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Nucleophilic addition to nitroacrylates: application towards the synthesis of 2,3-dehydroamino acids and 2,3-diamino acids

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ABSTRACT

The addition of the *N*-pronucleophiles to 2- or 3-nitro-2-alkenoates in the presence of base provided Michael addition products. In the case of 3-nitro compounds, reaction occurred via the formation of α-adducts and the subsequent elimination of nitrous acid to produce olefins with high *Z* stereoselectivity. 3-Phthalimido-2-nitrocinnamate adduct **8a** was converted into 2,3-diamino ester **11a**.

1. Introduction

The Michael addition between various nucleophiles and α,β-unsaturated alkenoates in most cases occurs regioselectively at the β-position to give the β-adduct.[1] The regioselectivity of the Michael reaction can be reversed by attaching groups with strongly electron-withdrawing properties at the β-carbon, which leads to the formation of the α-substituted products.[2] It was also predicted, based on the theoretical calculations that methyl 3-nitropropenoate should react with nucleophiles to give a α-substituted adduct.[3] This approach has been employed in the synthesis of aliphatic α-thioacrylates,[4a] polyfunctionalized α,β-unsaturated esters[4b] and very recently in the uncatalyzed α-addition of amines to β-nitroacrylates.[4c] We have decided to investigate the addition of nitrogen nucleophiles to β-nitroacrylates as α-Michael acceptors and α-nitroacrylates as conjugate Michael acceptors. The expected α-amino-β-nitro or β-amino-α-nitroadducts after subsequent reduction of nitro group would lead to the formation of α,β-diamino acids or to α,β-dehydroamino acids after β-elimination of HNO_2. α,β-Diaminocarboxylic acids[5] and α,β-dehydroamino acids[6] are constituents of several natural products and biologically active molecules. Considering the potential of these classes of amino acids, developing new methodologies for their synthesis have been undertaken.

Mioskowski and co-workers recently utilized the reaction of 3,3,3-trifluoro-1-nitropropene with *N*-nucleophiles for the synthesis of vicinal diamines.[7] In the past years a number of synthetic routes to 2,3-diaminocarboxylic acids of variable length, yields and complexity have been reported.[5] However, to the best of our knowledge, the conjugate addition of nitrogen nucleophiles to nitro-Michael acceptors towards the synthesis of 2,3-diamino acids has been only reported in a study for a synthesis of an angiotensin II analogue.[8] Herein, we report studies on the nucleophilic addition of *N*-pronucleophiles to α- and β-nitroacrylates as Michael acceptors in a new approach towards the synthesis of 2,3-diamino and *N*-protected 2,3-dehydroamino acid derivatives.

2. Results and discussion

We started with the investigation of anti-Michael addition of nitrogen pronucleophiles such as imides and carbamates to β-nitroacrylates. The 3-nitrocrotonate **1a** was prepared by reaction of the corresponding acrylic ester with $NaNO_2$–ceric ammonium nitrate (CAN) as reported.[9] The 3-nitropentenoate **1b** and β-nitrocinnamic esters **1c–d** were obtained by the nitroaldol (Henry) reaction between the appropriate nitroalkanes and ethyl glyoxalate as described.[10,11] The 3-nitroacrylates **1a–b** were obtained as single *E*-isomers while β-nitrocinnamates **1c–d** were prepared as mixtures of *E* and *Z* isomers. Initially, we studied nucleophilic addition of the anion derived from phthalimide as a source of the amino group. Thus, treatment of 3-nitrocrotonate (*E*)-**1a** with phthalimide in the presence of DBU (in acetonitrile at −10 °C) initially produced the anti-Michael addition product **4a** (TLC), which underwent subsequent in-situ elimination of HNO_2 to produce stable 2-*N*-phthalimido-2-butenoate **5a** as a single *Z*-isomer (84%; Table 1, entry 1). Analogous treatment of β-nitrocinnamate **1c** gave

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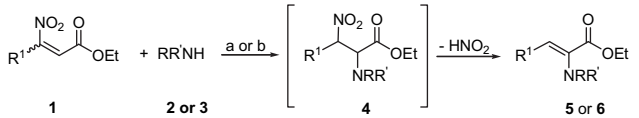
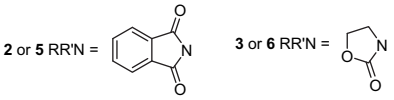
Table 1
Addition of nitrogen nucleophiles to ethyl-β-nitroacrylates



Series: **a** R^1 = Me; **b** R^1 = Et; **c** R^1 = Ph; **d** R^1 = 4-Me-Ph



Reagents and condition: (a) DBU/CH_3CN/0°C; (b) BuLi/THF/-20°C

Entry	Substrate	Nucleophile	Product	Yield[a] (%)	Condition
1	**1a** (*E*)	**2**	**5a**	84	a
2	**1b** (*E*)	**2**	**5b**	81	a
3	**1c** (*E*)	**2**	**5c**	98	a
4	**1d** (*E*/*Z*)	**2**	**5d**	87	a
5	**1a** (*E*)	**3**	**6a**	58	b
6	**1b** (*E*)	**3**	**6b**	48	b
7	**1c** (*E*)	**3**	**6c**	60	a
8	**1d** (*E*/*Z*)	**3**	**6d**	64	a

