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Diastereoselective Alkylation of an Oxazolidinone Chiral Auxiliary

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Abstract—Asymmetric synthesis, the part of diastereoselective alkylation of a chiral auxiliary is an important tool in organic synthesis. In this work an α-methyl, non-natural amino acid (NNAA) building block equipped with a phthalimide group tail was prepared. This work describes the generation of the lithium enolate oxazolidin-2-ones chiral auxiliary derived from non-natural amino acid and quenching this enolate with 2-chloromethyl-isoindole-1,3-dione, to provide an α-methyl, non-natural amino acid (NNAA) building block equipped with a phthalimide group in good yield in multistep synthesis with no sign of any minor diastereomers. The identity of new compound was confirmed by ^{1}H, ^{13}C NMR and mass spectrometry. With this building block in hand, peptides can be produced for evaluation in a variety of therapeutic areas in drug discovery.

Keywords: asymmetric synthesis, non-natural amino acids, chiral auxiliary

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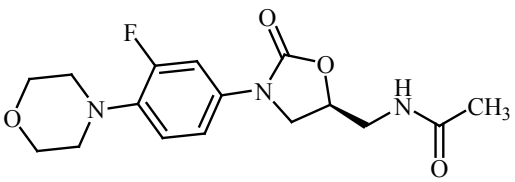
INTRODUCTION

An essential tool in contemporary organic chemistry synthesis is asymmetric synthesis, which is the process of constructing complicated compounds as single enantiomers from very easy and accessible starting materials [1]. Since practically all recently released chiral medications are sold as single enantiomers [2], these single enantiomers are crucial to drug development in the pharmaceutical business. The application of a chiral auxiliary is among the most often used techniques for asymmetric synthesis. Three crucial requirements must be fulfilled for the application of the chiral auxiliaries' approach to be advantageous: It should first mediate a transition that is very diastereoselective. Second, it needs to be simple to remove without causing the newly formed stereogenic center or centers to become racemized. Third, it must be easily bonded to the substrate in both enantiomerically pure forms.

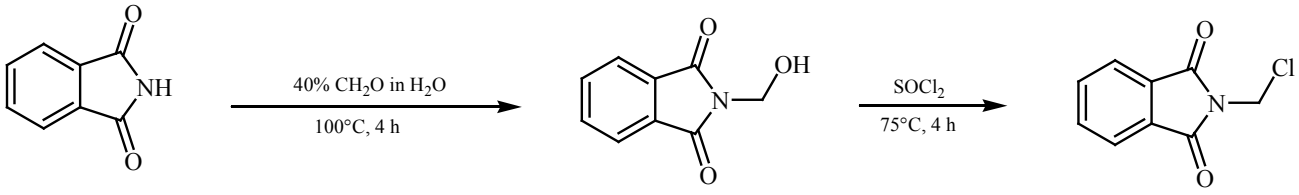
Several chiral auxiliaries that meet these requirements have been developed in the literature [3], however, the class of chiral oxazolidinones developed by David Evans have proved to be the gold standard [4]. These chiral auxiliaries have been successful in directing many diastereoselective alkylations, α-aminations, aldol additions, Diels-Alder cycloadditions, and Michael additions. Most significantly, these reactions can provide beneficial enantiopure intermediates that can be utilized in manufacturing and medication preparation. Compounds with an oxazolidine ring have great importance due to their presence in several biologically active synthetic products. An example of that is the linezolid compound which is oxazolidin-2-ones considered as a new antimicrobial class developed in the past 30 years (Scheme 1) [5].

Using chiral 8-phenylmenthol, Corey made the initial discovery and introduction of chiral auxiliaries in 1975 [6]. Trost then discovered chiral mandelic acid [7]. Since menthol is hard to make, Whitesell invented trans-2-phenyl-1-cyclohexanol in 1985 as a substitute [8]. The chiral oxazolidinones created and published by Evans are without a doubt the most effective and widely utilized chiral auxiliaries with several applications. One 2-oxazolidone is a component of the class of chemicals

Scheme 1.

