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The synthesis of optically enriched 2-benzyl-3-nitropropionic amide

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Abstract: The present communication describes a valuable procedure for the short and facile synthesis of a thermolysin inhibitor, i.e. optically enriched 2-benzyl-3-nitropropionic amide, successfully synthesized by virtue of a diastereoisomeric mixture intermediate, starting from commercially available *tert*-butyl acrylate; (S)-phenylethylamine is used as a source of the amino group in the amide. The reported synthetic route is substantially shorter than literature reports and provides the desired products in significantly higher overall yields. The whole process yields a significant reduction of waste products.

Keywords: 2-benzyl-3-nitropropionic amide; optically enriched; (S)-phenylethylamine; thermolysin inhibitor.

1 Introduction

Asymmetric compounds show great utility as tools for probing enzyme-associated biomolecule events as well as promising therapeutic leads. The mechanism by which chirality is introduced varies but includes screening of chiral libraries, incorporation of chiral centers during optimization efforts and the rational installation of a chiral moiety as guided by structural and modeling efforts. Stereochemistry plays an important role in terms of potency and selectivity [1–4].

β-Nitro carboxylic acids are valuable precursors for the synthesis of β-amino acids which have been used as non-natural chiral building blocks. β-Nitro carboxylic acids bearing an extra substituent in the α-position adjacent to the carboxyl moiety can be accessed in Michael addition reactions [5], enzymatic kinetic resolution [6], chemoenzymatic approach [7] and Pd-catalyzed asymmetric conjugate addition [8]. β-Nitro carboxylic acids and their derivatives are frequently found in enzyme inhibitors as optically active compounds with the chiral center at the α-position [9]. (R)-2-Benzyl-3-nitropropionic amide (*K*i=7.6 μm) is screened as an inhibitor to examine the thermolysin inhibition effect of stereochemistry, which was previously synthesized from commercially available diethylmalonate in 13 steps. Such a synthetic route is not only cumbersome, but also not very effective, with a yield of 2% (Table 1), departing from the core to green chemistry research [10]. At present, a number of preparative techniques used in the resolution of enantiomers are widely presented, for instance, crystallization techniques, chromatographic techniques and enzymatic kinetic resolution. The chromatographic separation process can be applied either to a mixture of enantiomers or to diastereomeric derivatives that are obtained by reaction with chiral derivatizing agents [11]. Thus, another pathway is designed to reduce the economic cost, and promote the following optical molecular to come into being (Scheme 1). An effective and new route is designed and synthesized.

2 Materials and methods

Flash chromatography was performed with 100–200 mesh silica gel (Qingdao Marine Chemical Plant, Qingdao City, Shandong, China) and thin layer chromatography (TLC) was carried out on silica coated glass sheets (Qingdao silica gel 60 F-254, Qingdao Marine Chemical Plant, Qingdao City, Shandong, China). Melting points were checked by a Thomas-Hoover capillary apparatus (Arthur H. Thomas Company, Beaver County, PA, USA). ^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR spectra were recorded with a Bruker AV300 (300 MHz, Bruker Corporation, Switzerland) instrument using tetramethylsilane as the internal standard. IR spectra were recorded on a Perkin-Elmer 1300 (PerkinElmer, MA, USA). Mass spectra were taken on Agilent 1100-HPLC/MSD (G1946A, Agilent Technologies, Santa Clara, CA, USA). Elemental analyses were performed on 2400 elemental analyzer (PerkinElmer, MA, USA).

2.1 *tert*-Butyl ester 3-nitropropionate

A round-bottomed flask (500 ml) was equipped with a magnetic stirring bar, and a pressure-equalizing dropping funnel (50 ml) charged with sodium nitrite (21.8 g, 0.3 mol), water (60 ml) and tetrahydrofuran (100 ml) was applied. Under the well-stirring solution at 0°C, *tert*-butyl acrylate (14.0 g, 0.3 mol), and then acetic acid (16.5 g,

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Table 1: Different synthetic route of (R)-2-benzyl-3-nitropropionic amide [10].

