Simple reduction of ethyl, isopropyl and benzyl aromatic esters to alcohols using sodium borohydride-methanol system

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Abstract
Several aromatic ethyl, isopropyl and benzyl esters were reduced to their corresponding alcohols in sodium borohydride-methanol system. The reductions were completed within 15-60 minutes in refluxing THF. The alcohol products were isolated after aqueous workup in good to excellent yields (63-100%). The general procedure presented is simple, safe, inexpensive and with good perspective in industrial scale.

Keywords: $NaBH_4$, aromatic esters, reduction

Introduction

Reduction plays a very important role in organic synthesis. One of the most common reagent used for this purpose is sodium borohydride.[1] Usually, the reactions carried out with $NaBH_4$ are safe, inexpensive and can be done in mild conditions.[2,3]

Although this reducing agent has been constantly used for reduction of aldehydes, ketones and other important functional groups, it is not common to use $NaBH_4$ itself for reduction of esters.[4-6]

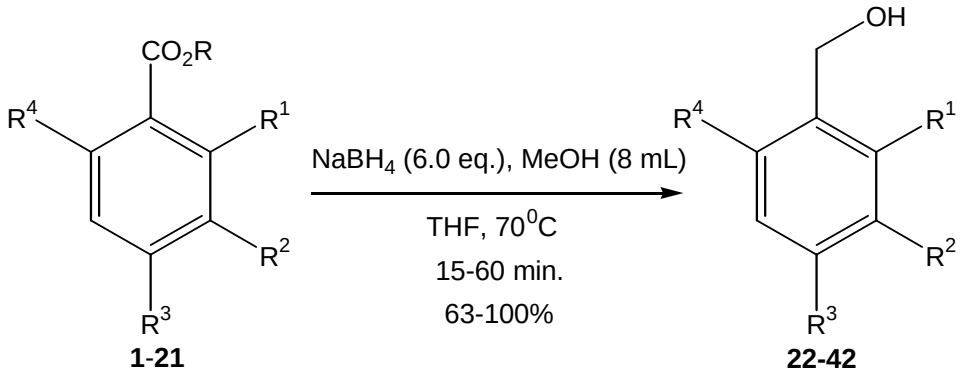
Due to this low reactivity towards esters, additives which enhance the activity of $NaBH_4$ have been reported.[7] For example, addition of iodine to $NaBH_4$ in THF provides H_3B–THF, which is useful for hydroborations, reduction of esters and various others functional groups.[8] Another example is the addition of zinc chloride in presence of tertiary amine that exhibits a reducing property toward ester function.[7]

In this context, the aim of the present article is to describe a simple one-pot different aromatic ethyl, isopropyl and benzyl esters reduction into the corresponding alcohol using $NaBH_4$-MeOH

system. The presence of different esters in this methodology is important due to these esters groups are able to enhance the solubility and cristallinity of some aromatic compounds. We have also tested this methodology with some aliphatic and heteroaromatic esters with good results.

Results and Discussion

The aromatic alcohols **22-42** were obtained by the method described in the general procedure (**Scheme 1**). The methodology presented is simple, safe, inexpensive, and raised the reduction of different aromatic ethyl, isopropyl and benzyl esters within 15 – 60 minutes after refluxing in THF. The respective alcohol products were isolated after aqueous workup in good to excellent yields (63-100%) (**Table 1**). The structures of the reduction products were confirmed by CG-MS, ^{1}H and ^{13}C RMN experiments, although they are already described in the literature.[9]



