Electronic Supplementary Information (ESI)

A novel approach to amino acid synthesis: acid-assisted reactions with dimethyl carbonate for efficient O-methylated, N,O-methylated and N-formylated derivatives

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Contents

The nature of amino acid

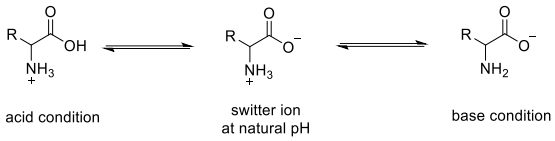


Table S1 The p*Ka* values of alanine, phenylalanine, leucine, methionine, H_2SO_4, $HClO_4$, HCl, HCO_2H, DMC, H_2O, RNH_3^+, MeOH and $MeOH^{+1–3}$

Compound		p*ka*
Alanine	α-COOH	2.35
	α -NH_3^+	9.87
Phenylalanine	α -COOH	2.58
	α -NH_3^+	9.24
Leucine	α -COOH	2.33
	α -NH_3^+	9.74
methionine	α -COOH	2.17
	α -NH_3^+	9.27
H_2SO_4		-2
HSO_4^-		2
$HClO_4$		-10
HCl		-7
HNO_3		-1.5
formic acid		3.75
H_2O		15.74
H_3O^+		-1.7
MeOH		15.54
$MeOH_2^+$		-2.2
R-NH_2		35-45

Table S2 The experimental results of monomethylation products synthesised from different amino acids (1 equivalent) with DMC (20 equivalent) promoted by stoichiometric amount (1.00 equivalent) of $HClO_4$ at 150 °C

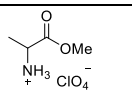
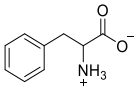
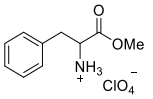
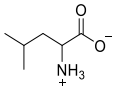
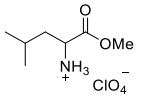
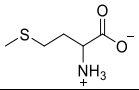
Substrate	Product	% conversion	yield
		>99	>99
		>99	>99
		>99	>99
	unknown	>99	-

Table S3 The experimental results of dimethylation products synthesised from different amino acids (1 equivalent) with DMC (40 equivalent) promoted by stoichiometric amount (1.00 equivalent) of H_2SO_4 at 150 °C

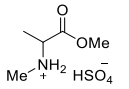
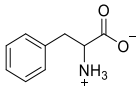
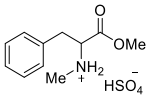
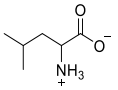
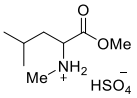
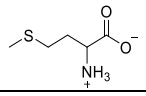
Substrate	Product	% conversion	yield
		>99	>99
		>99	>99
		>99	>99
	unknown	>99	-

Table S4 The experimental results of formylation products synthesised from different amino acids (1 equivalent) with DMC (20 equivalent) promoted by stoichiometric amount (1.00 equivalent) of formic acid at 150 °C

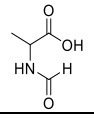
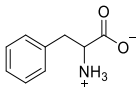
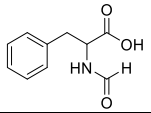
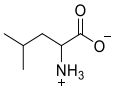
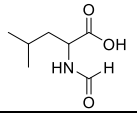
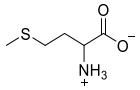
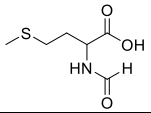
Substrate	Product	% conversion	yield
		>99	>99
		>99	>99
		>99	>99
		>99	>99

Table S5 All experimental results of reaction of amino acids promoted by stoichiometric amount (1.00 equivalent) of different acid catalysts with DMC (20, 40 and 80 equivalent) at 150 °C

Substrate (1 mmol)	Catalyst (1 mmol)	Product	DMC (mmol)		
			20	40	80
			%Conversion	%Conversion	%Conversion
alanine	$HClO_4$	A1	>99	79.38	53.70
phenylalanine	$HClO_4$	A2	>99	80.15	49.26
leucine	$HClO_4$	A3	>99	87.71	53.70
methionine	$HClO_4$	Decomposition			
alanine	H_2SO_4	B1	59.68	>99	73.04
phenylalanine	H_2SO_4	B2	50.00	>99	68.15
leucine	H_2SO_4	B3	53.92	>99	71.26
methionine	H_2SO_4	Decomposition			
alanine	formic	C1	>99	92.44	86.59
phenylalanine	formic	C2	>99	88.97	79.29
leucine	formic	C3	>99	92.68	86.34
methionine	formic	C4	>99	87.40	82.45
alanine	HNO_3	unknown	not selective		
phenylalanine	HNO_3	unknown	not selective		
leucine	HNO_3	unknown	not selective		
methionine	HNO_3	unknown	not selective		
alanine	HCl	unknown	not selective		
phenylalanine	HCl	unknown	not selective		
leucine	HCl	unknown	not selective		
methionine	HCl	unknown	not selective		
alanine	$FeCl_3$	unknown	not selective		
phenylalanine	$FeCl_3$	unknown	not selective		
leucine	$FeCl_3$	unknown	not selective		
methionine	$FeCl_3$	unknown	not selective		
alanine	$AlCl_3$	unknown	not selective		
phenylalanine	$AlCl_3$	unknown	not selective		
leucine	$AlCl_3$	unknown	not selective		
methionine	$AlCl_3$	unknown	not selective		
alanine	H_2SO_4-SiO_2	unknown	not selective		
phenylalanine	H_2SO_4-SiO_2	unknown	not selective		
leucine	H_2SO_4-SiO_2	unknown	not selective		
methionine	H_2SO_4-SiO_2	unknown	not selective		
alanine	$HClO_4$-SiO_2	unknown	not selective		
phenylalanine	$HClO_4$-SiO_2	unknown	not selective		
leucine	$HClO_4$-SiO_2	unknown	not selective		
methionine	$HClO_4$-SiO_2	unknown	not selective		

The products of reaction of amino acids with DMC in the acid catalyzed.

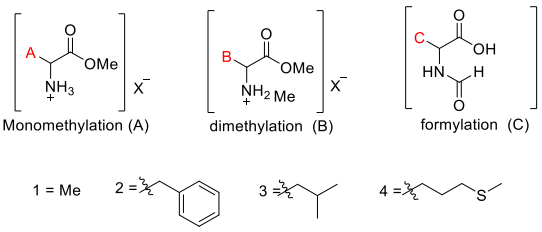


Table S6 Optical rotation experiment in EtOH

Substrate	Optical rotation of substrate	Optical rotation of product		
		$HClO_4$ condition	H_2SO_4 condition	HCO_2H condition
L-alanine	$[\alpha]^{27}$ +62.90 (*c* 0.6)	$[\alpha]^{27}$ +35.65 (*c* 0.6)	$[\alpha]^{27}$ +29.97 (*c* 0.6)	$[\alpha]^{27}$ +24.11 (*c* 0.5)
L-leucine	$[\alpha]^{27}$ +8.31 (*c* 0.25)	$[\alpha]^{27}$ +47.55 (*c* 1.0)	$[\alpha]^{27}$ +26.54 (*c* 0.3)	$[\alpha]^{27}$ +13.65 (*c* 0.8)
L-proline	$[\alpha]^{27}$ +19.39 (*c* 1.0)	$[\alpha]^{27}$ +47.55 (*c* 1.0)	$[\alpha]^{27}$ +25.18 (*c* 0.5)	$[\alpha]^{27}$ +9.03 (*c* 0.5)
L-histidine	$[\alpha]^{27}$ +19.39 (*c* 1.0)	$[\alpha]^{27}$ +10.12 (*c* 0.8)	-	$[\alpha]^{27}$ +22.81 (*c* 1.0)
L-tyrosine	$[\alpha]^{27}$ +31.1 (*c* 1.0)	$[\alpha]^{27}$ +78.14 (*c* 0.6)	[α]27 +40.37 (*c* 0.6)	$[\alpha]^{27}$ +72.18 (*c* 0.7)
L-glutamine	$[\alpha]^{27}$ +42.15 (*c* 0.7)	$[\alpha]^{27}$ +32.80 (*c* 1.0)	-	$[\alpha]^{27}$ +40.56 (*c* 0.7)
L-tryptophan	$[\alpha]^{27}$ +44.43 (*c* 0.6)	$[\alpha]^{27}$ +110.2 (*c* 1.0)	$[\alpha]^{27}$ +34.86 (*c* 0.2)	$[\alpha]^{27}$ +72.71 (*c* 0.7)

2. Characterization of structures of products

DL-alanine methyl ester. ^{1}H-NMR (CD_3OD): δ 4.13-4.08 (q, 1H), 3.82 (s, 3H), 1.53-1.51 (d, 3H); ^{13}C-NMR (CD_3OD): δ 170.08, 52.50, 48.64, 14.90.

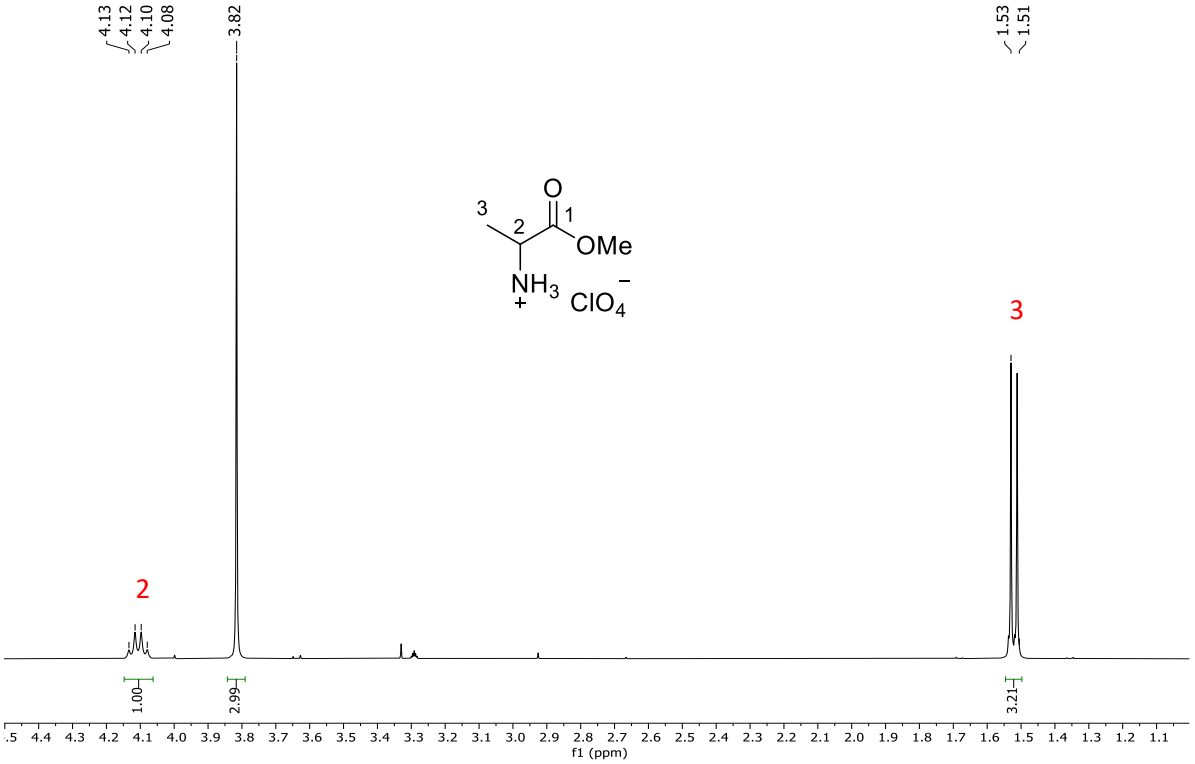


Figure S1. ^{1}H NMR of DL-alanine methyl ester in CD_3OD

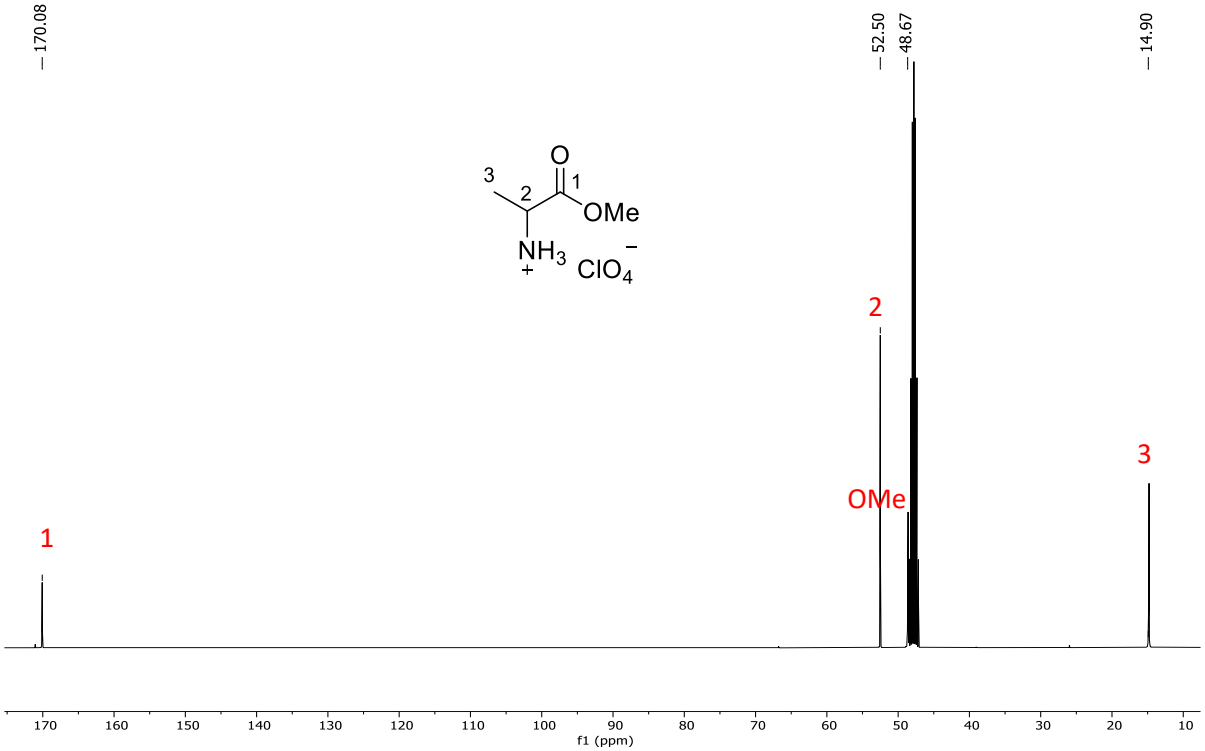


Figure S2. ^{13}C NMR of DL-alanine methyl ester in CD_3OD

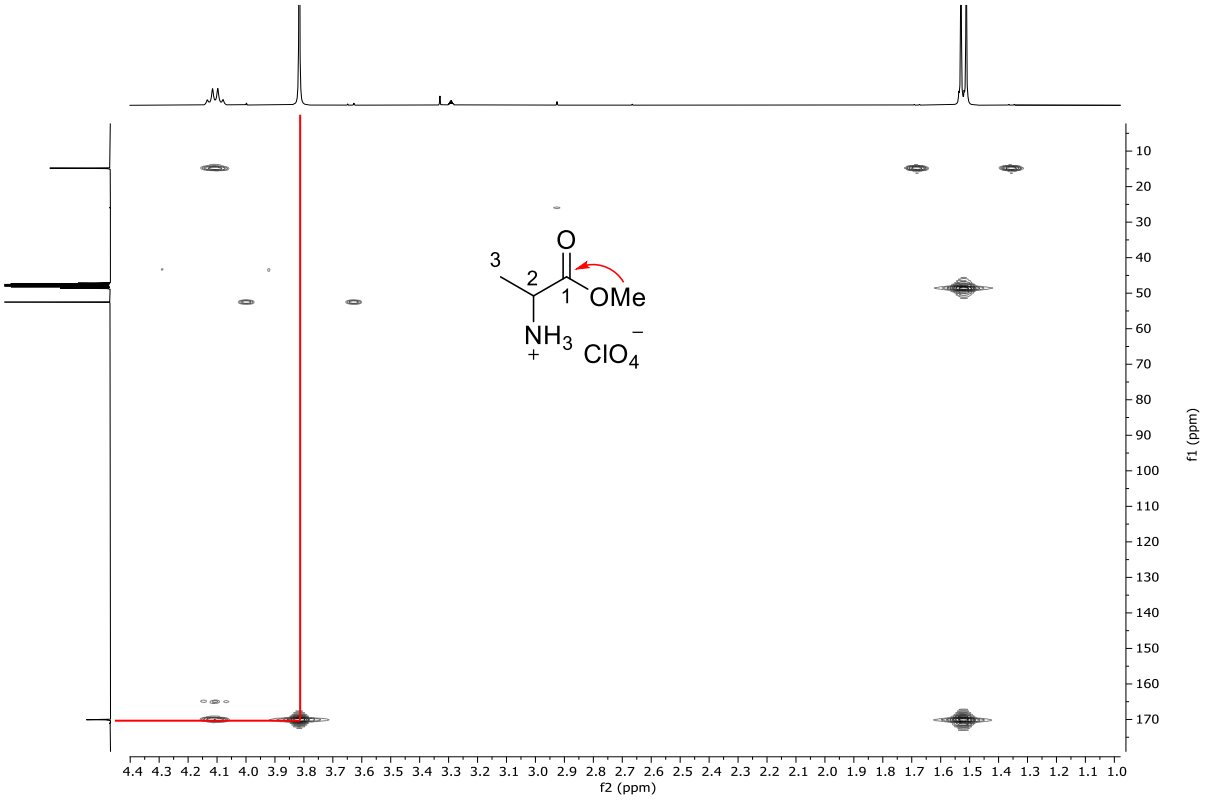


Figure S3. HMBC of DL-alanine methyl ester in CD_3OD

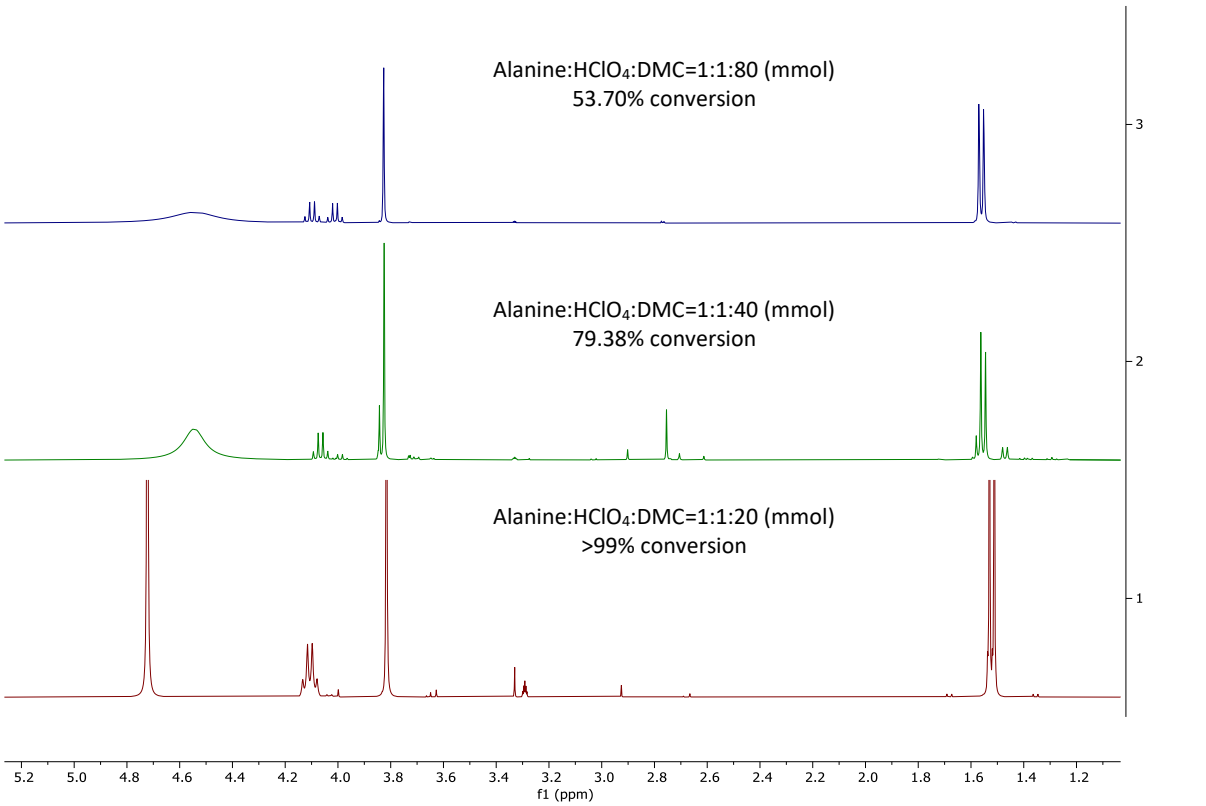


Figure S4. Compare the effect DMC assisted by $HClO_4$ in the reaction of alanine

DL-phenylalanine methyl ester. ^{1}H-NMR (DMSO-d_6+ CD_3OD): δ 7.44-7.30 (m, 5H), 4.40-4.35 (t, 1H), 3.75 (s, 3H), 3.24-3.12 (m, 2H); ^{13}C-NMR (DMSO-d_6+$CDCl_3$): δ 169.65, 134.32, 129.82, 129.34, 54.46, 53.45, 36.57.

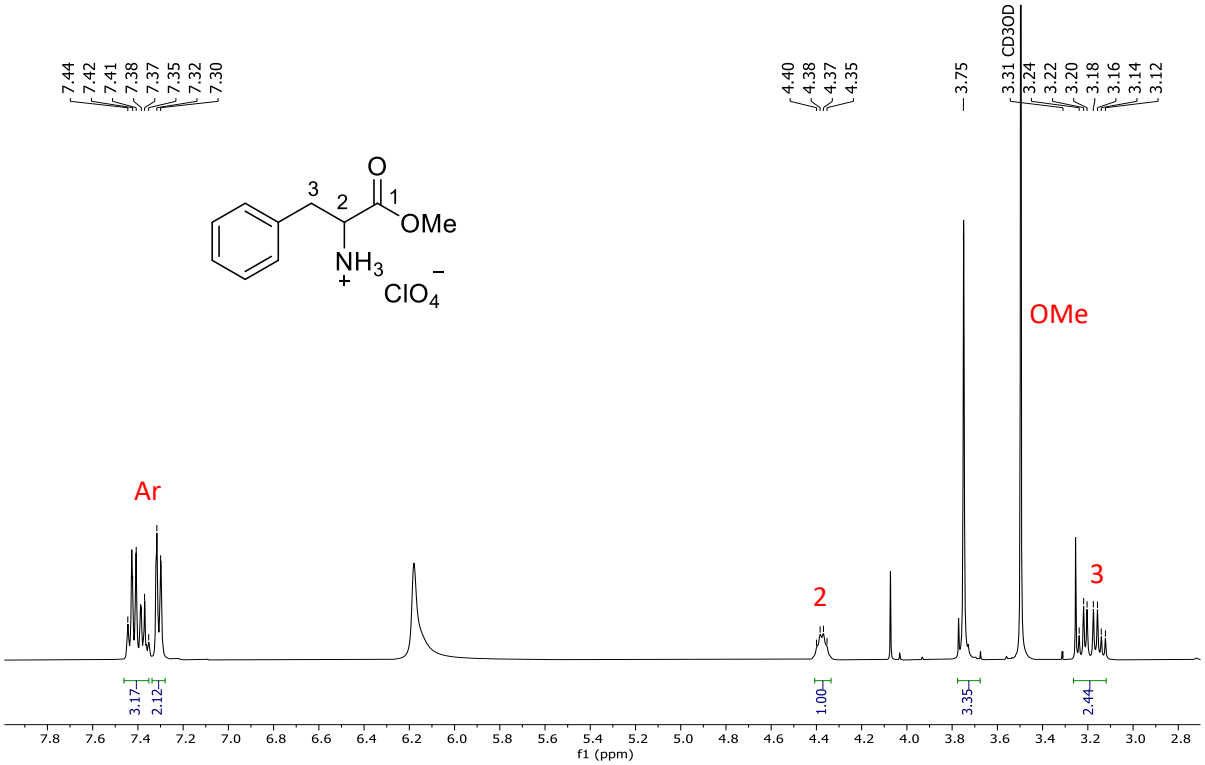


Figure S5. ^{1}H NMR of DL-phenylalanine methyl ester in DMSO-d_6+CD_3OD

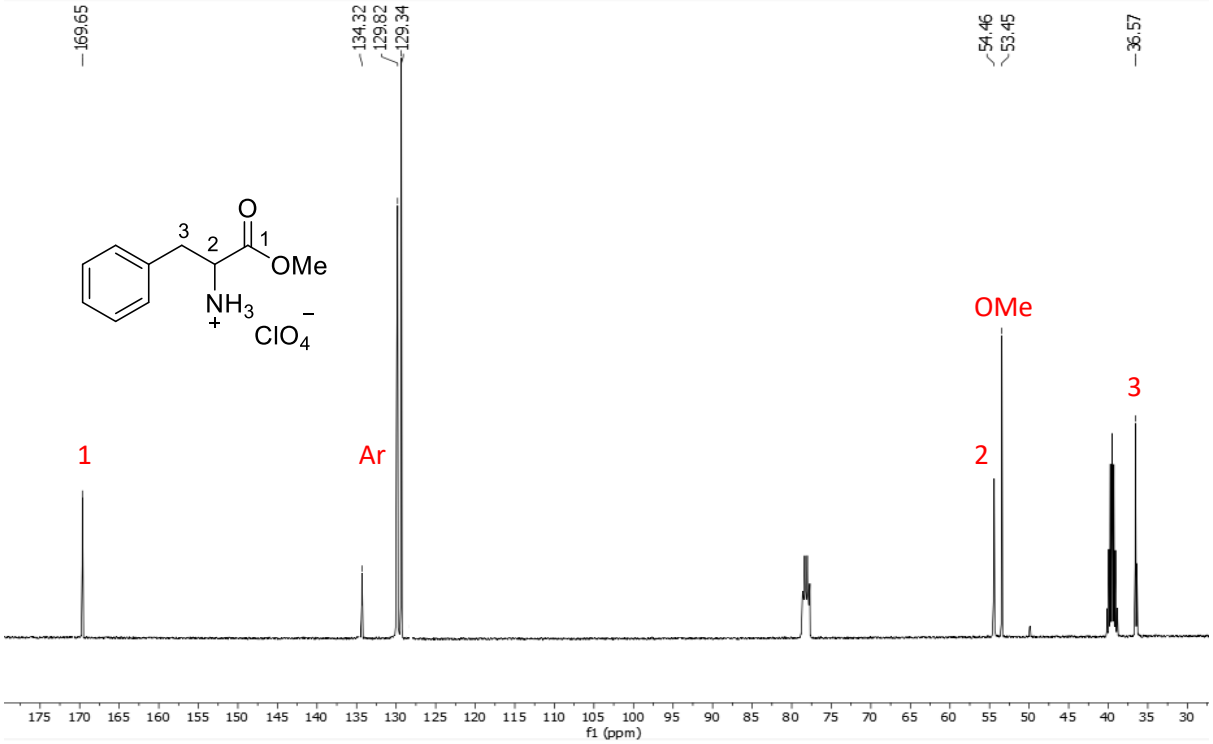


Figure S6. ^{13}C NMR of DL-phenylalanine methyl ester in DMSO-d_6+$CDCl_3$

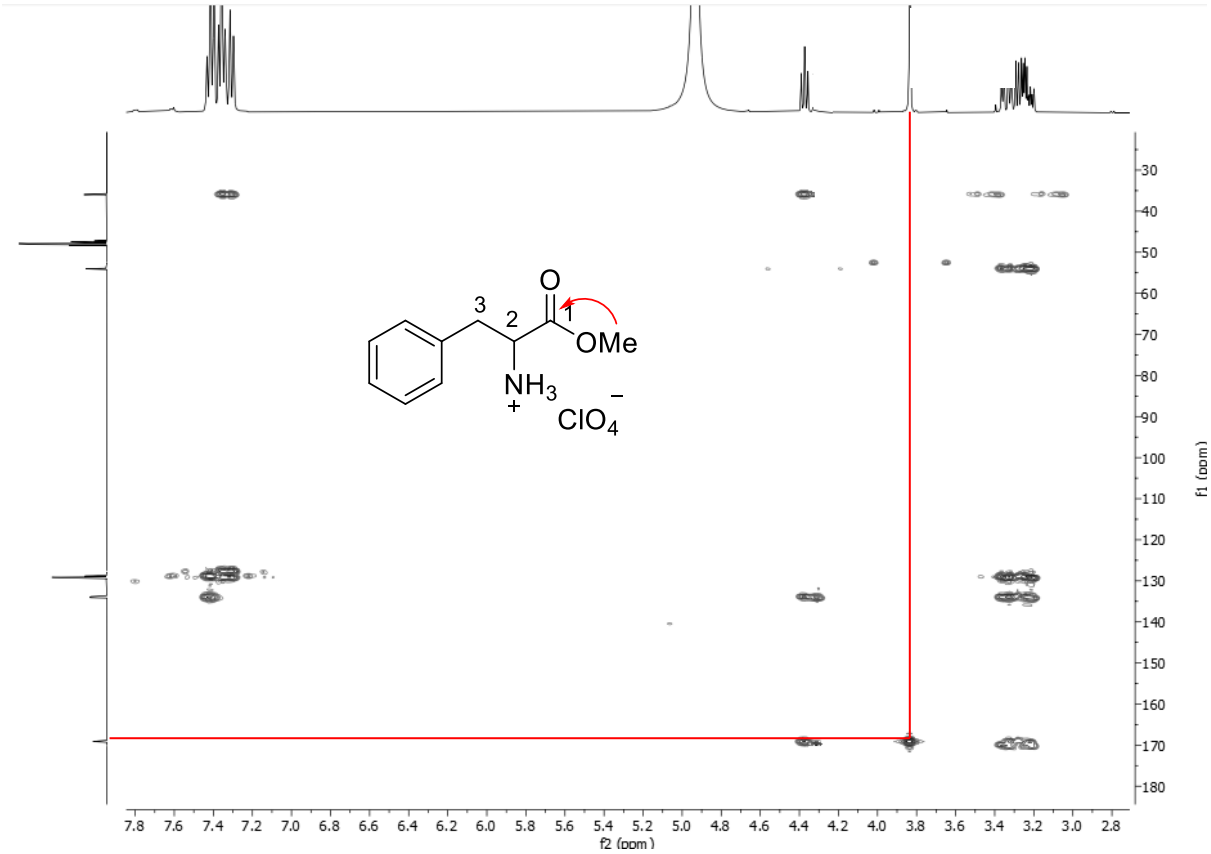


Figure S7. HMBC of DL- phenylalanine in CD_3OD

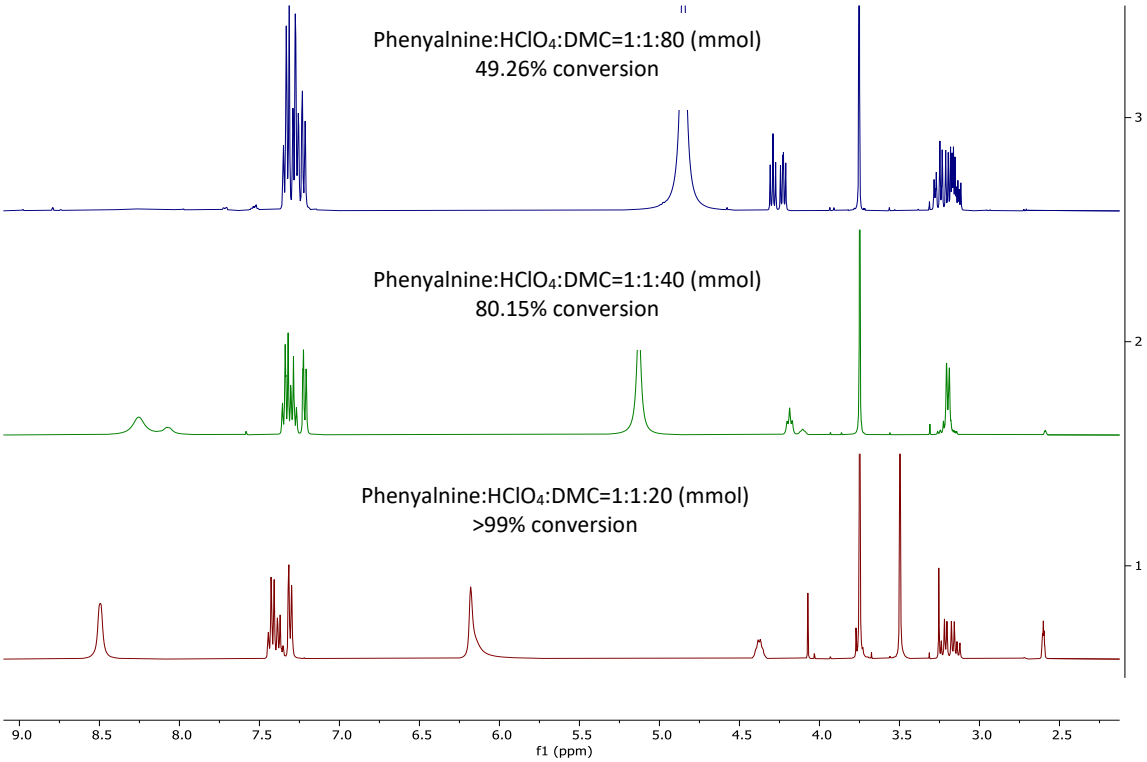


Figure S8. Compare the effect DMC assisted by $HClO_4$ in the reaction of phenylalanine

DL-leucine methyl ester. ^{1}H-NMR ($CD_3OD+CDCl_3$): δ 4.01 (t, 1H), 3.77 (s, 3H), 1.76-1.67 (m, 3H), 1.65 (m, 2H), 0.94 (m, 6H); 13C-NMR ($CD_3OD+CDCl_3$): δ 170.24, 53.29, 51.70, 39.28, 24.17, 21.81, 21.52.

