Short communication

Novel reduction of perfluoroalkyl ketones with lithium alkoxides

Yasser S. Sokeirik, Kazuyuki Sato, Masaaki Omote, Akira Ando *, Itsumaro Kumadaki **

Faculty of Pharmaceutical Sciences, Setsunan University, 45-1, Nagotoge-cho, Hirakata 573-0101, Japan

Abstract

The reaction of *tert*-butyl *N*-(2-bromophenyl)carbamate (**1**) with ethyl perfluorooctanoate in the presence of *tert*-butyllithium did not give the desired *N*-(2-perfluorooctanoylphenyl)carbamate (**3**) but gave 1-hydroxy-1H-perfluorooctyl compound (**4**), which was supposed to be formed by the reduction of **3**. A similar reaction of 2,2,2-trifluoroacetophenone with *tert*-butyllithium did not gave any reduction product. Detailed investigation showed that lithium ethoxide worked as the reducing agent of this abnormal reduction. By the reaction of lithium isopropoxide, an aldol product from 2,2,2-trifluoroacetophenone with acetone was isolated, while perfluoroheptyl or perfluoropropyl phenyl ketones were reduced by this alkoxide in a high yield without formation of the aldol adduct.
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1. Introduction

In our way to synthesize a new chiral ligand containing a perfluoroalkyl group [1], we needed to prepare some functionalized perfluoroalkyl aromatic ketones. For this purpose, we tried the reaction of *tert*-butyl *N*-phenylcarbamates (**1** or **2**) with perfluorocarboxylic esters in the presence of alkyllithium. During this synthesis, the secondary alcohols, the reduction products of the desired ketones, were obatined as a main product depending on the conditions (Scheme 1).

Here, we explored the condition for this abnormal reduction and clarified the mechanism leading to the unexpected products.

2. Results and discussion

The reaction of ethyl pentadecafluorooctanoate with *tert*-butyl *N*-(2-bromophenyl)carbamate (**1**) in the presence of *n*- or *sec*-butyllithium at low temperature gave only low yields of the desired perfluoroalkyl ketone (**3**) with a significant amount of by-product [2]. Then, we tried the reaction of *tert*-butyl

N-phenylcarbamate (**2**) in the presence of *tert*-butyllithium. The difficult metallation with this base at low temperature led us to carry out the reaction at higher temperature. At 0 °C to room temperature, metallation occurred. However, not the ketone (**3**) but 1H-perfluorooctyl secondary alcohol (**4**) was obtained in yields ranging from 38–60% according to the molar ratio of the *tert*-butyllithium, and none of the expected ketone (**3**) was observed at all [3]. We thought that the *tert*-butyllithium is responsible for this reduction, but the attempted reduction of 2,2,2-trifluoroacetophenone with *tert*-butyllithium did not gave any reduction product. These results are summarized in Table 1.

Tamborski and his coworkers studied the addition of phenyllithium to perfluorocarboxylic esters in various conditions, and reported that the similar reduction products as **4** were obtained [4]. They showed that the temperature was the key factor for the formation of the secondary alcohols. However, they did not suggest any mechanisms for the formation of these secondary alcohols.

We assumed that the lithium ethoxide formed by the reaction of aryllithium with ethyl perfluorocarboxylate might have concerned with the reduction of the perfluoroalkyl ketones in a mechanism like the Meerwein–Ponndorf–Verley reduction (see Scheme 2).

To prove this assumption, various perfluoroalkyl ketones were allowed to react with several lithium alkoxides.

First, 2,2,2-trifluoroacetophenone was chosen as a model compound to study the conditions and reagents (Table 2).

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* Corresponding author. Tel.: +81 72 866 3141; fax: +81 72 850 7020.
** Corresponding author. Tel.: +81 72 866 3140; fax: +81 72 850 7020.
  E-mail addresses: aando@pharm.setsunan.ac.jp (A. Ando),
kumadaki@pharm.setsunan.ac.jp (I. Kumadaki).

Scheme 1.

