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Reductive acetylation of carbonyl compounds to acetates with $NaBH_4/Cu(dmg)_2$ system

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ABSTRACT

Acetylation of carbonyl compounds is generally achieved via reduction followed by the acetylation. In addition, the combination systems of borohydrides have been also reported for one-pot reductive acetylation of carbonyl compounds. In this context, reductive acetylation of carbonyl compounds as a key synthetic protocol is a straightforward method for conversion of carbonyl compounds to the coressponding acetates. Reductive acetylation of a variety of carbonyl compounds such as aldehydes, ketones and α,β-unsaturated enals/enones was carried out efficiently with sodium borohydride /copper dimethylglyoxime, $Cu(dmg)_2$, in ethyl acetate under reflux condition. The corresponding acetates were obtained in high to excellent yields.

KEYWORDS

Acetylation;
Reduction;
Sodium borohydride;
(dimethylglyoximato) copper (II);
Ethyl acetate.

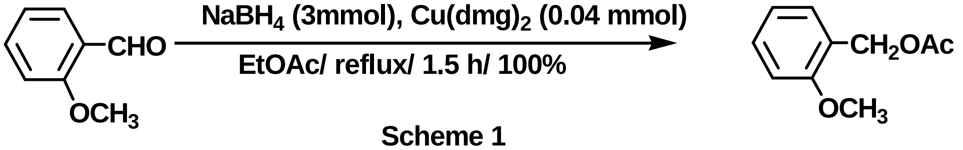
INTRODUCTION

During the past decades, sodium borohydride as a key reagent has played an important role in the reduction of organofunctional groups in modern organic synthesis[1-4]. This reagent is a relatively mild reducing agent and mostly used for reduction of aldehydes and ketones[5-10]. Reductive acetylation of carbonyl compounds as a key synthetic protocol is a straightforward method for conversion of carbonyl compounds to the corresponding acetates[11-13]. The literature review shows that the application of hydroborate agents for reductive acetylation of carbonyl compounds is rare. $NaBH_4$, $(Py)Zn(BH_4)_2$ and poly(4-vinylpyridine) supported $Zn(BH_4)_2$ are the reagents which have been reported for the titled transformation[14-19]. These methods generally suffer from some disadvantages such as low yield of products, occurrence of side reactions, less or unreactivity of ketones and preliminary preparation of the complex reducing agents[20-23]. Herein, we wish to introduce $NaBH_4$/(dimethylglyoximato) copper(II) in refluxing EtOAc as a very efficient protocol for reductive acetylation of various aldehydes and ketones to the corresponding acetates.

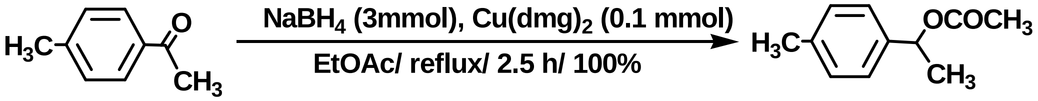
EXPERIMENTAL

General

All reagents and substrates were purchased from commercial sources with the best quality and were used without further purification. IR and ^{1}H NMR spectra were recorded on Thermo Nicolet Nexus 670 FT–IR and 300 MHz Bruker Avance spectrometers, respectively. The products were characterized by a comparison with authentic samples (melting or boiling points) and their ^{1}H NMR or IR spectra. All yields refer to isolated pure products. TLC was applied for the purity determination of substrates, products and reaction monitoring over silica gel 60 F254 aluminum sheet.



Scheme 1



Scheme 2

Preparation of catalyst (dimethylglyoximato) copper (II)

Dimethylglyoxime and Cu(OAc)$_2$.H$_2$O were added into absolute ethanol to get brown precipitates of Cu(dmg)$_2$[4].