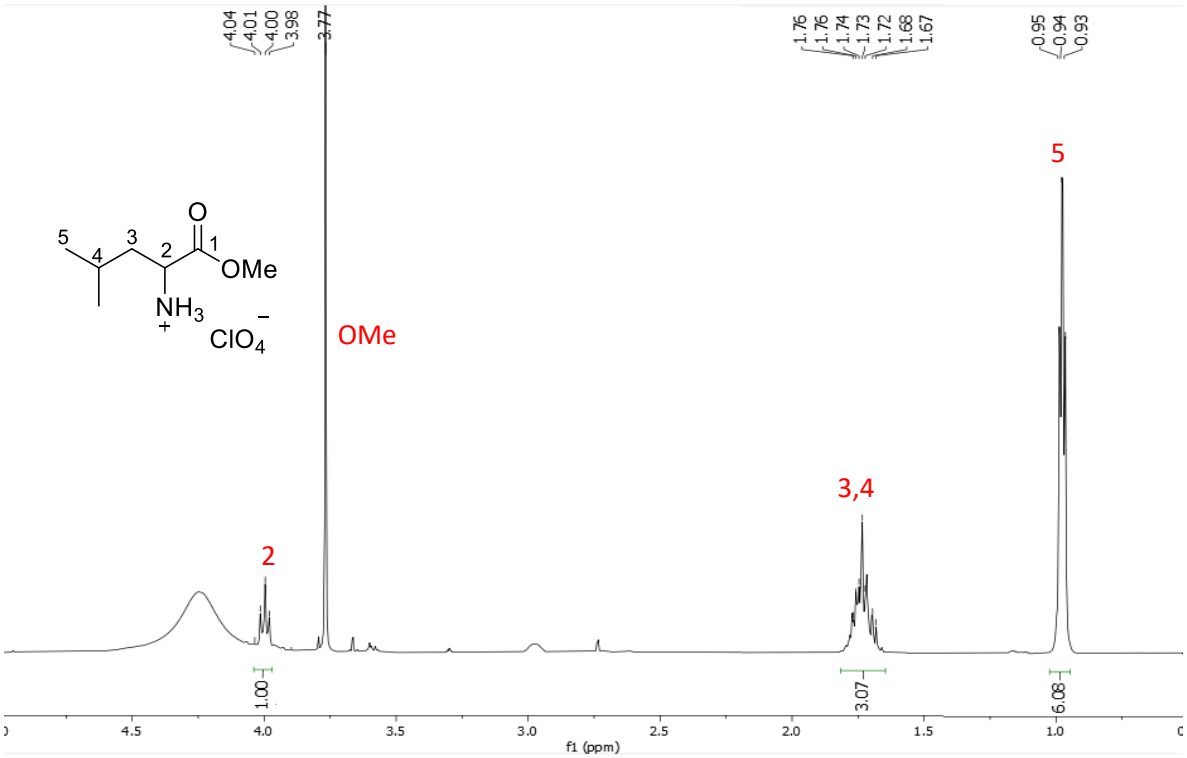


Figure S9. ^{1}H NMR of DL-leucine methyl ester in $CD_3OD+CDCl_3$

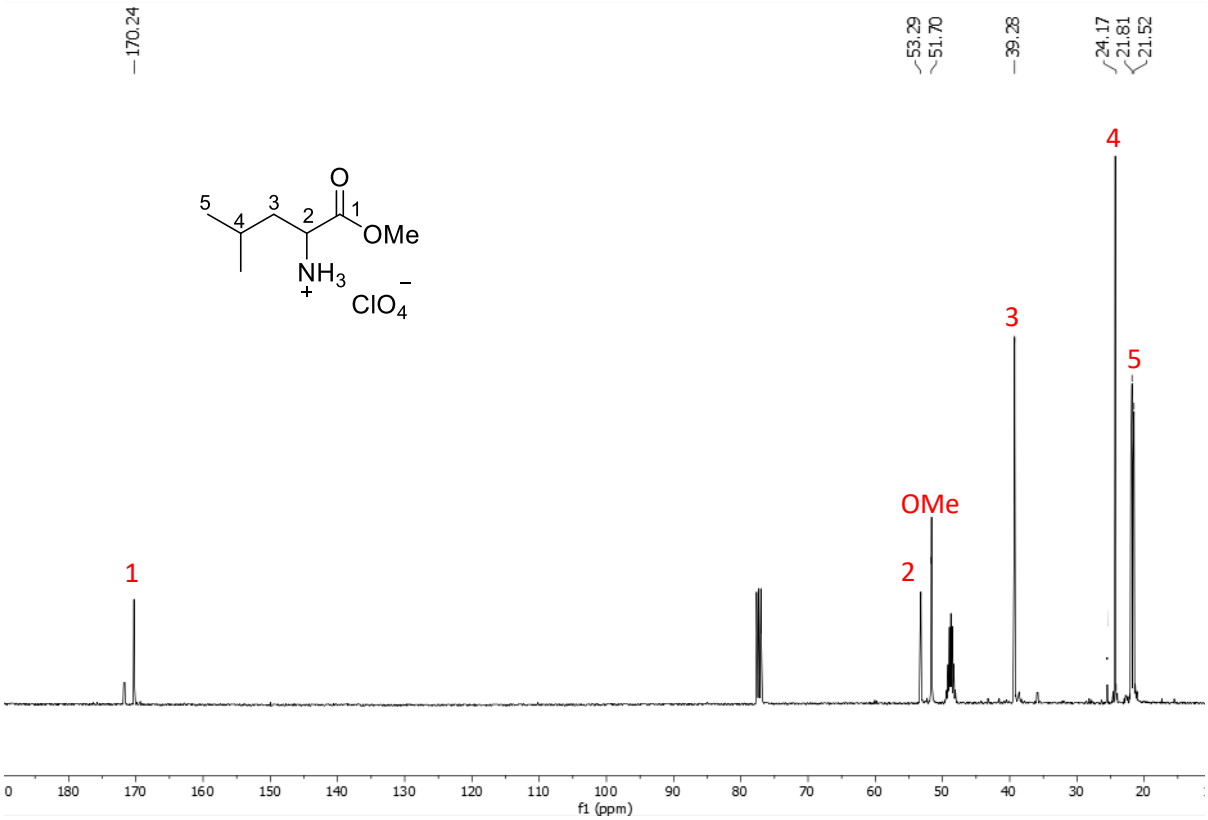


Figure S10. ^{13}C NMR of DL-leucine methyl ester in $CD_3OD+CDCl_3$

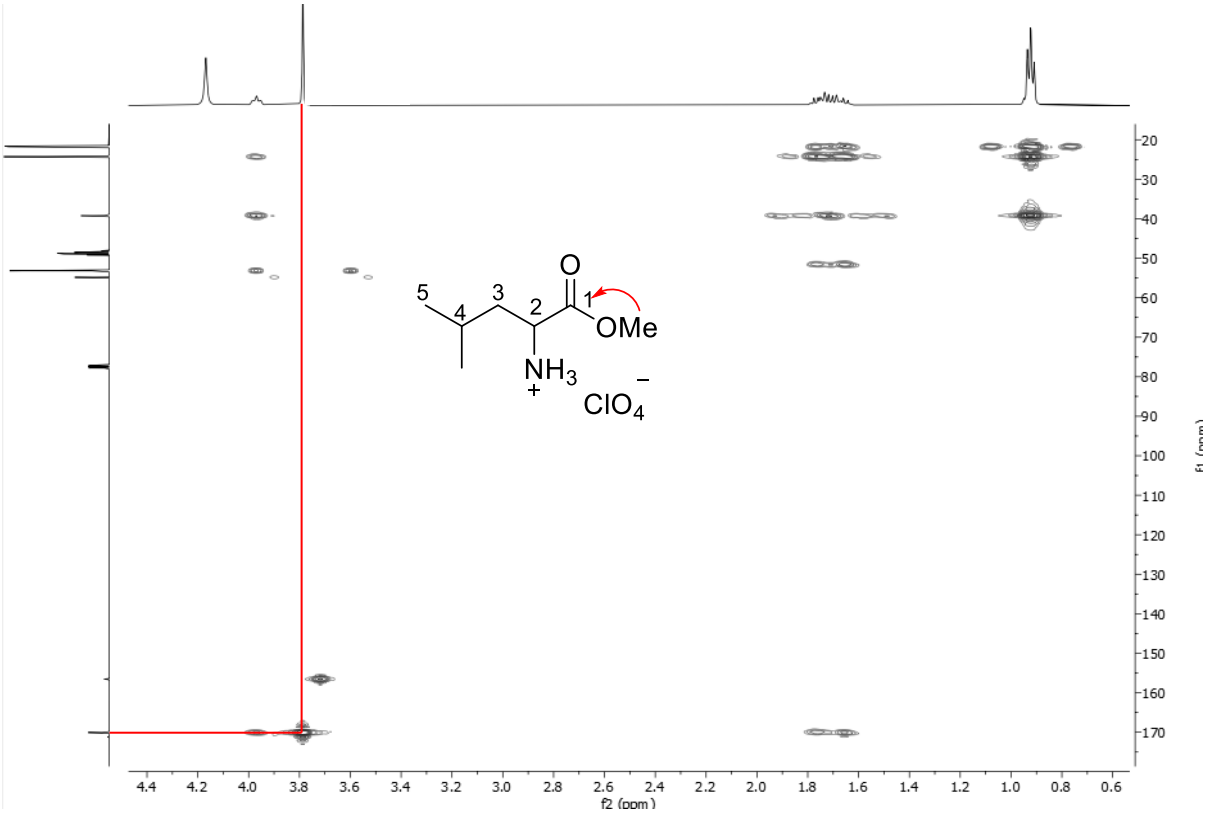


Figure S11. HMBC of DL- leucine methyl ester in CD_3OD

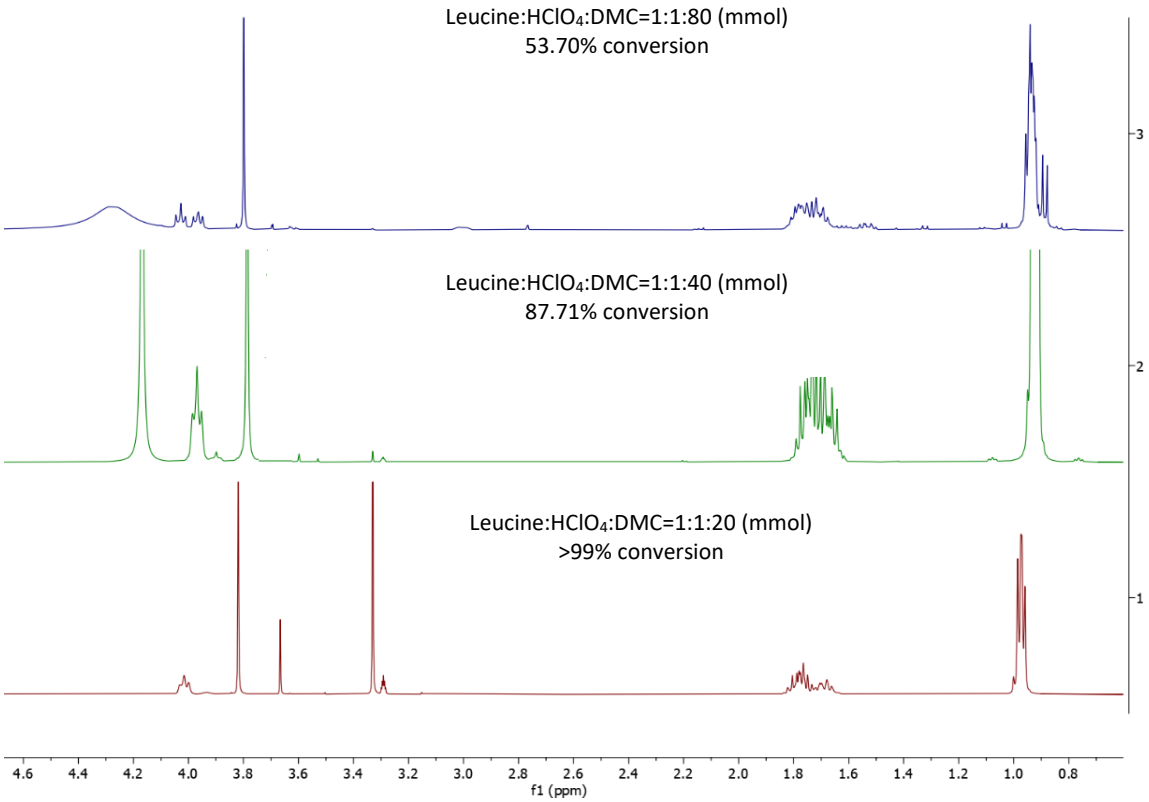


Figure S12. Compare the effect DMC assisted by $HClO_4$ in the reaction of leucine

DL-*N*-methyl alanine methyl ester ammonium. ^{1}H-NMR (CD_3OD): δ 4.12-4.07 (q, 1H), 3.82 (s, 3H), 3.67 (s, 3H), 1.54-1.53 (d, 3H); ^{13}C-NMR (CD_3OD+$CDCl_3$): δ 170.37, 54.77, 53.13, 48.84, 15.46.

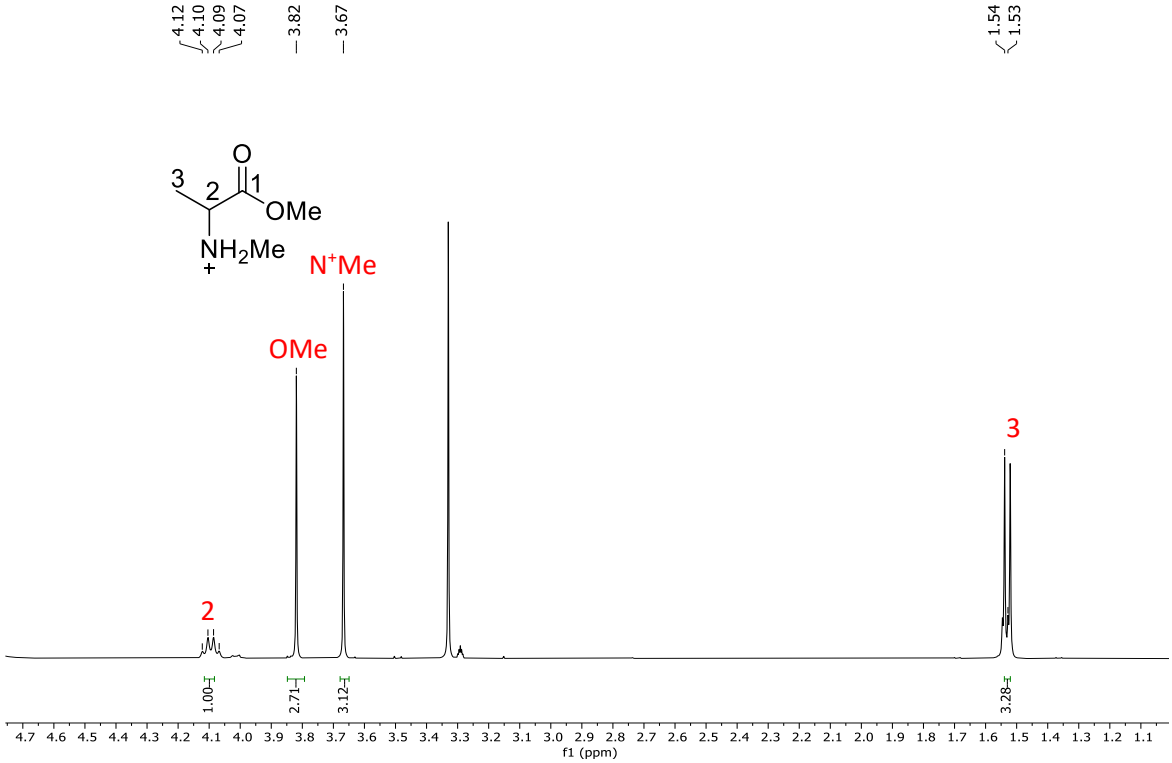


Figure S13. ^{1}H NMR of DL-*N*-methyl alanine methyl ester ammonium in CD_3OD+$CDCl_3$

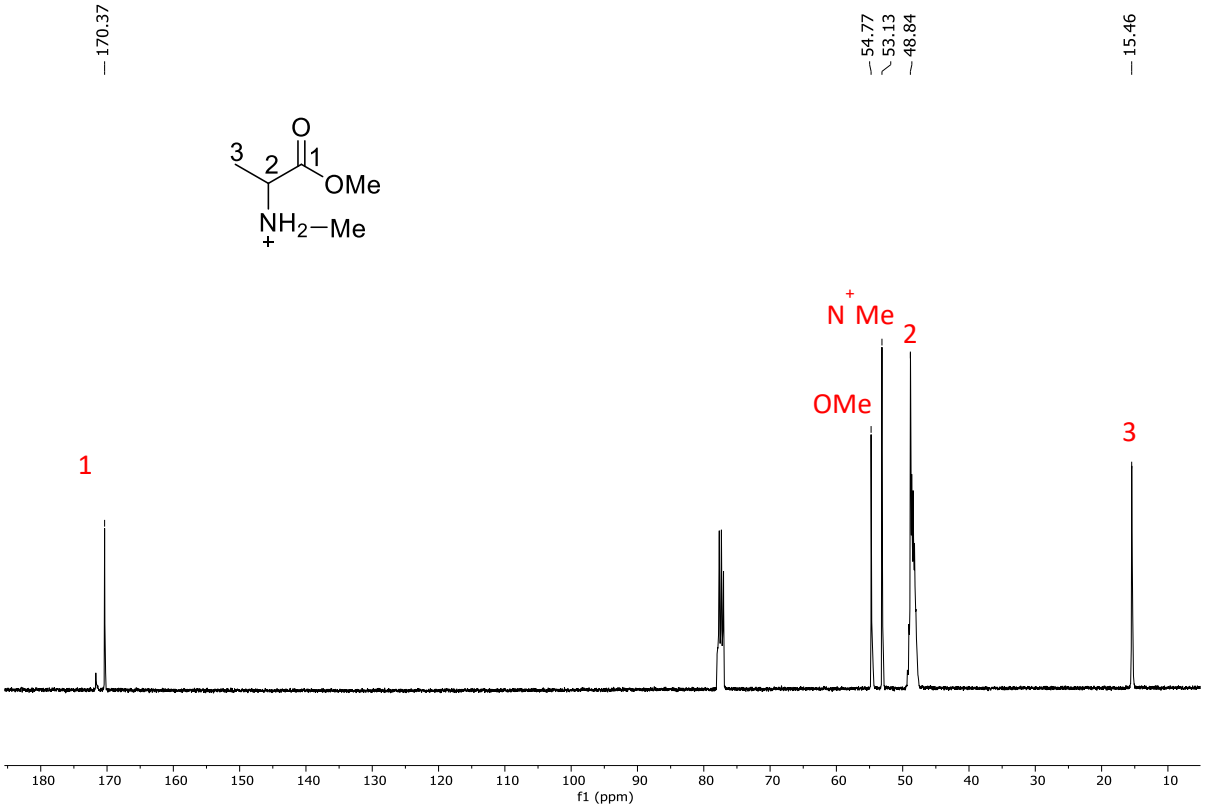


Figure S14. ^{13}C NMR of DL-*N*-methyl alanine methyl ester ammonium in CD_3OD+$CDCl_3$

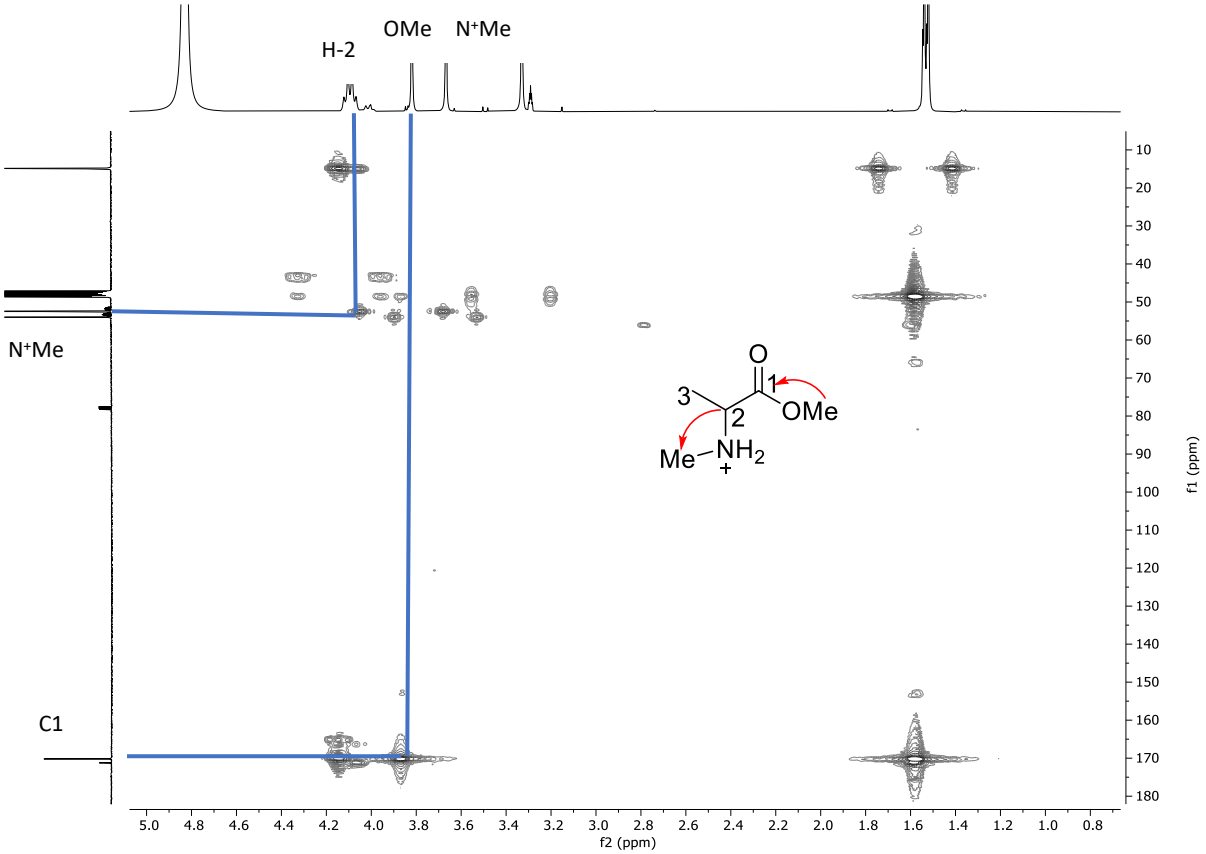


Figure S15. HMBC of DL-*N*-methyl alanine methyl ester ammonium in CD_3OD

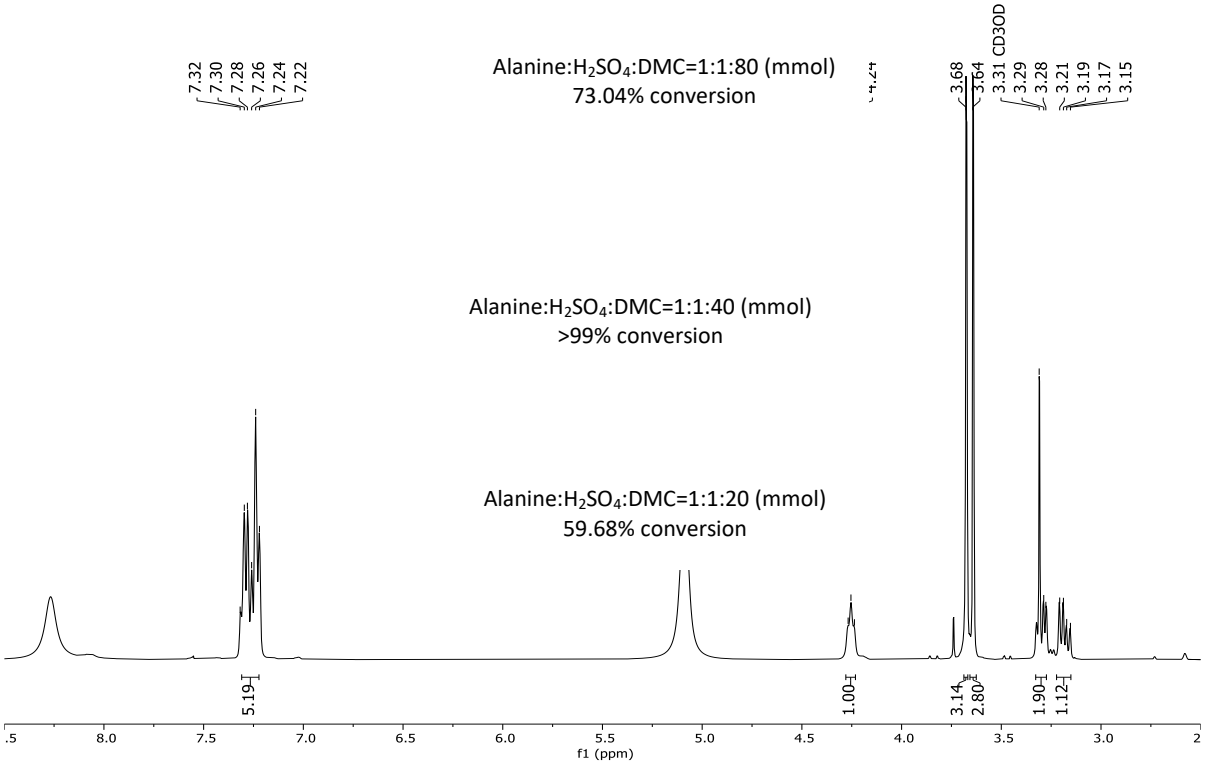


Figure S16. Compare the effect DMC assisted by H_2SO_4 in the reaction of alanine

DL-*N*-methyl phenylalanine methyl ester ammonium. ^{1}H-NMR (CD_3OD+DMSO-d_6): δ 7.32-7.22 (m, 5H),4.27 (t, 1H), 3.67 (s, 3H), 3.64 (s, 3H), 3.29-1.15 (m, 2H); ^{13}C-NMR (CD_3OD+DMSO-d_6): δ 169.55, 134.82, 129.92, 128.79, 127.65, 55.03, 54.37, 55.06, 36.48.

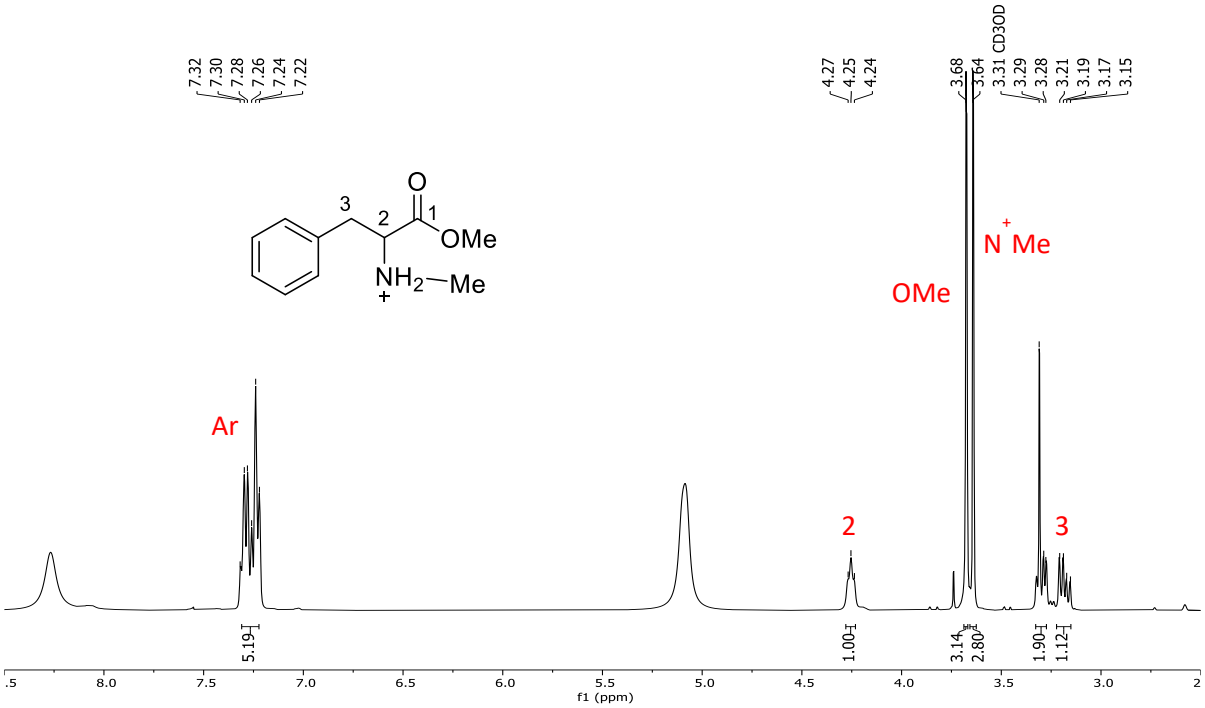


Figure S17. ^{1}H NMR of DL-*N*-methyl phenylalanine methyl ester ammonium in $CDCl_3$+DMSO-d_6

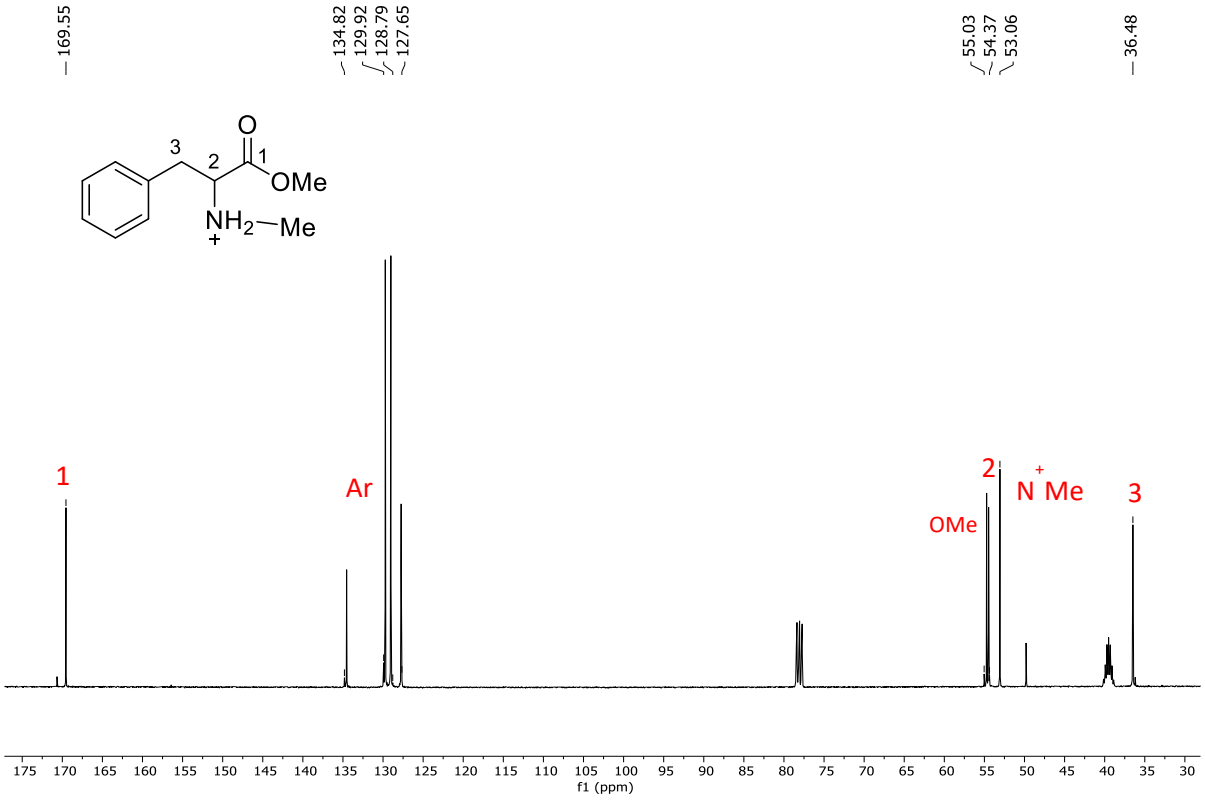


Figure S18. ^{13}C NMR of DL-*N*-methyl phenylalanine methyl ester ammonium in $CDCl_3$+DMSO-d_6

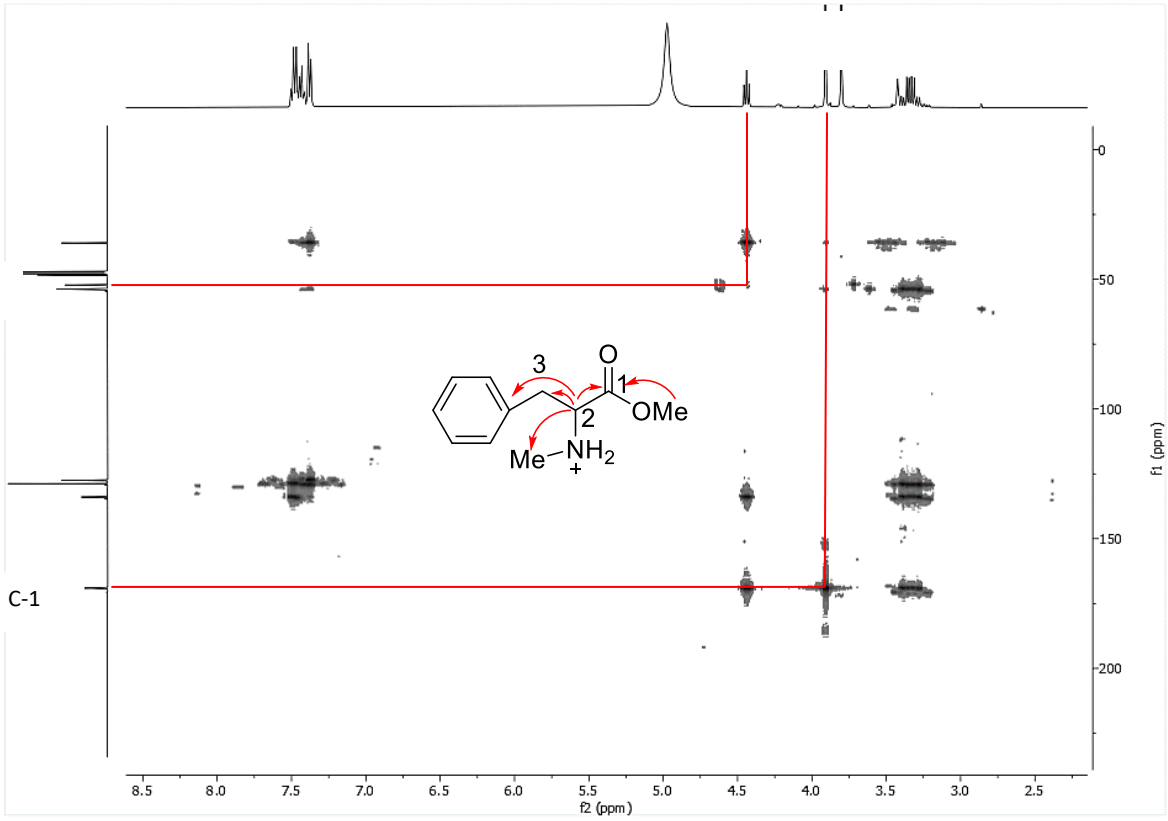


Figure S19. HMBC of DL-*N*-methyl phenylalanine methyl ester ammonium in CD_3OD

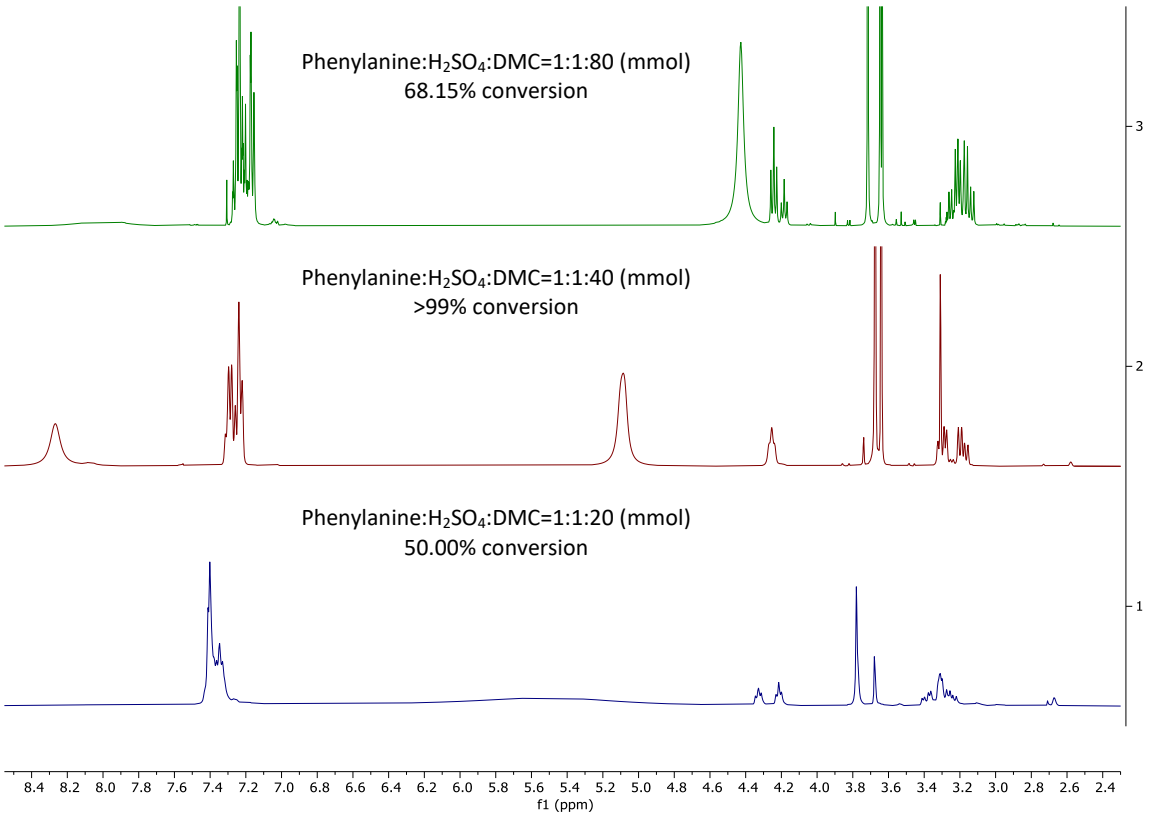


Figure S20. Compare the effect DMC assisted by H_2SO_4 in the reaction of phenylalanine

DL-*N*-methyl leucine methyl ester ammonium. ^{1}H-NMR ($CD_3OD+CDCl_3$): δ 3.90-3.86 (t, 1H),3.732 (s, 3H), 3.60 (s, 3H), 1.69-1.61 (m, 3H), 0.87-0.84 (m, 6H); ^{13}C-NMR ($CD_3OD+CDCl_3$): δ 170.31, 54.81, 52.90, 51.43, 24.28, 21.81.

