Supporting Information for

Catalyst-Free Ring Opening of Azlactones in Water Microdroplets†‡

Kumar Naveen,[a,§] Vishesh Singh Rawat,[a,§] Rahul Verma[a] and Elumalai Gnanamani*[a]

Department of Chemistry, Indian Institute of Technology Roorkee, Roorkee 247667, India

*Corresponding author. Email: gnanam@cy.iitr.ac.in

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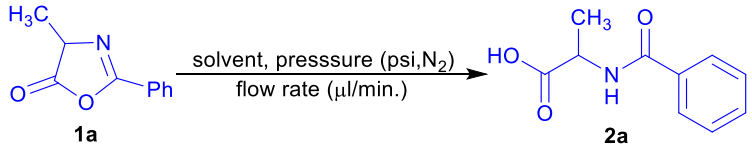
1. General information

All the amino acids were purchased from Avra synthesis Pvt. Ltd., India and used without further purification. All the solvents were purchased from Merck, India and distilled using standard procedures.[1a] For the microdropet spray used, the fused silica gel capillary for transfer of solution to the spray source (i.d. of 100 μm and o.d. of 360 μm from Ploymicro Technologies, Az, USA). TLC plate was performed on pre-coated 0.25 mm thick aluminium-backed silica gel plates purchased from Merck KGaA, Germany, and visualized with a UV lamp (λ = 254 nm) or ninhydrin stain. Flash chromatography was performed on Merck silica gel (230-400 mesh). Single crystal X-ray diffraction analysis (SC-XRD) analysis was performed on the Bruker D8 Quest model. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on JEOL ECZ500R/S1 instrument. All proton NMR chemical shifts are reported in ppm relative to tetramethylsilane (0.00 ppm) or the residual solvent peak (Chloroform-*d* δ 7.26 ppm and DMSO-d_6 δ 2.50). Multiplets are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. ^{13}C NMR spectra were recorded at 126 MHz, and data are reported as follows: a chemical shift in ppm from tetramethylsilane with the solvent as an internal indicator (Chloroform-*d* δ 77.16 ppm and DMSO-d_6 δ39.52). HRMS data were obtained in ESI mode by Agilent LC/Q-TOF instrument. Optical rotations were measured in an Rudolph Polarimeter AUTOPOL-V PLUS. The polarimeter optical rotation is consistent with that reported in the literature.[2-4] Enantiomeric excesses of the sample were determined on an Agilent HPLC instrument using the Dacel chiralpak columns (AD-H). All the azlactones (**1a-1e**) were prepared according to reported procedures, and the proton NMR data is consistent with that reported in the literature.[1b&c]

2. Optimization of reaction conditions:

General procedure I:

Azlactone (±-**1a**) was dissolved in a water-ACN or water-dioxane, or water-acetone solvent (1 mL, 1:1) and the solution loaded into an airtight glass syringe. The solution was delivered with a syringe pump (NE-300, New Era Pump Systems, Inc. Farmingdale, NY, USA) at a flow rate of 30 µl/min. to a fused silica gel glass capillary (i.d. of 100 µm and o.d. of 360 µm, capillary length: 20 cm). Dry nitrogen, which served as the sheath gas, was operated at 120 psi pressure or, as mentioned in Table S1. The distance between spray source and collecting surface kept as 40 mm. The microdroplets were sprayed for 33.3 minutes and collected. The collected crude material was then assayed by crude ^{1}H NMR to assess the conversion and purified through flash column chromatography (95:5→80:20, CH_2Cl_2/MeOH), afforded the title compound racemic *N*-benzoyl alanine **(2a).Table S1:** Optimization of reaction conditions.[a]



1a **2a**

Entry	Solvent ratio (1:1)	Pressure (psi)	Flow rate (µL/min.)	Concentration (mol L^{-1})	Conversion[b] (%)	Yield (%)[c]
1	H_2O: Dioxane	120	30	0.15	45	31
2	H_2O: Acetone	120	30	0.15	100	82
3	H_2O: ACN	120	30	0.15	100	90
4	H_2O: ACN	120	50	0.1	64	56
5	H_2O: ACN	120	30	0.1	100	94
6	H_2O: ACN	120	30	0.2	38	30
7	H_2O: ACN	50	30	0.1	42	36
8	H_2O: ACN	0	30	0.1	n.d.	n.d.

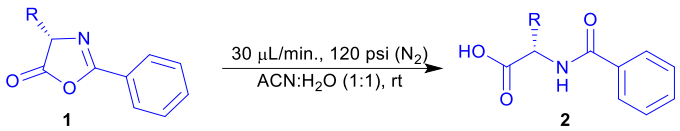
[a]All reactions were performed with *rac*-4-methyl-2-phenyloxazol-5(4*H*)-one for 33.3 minutes. [b]Conversion was determined by crude ^{1}H NMR analysis. [c]Yields of isolated products. n.d. = not detected.

3. Reaction in Bulk phase: *Control experiment:*

A 5 ml glass vial was charged with azlactone (±)-**1a** (0.1 mmol) and dissolved in 1 mL of water-acetonitrile (v:v = 1:1). The resulting mixture was stirred at room temperature for 6 hours and the organic solvent was evaporated *in vacuo,* and the reaction mixture was extracted with ethyl acetate (3×3 ml). The organic extracts were combined and dried over $MgSO_4$, and the organic solvent was concentrated *in vacuo* to afford corresponding crude (±)-**2a**. To determine the conversion, the crude sample was analyzed by using ^{1}H NMR and desired *N*-benzoyl alanine **(2a)** was not observed.

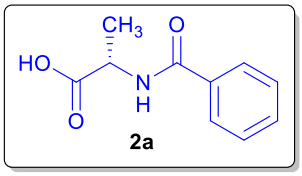
4. Microdroplet synthesis of *N*-benzoyl derivatives (2a-g):

General procedure II



0.1 mmol of azlactone (**1**) was dissolved in a water-acetonitrile in 1 mL of water/acetonitrile solvent (v:v = 1:1), and the solution was loaded into an airtight glass syringe. The solution was delivered with a syringe pump (NE-300, New Era Pump Systems, Inc. Farmingdale, NY, USA) at a flow rate of 30 µL/min to a fused silica gel capillary (i.d. of 100 µm and o.d. of 360 µm, capillary length: 20 cm). The end of the capillary was equipped with a sheath-gas-assisted spray emitter. Dry nitrogen, which served as the sheath gas, was operated at 120 psi. The distance between spray source and collecting surface kept as 40 mm. The microdroplets were sprayed for 33.3 minutes and collected. The collected crude material was purified through flash column chromatography to afford the corresponding *N*-benzoyl amino acid (**2**).

N-benzoyl-*L*-alanine (2a)



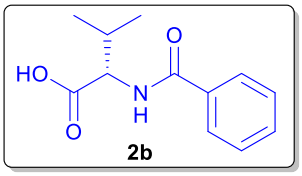
The title compound was prepared according to the general procedure II, using (*S*)-4-methyl-2-phenyloxazol-5(4*H*)-one **1a** (17.5 mg, 0.1 mmol). The crude product was subjected to flash column chromatography (95:5→80:20, CH_2Cl_2/MeOH), afforded the title compound **2a** as a white solid (18.2 mg, 94% yield). The structure of the compound was determined by using ^{1}H NMR data.

^{1}H NMR (DMSO-d$_6$, 400 MHz): δ 8.67 (d, *J* = 7.3 Hz, 1H), 7.88 (m, 2H), 7.52 (m, 1H), 7.47 (m, 2H), 4.42 (qn, *J* = 7.3 Hz, 1H), 1.39 (d, *J* = 7.3 Hz, 3H). The ^{1}H NMR data is consistent with that reported in the literature.[2]

HRMS: Calculated for $C_{10}H_{10}NO_3^-$[M–H] 192.0666, found 192.0670.

[α]$_D^{22}$: +24.1° (*c* 1.0, $CHCl_3$), lit. **[α]$_D^{22}$**: +29.1° (*c* 1.0, $CHCl_3$)[3]

N-benzoyl-*L*-valine (2b)

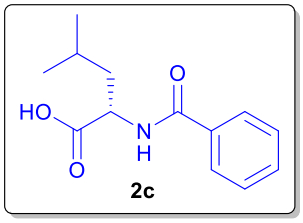


The title compound was prepared according to the general procedure II, using (*S*)-4-isopropyl-2-phenyloxazol-5(4*H*)-one **1b** (20.3 mg, 0.1 mmol). The crude product was subjected to flash column chromatography (95:5→85:15 CH_2Cl_2/MeOH), afforded the title compound **2b** as a white solid (17.9 mg, 81% yield). The structure of the compound was determined by using ^{1}H NMR data.

^{1}H NMR (DMSO-d$_6$, 400 MHz): δ 8.41 (d, *J* = 8.1 Hz, 1H), 7.91 – 7.84 (m, 2H), 7.56 – 7.50 (m, 1H), 7.49 – 7.44 (m, 2H), 4.29 (t, *J* = 7.6 Hz, 1H), 2.31 – 2.11 (m, 1H), 0.97 (t, *J* = 6.8 Hz, 6H). The ^{1}H NMR data is consistent with that reported in the literature.[2]

[α]$_D^{20}$: +10.4 (*c* 1.09, MeOH), lit. **[α]$_D^{20}$**: +10.0 (*c* 1.03, MeOH)[2]

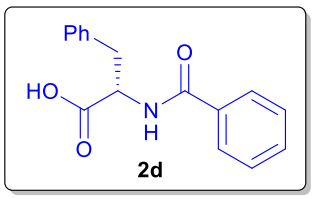
N-benzoyl-*L*-leucine (2c)



The title compound was prepared according to the general procedure II, using (*S*)-4-isobutyl-2-phenyloxazol-5(4*H*)-one **1c** (21.7 mg, 0.1 mmol). The crude product was subjected to flash column chromatography (95:5→85:15 CH_2Cl_2/MeOH), afforded the title compound **2c** as a light yellow solid (20 mg, 85% yield). The structure of the compound was determined by using ^{1}H NMR data.