Reductive acetylation of aldehydes with NaBH$_4$/Cu(dmg)$_2$ system, a typical procedure

In a round-bottom flask (10 mL) equipped with a magnetic stirrer, a mixture of benzaldehyde (0.106 g, 1 mmol) in EtOAc (2 mL) was prepared. Cu(dmg)$_2$ (0.01 mmol) was then added and the resulting mixture was stirred for 10 min under reflux conditions. Afterward, NaBH$_4$ (2 mmol) was added and the mixture was continued to stirring for 1.25 h. TLC monitored the progress of the reaction (eluent: CH$_2$Cl$_2$/Et$_2$O: 5/2). The mixture was then extracted with CH$_2$Cl$_2$ (3 × 8 mL) and dried over anhydrous Na$_2$SO$_4$. Evaporation of the solvent affords the pure benzyl acetate in 97% yield (TABLE 1, entry 1).

Reductive acetylation of ketones with NaBH$_4$/Cu(dmg)$_2$ system, a typical procedure

In a round-bottom flask (10 mL) equipped with a magnetic stirrer, a mixture of acetophenone (0.12 g, 1 mmol) in EtOAc (2 mL) was prepared. Cu(dmg)$_2$ (0.1 mmol) was then added and the resulting mixture was stirred for 10 min under reflux conditions. Afterward, NaBH$_4$ (3 mmol) was added and the mixture was continued to stirring for 2.5 h. TLC monitored the progress of the reaction (eluent: CH$_2$Cl$_2$/Et2O: 5/2). The mixture was then extracted with CH$_2$Cl$_2$ (3 × 8 mL) and dried over anhydrous Na$_2$SO$_4$. Evaporation of the solvent affords the pure 1- phenylethyl acetate in 94% yield (TABLE 2, entry 1).

Reductive acetylation of conjugated carbonyl compounds with NaBH$_4$/Cu(dmg)$_2$ system, a typical procedure

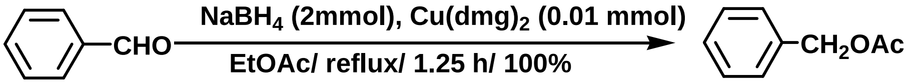
In a round-bottom flask (10 mL) equipped with a magnetic stirrer, a mixture of cinnamaldehyde (0.132 g, 1 mmol) in EtOAc (2 mL) was prepared. Cu(dmg)$_2$ (0.2 mmol) was then added and the resulting mixture was stirred for 10 min under reflux conditions. Afterward, NaBH$_4$ (3 mmol) was added and the mixture was continued to stirring for 2.25 h. TLC monitored the progress of the reaction (eluent: CH$_2$Cl$_2$/Et2O: 5/2). The mixture was then extracted with CH$_2$Cl$_2$ (3 × 8 mL) and dried over anhydrous Na$_2$SO$_4$. Evaporation of the solvent affords the pure cinnamyl acetate in 93% yield (TABLE 3, entry 2).

RESULT AND DISCUTION

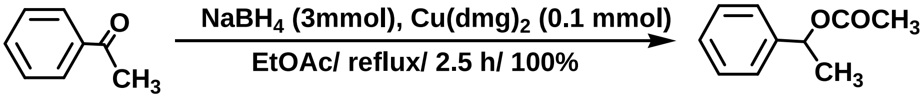
The optimization experiments showed that reductive acetylation of benzaldehyde (1 mmol) as a model compound was carried out perfectly with 3 mmol of NaBH$_4$ in the presence of Cu(dmg)$_2$ (0.01 mmol) in refluxing EtOAc (2 mL). The capability of NaBH$_4$/Cu(dmg)$_2$ in refluxing EtOAc was further explored by the reaction of various aromatic and aliphatic carbonyl compounds. As shown in TABLES 1 and 2, completion of the reactions required 3 mmol of NaBH$_4$ and 0.01-0.1 mmol of Cu(dmg)$_2$ to give the corresponding acetates in 91-98% yields during 1.25-3.25 h (Schemes 3 and 4).