[a] Isolated yield.

a separable mixture of the olefin **5c** and the unstable α-addition product **4c** (2:1, estimated by ^{1}H NMR spectroscopy). The ^{1}H NMR spectrum of **4c** showed that the adduct (3:1 mixture of two diastereoisomers) is derived from α-addition of phthalimide to β-nitrocinnnamate **1c**. The presence of two sets of doublets (d, J=10.7 Hz for the major isomer, and J=11.4 Hz for the minor one) corresponds to the hydrogens at C2 and C3 instead of signals for two hydrogens at C2. Numerous attempts to prepare exclusively the α-addition product **4c** failed. On the other hand, we found that reaction of **1c** with 3.6 equiv of phthalimide in the presence of DBU/MeCN afforded exclusively product (*Z*)-**5c** (98%, entry 3). The ^{1}H NMR spectrum of (*Z*)-**5c** reveals that the chemical shift of the β-vinyl proton signal occurs at 8.11 ppm in agreement with the literature value.[12] Analogous reaction of 3-nitroalkenoates **1b** and **1d** with phthalimide produced olefinic products **5b** and **5d** with good yields and *Z*-stereochemistry (entries 2 and 4).

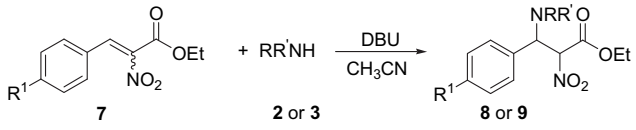
We then turned our attention to the anion resulting from 2-oxazolidinone, which is a moderately basic nitrogen nucleophile, and can be conveniently cleaved from the addition adducts to generate an amino group.[13] Moreover the 4-phenyl-2-oxazolidinone derivative in both enantiomeric forms has been shown to offer control of diastereoselectivity in the Michael addition to nitroalkenes[14] and fluorinated nitroalkenes.[7] However, reaction of β-nitrocinnamate **1c** with 2-oxazolidinone (1.2 equiv) in the presence of DBU (1.2 equiv) in acetonitrile at 0 °C led to the formation of elimination product **6c** as a single *Z*-isomer. The *Z*-stereochemistry for **6c** was established by comparison of the chemical shift of the β-vinyl proton signal (7.71 ppm) with the known[15] *E*-isomer (6.21 ppm). Different reaction conditions (3.6 equiv of 2-oxazolidinone) resulted in the formation of alkenoate **6c** in higher yield (60%, entry 7) rather than affording α-oxazolidin-2-yl addition product of type **4**. Analogous treatment of **1d** with 2-oxazolidinone gave **6d** (64%, entry 8).

Reactions of 2-oxazolidinone with 3-nitroacrylates **1a** and **1b** in the presence of DBU/MeCN also afforded the olefins **6a** and **6b** after β-elimination of HNO_2 but in low yield. Various bases, as well as different solvents and temperatures were tested to optimize the reaction conditions towards the formation these interesting *N*-protected 2,3-dehydroamino acids. It was found the BuLi in THF at −20 °C produced the olefins **6a**–**b** in better yields (entries 5 and 6).

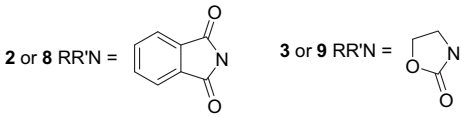
We have envisioned that addition of *N*-pronucleophiles to 2-nitroalkenoates could be utilized as efficient route to β-amino addition products. Very recently, Buevich et al.[10] reported that α-nitrocinnamic esters can be efficiently prepared by the addition of a nitro group to cinnamic esters utilizing $NaNO_2$–ceric ammonium nitrate ($NaNO_2$–CAN) method.[9] Using this methodology the α-nitrocinnamates **7a**–**c** were prepared as a mixture of *E* and *Z* isomers.

Thus, treatment of α-nitrocinnamate (*E*/*Z*)-**7a** with phthalimide (1.2 equiv) in the presence of DBU (1.2 equiv) in acetonitrile, at 0 °C gave stable α-nitro-β-phthalimido product **8a** in 94% yield as a mixture of two diastereoisomers (1:2; Table 2, entry 1). Analogous treatment of the substituted α-nitrocinnamates (*E*/*Z*)-**7b**–**c** also afforded β-adducts **8b**–**c** (entries 2 and 3). Reaction of the α-nitrocinnamates **7a**–**c** with 2-oxazolidinone (1.2 equiv) in the presence of DBU (1.2 equiv) in acetonitrile at 0 °C also provided the α-nitro-β-oxazolidin-2-yl products **9a**–**c** in 56–72% yields (entries 4–6).