^{1}H NMR (DMSO-d$_6$, 400 MHz): δ 8.57 (d, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 7.3 Hz, 2H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.46 (t, *J* = 7.3 Hz, 2H), 4.44 (ddd, *J* = 10.8, 8.0, 4.3 Hz, 1H), 1.83 – 1.65 (m, 2H), 1.58 (ddd, *J* = 12.8, 8.8, 4.3 Hz, 1H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.87 (d, *J* = 6.4 Hz, 3H). The ^{1}H NMR data is consistent with that reported in the literature.[2]
[α]$_D^{22}$: –9.0 (*c* 1.08, MeOH), lit. **[α]$_D^{20}$**: –12.8 (*c* 1.08, MeOH)[2]

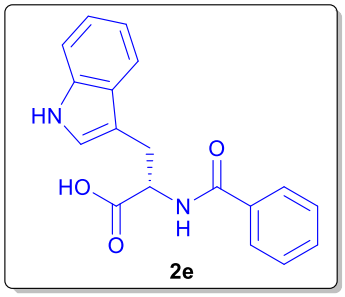
N-benzoyl-*L*-phenylalanine (2d)



The title compound was prepared according to the general procedure II, using (*S*)-4-benzyl-2-phenyloxazol-5(4*H*)-one **1d** (17.5 mg, 0.1 mmol). The crude product was subjected to flash column chromatography (95:5→80:20 CH_2Cl_2/MeOH), afforded the title compound **2d** as a white solid (23.7 mg, 88% yield). The structure of the compound was determined by using ^{1}H NMR data.

^{1}H NMR (DMSO-d$_6$, 400 MHz): δ 8.59 (d, *J* = 8.1 Hz, 1H), 7.80 – 7.75 (m, 2H) 7.51 (t, *J* = 7.3 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.30 (d, *J* = 6.9 Hz, 2H), 7.24 (t, *J* = 7.6 Hz, 2H), 7.16 (t, *J* = 7.1 Hz, 1H), 4.59 (m, 1H), 3.21 (dd, *J* = 13.7, 4.3 Hz, 1H), 3.07 (dd, *J* = 13.7, 10.2 Hz, 1H). The ^{1}H NMR data is consistent with that reported in the literature.[2]
[α]$_D^{20}$: –32.0 (*c* 1.09, MeOH), lit. **[α]$_D^{20}$**: –31.4 (*c* 1.09, MeOH)[2]

N-benzoyl-*L*-tryptophan (2e)

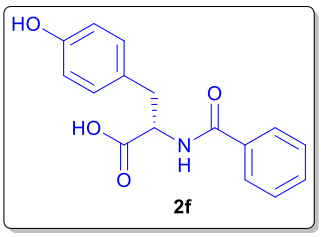


The title compound was prepared according to the general procedure II, using (*S*)-4-((1H-indol-3-yl)methyl)-2-phenyloxazol-5(4*H*)-one **1e** (29 mg, 0.1 mmol). The crude product was subjected to flash column chromatography (95:5→80:20 CH_2Cl_2/MeOH), afforded the title compound **2e** as a brown solid (24 mg, 78% yield).

^{1}H NMR (DMSO-d$_6$, 400 MHz): δ 10.82 (d, *J* = 2.5 Hz, 1H), 8.63 (d, *J* = 7.9 Hz, 1H), 7.82 (dd, *J* = 7.2, 1.7 Hz, 2H), 7.61 (d, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.3 Hz, 1H), 7.44 (t, *J* = 7.3 Hz, 2H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.22 (d, *J* = 2.3 Hz, 1H), 7.06 (t, *J* = 7.3 Hz, 1H), 6.99 (t, *J* = 7.6 Hz, 1H), 4.67 (m, 1H), 3.33 (dd, *J* = 14.6, 4.6 Hz, 1H), 3.22 (dd, *J* = 14.6, 9.9 Hz, 1H). The ^{1}H NMR data is consistent with that reported in the literature.[2]

HRMS: Calculated for $C_{18}H_{17}N_2O_3^+$ [M+H] 309.1234, found 309.1240.
[α]$_D^{20}$: –32.3 (c = 1.08, MeOH), lit. **[α]$_D^{20}$**: –35.7 (*c* 1.08, MeOH)[2]

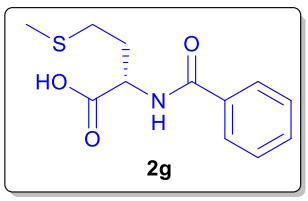
N-benzoyl-*L*-tyrosine (2f)



The title compound was prepared according to the general procedure II, using (S)-4-(4-hydroxybenzyl)-2-phenyloxazol-5(4*H*)-one **1f** (26.7 mg, 0.1 mmol). The crude product was subjected to flash column chromatography (95:5→80:20 $CHCl_3$/MeOH), afforded the title compound **2d** as a white solid (21.4 mg, 75% yield). The structure of the compound was determined by using ^{1}H NMR data.

^{1}H NMR (DMSO-d$_6$, 500 MHz): δ 9.21 (s, 1H), 8.62 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.6 Hz, 2H), 7.52 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 2H), 7.10 (d, *J* = 8.6 Hz, 2H), 6.64 (d, *J* = 8.6 Hz, 2H), 4.52 (ddd, *J* = 10.5, 8.0, 4.5 Hz, 1H), 3.06 (dd, *J* = 13.8, 4.5 Hz, 1H), 2.94 (dd, *J* = 13.8, 10.5 Hz, 1H). The ^{1}H NMR data is consistent with that reported in the literature.[4]
[α]$_D^{25}$: –33.4 (*c* 1.00, MeOH), lit. **[α]$_D^{23}$**:–36.0 (*c* 1.1, MeOH)[4]

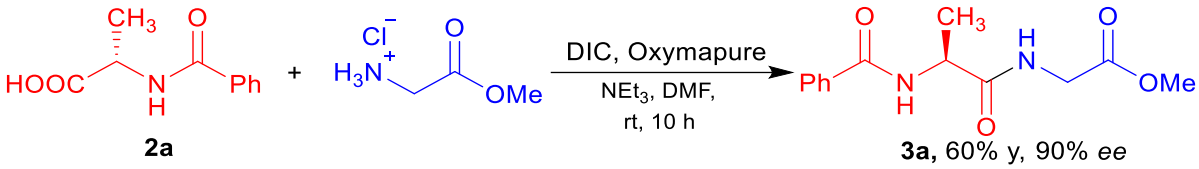
N-benzoyl-*L*-methionine (2g)



The title compound was prepared according to the general procedure II, using (*S*)-4-(2-(methylthio)ethyl)-2-phenyloxazol-5(4*H*)-one **1g** (23.5 mg, 0.1 mmol). The crude product was subjected to flash column chromatography (95:5→85:15 CH_2Cl_2/MeOH), afforded the title compound **2g** as a white solid (20.2 mg, 80% yield). The structure of the compound was determined by using ^{1}H NMR data.

^{1}H NMR (DMSO-d$_6$, 500 MHz): δ 8.64 (d, *J* = 7.8 Hz, 1H), 7.88 (d, *J* = 7.0 Hz, 2H), 7.59 – 7.50 (m, 1H), 7.48 (t, *J* = 7.3 Hz, 2H), 4.58 – 4.47 (m, 1H), 2.65 – 2.49 (m, 2H), 2.12 – 2.04 (m, 2H), 2.05 (s, 3H). The ^{1}H NMR data is consistent with that reported in the literature.[2]
[α]$_D^{25}$: –14.5° (*c* 1.00, MeOH), lit. **[α]$_D^{20}$**:–21.0 (*c* 1.03, MeOH)[2]

5. Synthesis of dipeptide 3a:[5a]



In a 25 mL round bottom flask charged with benzoyl-*L*-alanine (19.3 mg, 0.1 mmol), methyl glycinate hydrochloride (12.5 mg, 0.1 mmol), oxymapure (0.11 mmol., 1.1 equiv.), and DMF (2 ml) at room temperature in a nitrogen atmosphere. DIC (18.9 mg, 0.15 mmol, 1.5 equiv.) and NEt_3 (3.0 equiv.) were added to the reaction mixture at room temperature and stirred for 10 h. Quenched the reaction mixture with cold water and extracted with dichloromethane (3×5 ml), dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography (CH_2Cl_2: MeOH = 40:1), afforded the title compound (*S*)-**3a** as a white solid (15.8 mg, 60% yield). For HPLC analysis, the racemic sample of **3a** has been synthesised from racemic **2a**.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.80 (d, *J* = 8.3 Hz, 2H), 7.58 – 7.42 (m, 2H), 7.43 – 7.30 (m, 3H), 4.83 (qn, *J* = 7.1 Hz, 1H), 4.01 (d, *J* = 4.7 Hz, 2H), 3.69 (s, 3H), 1.47 (d, *J* = 6.9 Hz, 3H).

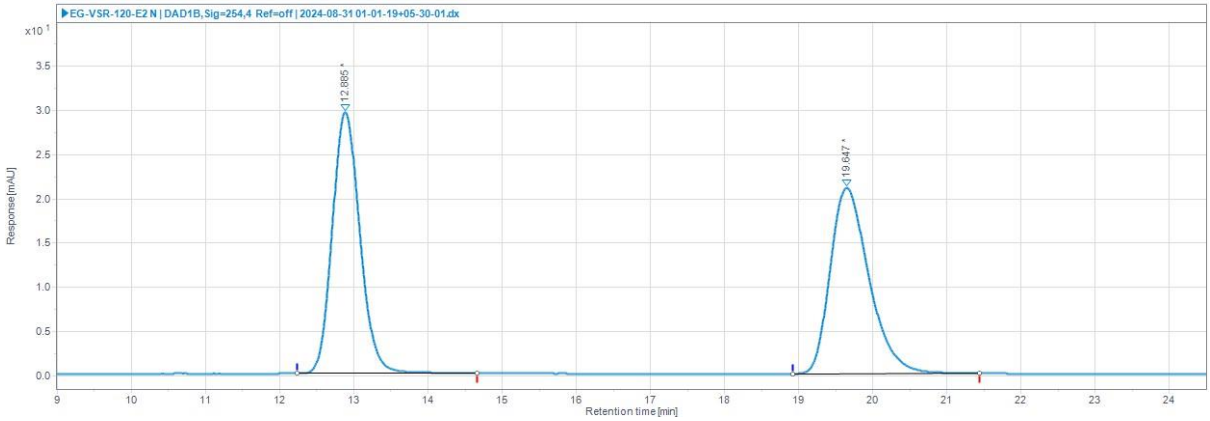
^{13}C NMR ($CDCl_3$, 126 MHz): δ 173.2, 170.3, 167.5, 133.7, 131.9, 128.6, 127.5, 52.4, 49.1, 41.3, 18.4. The NMR data is consistent with that reported in the literature.[5a]

HRMS: Calculated for $C_{13}H_{17}N_2O_4^+$ [M+H] 265.1183, found 265.1187.