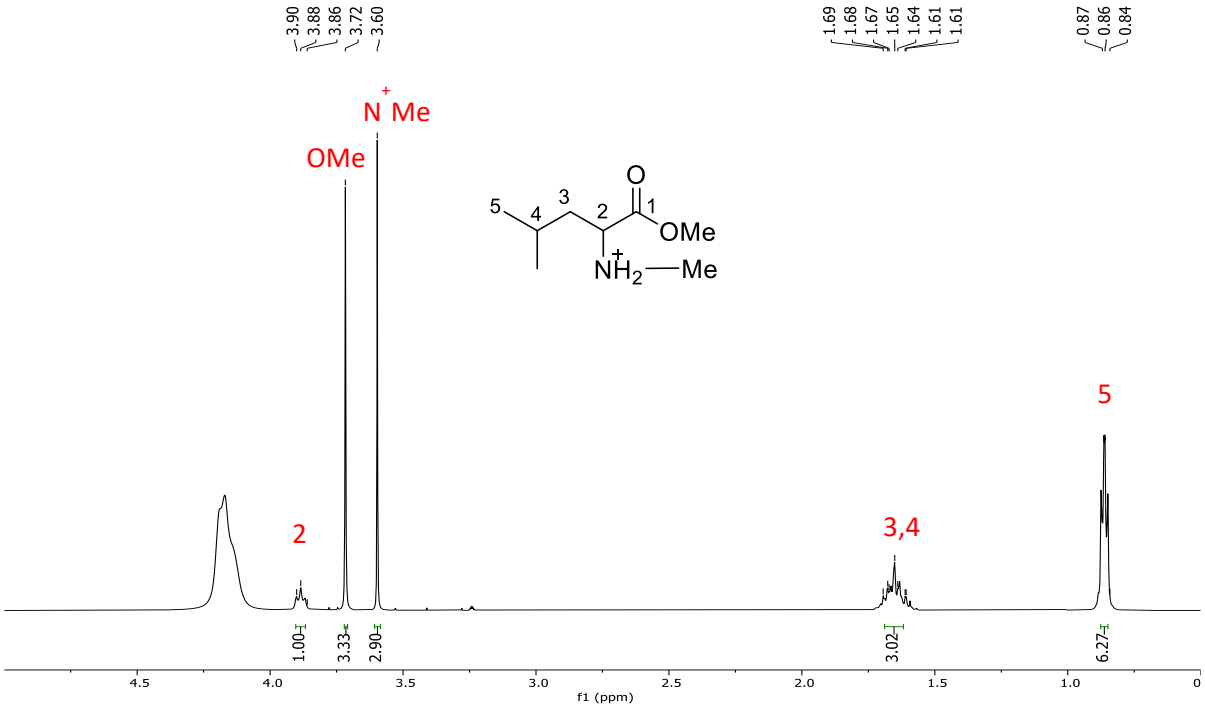


Figure S21. ^{1}H NMR of DL-*N*-methyl leucine methyl ester ammonium in $CD_3OD+CDCl_3$

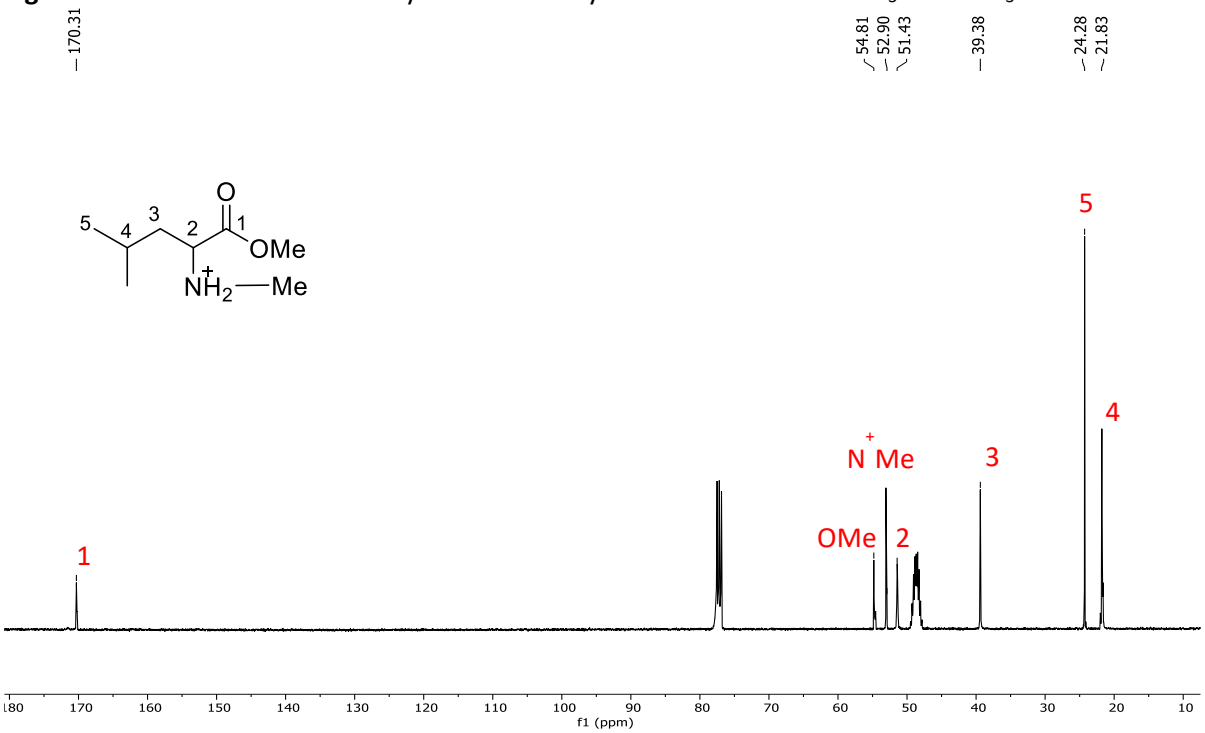


Figure S22. ^{13}C NMR of DL-*N*-methyl leucine methyl ester ammonium in $CD_3OD+CDCl_3$

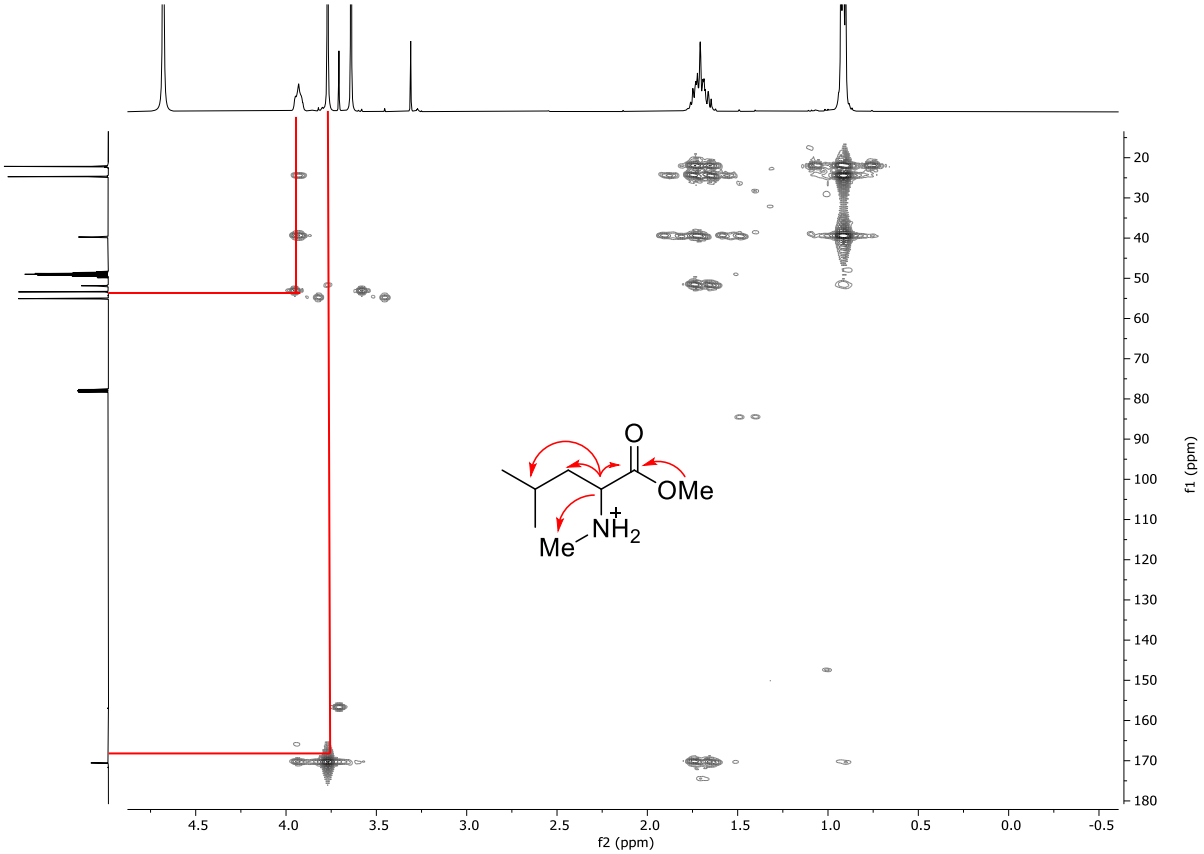


Figure S23. HMBC of DL-*N*-methyl leucine methyl ester ammonium in CD_3OD

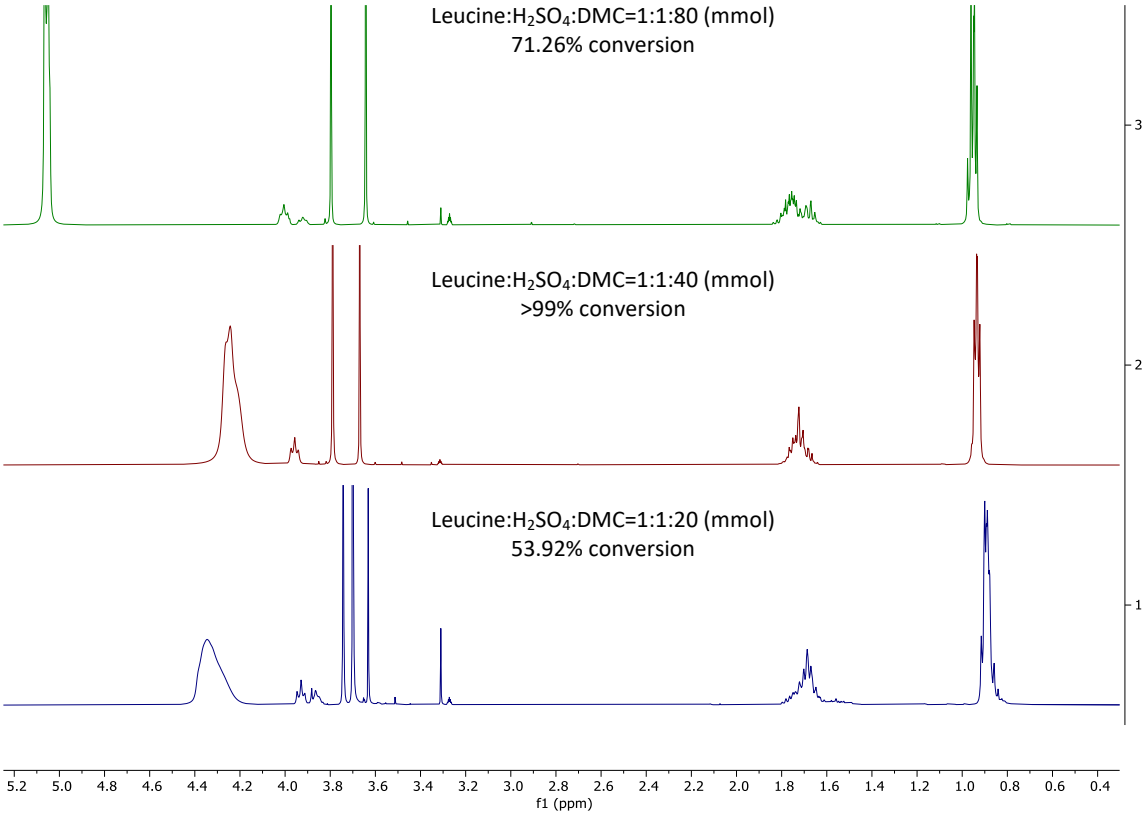


Figure S24. Compare the effect DMC assisted by H_2SO_4 in the reaction of leucine

DL- formylalanine. ^{1}H-NMR ($CD_3OD+CDCl_3$): δ 8.08 (s, 1H), 4.54-4.47 (t, 1H), 1.44-1.29 (d, 3H); ^{13}C-NMR ($CD_3OD+CDCl_3$): δ 174.31, 162.03, 46.76, 17.02.

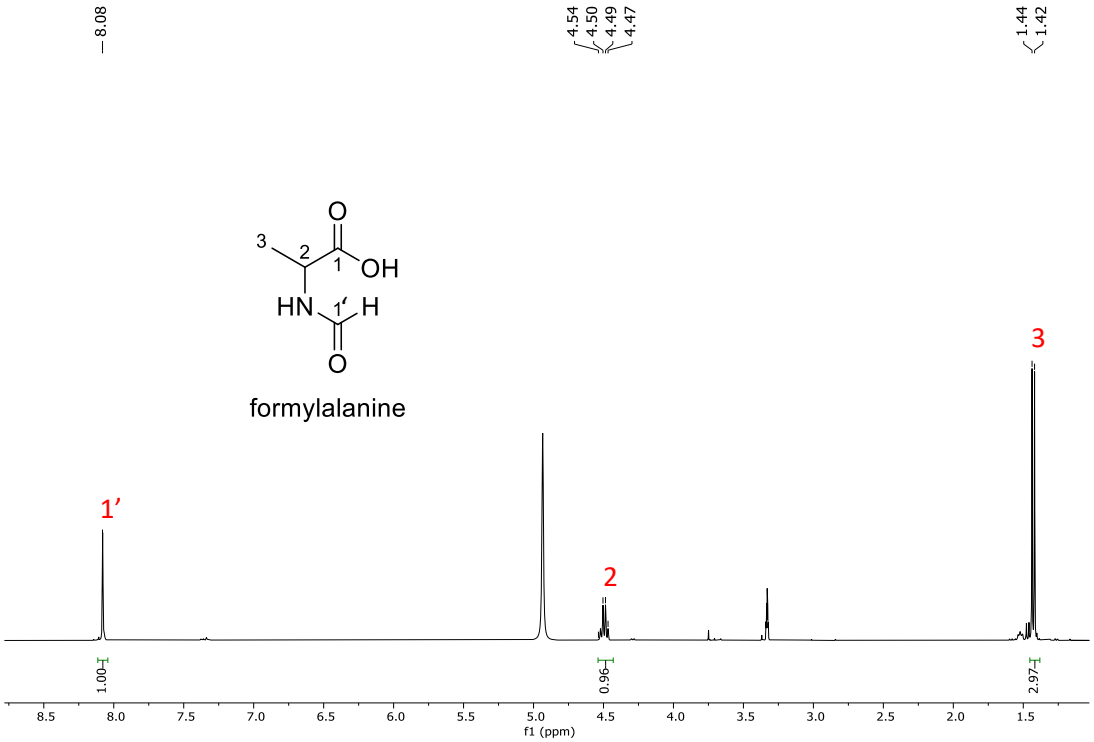


Figure S25. ^{1}H NMR of DL- formylalanine in CD_3OD

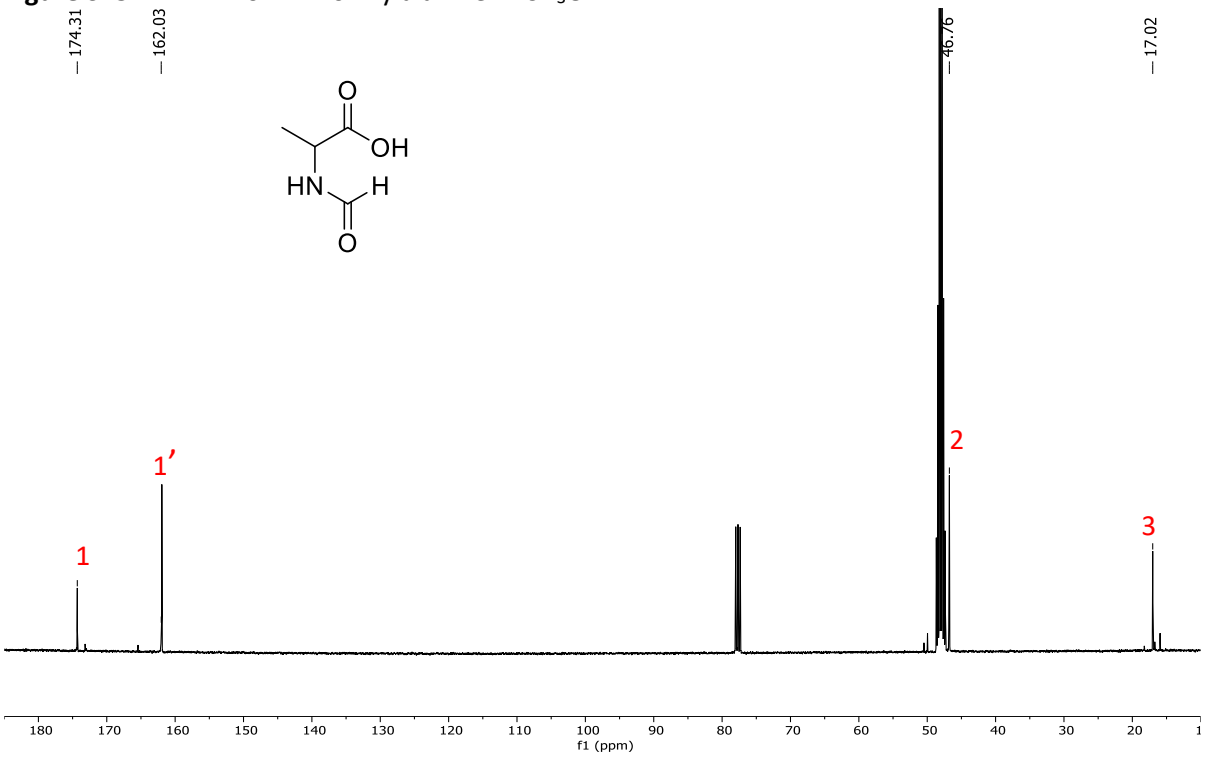


Figure S26. ^{13}C NMR of DL- formylalanine in $CD_3OD+CDCl_3$

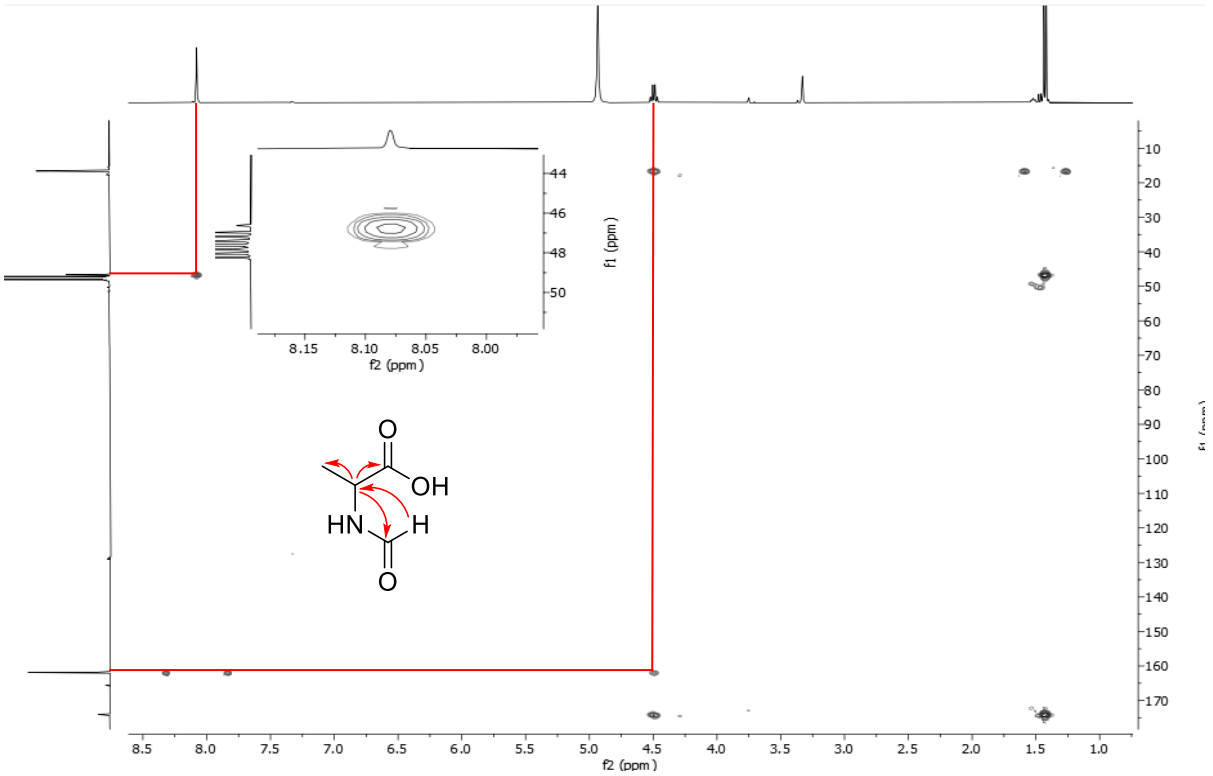


Figure S27. HMBC of DL- formylalanine in CD_3OD

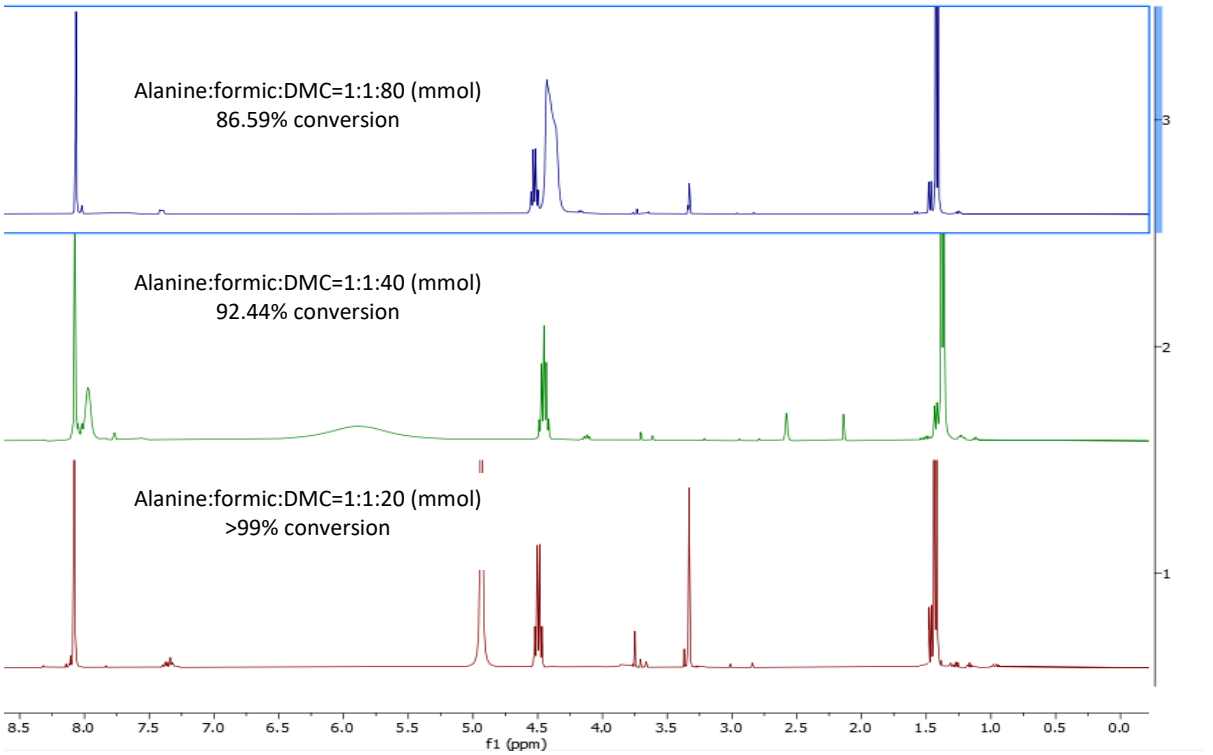


Figure S28. Compare the effect DMC assisted by formic acid in the reaction of alanine

DL-formylleucine. ^{1}H-NMR (CD_3OD+$CDCl_3$): δ 8.12 (s, 1H), 4.56-4.53 (m, 1H), 1.76-1.73 (m, 2H), 1.71-1.59 (m, 1H), 0.99-0.95 (m, 6H); ^{13}C-NMR (CD_3OD+$CDCl_3$): δ 174.33, 162.36, 49.53, 40.58, 24.67, 21.99, 20.73.

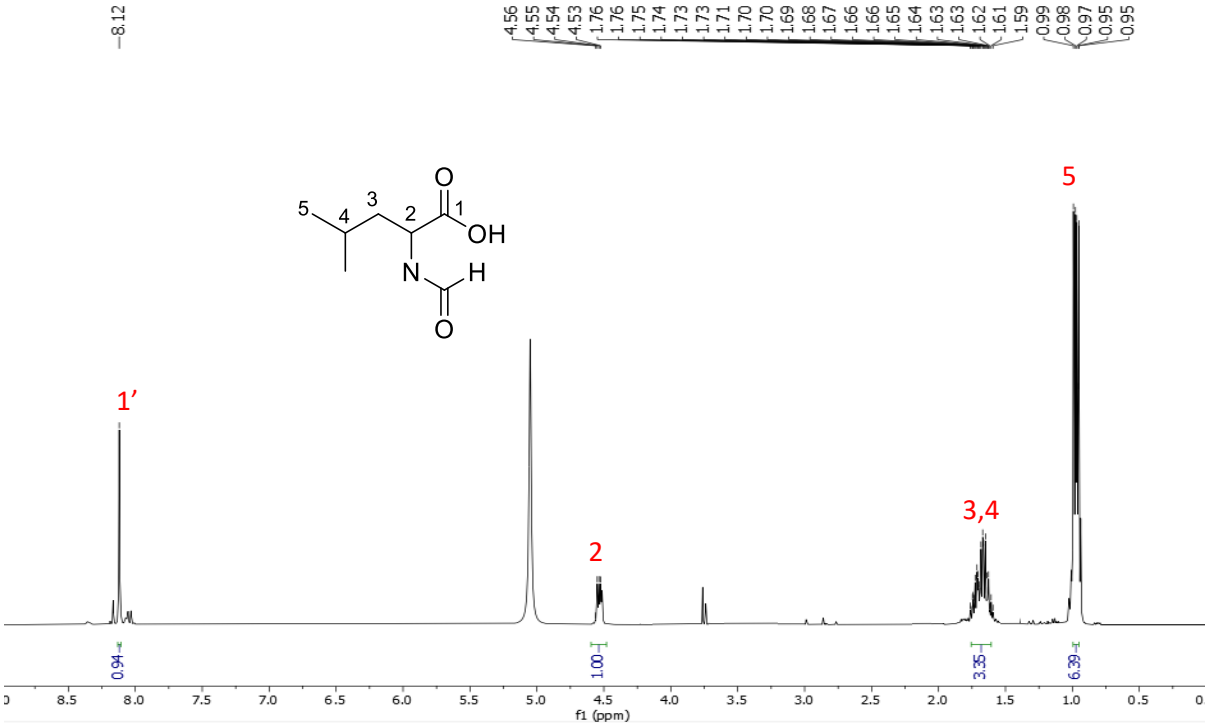


Figure S29. ^{1}H NMR of DL-formylleucine in $CDCl_3$+CD_3OD

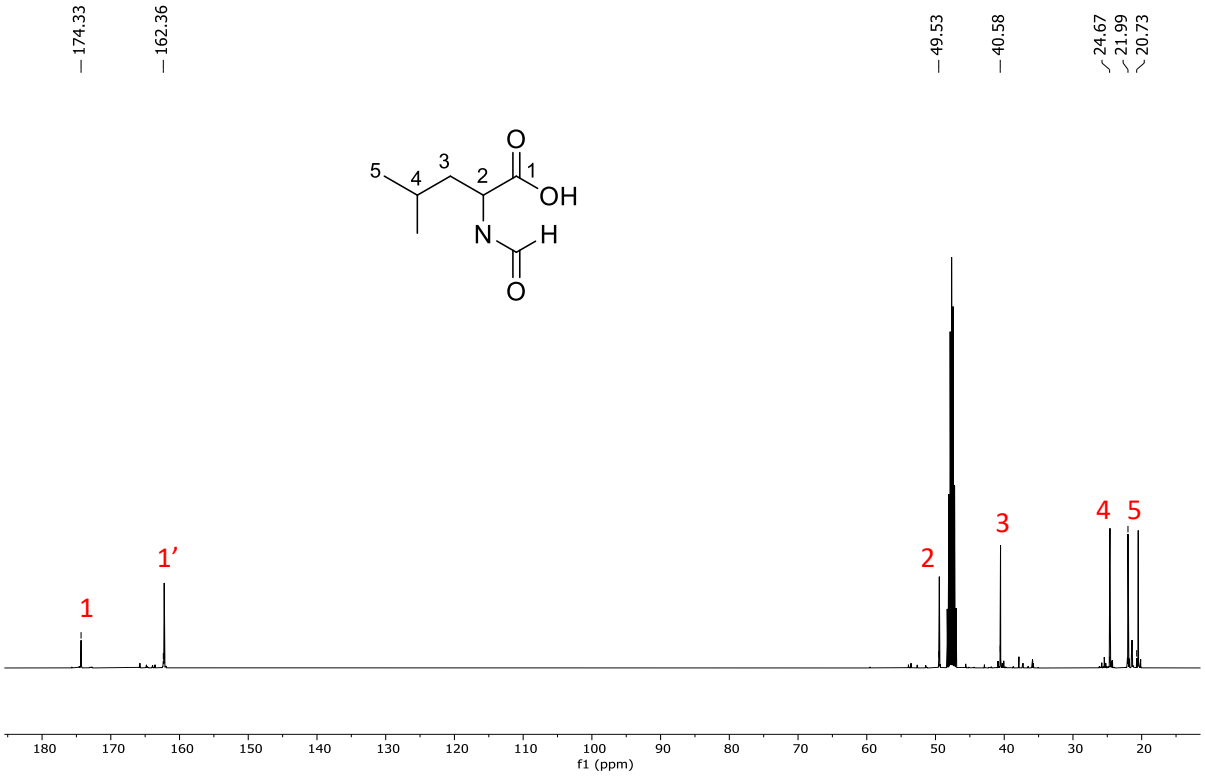


Figure S30. ^{13}C NMR of DL-formylleucine in $CDCl_3$+CD_3OD

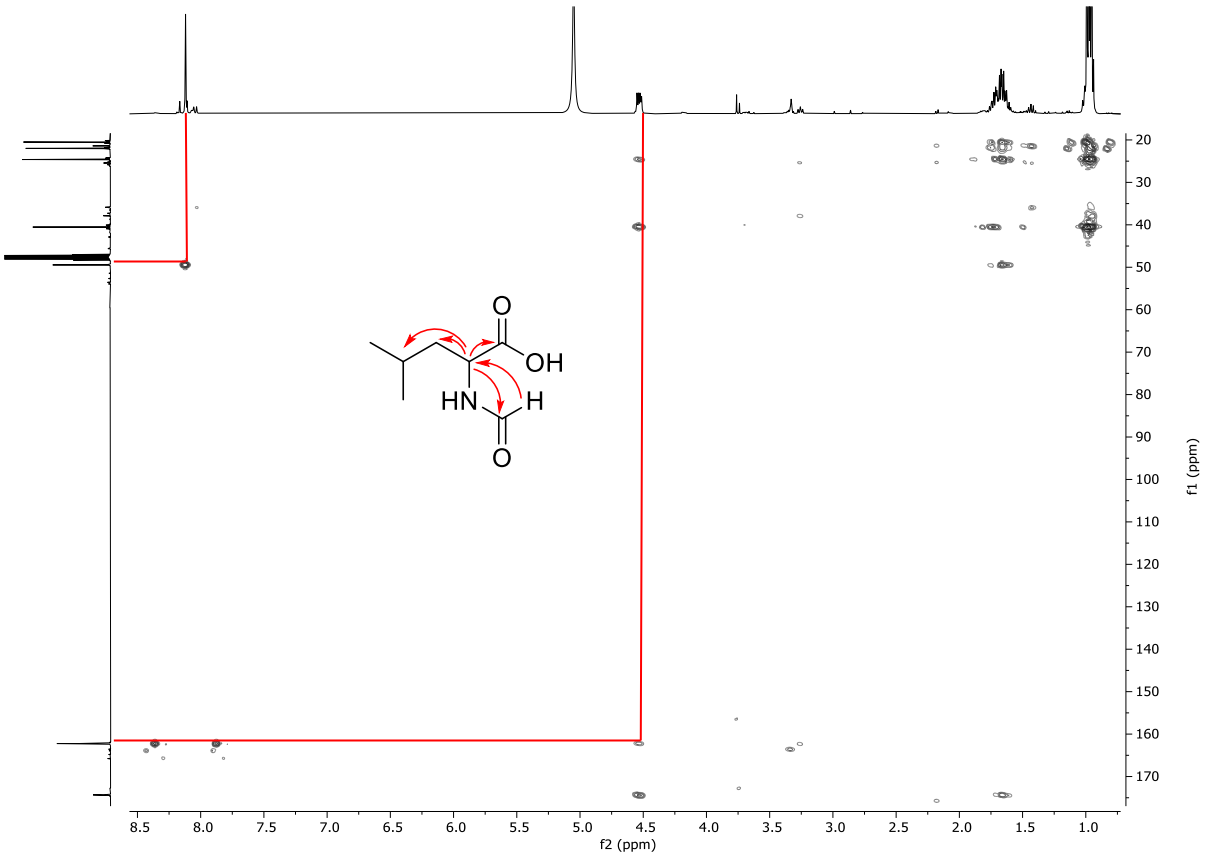


Figure S31. HMBC of DL-formylleucine in CD_3OD

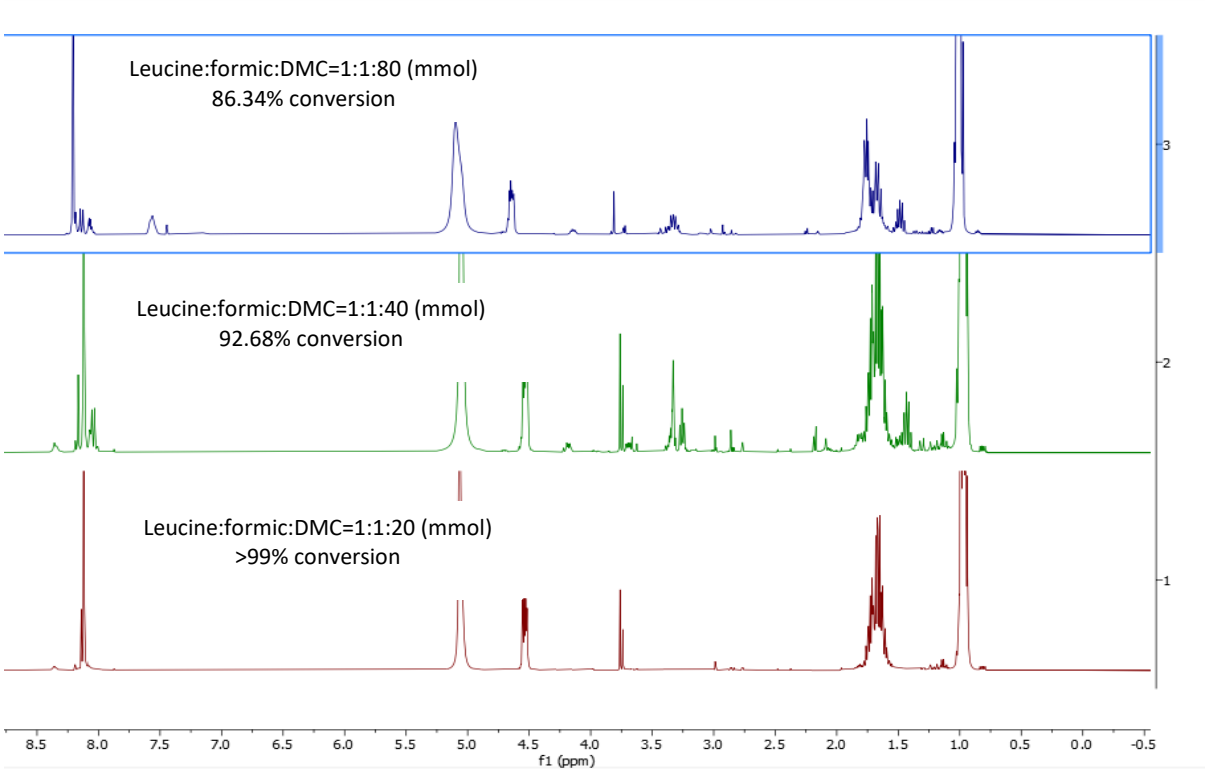


Figure S32. Compare the effect DMC assisted by formic acid in the reaction of leucine

DL-formylphenylalanine. ^{1}H-NMR (CD_3OD+$CDCl_3$): δ 8.78 (s, 1H),7.80 (m, 5H), 5.41 (m, 2H), 3.73-3.92 (2 set of dd, 2H); ^{13}C-NMR (CD_3OD+$CDCl_3$): δ 173.66, 162.31, 137.98, 130.05, 129.08, 127.35, 53.03, 38.22.

