Reduction of Carbonyl Function to a Methyl Group

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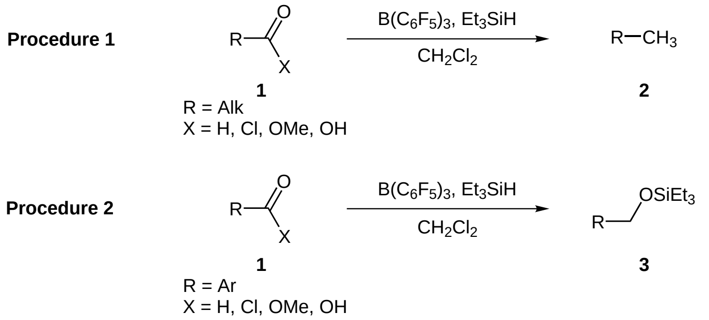
Abstract: A direct exhaustive reduction of aliphatic carbonyl functions (aldehydes, acyl chlorides, esters and carboxylic acids) to a methyl group by triethylsilane (Et_3SiH) in the presence of catalytic amount of tris(pentafluorophenyl)borane [$B(C_6F_5)_3$] is described. Aromatic carbonyl functions could undergo partial reduction to the corresponding TES-protected benzylic alcohols.

Key words: reductions, aldehydes, acyl chlorides, esters, carboxylic acids



Scheme 1

Introduction

Defunctionalization of organic functional groups is an equally important process as compared to functionalization. The carbonyl group can be reduced to a methylene group by Clemmensen[1] or Wolff–Kishner reduction.[2] Titanocene dichloride reduces carboxylic esters to produce alkanes and alcohols.[3] Complete reduction of carboxylic groups to methyl groups also can be achieved, however, reported procedures required multiple-step processes.[4] Most of these procedures require drastic reaction conditions and are often associated with low yields and structural limitations. On the other hand, Lewis acids are of great importance in various types of organic transformations.[5] It is well known that carbonyl compounds can be reduced with hydrosilanes in the presence of a Lewis acid.[6] Among the various Lewis acids, boron-based Lewis acids remain prominent due to their high Lewis acid strength and easy availability. In recent years, relatively unexplored $B(C_6F_5)_3$ has emerged as a viable alternative for boron-based Lewis acids, since it is (i) convenient to handle, (ii) commercially available, (iii) considerably more hydrolytically stable, and (iv) comparable in Lewis acidity to BF_3, but without the problems associated with reactive B–F bonds.[7] Recently, we[8] and Piers group[9] have observed the $B(C_6F_5)_3$-catalyzed reduction of alcohols and cleavage of aryl and alkyl ethers with hydrosilanes. We demonstrated that combination of $B(C_6F_5)_3/Et_3SiH$ efficiently reduced primary alcohols and ethers to give hydrocarbons.[8] Piers and co-workers recently reported a partial reduction of aromatic aldehydes, ketones and esters by using $B(C_6F_5)_3/Ph_3SiH$ combination.[10] In their protocol, one equivalent of the silane reagent was essential for clean reaction since further reduction of the silyl ether or silyl acetal products was observed when excess of silane was used. Encouraged by these findings, we then attempted to develop a convenient one-pot protocol for a direct defunctionalization of carbonyl functions into the corresponding hydrocarbons.[11]

Scope and Limitations

The procedure described here demonstrates an efficient, direct exhaustive reduction of the aliphatic carbonyl function (aldehyde, acyl chloride, ester and carboxylic acid) into a methyl group by using a catalytic amount of $B(C_6F_5)_3$ with stoichiometric amount of Et_3SiH. A partial

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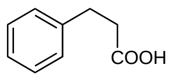
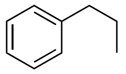
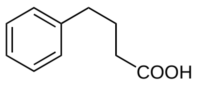
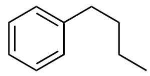
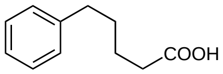
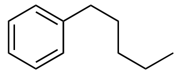
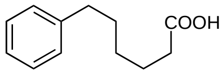
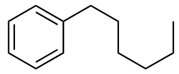
reduction of aromatic carbonyl functions into the silyl benzyl ethers is also described herein (Scheme 1).

A newly purchased $B(C_6F_5)_3$ can be used as received for present purpose. Since, $B(C_6F_5)_3$ is moisture- and air-sensitive, the use of old catalyst resulted to decrease of the chemical yield. However, old catalyst can be used with equal efficiency after purification by sublimation under argon atmosphere at 100 °C/1 Torr.