Then the direct acetylation of carbonyl compounds, α, β-unsaturated system using a combination NaBH$_4$/Cu(dmg)$_2$ was studied. Tests showed that the reaction of 1 mmol cinnamaldehyde with 3 mmol NaBH$_4$ and 0.15mmol Cu (dmg)$_2$ in refluxing ethyl acetate in

2 hours mixture of products cinnamyl acetate (75%) and 3- phenyl propyl acetate (25%) will produce. It can be concluded that the test was conducted under conditions of low reactivity and selectivity of the acetylation mixture of 1,2- and 1,4- is done. Next, it was decided that by controlling the reaction conditions used to increase or decrease the amount of moles of catalyst, the selectivity decreased cinnamaldehyde increase in acetylation. Experiment 1 mmol cinnamaldehyde with 3 mmol $NaBH_4$ and 0.2 mmol $Cu(dmg)_2$ in refluxing ethyl acetate during 2.45 hours, pure cinnamyl acetate produced (TABLE 3, items 1 and 2). The conditions for the reduction of various combinations of α, β-unsaturated carbonyl was studied and it was observed that the selectivity definitive acetylation reduction in the number of compounds of α, β-unsaturated be no mixture of acetylation of 1,2- and 1,4- significant dates. The results are shown in TABLE 3. However, in all cases, the reaction efficiency was very high (98% - 93%).

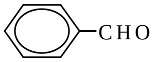
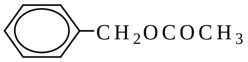
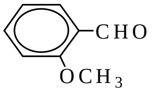
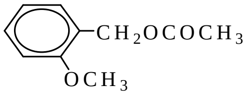
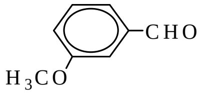
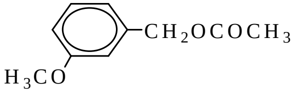
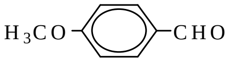
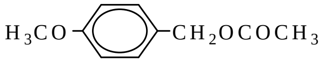
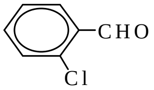
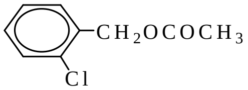
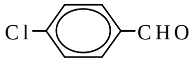
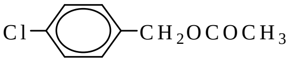
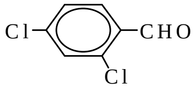
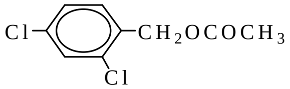
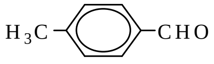
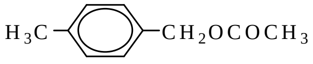
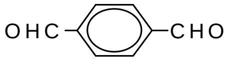
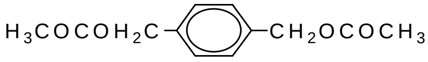
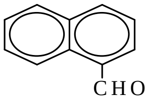
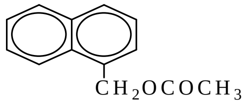


Scheme 3



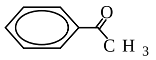
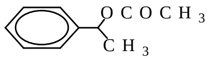
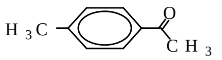
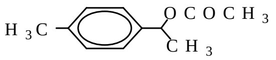
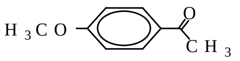
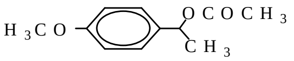
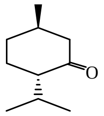
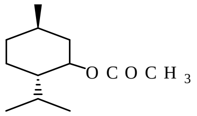
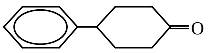
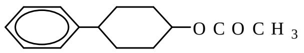
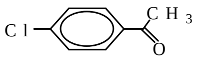
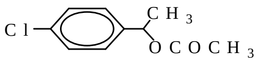
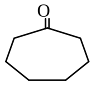
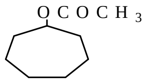
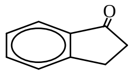
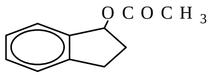
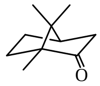
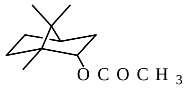
Scheme 4

TABEL 1 : Reductive acetylation of aldehydes with $NaBH_4/Cu(dmg)_2$ system[a].