HPLC: 90% *ee* (95:5 er) (Daicel CHIRALPAK AD-H, Hexane:^{i}PrOH (90:10) 1.0 mL/min; T_{major} = 19.6 min, T_{minor} = 12.8 min, 254 nm absorbance)

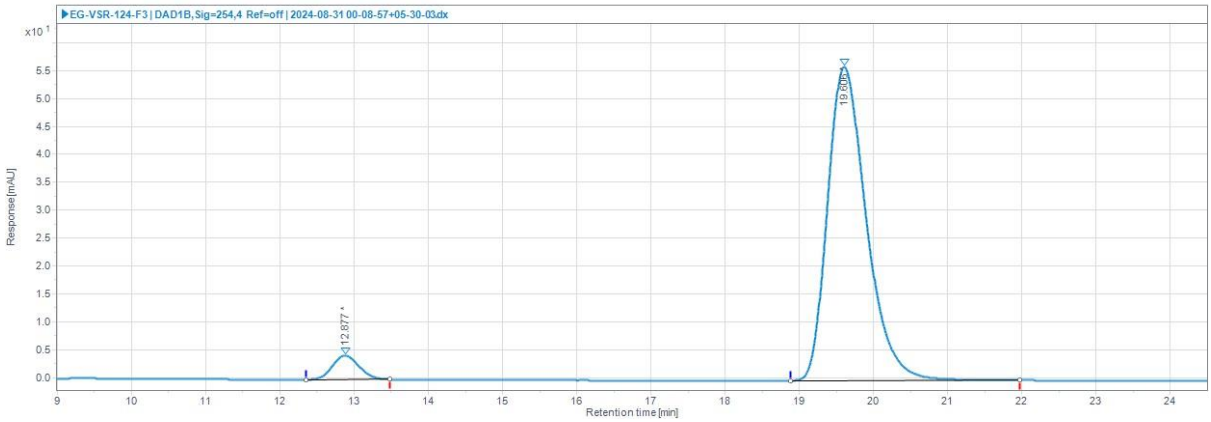
[α]$_D^{25}$: –23.7 (*c* 1.00, $CHCl_3$)

6. HPLC chromatogram of racemic and chiral dipeptide **3a**



Signal: DAD1B,Sig=254,4 Ref=off

Name	Peak Retention Time	Area	Area%	Height
	12.885	12821282	50.06	4946854.90
	19.647	12788340	49.94	3516759.59



Signal: DAD1B,Sig=254,4 Ref=off

Name	Peak Retention Time	Area	Area%	Height
	12.877	1801156	5.00	716442.20
	19.606	34222462	95.00	9428735.54

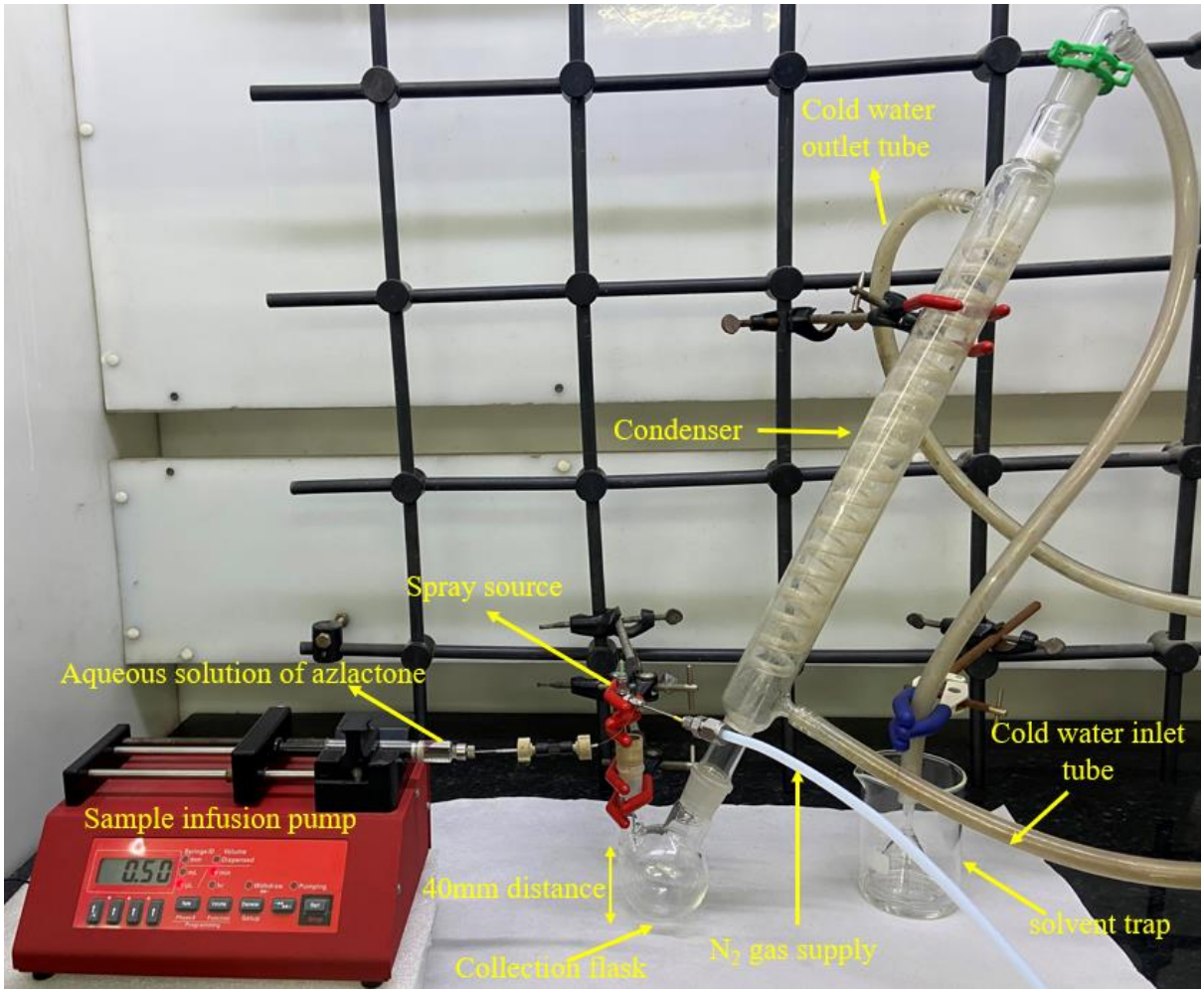
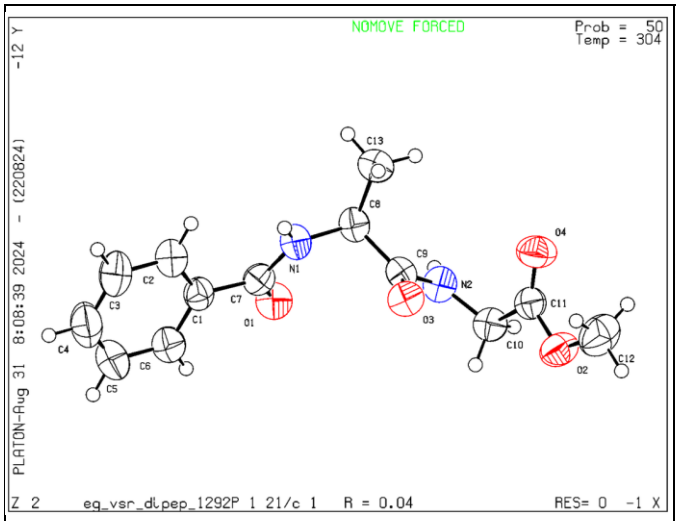
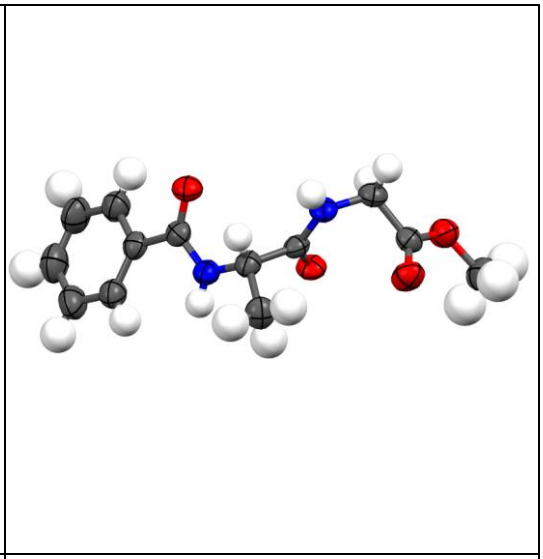


Figure S1: A picture of the experimental setup for the collection of the sprayed microdroplets in a round bottom flask (100 ml), connected to a condenser and solvent trap. The reaction duration calculated based on applied pressure, and the distance between spray source and collecting surface (40 mm). The calculated reaction duration found to be 483 µs (less than 0.5 ms).[5b]

7. X-ray crystallographic data:

Table S2. Crystal data and structure refinement of product **3a**[6]





ORTEP diagram of **3a**

Identification code	EG_VSR_DIPEP_1292_0ma_a
Empirical formula	$C_{13}H_{16}N_2O_4$
Formula weight	264.28
Temperature/K	304.0
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	13.5013(11)
b/Å	11.4480(10)
c/Å	9.0667(8)
α/°	90
β/°	100.556(4)
γ/°	90
Volume/Å^3	1377.7(2)
Z	4
ρ_{calc}g/cm^3	1.274
μ/mm^{-1}	0.095
F(000)	560.0

Crystal size/mm^3	0.146 × 0.049 × 0.021
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.698 to 50.092
Index ranges	-16 ≤ h ≤ 16, -13 ≤ k ≤ 13, -10 ≤ l ≤ 10
Reflections collected	33644
Independent reflections	2435 [R_{int} = 0.0721, R_{sigma} = 0.0336]
Data/restraints/parameters	2435/0/174
Goodness-of-fit on F^2	1.031
Final R indexes [I>=2σ (I)]	R_1 = 0.0398, wR_2 = 0.0862
Final R indexes [all data]	R_1 = 0.0682, wR_2 = 0.1037
Largest diff. peak/hole / e Å^{-3}	0.14/-0.14