The results are summarized in Table 1. 1-Dodecanal (**1a**) was exhaustively reduced into *n*-dodecane (**2a**) in the presence of 5 mol% of $B(C_6F_5)_3$ and three equivalents of Et_3SiH with excellent isolated yield (Procedure 1, Scheme 1, Table 1, entry 1). Likewise, *n*-hexadecanoyl chloride (**1b**) and methyl *n*-octadecanoate (**1c**) underwent smooth exhaustive reduction into the corresponding *n*-hexadecane (**2b**) and *n*-octadecane (**2c**), respectively, in virtually quantitative yields (entries 2 and 3). To the best of our knowledge, only aromatic carboxyl moiety has been reduced into a methyl group,[4] however, such a transformation of an aliphatic carboxyl group is unknown. In contrast, this methodology provides an effective reduction of aliphatic carboxyl group into the corresponding hydrocarbon in very high yield. Thus, dodecanoic acid (**1d**) and octadecanoic acid (**1e**) smoothly underwent exhaustive reduction to give *n*-dodecane (**2a**) and *n*-octadecane (**2c**), respectively (entries 4 and 5). In our previously reported procedure,[11a] use of hydrofluoric acid was essential in the work-up process for these transformations. Since hydrofluoric acid is highly poisonous and one of the most hazardous chemicals, we sought a milder, safer and equally efficient condition to utilize our methodology for practical synthetic purpose. We found that, use of conc. H_2SO_4 and NH_4F is equally effective, quick, safer and milder than use of hydrofluoric acid (see Procedure 1 for details).

Table 1 Reduction of Aliphatic Carbonyl Functions into Hydrocarbons[a]

Entry	Substrate **1**	Et_3SiH (equiv)	Product **2**	Yield (%)[b]
1	$n\text{-}C_{11}H_{23}CHO$ **1a**	3.0	$n\text{-}C_{12}H_{26}$ **2a**	96 (95)
2	$n\text{-}C_{15}H_{31}COCl$ **1b**	4.0	$n\text{-}C_{16}H_{34}$ **2b**	97 (95)
3	$n\text{-}C_{17}H_{35}CO_2Me$ **1c**	6.0	$n\text{-}C_{18}H_{38}$ **2c**	96 (98)
4	$n\text{-}C_{11}H_{23}CO_2H$ **1d**	6.0	**2a**	91 (94)
5	$n\text{-}C_{17}H_{35}CO_2H$ **1e**	6.0	**2c**	94 (91)
6	 COOH **1f**	6.0	 **2d**	94 (91)
7	 COOH **1g**	6.0	 **2e**	37[c]
8	 COOH **1h**	6.0	 **2f**	93 (86)
9	 COOH **1i**	6.0	 **2g**	93 (88)

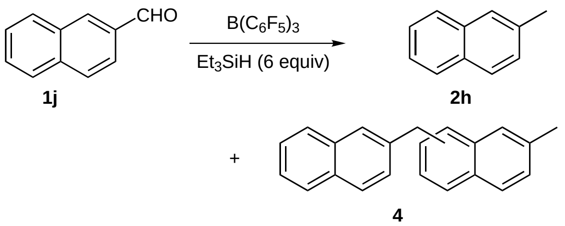
[a] All reactions were carried out in the presence of 5 mol% of $B(C_6F_5)_3$ with stoichiometric amount of Et_3SiH under argon.

[b] Isolated yield of the products in 5 mmol scale synthesis. Yields in parentheses show isolated yield of the product in 50 mmol scale synthesis.

[c] 1,2,3,4-Tetrahydronaphthalene (63%) was obtained.

Following the Procedure 1, exhaustive reduction of hydrocinnamic acid (**1f**) was achieved (Table 1, entry 6). On the other hand, the same reaction proceeded smoothly and product **2d** could be purified in high yield without using fluorine source at the work-up stage. With this method, unlike the homologues with shorter (**1f**) or longer (**1h, 1i**) chains, 4-phenylbutyric acid (**1g**) produced a significant amount (63%) of 1,2,3,4-tetrahydronaphthalene (the product of intramolecular Friedel–Crafts type alkylation process), together with the normal reduction product **2e** in 37% yield.

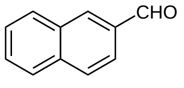
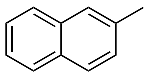
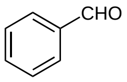
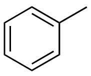
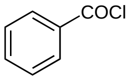
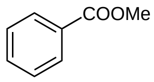
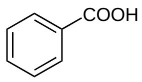
We then investigated the possibility of similar transformation for aromatic substrates. As shown in Table 2, various aromatic substrates **1j**–**n** underwent reduction to give the corresponding hydrocarbons (Table 2, entries 1–5). Although GC/MS and NMR analyses of the crude reaction mixtures indicated that aromatic carbonyl functions exhaustively reduced into methyl groups, purification of the products proved apparently not so simple. For example, reduction of 2-naphthaldehyde (**1j**) with six equivalents of Et_3SiH in the presence of 5 mol% of $B(C_6F_5)_3$ afforded the desired 2-methylnaphthalene (**2h**) as a major product (Equation 1, Table 2, entry 1). However, it was formed, accompanied with inseparable mixture of the dimeric by-product **4**, the formation of which was confirmed by GC/MS and NMR analyses of the crude reaction mixture. The dimeric by-product **4** had formed via partial Friedel–Crafts type alkylation of 2-methylnaphthalene (**2h**).



