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A new synthetic route to polyfluorobenzyl alcohol

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ABSTRACT

The synthesis of polyfluorinated benzyl alcohol from pentafluorobenzoic acid has been developed. An economical and effective direct reduction method of polyfluorobenzoic acid by zinc borohydride is described.

1. Introduction

Polyfluorinated benzyl alcohols such as 2,3,5,6-tetrafluorobenzyl alcohol **1**, 2,3,5,6-tetrafluoro-4-methylbenzyl alcohol **2** and 2,3,5,6-tertrafluoro-4-(methoxymethyl)benzyl alcohol **3** are useful intermediates in synthesis of pharmaceutical, agrochemical and novel materials [1–3]. Therefore, methods to prepare polyfluorobenzyl alcohols, especially the route which is suitable for industrialization attracted many interests. Most of the polyfluorobenzyl alcohols were produced by the route from tetrafluoroterephthalonitrile. For example, 2,3,5,6-tetrafluorobenzyl alcohol **1** was synthesized through hydrolysis, decarboxylation and reduction [4,5]. 2,3,5,6-Tertrafluoro-4-methylbenzyl alcohol **2** was prepared by substitution, reduction and diazotization [6,7]. Using hydrogen and nickel in methanol, 2,3,5,6-tetrafluoroterephthalonitrile was reduced to 2,3,5,6-tetrafluoroterephthalaldehyde dimethylacetal [8]. Through hydrolysis, bromination and methoxylation, 2,3,5,6-tertrafluoro-4-(methoxymethyl)benzyl alcohol **3** was obtained [9–11]. The present routes are summarized in Scheme 1.

In these reactions, the key point is how to reduce carboxyl group to hydroxymethyl group. It could be successfully achieved when using $LiAlH_4$, a strong reducing reagent [12]. However, $LiAlH_4$ is not suitable for industrialization because of its high cost. Therefore, some indirect reduction methods were reported in which $NaBH_4$ that is cheaper than $LiAlH_4$ was used as a reducing reagent. For example, after the carboxyl group was converted to the acyl halides [13,14] or the esters [15–17], they were reduced to the corresponding alcohol by $NaBH_4$. Recently, Rodefeld claimed a preparation process of 2,3,5,6-tetrafluorobenzyl alcohol **1** by direct reduction of 2,3,5,6-tetrafluorobenzoic acid with sodium borohydride in the existence of dimethyl sulfate [18].

In this paper, we describe a new synthetic route to polyfluorobenzyl alcohols using pentafluorobenzoic acid which is easily obtained in the industry as a starting material and discuss about the reduction of polyfluorobenzoic acid using $Zn(BH_4)_2$ and $LiAlH_4$ as reducing reagents.

2. Results and discussion

In order to obtain various polyfluorobenzyl alcohols such as 2,3,5,6-tetrafluorobenzyl alcohol **1**, 2,3,5,6-tertrafluoro-4-methylbenzyl alcohol **2**, 2,3,5,6-tetrafluoro-4-(methoxymethyl)benzyl alcohol **3** and 2,3,4,5,6-pentafluorobenzyl alcohol **4**, we contrived a novel synthetic route using pentafluorobenzoic acid, a facile industrial product as a starting material (Scheme 2).

Firstly, we tried to use $LiAlH_4$ to reduce 2,3,4,5,6-pentafluorobenzoic acid to 2,3,4,5,6-pentafluorobenzyl alcohol. The fluorine atom on the benzene ring was also replaced by hydrogen atom in the reduction reaction. It is similar to the literature [19] which used polyfluorobenzoyl fluoride. The fluorine atom on the polyfluorinated benzene is known to be easily substituted by nucleophilic reagent, especially when other electron-withdrawing groups on the polyfluorinated benzene ring. In the case of 1-substituented pentafluorobenzenes, fluorine at 4-position is readily replaced with nucleophiles even though the substituents are electron-donating group such an alkyl group [20,21]. Furthermore, mechanism, scope, and synthetic applications of nucleophilic substitution on aromatic fluorides are well summarized by Uneyama [22]. Since pentafluorobenzoic acid has a strong

