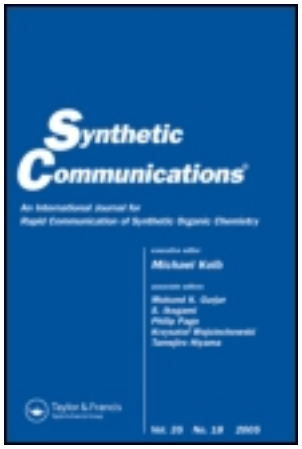

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Chemoselective Reduction and Transesterification of α-Keto Propargylic Esters Mediated by $NaBH_4$ and $CeCl_3 \cdot 7H_2O$

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CHEMOSELECTIVE REDUCTION AND TRANSESTERIFICATION OF α-KETO PROPARGYLIC ESTERS MEDIATED BY $NaBH_4$ and $CeCl_3 \cdot 7H_2O$

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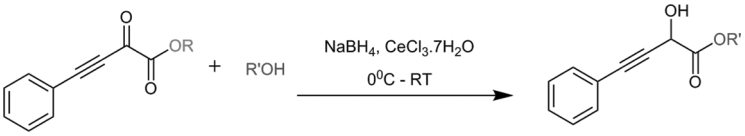
GRAPHICAL ABSTRACT



R = Me, Et
R' = Me, Et, *n*-Pro, *iso*-Pro,*n*-Bu,Allyl,Propargyl

Abstract *An efficient one-pot synthesis of α -hydroxy propargylic esters by chemoselective reduction followed by transesterification using $NaBH_4$ in combination with $CeCl_3 \cdot 7H_2O$ is described.*

Keywords $NaBH_4/CeCl_3.7H_2O$; reduction; transesterification

INTRODUCTION

Propargylic alcohols and esters are versatile building blocks as they allow for facile conversion to a variety of functional groups in the synthesis of allenes, lactones, and heterocycles, which are part of biologically active molecules[1] such as thrombin receptor antagonists[2] and reverse transcriptase inhibitors.[3] These key intermediates can be obtained by various chemical methods, which include direct coupling reaction[4] or coupling followed by reduction.[5] Selective 1,2-reduction of conjugated aldehydes and ketones by $NaBH_4/CeCl_3 \cdot 7H_2O$ are known.[6] Because of its unique catalytic properties (i.e., inexpensive, nontoxic, and water tolerant), catalyst $CeCl_3 \cdot 7H_2O$ was used as a potential Lewis acid which imparts high region- and chemoselectivity[7] in organic transformations such as hydro oxacyclization of unsaturated 3-hydroxy esters,[8] Michael addition,[9] esterification of phenolic alcohols,[10] enamination of β-dicarbonyl compounds,[11] allylation of aldehydes,[12]

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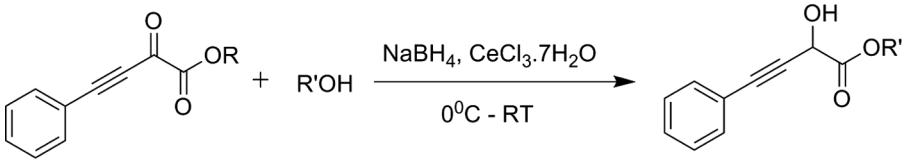


Scheme 1. Reduction cum transesterification of α-keto propargylic esters using $NaBH_4/CeCl_3 \cdot 7H_2O$.

