Cu(I)-Mediated Alkyl Group Transfer of Alkylboranes to Carboxylic Acid Chlorides

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The alkyl group transfer reaction of alkylboranes with carboxylic acid chlorides affords the corresponding ketones in moderate yields in the presence of potassium *tert*-butoxide and copper(I) iodide.

We reported previously that the electrochemical alkyl group transfers from trialkylboranes to carbonyl compounds,[1] carboxylic acid compounds[2] and epoxide compounds[3] by implementing an electrochemical procedure using copper as a sacrificial anode in an undivided cell. As soon as it was published, this method drew great attention because of its enormous potential in synthetic utility.[4] Therefore, based on this method, we examined the alkyl group transfer reaction of alkylboranes with carboxylic acid chlorides by the electrochemical procedure[2] and also by the general organic chemistry procedure.

Now, we report a new methodology for the alkyl group transfer reaction of alkylboranes with carboxylic acid chlorides *via* the reactive copper(I) alkylborate complexes in the presence of potassium *tert*-butoxide and copper(I) iodide by a mild organic chemistry process. Although alkylmagnesium, -zinc, -tin, and aluminum reagents have been successfully used for alkyl transfer reactions with acid chloride,[5] the result comprises an excellent carbon-carbon bond formation synthesis since alkylboranes are readily prepared by hydroboration from alkenes, unlike alkyl transfer reactions reported by Suzuki *et al.*[6] And this reaction was also successful in carbon-carbon bond formation without expensive palladium catalysts.

First of all, a variety of solvents, such as tetrahydrofuran (THF) - hexamethylphosphoric triamide (HMPA) (1 : 1, 2 : 1, 5 : 1), tetrahydrofuran (THF) - dimethylformamide (DMF) (2 : 1), and tetrahydrofuran (THF) as a solvent, copper(I) halides, such as copper(I) bromide, copper(I) iodide, and copper(I) chloride, and bases, such as potassium *tert*-butoxide, sodium methoxide, and sodium ethoxide were examined to find the combination that affords the best yield.

As a result, we found that THF-HMPA (2 : 1) as a solvent, copper(I) iodide as a copper(I) halide, and potassium *tert*-butoxide as a base gave the best yield (Table 1).

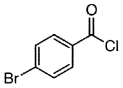
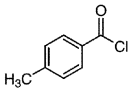
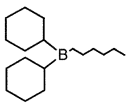
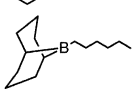
As shown in Table 1, the ethyl group transfer reaction of triethylborane was especially affected not by sodium methoxide (entry 9) and sodium ethoxide (entry 10) but by potassium *tert*-butoxide (entry 1). Also copper(I) halides

Table 1. Optimization of organyl group transfer reaction condition of triethylborane to octanoyl chloride[a]

entry	solvent	copper(I) halide	base	reaction time (h)	yield (%)[b]
1	THF-HMPA(2:1)	CuI	$KOC(CH_3)_3$	4	63
2	THF-HMPA(5:1)	CuI	$KOC(CH_3)_3$	14	44
3	THF-HMPA(1:1)	CuI	$KOC(CH_3)_3$	15	27
4	THF	CuI	$KOC(CH_3)_3$	14	39
5	THF-DMF(2:1)	CuI	$KOC(CH_3)_3$	14	27
6	THF-HMPA(2:1)	CuBr	$KOC(CH_3)_3$	4	54
7	THF-HMPA(2:1)	CuCl	$KOC(CH_3)_3$	6	29
8	THF-HMPA(2:1)	–	$KOC(CH_3)_3$	14	no reaction
9	THF-HMPA(2:1)	CuI	$NaOCH_3$	14	3
10	THF-HMPA(2:1)	CuI	$NaOCH_2CH_3$	14	trace

[a]Reactions of octanoyl chloride (10 mmole) with triethylborane (5 mmole) were carried out using potassium *tert*-butoxide (1 eq.) and copper(I) halides (1 eq.) at room temperature. [b]Isolated yields are based on triethylborane.

