Oxidative Amidation of Benzyl alcohols with Amino acid Esters mediated by N-hydroxysuccinimide/phenyliodine diacetate

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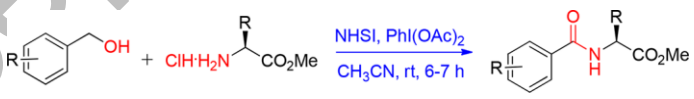
Abstract

A simple protocol involving metal free oxidative amidation of benzyl alcohols with amino acid esters has been presented. The amidation proceeds in a radical pathway unlike in conventional metal mediated extrusion of dihydrogen. The method is advantageous in terms of metal free conditions, non expensive commercial starting substrates. Also various substituents in the starting materials are tolerated and sterically hindered amino acid side chains could provide good yields of amide products.

Graphical Abstact



KEYWORDS: *N*-hydroxysuccinimide; phenyliodine diacetate; amide; oxidation; benzyl alcohol & amino acid.

INTRODUCTION

The amide bond is ubiquitous in organic and biological chemistry.[1] It is a key functional group in peptides, polymers, and many natural products.[2] Amides are present in a broad spectrum of compounds of pharmaceutical, agricultural, and material interests.[3] The most common prevalent method for the synthesis of the amides is treatment of activated carboxylic acid derivatives with amine precursors.[4] Emerging methods for oxidative amide formation have been reviewed in several recent reviews.[5] Various alternative strategies such as the Staudinger reaction,[6] Schmidt reaction[7] and the Beckmann rearrangement[8] have been developed. However, in most of these methods, use of excess of coupling partners, stoichiometric amounts of various reagents are required and equimolar amounts of by-products are produced as waste. Other methodologies to access amides include hydrative amide synthesis with alkynes,[9] thioacid/ester ligation methods,[10] aminocarbonylation of aryl halides.[11]

One of the most attractive methods include oxidative amidation of alcohols and aldehydes that can circumvent carboxylic acid isolation. Catalytic amidation of aldehydes employ metal catalysts such as ruthenium, rhodium, copper and stoichiometric amounts of bases.[12] In addition, coupling of primary amines and alcohols make use of expensive metal catalysts such as ruthenium, rhodium, gold and silver complexes.[13] Presumably, the reaction proceeds through the intermediate aldehyde which reacts with the amine to give a hemiaminal that is subsequently dehydrogenated to the amide. However the

drawbacks include limited activity with sterically hindered alcohols or amines and less basic aromatic amines.

Despite elegant protocols in metal catalysed oxidative amide bond formation, there are limited reports for metal free variations.[14-16] Metal free processes involving tandem oxidative amidation of aldehydes which are particularly attractive from environmental and economical stand point. Yao et al. reported oxidative amide formation from aldehydes using N-hydroxysuccinimide and $PhI(OAc)_2$ under mild conditions in moderate to good yields.[14] Also few examples of oxidative amide formation from alcohols and amines using *o*-iodoxybenzoic acid were reported. In another report novel glycosyl carboxamides were prepared from aldehydes and amines using $PhI(OAc)_2$ in the presence of ionic liquid at ambient temperature.[15] Other metal free oxidative amidation of alcohols using peroxide as oxidant have also been reported albeit at high temperature conditions.[16] We envisaged preparing metal free amide formation from benzyl alcohols with chiral systems viz. amino acid esters. The amino acid esters were chosen as amine components for our study so as to determine the viability of the protocol with steric effects of amino acid side chains as well as to find the possibility of epimerization under the present conditions.

RESULTS AND DISCUSSION

Initially, several amino acids were converted to the corresponding esters **ii** employing reported protocol. In a typical experiment, benzyl alcohol **i** in MeCN was treated with $PhI(OAc)_2$ at room temperature (Scheme 1). After 10 min, N-hydroxysuccinimide was

added followed by amino acid ester **ii** and then the reaction mixture was stirred for 1-2 h until the TLC showed complete disappearance of the NHSI ester. Gratifyingly, the reaction completed within 30 min. The desired amide product **iii** was isolated in 90% yield after simple aqueous work up followed by purification over silica gel column chromatography. The optimization of reaction with respect to the solvent, temperature and molar equivalents of NHSI and $PhI(OAc)_2$ was then investigated. Importantly no product was observed in the absence $PhI(OAc)_2$ or with $PhI(OAc)_2$ alone. Screening of various solvents such as dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), ethyl acetate (EtOAc) and *N*,*N*-dimethylformamide (DMF) revealed MeCN to be the optimum solvent (Table 1 Scheme 1). Higher equivalents of NHSI and $PhI(OAc)_2$ did not improve the output of the reaction (Table 1 Scheme1), whereas lesser equivalent of $PhI(OAc)_2$ led to a decrease in the yield of the product.