Table S3 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for EG_VSR_DIPEP_1292_0ma_a. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
O1	1878.1(10)	6571.2(12)	1902.8(14)	60.8(4)
O2	6612.7(11)	5882.5(12)	5947.3(15)	68.4(4)
O3	4029.3(10)	6740.6(11)	5382.7(13)	54.4(4)
O4	6175.0(12)	7749.0(13)	5556.3(16)	71.4(4)
N1	2173.0(11)	7742.5(14)	3914.5(16)	51.2(4)
N2	4614.7(12)	7027.9(14)	3252.0(16)	52.3(4)
C1	597.7(14)	6667.3(17)	3380(2)	50.3(5)
C2	105.5(16)	7341.3(19)	4287(2)	61.3(6)
C3	-820.9(17)	7001(2)	4574(3)	78.2(7)
C4	-1263.5(18)	5989(3)	3962(3)	85.6(8)
C5	-787.8(19)	5322(2)	3060(3)	83.3(7)
C6	139.4(16)	5658.8(19)	2756(2)	67.3(6)
C7	1597.8(14)	6986.2(16)	3015(2)	48.4(5)
C8	3142.1(14)	8120.1(16)	3607(2)	50.4(5)

C9	3953.6(14)	7220.0(16)	4149.4(19)	46.4(5)
C10	5478.7(15)	6295.3(17)	3744(2)	53.4(5)
C11	6111.4(14)	6747.7(18)	5168(2)	50.6(5)
C12	7257.4(19)	6202(2)	7353(3)	86.2(8)
C13	3451.0(16)	9274.3(17)	4388(2)	67.4(6)

Table S4 Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for EG_VSR_DIPEP_1292_0ma_a. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	67.5(9)	69.6(9)	47.0(8)	-4.6(7)	15.2(7)	0.4(7)
O2	76(1)	59.6(9)	64.8(9)	-2.3(7)	0.1(8)	13.3(8)
O3	67.1(9)	62.4(8)	35.9(7)	5.1(6)	15.0(6)	2.7(7)
O4	85.1(11)	51.6(9)	72(1)	-4.6(8)	0.1(8)	-2.0(8)
N1	49.6(10)	63.6(10)	41.7(8)	-2.4(8)	11.9(7)	-3.6(8)
N2	57.6(10)	66.3(11)	34.7(8)	3.5(7)	13.3(8)	1.8(8)
C1	46.2(11)	57.6(12)	44.7(10)	6.6(9)	2.2(9)	0(1)
C2	53.0(13)	73.5(14)	57.3(12)	-1.2(11)	9.7(10)	-2.3(11)
C3	53.9(14)	107(2)	76.7(16)	1.4(14)	18.6(12)	3.1(14)
C4	52.0(15)	106(2)	97.8(19)	10.4(17)	10.3(14)	-11.2(15)
C5	60.6(16)	79.8(17)	104(2)	-4.7(15)	1.8(14)	-16.9(13)
C6	58.2(14)	66.3(14)	75.1(15)	-4.4(12)	6.0(11)	-2.1(11)
C7	51.7(12)	52.2(11)	40.2(10)	6.2(9)	5.2(9)	4.2(9)
C8	48.4(12)	61.5(13)	41.7(10)	3.9(9)	9.7(9)	-4.3(10)
C9	50.0(12)	53.5(11)	36(1)	-5.3(9)	8.9(9)	-7.5(9)
C10	59.9(13)	57.8(12)	45.6(11)	-3.6(9)	17.8(10)	0.9(10)
C11	50.7(12)	53.1(13)	51.2(11)	1.5(10)	17.9(9)	0.9(10)
C12	86.4(18)	91.7(18)	70.0(15)	-3.2(13)	-13.3(13)	19.3(14)
C13	66.7(14)	55.2(13)	79.5(15)	4.1(11)	11.4(12)	-5.8(11)

Table S5 Bond Lengths for EG_VSR_DIPEP_1292_0ma_a.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O1	C7	1.235(2)	C1	C6	1.381(3)
O2	C11	1.328(2)	C1	C7	1.493(3)
O2	C12	1.452(3)	C2	C3	1.379(3)
O3	C9	1.233(2)	C3	C4	1.373(3)
O4	C11	1.198(2)	C4	C5	1.363(3)
N1	C7	1.337(2)	C5	C6	1.385(3)
N1	C8	1.453(2)	C8	C9	1.519(3)
N2	C9	1.332(2)	C8	C13	1.521(3)
N2	C10	1.440(2)	C10	C11	1.504(3)
C1	C2	1.384(3)			

Table S6 Bond Angles for EG_VSR_DIPEP_1292_0ma_a.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C11	O2	C12	116.35(16)	O1	C7	C1	120.78(18)
C7	N1	C8	121.24(15)	N1	C7	C1	118.09(17)
C9	N2	C10	120.18(15)	N1	C8	C9	110.95(15)
C2	C1	C7	123.22(18)	N1	C8	C13	110.42(16)
C6	C1	C2	118.81(19)	C9	C8	C13	108.59(15)
C6	C1	C7	117.96(18)	O3	C9	N2	121.81(17)
C3	C2	C1	120.4(2)	O3	C9	C8	122.06(16)
C4	C3	C2	120.3(2)	N2	C9	C8	116.02(16)
C5	C4	C3	119.8(2)	N2	C10	C11	111.47(15)
C4	C5	C6	120.4(2)	O2	C11	C10	110.73(17)
C1	C6	C5	120.3(2)	O4	C11	O2	123.77(19)
O1	C7	N1	121.13(18)	O4	C11	C10	125.50(19)

Table S7 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for EG_VSR_DIPEP_1292_0ma_a.

Atom	*x*	*y*	*z*	U(eq)
H1	1965.48	8010.59	4690.2	61
H2	4525.29	7342.32	2376.19	63
H2A	401.01	8027.3	4706.58	74
H3	-1147.42	7459.9	5183.49	94
H4	-1886.03	5759.35	4163.1	103
H5	-1087.51	4636.29	2646.37	100
H6	454.74	5203.93	2128.08	81
H8	3087.96	8224.72	2522.23	60
H10A	5884.2	6261.66	2965.54	64
H10B	5254.98	5508.8	3909	64
H12A	7643.61	5534.85	7760.49	129
H12B	6849.63	6466.03	8050.08	129
H12C	7705.08	6817	7176.68	129
H13A	4101.93	9499.52	4201.9	101
H13B	3479.61	9187.34	5447.86	101
H13C	2966.26	9864.65	4006.48	101

Experimental

Single crystals of $C_{13}H_{16}N_2O_4$ **[EG_VSR_DIPEP_1292_0ma_a]** were **[]**. A suitable crystal was selected and **[]** on a **'Bruker APEX-II CCD'** diffractometer. The crystal was kept at 304.0 K during data collection. Using Olex[7], the structure was solved with the XT[8] structure solution program using Intrinsic Phasing and refined with the XL[9] refinement package using Least Squares minimisation.

Crystal structure determination of [EG_VSR_DIPEP_1292_0ma_a]

Crystal Data for $C_{13}H_{16}N_2O_4$ (M =264.28 g/mol): monoclinic, space group $P2_1/c$ (no. 14), a = 13.5013(11) Å, b = 11.4480(10) Å, c = 9.0667(8) Å, β = 100.556(4)°, V = 1377.7(2) Å^3, Z = 4, T = 304.0 K, μ(MoKα) = 0.095 mm^{-1}, *Dcalc* = 1.274 g/cm^3, 33644 reflections measured (4.698° ≤ 2Θ ≤ 50.092°), 2435 unique (R_{int} = 0.0721, R_{sigma} = 0.0336) which were used in all calculations. The final R_1 was 0.0398 (I > 2σ(I)) and wR_2 was 0.1037 (all data).

