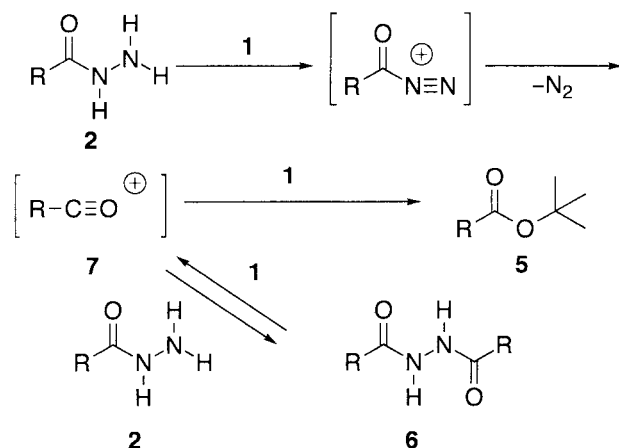
Table 2. The transformation of hydrazides **2** or *N*'-phenylhydrazides **3** to *t*-butyl esters **5**^a

Run	Substrate	1 /equiv	Temp.	Time /min	Product	Yield /%
1	2b	6.2	RT	20	5b	68
2	3b	4.0	RT	20		72 ^b
3		6.0	50 °C	10		86 ^c
4	2c	8.0	RT	20	5c	29
5	3c	6.2	RT	20		83
6	2d	6.2	RT	20	5d	49
7	3d	4.2	RT	20		84
8	3e	4.2	RT	20	5e	83
9	3f	4.0	50 °C	20	5f	76
10	3g	5.0	RT	30	5g	56
11	3h	4.0	RT	120	5h	67
12	3i	4.0	RT	90	5i	73
13	3j	4.0	RT	120	5j	78

^aAll reactions were performed by a similar procedure as described in the text, unless otherwise noted. ^b*N,N'*-Diphenyl-4-methylbenzhydrazide was obtained in 8% yield. ^cCopper(II) chloride was used instead of copper(II) bromide.

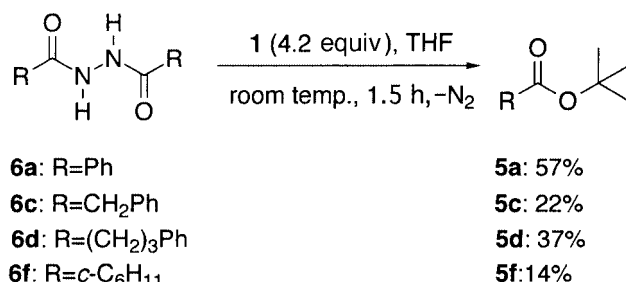
min. Then benzhydrazide **2a** (68 mg, 0.5 mmol) was added to the reaction mixture. After being stirred for 20 min, the reaction was quenched by addition of 7.5% aqueous solution of ammonia. The organic materials were extracted with CH₂Cl₂, and the extract was dried over Na₂SO₄. After removal of the solvent under reduced pressure, the residue was purified by preparative TLC (*n*-hexane:EtOAc 9:1) and *t*-butyl benzoate **5a** (78 mg) was isolated in 88% yield.

The mechanism of the reaction of **2** or **3** with **1** seems to be complicated. Although the details of the reaction process are uncertain at the present time, a probable mechanism of the formation of *t*-butyl ester **5** is outlined in Scheme 2. Regarding the evolution of nitrogen, an acyldiazonium salt may be generated

**Scheme 2.**

by the oxidation of **2** with **1**, and decomposed to form an acyl cation-like species (**7**). *t*-Butoxide attacked **7** to give *t*-butyl ester **5**. By competing with *t*-butoxide, **7** may react with starting material **2** to form *N,N'*-diacylhydrazine **6**. Reactions using **3** as the starting material generally give better results because the phenyl group could suppress formation of the corresponding diacylhydrazine.

From the above proposed pathway, it was expected that **1** had the ability to react with *N,N'*-diacylhydrazine **6**, so that treatment of **6** with **1** under similar conditions was examined (Scheme 3). The results, however, showed that all yields of **5** were low.

**Scheme 3.**

Further investigation using **1** is now in progress.

References and Notes

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- N,N'*-diphenylbenzhydrazide, ¹H NMR (DMSO-*d*₆, 300 MHz) δ 11.07 (1H, s), 8.07 (2H, d, *J* = 8.2 Hz), 7.62 (1H, t, *J* = 8.2 Hz), 7.56 (2H, t, *J* = 8.2 Hz), 7.33 (4H, t, *J* = 7.8 Hz), 7.25 (4H, d, *J* = 7.8 Hz), 7.01 (2H, t, *J* = 7.8 Hz); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 166.73, 147.02, 133.72, 132.63, 129.67, 129.29, 128.20, 122.86, 119.77.
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