Scheme 2.
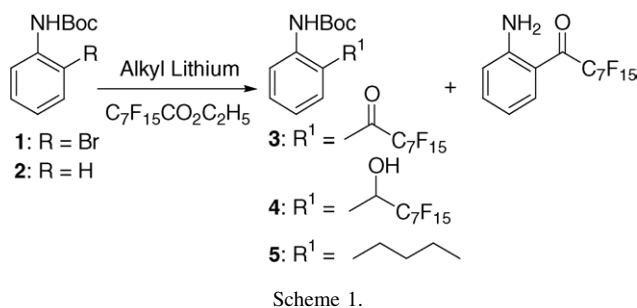
Reaction with one equivalent of lithium ethoxide in diethyl ether resulted in formation of 2,2,2-trifluoro-1-phenylethanol, a reduction product, in a low yield (21%) with a fairly large amount of benzoic acid, which might be formed through the haloform-type reaction. When two equivalents of lithium ethoxide was used, the yield of the alcohol was increased to 65% [5]. Solvent effect for this reduction was examined using two equivalents of lithium ethoxide, as shown in Runs 3–6 in Table 2. Toluene gave a fairly good yield of the reduction product, while THF and hexane gave benzoic acid mainly. In

ethanol, no reaction was observed, and the unreacted ketone was recovered. A similar reaction with lithium methoxide gave a very low yield (8%) of the alcohol (Run 7). Similarly, sodium ethoxide gave a small amount of the reduction product (Run 8).

Ashby et al. reported that lithium isopropoxide is a good reducing agent for benzophenone [6]. This led us to try lithium isopropoxide for the reduction of perfluoroalkyl ketones. Moderate yields of the reduction product was obtained in low polar solvents at room temperature. Significant amounts of the aldol from reaction of 2,2,2-trifluoroacetophenone with acetone was separated as a by-product (Runs 9–11). Higher temperature gave a better yield (Run 12) [7]. This reduction did not proceed at 0 °C (Run 13). The fact that lithium tert-butoxide did not give any reduction products shows that an α-proton is necessary for the reduction (Run 14).

n-Butyllithium gave a moderate yield of the reduced product with the addition product of butyl group to the carbonyl group (Run 15). sec-Butyllithium was found to be less reactive (Run 16). While tert-butyllithium has nine α-hydrogens and was expected to be most reactive, it was found to be unreactive (Run 17). That may be due to steric factor [5].

Finally, we examined the reaction of ketones with a more bulky perfluoroalkyl groups (see Table 3) [8]. Thus, the reaction of heptafluoropropyl and pentadecafluoroheptyl phenyl ketones with lithium isopropoxide gave high yields of the corresponding secondary alcohols. No aldol product was observed, probably because the large perfluoroalkyl groups hindered the addition of the enolate to the carbonyl group. These results

Table 1
Reaction of N-arylcarbamate (1 or 2) with alkyllithiums

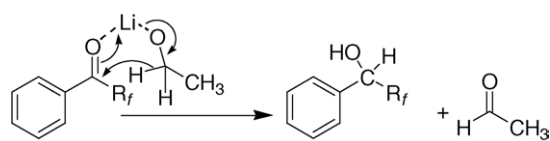| Substrate	Alkyllithium (eq.)	Time (h)	Temperature (°C)	Product (yield %)[a]
1	n-BuLi (2.6)	24	−80	3 (35), 5 (33)
1	sec-BuLi (2.6)	24	−80	3 (43), deprotected ketone (45)
2	tert-BuLi (2.4)	24	0 to rt	4 (38)
2	tert-BuLi (3.0)	24	0 to rt	4 (60)
2	MeLi (1.2) then tert-BuLi (1.2)	24	0 to rt	4 (37)

[a] Isolated yield.