The optimized protocol was then generalized to benzyl alcohols with differently substituted aryl moieties with both electron donating as well as withdrawing nature. Also various sterically hindered amino acid esters were employed to obtain the desired amide products in moderate to good yields (Table 2).

All the reactions had clean profile and the products were obtained in good yields after purification by column chromatography on silica gel. The structures of the product amides were confirmed by ^1H NMR, ^{13}C NMR and mass spectrometric analyses. Though the present reaction conditions were mild, the possibility of racemization was studied in

the case of two enantiomeric amides Bn-L-Ala-OMe **4** and Bn-D-Ala-OMe **4***. The chiral-HPLC profiles of **4** and its enantiomer **4*** showed retention times of R_t 12.740 and 18.078 min respectively. The equimolar mixture of **4** & **4*** showed distinct retention times R_t 12.267 and 18.248 min, thus confirming the absence of racemisation.

A possible reaction mechanism is presented in scheme 2, in which alcohol **a** is oxidized (after a ligand exchange around the iodine atom)[17] to corresponding aldehyde **b** with NHSI as a catalyst. Then aldehyde **b** reacts with NHSI giving the corresponding hemiaminal **c**. NHSI is oxidized to the corresponding succinimide *N*-oxy radical (SINO) which abstracts a proton from the hemiaminal **c** generating the corresponding hemiaminal radical **d**,[14] which on rapid oxidation provide ester **e.** Finally ester **e** undergoes a nucleophilic substitution by the amino acid ester to amides.

In summary, a simple metal free protocol for oxidative amidation of benzyl alcohols with amino acid esters has been developed. The $PhI(OAc)_2$ acts as stoichiometric oxidant for the formation of *N*-hydroxysuccinimide ester which then undergoes amidation by reaction with amino acid esters. The method has several advantageous such as metal free conditions, non expensive commercial starting substrates, broad substrate scope in both alcohols with various substituents and sterically hindered amino acid esters in providing good yields of amide products.

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SUPPLEMENTARY DATA

Spectroscopic data (^{1}H, ^{13}C NMR and mass spectra) of compounds can be found in the online version at ……

EXPERIMENTAL SECTION

General procedure for the synthesis of amides derived from benzyl alcohols and amino acid esters:

To a solution of benzyl alcohol (1 mmol) in MeCN (10 mL) was added $PhI(OAc)_2$ (1 mmol) and the reaction was stirred for 10 min. Then NHSI (1.5 mmol) was added and stirring was continued for 15 min. To this mixture, amino acid ester (1 mmol) was added under nitrogen atmosphere. The reaction was stirred for 1-2 h at room temperature till the completion of reaction (consumption of NHSI ester by TLC analysis). The reaction mixture was quenched with water and extracted with EtOAc. (10 mL X 3). The combined organic layer was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography on silica gel (*n*-hexane-EtOAc).