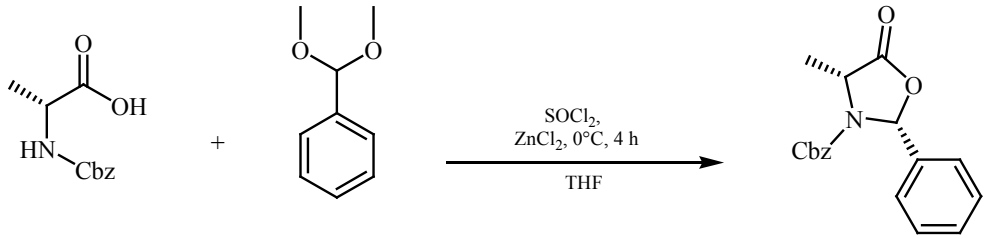


Scheme 2.



1 **2** quantitative yield **3** quantitative yield

Scheme 3.



4 **5** **6** (56%)

known as oxazolidinones. 2-Oxazolidone is a heterocyclic molecule with a 5-membered ring that contains both nitrogen and oxygen. Typically, chiral natural amino acids are used to make them [9–15].

Diastereoselective alkylation is one of the most well-known and best-executed processes of acylated Evans' oxazolidinones. Evans' approach is widely used by organic synthetic chemists despite the benefits of asymmetric catalysis, particularly when optically pure carboxylic acid derivatives are needed as intermediate or end products. The use of chiral auxiliaries is still a highly important and common method for asymmetric synthesis, even though it is not as elegant as asymmetric catalysis. Accordingly, Evans and colleague's complete synthesis of cytovaricin is regarded as a classic use of oxazolidinones as chiral auxiliaries for the four asymmetric aldol reactions and one asymmetric alkylation needed to install of the nine stereogenic centers found in cytovaricin [16–19].

Peptide-based therapeutic initiatives have closed the gap with small-molecule-focused pharmaceutical initiatives. Backbone modifications, such as α-methylation with non-natural amino acids (NNAAs), have contributed to peptide longevity [20–22]. Nevertheless, there are very few α-methyl amino acids present commercially but they are highly costly. By using peptide-based prospects, the creation of a universal synthetic technique to prepare a broad range of α-methyl NNAAs would be a major advancement in drug discovery.

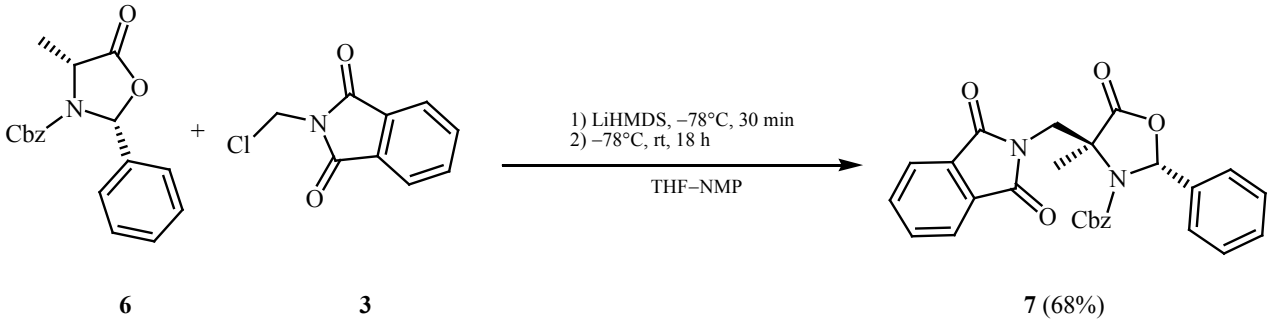
In this work, by using 2-chloromethyl-isoindole-1,3-dione **3** with (2*R*,4*R*)-4-methyl-5-oxo-2-phenyl-1,3-oxazolidine-3-carboxylate **6**, we introduce a novel diastereoselective alkylation procedure for the Evans chiral auxiliary.

