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SILICA GEL PROMOTED SOLVENT-FREE SYNTHESIS OF ARYLCARBINOLS AND FERROCENYLCARBINOLS

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SILICA GEL PROMOTED SOLVENT-FREE SYNTHESIS OF ARYLCARBINOLS AND FERROCENYLCARBINOLS

Submitted by (09/25/00)

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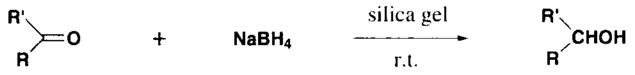
In general, $NaBH_4$ is a popular reagent of choice for its ease of manipulation and its insensitivity to moisture compared to other metal hydride reducing reagents.[1-3] However the activity of the $NaBH_4$ is relatively poor and the reduction process requires higher temperature or longer reaction time compared with those using $LiAlH_4$ and $LiBH_4$. Therefore an improvement of the reducing potency of $NaBH_4$ would provide an added tool for synthetic chemists. Ranu and co-workers described silica gel-supported zinc borohydride as an efficient and highly selective reagent for the reduction of conjugated ketones and aldehydes to the corresponding allylic alcohols, but this method requires keeping the reaction mixture at -5 to -10° for 7-8 h.[4] Recently, it has also been demonstrated that silica gel has a remarkable ability to promote the various reactions.[5, 6] Hirano and co-workers reported the reduction of ketones and aldehydes with $NaBH_4$ in hexane in the presence of silica gel.[6] This method requires dry hexane as solvent and is carried out under a dry argon atmosphere at 40° for several hours. This tedious, inconvenient, and lengthy procedure may therefore, reduce its value.

It is well known that solvent-free syntheses have many advantages over conventional solution procedures. Typically, solvent-free synthesis features short reaction time, cleaner reaction and easier work-up. In recent years, various applications of solvent-free organic chemistry have attracted great attention.[7-10] Though the reduction of ketones under solvent-free conditions with $NaBH_4$ was investigated long ago, this process has not been used widely, because it requires a ten-fold molar amount of $NaBH_4$ and a very long reaction time.[11]

The present work reports a convenient and effective method for the reduction of carbonyl compounds to the alcohols with $NaBH_4$ supported on silica gel as reducing reagent without solvent at room temperature. The procedure involves grinding a mixture of $NaBH_4$, silica gel and the carbonyl compound in a mortar. The reduction is completed within 10-30 min. and the reaction may be monitored by TLC, and in some cases by disappearance of the orange color of the carbonyl compounds, such as in case of the acylferrocene; its orange color changed into yellowish color when the reduction was completed. In general, a pure product was obtained in high yield without further purification (Table 1).



1 **2**

a) R = H, R' = C_6H_5; ***b***) R = Me, R' = C_6H_5; ***c***) R = H, R' = 3-$O_2NC_6H_4$; ***d***) R = H, R' = 4-$O_2NC_6H_4$;
e) R = H, R' = 4-ClC_6H_4; ***f***) R = H, R' = 4-BrC_6H_4; ***g***) R = H, R' = 4-HOC_6H_4; ***h***) R = H, R' = 4-CNC_6H_4;
i) R = H, R' = 3,4-$CH_2OCH_2C_6H_4$; ***j***) R = H, R' = 4-$NH_2C_6H_4$; ***k***) R = H, R' = 4-$Me_2NC_6H_4$;
l) R = H, R' = 4-HO-3-$MeOC_6H_3$; ***m***) R = Me, R' = 2-HOC_6H_4; ***n***) R = C_6H_5, R' =C_6H_5;
o) R = 2-C_5H_4N, R' = C_6H_5; ***p***) R = H, R' = *trans*-$C_6H_5CH=CH$; ***q***) R = H, R' = $C_5H_5FeC_5H_4$;
r) R = Me, R' = $C_5H_5FeC_5H_4$; ***s***) R = Et, R' = $C_5H_5FeC_5H_4$; ***t***) R = C_6H_5, R' = $C_5H_5FeC_5H_4$;