Route	Synthetic steps	Total yields	Conditions
Previous	13	2%	Cumbersome
This work	5	13%, 15%	Viable

0.3 mol) were added by droplet over a period of 45 min. The reaction mixture was continuously stirred at 0°C for another 3 h. Then, ethyl acetate (125 ml) and aqueous saturated sodium bicarbonate (50 ml) were added for complete neutralization. The organic layers were combined, and dried with anhydrous magnesium sulfate. The yellow oil was obtained after the organic phase was submitted to azeotropic distillation with toluene (2×25 ml) in order to remove residual water and acetic acid, which yielded 9.4 g (49%) of crude product.

IR (film) 2980, 2934, 1731, 1560, 1159 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 4.60 (t, 2H, *J*=6.0 Hz), 2.88 (t, 2H, *J*=6.0 Hz), 1.46 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.52, 82.17, 70.01, 32.17, 27.91.

2.2 *tert*-Butyl ester 2-benzyl-3-nitropropanoate

Butyl lithium (4.0 ml, 1.6 mol/ml in hexane, 0.6 mmol) was added to a solution of diisopropylamine (0.9 ml, 0.6 mmol) and hexamethyl phosphoryl triamide (1.8 g, 14 mmol) in dry tetrahydrofuran (40 ml) at -78°C. The solution was stirred for 50 min, and then *tert*-butyl ester 3-nitropropionate (0.4 g, 2.8 mmol) and benzyl bromide (4 ml, 3.5 mmol) were added. Diethyl ether (50 ml) was added after 5 h of stirring. The combined organic layers were washed with water (100 ml), and dried over anhydrous magnesium sulfate. The crude reaction mixture was purified by column chromatography eluting with ethyl acetate: light petroleum=1:9 to give the desired product (70%).

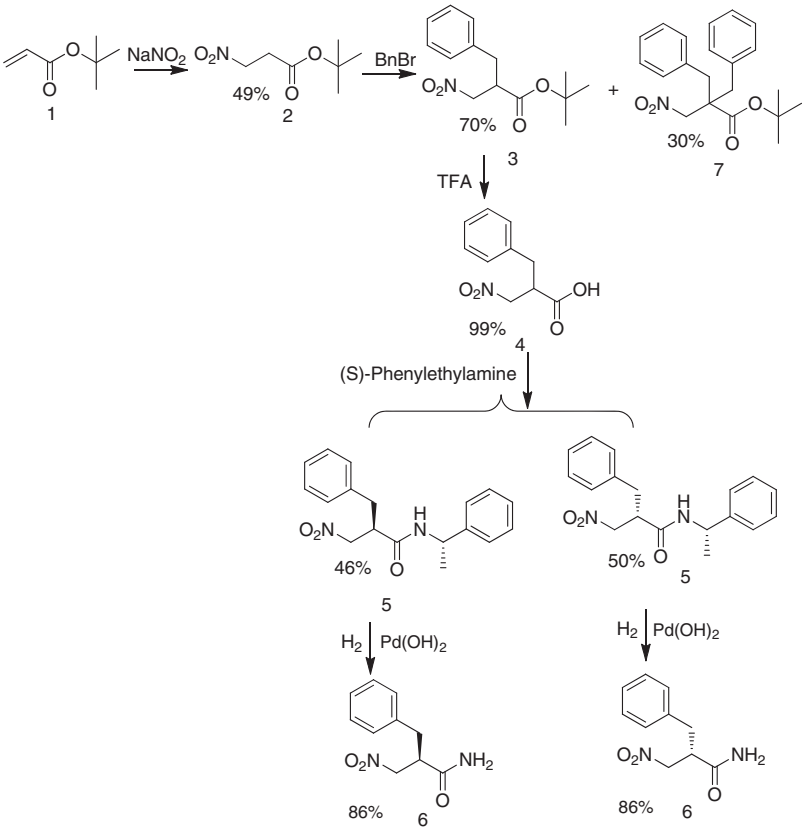
Rf: 0.5 (ethyl acetate: light petroleum=10:1). IR (KBr) 3300, 1735, 1563, 1370 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.18 (m, 5H), 4.62 (dd, *J*=4.3, 10.0 Hz, 1H), 4.32 (dd, *J*=4.3, 10.0 Hz, 1H), 3.39–3.34 (m, 1H), 3.08 (dd, *J*=5.3, 8.0 Hz, 1H), 2.81 (dd, *J*=5.3, 8.0 Hz, 1H), 1.38 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.61, 136.73, 128.98, 128.81, 127.29, 82.24, 74.52, 45.31, 35.19, 27.72. MS (APCI), m/e=264 $[M-1]^+$. Anal. Calcd. for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.38; H, 7.21; N, 5.29.