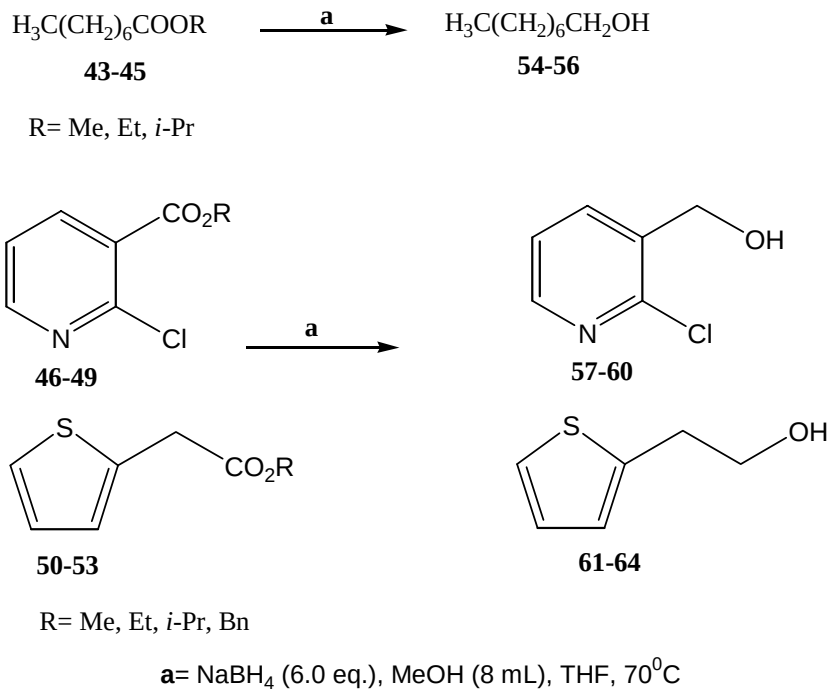
Scheme 1

Table 1. Reduction of aromatic ethyl, isopropyl and benzyl esters to alcohols using sodium borohydride-methanol system

Number	Substrate	R	Time(min)	Yield(%)	mp_{exp} (mp_{lit}) (°C)	CG/MS* (%)
22	R^1=R^2=R^3=R^4=H	Et	20	96	*oil*	100
23	R^1=R^2=R^3=R^4=H	*i*-Pr	20	68	*oil*	100
24	R^1=R^2=R^3=R^4=H	Bn	15	100	*oil*	100
25	R^1=R^4=Cl, R^2=R^3=H	Et	15	100	96-97 (95-98)	100
26	R^1=R^4=Cl, R^2=R^3=H	*i*-Pr	15	100	93-95 (95-98)	90
27	R^1=R^4=Cl, R^2=R^3=H	Bn	15	98	95-96 (96-98)	97
28	R^1=R^2=Cl, R^3=R^4=H	Et	20	95	90-92 (94-95)	95
29	R^1=R^2=Cl, R^3=R^4=H	*i*-Pr	20	88	95-96 (93-95)	98
30	R^1=R^2=Cl, R^3=R^4=H	Bn	15	93	91-92 (94-95)	91
31	R^1=R^3=Cl, R^2=R^4=H	Et	20	76	53-55 (56-58)	98
32	R^1=R^3=Cl, R^2=R^4=H	*i*-Pr	20	82	56-57 (55-58)	88
33	R^1=R^3=Cl, R^2=R^4=H	Bn	20	88	57-59 (57-58)	98
34	R^1=R^3=F, R^2=R^4=H	Et	60	63	*oil*	92
35	R^1=R^3=F, R^2=R^4=H	*i*-Pr	60	74	*oil*	94
36	R^1=R^3=F, R^2=R^4=H	Bn	20	87	*oil*	98
37	R^1=R^2=R^4=H, R^3=F	Et	30	83	*oil*	95
38	R^1=R^2=R^4=H, R^3=F	*i*-Pr	30	88	*oil*	97
39	R^1=R^2=R^4=H, R^3=F	Bn	20	92	*oil*	98
40	R^1=R^2=R^4=H, R^3=Cl	Et	40	98	71-73 (70-72)	89
41	R^1=R^2=R^4=H, R^3=Cl	*i*-Pr	40	92	68-70 (70-72)	92
42	R^1=R^2=R^4=H, R^3=Cl	Bn	20	86	69-70 (70-72)	99

*****determined by area normalization

Additionally, this methodology has been also applied to aliphatic and heteroaromatic esters (**Scheme 2**) with good results, as shown in **Table 2**.