When the reaction was carried out by grinding a mixture of aldehyde or ketone, silica gel and $NaBH_4$ with pestle and mortar at room temperature, aromatic aldehydes were converted to corresponding alcohols in better than 96% of yield within 10 min (Run 1, 8, 10). The reduction of ketones was slower and required 15-20 min. for completion. The reduction of ferrocenylcarbonyl compounds was even slower than that of ketones and required about 20-30 min. for complete reduction. It is to be noted that the reduction of *trans*-cinnamyl aldehyde (Run 23) gives exclusively *trans*-cinnamyl alcohol. The reduction of benzophenone and benzoylferrocene was difficult and the yields of corresponding products were 70 and 35%, respectively (Run 20 and 27). Steric hindrance around the carbonyl group might account for the low yields of products ***2n*** and ***2t***. However, when the reaction was carried out at ca 40-45°, it proceeded much faster and was complete within 5-15 min. in excellent yields (Run 2, 6, 21, 28). On the other hand, when a mixture of aldehyde or ketone, silica gel and $NaBH_4$ was ground in a mortar with a pestle, then the mixture was kept at 40-45° for 15-120 min., the reduction also proceeded in excellent yields (Run 11, 12, 14-19). Esters (ethyl benzoate) did not react under the same conditions. In addition, it was found that the reduction of aldehydes containing electron-withdrawing groups (***1d-1f***, ***1h***) was much more rapid than of those containing electron donating groups (***1g***, ***1i-1m***).

Table 1. Reduction of Carbonyl Compounds with $NaBH_4$ and SiO_2

Run	Cmpd	Yield[a] (%)	Temp (°C)	$NaBH_4$ (mmol)	SiO_2 (g)	Time (min.)	mp(bp)/(°C)	*lit.* mp(bp)/(°C)
1	***2a***	96	rt	1.2	1.0	10	(92-94/10mmHg)	(93/10mmHg)[13a]
2	***2a***	96	40-45[b]	1.2	1.0	5	"	"
3	***2a***	92	rt	0.3	0.5	30	"	"
4	***2a***	90	40-45[b]	10.0	15.0	30	"	"
5	***2b***	95	rt	1.0	1.0	15	(85-86/7mmHg)	(85-86/7mmHg)[13b]
6	***2b***	95	40-45[b]	1.0	1.0	10	"	"
7	***2b***	93	rt	0.3	0.5	50	"	"
8	***2c***	96	rt	1.3	1.0	10	27	27[13c]
9	***2c***	95	rt	0.4	0.5	40	"	"
10	***2d***	96	rt	1.2	1.0	10	91-92	92-93[13c]
11	***2e***	96	40-45[c]	1.2	0.5	15	74-75	75[12d]
12	***2f***	93	40-45[c]	1.2	1.0	15	76-77	76.5-77[14]
13	***2g***	94	rt	1.2	1.0	30	125-127	124.5-128.5[13e]
14	***2h***	95	40-45[c]	1.2	1.0	15	132-133	133-134[13f]
15	***2i***	93	40-45[c]	1.2	0.8	60	57-58	58[13g]
16	***2j***	94	40-45[c]		0.8	90	65	65[13h]
17	***2k***	92	40-45[c]	1.2	0.8	120	68-70	68-70[13h]
18	***2l***	95	40-45[c]	1.2	1.0	120	114-115	114-115[13i]
19	***2m***	93	40-45[c]	1.2	0.8	60	53-54	53-54[13j]
20	***2n***	70	rt	1.2	1.0	30	68-69	68[13k]
21	***2n***	90	40-45[c]	1.2	1.0	15	"	"
22	***2o***	85	40-45[c]	1.2	1.0	120	123-125	125[15]
23	***2p***	91	rt	1.0	1.0	30	33	33[13l]
24	***2q***	92	rt	1.2	1.0	20	80-81	81-82[12a]
25	***2r***	96	rt	2.0	2.0	20	74-76	73-75[12b]
26	***2s***	95	rt	1.5	1.0	30	63-64	64-65[12c]
27	***2t***	35	rt	1.5	1.0	30	80-81	81-82[12d]
28	***2t***	90	40-45[b]	1.6	1.0	15	"	"