Table 2
Reaction of 2,2,2-trifluoroacetophenone with bases

Run	Base (eq.)	Solvent	Temperature (°C)	Time (h)	Reduction product (%)[a]	By-product
1	EtOLi (1.0)	Et$_2$O	rt	96	21	PhCOOH[b]
2	EtOLi (2.0)	Et$_2$O	rt	96	65	PhCOOH[b]
3	EtOLi (2.0)	THF	rt	96	25	PhCOOH[b]
4	EtOLi (2.0)	EtOH	rt	96	No reduction	
5	EtOLi (2.0)	n-Hexane	rt	96	23	PhCOOH[b]
6	EtOLi (2.0)	Toluene	rt	96	61	
7	MeOLi (2.0)	THF	rt	96	8	PhCOOH[b]
8	EtONa (2.0)	THF	rt	96	14	PhCOOH[b]
9	isoPrOLi (2.0)	Et$_2$O	rt	18	54	Aldol 37%[a]
10	isoPrOLi (2.0)	n-Hexane	rt	18	56	Aldol 26%[a]
11	isoPrOLi (2.0)	Toluene	rt	18	50	Aldol 40%[a]
12	isoPrOLi (2.0)	Toluene	80	6	77	Aldol 23%[a]
13	isoPrOLi (2.0)	Toluene	0	24	No reduction	
14	tert-BuOLi (2.4)	THF	rt	24	No reduction	
15	n-BuLi (2.4)	Et$_2$O	rt	18	44	Adduct of Bu[c] 52%[a,c]
16	sec-BuLi (2.4)	Et$_2$O	rt	18	41	
17	tert-BuLi (2.4)	Et$_2$O	rt	18	No reduction	

[a] Yields were estimated by ^{19}F NMR.
[b] Traces to very small amounts. Identified ^{1}H NMR and mixture-melting point with the authentic sample.
[c] Identified ^{1}H NMR, IR and MS.

Table 3
Reaction of perfluoroalkyl phenyl ketones with lithium isopropoxide

Substrate	Reducing agent	Temperature (°C)	Time (h)	Yield (%)[a]
$C_6H_5COC_3F_7$	isoPrOLi (2eq)	80	6	85
$C_6H_5COC_7F_{15}$	isoPrOLi (2eq)	80	6	90

[a] Isolated yield.

show that lithium isopropoxide is a good reducing agents for bulky perfluoroalkyl ketones.

3. Conclusion

We observed abnormal reaction of aryllithiums with ethyl perfluoroalkanoate, where aryl perfluoroalkyl carbinols were obtained. Detailed examination of this reaction showed that lithium ethoxide caused the reduction of the primary products, aryl perfluoroalkyl ketone. This reduction was found to be applicable for some aromatic perfluoroalkylketones. The experimental procedure is simple and the yields are moderate to excellent. So, this reaction can be used for synthesis of aryl perfluoroalkyl carbinols.

References

[1] Concerning the synthesis and application of chiral ligands containing perfluoroalkyl groups by our group, see: M. Omote, Y. Nishimura, K. Sato, A. Ando, I. Kumadaki, J. Fluorine Chem. 126 (2005) 407–409, and references therein.

[2] Detailed description of the first reaction in Table 1; To a stirred solution of *tert*-butyl *N*-(2-bromophenyl)carbamate (272 mg, 1 mmol) in 5 mL dry Et$_2$O at −80 °C was added over a period of 30 min a hexane solution of *n*-BuLi (1.64 mL, 1.58 M solution, 2.6 mmol). After 2 h's stirring at the same temperature, ethyl pentadecafluorooctanoate (486 mg, 1.1 mmol) was added slowly. The resulting mixture is kept under stirring at the same temperature for 24 h. The reaction mixture is quenched with 2 M HCl and stirred at room temperature for 1 h. After separation of the two phases, the aqueous phase was extracted with Et$_2$O three times. The combined organic extracts were dried over MgSO$_4$ and evaporated under vacuum to yield an oily mass, which was purified with a column chromatography (SiO$_2$, 5% Et$_2$O in hexane) to yield 206 mg (35%) of compound **3** and 82 mg (33%) of compound **5**. Compound **3**. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 10.15 (1H, s, disappeared with D$_2$O), 8.52–8.50 (1H, m), 7.94–7.88 (1H, m), 7.66–7.54 (1H, m), 7.04–6.98 (1H, m), 1.46 (9H, s). ^{19}F NMR (56.4 MHz, CDCl$_3$) δ (from $C_6H_5CF_3$): −17.30 to −18.50 (3F, m), −58.22 to −62.53 (10F, m), −63.12 to −64.17 (2F, m). HRMS Calcd. for $C_{19}H_{14}F_{15}NO_3$: 589.073 (M^+), Found: 589.074. IR (neat) cm^{-1}: 3325, 1744, 1678, 1242. Compound **5**. ^{1}H NMR (CDCl$_3$) δ: 7.67–7.66 (1H, m), 7.12–7.05 (2H, m), 6. 96–6.92 (1H, m), 6. 23 (1H, s, disappeared with D$_2$O), 2.25 (2H, t, *J* = 7.5 Hz), 1.52–1.44 (11H, m), 1.31 (2H, sex, *J* = 7.5 Hz), 0. 87 (3H, t, *J* = 7.3 Hz). MS *m/z* 249 (M^+). HRMS Calcd. for $C_{15}H_{23}NO_2$: 249.173 (M^+), Found: 249.173. IR (neat) cm^{-1}: 3360, 1706.