Table 2
Addition of nitrogen nucleophiles to ethyl-α-nitroacrylates



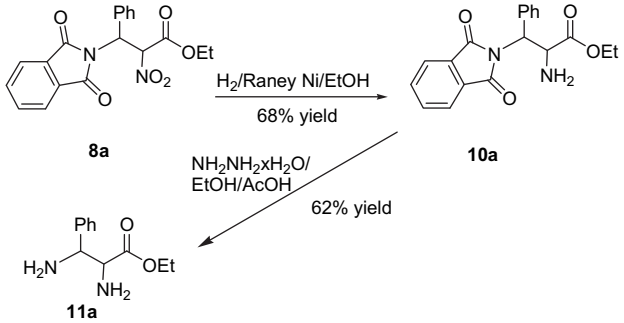
Series: **a** R^1 = H; **b** R^1 = MeO; **c** R^1 = Me



Entry	Substrate	Nucleophile	Product	Yield[a] (%)	Isomers ratio[b]
1	**7a** *E*/*Z* (2:1)	**2**	**8a**	94	2:1
2	**7b** *E*/*Z* (5:2)	**2**	**8b**	81	1.4:1
3	**7c** *E*/*Z* (2:1)	**2**	**8c**	84	1.4:1
4	**7a**	**3**	**9a**	56	3:1
5	**7b**	**3**	**9b**	58	1:1
6	**7c**	**3**	**9c**	72	1:1

[a] Isolated yield.
[b] Estimated from the ^{1}H NMR.

These results clearly indicate that the nitro group at the β-position of the Michael acceptor is an important factor contributing to the stabilization of the α-addition product of type **4**, in which the presence of an acidic hydrogen atom at the α-position to the ester group induces the β-elimination of nitrous acid to form the α,β-unsaturated product of type **5** or **6** in basic conditions. Therefore the 3-nitroacrylates **1a**–**b** and β-nitrocinnamates **1c**–**d** could serve as a convenient precursors to *N*-phthalimido-2,3-dehydroamino acids[16] or enamides of type **6**. α-Nitrocinnamates **7a**–**c**, however, can be converted to 2,3-diamino acids derivatives by reduction of the nitro group and cleavage of the imide[17] or carbamate[13] functionalities in the addition products. To illustrate this approach, the



Scheme 1.

addition product **8a** was transformed into an amino derivative **11a**. Thus, the reduction of nitro group with hydrogen over Raney Ni led to the formation of a 3-*N*-protected 2,3-diamino acid derivative **10a**. Subsequent deprotection with hydrazine[17] afforded 2,3-diamino ester **11a** with spectroscopic data consistent with literature[18] (Scheme 1).

In conclusion, we have demonstrated that the α-addition of *N*-nucleophiles such as phthalimide or 2-oxazolidinone to β-nitroacrylates produced 2-*N*-phthalimido or 2-oxazolidinyl alkenoate derivatives with good yields and excellent *Z* stereoselectivity. Addition of such *N*-nucleophiles to α-nitrocinnamates provided stable β-addition products, which served as precursors to 2,3-diamino esters. Access to the asymmetric synthesis of 2,3-diamino acids using a Michael β-addition approach is currently in progress.

3. Experimental

3.1. General

THF was distilled from sodium/benzophenone and CH_3CN was distilled from CaH_2 under an argon atmosphere. ^1H (400 or 300 MHz) and ^{13}C (100 or 75 MHz) NMR spectra were determined in $CHCl_3$. Mass spectra (MS) and HRMS were obtained with electron impact (EI, 20 eV) unless otherwise noted. Merck Kieselgel 60-F_{254} sheets were used for TLC and products were detected with 254 nm light. Merck Kieselgel 60 (230–400 mesh) was used for column chromatography.

3.2. Ethyl 2-*N*-phthalimido-2(*Z*)-butenoate (5a)

3.2.1. Procedure A. DBU (0.04 mL, 41 mg, 0.27 mmol) was added to a stirred solution of phthalimide (40 mg, 0.27 mmol) in CH_3CN (6 mL) at 0 °C under an argon atmosphere. After 1 h at 0 °C, the reaction mixture was cooled to −10 °C and a solution of **1a** (36 mg, 0.23 mmol) in CH_3CN (1 mL) was added. The resulting mixture was stirred for 30 min at which time TLC showed complete disappearance of **1a**. The reaction mixture was quenched with saturated aqueous NH_4Cl (3 mL) and after being warmed to room temperature, the mixture was extracted with EtOAc (2×8 mL). The combined organic layer was washed with water, brine, dried (Na_2SO_4) and evaporated to dryness under vacuum. The oily residue was column chromatographed ($CHCl_3$) to give **5a** as an oil (49 mg, 84%): IR ($CHCl_3$) 2928, 1790, 1740 cm^{-1}; ^1H NMR δ 1.25 (t, J=7.1 Hz, 3H), 1.83 (d, J=7.1 Hz, 3H), 4.22 (q, J=7.1 Hz, 2H), 7.38 (q, J=7.1 Hz, 1H), 7.74–7.80 (m, 2H), 7.90–7.96 (m, 2H); ^{13}C NMR δ 14.1, 14.5, 61.7, 123.6, 123.8, 132.1, 134.4, 142.9, 162.5, 166.7; HRMS m/z Calcd for $C_{14}H_{13}NO_4$ (M^+) 259.0845, found 259.0839.