Scheme 2

Table 2. Reduction of some aliphatic and heteroaromatic esters to alcohols using sodium borohydride-methanol system

Number	R	Time(min)	Yield (%)	CG/MS* (%)
54	Me	15	81	92
55	Et	15	74	94
56	i- Pr	15	80	90
57	Me	15	93	97
58	Et	15	91	97
59	i-Pr	15	88	95
60	Bn	15	60	97
61	Me	15	97	99
62	Et	15	94	99
63	i-Pr	15	72	97
64	Bn	15	80	94

*determined by area normalization

In conclusion, we have developed an inexpensive, simple, safe and general protocol for one-pot reduction of aromatic esters with good perspective for use in reduction of aliphatic and heteroaromatic esters too.

Experimental Section

General Procedures. Mass spectra (CG/MS) were recorded on a Agilent Tecnologies 61530A / 5792A mass spectrometer. NMR spectra were recorded on a Bruker Avance 500 spectrometer operating at 500.00 MHz (^{1}H) and 125.0 MHz (^{13}C), in deuterated chloroform. Proton and carbon spectra were typically obtained at room temperature. For TLC plates coated with silica gel were run in ethyl acetate/hexane mixture and spots were developed in Ultraviolet and alcoholic phosphomolibdic acid solution 7% p/v.

General procedures for the synthesis of the alcohols 22-42, **54-56**, **57-60** and **61-64** The esters used in this study are commercially available or can be simply made by their corresponding carboxylic acids in presence of thionyl chloride.[9]

Finely powdered sodium borohydride (6 eq.; 24-30 mmol) was suspended in THF in presence of the respective ester (1g; 4-5 mmol) during a period of 15 minutes under reflux (70ºC) and stirring. Then methanol (8mL) was added dropwise during a period of 15 minutes with effervescence being observed. Stirring and reflux were maintained during a period of 15 to 60 minutes. The reactions were monitored by TLC using mixtures of ethyl acetate/*n*-hexane as eluants. After the end of reaction, the alcohol was cooled to room temperature and quenched with a saturated solution of NH_4Cl (10mL) for further period of 1.5 hour. For purification of alcohols, the organic layer was separated and the aqueous phase extracted with ethyl acetate (2x25mL). The organic extracts were combined and dried over Na_2SO_4 and concentrated under low pressure to give the respective alcohols. The alcohols obtained from benzilic esters were purified by column chromatography on silica gel, eluting with hexane:ethyl acetate gradient (up to 50%) afforded the pure derivatives **24, 27, 30, 33, 36, 39, 42, 60** and **64**. All the alcohols were fully characterized by CG-MS, ^{1}H and ^{13}C RMN spectra and are known in the literature[10].

(2,6-Dichloro-phenyl)-methanol (27). ^{1}H NMR [500.00 MHz, $CDCl_3$] δ: 7.35 (2H; d; *J*= 8.0 Hz; H_3 e H_5); 7.18 (1H; dd; *J*= 8.0 and 8.0 Hz; H_4); 4.82 (2H; s; C$\underline{H}_2$) ppm. ^{13}C NMR (100.0 MHz, $CDCl_3$) δ: 139.4; 134.1; 134.0; 130.1; 129.5; 127.2; 59.4 ppm.

(2,3-Dichloro-phenyl)-methanol (30). ^{1}H NMR [500.00 MHz, $CDCl_3$] δ: 7.42 (1H; d; *J*= 7.5 Hz; H_6); 7.41 (1H; d; 7.5 Hz; H_4); 7.23 (1H; dd; *J*= 7.5 and 8.0 Hz; H_5); 4.79 (2H; s; C$\underline{H}_2$) ppm. ^{13}C NMR (100.0 MHz, $CDCl_3$) δ: 140.5; 129.4; 128.6; 127.5; 127.0; 127.0; 63.1 ppm.