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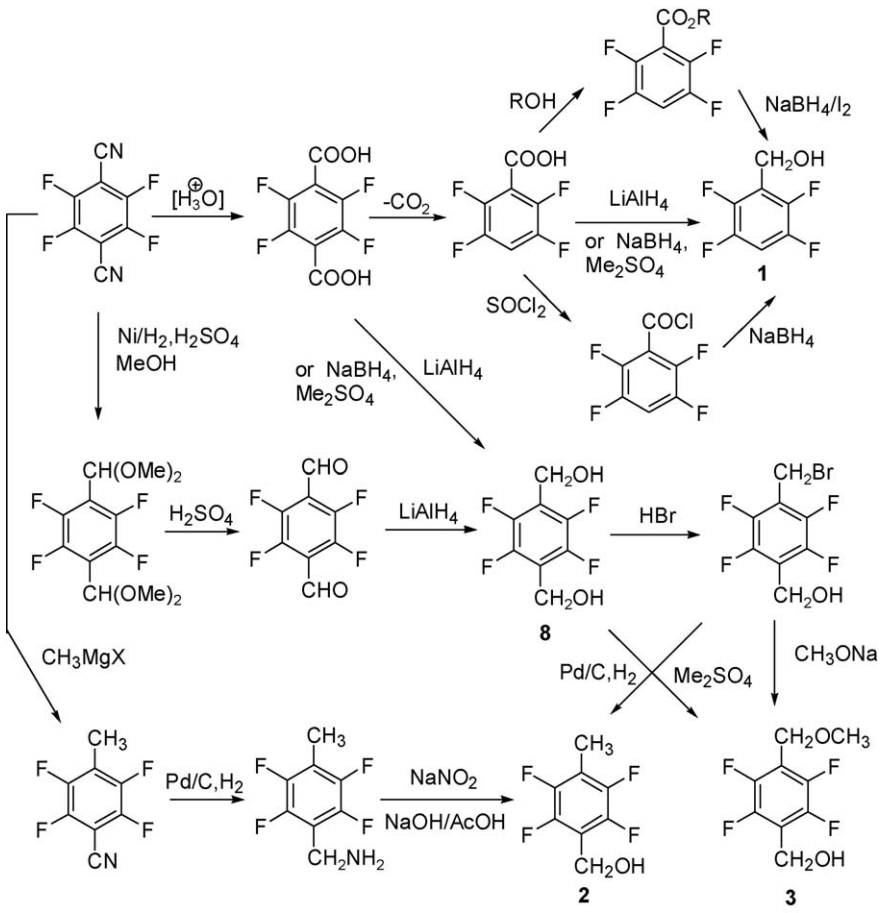
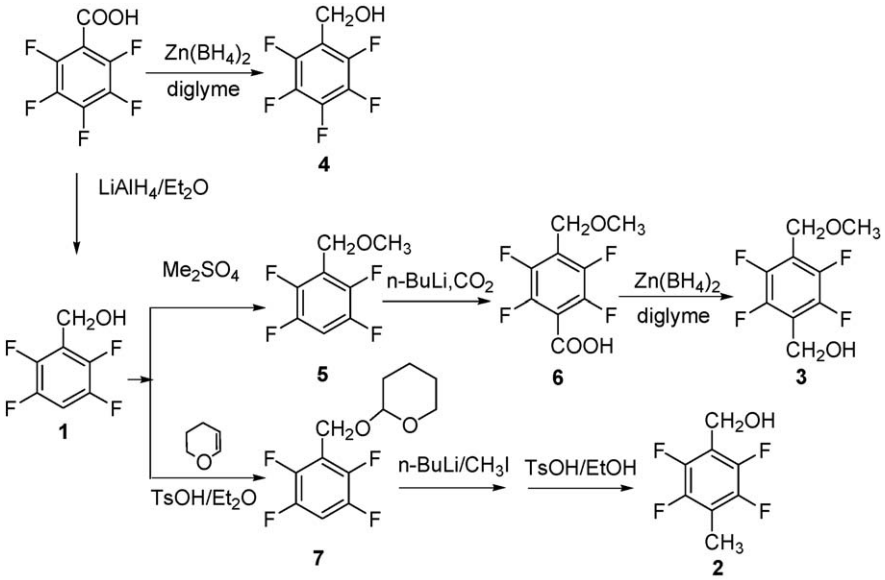