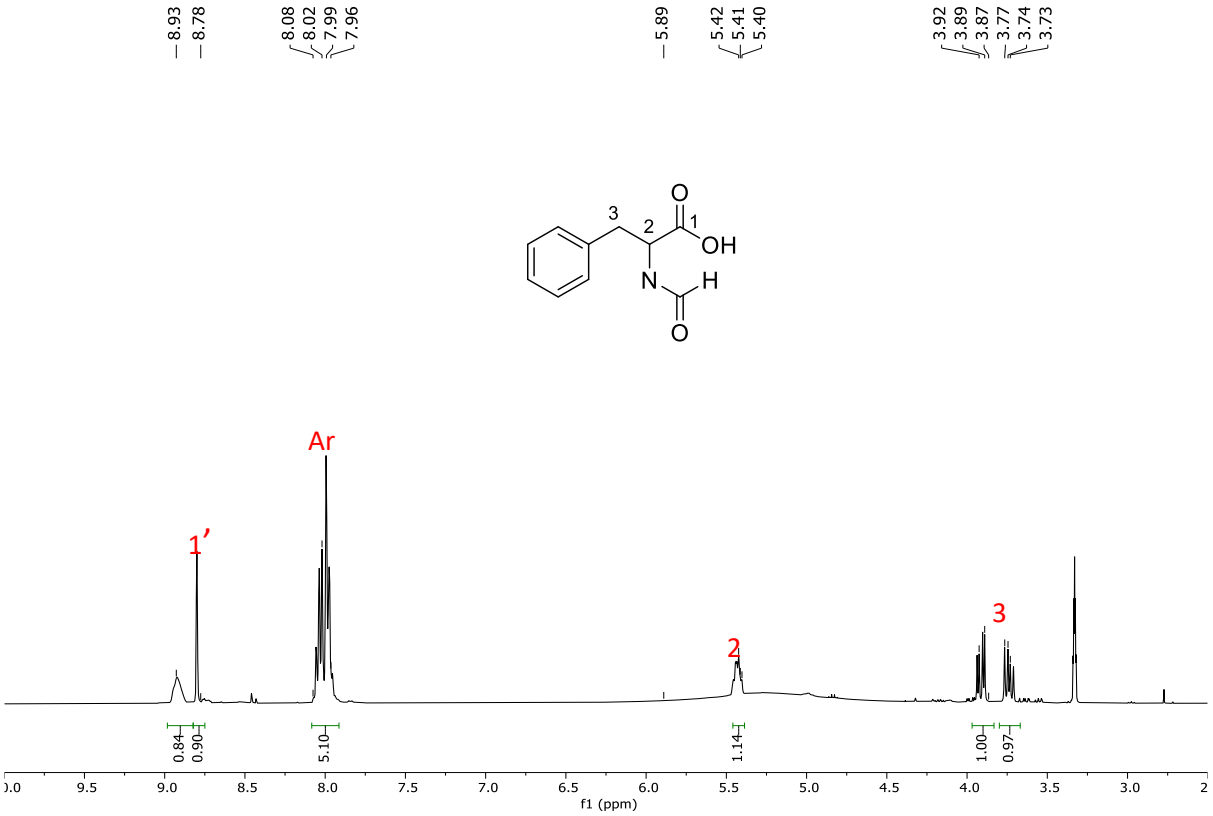


Figure S33. ^{1}H NMR of DL-formylphenylalanine in $CDCl_3$+CD_3OD

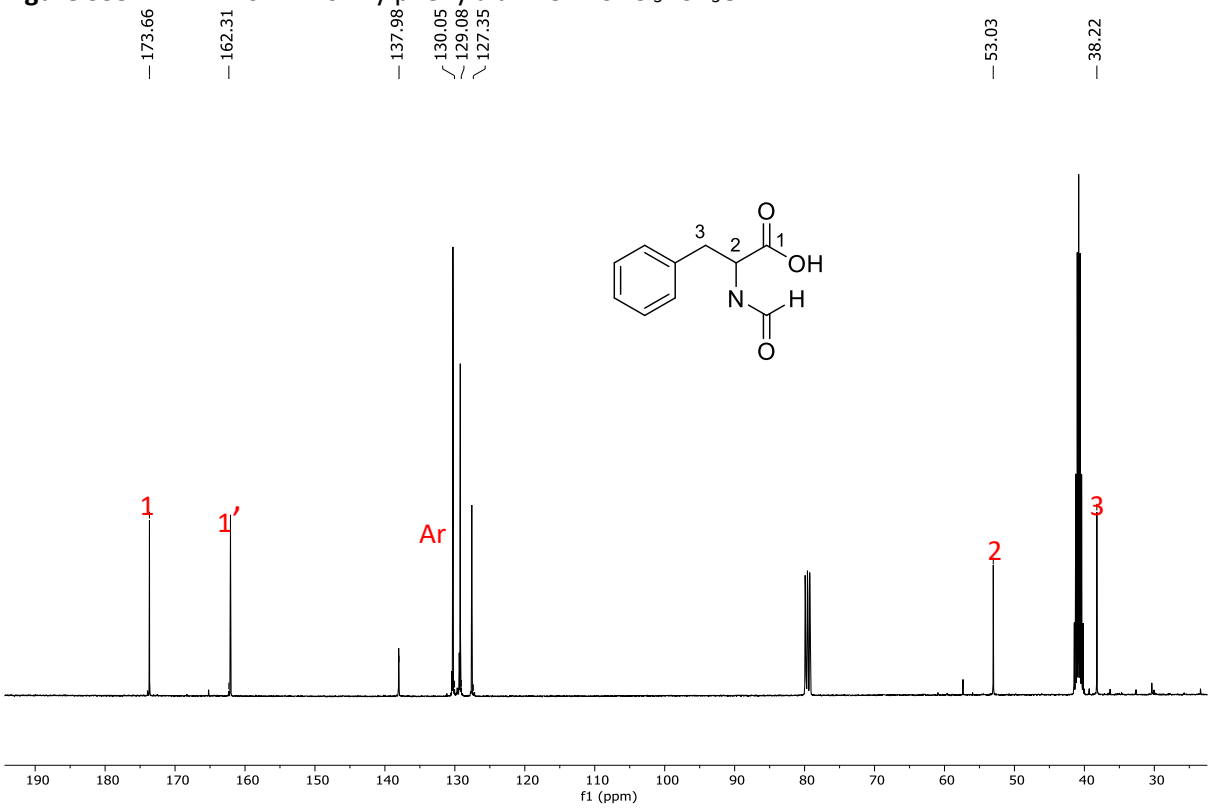


Figure S34. ^{13}C NMR of DL-formylphenylalanine in $CDCl_3$+CD_3OD

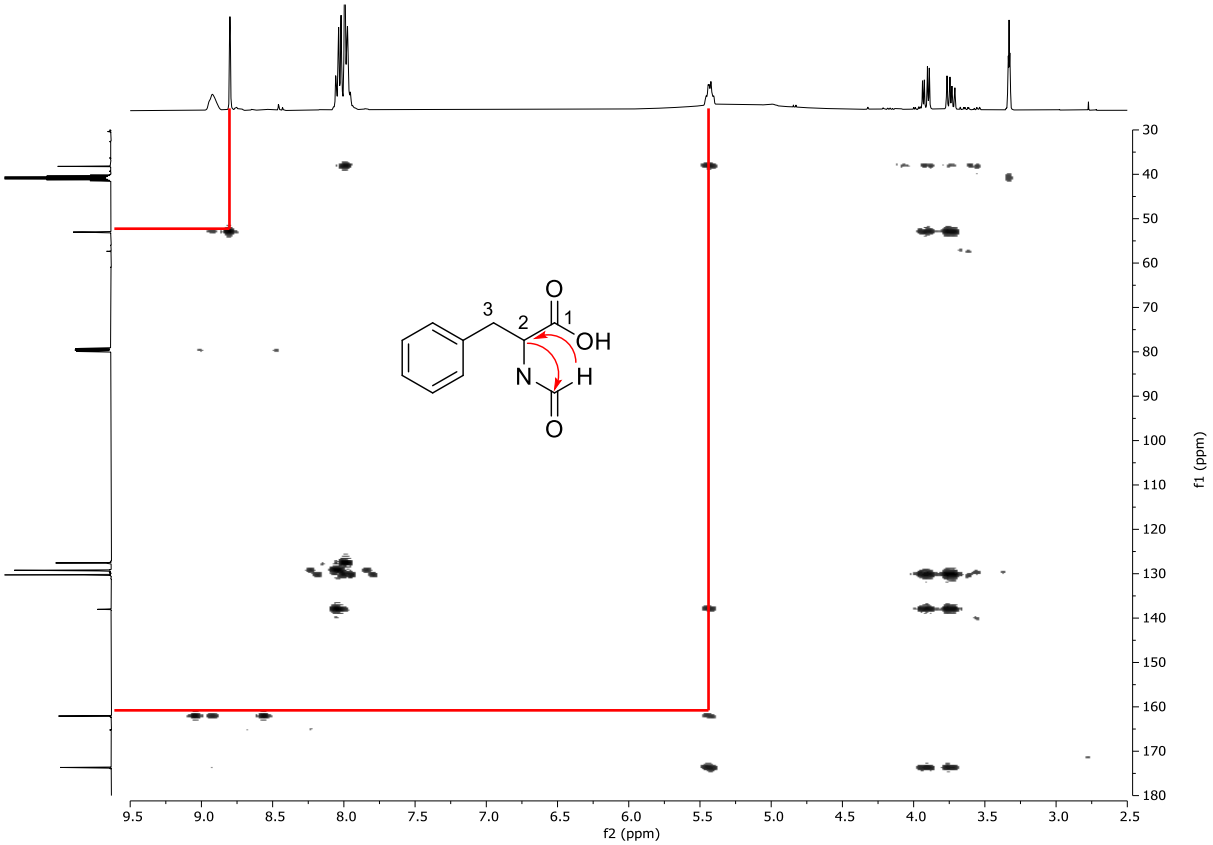


Figure S35. HMBC of DL-formylphenylalanine in CD_3OD

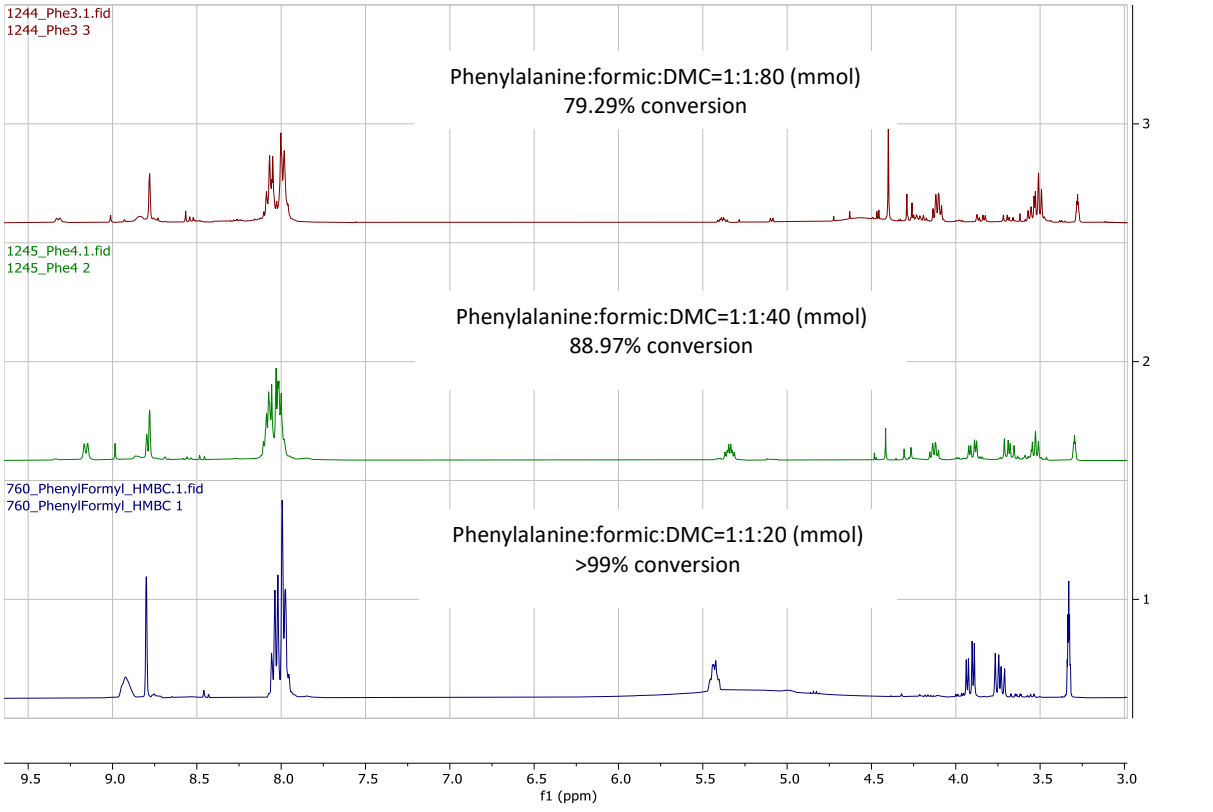


Figure S36. Compare the effect DMC assisted by formic acid in the reaction of phenylalanine

DL-formylmethionine. ^{1}H-NMR ($CD_3OD+CDCl_3$): δ 8.14 (s, 1H), 4.67-4.64 (q, 1H), 2.68-2.50 (m, 2H), 2.16-1.97 (m, 2H), 2.14 (s, 3H); ^{13}C-NMR ($CD_3OD+CDCl_3$): δ 173.32, 162.05, 50.23, 31.37, 29.83, 14.88.

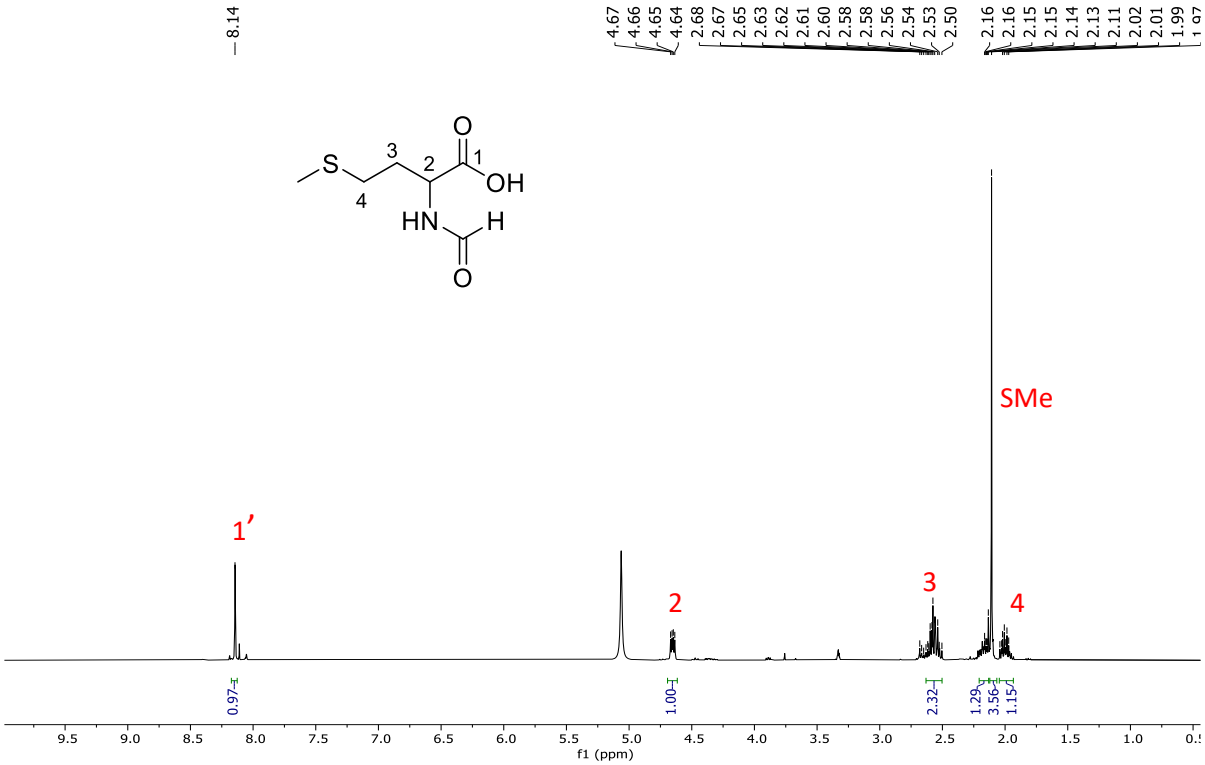


Figure S37. ^{1}H NMR of DL-formymethionine in $CDCl_3+CD_3OD$

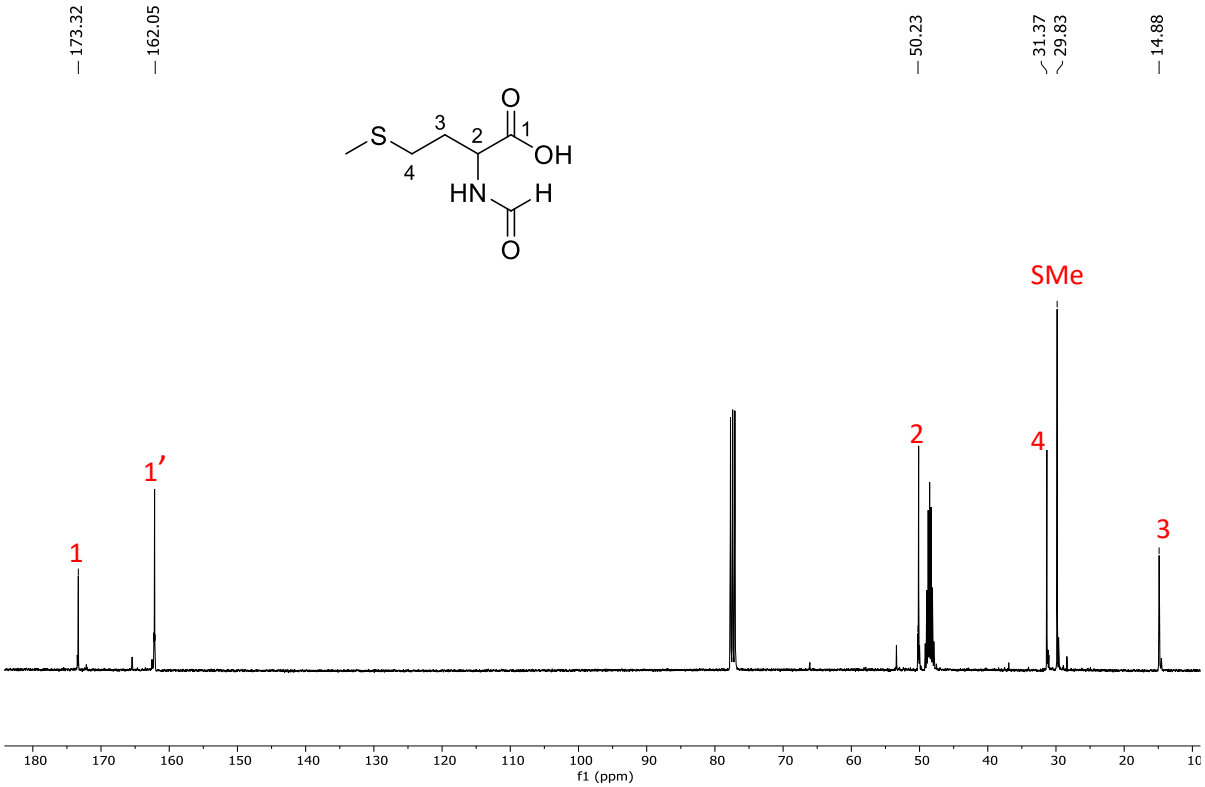


Figure S38. ^{13}C NMR of DL-formymethionine in $CDCl_3+CD_3OD$

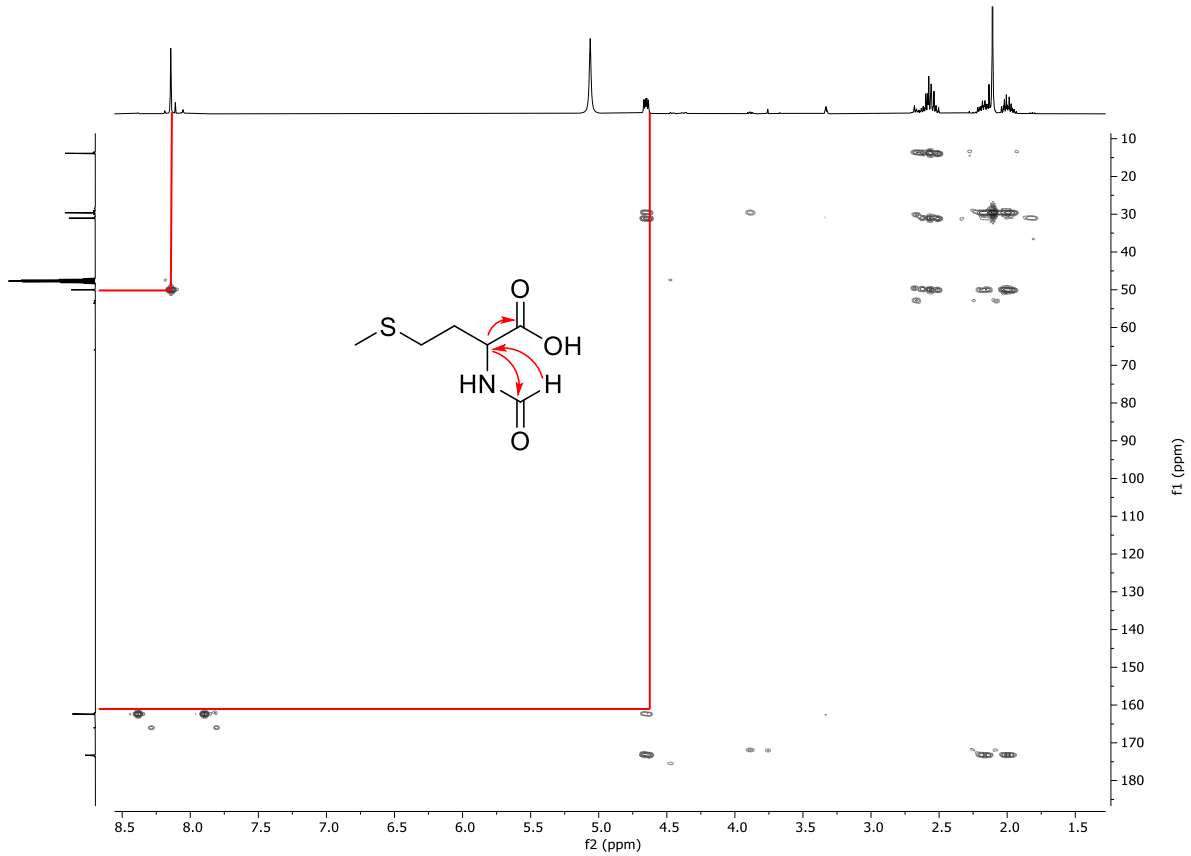


Figure S39. HMBC of DL- formymethionine in CD_3OD

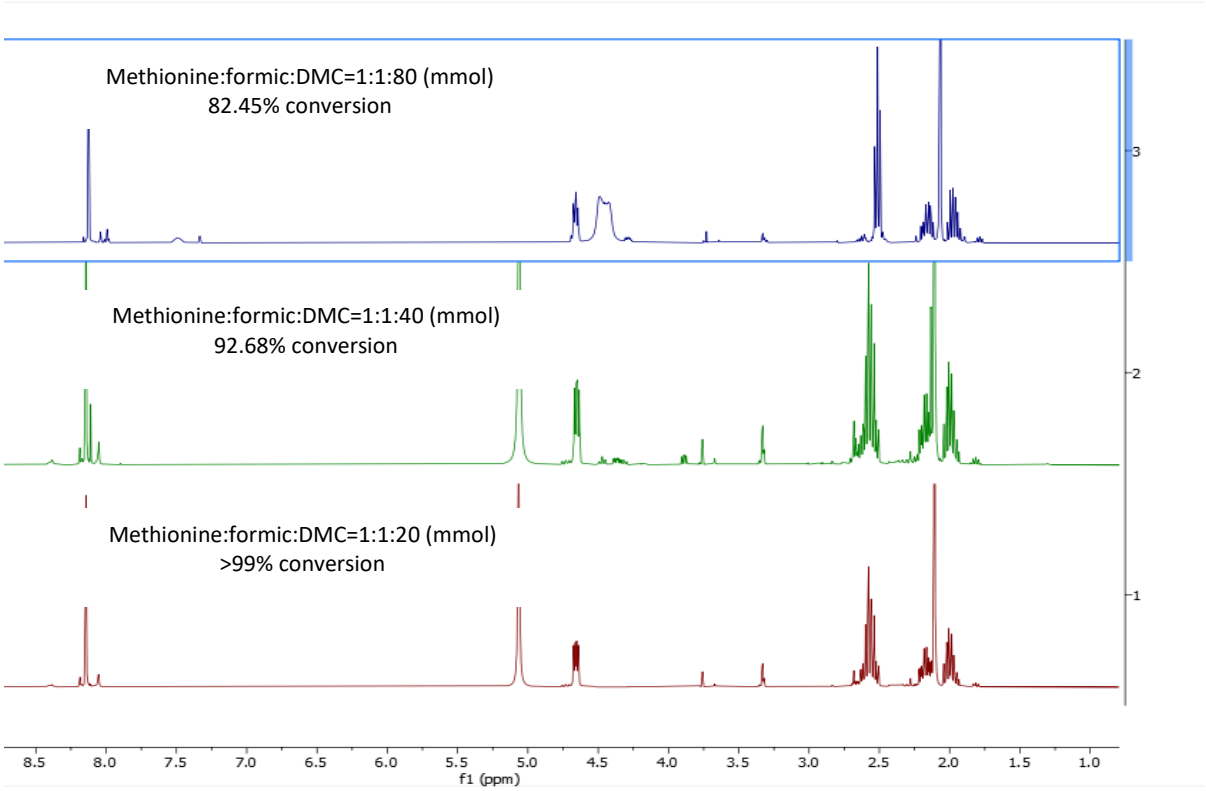


Figure S40. Compare the effect DMC assisted by formic acid in the reaction of methionine

DL-alanine. ^{1}H-NMR (D_2O): δ 3.79-3.74 (q, 1H), 1.47-1.45 (d, 3H); ^{13}C-NMR (D_2O): δ 178.61, 53.08, 18.87.

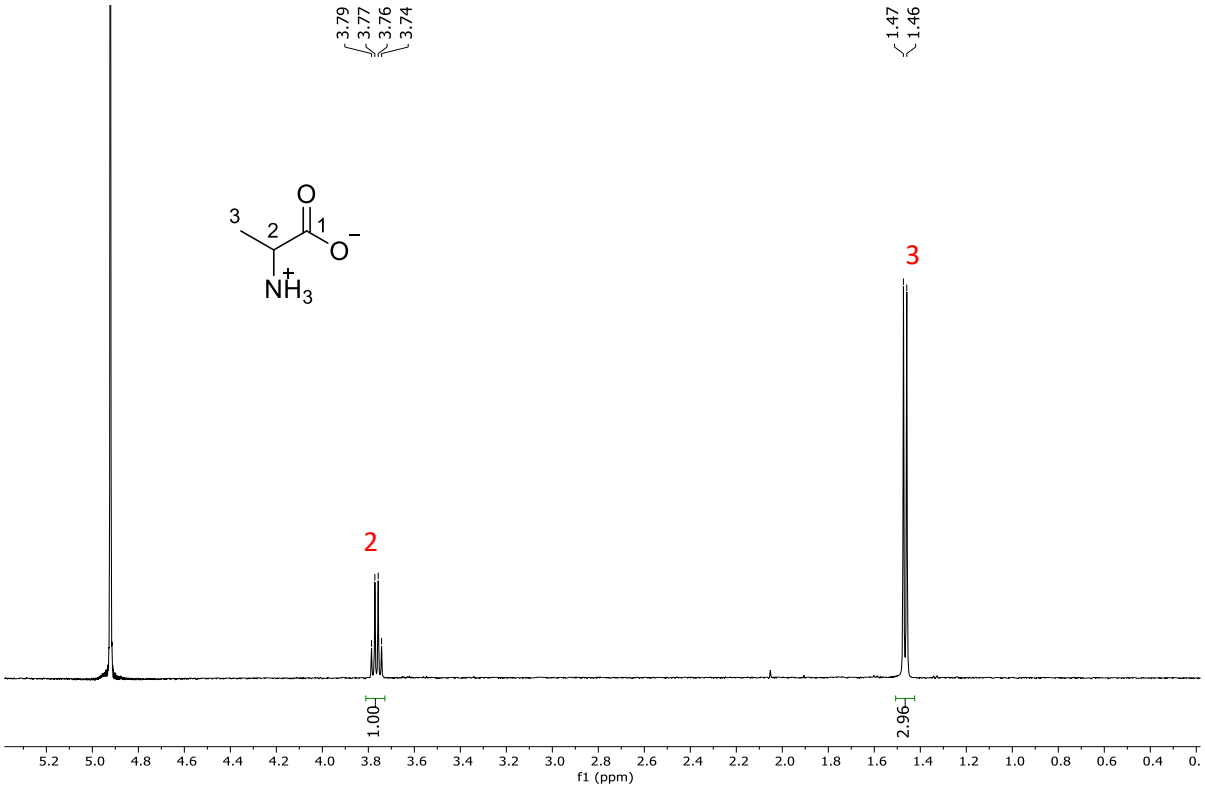


Figure 41. ^{1}H NMR of DL-alanine in D_2O

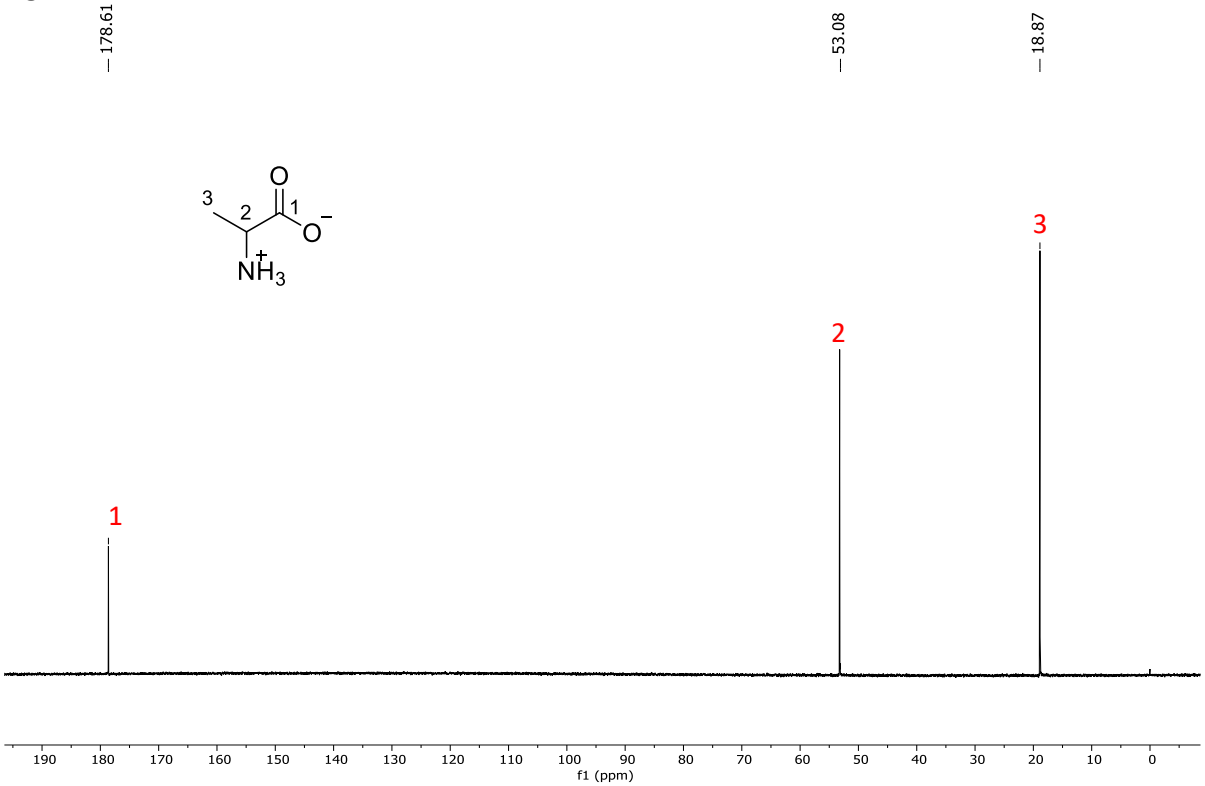


Figure S42. ^{13}C NMR of DL-alanine in D_2O

DL-phenylalanine. ^{1}H-NMR (D_2O): δ 7.43-7.31 (m, 5H), 3.99-3.97 (q, 1H), 3.29-3.10 (m, 2H); ^{13}C-NMR (D_2O): δ 176.78, 138.02, 132.09, 131.84, 130.42, 58.75, 39.10.

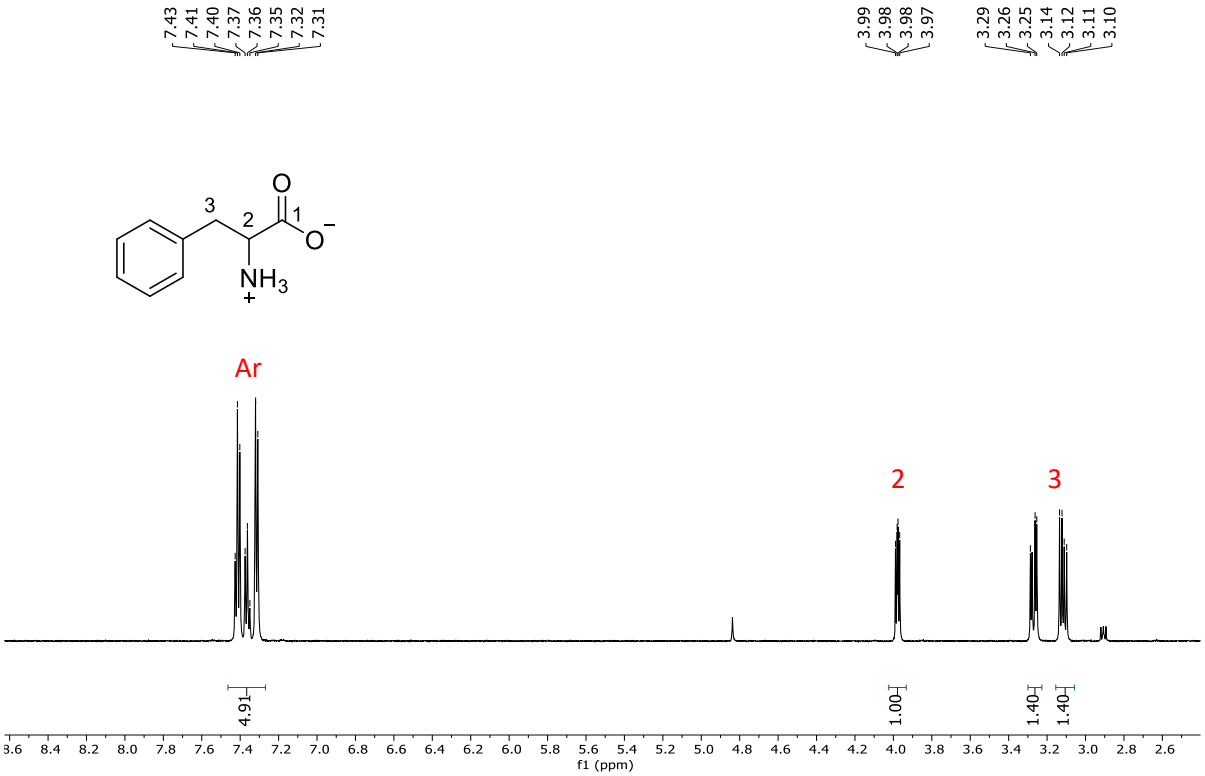


Figure S43. ^{1}H NMR of phenylalanine in D_2O

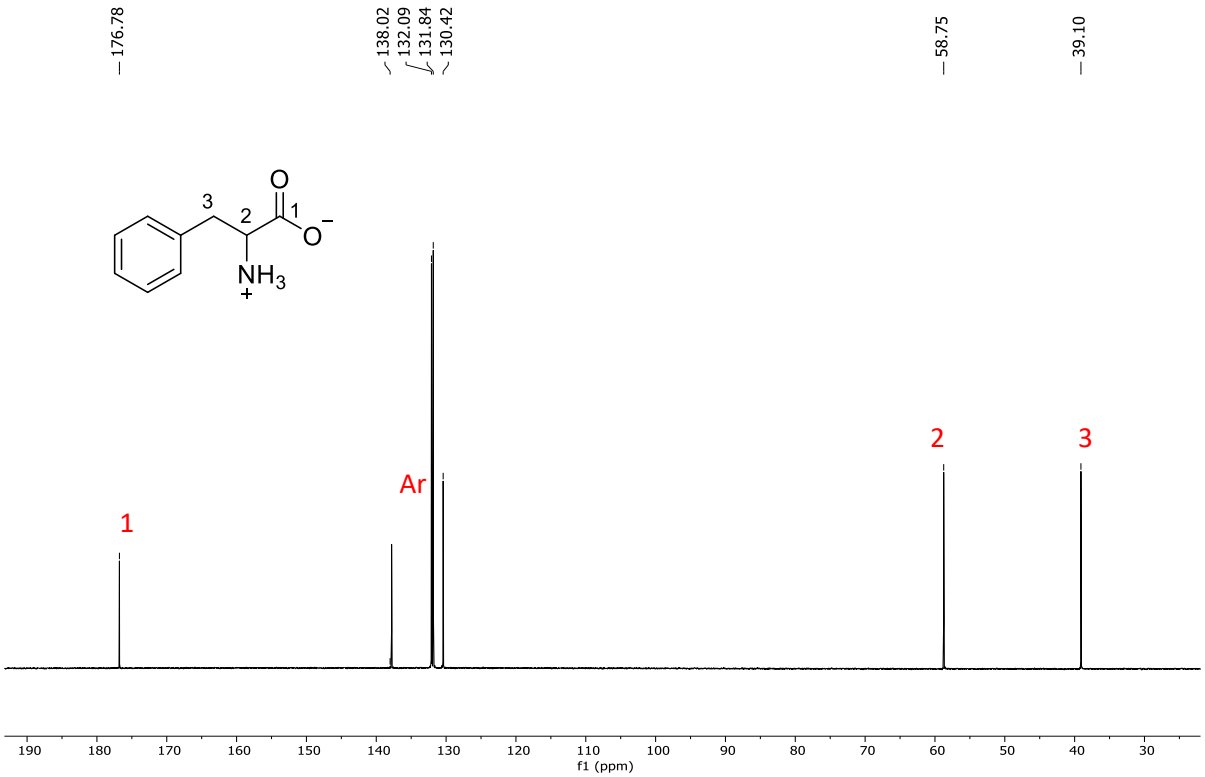


Figure S44. ^{13}C NMR of DL-phenylalanine in D_2O

DL-leucine. ^{1}H-NMR (D_2O): δ 3.72-3.70 (t, 1H), 1.74-1.65.(m, 3H), 0.96-0.94 (d, 6H); ^{13}C-NMR (D_2O): δ 178.38, 56.12, 42.53, 27.01, 24.76, 23.59.