3.3. Ethyl 2-*N*-phthalimido-2(*Z*)-pentenoate (5b)

Treatment of **1b** (30 mg, 0.18 mmol) with phthalimide (31 mg, 0.21 mmol) and DBU (31 μL, 32 mg, 0.21 mmol) by procedure A [column chromatographed (EtOAc/hexane 20%→25%)] gave **5b** as an oil (38 mg, 81%): IR ($CHCl_3$) 2930, 1784, 1740 cm^{-1}; ^1H NMR δ 1.11 (t, J=7.7 Hz, 3H), 1.27 (t, J=7.1 Hz, 3H), 2.17 (quintet, J=7.7 Hz, 2H), 4.22 (q, J=7.1 Hz, 2H), 7.30 (t, J=7.7 Hz, 1H), 7.74–7.81 (m, 2H), 7.90–7.97 (m, 2H); ^{13}C NMR δ 12.5, 14.1, 22.2, 61.5, 121.6, 123.8, 132.1, 134.4, 149.8, 162.8, 167.1; HRMS m/z Calcd for $C_{15}H_{15}NO_4$ (M^+) 273.1001, found 273.1027.

3.4. Ethyl 3-nitro-3-phenyl-2-(*N*-phthalimido)propanoate (4c)

Treatment of **1c**(*E*) (38 mg, 0.17 mmol) with phthalimide (30.5 mg, 0.21 mmol) and DBU (31 μL, 31.5 mg, 0.21 mmol) by procedure A gave a mixture (59 mg, non-separable by using EtOAc/hexane 35%→40% system as eluent) of **4c** and **5c** (31:69 based on ^1H NMR spectrum). The mixture of products was separated in 90% CH_2Cl_2/hexane as eluent. Compound **4c** has ^1H NMR (isomers ratio 3:1) major isomer: δ 1.24 (t, J=7.1 Hz, 3H), 4.28 (q, J=7.1 Hz, 2H), 6.14 (d, J=10.7 Hz, 1H), 6.43 (d, J=10.7 Hz, 1H), 7.23–7.29 (m, 3H), 7.39–7.49 (m, 2H), 7.66–7.70 (m, 2H), 7.73–7.76 (m, 2H); ^{13}C NMR δ 13.7, 52.0, 63.1, 87.3, and signals for both of diastereomers: 123.8, 124.0, 128.0, 128.6, 129.1, 130.5, 130.6, 130.8, 131.0, 134.5, 134.7, 165.0, 166.6, 166.61, 166.8; minor isomer: δ 0.97 (t, J=7.1 Hz, 3H), 4.01 (dq, J=3.1, 7.1 Hz, 2H), 5.92 (d, J=11.4 Hz, 1H), 6.66 (d, J=11.4 Hz, 1H), 7.23–7.29 (m, 3H), 7.39–7.49 (m, 2H), 7.78–7.81 (m, 2H), 7.91–7.94 (m, 2H); ^{13}C NMR δ 13.6, 53.6, 62.5, 88.0, and signals listed above; FABMS 369 $[M+H]^+$, 391 $[M+Na]^+$.

3.5. Ethyl 3-phenyl-2-*N*-phthalimido-2(*Z*)-propenoate (5c)

Treatment of **1c** (22 mg, 0.10 mmol) with phthalimide (50 mg, 0.34 mmol) and DBU (17 μL, 17 mg, 0.11 mmol) by procedure A (excess of phthalimide was gel filtered using CH_2Cl_2) gave **5c**[12a] (31 mg, 98%): IR ($CHCl_3$) 2927, 1788, 1723 cm^{-1}; ^1H NMR δ 1.30 (t, J=7.1 Hz, 3H), 4.30 (q, J=7.1 Hz, 2H), 7.27–7.34 (m, 3H), 7.39–7.43 (m, 2H), 7.75–7.80 (m, 2H), 7.86–7.94 (m, 2H), 8.11 (s, 1H); ^{13}C NMR δ 14.5, 62.4, 120.8, 123.9, 124.3, 129.3, 129.7 130.8, 132.5, 132.8, 133.0, 134.7, 134.8, 143.1, 163.50, 167.2, 168.2.

3.6. Ethyl 3-(4-methylphenyl)-2-*N*-phthalimido-2(*Z*)-propenoate (5d)

Treatment of **1d**(*E*/*Z*) (23 mg, 0.1 mmol) with phthalimide (53 mg, 0.36 mmol) and DBU (18 μL, 18.5 mg, 0.12 mmol) by procedure A (using 90:100 CH_2Cl_2/hexane as eluent for column chromatography) gave **5d** as a solidifying oil (29 mg, 87%): IR ($CHCl_3$) 2926, 1794, 1723 cm^{-1}; ^1H NMR: δ 1.30 (t, J=7.1 Hz, 3H), 2.30 (s, 3H), 4.29 (q, J=7.1 Hz, 2H), 7.10 (d, J=8.1 Hz, 2H), 7.31 (d, J=8.1 Hz, 2H), 7.76–7.82 (m, 2H), 7.90–7.96 (m, 2H), 8.08 (s, 1H); ^{13}C NMR δ 14.2, 21.5, 61.9, 119.3, 123.9, 129.5, 129.6 129.7, 132.2, 134.4, 141.1, 142.6, 163.5, 166.9; HRMS m/z Calcd for $C_{20}H_{17}NO_4$ (M^+) 335.1158, found 335.1123.