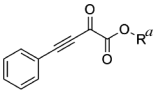
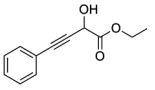
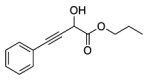
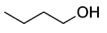
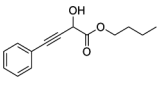
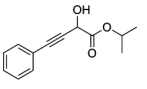
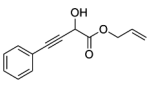
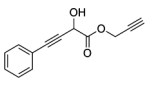
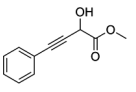
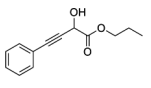
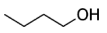
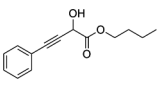
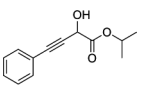
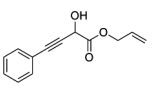
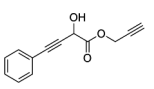
dihydroxylation of unreactive olefins,[13] and Julia olefination of cyclopropyl carbinols,[14] synthesis of N,N-disubtituted ureas,[15] and quinoline derivatives.[16] Recently, Meng et al. developed the Ru-catalyzed enantioselective hydrogenation of aromatic α-ketoesters with $CeCl_3 \cdot 7H_2O$ as an effective additive.[17] To prepare racemic α-hydroxy propargylic esters as substrates[18] for *Candida parapsilosis* ATCC 7330, which is known to efficiently catalyze deracemization,[19] we followed the reported procedure[5] using $NaBH_4/CeCl_3 \cdot 7H_2O$. Significantly, in addition to reduction, a transesterfied product was formed; that is, reduction of methyl 2-oxo-phenylbut-3-ynoate in ethanol with $NaBH_4/CeCl_3 \cdot 7H_2O$ resulted in the formation of ethyl 2-hydroxy-4-phenylbut-3-ynoate. This interesting result prompted us to study the importance of $NaBH_4/CeCl_3 \cdot 7H_2O$ as a reducing cum transesterifiying agent for various α-keto propargylic esters.

Esters are generally synthesized either from reaction of carboxylic acid with alcohol[20] and/or by transesterification of an ester with an alcohol.[21] Poor solubility of some acids in organic solvents makes transesterification more advantageous than ester synthesis.[22] Transesterification is an important reaction as it used to prepare organic intermediates in the synthesis of biologically important molecules and also in the preparation of biodiesel.[21a,23] Thus, a number of useful procedures catalyzed by a variety of protic and Lewis acids,[22,24] organic and inorganic bases,[25] enzymes and antibodies[21c,26] have been developed for transesterification. However, methods for the transesterification of α-keto esters[27] are rather few. Despite the numerous methods of transesterification reported in literature, there is a constant need to develop new protocols that require mild conditions, especially for compounds with acid- and base-sensitive functionalities such as hydroxy, ester, and alkyne moieties. To the best of our knowledge, there has been no report on transesterification of α-keto propargylic esters using $NaBH_4/CeCl_3 \cdot 7H_2O$. Earlier work from our laboratory reported the reduction cum transesterification of β-keto esters using $NaBH_4$.[28] Herein, we report an efficient one-pot reaction to obtain different types of α-hydroxy propargylic esters from α -keto propargylic esters by using $NaBH_4/CeCl_3 \cdot 7H_2O$ in different alcohols at room temperature under mild reaction conditions (Scheme 1).

RESULTS AND DISCUSSION

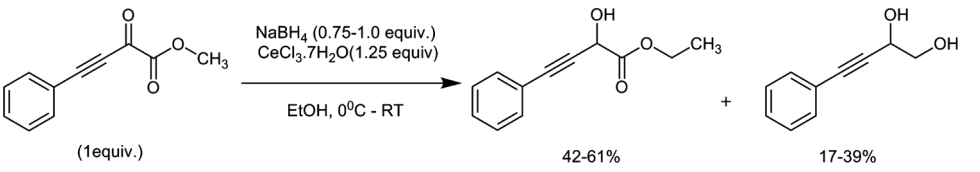
In a typical experiment, α-keto propargylic esters were treated with the desired alcohols, and the corresponding reduced cum transesterfied products were obtained in moderate to good yields. The results are summarized in Table 1. In optimization studies, we tried the reaction with various concentration of $NaBH_4$ for methyl

Table 1. Reduction cum transesterification of α-keto propargylic esters using $NaBH_4/CeCl_3 \cdot 7H_2O$

Entry		Solvent	Product	Time (h)	Isolated yield (%)
1	CH_3	CH_3CH_2OH		3	71
2	CH_3			6	65
3	CH_3			6	67
4	CH_3			12	61
5	CH_3			12	58
6	CH_3			12	51
7	CH_3CH_2	CH_3OH		3	69
8	CH_3CH_2			6	62
9	CH_3CH_2			12	63
10	CH_3CH_2			24	20
11	CH_3CH_2			12	41
12	CH_3CH_2			12	37