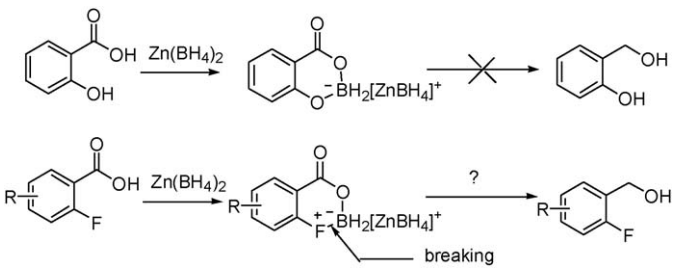
Scheme 1.

electron-withdrawing group, fluorine atom at para-position was substituted by hydride ion of $LiAlH_4$ during $LiAlH_4$ reduction of carboxyl group. Using excess amount of $LiAlH_4$, the alcohol **1** was obtained in over 90% yield.

In order to develop a method for the cost-effective preparation of polyfluorobenzyl alcohols from polyfluorobenzoic acids, we tried to use zinc borohydride in THF according to the literature [23]. However, when using THF as a solvent, we failed to reduce pentafluorobenzoic acid. In the literature, salicylic acid was reported as an exceptional case leading to a failure due to the formation of a stable intermediate. We supposed that our compound might form a stable intermediate that leads to the



Scheme 2.



Scheme 3.

Table 1
The solvent effect of the reduction of pentafluorobenzoic acid using $Zn(BH_4)_2$[a].

Entry	Solvent	Condition	Yield
1	Tetrahydrofuran	Reflux, 24 h	0
2	Dioxane	Reflux, 24 h	Trace
3	Diglyme	Reflux, 5 h	86%[b]

[a] The molar quantity of pentafluorobenzoic acid and $Zn(BH_4)_2$ was 5.2 and 2.4 mmol respectively and 20 ml of solvent was used.
[b] Isolated yield.

failure of the reaction. So perhaps breaking the B–F bond in the intermediate was a key to the success of this reduction process (Scheme 3).

When using dioxane as the solvent which has high boiling point, trace amount of target product was observed by TLC. However, when using diglyme which has higher boiling point, 2,3,4,5,6-pentafluorobenzyl alcohol **4** was successfully obtained in 86% yield (Table 1).

The same method was used in the reduction of 2,3,5,6-tetrafluoro-4-(methoxymethyl)benzoic acid **6** and 2,3,5,6-tetrafluoroterephthalic acid to give the corresponding alcohol in good yields (Sections 4.5 and 4.7).

2,3,5,6-Tetrafluorobenzyl alcohol **1** was methylated to obtain 2,3,5,6-tetrafluoro-4-(methoxymethyl)benzene **5**. The compound **5** was treated by *n*-BuLi and carbon dioxide to prepare the acid **6**. The acid **6** was reacted with zinc borohydride to give 2,3,5,6-tertrafluoro-4-(methoxymethyl)benzyl alcohol **3**. After hydroxyl group of alcohol **1** was protected as its THP ether, the compound **7** was treated by *n*-BuLi and CH_3I to prepare the methylated compound that was deprotected using TsOH and ethanol to give one of our target molecule, 2,3,5,6-tertrafluoro-4-methyl-benzyl alcohol **2**.