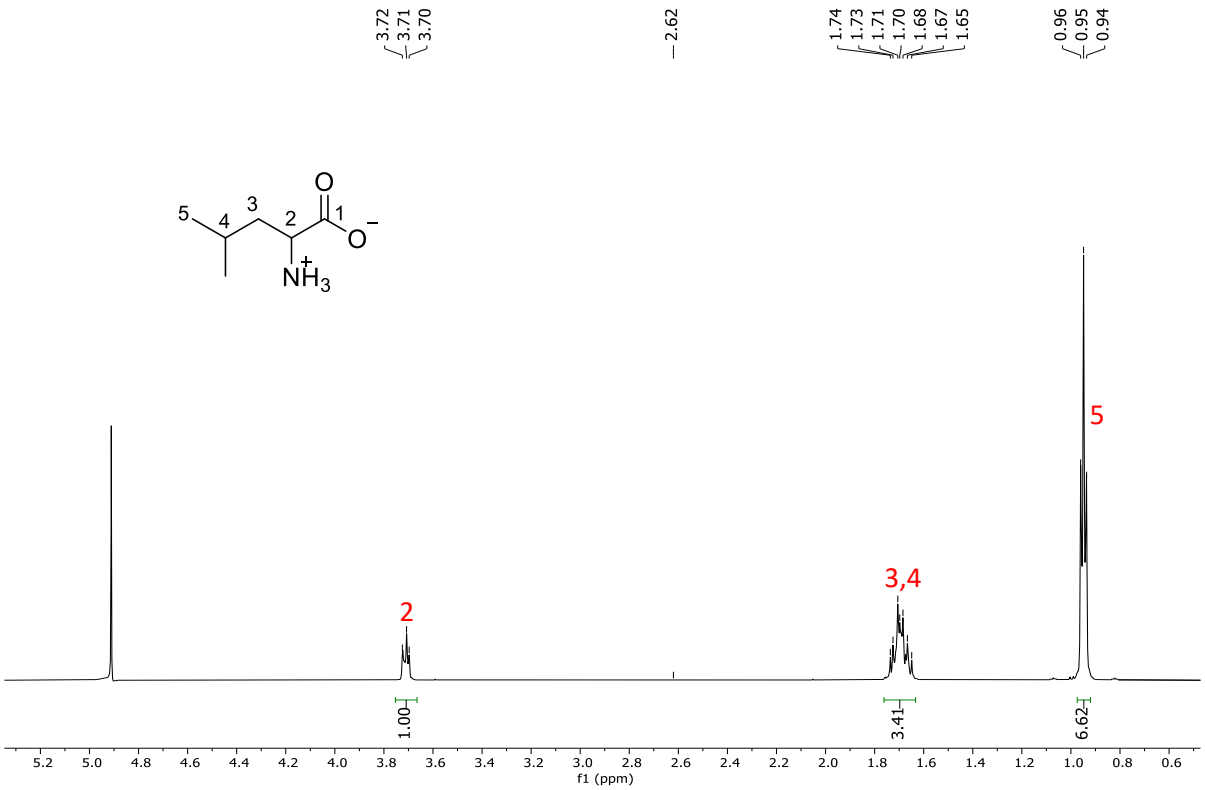


Figure S45. ^{1}H NMR of DL-leucine in D_2O

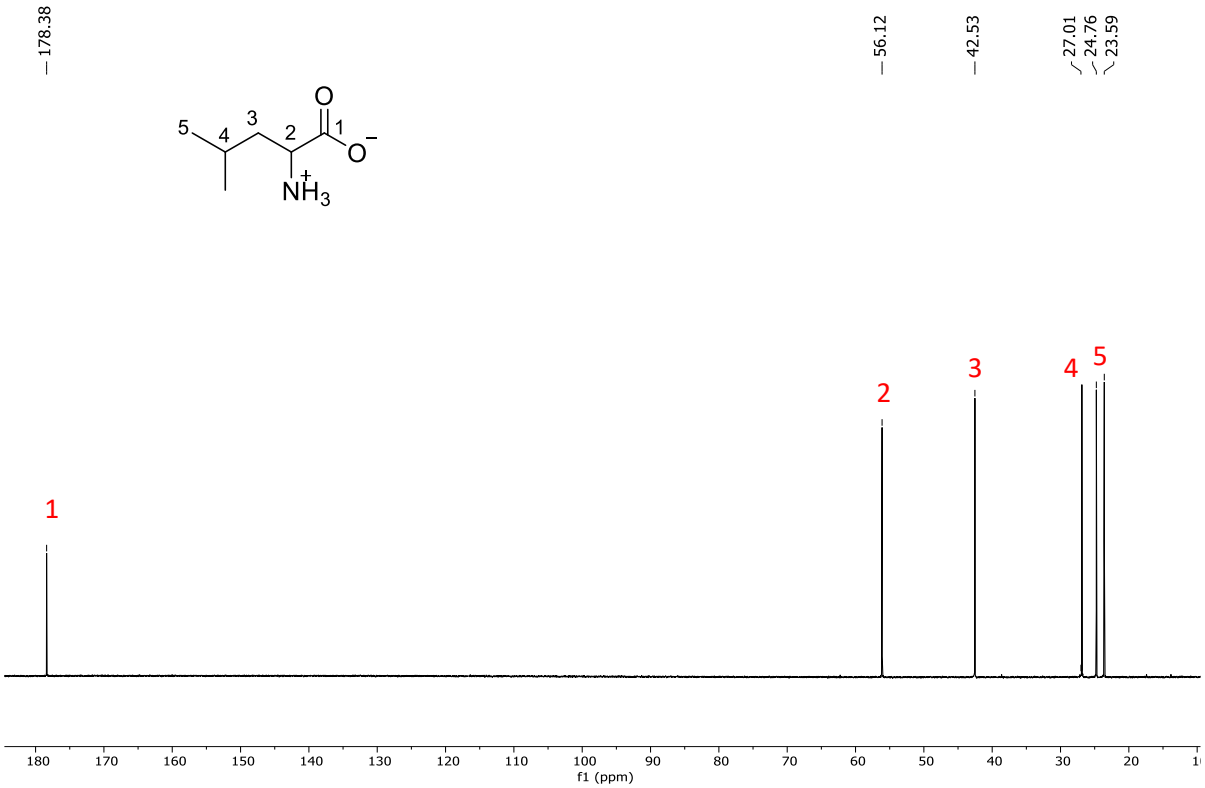


Figure S46. ^{13}C NMR of DL-leucine in D_2O

DL-methionine. ^{1}H-NMR (D_2O): δ 3.72-3.70 (t, 1H), 2.55-2.52 (t, 2H), 2.02-1.97.(m, 2H), 2.03 (s, 3H); ^{13}C-NMR (D_2O): δ 171.10, 56.59, 32.40, 31.52, 16.64.

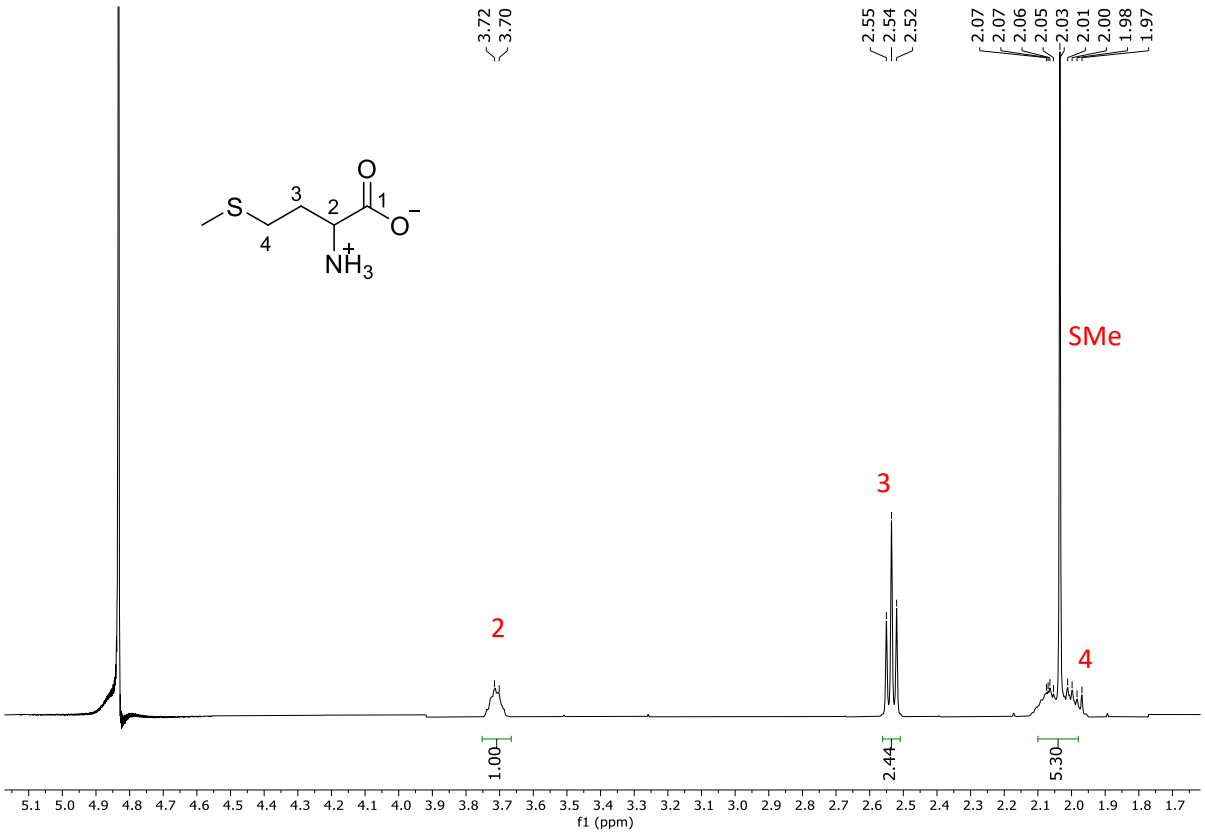


Figure S47. ^{1}H NMR of DL-methionine in D_2O

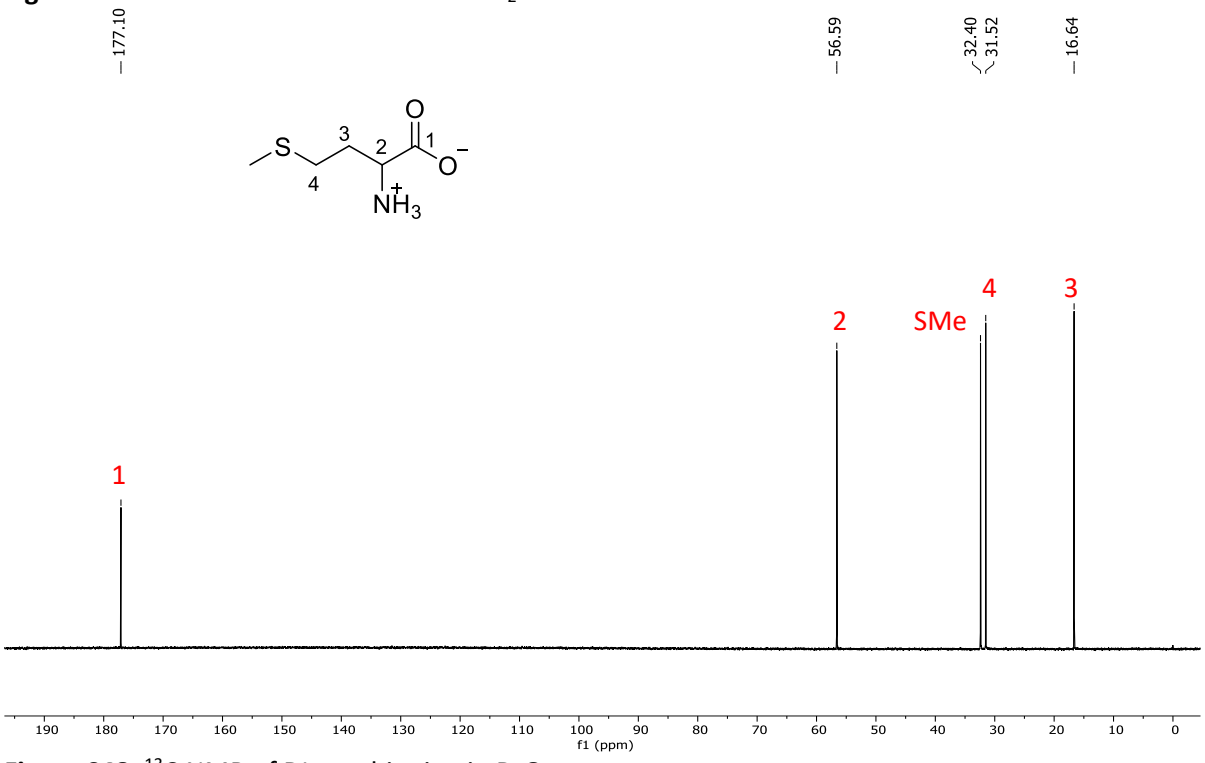


Figure S48. ^{13}C NMR of DL-methionine in D_2O

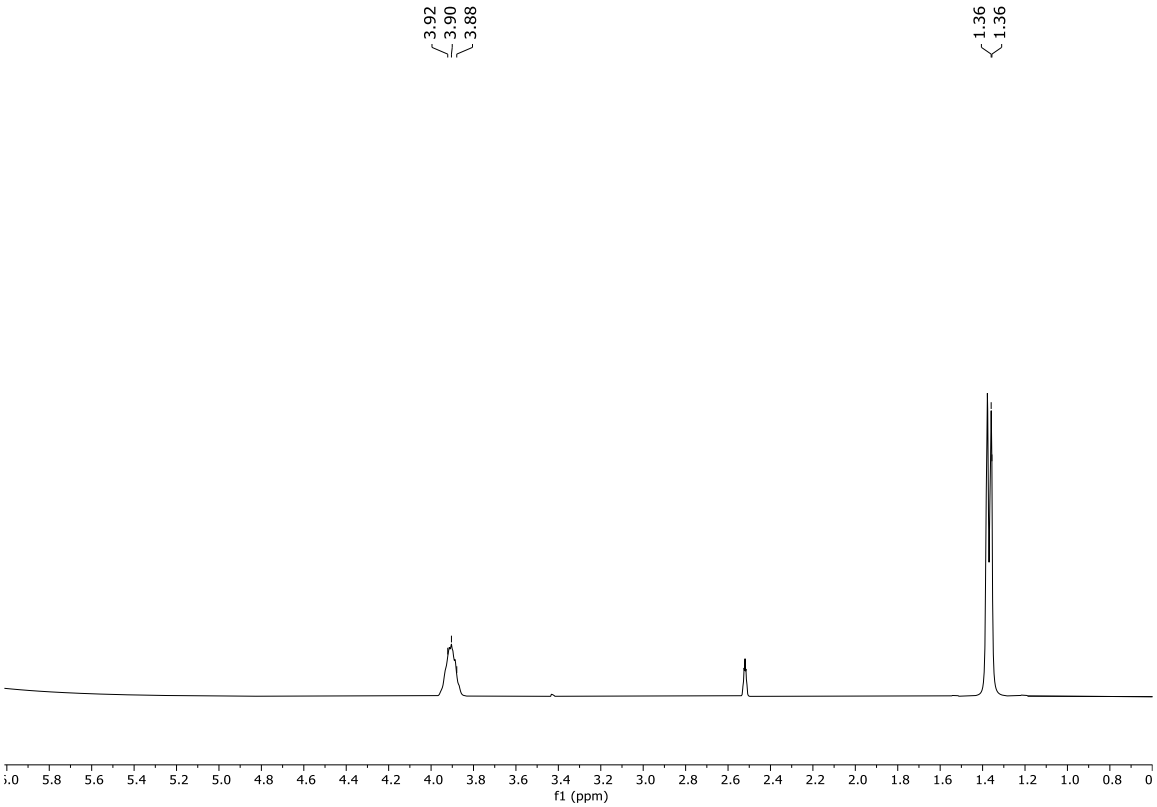


Figure S49. ^{1}H NMR of reaction of DL-alanine using $HClO_4$ under reflux (90 °C) in DMSO

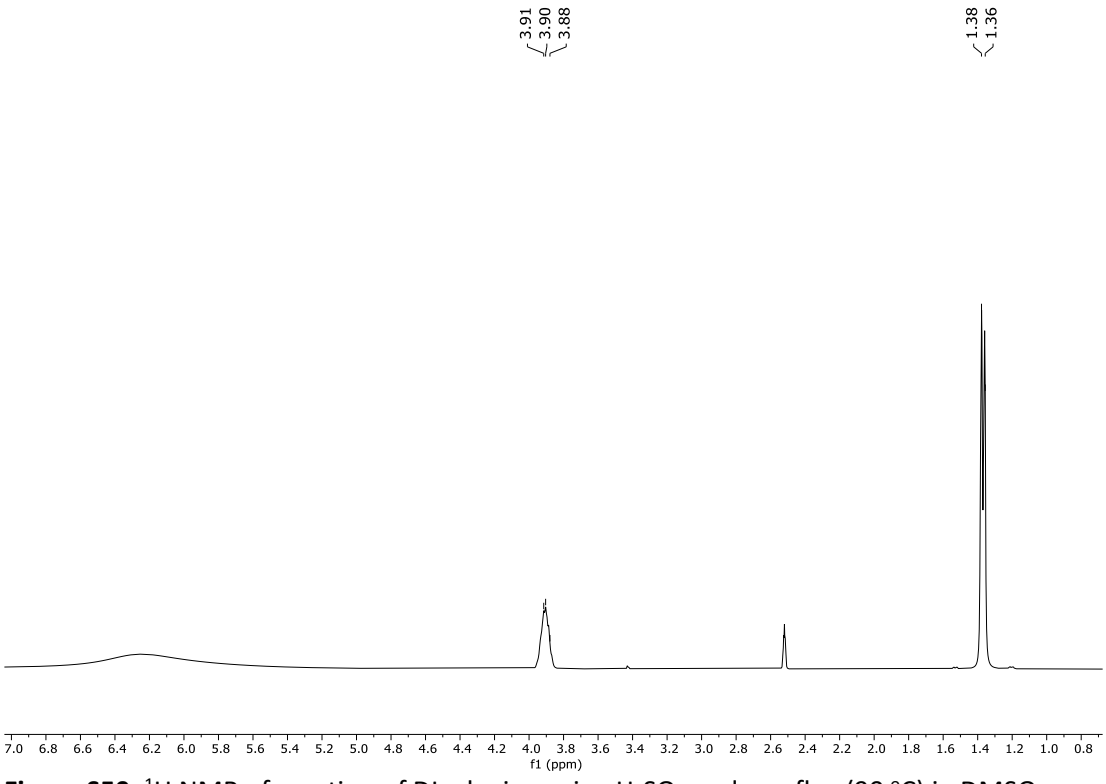


Figure S50. ^{1}H NMR of reaction of DL-alanine using H_2SO_4 under reflux (90 °C) in DMSO

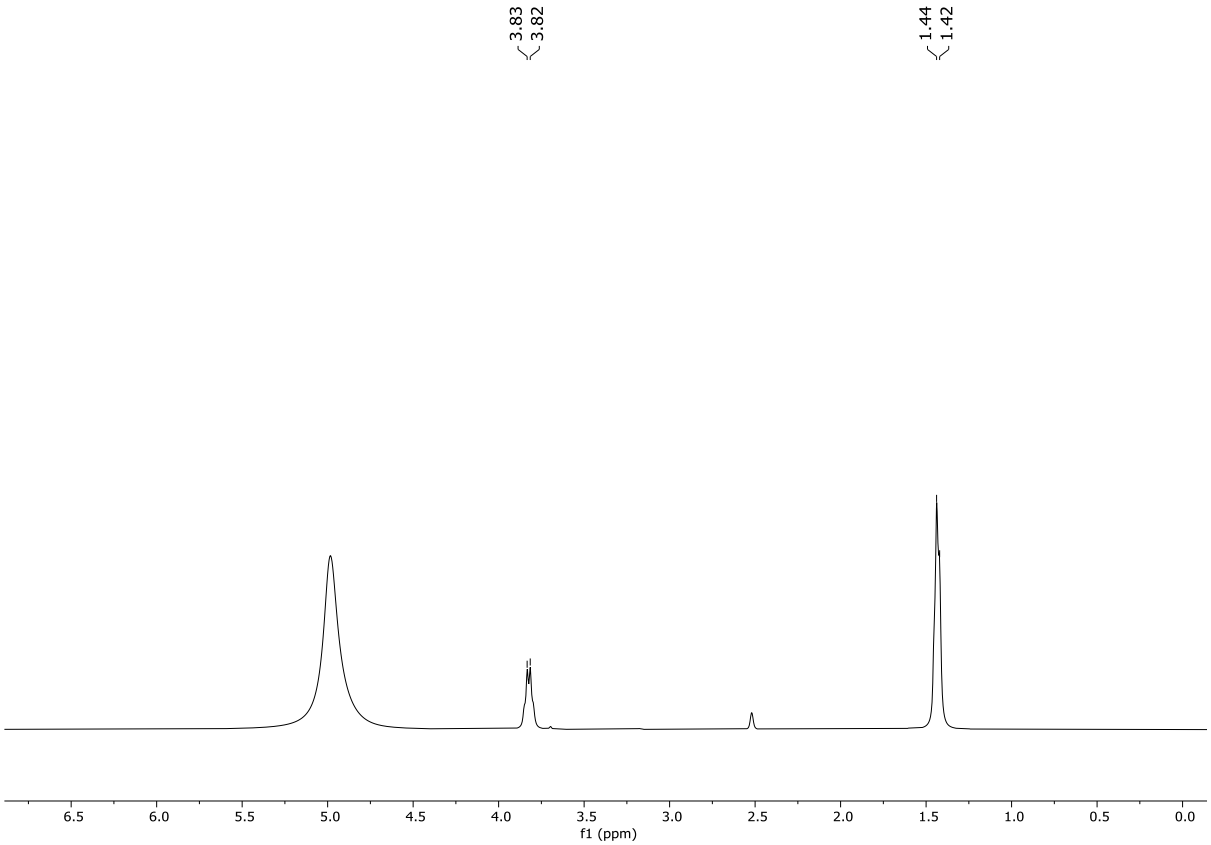


Figure S51. ^{1}H NMR of reaction of DL-alanine using HCl under reflux (90 ^{o}C) in DMSO

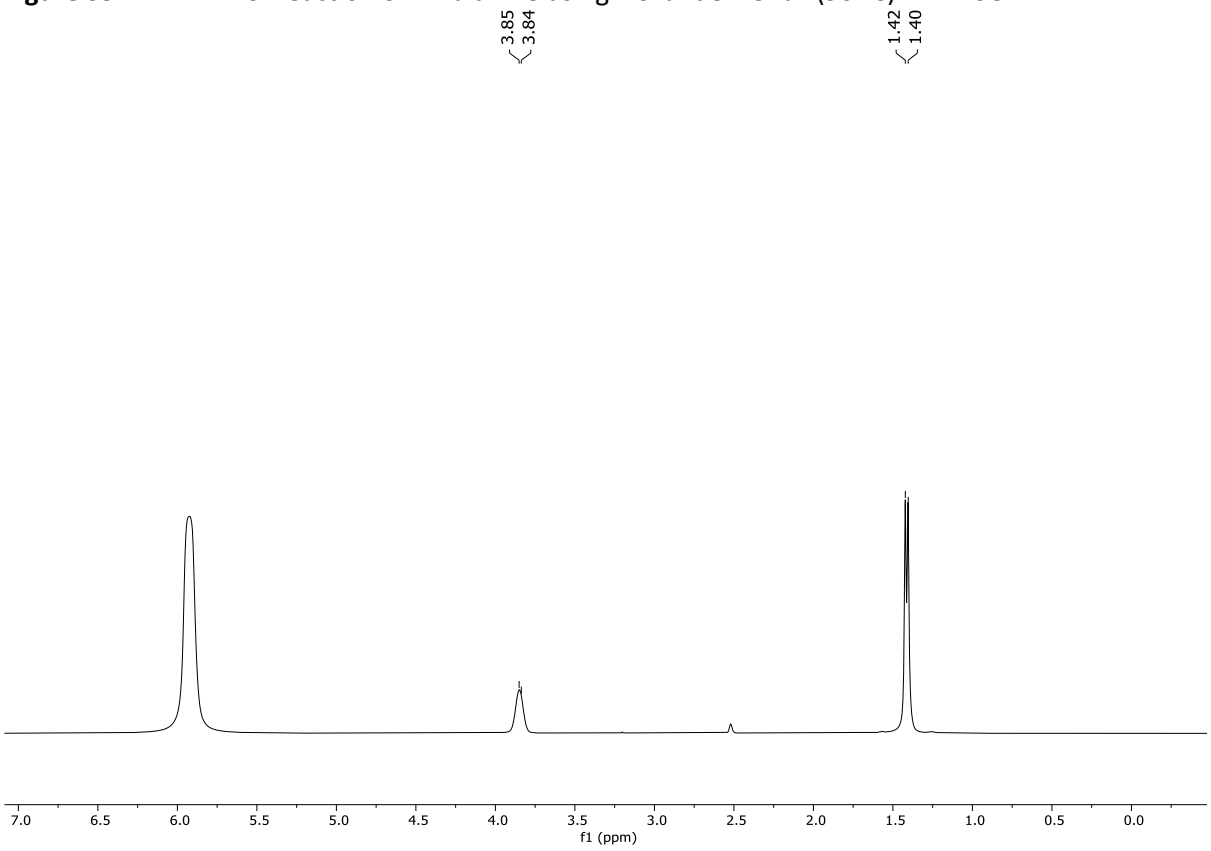


Figure S52. ^{1}H NMR of reaction of DL-alanine using HNO_3 under reflux (90 ^{o}C) in DMSO

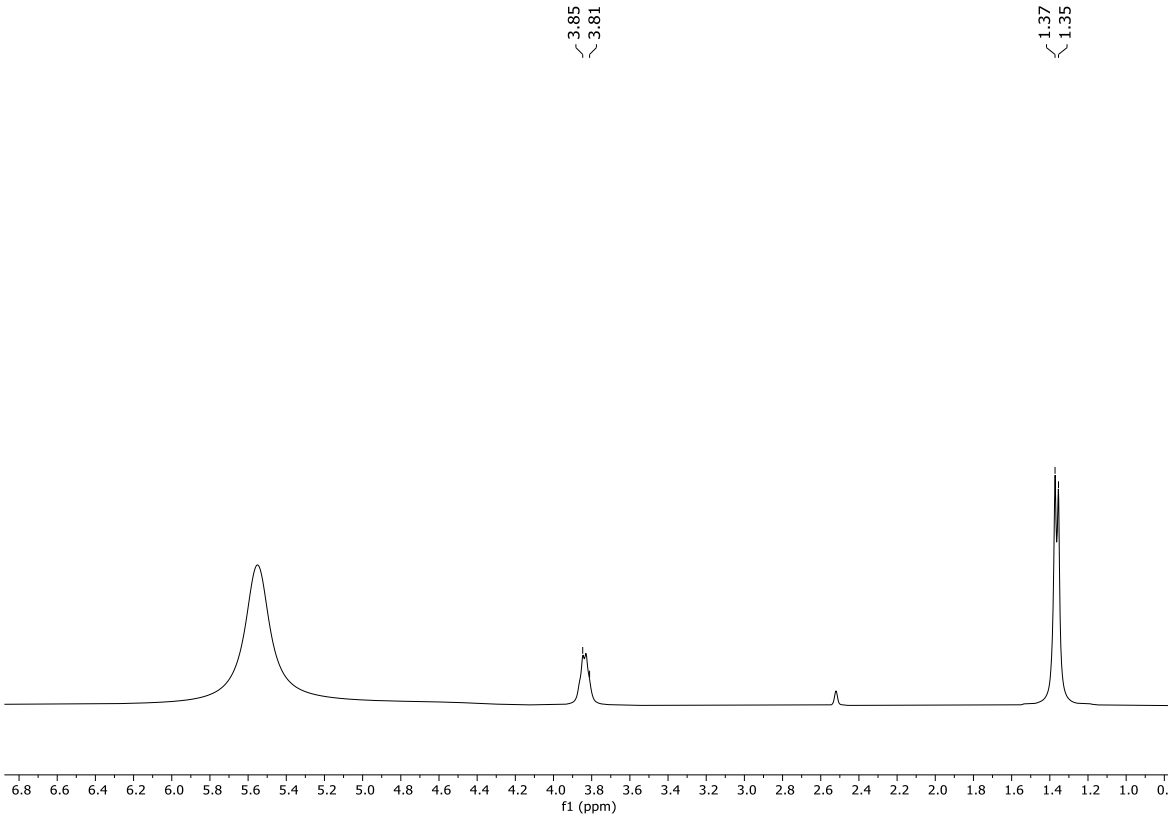


Figure S53. ^{1}H NMR of reaction of DL-alanine using HCO_2H under reflux (90 °C) in DMSO

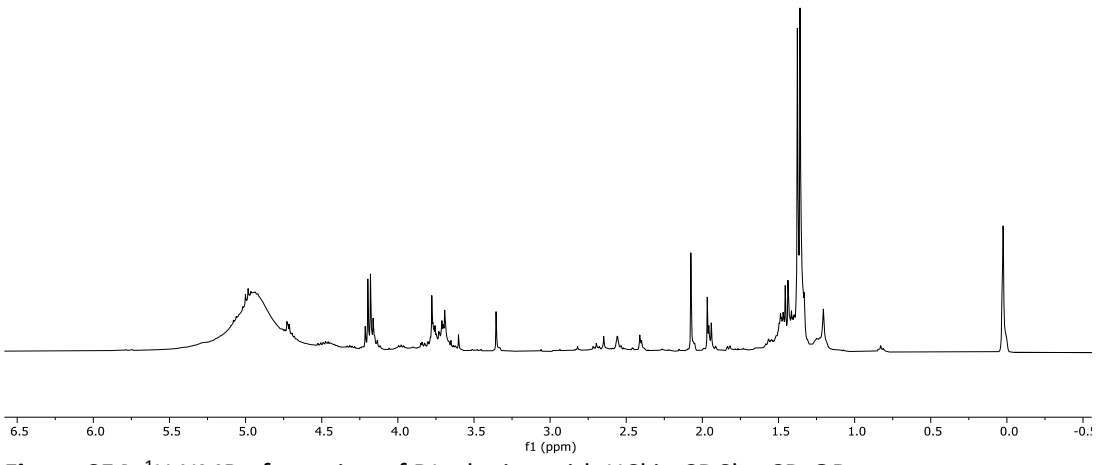


Figure S54. ^{1}H NMR of reaction of DL-alanine with HCl in $CDCl_3$ +CD_3OD

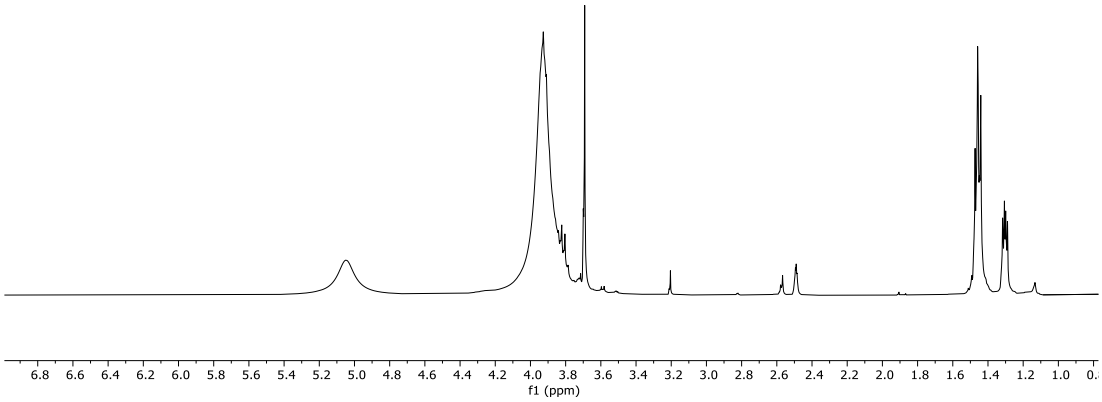


Figure S55. ^{1}H NMR of reaction of DL-alanine with HNO_3 in $CDCl_3$ +CD_3OD

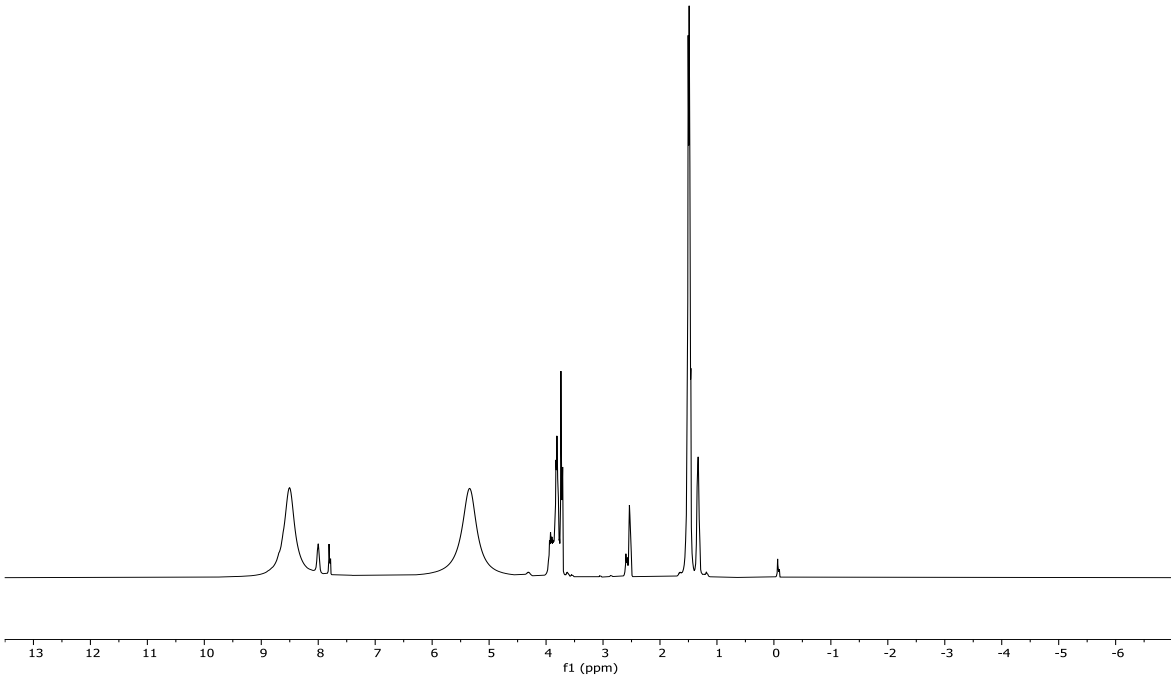


Figure S56. ^{1}H NMR of reaction of DL-alanine with $FeCl_3$ in $CDCl_3$ +CD_3OD

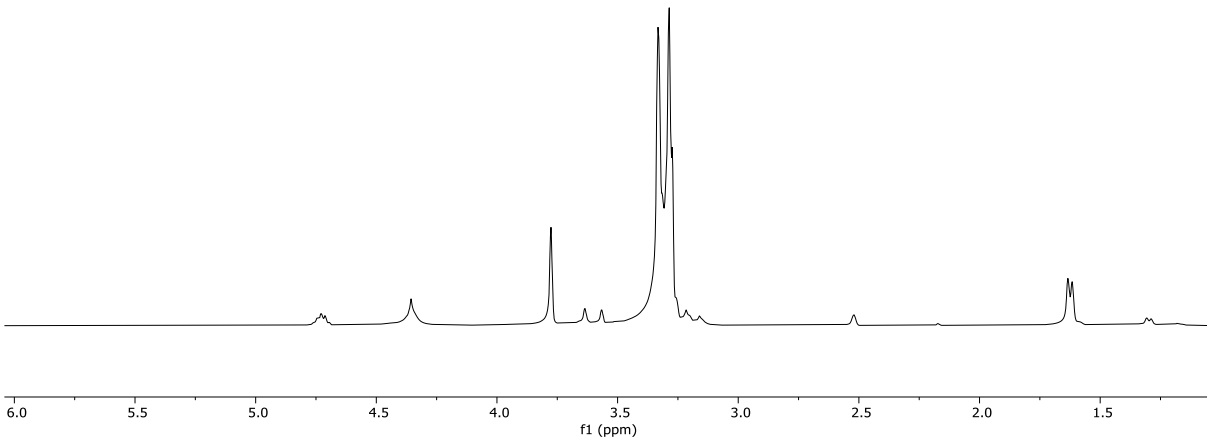


Figure S57. ^{1}H NMR of reaction of DL-alanine with $AlCl_3$ in $CDCl_3$ +CD_3OD