[a]Methyl 4-phenyl-2-oxobut-3-ynoate and ethyl 4-phenyl-2-oxobut-3-ynoate were synthesized according to the literature report.[5]

2-oxo-4-phenylbut-3-ynoate in ethanol (with 1.2 equiv. of $CeCl_3 \cdot 7H_2O$ in 3 h reaction time). The yields obtained for 0.25, 0.5, 0.75, and 1.0 equiv. of $NaBH_4$ were 53%, 71%, 61%, and 42% respectively. The reaction was not complete with 0.25



Scheme 2. Reduction cum transesterification of methyl 2-oxo-4-phenylbut-3-ynoate using $NaBH_4$/$CeCl_3 \cdot 7H_2O$.

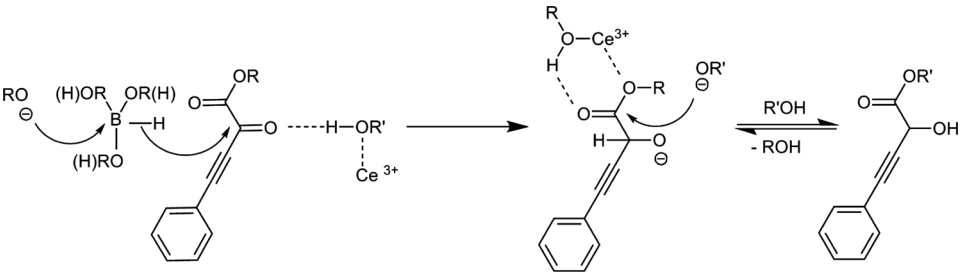
equiv., and 38% of starting material was recovered. With 0.75 and 1.0 equiv. of $NaBH_4$, the corresponding diol product was also observed in 17% and 39% yields respectively because of the reduction of both keto and ester groups (Scheme 2). With 0.5 equiv., a maximum yield of 71% was observed because of the selective reduction of the keto group. On the basis of these results, all the experiments were done with 0.5 equiv. of $NaBH_4$.

According to these optimized reaction conditions, methyl 2-oxo-4-phenylbut-3-ynoate on treatment with ethanol in the presence of $NaBH_4/CeCl_3 \cdot 7H_2O$ led to the corresponding reduced cum transesterfied product with 71% yield in 3 h due to the good solubility of catalyst (entry 1). Furthermore, methyl 2-oxo-4-phenylbut-3-ynoate with *n*-propanol, *n*-butanol, and *iso*-propanol gave the corresponding transesterfied hydroxy (reduced) products with yields ranging from 61 to 67% (entries 2–4). In the presence of allyl and propargyl alcohols, the formation of the corresponding products, allyl 2-hydroxy-4-phenylbut-3-ynoate, and prop-2-ynyl 2-hydroxy-4-phenylbut-3-ynoate in 58% and 51% yield respectively (entries 5 and 6) were observed. These two compounds are reported here for the first time.

Ethyl 2-oxo-4-phenylbut-3-ynoate with methanol, *n*-propanol, and *n*-butanol led to the formation of corresponding transesterfied reduced products in 62–69% yields (entries 7–9) while with allyl and propargyl alcohols, the transesterfied reduced products were isolated in 41% and 37% yields respectively (entries 11 and 12). With *iso*-propanol, the reduction was completed within 15 min, but the transesterfied product was obtained only after 24 h in 20% yield (entry 10). Use of *tert*-butanol, 2-methoxyethonol, and benzyl alcohol with methyl and ethyl 2-oxo-4-phenylbut-3-ynoate did not give the desired transesterfied product even after 24 h, possibly because of the poor solubility of the catalyst but the reduced untransesterfied product formed within 30 min.

To ensure that $CeCl_3 \cdot 7H_2O$ facilitated the transesterification process, the reaction (entry 1) was carried out in the absence of $CeCl_3 \cdot 7H_2O$. The reaction did not proceed even after 24 h. On the other hand, the same reaction in the absence of $NaBH_4$, after 24 h reaction time, gave only 18% of the transesterfied product without reduction. The results of these experiments confirmed that both $NaBH_4$ and $CeCl_3 \cdot 7H_2O$ are necessary for the reduction cum transesterification reaction.