3. Conclusion

In conclusion, we developed a novel synthetic route for the preparation of polyflurorobenzyl alcohols from pentafluorobenzoic acid. The route was shortened by direct reduction of polyfluorobenzoic acid using zinc borohydride as a reductive agent.

4. Experimental

Boiling points and melting points were uncorrected. Melting points were measured on a Yanaco Mp-500 instrument. ^{1}H NMR spectra were obtained at 500 MHz (IMOVA-500) using Me_4Si as an internal standard. All reactions were monitored by TLC.

4.1. Preparation of 2,3,5,6-tetrafluorobenzyl alcohol (1)

$LiAlH_4$ (2.0 g, 52 mmol) and dried ether (40 ml) was added to a dry 100 ml three-necked flask fitted with a reflux condenser and a dropping funnel under N_2 atmosphere. Pentafluorobenzoic acid (7.8 g, 37 mmol) dissolved in dry ether was added dropwise to the mixture for 20 min in an ice-water bath. The reaction mixture was then stirred at room temperature for 20 min and heated under reflux for another 2 h. After being cooled to room temperature, ice-water (10 ml) and H_2SO_4 (10 ml, 2 M) was added to the mixture in the ice-water bath. The organic layer was separated and the aqueous layer was extracted with Et_2O (2× 20 ml). The combined organic extract was dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure to give alcohol **1** as colorless liquid (6.1 g, 91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.30 (br, 1H, –OH), 4.69 (s, 2H, $-CH_2$), 7.01–7.08 (m, 1H, ArH).

4.2. Preparation of 2,3,4,5,6-pentafluorobenzyl alcohol (4)

Freshly fused $ZnCl_2$ (0.33 g, 2.4 mmol), $NaBH_4$ (0.2 g, 4.8 mmol) and dry diglyme (20 ml) was added to a dried 100 ml three-necked flask fitted with a reflux condenser and connected to a mercury bubbler. The mixture was stirred for 24 h at room temperature. Then pentafluorobenzoic acid (1.1 g, 5.2 mmol) dissolved in dry diglyme was added. The mixture was stirred and heated under reflux for 5 h. The solvent was distilled off and recycled. The excess hydride was quenched with H_2SO_4 (10 ml, 2 M). Then the reaction mixture was treated with anhydrous K_2CO_3 and was extracted with CH_2Cl_2 (3× 10 ml). The organic layer was dried on Na_2SO_4, filtered and solvent was removed to give the alcohol **4** of crude product (0.8 g, 86%). After the crude product was purified by silica gel column, a white solid was obtained. m.p.: 34–37 °C (lit. oil [19]). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 4.82 (s, 2H, $-CH_2$).

4.3. Preparation of 1,2,4,5-tetrafluoro-3-(methoxymethyl)benzene (5)

The compound **1** (8.4 g, 47 mmol), finely ground NaOH (1.87 g, 47 mmol) and 40 ml CH_2Cl_2 was added to a round-bottom flask. The mixture was stirred in an ice-water bath for 30 min. After a small amount of benzyltrimethylammonium chloride was added, the mixture was stirred for another 30 min. Then dimethyl sulfate (4.5 ml, 47 mmol) diluted in 10 ml CH_2Cl_2 was added dropwise. The mixture was stirred for 2 h at 4–5 °C. After that, the mixture was filtered and washed with water. The filtrate was separated and the aqueous layer was extracted with CH_2Cl_2 (2× 10 ml). The combined organic layer was dried and solvent was removed under reduced pressure to give crude product. The crude product was distilled (37 °C/170 Pa; lit. 138 °C/760 mmHg [24]) to give the compound **5** as colorless liquid (6.8 g, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.40 (s, 3H, $-OCH_3$), 4.46 (s, 2H, $-CH_2$), 7.04–7.06 (m, 1H, ArH).