a) All products are known compounds and their physical constants, IR and ^1H NMR spectra correspond to those reported in the literature. *b*) Ground in a mortar preheated in an oven at 40-45° for 5-30 min. *c*) The ground mixture in the mortar was placed in the oven for 15-120 min.

The reduction can be completed by grinding a mixture of aldehyde (or ketone), $NaBH_4$ (their molar ratio=1:0.3) and silica gel (optimal amount 0.5 g), but it requires relatively long reaction time (Run 3, 7, 9). Some experiments demonstrate that nearly all of the hydride was utilized in the reduction process. In addition, the synthesis of benzyl alcohol was also carried out on a thirty-fold scale (gram-scale) (Run 4), but the yield (90%) did not increase as compared to that obtained in the small scale experiment (Run 3).

In conclusion, the reduction of carbonyl compounds using $NaBH_4/SiO_2$ in dry media provides a very convenient and effective method for the preparation of a variety of arylcarbinols and ferrocenylcarbinols. The operational simplicity, high yields and low cost will certainly make this procedure an attractive method for reduction of carbonyl compounds.

EXPERIMENTAL SECTION

Ferrocenecarboxaldehyde, acetylferrocene, propionylferrocene and benzoylferrocene were prepared by a general procedure.[12] The purity of these compounds was checked by TLC and their physical constants were confirmed with those reported in the literature. All other reagents are AR grade.

General Procedure for the Reduction of Carbonyl Compounds. ***Method A***.- In a typical experiment, a mixture of acetylferrocene (0.22g, 1mmol), silica gel (1g, chromatographic grade, particle size 0.2-0.5mm) and $NaBH_4$ (0.045g, 1.2 mmol) was ground thoroughly in a mortar and pestle for 20 min. at room temperature (Table 1) until the reduction was complete by TLC monitoring. After the mixture had cooled to room temperature, it was extracted with ether (20 mL x 3). The combined extracts were dried over anhydrous $MgSO_4$ and the solvent removed under vacuum to give 1-hydroxyethylferrocene in 96% yield (0.22g, mp. 74-76°, *lit.*[12b] 73-75°). The product could be further purified by recrystallization from *n*-hexane. In addition, the reaction may also be carried out by introducing the reaction mixture into a mortar preheated to 40-45° for 10-30 min. and ground immediately and thoroughly until the reduction is complete by TLC examination (Run 2, 6, 21 and 28).

Method B.- A mixture of aldehyde or ketone (Run 11, 12, and 14-19)(1 mmol), silica gel (0.8-1g). $NaBH_4$ (1.2 mmol) was ground thoroughly with a pestle in a mortar, then the mixture was kept at 40-45° in an oven for 15-120 min. The products were isolated as described previously.

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SYNTHESIS OF THYMYL ETHERS AND ESTERS USING POLYMER-SUPPORTED THYMOL ANION

Submitted by
(09/05/00)

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Terpenoids play an important role in the enzyme system of plants and are one of the most abundant and potent groups of naturally occurring substances having biological activity on various pests. Monoterpenoids are natural substances and secondary metabolites of plants which are generally considered as self-defense tactics against the plant's enemies. The biological activity of monoterpenoids[1-4] against insects, nematodes, phytopathogenic fungi and other pest species is believed to be related to the nature and position of specific groups or substituents. The chemical modification[5-9] of natural monoterpenoids to various ether and ester derivatives has been reported[1-3, 8, 9] to result in modi-