Mechanistically, $NaBH_4$ alone acts as a soft reducing agent, and the active species during the Luche reduction was believed to be an alkoxy borohydride, which in combination with the hard Ce^{3+} cation acts as a hard reducing agent.[6c,29] The cerium plays an important role as catalyst in the formation of alkoxy borohydrides and increases the electrophilicity of the carbonyl carbon atom.[6c,29] From a mechanistic



Scheme 3. Plausible mechanism.

standpoint, cerium ions preferentially coordinate to the oxygen atom of solvent and increase the acidity of the medium,[30] thus helping to activate the carbonyl carbon of the ketone in the reduction and also activating the carbonyl carbon of the ester in the transesterification (Scheme 3).

CONCLUSIONS

In conclusion, we have developed a highly efficient method for the chemoselective reduction and transesterification for α -keto propargylic esters mediated by $NaBH_4/CeCl_3 \cdot 7H_2O$. The notable advantages of the procedure are (a) simple and one-pot reaction, (b) easy availability and nontoxic nature of the reagent, (c) mild reaction conditions (tolerance to sensitive functionalities such as hydroxy, ester, and alkyne moieties during transesterification), (d) the solvents need not to be dried, (e) $CeCl_3$ can be used directly as its heptahydrate and no drying is needed, and (f) neither inert atmosphere not the protection of hydroxy group is required.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Bruker AV-400 spectrometer operating at 400 and 100 MHz, respectively. Chemical shifts are expressed in parts per million (ppm) values using tetramethylsilane (TMS) as an internal standard. TLC was carried out on Kieselger 60 F254 aluminium sheets (Merck1.05554). All chemicals were obtained from Aldrich and Merck.

General Procedure for the Reduction Cum Transesterification Reaction

The α-keto propargylic ester (2.50 mmol) was treated with the desired alcohol (15 ml) in the presence of $NaBH_4$ (1.25 mmol) and $CeCl_3 \cdot 7H_2O$ (3.13 mmol) at room temperature. The reaction was monitored by TLC, and after completion, excess alcohol was stripped off. The reaction mixture was quenched with dilute HCl and extracted with dechloremethane (DCM). The organic layer was dried, concentrated, purified by silica-gel column chromatography, and characterized by infrared (IR), ^1H and ^{13}C NMR, and high-resolution mass spectrometry (HRMS).

Some Selected Spectral Data of the Products

Allyl 2-Hydroxy-4-phenylbut-3-ynoate (entries 5 and 11). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.16$ (1H, d, $J = 7.2$ Hz), 4.78 (2H, m), 5.10 (1H, d, $J = 7.2$ Hz), 5.30 (1H, dd, $J = 10.4$ Hz & 1.6 Hz), 5.41 (1H, dd, $J = 17.2$ Hz & 1.6 Hz), 5.96 (1H, m), 7.31–7.33 (3H, m), 7.44–7.46 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 170.0, 131.9, 131.0, 128.9, 128.3, 121.7, 119.1, 85.6, 84.1, 67.0, 61.9. IR (ν, cm^{-1}): 3451, 2926, 2155, 1742, 1602, 1489, 1445, 1263, 1197, 1079, 756. HRMS: m/z, calcd. Mass: 239.0684 [$(M + Na)^+$]; found: 239.0689 [$(M + Na)^+$].

Prop-2-ynyl 2-Hydroxy-4-phenylbut-3-ynoate (entries 6 and 12). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.55$ (1H, t, $J = 2$ Hz), 3.08 (1H, d, $J = 7.6$ Hz), 4.87 (2H, dq, $J = 15.2$ Hz & 2 Hz), 5.12 (1H, d, J = 7.6 Hz), 7.29–7.36 (3H, m), 7.45–7.47 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 132.1, 129.1, 128.4, 121.7, 86.2, 83.6, 76.5, 76.1, 62.1, 54.0 IR (ν, cm^{-1}): 3417, 3290, 2955, 2233, 2188, 2164, 1754, 1441, 1192, 1082, 994, 761. HRMS: m/z, calcd. Mass: 237.0528 [$(M + Na)^+$], found: 237.0515 [$(M + Na)^+$].

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