3.7. Ethyl 2-(2-oxazolidinyl)-2(*Z*)-butenoate (6a)

3.7.1. Procedure B. BuLi (0.12 mL (1.6 M/hexane), 0.20 mmol) was added to a stirred solution of 2-oxazolidone (17 mg, 0.20 mmol) in THF (6 mL) at −20 °C under an argon atmosphere. After 1 h, the solution of **1a** (32 mg, 0.20 mmol) in THF (1 mL) was added and resulting mixture was stirred for 30 min at 0 °C than for 12 h at rt at which time TLC showed complete disappearance of **1a**. The reaction mixture was quenched with saturated aqueous NH_4Cl (3 mL) and resulting mixture was extracted with EtOAc (2×6 mL). The combined organic layer was washed with water, brine, dried (Na_2SO_4) and evaporated to dryness under vacuum. The oily residue was column chromatographed (EtOAc/hexane 20%→35%) to give **6a** as an oil (29 mg, 58%): IR ($CHCl_3$) 2926, 1750, 1700 cm^{-1}; ^1H NMR δ 1.31 (t, J=7.1 Hz, 3H), 1.88 (d, J=7.1 Hz, 3H), 3.67–3.84 (m, 2H), 4.24 (q, J=7.1 Hz, 2H), 4.44–4.52 (m, 2H), 7.38 (q, J=7.1 Hz, 1H); ^{13}C NMR δ 13.9, 14.2, 45.9, 61.3, 62.7, 128.0, 140.9, 156.8, 163.1; HRMS m/z Calcd for $C_9H_{13}NO_4$ (M^+) 199.0845, found 199.0839.

3.8. Ethyl 2-(2-oxazolidinyl)-2(*Z*)-pentenoate (6b)

Treatment of **1b** (44 mg, 0.25 mmol) with 2-oxazolidone (22 mg, 0.25 mmol) and BuLi (0.16 mL (1.6 M/hexane), 0.25 mmol) by procedure B gave **6b** as an oil (26 mg, 48%): IR ($CHCl_3$) 2996, 1757, 1702 cm^{-1}; ^1H NMR δ 1.11 (t, J=7.7 Hz, 3H), 1.32 (t, J=7.1 Hz, 3H), 2.28 (quintet, J=7.7 Hz, 2H), 3.76–3.82 (m, 2H), 4.25 (q, J=7.1 Hz, 2H), 4.44–4.49 (m, 2H), 7.00 (t, J=7.7 Hz, 1H); ^{13}C NMR

δ 12.6, 14.2, 21.6, 46.2, 61.4, 62.6, 126.5, 147.2, 156.9, 162.3; HRMS *m*/*z* Calcd for $C_{10}H_{15}NO_4$ (M^+) 213.1001, found 213.0879.

3.9. Ethyl 3-phenyl-2-(2-oxazolidinyl)-2(*Z*)-propenoate (6c)

Treatment of **1c** (42 mg, 0.19 mmol) with 2-oxazolidone (59 mg, 0.68 mmol) and DBU (34 μL, 35 mg, 0.23 mmol) by procedure A (reaction mixture was kept at 6 °C for overnight for complete consumption of **1c**) gave **6c**[15] (30 mg, 60%): ^{1}H NMR δ 1.37 (t, *J*=7.1 Hz, 3H), 3.72 (t, *J*=7.8 Hz, 2H), 4.33 (q, *J*=7.1 Hz, 2H), 4.49 (t, *J*=7.8 Hz, 2H), 7.39–7.43 (m, 3H), 7.55–7.61 (m, 2H), 7.71 (s, 1H).

3.10. Ethyl 3-(4-methylphenyl)-2-(2-oxazolidinyl)-2(*Z*)-propenoate (6d)

Treatment of **1d** (43 mg, 0.18 mmol) with 2-oxazolidone (57 mg, 0.66 mmol) and DBU (32 μL, 33 mg, 0.22 mmol) by procedure A (reaction mixture was kept at 6 °C for overnight for complete consumption of **1d**) gave **6d** as an oil (32 mg, 64%): IR ($CHCl_3$) 2956, 1762, 1714 cm^{-1}; ^{1}H NMR δ 1.35 (t, *J*=7.1 Hz, 3H), 2.37 (s, 3H), 3.72 (t, *J*=7.8 Hz, 2H), 4.32 (q, *J*=7.1 Hz, 2H), 4.48 (t, *J*=7.8 Hz, 2H), 7.21 (d, *J*=8.0 Hz, 2H), 7.48 (d, *J*=8.0 Hz, 2H), 7.67 (s, 1H); ^{13}C NMR δ 14.3, 21.5, 45.4, 61.7, 62.9, 124.8, 129.7, 129.8, 130.0, 139.6, 141.1, 157.6, 164.1; HRMS *m*/*z* Calcd for $C_{15}H_{17}NO_4$ (M^+) 275.1158, found 275.1209.