8. References:

1. (a) Armarego, W. L. F; Chai, C. L. L. purification of Laboratory Chemicals, 6th ed.; Elsevier, UK, 2009. (b) C. Macovei, P. Vicennati, J. Quinton, M.-C. Nevers, H. Volland, C. Créminon and F. Taran, *Chem. Commun.*, 2012, **48**, 4411. (c) S. Dong, X. Liu, Y. Zhu, P. He, L. Lin and X. Feng, *J. Am. Chem. Soc.*, 2013, **135**, 10026–10029.
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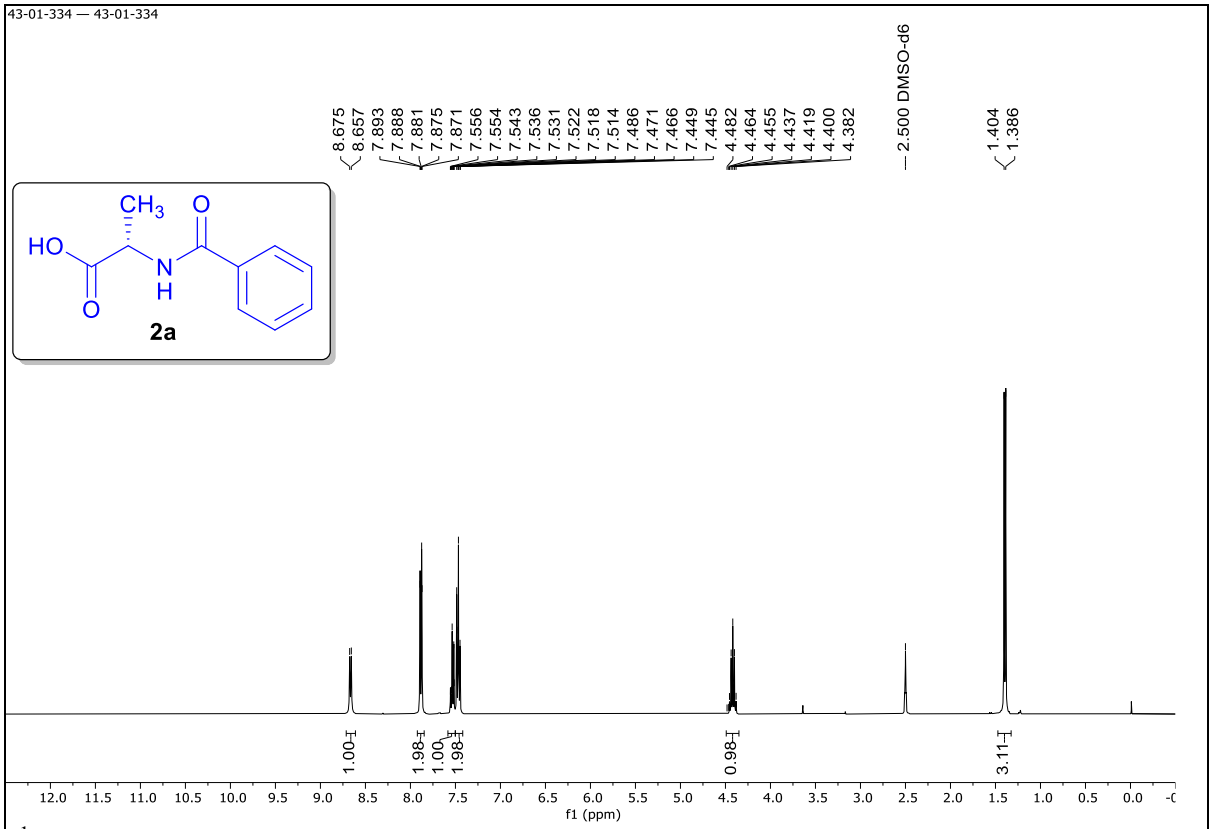
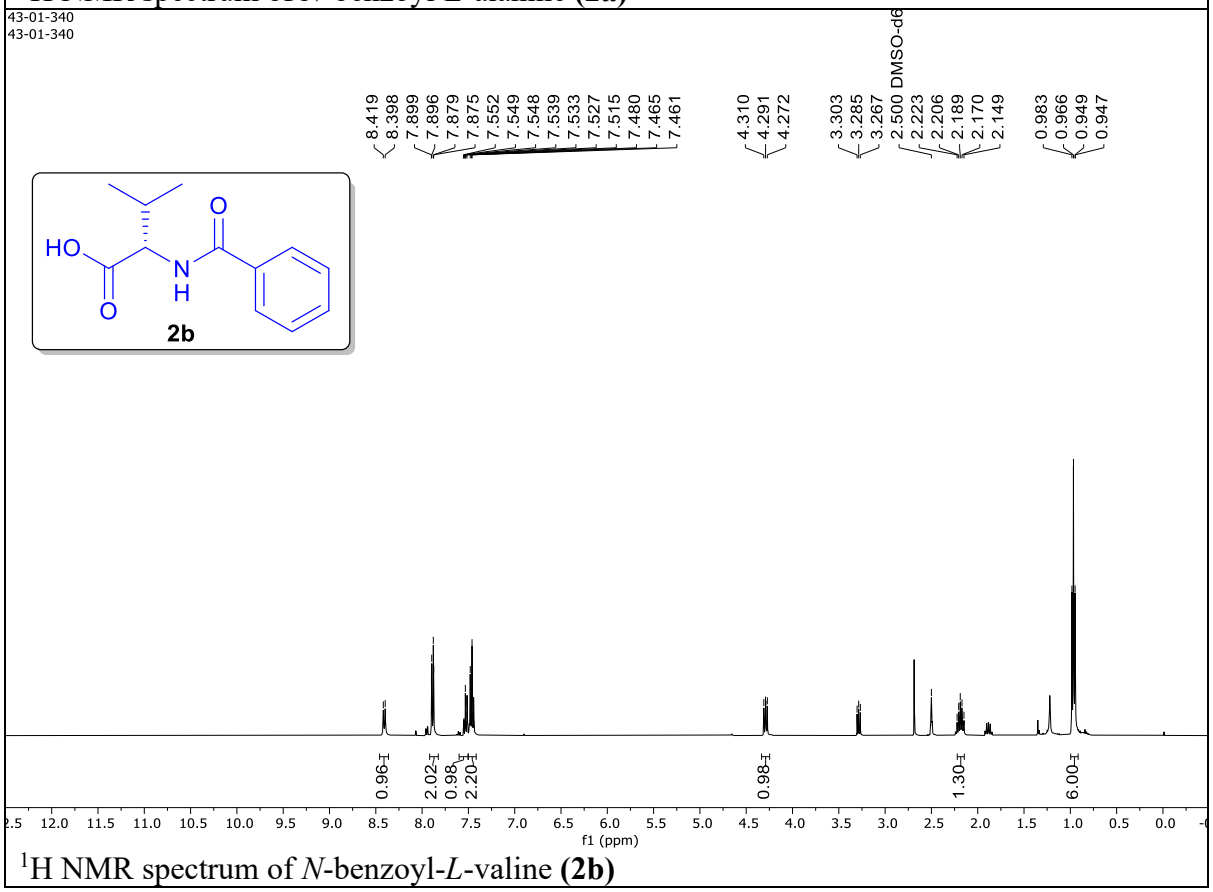
5. (a) W. Xiong, G. Lai and W. H. Liu, *Chem. Eur. J.*, 2024, **30**, e202401619. (b) J. K. Lee, S. Kim, H. G. Nam and R. N. Zare, *Proc. Natl. Acad. Sci. U. S.A.* 2015, **112**, 3898.
6. Detailed X-ray crystallographic data (CCDC No.2380911) are available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK
7. O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard, H. Puschmann, *J. Appl. Cryst.* 2009, **42**, 339-341.
8. G. M. Sheldrick, *Acta Cryst.* 2015, *A71*, 3-8.
9. G. M. Sheldrick, *Acta Cryst.* 2015, *C71*, 3-8.

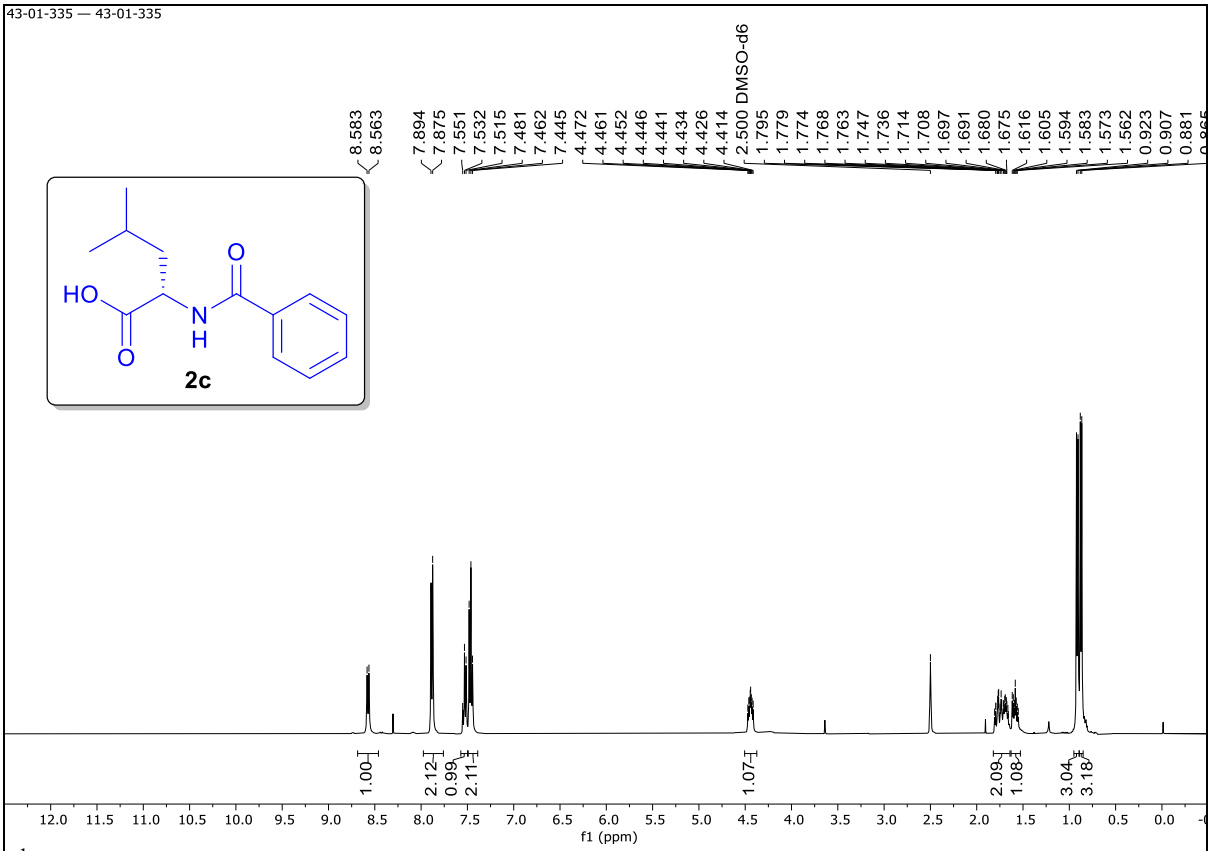
9. NMR Spectra:



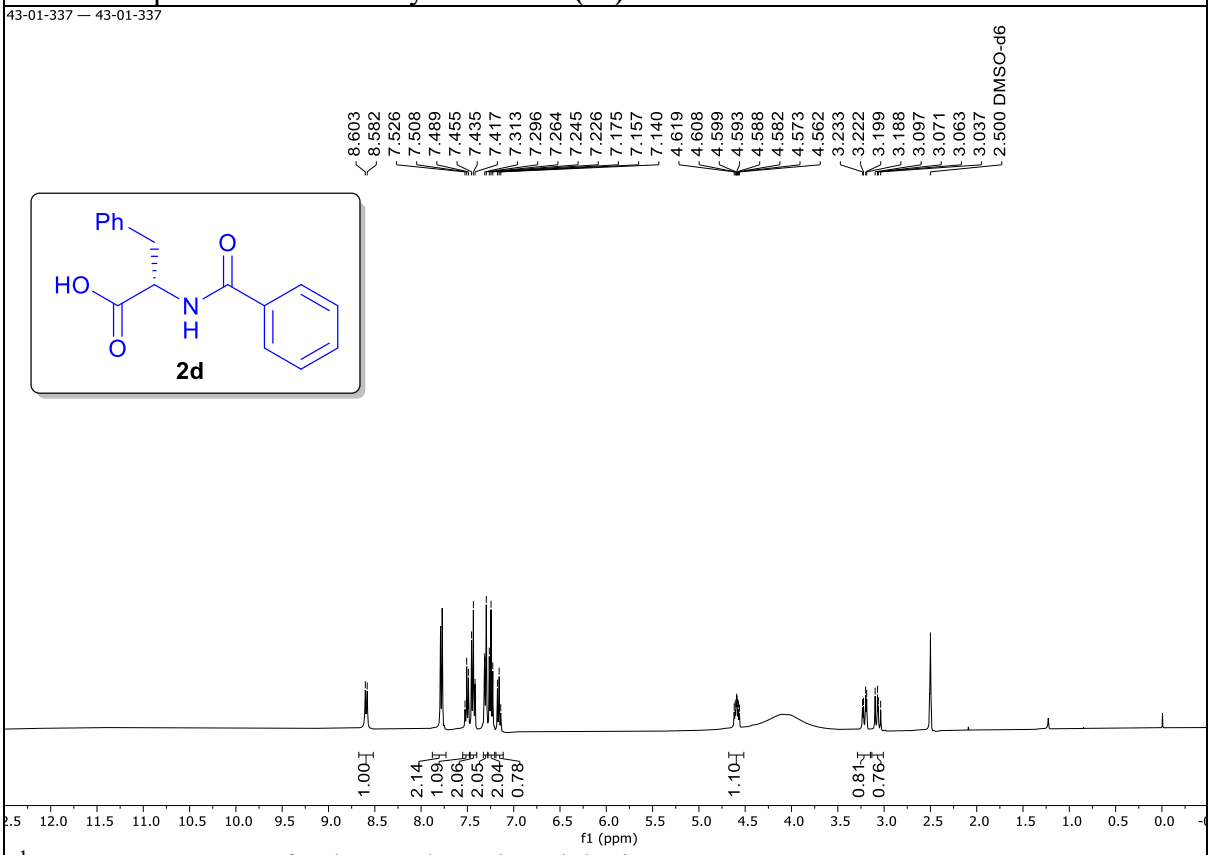
^{1}H NMR spectrum of *N*-benzoyl-*L*-alanine **(2a)**



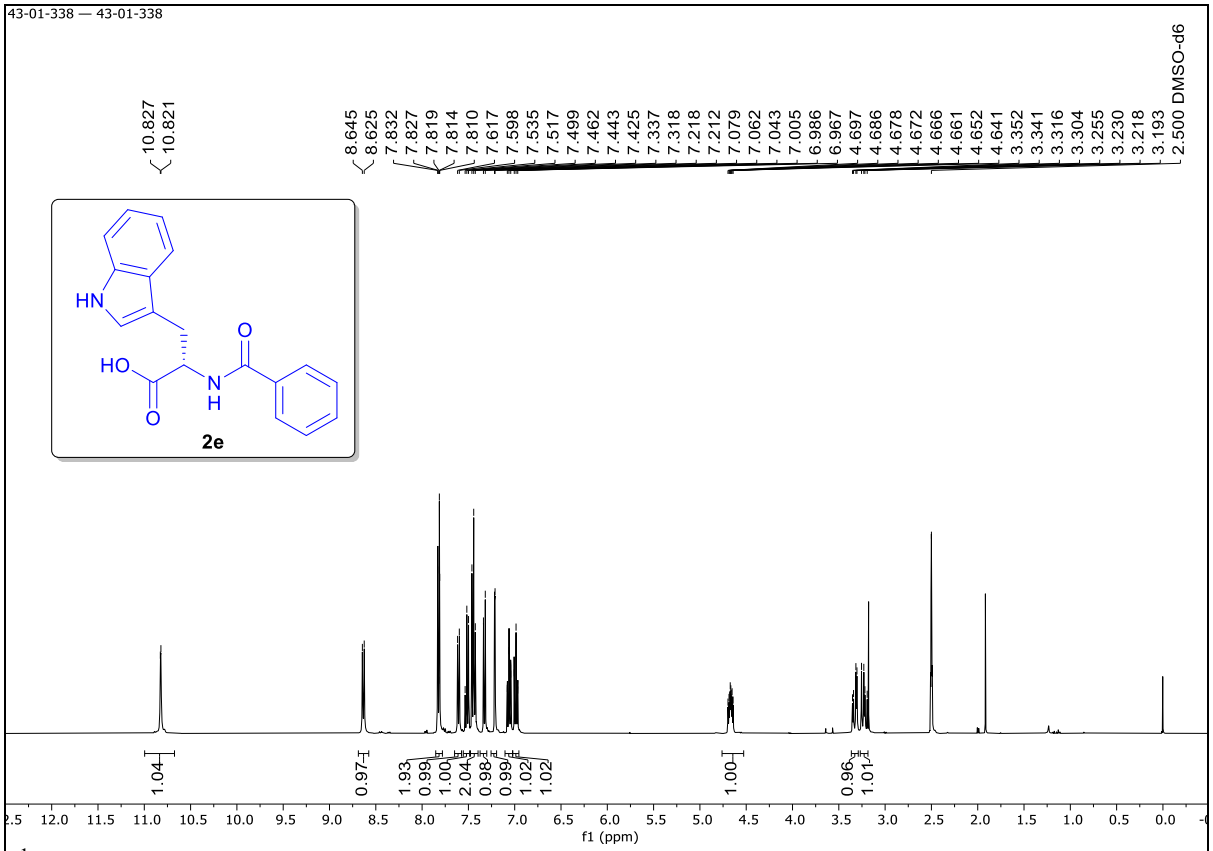
^{1}H NMR spectrum of *N*-benzoyl-*L*-valine **(2b)**



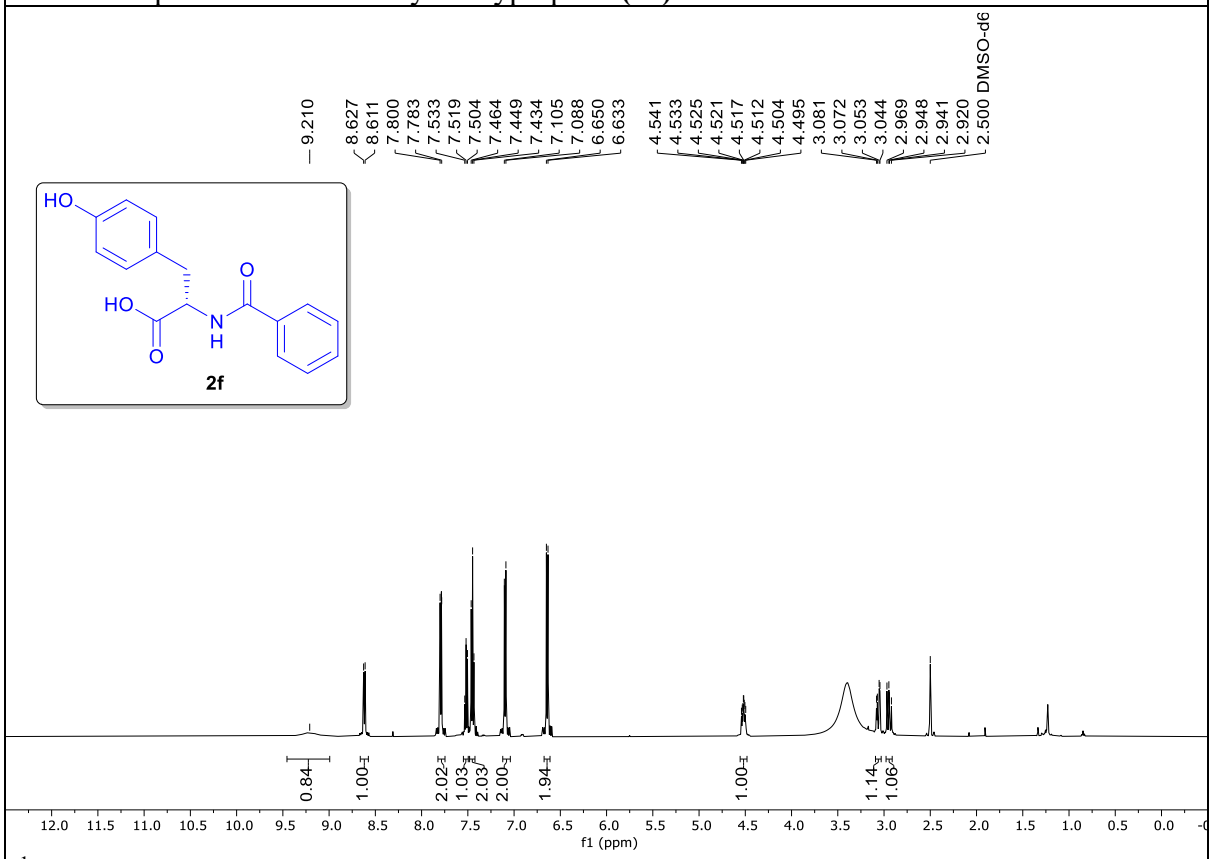
^{1}H NMR spectrum of *N*-benzoyl-*L*-leucine **(2c)**