2.3 *tert*-Butyl ester 2,2-dibenzyl-3-nitropropanoate

Yield, 30%. Rf: 0.7 (ethyl acetate:light petroleum=10:1). IR (KBr) 3300, 1735, 1563, 1370 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55–7.14 (m, 10H), 4.39 (s, 2H), 3.32 (d, *J*=13.8 Hz, 2H), 3.06 (d, *J*=13.8 Hz, 2H), 1.32 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.20, 135.57, 130.49, 128.48, 127.25, 82.84, 75.18, 51.46, 40.96, 27.72. Anal. Calcd. for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.96; H, 7.08; N, 3.93.

2.4 (R,S)-2-Benzyl-3-nitropropanoic acid

Trifluoroacetic acid (3.6 ml, 47.2 mmol) was added to a solution of *tert*-butyl ester 2-benzyl-3-nitropropionate (40 mg, 1.5 mmol) in



Scheme 1: The synthesis of optically enriched 2-benzyl-3-nitropropionic amide.

dichloromethane (10 ml). The mixture was stirred at room temperature for 24 h and then concentrated to produce the acid as an oil (99%).

IR (KBr) 3429, 1718, 1563, 1370, 1016 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 9.22 (br, 1H), 7.39–7.19 (m, 5H), 4.66 (dd, *J*=5.2, 12.6 Hz, 1H), 3.90 (dd, *J*=5.2, 12.6 Hz, 1H), 3.70–3.30 (m, 1H), 3.41 (dd, *J*=5.3, 13.9 Hz, 1H), 2.88 (dd, *J*=5.3, 13.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.01, 136.08, 129.11, 128.87, 127.57, 73.52, 44.3, 34.78. MS (ACPI), m/e=208 $[M-1]^+$.

2.5 Diastereoisomeric mixture

Isobutyl chloroformate (700 µl, 0.9 mmol) and 4-methylmorpholine (700 µl, 0.9 mmol) were added to an ice-chilled stirred solution of 2-benzyl-3-nitropropanoic acid (177 mg, 0.9 mmol) in dichloromethane (5 ml). The resulting mixture was stirred for 30 min at 0°C. After that, (S)-phenyl ethylamine (110 µl, 0.9 mmol) was added to the mixture, and then was stirred for 1 h at room temperature. After removal of the solvent, the residue was extracted with ethyl acetate (50×3 ml), and the organic layer dried over anhydrous magnesium sulfate. The crude product was obtained as the diastereoisomeric mixture (2R,1′R)-2-nitro-3-phenyl-N-(1′-phenylethyl)-propionic amide and (2S,1′R)-2-nitro- 3-phenyl-N-(1′-phenylethyl)-propionic amide (96%).

IR (KBr) 3457, 1736, 1570, 1363 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.12 (m, 20H), 5.57 (d, *J*=6.9 Hz, 1H), 5.41 (d, *J*=6.9 Hz, 1H), 5.12–4.95 (m, 2H), 4.92 (d, *J*=9.6 Hz, 1H), 4.87 (d, *J*=9.6 Hz, 1H), 4.43 (t, *J*=5.0 Hz, 1H), 4.38 (t, *J*=5.0 Hz, 1H), 3.25–3.09 (m, 2H), 2.99–2.71 (m, 4H), 1.44 (d, *J*=6.9 Hz, 1H), 1.21 (d, *J*=6.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.67, 169.58, 142.30, 142.20, 137.16, 136.88, 128.97, 128.85, 128.68, 128.56, 127.46, 127.34, 127.17, 126.12, 125.98, 75.71, 75.44, 48.94, 48.89, 46.99, 46.97, 36.31, 36.04, 21.22, 21.12.