3.11. Ethyl 2-nitro-3-phenyl-3-(*N*-phthalimido)-propanoate (8a)

3.11.1. Procedure C. DBU (35 μL, 35 mg, 0.23 mmol) was added to a stirred solution of phthalimide (34 mg, 0.23 mmol) in CH_3CN (6 mL) at 0 °C under an argon atmosphere. After 1 h, the solution of **7a** (*E*/*Z*, 2:1; 43 mg, 0.19 mmol) in CH_3CN (1 mL) was added and resulting mixture was stirred for 10 min at which time TLC showed complete disappearance of **7a**. The reaction mixture was then quenched with saturated aqueous NH_4Cl (3 mL) and after being warmed to rt, the mixture was extracted with EtOAc (2×8 mL). The combined organic layer was washed with water, brine, dried (Na_2SO_4) and was evaporated to dryness under vacuum. The oily residue was column chromatographed (EtOAc/hexane 20%→25%) to give **8a** (68 mg, 94%) (2:1) as a mixture of two diastereoisomers. Crystallization (EtOH) yielded white crystals (mp 147–150 °C) as a mixture of diastereoisomers (3:1). The minor isomer had: ^{1}H NMR δ 1.13 (t, *J*=7.1 Hz, 3H), 4.20 (q, *J*=7.1 Hz, 2H), 6.21 (d, *J*=12.1 Hz, 1H), 6.83 (d, *J*=12.1 Hz, 1H), 7.32–7.38 (m, 3H), 7.60–7.65 (m, 2H), 7.71–7.76 (m, 2H), 7.81–7.87 (m, 2H); ^{13}C NMR δ 13.5, 54.7, 63.3, 85.9, 123.8, 128.6, 129.1, 129.5, 131.4, 133.6, 134.5, 162.5, 167.4. The major isomer had: ^{1}H NMR δ 1.02 (t, *J*=7.1 Hz, 3H), 4.08 (dq, *J*=1.2, 7.1 Hz, 2H), 6.22 (d, *J*=11.5 Hz, 1H), 6.85 (d, *J*=11.5 Hz, 1H), 7.32–7.38 (m, 3H), 7.60–7.65 (m, 2H), 7.71–7.76 (m, 2H), 7.81–7.87 (m, 2H); ^{13}C NMR δ 13.6, 53.5, 63.6, 85.7, 123.8, 128.6, 129.2, 129.5, 131.4, 134.0, 134.5, 162.5, 167.4; IR ($CHCl_3$) 2926, 1752, 1720, 1568 cm^{-1}; HRMS *m*/*z* Calcd for $C_{19}H_{16}N_2O_6$ (M^+) 368.1008, found 368.0981.

3.12. Ethyl 3-(4-methoxyphenyl)-2-nitro-3-(*N*-phthalimido)-propanoate (8b)

Treatment of **7b** (*E*/*Z*, 5:2; 68 mg, 0.27 mmol) with phthalimide (48 mg, 0.32 mmol) and DBU (48 μL, 49 mg, 0.32 mmol) by procedure C gave **8b** (87 mg, 81%) as a mixture of two isomers (1.4:1) as an oil. The major isomer had: ^{1}H NMR δ 1.06 (t, *J*=7.1 Hz, 3H), 3.77 (s, 3H), 4.09 (dq, *J*=2.6, 7.1 Hz, 2H), 6.18 (d, *J*=11.5 Hz, 1H), 6.81 (d, *J*=11.5 Hz, 1H), 6.83–6.89 (m, 2H), 7.54–7.58 (m, 2H), 7.70–7.74 (m, 2H), 7.81–7.87 (m, 2H); ^{13}C NMR δ 13.5, 54.2, 55.3, 63.3, 86.1, 114.4, 123.7, 126.0, 130.6, 131.4, 134.4, 160.3, 162.0, 167.5. The minor isomer had: ^{1}H NMR δ 1.12 (t, *J*=7.1 Hz, 3H), 3.78 (s, 3H), 4.19 (q, *J*=7.1 Hz, 2H), 6.15 (d, *J*=11.8 Hz, 1H), 6.78 (d, *J*=11.8 Hz, 1H), 6.83–6.89 (m, 2H), 7.54–7.58 (m, 2H), 7.70–7.74 (m, 2H), 7.81–7.87 (m, 2H); ^{13}C NMR δ 13.6, 53.1, 55.3, 63.5, 86.0, 114.5, 123.7, 125.6, 130.0, 131.5, 134.5, 160.2, 162.5, 167.4; IR ($CHCl_3$) 2927, 1752, 1720, 1566 cm^{-1}; HRMS *m*/*z* Calcd for $C_{20}H_{18}N_2O_7$ (M^+) 398.1114, found 398.1087.