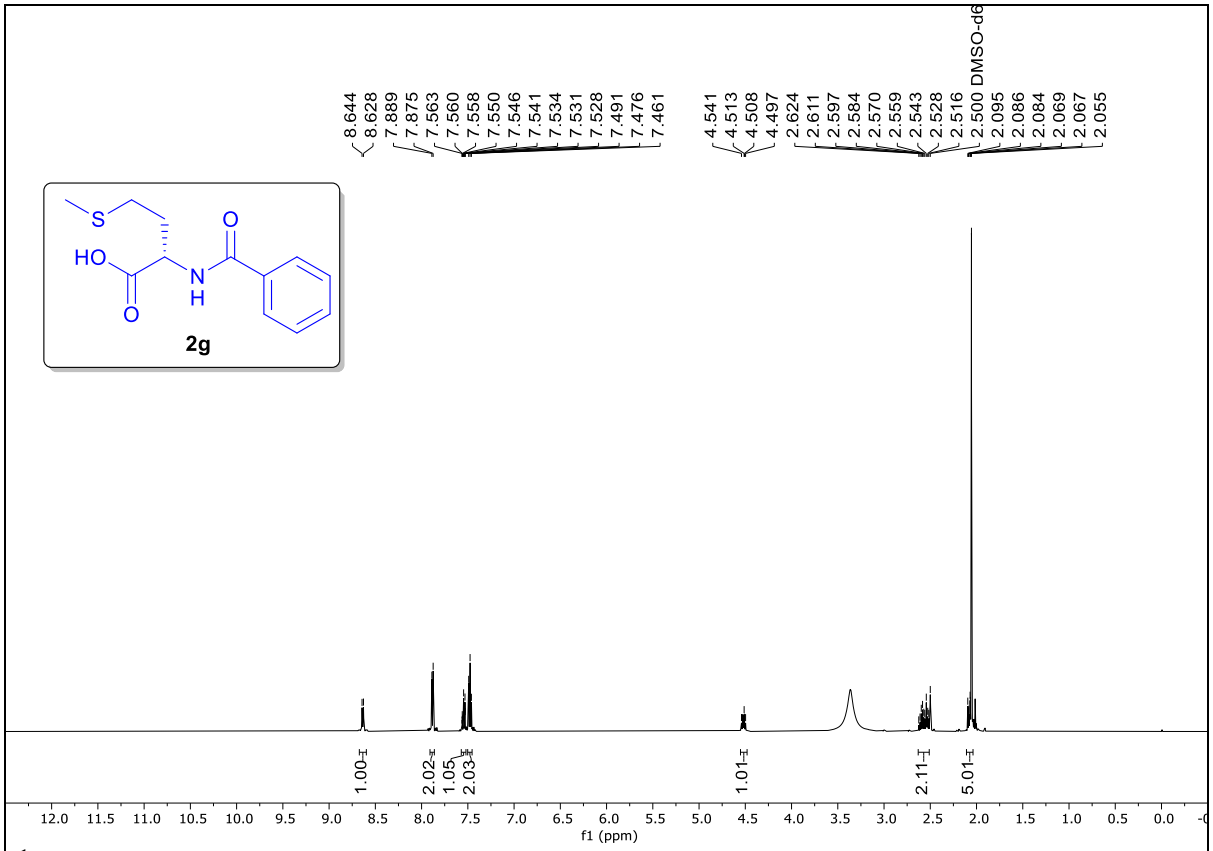
^{1}H NMR spectrum of *N*-benzoyl- *L*-phenylalanine **(2d)**



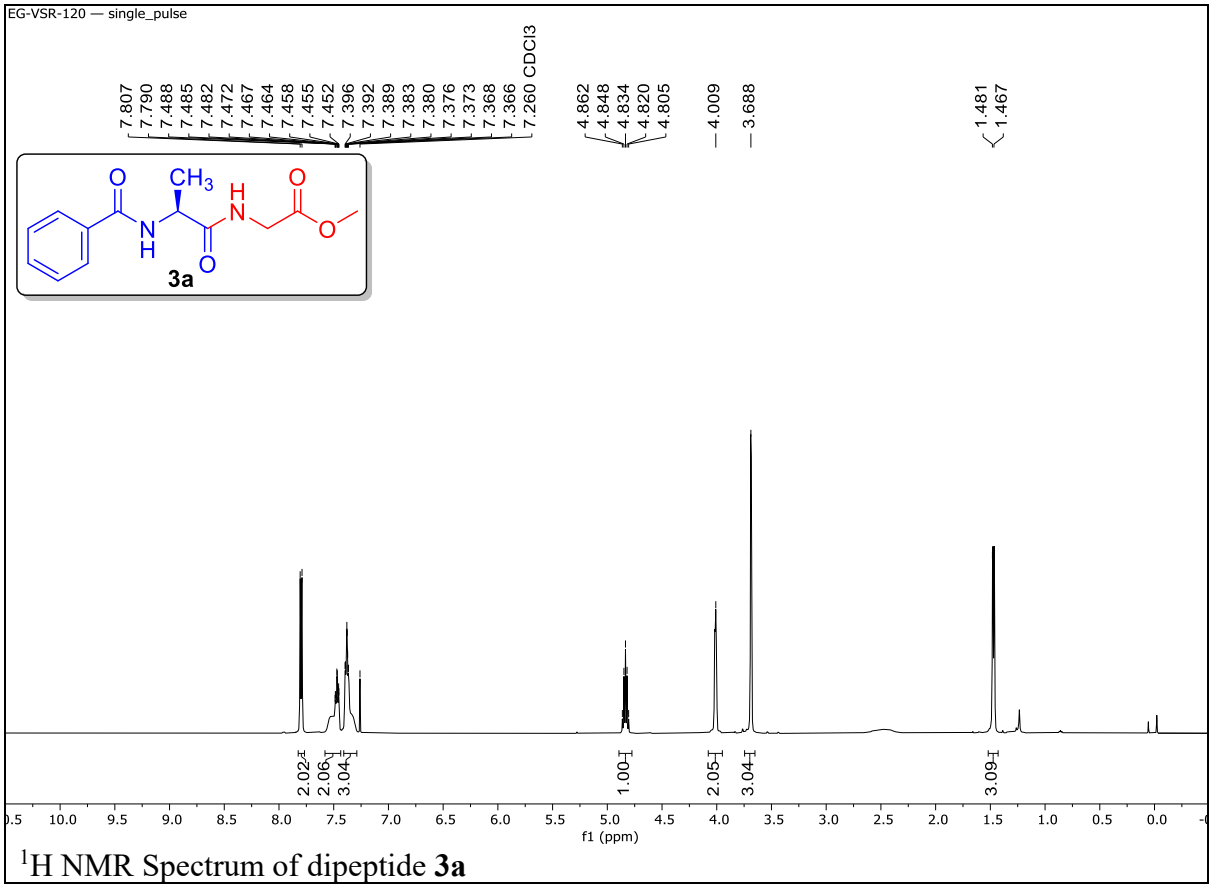
^{1}H NMR spectrum of *N*-benzoyl-*L*-tryptophan **(2e)**



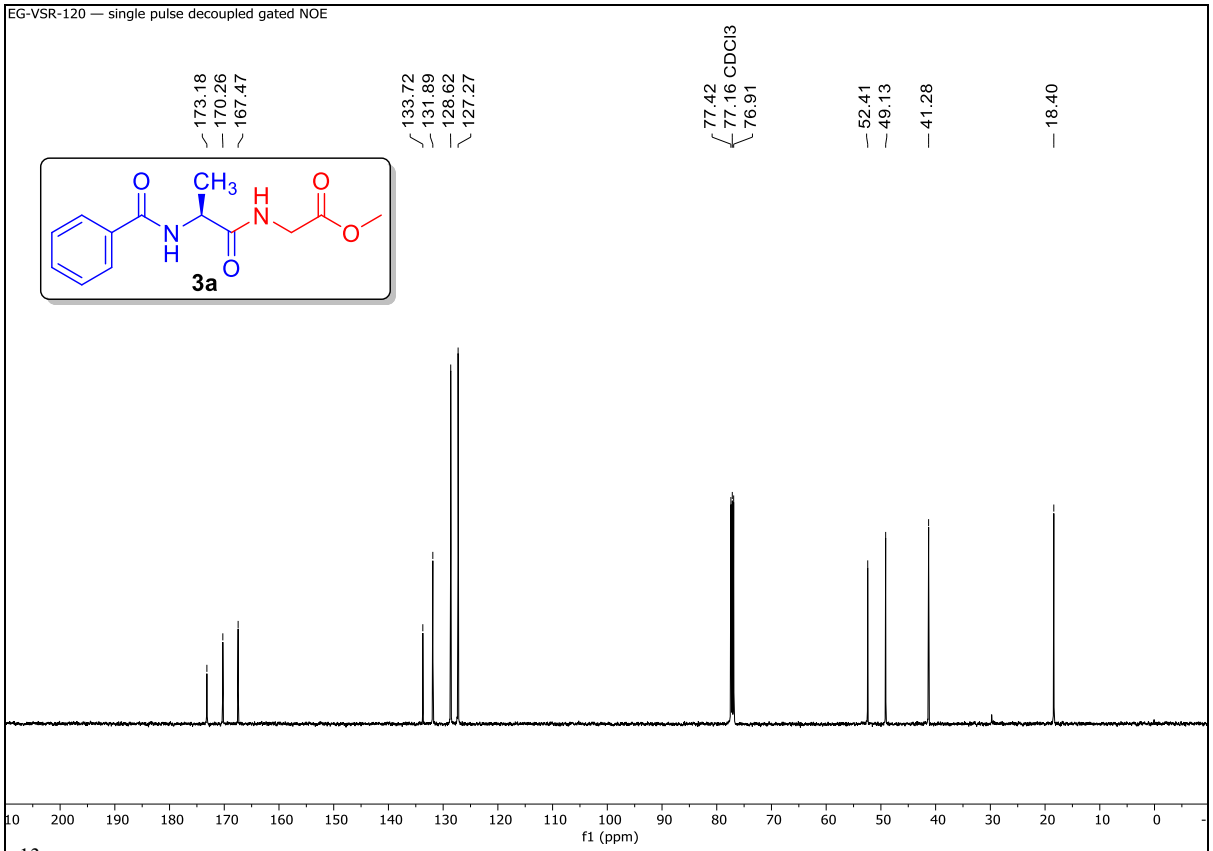
^{1}H NMR spectrum of *N*-benzoyl- *L*-tyrosine **(2f)**



^{1}H NMR spectrum of *N*-benzoyl- *L*- methionine **(2g)**



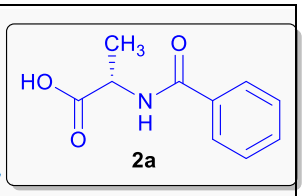
^{1}H NMR Spectrum of dipeptide **3a**



^{13}C NMR spectrum of dipeptide *L*-Ala-Gly **(3a)**

10. Polarimeter data of chiral 2 and 3a:

IIT Roorkee
Thursday, 30-AUG-2024



2a

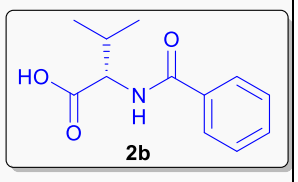
This sample was measured on an Autopol V Plus, Serial #85232
Manufactured by Rudolph Research Analytical, Hackettstown, NJ, USA.