Equation 1

It was found that aromatic carbonyl functions underwent partial reduction by decreasing the amount of Et_3SiH to cleanly afford silyl ethers **3** as sole products without any complication (Procedure 2, Scheme 1). Thus obtained si-

Table 2 Reduction of Aromatic Carbonyl Functions into Hydrocarbons[a]

Entry	Substrate **1**	Et_3SiH (equiv)	Product **2**	Yield (%)[b]
1	 **1j**	6.0	 **2h**	91
2	 **1k**	6.0	 **2i**	82
3	 **1l**	6.0	**2i**	84
4	 **1m**	6.0	**2i**	87
5	 **1n**	6.0	**2i**	85

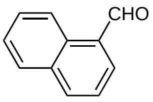
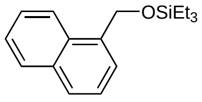
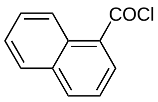
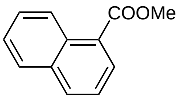
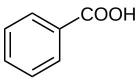
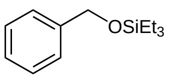
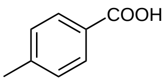
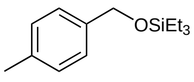
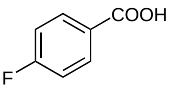
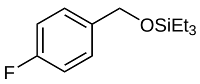
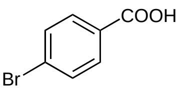
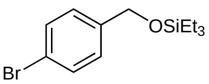
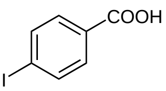
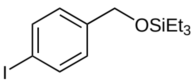
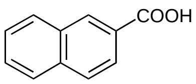
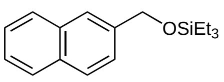
[a] All reactions were carried out by using 1 mmol of substrate in the presence of 5 mol% of $B(C_6F_5)_3$ with six equivalents of Et_3SiH under argon atmosphere.
[b] NMR yields.

lyl ethers **3** can be easily deprotected into the benzylic alcohols upon hydrolysis.[12]

The results of partial reduction of aromatic carbonyl functions are summarized in Table 3. The reduction of aromatic carbonyl compounds 1-naphthaldehyde (**1o**), 1-naphthoyl chloride (**1p**) and 1-naphthoic acid methyl ester (**1q**) with 1.1, 2.2, and 3.3 equivalents of Et_3SiH, respectively, in the presence of 5 mol% of $B(C_6F_5)_3$ proceeded cleanly to form the TES-ether of naphthylmethanol (**3a**) in almost quantitative yields (Table 3, entries 1–3).[13] Furthermore, this method is equally effective for partial reduction of aromatic carboxylic acids. Employing 3.3 equivalents of Et_3SiH, various aromatic substrates **1n**–**v** under mild reaction condition cleanly provided the silyl ethers of the benzyl series **3b**–**f** and the silyl ether of naphthylmethanol (**3g**) in excellent yields (entries 4–9).

Recently, Chandrasekhar and co-workers reported the polymethylhydrosiloxane/$B(C_6F_5)_3$-catalyzed reduction of carbonyl groups (ketones and aldehydes) into methylenes[14] albeit in comparatively lower yields. In summary, we have developed an efficient and mild practical synthetic method for the exhaustive reduction of aliphatic aldehydes, acyl chlorides, esters, and carboxylic acids into hydrocarbons. Furthermore, we elaborated an effective protocol for the partial reduction of aromatic aldehydes, acyl chlorides, esters, and carboxylic acids into the corresponding TES-protected benzylic alcohols.

Table 3 Reduction of Aromatic Carbonyl Functions into Silyl Benzyl Ethers[a]

Entry	Substrate **1**	Et_3SiH (equiv)	Product **3**	Yield (%)[b]
1	 **1o**	1.1	 **3a**	96
2	 **1p**	2.2	**3a**	95
3	 **1q**	3.3	**3a**	92 (96)
4	 **1n**	3.3	 **3b**	95
5	 **1r**	3.3	 **3c**	91
6	 **1s**	3.3	 **3d**	93
7	 **1t**	3.3	 **3e**	93
8	 **1u**	3.3	 **3f**	94
9	 **1v**	3.3	 **3g**	96

[a] All reactions were carried out in the presence of 5 mol% of $B(C_6F_5)_3$ with stoichiometric amount of Et_3SiH under argon atmosphere.
[b] Isolated yield of the products in 5 mmol scale synthesis. Yield in parenthesis shows isolated yield of the product in 30 mmol scale synthesis.