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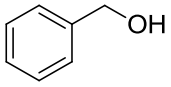
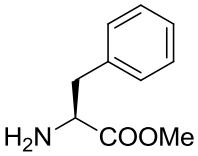
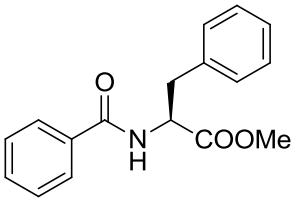
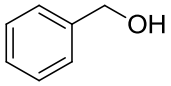
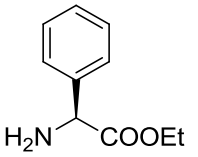
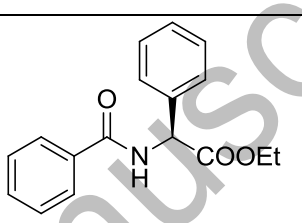
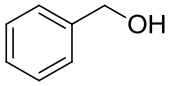
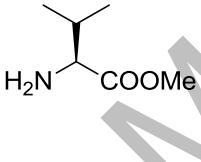
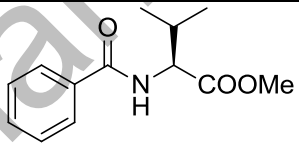
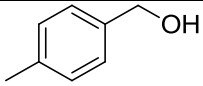
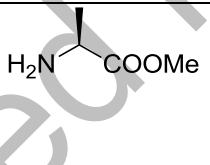
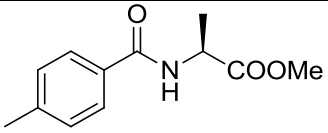
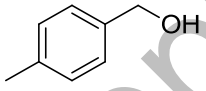
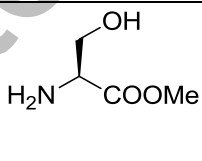
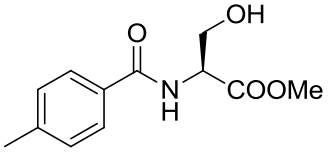
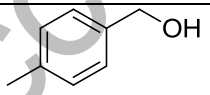
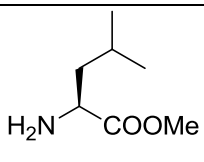
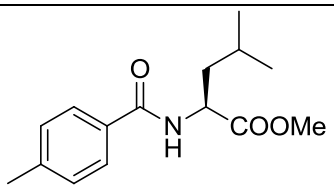
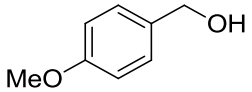
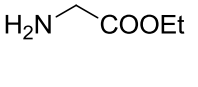
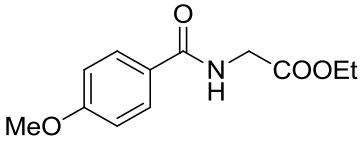
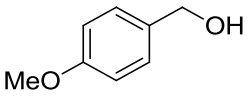
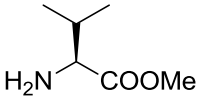
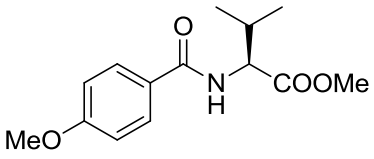
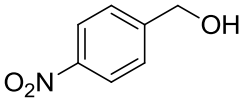
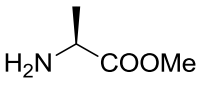
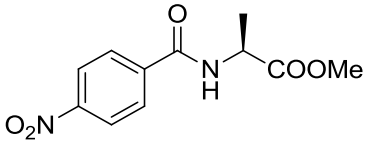
Table 1 Optimization of reaction conditions for oxidative amidation of benzyl alcohols[a]

Entry	Solvent	Equivalents of NHSI/PhI(OAc)$_2$	Time (min)	Yield (%)[b]
1	MeCN	1.5/1	30	90
2	THF	2/1.5	45	84
3	CH_2Cl_2	2/1.5	60	76
4	EtOAc	2/1.5	110	65
5	DMF	2/1.5	120	60
6	MeCN	1.5/1.5	30	88
7	MeCN	2/2	60	55
8	MeCN	1.5/0.5	60	40

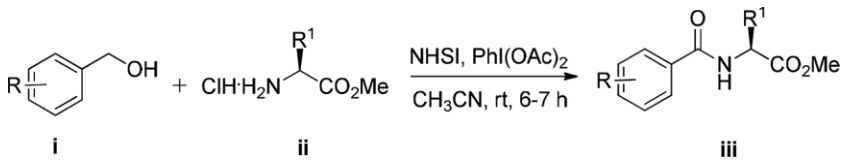
[a] Reactions were monitored by TLC. [b] Isolated yield after column chromatography

Table 2 NHSI/PIDA mediated oxidative amidation of benzyl alcohols with amino acid esters

Entry	Benzyl alcohol	Amino acid ester	Amide	Yield
1				95
2				88
3				90
4				92
5				89
6				91
7				94

8				92
9				85

Scheme 1. Oxidative amidation of benzyl alcohols with amino acid esters



Scheme 2. Possible mechanism for amidation