RESULTS AND DISCUSSION

The purpose of this article is to report a new procedure regarding Evans' diastereoselective alkylation of (2*R*,4*R*)-4-methyl-5-oxo-2-phenyl-1,3-oxazolidine-3-carboxylate **6** with 2-chloromethyl-isoindole-1,3-dione **3**. The diastereoselective alkylation of (2*R*,4*R*)-4-methyl-5-oxo-2-phenyl-1,3-oxazolidine-3-carboxylate **6** with 2-chloromethyl-isoindole-1,3-dione **3** is the last stage of the multistep synthesis to give compound **7** as a white solid (68% yield) as shown in Schemes 2–4.

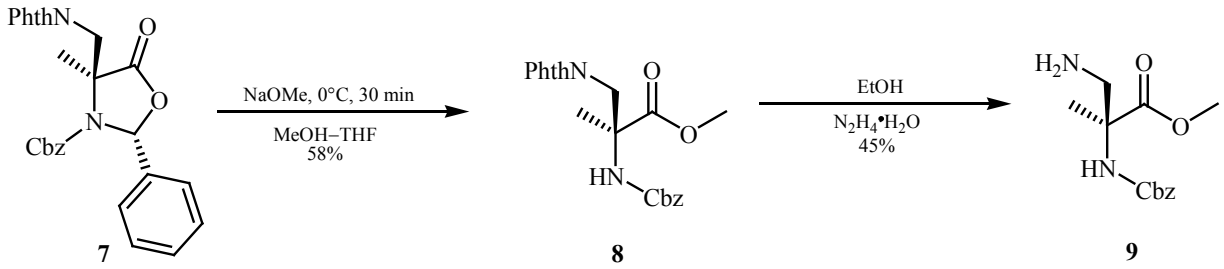
In the first case, I envisioned beginning with a starting substance that was available in both enantiomeric form and chiral, as well as optically pure. cyclization of Cbz-protected D-alanine with benzaldehyde dimethyl acetal yielded **6** after recrystallization as a single isomer. After compound **6**'s lithium enolate was generated

Scheme 4.



6 **3** **7** (68%)

Scheme 5.



7 **8** **9**

and quenched with compound **3** chirality transfer was accomplished, yielding compound **7**, with no indication of any minor diastereomers [23].

The identity of the α-methyl, non-natural amino acid (NNAA) building block equipped with a phthalimide moiety compound **7** has been confirmed by NMR and HRMS. The experiments have been carried out in DMSO-d_6 at 100°C. This product **7** is a potential building block for peptide synthesis, as shown in Scheme 5, transesterification of compound **7** leads to compound **8** in 58% yield, which can be transformed into amino acid derivatives upon the removal of the phthalimide moiety to yield compound **9** in 45% yield.

In summary, a multistep synthesis was used to prepare compound **7**, an α-methyl non-natural amino acid (NNAA) building block with a phthalimide group tail, in good yield. Generation of the lithium enolate for compound **6** and quenching with chloride **3**, completing chirality transfer yielding compound **7**, and showing no signs of minor diastereomers. The non-natural amino acid (NNAA) building block α-methyl can be utilized in the drug discovery and peptide production processes [24–28].

CONCLUSIONS

An α-methyl, non-natural amino acid (NNAA) building block with a phthalimide group tail compound **7** was prepared using a multistep synthetic route in high yield with no indication of minor diastereomers. The widely used and well-understood Evans oxazolidinone system is used to illustrate the power of chiral auxiliaries in asymmetric synthesis. In the future, this α-methyl non-natural amino acid (NNAA) building block may be a promising choice for peptide production and drug development.

EXPERIMENTAL

All reagents were obtained from commercial vendors (Sigma-Aldrich, Combi-Blocks, AmBeed, Fisher Scientific) and used as supplied. NMR spectra (^{1}H, ^{13}C) were obtained on an Agilent VNMRS Varian VNMRS 500 MHz spectrometer. The chemical shifts are referenced to the residual solvent signal (DMSO-d_6). HRMS analyses of compounds were performed on an Agilent Technologies 6220 oaTOF instrument (ESI, APPI, APCI) in positive or negative ionization mode.

LiHMDS is a moisture sensitive material and should be handled under an inert atmosphere, such as nitrogen or argon, to prevent exposure to air.