Table 2. The alkyl transfer of various alkylboranes to various carboxylic acid chlorides in the presence of potassium tert-butoxide and copper(I) iodide[a]

entry	substrate	borane	additive compound[b]	yield (%)[c]
1	$CH_3(CH_2)_6COCl$	$(CH_3CH_2)_3B$	–	63
2	$Br(CH_2)_4COCl$	$(CH_3CH_2)_3B$	–	53
3		$(CH_3CH_2)_3B$	–	68
4		$(CH_3CH_2CH_2CH_2)_3B$	TMEDA	63
5		$(CH_3CH_2)_3B$	TMEDA	64
6		$(CH_3CH_2)_3B$	TMEDA	68
7[d]	$CH_3(CH_2)_6COCl$		–	44
8[d]			–	59

[a]Reactions of carboxylic acid chlorides (10 mmole) with alkylboranes (5 mmole) were carried out in THF : HMPA (2 : 1) of solvent by using potassium *tert*-butoxide (1 eq.) and copper(I) halides (1 eq.). [b]Isolated yields are based on alkylboranes. [c]2 eq additive compound TMEDA was utilized. [d]Hydroboration of dicyclohexene and 9-BBN and 1-hexene were arried out by modifying the literature procedure.

played an important role in successfully achieving ethyl group transfer reaction of triethylborane (entries 1, 6, 7, and 8).

Finally, to evaluate the alkyl group transfer reaction various caroxylic acid chlorides and a variety of organoboron compounds were evaluated under our standard condition [THF-HMPA (2 : 1), copper(I) iodide, and potassium *tert*-butoxide]. The results of the alkyl transfer reaction are summarized in Table 2.

When the alkyl groups transfer reaction of trialkylboranes was conducted with the alipatic carboxylic acid chlorides octanoyl chloride, 5-bromo-valeroyl chloride, and cyclohexa carbonyl chloride, and the aromatic carboxylic chlorides benzoyl chloride, 4-methyl benzoyl chloride, and 4-bromo-benzoyl chloride, the desired ketones were obtained in the yield range of 63-53% in 4h (entries 1-6). In contrast, when B-hexyl-dicyclohexylborane and B-hexyl-9-BBN were used as a alkylboranes to a hexyl group transfer reaction, yields more or less decreased (entries 7, 8). Futhermore, aromatic acid chlorides, such as benzoyl chloride (entry 4), 4-methyl benzoyl chloride (entry 6), and 4-bromo benzoyl chloride (entry 5), generated the corresponding ketones more successfully when an additive compound, TMEDA, was added to the reaction vessel.

In view of the results so far achieved, the experiments show no distinguishable differences in reaction rate for any structural change for both alkylboranes and substrates. Moreover, despite the absence of any systematic study to find out the mechanism, the most probable mechanism of alkyl transfer reaction involves the nucleophilic addition of alkyl anions which are generated from alkylboranes in the presence of potassium *tert*-butoxide and copper(I) iodide.

We have found that the reactive copper alkylborate complexes generated from alkylboranes easily undergo alkyl group transfer reaction to carboxylic acid chlorides in moderate yields under a mild condition. Further studies of the mechanism and scope of this reaction are in progress. A detailed study of the scope and limitations of the synthesis is also in progress.

Experimental Section

General Method. All reactions were performed in flame or oven dried glassware under a positive nitrogen pressure. Air and moisture sensitive compounds were introduced through a syringe or cannula through a rubber septum. Compounds 9-BBN (1 *M*, THF), potassium *tert*-butoxide, and copper(I) halides were purchased from Aldrich. Hydroborations were prepared according to or by modifying documented procedures. Products were consistent with the documented reports. THF was distilled from sodium/ benzophenone kethyl under a nitrogen atmosphere. Analytical thin-layer chromatography was performed with E. Merck silica gel 60F glass plates and flash chromatography using E. Merck silica gel 60 (230-400 mesh). ^{1}H spectra were recorded on a Varian Unit Inova 400 spectrometer. All NMR data were obtained in $CDCl_3$ solution, chemical shifts (δ) are given in ppm relative to TMS.