Set Temperature : 22.0
Temperature Correction : Sucrose

n	Average	Std.Dev.	Maximum	Minimum
5	24.056	0.5128	23.869	23.247

S.No	Sample ID	Time	Result	Scale	OR °Arc	WLG	Conc.	Temp.
1	N-Bz-Ala	03:33:35 PM	24.771	SR	0.247	589	1.000	22.4
2	N-Bz-Ala	03:33:46 PM	24.393	SR	0.243	589	1.000	22.4
3	N-Bz-Ala	03:33:57 PM	24.001	SR	0.240	589	1.000	22.3
4	N-Bz-Ala	03:34:08 PM	23.247	SR	0.232	589	1.000	22.3
5	N-Bz-Ala	03:34:19 PM	23.869	SR	0.238	589	1.000	22.3

IIT Roorkee
Thursday, 29-AUG-2024



2b

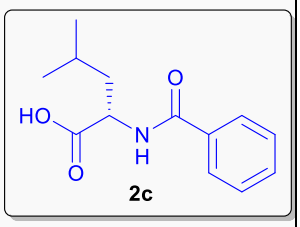
This sample was measured on an Autopol V Plus, Serial #85232
Manufactured by Rudolph Research Analytical, Hackettstown, NJ, USA.

Set Temperature : 20.0
Temperature Correction : Sucrose

n	Average	Std.Dev.	Maximum	Minimum
5	10.370	0.1208	10.555	10.267

S.No	Sample ID	Time	Result	Scale	OR °Arc	WLG	Conc.	Temp.
1	N-Bz-Val	03:44:26 PM	10.339	SR	0.113	589	1.090	20.4
2	N-Bz-Val	03:44:37 PM	10.269	SR	0.112	589	1.090	20.4
3	N-Bz-Val	03:44:48 PM	10.555	SR	0.115	589	1.090	20.3
4	N-Bz-Val	03:44:59 PM	10.267	SR	0.112	589	1.090	20.3
5	N-Bz-Val	03:45:10 PM	10.419	SR	0.114	589	1.090	20.3

IIT Roorkee
Thursday, 29-AUG-2024



2c

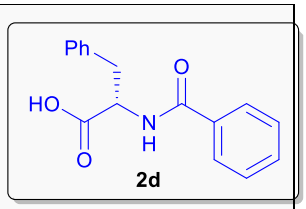
This sample was measured on an Autopol V Plus, Serial #85232
Manufactured by Rudolph Research Analytical, Hackettstown, NJ, USA.

Set Temperature : 22.0
Temperature Correction : Sucrose

n	Average	Std.Dev.	Maximum	Minimum
5	-9.003	0.1995	-9.197	-8.700

S.No	Sample ID	Time	Result	Scale	OR °Arc	WLG	Conc.	Temp.
1	N-Bz-Leu	04:05:52 PM	-9.197	SR	-0.099	589	1.080	22.0
2	N-Bz-Leu	04:06:03 PM	-8.915	SR	-0.096	589	1.080	22.0
3	N-Bz-Leu	04:06:14 PM	-9.065	SR	-0.098	589	1.080	22.1
4	N-Bz-Leu	04:06:25 PM	-8.700	SR	-0.094	589	1.080	22.1
5	N-Bz-Leu	04:06:36 PM	-9.138	SR	-0.099	589	1.080	22.1

IIT Roorkee
Thursday, 29-AUG-2024



2d

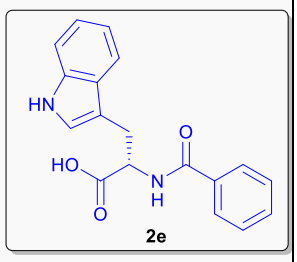
This sample was measured on an Autopol V Plus, Serial #85232
Manufactured by Rudolph Research Analytical, Hackettstown, NJ, USA.

Set Temperature : 20.0
Temperature Correction : Sucrose

n	Average	Std.Dev.	Maximum	Minimum
5	-32.016	0.5289	-32.671	-31.247

S.No	Sample ID	Time	Result	Scale	OR °Arc	WLG	Conc.	Temp.
1	N-Bz-PhAla	03:33:35 PM	-32.671	SR	-0.356	589	1.090	20.4
2	N-Bz-PhAla	03:33:46 PM	-32.293	SR	-0.352	589	1.090	20.4
3	N-Bz-PhAla	03:33:57 PM	-32.001	SR	-0.349	589	1.090	20.3
4	N-Bz-PhAla	03:34:08 PM	-31.247	SR	-0.341	589	1.090	20.3
5	N-Bz-PhAla	03:34:19 PM	-31.869	SR	-0.347	589	1.090	20.3

IIT Roorkee
Thursday, 29-AUG-2024



2e

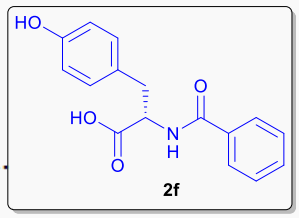
This sample was measured on an Autopol V Plus, Serial #85232
Manufactured by Rudolph Research Analytical, Hackettstown, NJ, USA.

Set Temperature : 20.0
Temperature Correction : Sucrose

n	Average	Std.Dev.	Maximum	Minimum
5	-32.250	0.0909	-32.363	-32.116

S.No	Sample ID	Time	Result	Scale	OR °Arc	WLG	Conc.	Temp.
1	N-BZ-Trp	03:24:56 PM	-32.225	SR	-0.348	589	1.080	20.4
2	N-BZ-Trp	03:25:07 PM	-32.291	SR	-0.349	589	1.080	20.4
3	N-BZ-Trp	03:25:18 PM	-32.363	SR	-0.350	589	1.080	20.3
4	N-BZ-Trp	03:25:29 PM	-32.116	SR	-0.347	589	1.080	20.3
5	N-BZ-Trp	03:25:40 PM	-32.253	SR	-0.348	589	1.080	20.2

IIT Roorkee
Thursday, 10-OCT-2024



2f

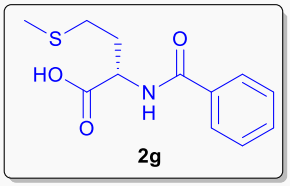
This sample was measured on an Autopol V Plus, Serial #85232
Manufactured by Rudolph Research Analytical, Hackettstown, NJ, USA.

Set Temperature : 25.0
Temperature Correction : Sucrose

n	Average	Std.Dev.	Maximum	Minimum
5	-33.410	1.4177	-35.775	-32.324

S.No	Sample ID	Time	Result	Scale	OR °Arc	WLG	Conc.	Temp.
1	N_Bz_Tyro	11:00:39 AM	-32.999	SR	-0.330	589	1.000	25.4
2	N_Bz_Tyro	11:00:49 AM	-33.575	SR	-0.336	589	1.000	25.3
3	N_Bz_Tyro	11:01:00 AM	-35.775	SR	-0.358	589	1.000	25.3
4	N_Bz_Tyro	11:01:10 AM	-32.375	SR	-0.324	589	1.000	25.2
5	N_Bz_Tyro	11:01:20 AM	-32.324	SR	-0.323	589	1.000	25.2

IIT Roorkee
Thursday, 10-OCT-2024



2g

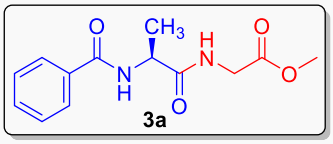
This sample was measured on an Autopol V Plus, Serial #85232
Manufactured by Rudolph Research Analytical, Hackettstown, NJ, USA.

Set Temperature : 25.0
Temperature Correction : Sucrose

n	Average	Std.Dev.	Maximum	Minimum
5	-14.501	0.0635	-14.562	-14.410

S.No	Sample ID	Time	Result	Scale	OR °Arc	WLG	Conc.	Temp.
1	N_BZ_Meth	10:48:53 AM	-14.486	SR	-0.145	589	1.000	25.2
2	N_BZ_Meth	10:49:04 AM	-14.562	SR	-0.146	589	1.000	25.2
3	N_BZ_Meth	10:49:14 AM	-14.562	SR	-0.146	589	1.000	25.2
4	N_BZ_Meth	10:49:24 AM	-14.487	SR	-0.145	589	1.000	25.1
5	N_BZ_Meth	10:49:34 AM	-14.410	SR	-0.144	589	1.000	25.1

IIT Roorkee
Saturday, 31-AUG-2024



3a

This sample was measured on an Autopol V Plus, Serial #85232
Manufactured by Rudolph Research Analytical, Hackettstown, NJ, USA.

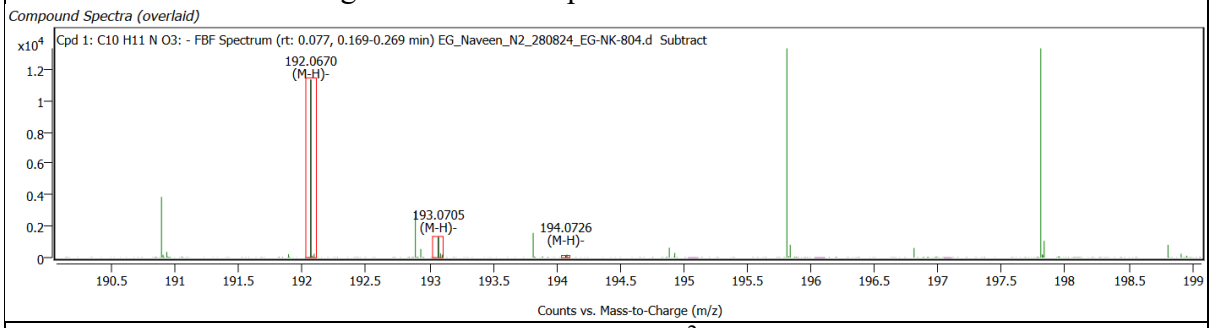
Set Temperature : 25.0
Temperature Correction : Sucrose

n	Average	Std.Dev.	Maximum	Minimum
5	-23.740	0.4370	-24.209	-23.168

S.No	Sample ID	Time	Result	Scale	OR °Arc	WLG	Conc.	Temp.
1	Me BEZ-L-ALAGLY	12:29:36 PM	-23.168	SR	-0.232	589	1.000	25.1
2	Me BEZ-L-ALAGLY	12:29:46 PM	-23.398	SR	-0.234	589	1.000	25.0
3	Me BEZ-L-ALAGLY	12:30:01 PM	-23.954	SR	-0.240	589	1.000	25.0
4	Me BEZ-L-ALAGLY	12:30:11 PM	-24.209	SR	-0.242	589	1.000	24.9
5	Me BEZ-L-ALAGLY	12:30:21 PM	-23.972	SR	-0.240	589	1.000	24.9

11. MS and MS^2 data of 2a:

Negative ion mode spectrum of MS data of **2a:**



Positive ion mode of MS^2 data of **2a:**