2-Chloromethyl-isoindole-1,3-dione (3). Compound **3** was prepared according to a literature procedure [29]. A solution of phthalimide **1** and formaldehyde (40% M/V solution in water) in water (40 mL) was stirred at 100°C for 6 h. The mixture was then cooled to room temperature and filtered. The precipitate was washed several times with water and pentane and dried to provide 2-hydroxymethyl-isoindole-1,3-dione **2** in quantitative yield. In the next step, compound **2** and thionyl chloride were stirred under argon at 75°C for 4 h. The mixture was then cooled to room temperature. Thionyl chloride was removed under reduced pressure. The residue was diluted with dichloromethane and the solvent was evaporated under reduce pressure. This procedure was repeated 5 times to afford 2-chloromethyl-isoindole-1,3-dione **3** in quantitative yield.

(2*R*,4*R*)-4-Methyl-5-oxo-2-phenyl-1,3-oxazolidine-3-carboxylate (6). Compound **6** was synthesized according to a literature procedure [30]. In a dry flask under N_2, Cbz-D-alanine **4** (1.0 equiv.) and benzaldehyde dimethyl acetal **5** (1.025 equiv.) were dissolved in dry tetrahydrofuran and cooled to 0°C. $SOCl_2$ (1.1 equiv.) was added dropwise, and after stirring 10 min, $ZnCl_2$ (1.1 equiv.) was added, and the solution further stirred for 4 h at 0°C. The reaction was quenched with the dropwise addition of ice water, followed by the addition of sodium bicarbonate solution until pH = 4. The mixture was diluted in water and extracted with ether three times, and the organic layers were washed with brine, dried over anhydrous sodium sulfate, and evaporated to dryness in vacuum. Crude product was dissolved in a minimum of ether, cooled to room temperature, and product was precipitated by the dropwise addition of hexanes over 6 h to yield the product in 56% yield.

Benzyl (2*R*,4*S*)-4-[(1,3-dioxoisoindolin-2-yl)-methyl]-4-methyl-5-oxo-2-phenyloxazolidine-3-carboxylate (7). In a dry flask under N_2, (2*R*,4*R*)-4-methyl-5-oxo-2-phenyl-1,3-oxazolidine-3-carboxylate **6** (9.2 g, 29.6 mmol, 1.0 equiv.) was dissolved in dry THF (144 mL) and *N*-methyl-2-pyrrolidone (NMP) (24 mL), and the solution was cooled to –78°C. Lithium bis(trimethylsilyl)amide (LiHMDS) (1.0 M) in THF (30.8 mL, 30.8 mmol, 1.3 equiv.) was added dropwise to the solution, and after stirring for 10 min, compound **3** (13.9 g, 71.1 mmol, 3.0 equiv.) was added dropwise. The reaction was allowed to warm gradually to rt over 18 h and quenched with ammonium chloride (NH_4Cl) solution, after which it was diluted with H_2O, and extracted with DCM (×3). Organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4, and evaporated to dryness in vacuum. The residue was purified by column chromatography with a gradient of 0–30% ethyl acetate in hexanes (v/v) to yield 9.5 g (20.1 mmol) of **7** as a white solid (68% yield). ^{1}H NMR spectrum (500 MHz, DMSO-d_6, 100°C), δ, ppm: 1.87 s (3H), 4.16 d (1H, *J* 14.4 Hz), 4.38 d (1H, *J* 14.4 Hz), 5.05 s (2H), 6.40 s (1H), 6.93–7.34 m (5H), 7.34–7.52 m (5H), 7.78–8.02 m (4H). ^{13}C NMR spectrum (126 MHz, DMSO-d_6, 100°C), δ_C, ppm: 22.66, 61.88, 67.44, 89.15, 123.81, 127.22, 127.90, 128.28, 128.64, 129.06, 130.15, 135.13, 131.90, 136.04, 137.40, 151.96, 168.02, 172.05. Mass-spectrum (HRMS-ESI): 493.1383 $[M + Na]^+$ (calcd for $C_{27}H_{22}N_2O_6$: 493.1370).

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CONFLICT OF INTEREST

The authors of this work declare that they have no conflicts of interest.

SUPPLEMENTARY INFORMATION

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