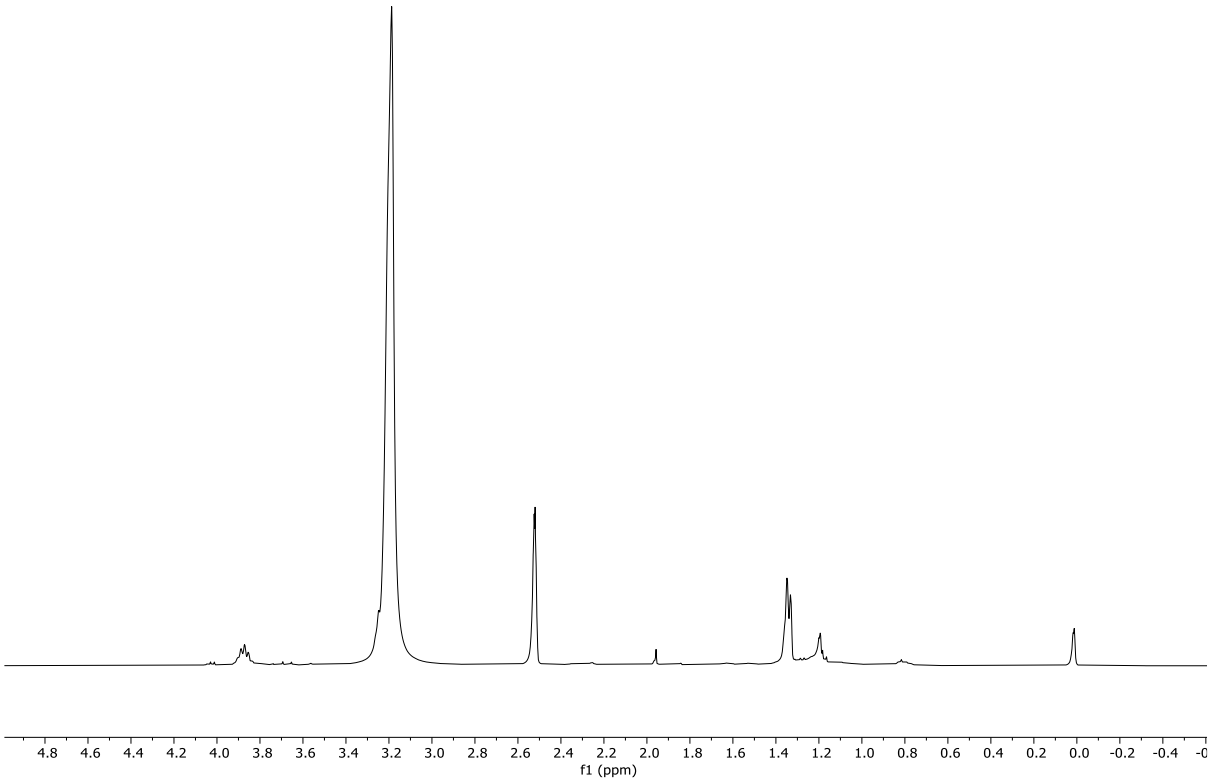


Figure S58. ^{1}H NMR of reaction of DL-alanine with H_2SO_4-SiO_2 in $CDCl_3$ +CD_3OD

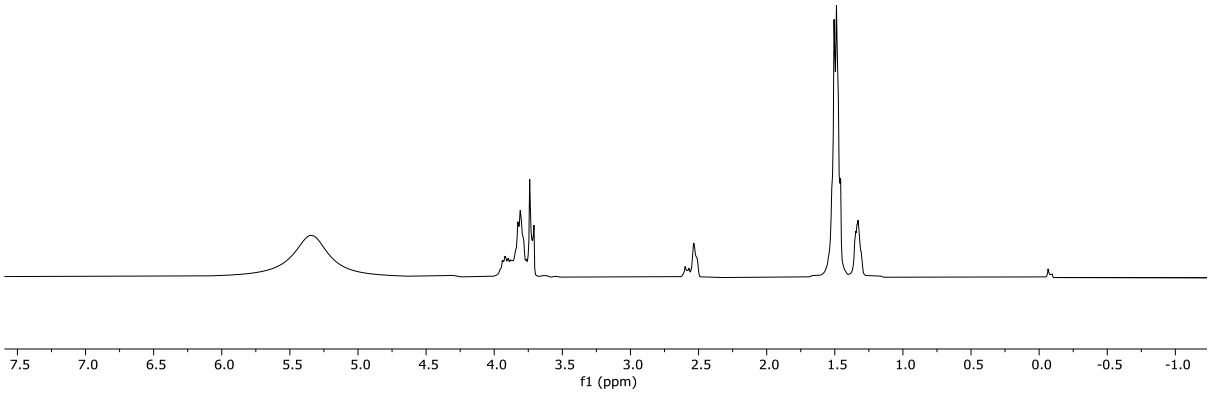


Figure S59. ^{1}H NMR of reaction of DL-alanine with $HClO_4$-SiO_2 in $CDCl_3$ +CD_3OD

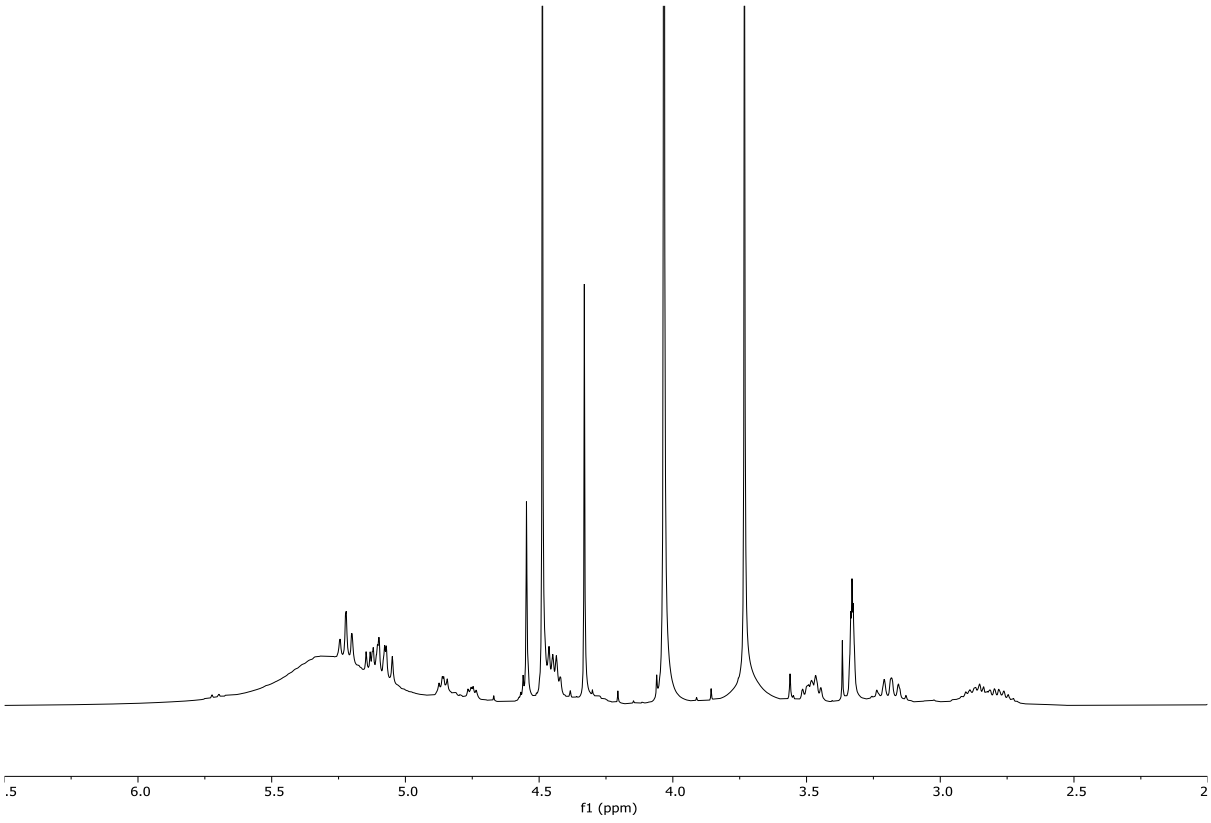


Figure S60. ^{1}H NMR of decomposition of methionine with $HClO_4$ (water as solvent instead of DMC) in $CDCl_3$ +CD_3OD

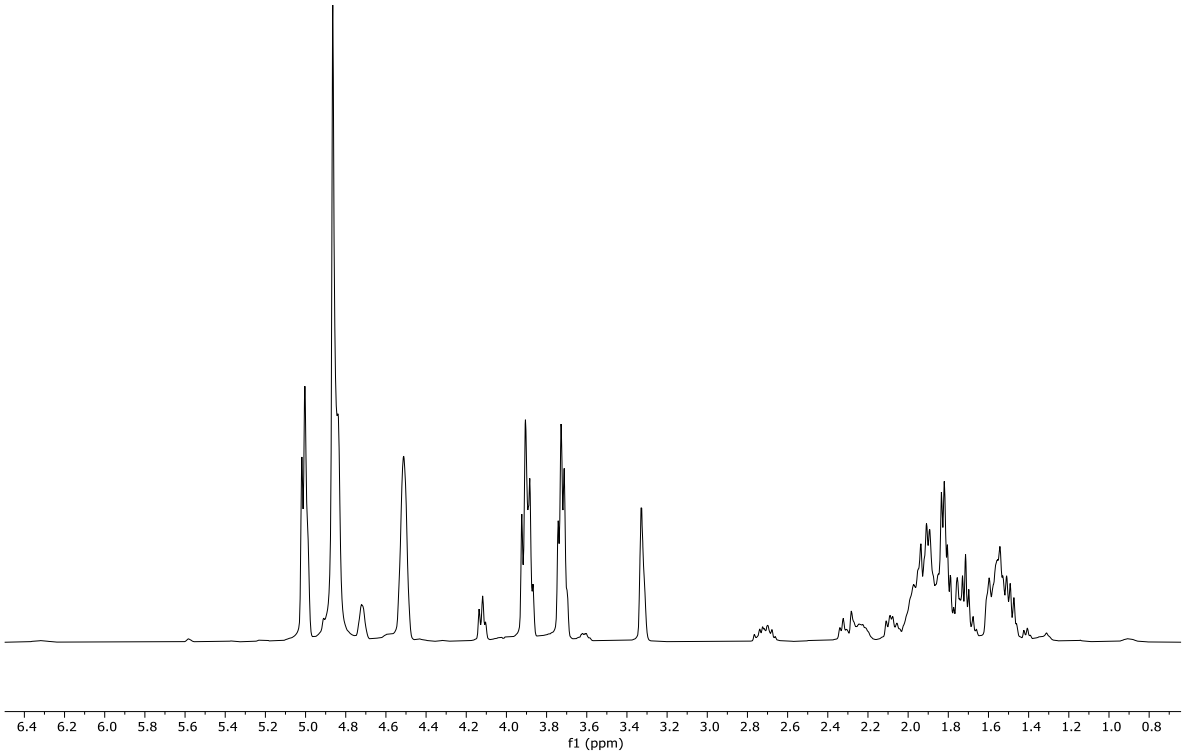


Figure S61. ^{1}H NMR of decomposition of methionine with H_2SO_4 (water as solvent instead of DMC) in $CDCl_3$ +CD_3OD

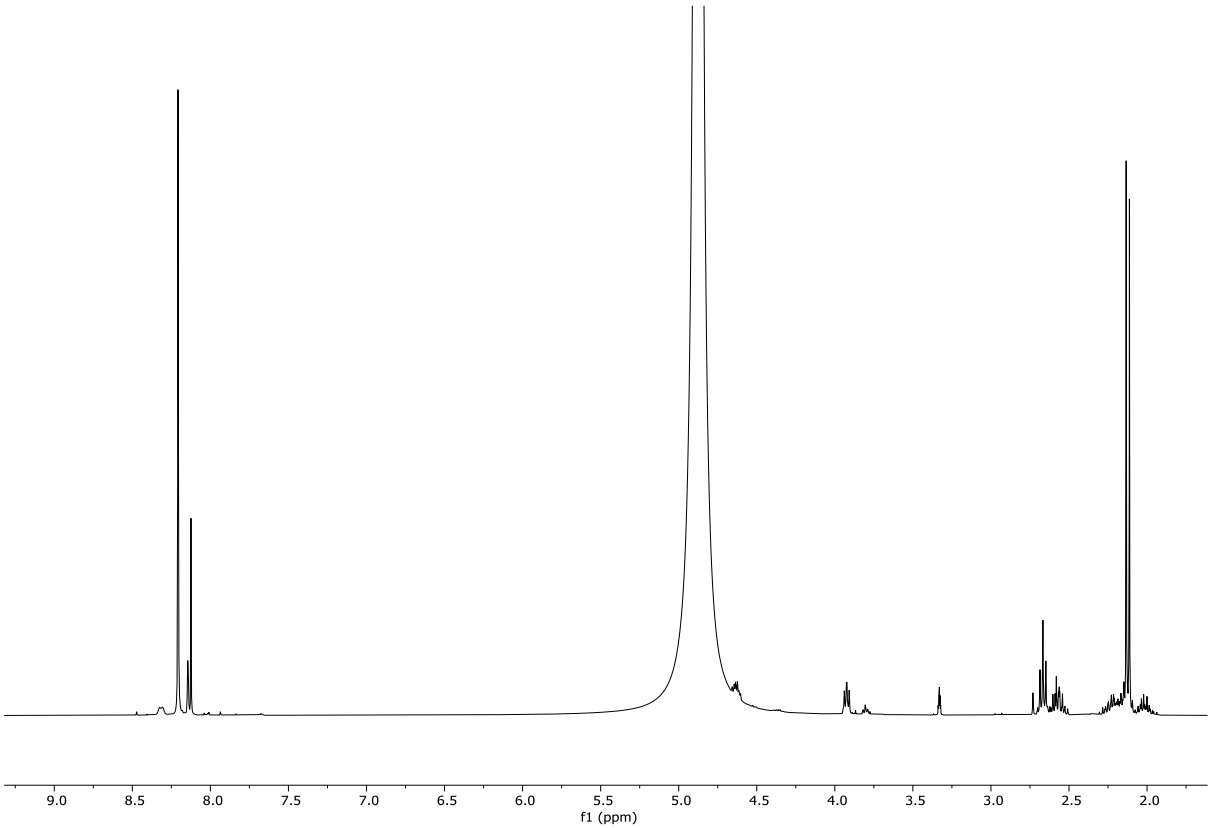


Figure S62. ^{1}H NMR of uncomplete reaction of methionine with HCO_2H (water as solvent instead of DMC) in $CDCl_3$ +CD_3OD

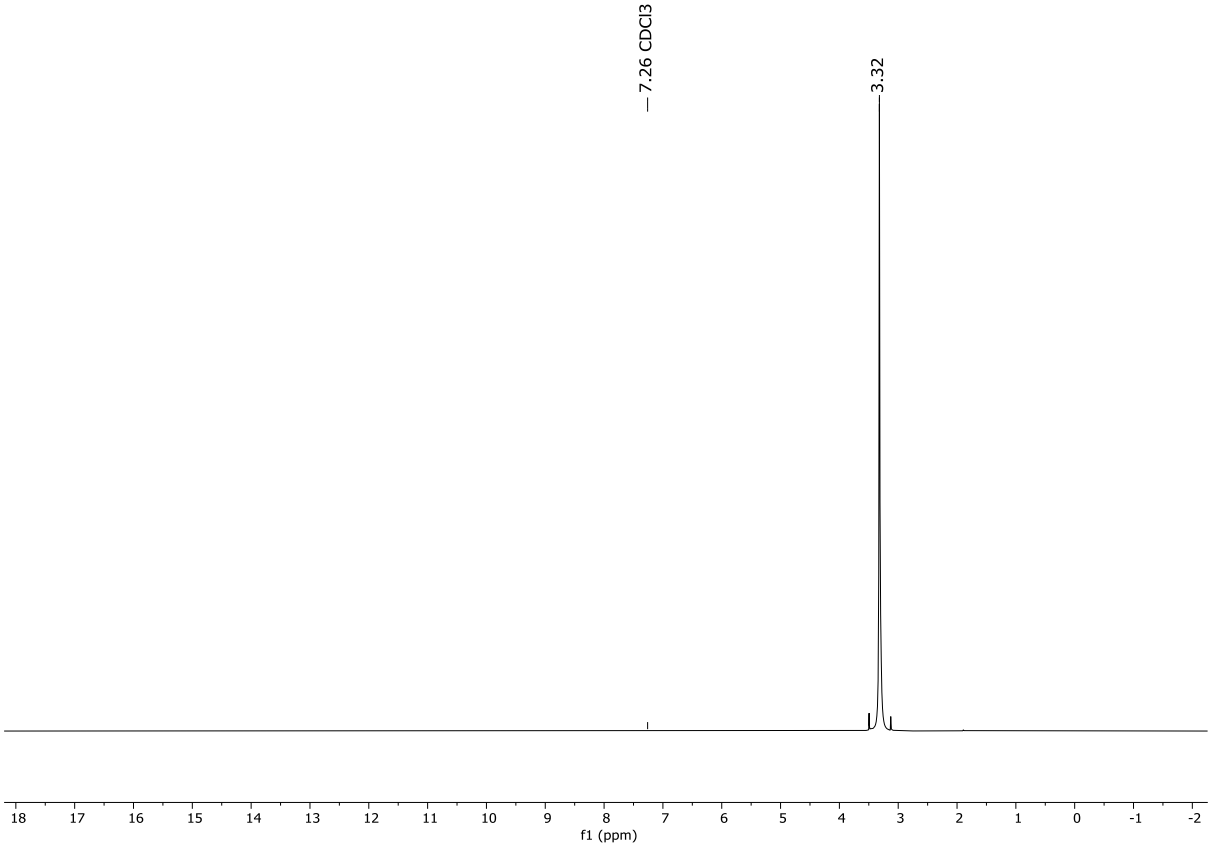


Figure S63. ^{1}H NMR of DMC in $CDCl_3$

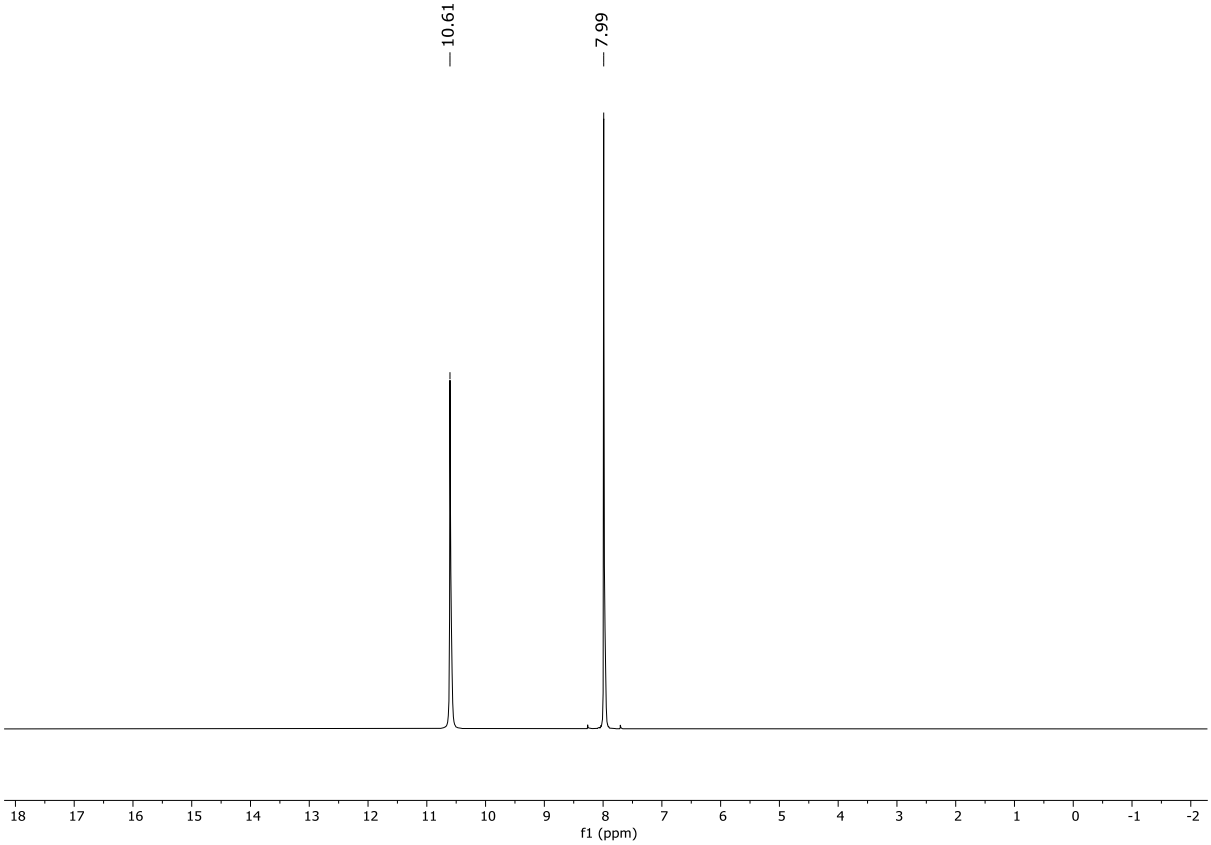


Figure S64. ^{1}H NMR of HCO_2H in $CDCl_3$

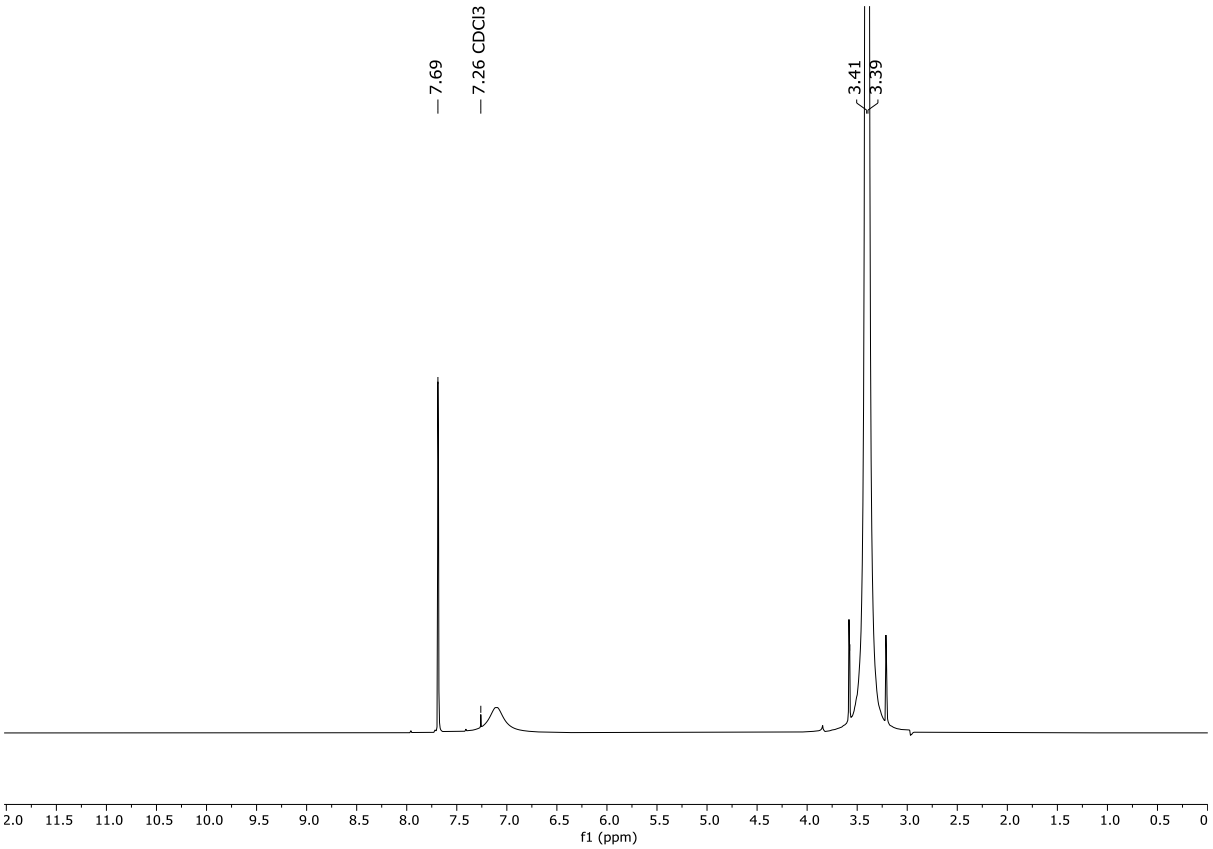


Figure S65. ^{1}H NMR of reaction of DMC and HCO_2H (20:1) in $CDCl_3$

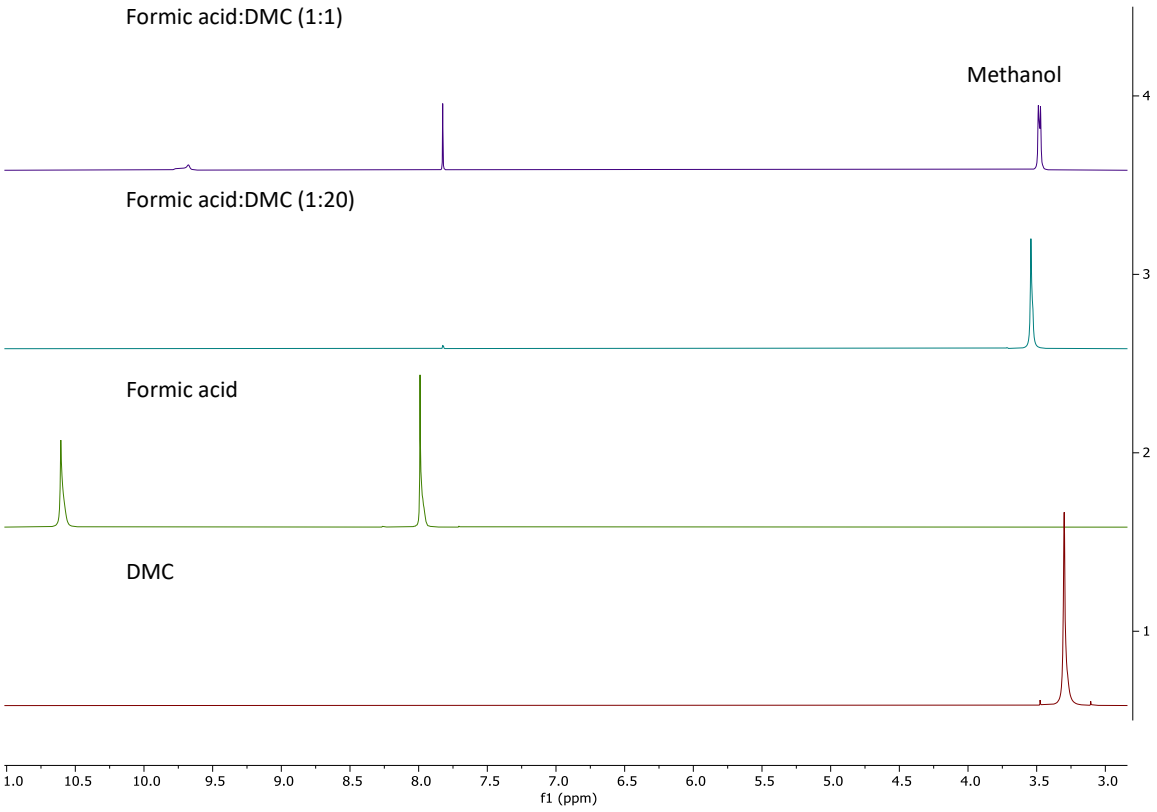


Figure S66. ^{1}H NMR of reaction of DMC and HCO_2H (1:1) in $CDCl_3$

L-alanine methyl ester. ^{1}H-NMR (CD_3OD+$CDCl_3$): 4.11-4.05 (t, 1H), 3.83 (s, 3H) 1,57-1.55 (d, 3H).

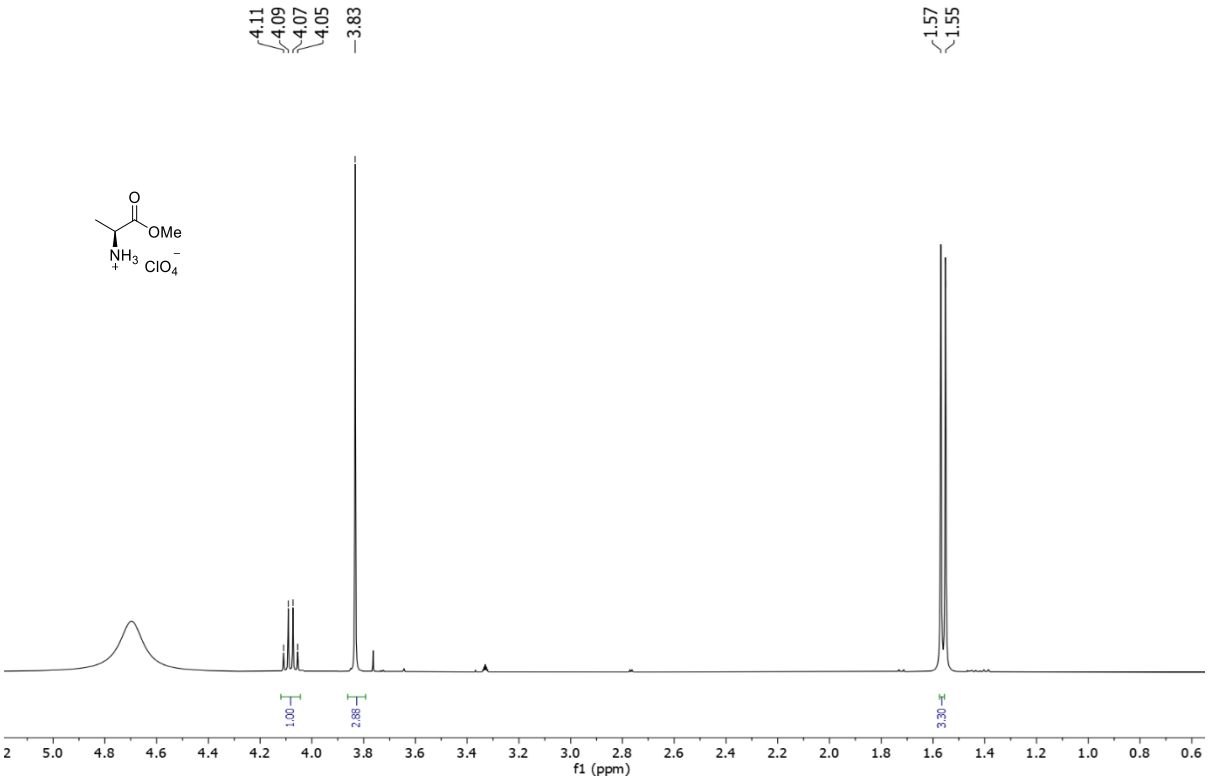


Figure S67. ^{1}H NMR of L-alanine methyl ester in CD_3OD + $CDCl_3$

L-leucine methyl ester. ^{1}H-NMR (CD_3OD+$CDCl_3$): 4.06-4.02 (t, 1H), 3.85 (s, 3H) 1,85-1.68 (m, 2H), 0.99-0.98 (d, 6H).

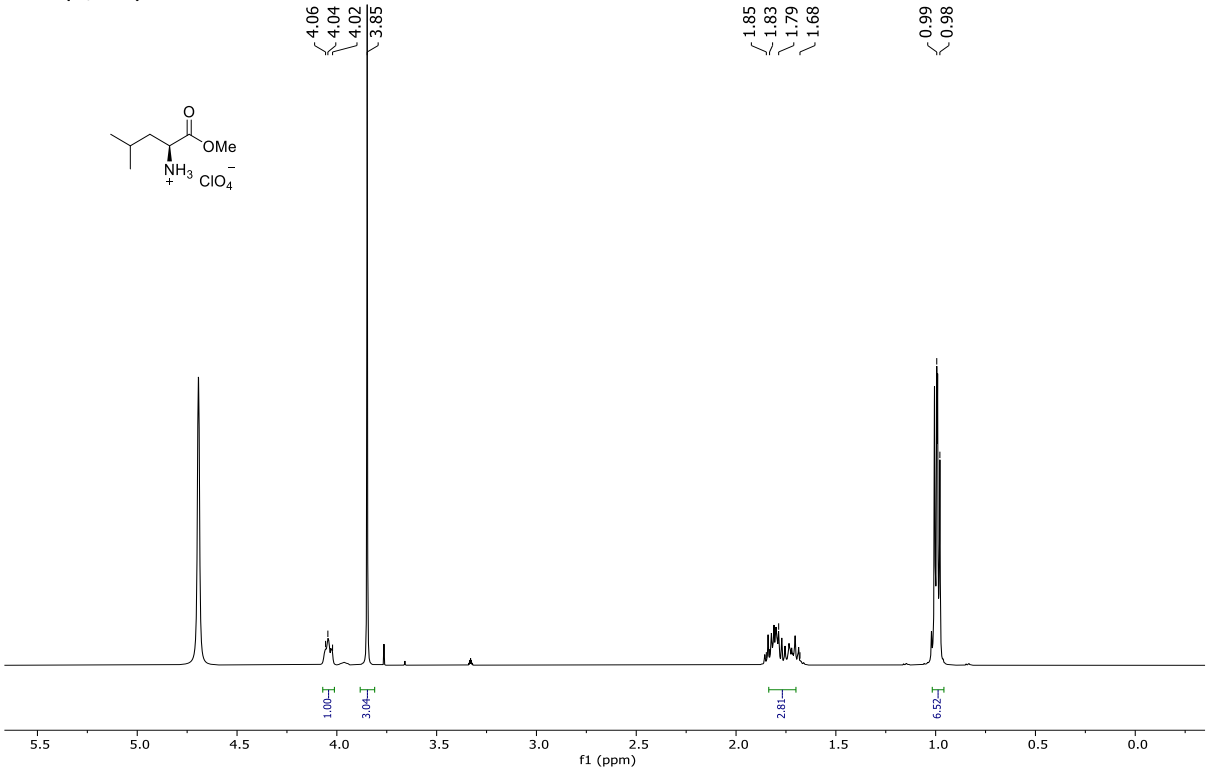


Figure S68. ^{1}HNMR of L-leucine methyl ester in CD_3OD + $CDCl_3$

L-proline methyl ester. ^{1}H-NMR (CD_3OD+$CDCl_3$): 4.35-4.31 (t, 1H), 3.76 (s, 3H) 3.37-3.28 (m, 2H), 2.40-2.32 (m, 1H), 2.08-1.97 (m, 3H); ^{13}C-NMR: δ 169.25, 59.49, 53.26, 46.30, 27.99, 23.21.