2.6 Preparative liquid chromatography

Diastereoisomer mixture (71 mg) was detected at a wavelength of 240 nm. The HPLC system consisted of HITACHI Model L-7100 pumps (Tokyo, Japan), Tosoh Model AS-8020 auto injector (Tokyo, Japan), SHIMAZU Model SPD-10AV detector (Tokyo, Japan) and HITACHI Model D-7500 integrator (Tokyo, Japan). The guard column, Inertsil ODS-3 (1.0×4.0 cm I.D., 3 mm) was placed between the auto injector and the separative column, Inertsil ODS-3 (250×4.6 mm I.D., 3 mm). The mobile phase was methanol-water=3:1 and was degassed by sonication. The column was maintained at 40°C with a flow rate of 0.5 ml/min. The entire mobile phase contained target compounds combined, and dried over anhydrous magnesium sulfate.

2.7 (2S,1′R)-2-Nitro-3-phenyl-N-(1′-phenylethyl)-propionic amide

(46%, 32 mg); Mp 147–148.5°C; IR (KBr) 3457, 1736, 1570, 1363 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.18 (m, 10H), 5.41 (d, *J*=6.9 Hz, 1H), 5.00–4.95 (m, 1H), 4.87 (d, *J*=6.9 Hz, 1H), 4.38 (t, *J*=4.8 Hz, 1H), 3.25–3.09 (m, 1H), 2.80–2.71 (m, 2H), 1.21 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.58, 142.30, 137.16, 128.85, 128.68, 127.46, 127.34, 125.98, 75.44, 48.89, 46.97, 36.31, 21.12. Anal. Calcd. for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.21; H, 6.44; N, 8.96.

2.8 (2R,1′R)-2-Nitro-3-phenyl-N-(1′-phenylethyl)-propionic amide

(50%, 35 mg); Mp 147–148.5°C; IR (KBr) 3457, 1736, 1570, 1363 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26–7.12 (m, 10H), 5.57 (d, *J*=6.9 Hz, 1H), 5.12–5.00 (m, 1H), 4.92 (d, *J*=6.9 Hz, 1H), 4.43 (t, *J*=5.0 Hz, 1H), 3.25–3.09 (m, 1H), 2.89–2.86 (m, 2H), 1.44 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.67, 142.20, 136.88, 128.97, 128.56, 127.46, 127.17, 126.12, 75.71, 48.94, 46.99, 36.04, 21.22. Anal. Calcd. for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.21; H, 6.44; N, 8.96.

2.9 (R)-2-Benzyl-3-nitro-propionic amide

(2R,1′R)-2-Nitro-3-phenyl-N-(1′-phenylethyl)-propionic amide (35 mg, 0.1 mmol) was dissolved in methanol (1 ml) containing water (100 µl) and acetic acid (30 µl), and was subjected to hydrogenolysis in the presence of palladium hydroxide (20 wt.%, 20 mg) under hydrogen for 24 h at room temperature. Recrystallization in diethyl ether provided a white solid as a product (86%).

Mp 106–107°C; [α]=+40.5° (*c* 0.49, methanol). IR (KBr) 3457, 1736, 1570, 1363 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16–7.34 (m, 5H), 5.61 (s, 1H), 5.48 (s, 1H), 4.81 (dd, *J*=4.8, 9.7 Hz, 1H), 4.49 (dd, *J*=4.8, 9.7 Hz, 1H), 3.30–3.37 (m, 1H), 3.00 (dd, *J*=5.2, 7.7 Hz, 1H), 2.78 (dd, *J*=5.2, 7.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.23, 136.77, 129.03, 128.87, 127.41, 75.12, 45.84, 36.06. MS (APCI) m/e: 209 $[M+1]^+$. Anal. Calcd for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81; N, 13.45. Found: C, 57.67; H, 5.80; N, 13.46.

2.10 (S)-2-Benzyl-3-nitro-propionic amide

With the same procedure, (2S,1′R)-2-nitro-3-phenyl-N-(1′-phenylethyl)-propionic amide (32 mg, 0.1 mmol) is converted to the target product (18.6 mg, 86%) .