Typical Experimental Procedure. 10 mL of triethylborane (1 M, 10 mmole) was placed in 100 mL flask. Potassium *tert*-butoxide (1.22 g, 10 mmole), 10 mL of THF, and 5 mL of HMPA were added to the flask under a nitrogen atmosphere and stirred at room temperature for 30 min. Copper iodide (1.90 g, 10 mmole) was added to the reaction mixture which was then stirred for 30 min. After the color changing to dark blue-black, octanoyl chloride (3.4 mL, 20 mmole) was added to the reactants which were then stirred again at room temperature for 4 h. The products were isolated in the following manner. The reactants were quenched with 50 mL of water and the product extracted in *n*-hexane (3 × 20 mL). The combined organic extracts ware dried over anhydrous magnesium sulfate before solvent removal under reduced pressure. The product was purified by column chromatography (hexane : ethyl acetate : ether = 30 : 1 : 1) to yield 0.98 g (63%) of the desired decan-3-one. Other products followed the same procedure. ^{1}H NMR ($CDCl_3$) δ 2.4 (t, J = 7.6 Hz, 4H), 1.6-1.5 (t, J = 6.8 Hz, 2H), 1.1-1.0 (t, J = 7.2 Hz, 3H), 1.3 (m, 8H), 0.9 (t, J = 6.8 Hz, 3H).

6-Bromo-hexan-3-one: The product was isolated by flash chromatography (hexane : ethyl acetate : ether = 100 : 1 : 1) to give 0.94 g (53%) ^{1}H NMR ($CDCl_3$) δ 3.4 (t, J = 6.6 Hz, 2H), 2.4 (m, 4H), 1.9 (m, 2H), 1.7 (m, 2H), 1.1 (t, J = 7.2 Hz, 3H).

1-Cyclohexyl-propane-1-one: The product was isolated by flash chromatography (hexane : ethyl acetate : ether = 30 : 1 : 1) to give 0.95 g (68%) ^{1}H NMR ($CDCl_3$) δ 2.5 (q, J = 7.2 Hz, 2H), 2.3 (m, 1H), 1.9 (m, 4H), 1.4-1.2 (m, 6H), 1.0 (t, J = 7.2 Hz, 3H).

Tetradecan-3-one: The product was isolated by flash chromatography (hexane : ethyl acetate : ether = 30 : 1 : 1) to give 0.93 g (44%) ^{1}H NMR ($CDCl_3$) δ 2.4 (m, 4H), 1.9 (m, 2H), 1.6 (m, 4H), 1.4-1.2 (m, 14H), 0.9 (m, 3H).

Phentanophenone: The product was isolated by flash chromatography (hexane : ethyl acetate = 8 : 1) to give 1.02 g (63%) ^{1}H NMR ($CDCl_3$) δ 7.95 (d, J = 6.8 Hz, 2H), 7.55 (m, 1H), 7.46 (m, 2H), 2.97 (t, J = 7.2 Hz, 2H), 1.41 (m, 2H), 0.95 (t, J = 7.6 Hz, 3H).

4-Methyl propiophenone: The product was isolated by flash chromatography (hexane : ethyl acetate = 8 : 1) to give 1.02 g (68%) ^{1}H NMR ($CDCl_3$) δ 7.86 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 2.97 (q, J = 7.2 Hz, 2H), 2.93 (s, 3H), 1.21 (t, J = 7.6 Hz, 3H).

4-Bromo propiophenone: The product was isolated by flash chromatography (hexane : ethyl acetate = 4 : 1) to give 1.36 g (64%) ^{1}H NMR ($CDCl_3$) δ 7.93 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 2.98 (q, J = 7.6 Hz, 2H), 1.22 (t, J = 7.2 Hz, 3H).

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