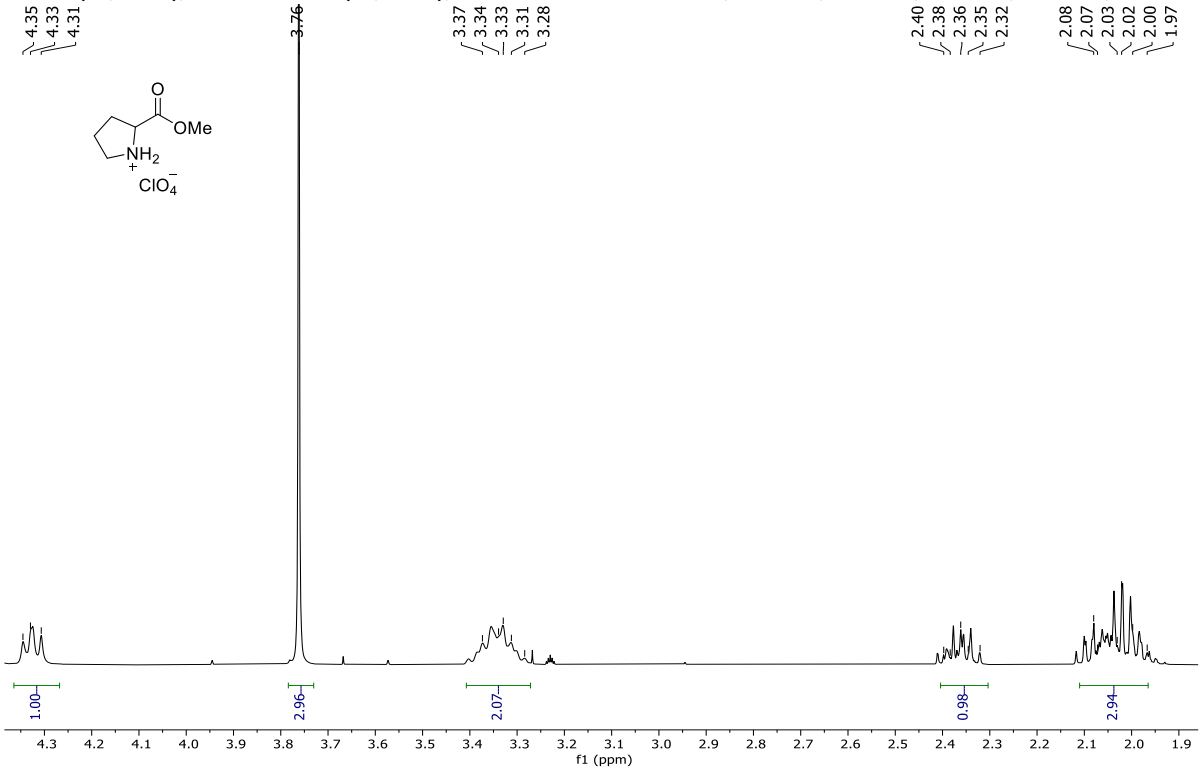


Figure S69. ^{1}HNMR of L-proline methyl ester in CD_3OD + $CDCl_3$

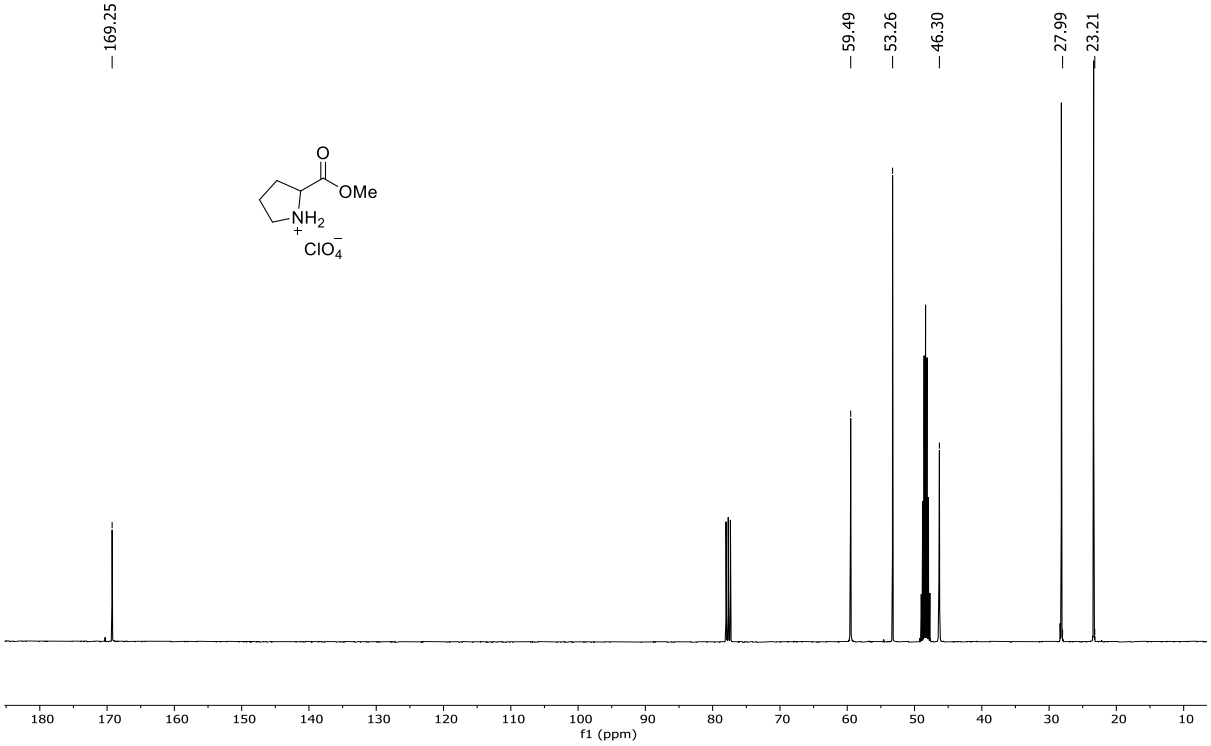


Figure S70. ^{13}C NMR of L-proline methyl ester in CD_3OD + $CDCl_3$

L-glysine methyl ester. ^{1}H-NMR (CD_3OD+$CDCl_3$): δ 3.82 (brs, 2H), 3.80 (s, 3H); ^{13}C-NMR: δ 167.79, 57.92, 40.14.

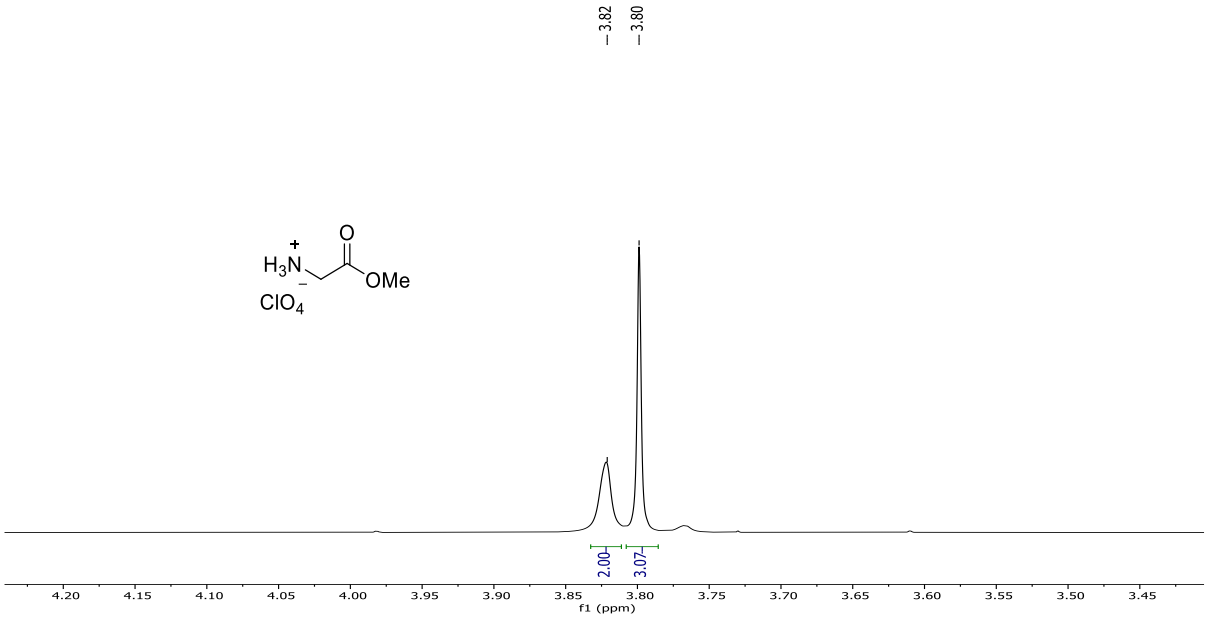


Figure S71. ^{1}H NMR of L-glycine methyl ester in CD_3OD + $CDCl_3$

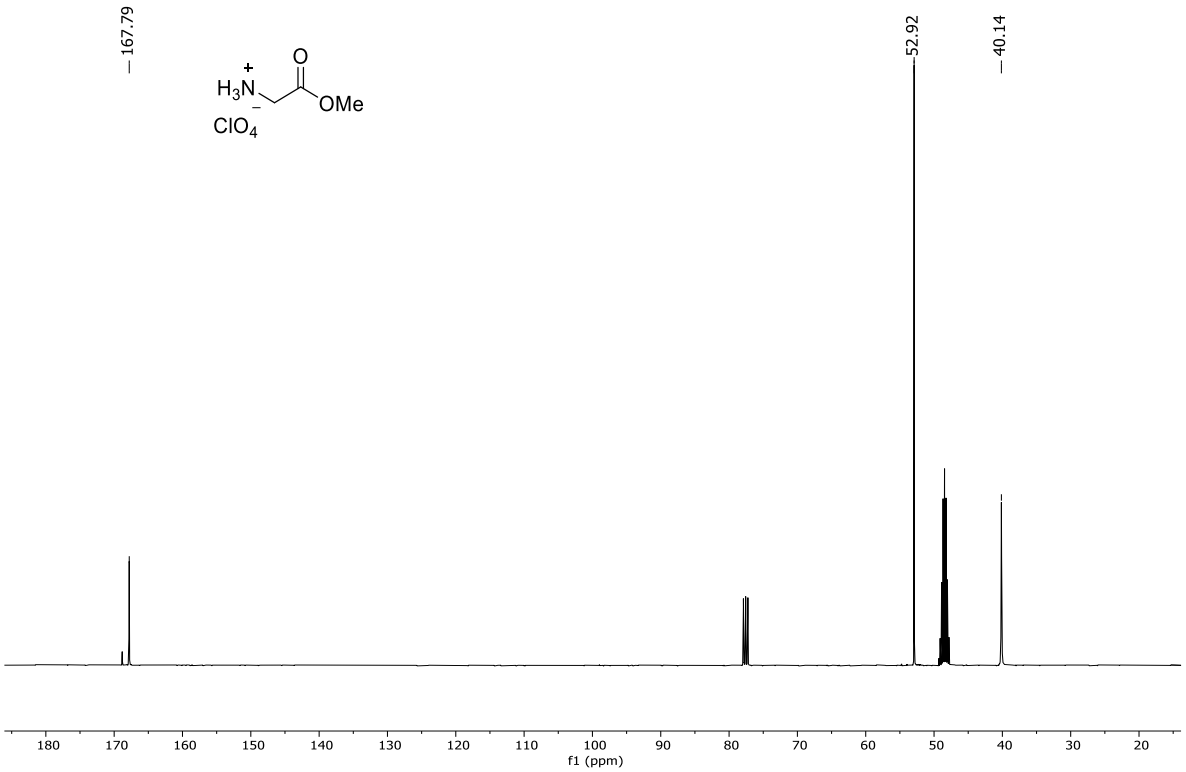


Figure S72. ^{13}C NMR of glycine methyl ester in CD_3OD + $CDCl_3$

L-histidine methyl ester. ^{1}H-NMR (CD_3OD+$CDCl_3$): δ 8.16 (s, 1H), 7.51 (s, 2H), 4.24-4.18 (t, 1H), 3.76 (s, 3H) 3.26-3.118 (d, 2H); ^{13}C-NMR: δ 168.09, 134.63, 127.80, 117.94, 53.22, 51.87, 25.73.

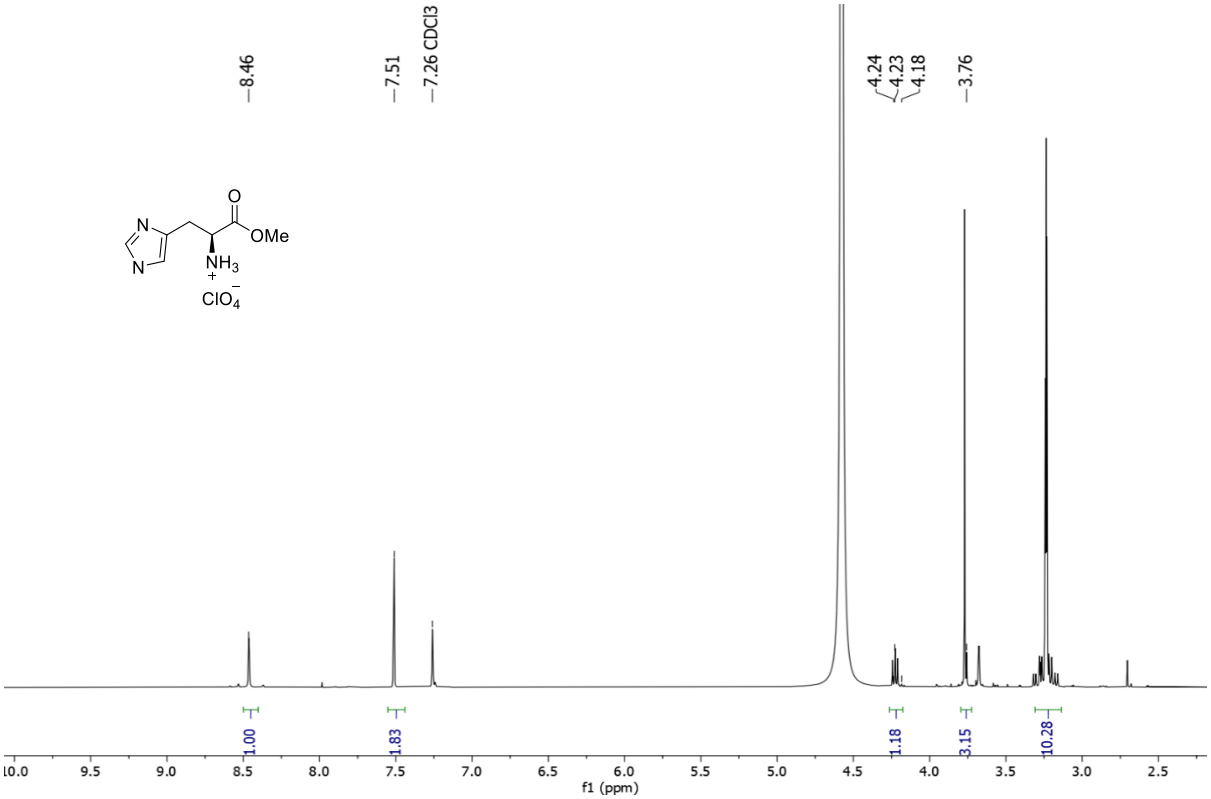


Figure S73. ^{1}H NMR of L-histidine methyl ester in CD_3OD

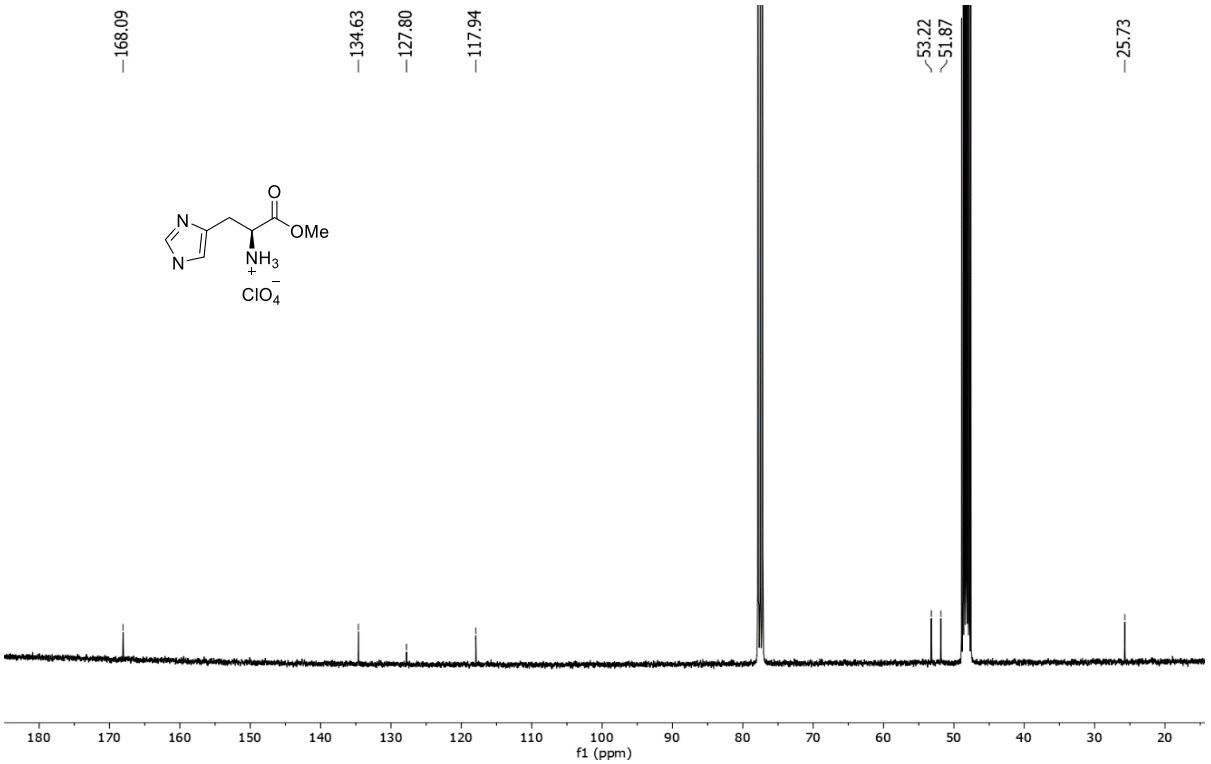


Figure S74. ^{13}CNMR of L-histidine methyl ester in CD_3OD

L-tyrosine methyl ester. ^{1}H-NMR (CD_3OD+$CDCl_3$): δ 7.24-7.21 (d, 2H), 6.98-6.95 (d, 2H), 4.40-4.36 (t, 1H), 3.96 (s, 3H) 3.26-3.118 (d, 2H); ^{13}C-NMR: δ 168.92, 156.11, 130.21, 124.06, 115.54, 54.35, 52.98, 35.29.

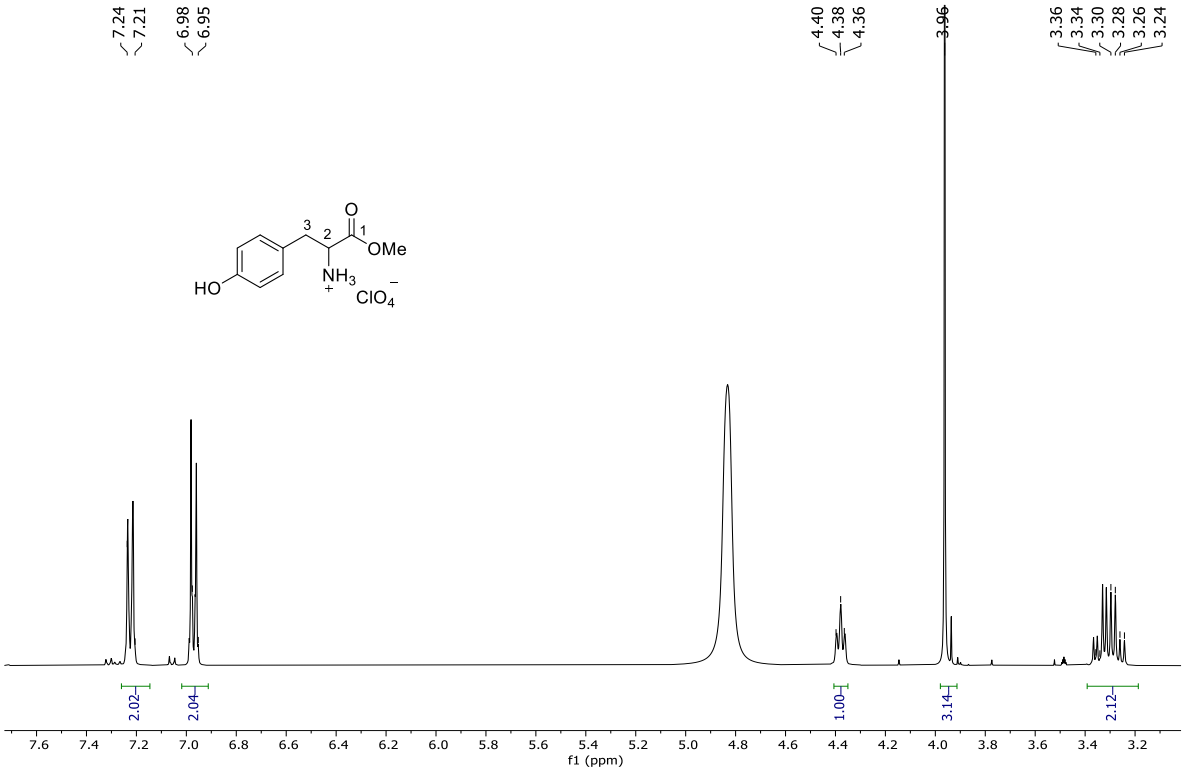


Figure S75. ^{1}H NMR of L-tyrosine methyl ester in CD_3OD + $CDCl_3$

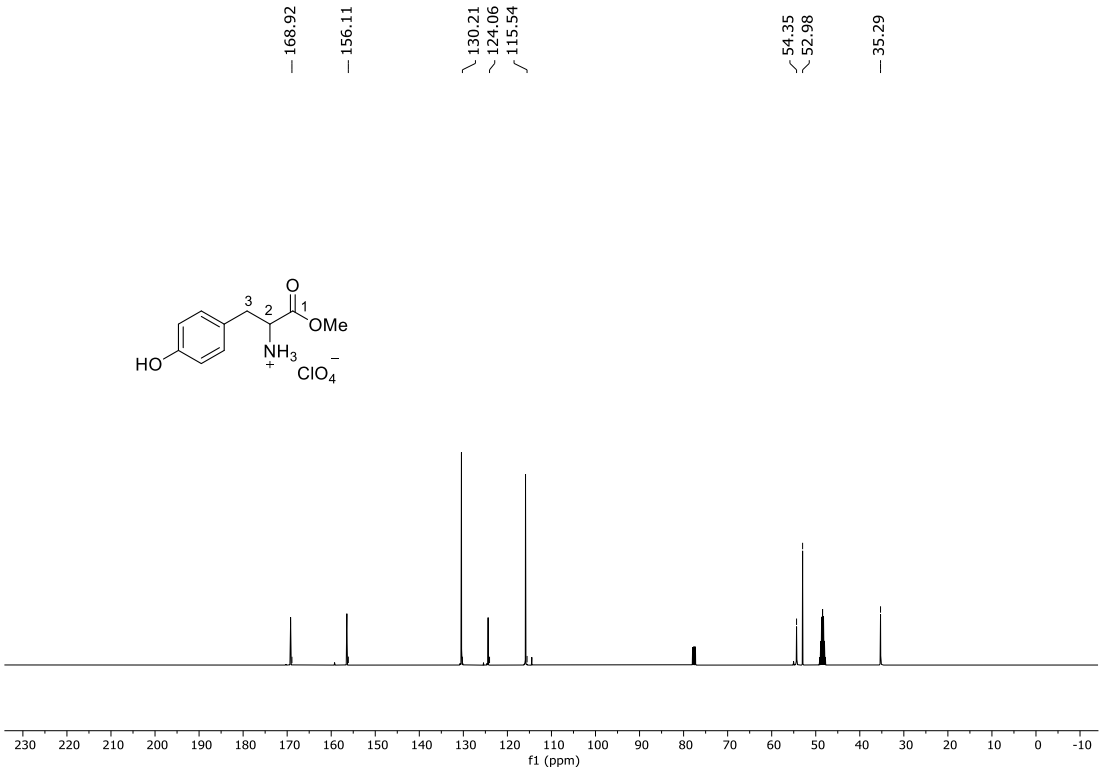


Figure S76. ^{13}C NMR of L-tyrosine methyl ester in CD_3OD + $CDCl_3$

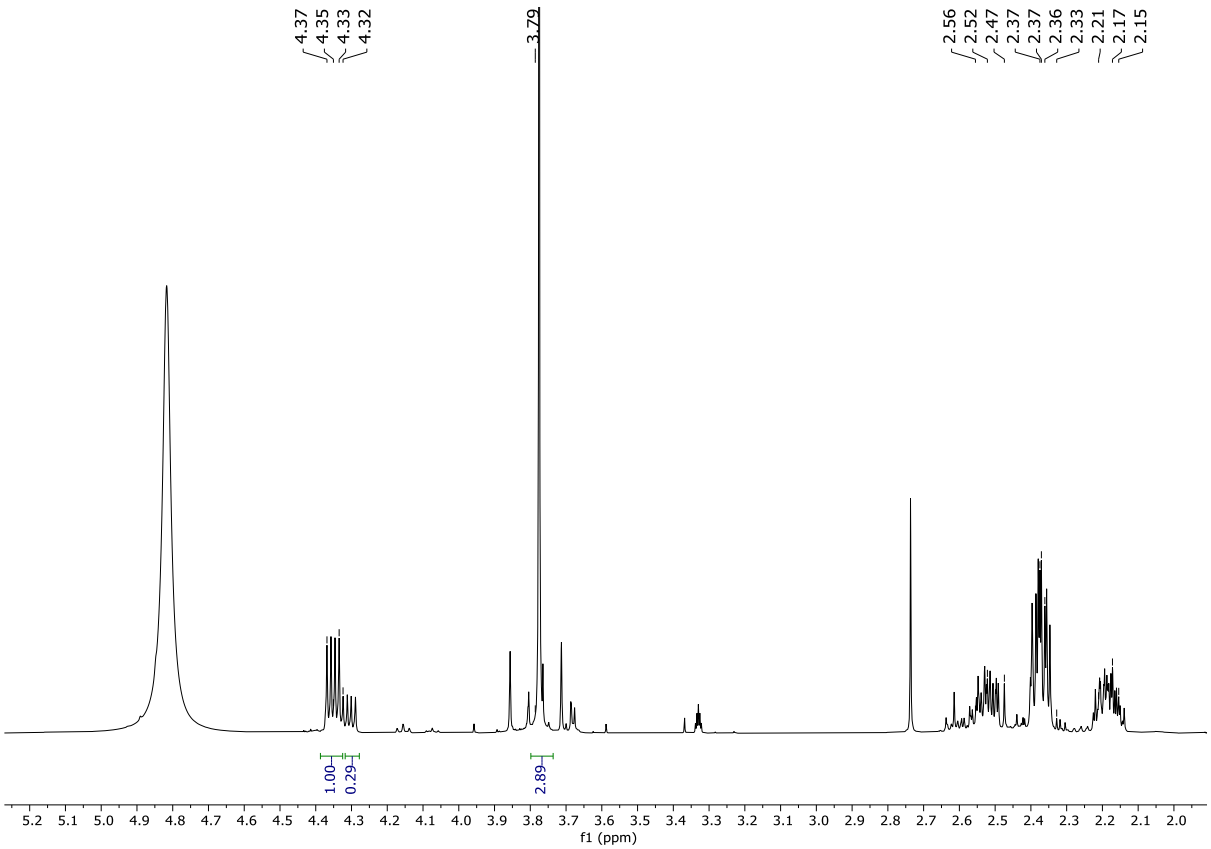


Figure S77. ^{1}H NMR of L-glutamine methyl ester in CD_3OD + $CDCl_3$

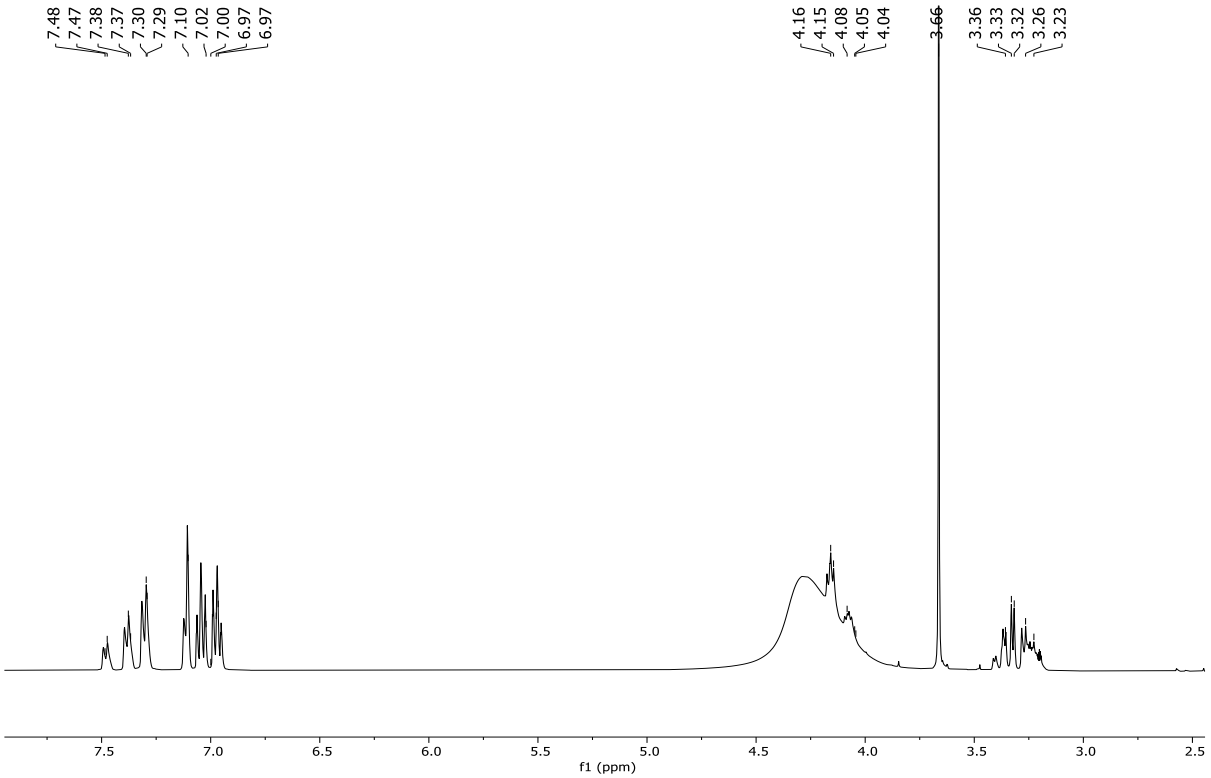


Figure S78. ^{1}H NMR of L-tryptophan methyl ester in CD_3OD + $CDCl_3$

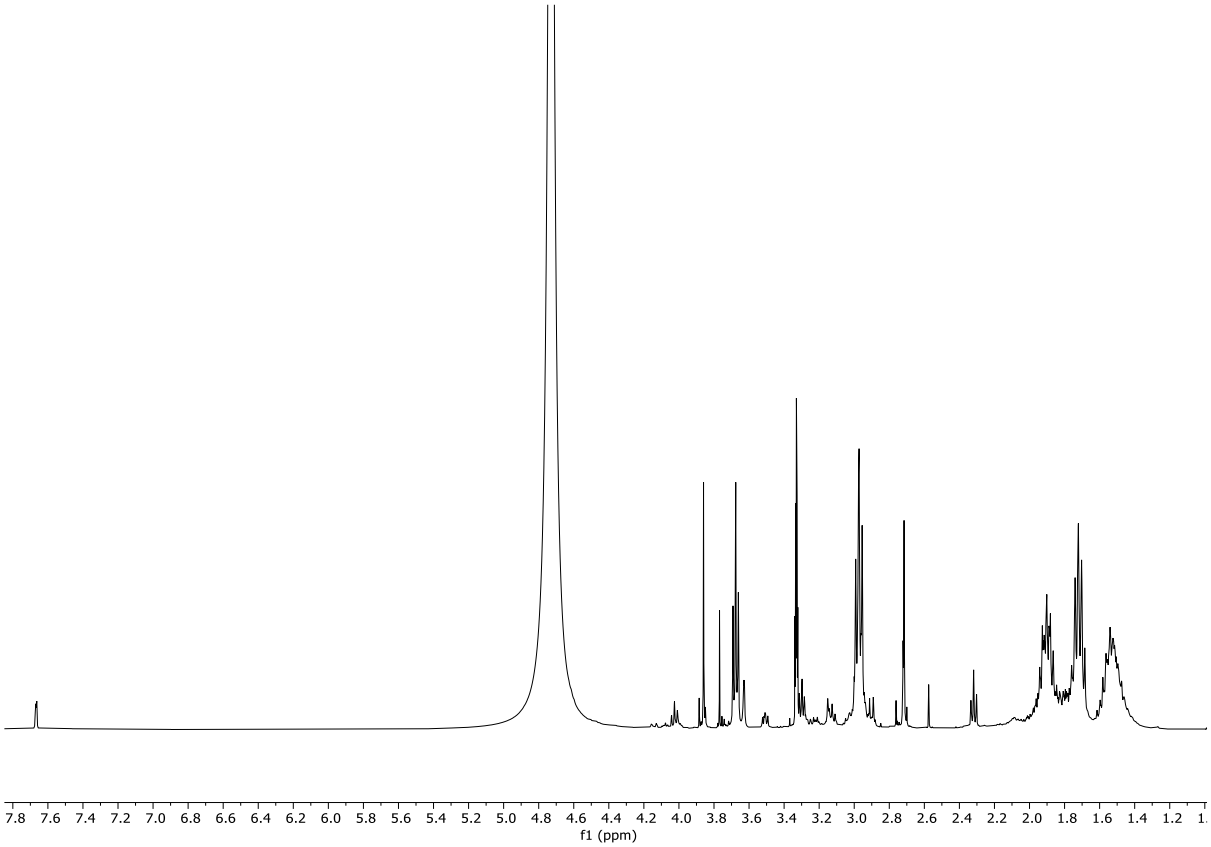


Figure S79. ^{1}H NMR of L-lysine in $HClO_4$ condition

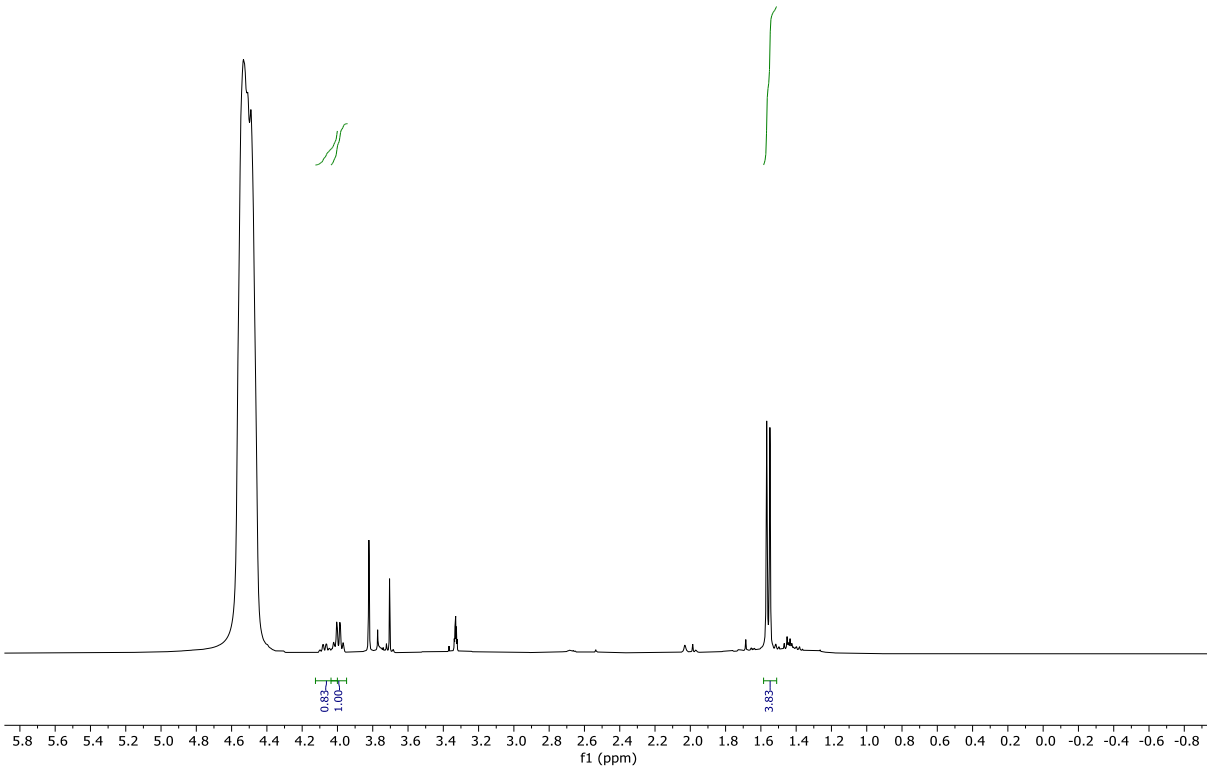


Figure S80. ^{1}H NMR of L-cystine in $HClO_4$ condition

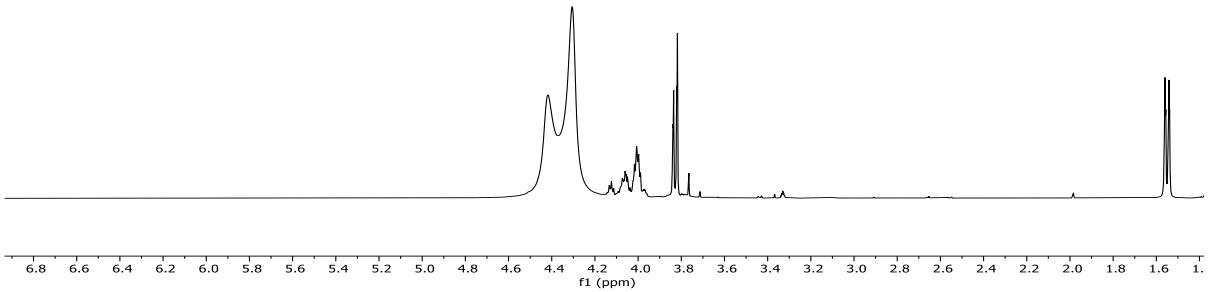


Figure S81. ^{1}H NMR of D-serine $HClO_4$ condition

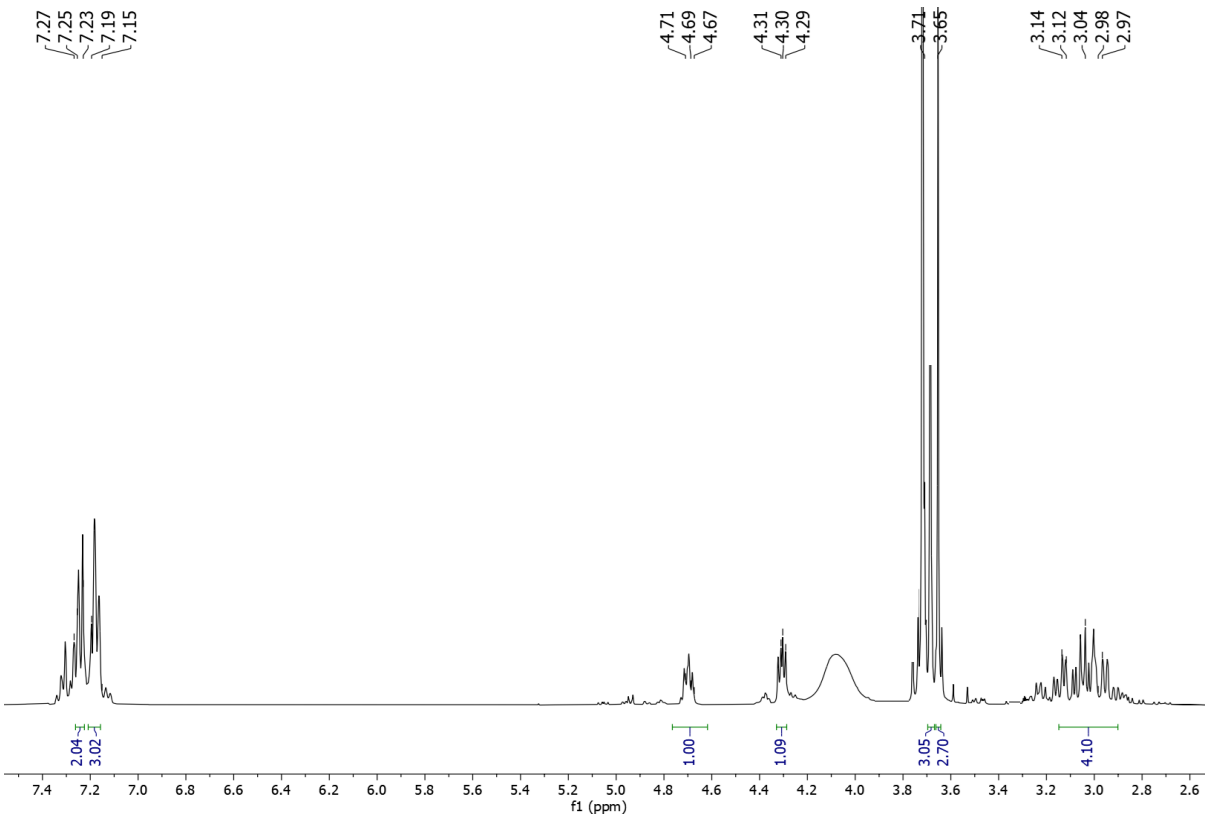


Figure S82.^{1}H NMR of aspartame in $HClO_4$

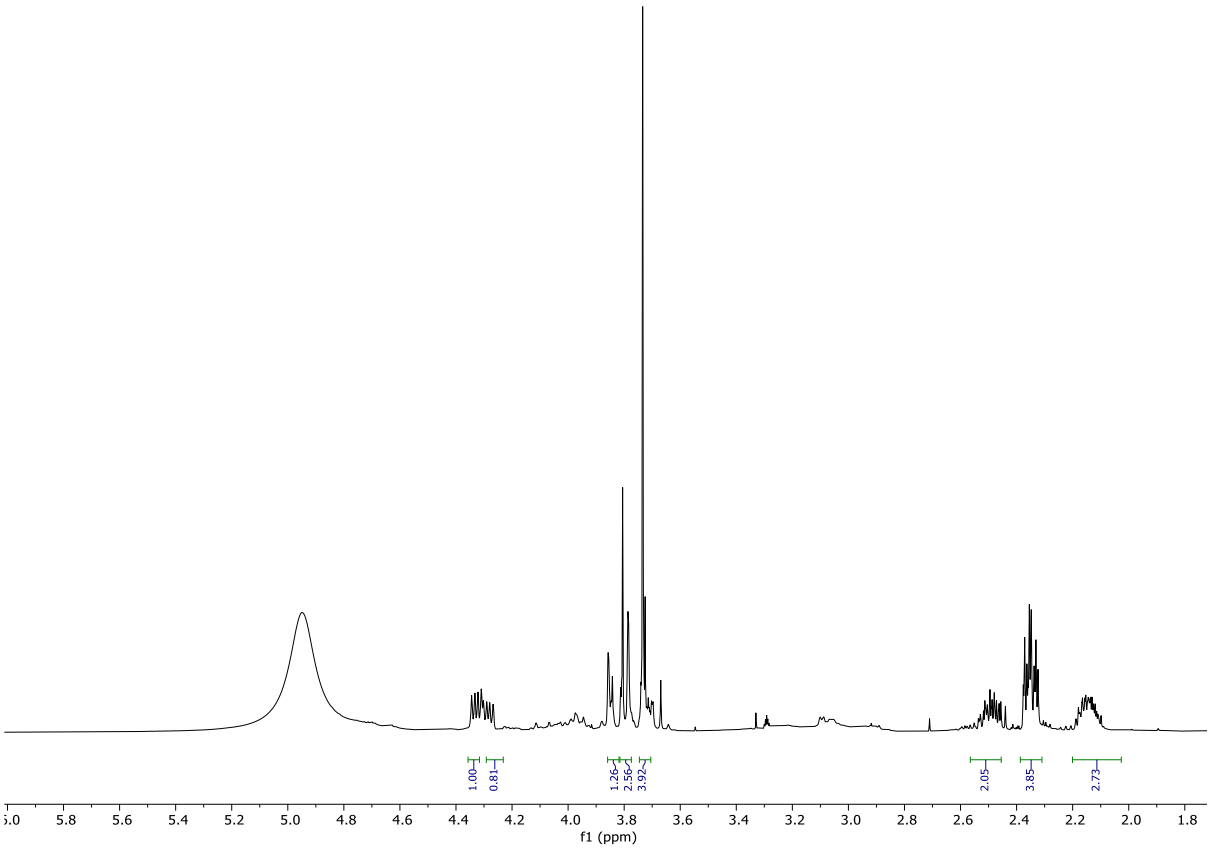


Figure S83. ^{1}H NMR of L-glutathione in $HClO_4$ condition

N-methyl-L-alanine methyl ester ammonium. ^{1}H-NMR (CD_3OD+$CDCl_3$): 4.01-3.97 (q, 1H), 3.71(s, 3H), 3.52 (s, 3H), 1.44-1.43 (d, 3H); ^{13}C-NMR: δ 167.83, 54.57, 52.70, 40.03.