(2,4-Dichloro-phenyl)-methanol (33). ^{1}H NMR [500.00 MHz, $CDCl_3$] δ: 7.43 (1H; s; H_3); 7.37 (1H; dd; *J*= 2.0 and 9.0 Hz; H_5); 7.27 (1H; d; *J*= 9.0 Hz; H_6); 4.75 (2H; s; C$\underline{H}_2$) ppm. ^{13}C NMR (100.0 MHz, $CDCl_3$) δ: 136.7; 133.8; 133.2; 129.4; 129.1; 127.3; 62.2 ppm.

(2,4-Difluoro-phenyl)-methanol (36). ^{1}H NMR [500.00 MHz, $CDCl_3$] δ: 7.43 (1H; dd; *J*= 8.5 and 9.5 Hz; H_3); 7.37 (1H; dd; *J*= 5.5 and 9.0 Hz; H_6); 7.27 (1H; dd; *J*= 9.0 and 9.5 Hz; H_5); 4.68 (2H; s; C$\underline{H}_2$) ppm. ^{13}C NMR (100.0 MHz, $CDCl_3$) δ: 161.6; 161.3; 128.5; 124.5; 110.1; 104.3; 57.1 ppm.

(4-Fluorophenyl)-methanol (39). ^{1}H NMR [500.00 MHz, $CDCl_3$] δ: 7.21 (2H; d; *J*=8.3 Hz; H_2 and H_6); 6.89 (2H; dd; *J*= 8.3 and 7.5 Hz; H_3 and H_5); 4.49 (2H; s; C$\underline{H}_2$) ppm. ^{13}C NMR (100.0 MHz, $CDCl_3$) δ: 161.8; 137.1; 127.7; 114.9; 67.7 ppm.

(4-Chlorophenyl)-methanol (42). ^{1}H NMR [500.00 MHz, $CDCl_3$] δ: 7.31 (2H; d; *J*= 7.5 Hz; H_3 and H_5); 7.10 (2H; d; *J*= 7.5 Hz; H_2 and H_6); 4.51 (2H; s; C$\underline{H}_2$) ppm. ^{13}C NMR (100.0 MHz, $CDCl_3$) δ: 139.4; 130.4; 128.9; 128.1; 66.8 ppm.
(2-Chloro-pyridin-3-yl)-methanol (60). ^{1}H NMR [500.00 MHz, $CDCl_3$] δ: 7.65 (1H; dd; *J*= 5.5 and 2.0 Hz; H_6); 7.32 (1H; dd; *J*= 2.0 and 7.5 Hz; H_4); 7.20 (1H; dd; *J*= 5.5 and 7.5 Hz; H_5); 4.74 (2H; s; C$\underline{H}_2$) ppm. ^{13}C NMR (100.0 MHz, $CDCl_3$) δ: 161.3; 150.5; 139.5; 122.7; 119.1; 64.2 ppm.
2-Thiophen-2-yl-ethanol (64). ^{1}H NMR [500.00 MHz, $CDCl_3$] δ: 7.12 (1H; dd; *J*= 1.0 and 5.0 Hz; H_5); 6.92 (1H; dd; *J*= 3.5 and 5.0 Hz; H_4); 6.83 (1H; d; *J*= 3.5 Hz; H_3); 3.77 (2H; t; *J*= 6.5 Hz; C$\underline{H}_2$-OH); 3.01 (2H; *J*= 6.5 Hz; C$\underline{H}_2$) ppm. ^{13}C NMR (100.0 MHz, $CDCl_3$) δ: 140.8; 126.9; 125.4; 123.8; 63.3; 33.1 ppm.

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