3.13. Ethyl 3-(4-methylphenyl)-2-nitro-3-(*N*-phthalimido)-propanoate (8c)

Treatment of **7c** (*E*/*Z*, 2:1; 72 mg, 0.31 mmol) with phthalimide (54 mg, 0.37 mmol) and DBU (55 μL, 56 mg, 0.37 mmol) by procedure C gave **8c** (98 mg, 84%) as a mixture of two isomers (1.4: 1) as an oil. The major isomer had: ^{1}H NMR δ 1.05 (t, *J*=7.1 Hz, 3H), 2.31 (s, 3H), 4.08 (dq, *J*=1.1, 7.1 Hz, 2H), 6.19 (d, *J*=11.5 Hz, 1H), 6.83 (d, *J*=11.5 Hz, 1H), 7.15–7.20 (m, 2H), 7.48–7.55 (m, 2H), 7.70–7.74 (m, 2H), 7.81–7.87 (m, 2H); ^{13}C NMR δ 13.5, 21.2, 54.4, 63.3, 85.9, 123.7, 129.0, 129.7, 130.5, 131.3, 134.5, 139.5, 161.9, 167.4. The minor isomer had: ^{1}H NMR δ 1.13 (t, *J*=7.1 Hz, 3H), 2.30 (s, 3H), 4.19 (q, *J*=7.1 Hz, 2H), 6.17 (d, *J*=11.8 Hz, 1H), 6.81 (d, *J*=11.8 Hz, 1H), 7.15–7.20 (m, 2H), 7.48–7.55 (m, 2H), 7.70–7.74 (m, 2H), 7.81–7.87 (m, 2H); ^{13}C NMR δ 13.6, 21.2, 53.3, 63.5, 85.7, 123.7, 128.5, 129.8, 131.0, 131.4, 134.4, 139.4, 162.5, 167.3; IR ($CHCl_3$) 2987, 1752, 1720, 1566 cm^{-1}; HRMS *m*/*z* Calcd for $C_{20}H_{18}N_2O_6$ (M^+) 382.1165, found 382.1189.

3.14. Ethyl 2-nitro-3-(2-oxazolidinyl)-3-phenylpropanoate (9a)

Treatment of **7a** (*E*/*Z*, 2:1; 36 mg, 0.16 mmol) with 2-oxazolidone (17 mg, 0.19 mmol) and DBU (30 μL, 30 mg, 0.19 mmol) by procedure C (reaction mixture was quenched after overnight at rt) gave **9a** (28 mg, 56%) as a mixture of two diastereoisomers (3:1). Crystallization (EtOH) yielded white crystals (mp 128–130 °C) as a mixture of diastereoisomers (9:1). The major isomer had: ^{1}H NMR δ 1.01 (t, *J*=7.1 Hz, 3H), 3.52–3.56 (m, 1H), 3.58–3.65 (m, 1H), 4.00–4.10 (m, 2H), 4.25–4.36 (m, 2H), 5.48 (d, *J*=11.4 Hz, 1H), 6.38 (d, *J*=11.4 Hz, 1H), 7.38–7.44 (m, 5H); ^{13}C NMR δ 13.5, 43.7, 58.9, 62.3, 63.3, 86.7, 127.8, 128.4, 129.3, 132.7, 157.4, 161.9. The minor isomer had: ^{1}H NMR δ 1.35 (t, *J*=7.1 Hz, 3H), 3.38–3.64 (m, 2H), 4.24–4.38 (m, 4H), 5.63 (d, *J*=11.5 Hz, 1H), 6.16 (d, *J*=11.5 Hz, 1H), 7.38–7.44 (m, 5H); ^{13}C NMR δ 13.7, 43.9, 57.4, 62.3, 63.5, 86.4, 127.8, 128.4, 129.3, 132.7, 157.4, 162.7; IR ($CHCl_3$) 2985, 1752, 1567 cm^{-1}; HRMS *m*/*z* Calcd for $C_{14}H_{16}N_2O_6$ (M^+) 308.1008, found 308.1020.

3.15. Ethyl 3-(4-methoxyphenyl)-2-nitro-3-(2-oxazolidinyl)-propanoate (9b)

Treatment of **7b** (*E*/*Z*, 5:2; 49 mg, 0.19 mmol) with 2-oxazolidone (20 mg, 0.23 mmol) and DBU (35 μL, 36 mg, 0.23 mmol) by procedure C gave **9b** (38 mg, 58%) as a mixture of two diastereoisomers (1:1) as an oil. ^{1}H NMR δ 1.04 (t, *J*=7.1 Hz, 3H), 1.33 (t, *J*=7.1 Hz, 3H), 3.38–3.66 (m, 2H), 3.40–3.58 (m, 2H), 381 (s, 3H), 3.82 (s, 3H), 4.00–4.12 (m, 2H), 4.23–4.30 (m, 2H), 4.24–4.32 (m, 4H), 5.42 (d, *J*=11.5 Hz, 1H), 5.54 (d, *J*=11.5 Hz, 1H), 6.12 (d, *J*=11.5 Hz, 1H), 6.32 (d, *J*=11.5 Hz, 1H), 6.88–6.93 (m, 4H), 7.31–7.37 (m, 4H); ^{13}C NMR δ 13.5, 13.8, 42.9, 43.6, 55.3, 57.2, 58.4, 62.3, 62.4, 63.3, 63.7, 86.7, 86.9, 114.5, 114.7, 124.5, 124.9, 129.2, 129.8, 157.4, 160.4, 160.5, 161.9, 162.6; IR ($CHCl_3$) 2926, 1753, 1566 cm^{-1}; HRMS *m*/*z* Calcd for $C_{15}H_{18}N_2O_7$ (M^+) 338.1114, found 338.1146.