Entry	Substrate	Product	Molar ratio[b]	Time (h)	Yield (%)[c]
1	 CHO	 CH_2OCOCH_3	1:2:0.01	1.25	97
2	 CHO OCH_3	 CH_2OCOCH_3 OCH_3	1:3:0.04	1.50	97
3	 CHO H_3CO	 CH_2OCOCH_3 H_3CO	1:3:0.1	1.50	93
4	 H_3CO CHO	 H_3CO CH_2OCOCH_3	1:3:0.1	2	97
5	 CHO Cl	 CH_2OCOCH_3 Cl	1:3:0.02	2	94
6	 Cl CHO	 Cl CH_2OCOCH_3	1:3:0.02	1.5	95
7	 Cl CHO Cl	 Cl CH_2OCOCH_3 Cl	1:3:0.02	2	97
8	 H_3C CHO	 H_3C CH_2OCOCH_3	1:3:0.04	1.45	92
9	 OHC CHO	 H_3COCOH_2C CH_2OCOCH_3	1:3:0.04	1.25	98
10	 CHO	 CH_2OCOCH_3	1:3:0.07	1.35	95

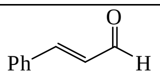
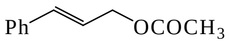
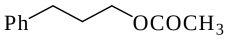
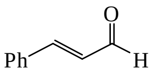
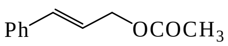
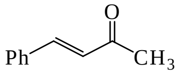
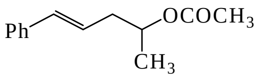
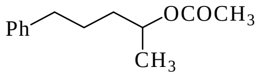
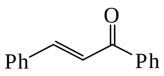
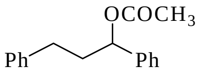
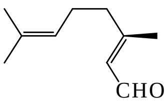
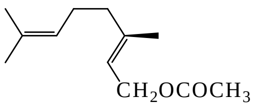
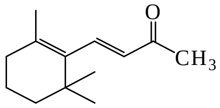
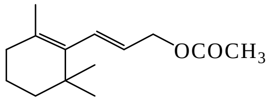
[a]All reactions were carried out in refluxing EtOAc (2 ml); [b]Molar ratio as $Subs./NaBH_4/Cu(dmg)_2$; [c]Isolated yields.

TABLE 2 : Reductive acetylation of ketones with $NaBH_4/Cu(dmg)_2$ system[a].

Entry	Substrate	Product	Molar ratio[b]	Time (h)	Yield (%)[c]
1			1:3:0.1	2.5	94
2			1:3:0.1	2.5	95
3			1:3:0.1	3	99
4			1:3:0.3	3.15	95
5			1:3:0.1	2.25	93
6			1:3:0.1	2.5	93
7			1:3:0.1	2.5	98
8			1:3:0.2	2.5	96
9			1:3:0.3	3.25	91

[a]All reactions were carried out in refluxing EtOAc (2 ml); [b]Molar ratio as Subs./$NaBH_4/Cu(dmg)_2$; [c]Isolated yields.

TABLE 3 : Reductive acetylation of conjugated carbonyl compounds with $NaBH_4/Cu(dmg)_2$ system[a]

Entry	Substrate	Products	Molar ratio[b]	Ratio of 1,2 /1,4	Time (h)	Yield (%)[c]
1		 	1:13:0.15	75:25	2	98
2			1:3:0.2	100:0	2.25	93
3		 	1:3:0.2	22:78	3.15	98
4			1:3:0.3	0:100	3.5	96
5			1:3:0.2	100:0	3	94
6			1:3:0.2	100:0	3.15	97

[a]All reactions were carried out in refluxing EtOAc (2 ml); [b]Molar ratio as Subs./$NaBH_4/Cu(dmg)_2$; [c]Isolated yields.

CONCLUSION

In conclusions we have shown the one-pot reductive acetylation of a variety of aldehydes, ketones and α, β-unsaturated with $NaBH_4/Cu(dmg)_2$ system. Also, the chemoselective reductive acetylation of aldehydes and ketones in the presence of ethyl acetate with this reducing agent was perfectly achieved. In view points of high efficiency, regio - and chemoselectivity of the reactions, mild reaction conditions and the easy work-up procedure, we believe that this reagent can be considered as a suitable and perfect reagent for one-pot reductive acetylation of various kinds of carbonyl compounds.

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