Procedures

Herein, we describe a typical practical synthetic procedure for the convenient, direct transformations of aliphatic carbonyl functions (aldehydes, acyl chlorides, esters, and carboxylic acids) to hydrocarbons (Procedure 1). In Procedure 2, aromatic carbonyl functions (aldehydes, acyl chlorides, esters, and carboxylic acids) are partially reduced to the TES-protected benzylic alcohol derivatives.

In Procedure 1, we report the exhaustive reduction of 1-dodecanal (**1a**) to *n*-dodecane (**2a**). In Procedure 2, the partial reduction of 1-naphthoic acid methyl ester (**1q**) to triethyl(naphthalen-1-ylmethoxy)silane (**3a**) is detailed.

n-Dodecane (2a); Typical Procedure 1

An oven-dried 300 mL three necked round-bottomed flask, equipped with stirring bar and dropping funnel was charged with $B(C_6F_5)_3$ (1.28 g, 2.5 mmol) under argon. An argon-filled balloon was used to maintain inert atmosphere. A solution of 1-dodecanal (**1a**; 9.22 g, 50 mmol) in anhyd CH_2Cl_2 (50 mL) was then added with a cannula. Et_3SiH (24 mL, 150 mmol) was introduced dropwise to the stirred mixture through the dropping funnel over 20 min. After stirring the mixture for 20 h at r.t., it was quenched with Et_3N (2.5 mL). The reaction mixture was concentrated by rotary evaporation then filtered through a Celite pad to remove solid particles and rinsed with pentane (50 mL). The filtrate was collected in 200 mL round-bottomed flask and concentrated under reduced pressure. The residue was cooled by using an ice-bath and conc. H_2SO_4 (50 mL) added slowly with magnetic stirring. NH_4F (6.0 g) was then added in several portions. After the final addition of NH_4F, the stirring was continued for 15 min, and then the temperature was raised to 40 °C. After heating for 1 hour, the reaction mixture was carefully poured in brine (200 mL) and the crude product was extracted with pentane (4×200 mL). The combined organic layers were washed with H_2O (4×200 mL), dried (Na_2SO_4), filtered and concentrated. The residue was purified by silica gel column chromatography using hexane as eluent to afford *n*-dodecane (**2a**) (8.05 g, 95%) as a colorless oil.

IR (neat): 2957, 2924, 2854, 1468, 1377, 721 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.85$ (t, $J = 6.4$ Hz, 6 H), 1.23 (s, 20 H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.07$, 22.67, 29.36, 29.69, 31.91.

Triethyl(naphthalen-1-ylmethoxy)silane (3a); Typical Procedure 2

An oven-dried 200 mL three necked round-bottomed flask, equipped with stirring bar and dropping funnel was charged with $B(C_6F_5)_3$ (0.77 g, 1.5 mmol) under argon. An argon-filled balloon was used to maintain inert atmosphere throughout the reaction period. Anhyd CH_2Cl_2 (30 mL) was added via syringe and the mixture was cooled to 0 °C followed by addition of 1-naphthoic acid methyl ester (**1q**; 4.8 mL, 30 mmol). Et_3SiH (16 mL, 99 mmol) was then introduced dropwise to the stirred mixture through a dropping funnel over 45 min. After stirring the mixture for 20 h at r.t., it was quenched with Et_3N (2 mL). The mixture was concentrated by rotary evaporation then filtered through a Celite pad to remove solid particles and rinsed with hexane (30 mL). The filtrate was concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography by using hexane–EtOAc (50:1) as eluent to afford **3a** (7.47 g, 96%).

^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.08$ (d, $J = 8.0$ Hz, 1 H), 7.92 (d, $J = 8.2$ Hz, 1 H), 7.83 (d, $J = 8.2$ Hz, 1 H), 7.67 (d, $J = 7.0$ Hz, 1 H), 7.59–7.51 (m, 3 H), 5.28 (s, 2 H), 1.06 (t, $J = 7.9$ Hz, 9 H), 0.76 (q, $J = 7.9$ Hz, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 137.06$, 133.98, 131.28, 129.05, 128.09, 126.29, 126.00, 125.93, 124.38, 123.77, 63.52, 7.31, 5.00.

GC/MS: *m/z* (%) = 272 (M^+, 3), 243 (M – Et, 34), 141 (100).

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