3.16. Ethyl 3-(4-methylphenyl)-2-nitro-3-(2-oxazolidinyl)-propanoate (9c)

Treatment of **7c** (*E*/*Z*, 2:1; 85 mg, 0.36 mmol) with 2-oxazolidone (38 mg, 0.43 mmol) and DBU (65 μL, 66 mg, 0.43 mmol) by procedure C gave **9c** (84 mg, 72%) as a mixture of two diastereoisomers (1:1) as an oil. ^{1}H NMR δ 1.05 (t, *J*=7.1 Hz, 3H), 1.33

(t, J=7.1 Hz, 3H), 2.35 (s, 6H), 3.35–3.66 (m, 2H), 3.41–3.58 (m, 2H), 4.00–4.15 (m, 2H), 4.22–4.38 (m, 4H), 4.23–4.36 (m, 2H), 5.48 (d, J=11.5 Hz, 1H), 5.60 (d, J=11.5 Hz, 1H), 6.12 (d, J=11.5 Hz, 1H), 6.33 (d, J=11.5 Hz, 1H), 7.18–7.21 (m, 4H), 7.27–7.31 (m, 4H); ^{13}C NMR δ 13.4, 13.7, 21.1, 42.7, 43.4, 57.2, 58.5, 62.2, 62.3, 63.2, 63.8, 86.4, 86.8, 127.6, 128.2, 129.5, 129.9, 130.0, 139.7, 157.4, 161.9, 162.6; IR ($CHCl_3$) 2982, 1752, 1566 cm^{-1}; HRMS m/z Calcd for $C_{15}H_{18}N_2O_6$ (M^+) 322.1165, found 322.1178.

3.17. Ethyl 2-amino-3-phenyl-3-(*N*-phthalimido)-propanoate (10a)

A suspension of **8a** (mixture of diastereoisomers 2:1, 40 mg, 0.11 mmol) and Raney nickel (~5 mg) in EtOH (4 mL) was hydrogenated over H_2 gas under balloon atmosphere for 8 h. The resulting solution was filtered over Celite, and washed with EtOH (5 mL). The organic layer was evaporated and purified by column chromatography (EtOAc/hexane 30%→50%) to afford **10a** as a separable mixture of two diastereoisomers 2:1 (25 mg, 68%) as a solidifying oil. The minor isomer (less polar) had: ^{1}H NMR δ 0.96 (t, J=7.2 Hz, 3H), 1.58 (br s, 2H), 4.11–3.98 (m, 2H), 4.98 (d, J=11.0 Hz, 1H), 5.35 (d, J=11.0 Hz, 1H), 7.33–7.41 (m, 3H), 7.64–7.73 (m, 4H), 7.80–7.86 (m, 2H); ^{13}C NMR δ 13.8, 53.9, 58.3, 61.3, 123.3, 128.6, 128.9, 129.5, 131.7, 134.1, 136.3, 167.7, 173.0. The major isomer (more polar) had: ^{1}H NMR δ 0.94 (t, J=7.2 Hz, 3H), 1.58 (br s, 2H), 3.95 (q, J=7.2 Hz, 2H), 4.87 (d, J=11.0 Hz, 1H), 5.40 (d, J=11.0 Hz, 1H), 7.27–7.34 (m, 3H), 7.57–7.62 (m, 2H), 7.67–7.71 (m, 2H), 7.82–7.84 (m, 2H); ^{13}C NMR δ 13.8, 55.1, 58.8, 60.9, 123.3, 128.4, 128.5, 129.1, 131.8, 134.0, 136.5, 168.5, 173.8; IR ($CHCl_3$) 3420, 1773, 1713 cm^{-1}; HRMS (LSIMS) m/z Calcd for $C_{19}H_{19}N_2O_4$ $[M+H]^+$ 339.1345, found 339.1340.

3.18. Ethyl 2,3-diamino-3-phenylpropanoate (11a)

Hydrazine monohydrate (0.007 mL, 7 mg, 0.14 mmol) was added to a stirred solution of **10a** (major isomer) (14 mg, 0.04 mmol) in EtOH (3 mL) at 0 °C. After 1.5 h, AcOH was added (few drops) and the mixture was stirred for 10 min at 0 °C and then allowed to warm to rt overnight. Concentration in vacuo and purification by column chromatography (CH_2Cl_2/MeOH/NH_4OH 100:5:0.5) afforded **11a**[18] (5.5 mg, 62%): ^{1}H NMR δ 1.15 (t, J=7.2 Hz, 3H), 1.76 (br s, 4H), 3.61 (d, J=5.1 Hz, 1H), 4.10 (dq J=1.3, 7.2 Hz, 2H), 4.25 (d, J=5.1 Hz, 1H), 7.33–7.37 (m, 5H); ^{13}C NMR δ 14.0, 58.4, 60.9, 61.0, 126.8, 127.4, 128.4, 142.5, 174.0.

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