Mp 106–107°C; [α]=-40.0° (*c* 0.32, methanol). IR (KBr) 3457, 1736, 1570, 1363 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16–7.34 (m, 5H), 5.61 (s, 1H), 5.48 (s, 1H), 4.81 (dd, *J*=4.8, 9.7 Hz, 1H), 4.49 (dd, *J*=4.8, 9.7 Hz, 1H), 3.30–3.37 (m, 1H), 3.00 (dd, *J*=5.2, 7.7 Hz, 1H), 2.78 (dd, *J*=5.2, 7.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.23, 136.77, 129.03, 128.87, 127.41, 75.12, 45.84, 36.06. MS (APCI) m/e: 209 $[M+1]^+$. Anal. Calcd for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81; N, 13.45. Found: C, 57.67; H, 5.80; N, 13.46.

3 Results and discussion

One thing that should be noted is that saponification of methyl ester 2-benzyl-3-nitropropionate gave an impure product that required purification by silica gel column chromatography, as reported [12]. However, acidic hydrolysis of methyl ester 2-benzyl-3-nitropropionate also gave impure nitro acid. The amount of this by-product increased when the reaction time or the HCl concentration was increased. Thus, the homologous *tert*-butyl ester is rational selective in this paper. *tert*-Butyl acrylate (**1**) is used as starting material in our five-step synthesis route [13].

tert-Butyl 3-nitropropionate (**2**) [14, 15] is obtained from **1** by nitration with a yield of 49%. Furthermore, *tert*-butyl ester 2-benzyl-3-nitropropionate (**3**) [16–18] is proceeded in a yield of 70% by means of the alkylation of the dianion of **2**. *tert*-Butyl 2,2-dibenzyl-3-nitropropanoate (**7**) is also formed due to carbon alkylation of α,α-doubly deprotonated nitroalkane (Scheme 1). Subsequently, **3** is treated with trifluoroacetic acid to produce 2-benzyl-3-nitropropionic acid (**4**) in 99% yield. Unfortunately, one observation is that diastereoisomeric salts of **4** which are obtained with (R)- or (S)-phenylethylamine obtained by optical resolution via crystallization, failed [19, 20].

Consequently, **4** is coupled with (S)-phenylethylamine using isobutyl chloroformate in the presence of 4-methylmorpholine [21, 22], resulting in clean conversion to the diastereoisomeric mixture of amides (**5**). The ratio of diastereomer (1:1) is calculated by ^{1}H NMR spectra in the mixture [23]. However, mixture **5** cannot be performed by most of the chromatography techniques, such as medium pressure liquid chromatography, thin layer chromatography or flash column chromatography. Furthermore, even by applying different adsorbent materials (such as silica gel, aluminum oxide, etc.) and mobile phase, i.e. different solvent or solvent mixture, in a similar result, separation of **5** was also not achieved. Fortunately, the first eluted component (retention time: 8.8 min), then the second (retention time: 13.0 min), can be produced by preparative HPLC from **5.** Good resolution for the chromatogram of **5** can be achieved when tuning the elution mobile to methanol:water=3:1. The configuration of the isolated amides is in agreement with the assignment of the two diastereoisomers (2S,1′R)-2-acetoxymethyl-3-phenyl-N-(1′-phenyl ethyl)-propionic amide and (2R,1′R)-2-acetoxymethyl-3-phenyl-N-(1′-phenyl ethyl)-propionic amide. The obtained amides were subjected to hydrogenolysis in methanol and palladium hydroxide on charcoal, respectively, to produce optically enriched 2-benzyl-3-nitropropionic amide (**6**) [10]. The nitro group is particularly insusceptible during the hydrogenolysis process.

In this work, the optical activity of **6** is identical to previous work. Compared with previous work, higher total yields have been achieved with a shorter synthetic route (Table 1); in other words, the new pathway is more effective and viable. This new facile synthetic route has shortened the process into a five-step pathway compared with the previous 13-step pathway, with total yields as high as 13%, 15%. Beyond that, the synthetic conditions are viable, not cumbersome. The approach offers attractive advantages including fewer steps, inexpensive cost, and withdrawal of susceptible acid-base conditions; effective tools for the synthesis of biologically relevant molecules are provided.

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Bionotes

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