[3] Detailed description of Run 3 in Table 1: a solution of *tert*-BuLi in pentane (4.17 mL, 1.49 M solution, 6.21 mmol) was added slowly to a stirred solution of *tert*-butyl *N*-phenylcarbamate (500 mg, 2.59 mmol) in dry Et$_2$O (10 mL) at 0 °C. The solution was stirred at 0 °C for further 2 h. To this solution was added ethyl pentadecafluorooctanoate (1259 mg, 2.85 mmol). The resulting mixture was stirred at 0 °C for additional 2 h and at room temperature for 24 h. The reaction was quenched with 2 M HCl. The organic phase was separated and the acidic phase was extracted with Et$_2$O. The combined organic extracts were dried over MgSO$_4$, and

evaporated under vacuum. The residue was purified with a column chromatography (SiO$_2$, 5% to 20% Et$_2$O in hexane) to give 581 mg (38%) of compound **4**. Compound **4**: colorless crystals from Et$_2$O–hexane. Mp 104–105 °C. ^{1}H NMR (CDCl$_3$) δ: 7.64–7.62 (1H, m), 7.42–7.36 (2H, m), 7.20–7.16 (1H, m), 7.11 (1H, s, disappeared with D$_2$O), 5.38 (1H, m), 4.79 (1H, s, disappeared with D$_2$O), 1.50 (9H, s). ^{19}F NMR (DMSO) δ: −19.52 to −20.24 (3F, m), −52.52 (1F, m), −59.17 to −62.41 (9F, m), −64.39 to −65.37 (2F, m). MS *m/z*: 591 (M^+). HRMS Calcd. for $C_{19}H_{16}F_{15}NO_3$: 591.089 (M^+), Found: 591.090. IR (KBr) cm^{-1}: 3384, 1686, 1212, 1148.

[4] L.S. Chen, G.J. Chen, C. Tamborski, J. Fluorine Chem. 18 (1981) 117–129.

[5] Experimental details of Run 2 in Table 2: to a solution of freshly prepared EtOLi (59.8 mg, 1.15 mmol) in 3 mL dry Et$_2$O, 2,2,2-trifluoroacetophenone (100 mg, 0.57 mmol) was added at room temperature under argon atmosphere. The reaction mixture was stirred at room temperature for 96 h. The mixture was cooled in an ice bath and quenched with 2 M HCl, and extracted by Et$_2$O three times. The combined organic extracts were dried over MgSO$_4$ and evaporated under vacuum. The mixture was separated by a flash column chromatography to give about 65 mg of crude 2,2,2-trifluoro-1-phenylethanol and 15 mg of benzoic acid. The crude 2,2,2-trifluoro-1-phenylethanol was purified with a column chromatography (SiO$_2$, 5% to 10% Et$_2$O in hexane) for spectral analysis. 2,2,2-Trifluoro-1-phenylethanol: ^{1}H NMR (CDCl$_3$) δ: 7.38–7.71 (5H, m), 4.98–5.06 (1H, m), 2.62 (1H, s, disappeared with D$_2$O). ^{19}F NMR (CDCl$_3$) δ: −15.25 (3F, d, *J* = 6.2 Hz). IR (neat) cm^{-1}: 3450. These data were consistent with the authentic sample.