4.4. Preparation of 2,3,5,6-tetrafluoro-4-(methoxymethyl)benzoic acid (6)

Under N_2 atmosphere, a mixture of the compound **5** (2.4 g, 12 mmol) and 30 ml ether was cooled to −78 °C. *n*-BuLi (5 ml, 2.57 M, 12 mmol) was added dropwise for 20 min. The mixture was stirred for 1 h. Then dry CO_2 was bubbled into the reaction system for 1 h and the temperature was kept at about −60 °C. After that, the mixture was warmed to room temperature and dry CO_2 was bubbled into reaction system for another 40 min. The solution of HCl (10 ml, 6 M) was added to the mixture. After simple work-up procedure, the compound **6** was obtained as oil (1.8 g, 66%), which was used for the next step directly. The oil was purified by silica gel column (ethyl acetate) to give a white solid. m.p.: 93–95 °C (lit. 92–95 °C [25]).

4.5. Preparation of 2,3,5,6-tetrafluoro-4-(methoxymethyl)benzyl alcohol (3)

The reaction was carried out as described in Section 4.2. $Zn(BH_4)_2$ (10 mmol) and 2,3,5,6-tetrafluoro-4-(methoxymethyl)-

benzoic acid **6** (4.7 g, 20 mmol) was used to give the alcohol **3** as colorless liquid (3.6 g, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.43 (s, 3H, $-OCH_3$), 4.64 (d, 2H, J = 2 Hz, $-CH_2OMe$), 4.71 (d, 2H, J = 3 Hz, $ArCH_2OH$).

4.6. Preparation of 2,3,5,6-tetrafluoro-4-methylbenzyl alcohol (2)

Under N_2 atmosphere, a mixture of 2,3,5,6-tetrafluorobenzyl alcohol **1** (5.2 g, 29 mmol), TsOH (catalytic amount), 3,4-dihydro-2H-pyran (3.9 g, 43 mmol) and dry THF (20 ml) was placed in a flask equipped with a magnetic stirring bar. The mixture was stirred at room temperature for 30 min. After the solvent was distilled under reduced pressure, the residue was dissolved in Et_2O (20 ml) and washed with H_2O. The aqueous layer was extracted with Et_2O (2× 10 ml) and the ether layers were combined. The organic layer was dried over Na_2SO_4, and then filtered and distilled under reduced pressure to give the crude ether **7** (7 g). The crude product **7** was used directly in the next step without any further purification.

The ether **7** was dissolved in dry THF (40 ml) and the solution was cooled to −78 °C. After cooling, *n*-BuLi (18.2 ml, 1.60 M, 29.2 mmol) was added dropwise for 30 min and the mixture was stirred for 2 h. CH_3I (2 ml) was then added and the mixture was stirred for 1 h. When the temperature of the mixture returned to room temperature, H_2O (20 ml) was slowly added and the organic layer was separated and dried over Na_2SO_4. The organic layer was then filtered and solvent was distilled under reduced pressure to give the product (5.9 g).

The product was dissolved in ethanol (20 ml) and TsOH (catalytic amount) was added to the solution. The mixture was then heated to reflux for 30 min. After the ethanol was removed, the residue was dissolved in CH_2Cl_2 (20 ml), washed with H_2O and dried on Na_2SO_4. The solvent was then removed under reduced pressure to give the product **2** (3.8 g, 68%). After purified by silica gel column, a white solid was obtained. m.p.: 50–51 °C (lit. 48 °C [7]).^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 2.35–2.37 (m, 3H, $-CH_3$), 4.75 (d, 2H, J = 2 Hz, $-CH_2$).

4.7. Preparation of 2,3,5,6-tetrafluorodibenzyl alcohol (8)

The reaction was carried out as described in Section 4.2. $Zn(BH_4)_2$ (20 mmol) and 2,3,5,6-tetrafluoroterephthalic acid (2.4 g, 10 mmol) was used to give a white solid **8** (1.5 g, 71%). m.p.: 106–107 °C (lit. 106 °C [8]), ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 4.60 (s, 1H, –OH), 4.73 (d, 2H, J = 6 Hz, $-CH_2$).

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