[6] E.C. Ashby, A.B. Goel, J.N. Argyropoulos, Tetrahedron Lett. 21 (1982) 2273–2276.

[7] Experimental details of Run 12 in Table 2: in a dry flask fitted with a calcium chloride guard tube, 2,2,2-trifluoroacetophenone (100 mg, 0.57 mmol) was added into a solution of freshly prepared isoPrOLi (75.9 mg, 1.15 mmol) in dry toluene (3 mL) at room temperature. The mixture was heated gradually to 80 °C. After disappearance of the peak of the starting material on GLC, the mixture was cooled by an ice bath and the reaction was quenched with saturated NH$_4$Cl. The two phases were separated, and the aqueous phase was extracted with Et$_2$O. The combined organic layer was dried over MgSO$_4$ and evaporated under vacuum. The residue was separated by a column chromatography (SiO$_2$, 5% Et$_2$O in hexane) to yield about 77 mg of 2,2,2-trifluoro-1-phenylethanol. By eluating with 10% Et$_2$O in hexane, the aldol product, 5,5,5-trifluoro-4-hydroxy-4-phenylpentan-2-one, (about 30 mg) was obtained. 5,5,5-Trifluoro-4-hydroxy-4-phenylpentan-2-one (purified by further chromatography): ^{1}H NMR (CDCl$_3$) δ: 7.58–7.54 (2H, m), 7.42–7.35 (3H, m), 5.43 (1H, s, disappeared with D$_2$O), 3.37 (1H, d, *J* = 18 Hz), 3.21 (1H, d, *J* = 18 Hz), 2.21 (3H, s). ^{19}F NMR (CDCl$_3$) δ: −17.16 (s, CF$_3$). MS *m/z* 232 (M^+). HRMS Calcd. for $C_{12}H_{15}F_3O$: 232.071 (M^+), Found: 232.070. IR (neat) cm^{-1}: 3500, 1712.

[8] Detailed description of the second reaction in Table 3: in a dry flask fitted with calcium chloride guard tube, 1-phenylpentadecafluorooctan-1-one (100 mg, 0.21 mmol) was added to a solution of freshly prepared isoPrOLi (27.8 mg, 0.42 mmol) in dry toluene (3 mL) at room temperature. The mixture was heated gradually to 80 °C. After disappearance of the peak of the starting material on GLC, the mixture was cooled in an ice bath and the reaction was quenched with saturated NH$_4$Cl. The two phases were separated, and the aqueous phase was extracted with Et$_2$O. The combined organic layer was dried over MgSO$_4$, and evaporated under vacuum. The residue was purified by a column chromatography (SiO$_2$, 5% Et$_2$O in hexane) to yield 90 mg (90%) of 1-phenyl-1H-perfluorooctan-1-ol as white solid, which was recrystallized from hexane to give colorless crystals. M.p. 60 °C. ^{1}H NMR (CDCl$_3$) δ: 7.49–7.36 (5H, m), 5.23–5.18 (1H, m), 2.53 (1H, s, disappeared with D$_2$O). ^{19}F NMR (CDCl$_3$) δ: −18.36 (3F, m), −53.50 (1F, m), −57.10 to −60.35 (8F, m), −62.50 (2F, m), −63.25 (1F; m). IR (neat) cm^{-1}: 3480. A similar reaction of 1-phenylperfluorobutan-1-one gave 1-phenyl-1H-perfluorobutan-1-ol: colorless oil. ^{1}HNMR (CDCl$_3$) δ: 7.48–7.39 (5H, m), 5.06-4.98 (1H, m), 2.62 (1H, s, disappeared with D$_2$O). ^{19}F NMR (CDCl$_3$) δ: −18.75 (3F, m), −55.31 (1F, m), −62.21 (2F, m), −64.52 (1F, m). IR (neat) cm^{-1}: 3450.