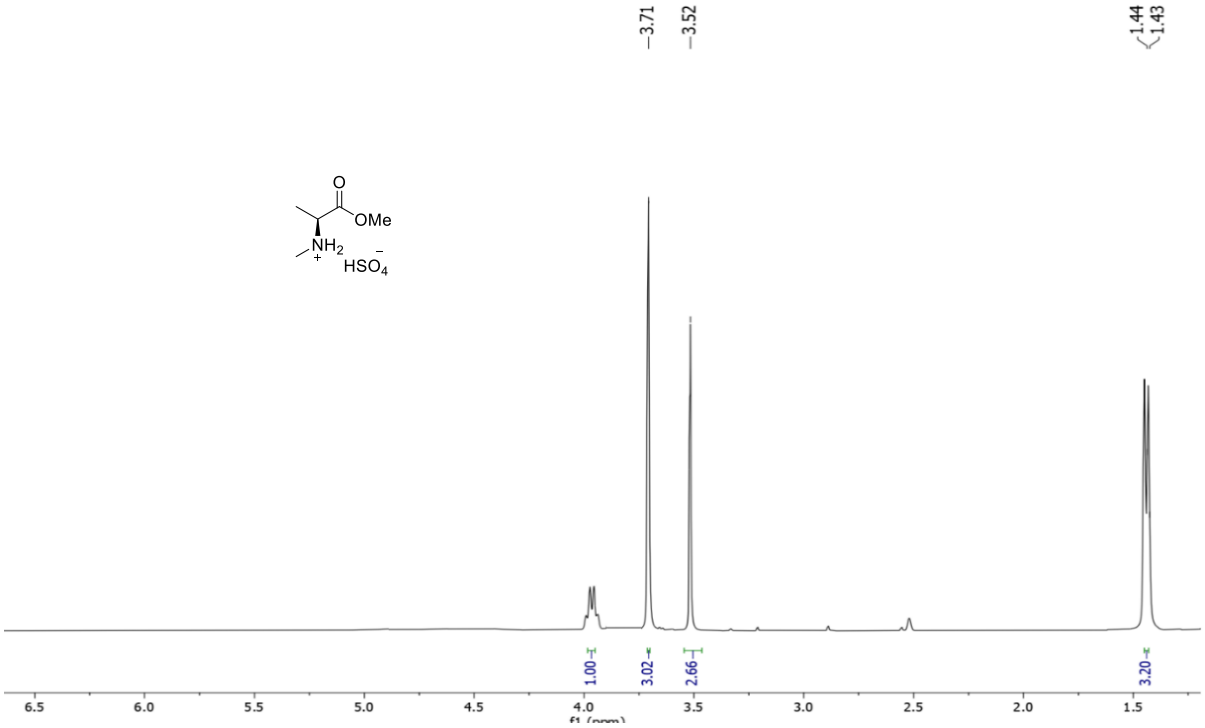


Figure S84 ^{1}H NMR of L-*N*-methyl alanine methyl ester ammonium in CD_3OD + $CDCl_3$

N-methyl-L-leucine methyl ester ammonium. ^{1}H-NMR ($CD_3OD+CDCl_3$): 3.93 (brs, 1H), 3.76(s, 3H), 3.66 (s, 3H), 1.75-1.68 (m, 3H), 0.89-0.88 (d, 6H).

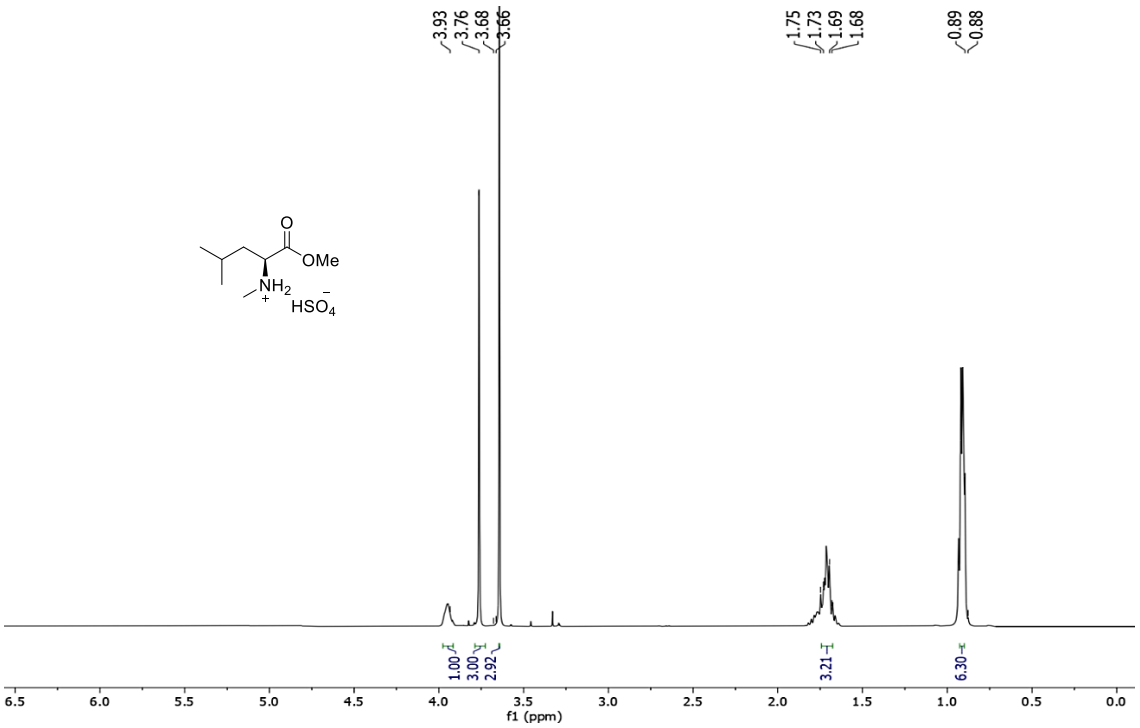


Figure S85 ^{1}H NMR of L-*N*-methyl alanine methyl ester ammonium in CD_3OD + $CDCl_3$

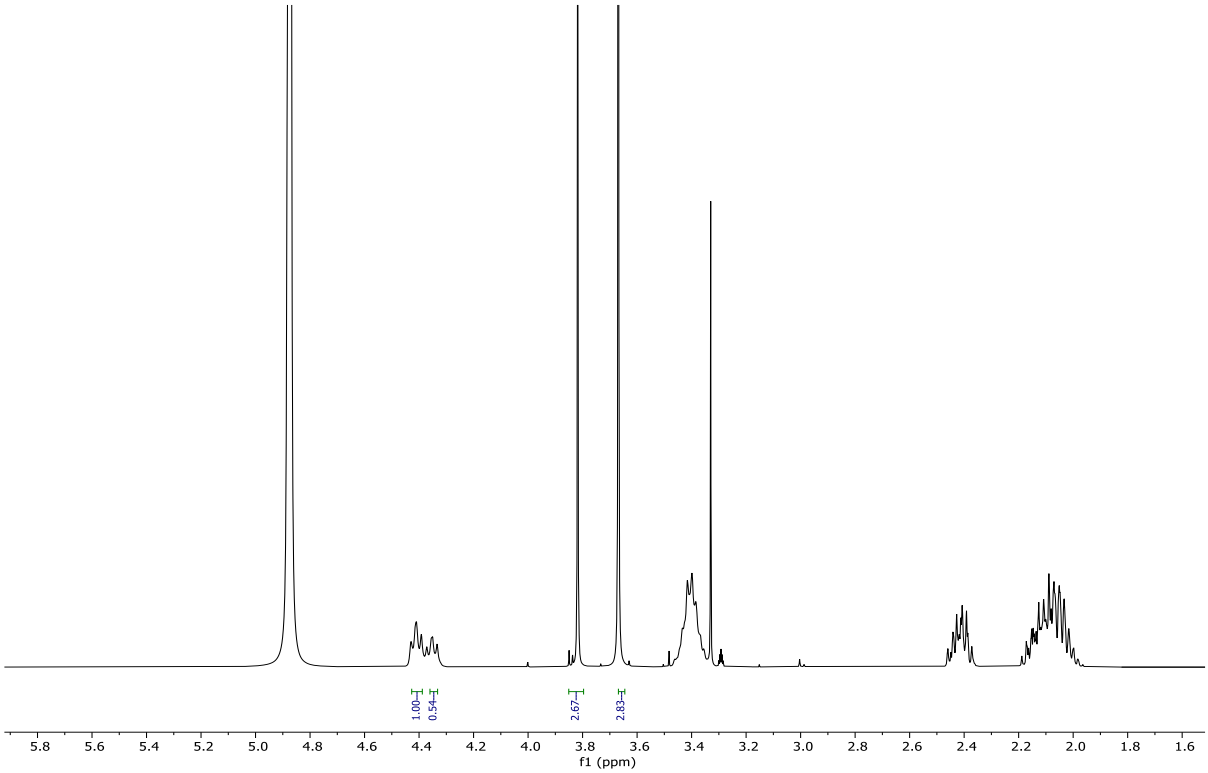


Figure S86 ^{1}H NMR of L-*N*-methyl Proline in H_2SO_4

N-methyl-L-glycine methyl ester ammonium. ^{1}H-NMR (CD_3OD+$CDCl_3$): 3.83 (brs, 2H),3.79(s, 3H), 3.66 (s, 3H); ^{13}C-NMR: δ 167.83, 54.57, 52.70, 40.03.

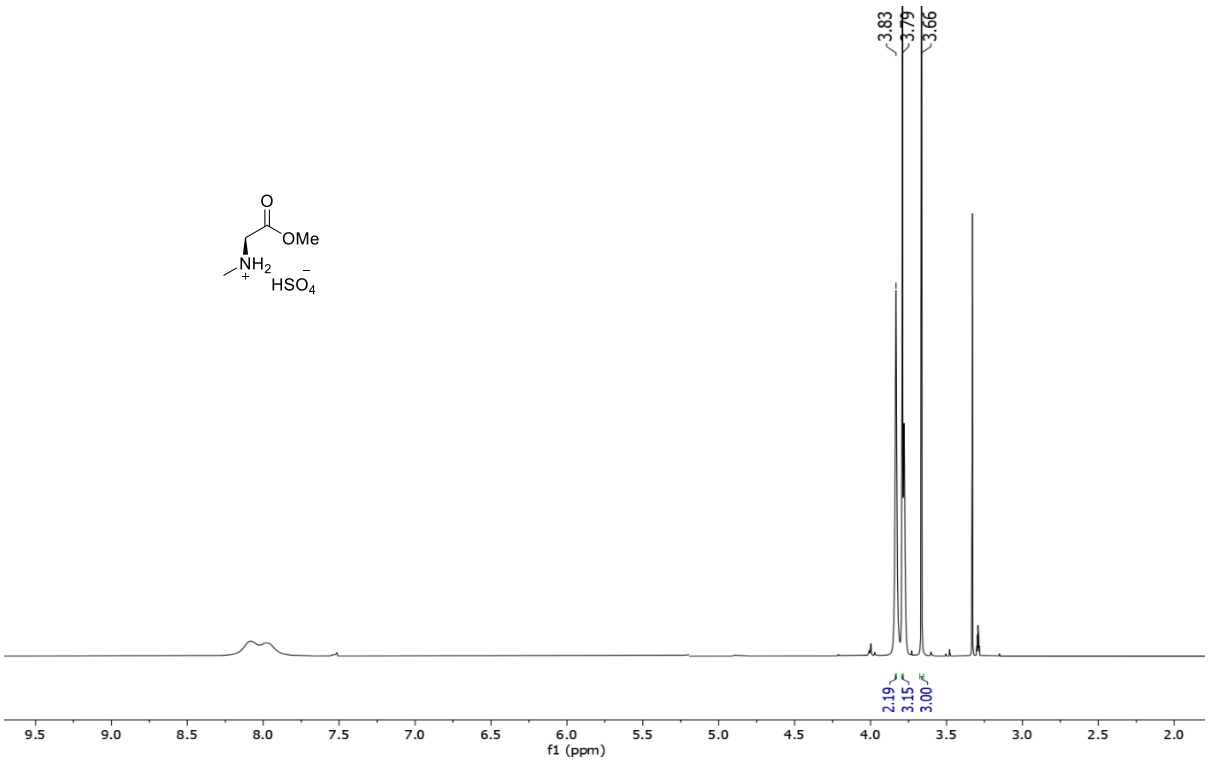


Figure S87 ^{1}H NMR of L-*N*-methyl glycine methyl ester ammonium in CD_3OD + $CDCl_3$

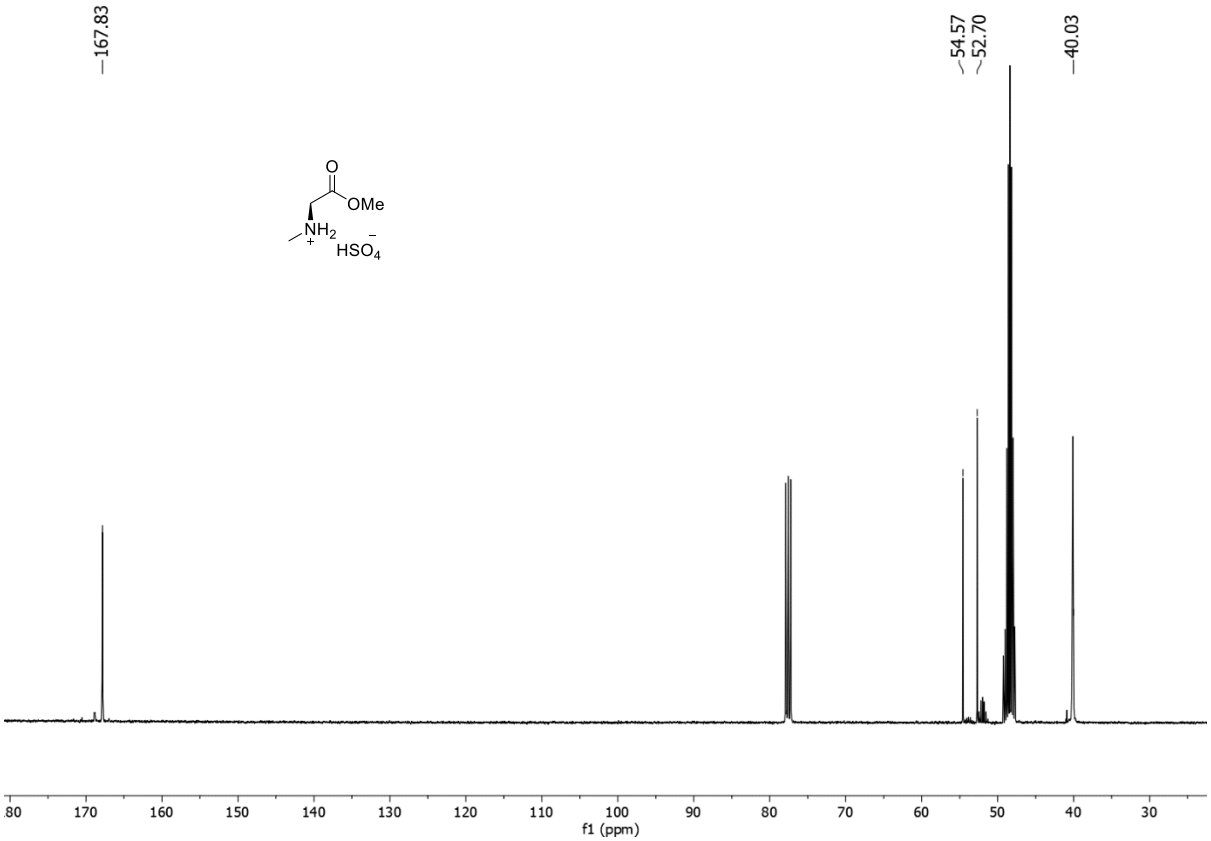


Figure S88 ^{13}C NMR of L-*N*-methyl glycine methyl ester ammonium in CD_3OD + $CDCl_3$

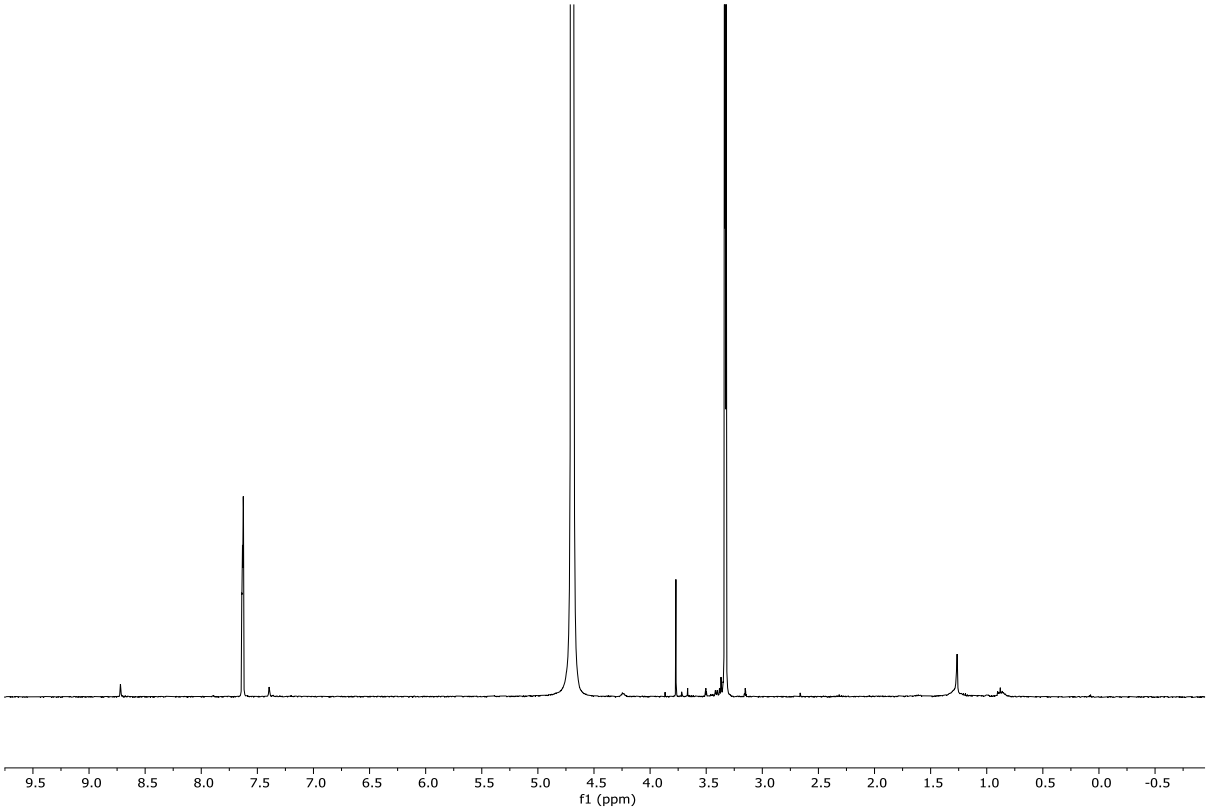


Figure S89. ^{1}H NMR of L-histidine in H_2SO_4

N-methyl-L-tyrosine methyl ester ammonium. ^{1}H-NMR (CD_3OD+$CDCl_3$): 7.26-7.22 (d, 2H), 7.00-6.98 (d, 2H), 4.40-4.37(t, 1H), 3.96 (s, 3H) 3.90 (s, 3H), 3.35-3.33 (m, 2H); ^{13}C-NMR: δ 168.99, 156.62, 130.36, 124.26, 116.06, 54.50, 54.23, 52.72, 35.33.

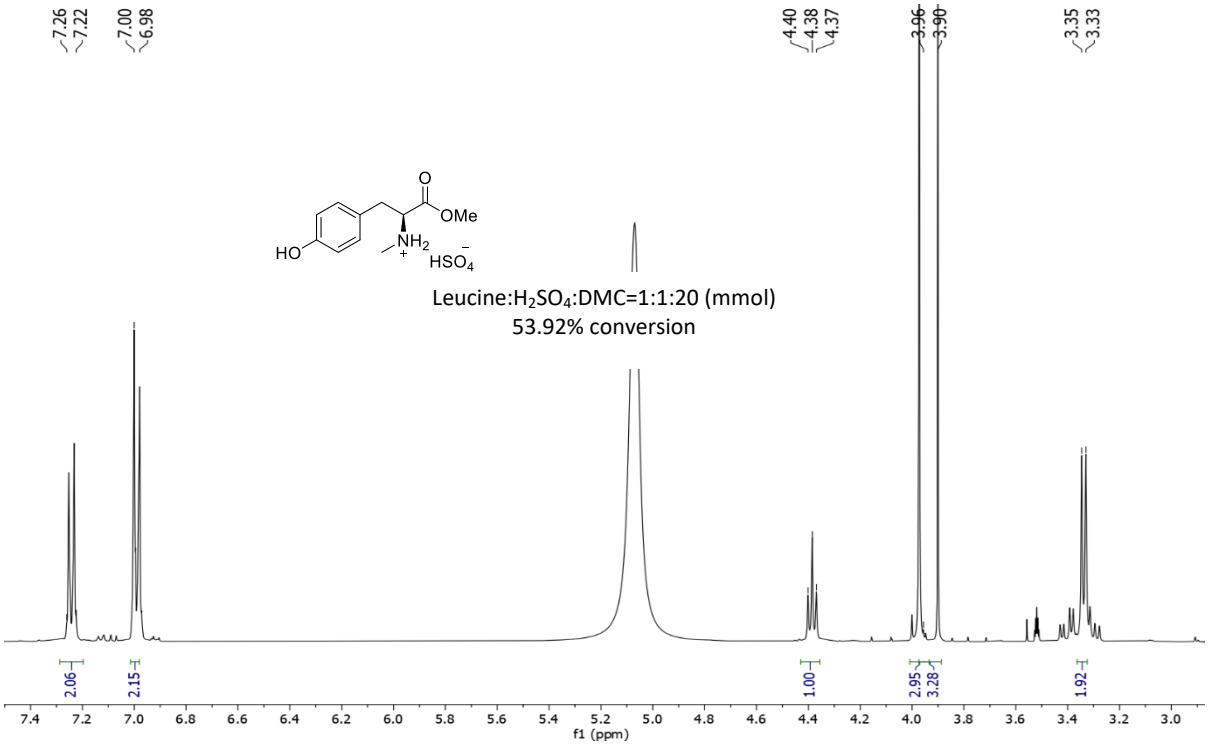


Figure S90 ^{1}H NMR of *N*-methyl-L- tyrosine methyl ester ammonium in CD_3OD + $CDCl_3$

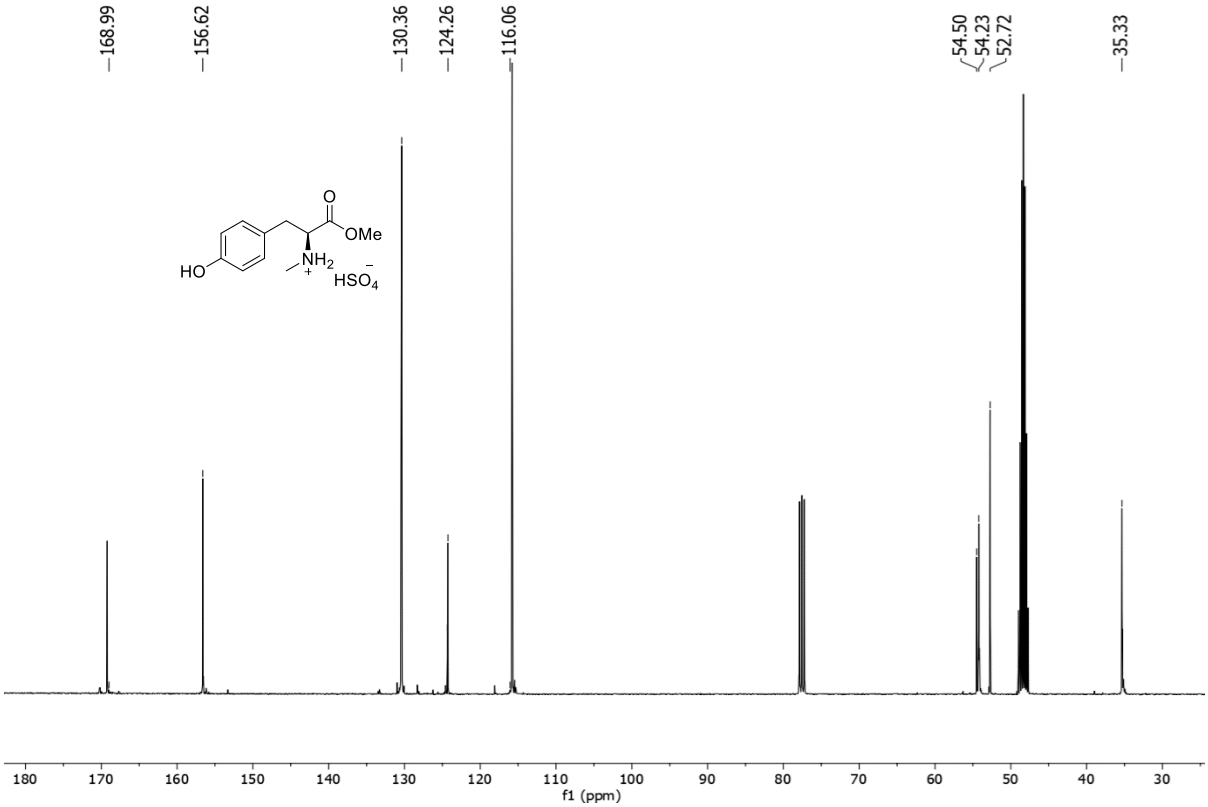


Figure S91. ^{13}C NMR of L-*N*-methyl tyrosine methyl ester ammonium in CD_3OD + $CDCl_3$

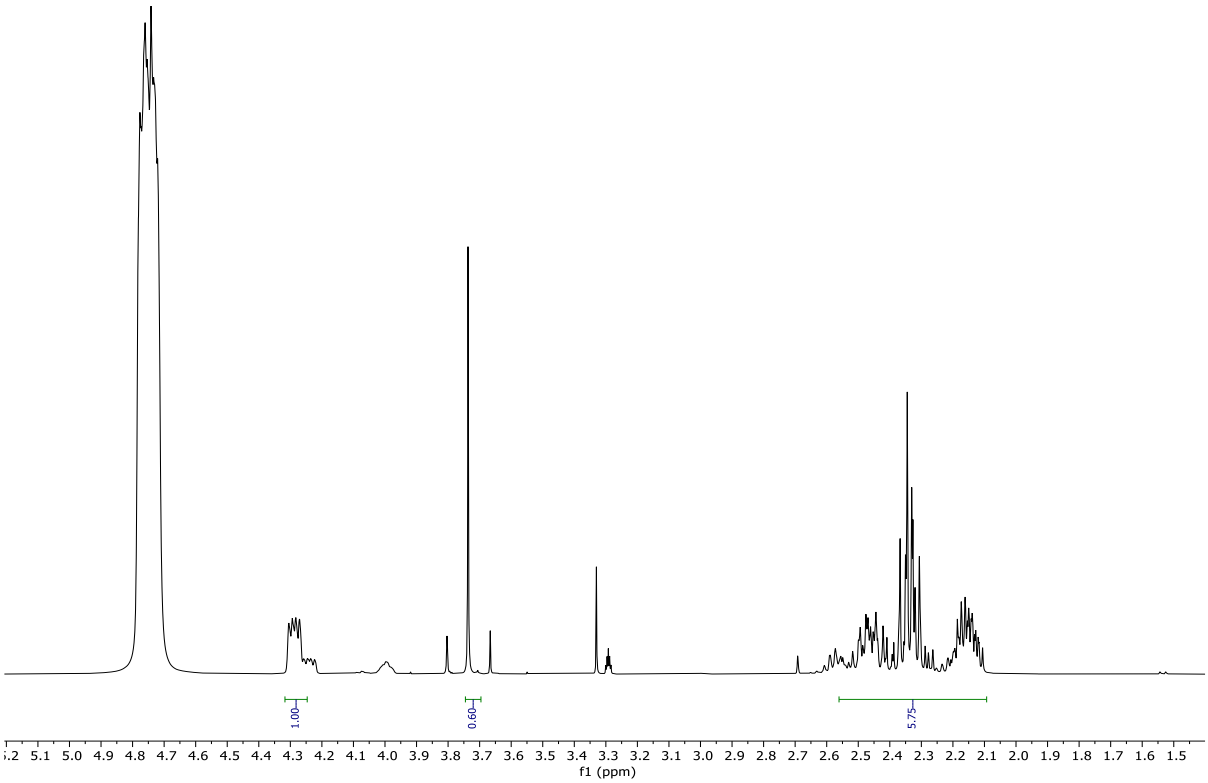


Figure S92 ^{1}H NMR of L-Glutamine in H_2SO_4

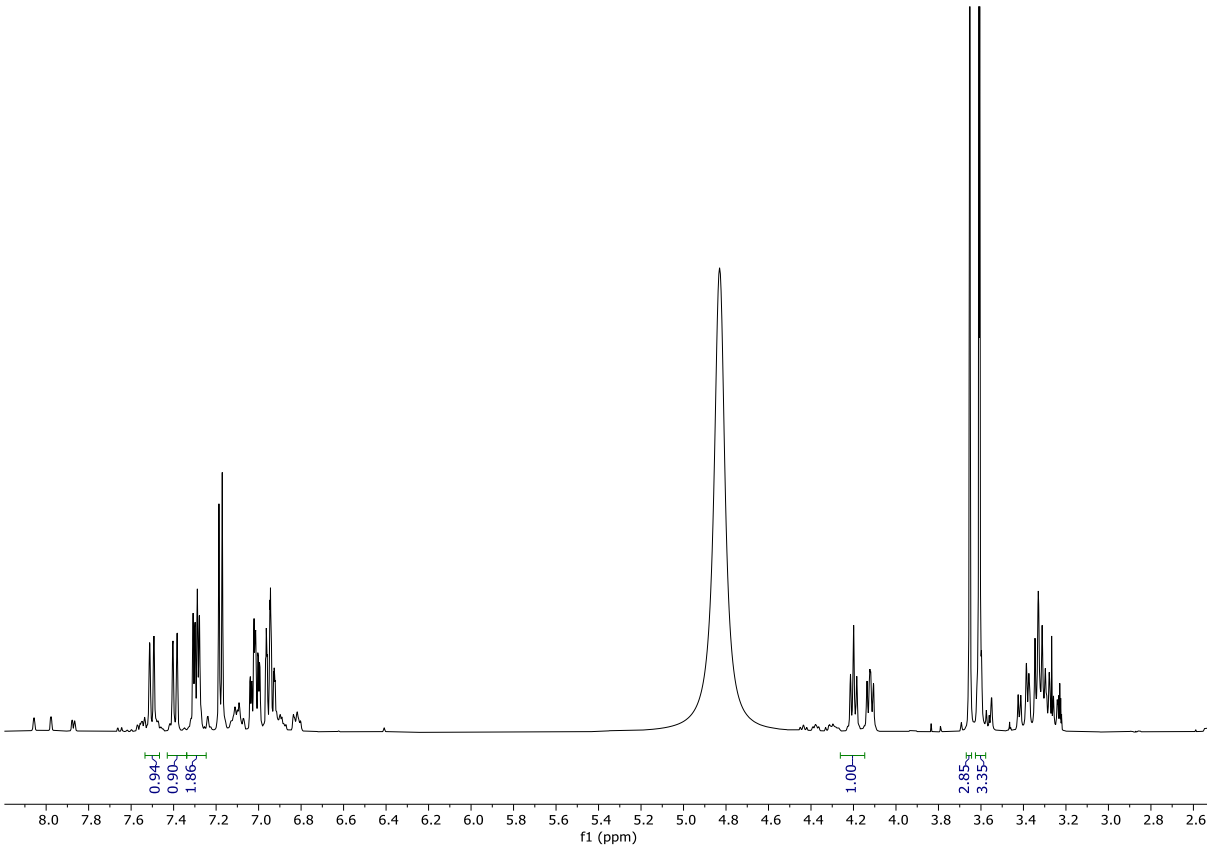


Figure S93 ^{1}H NMR of L-Tryptophan in H_2SO_4

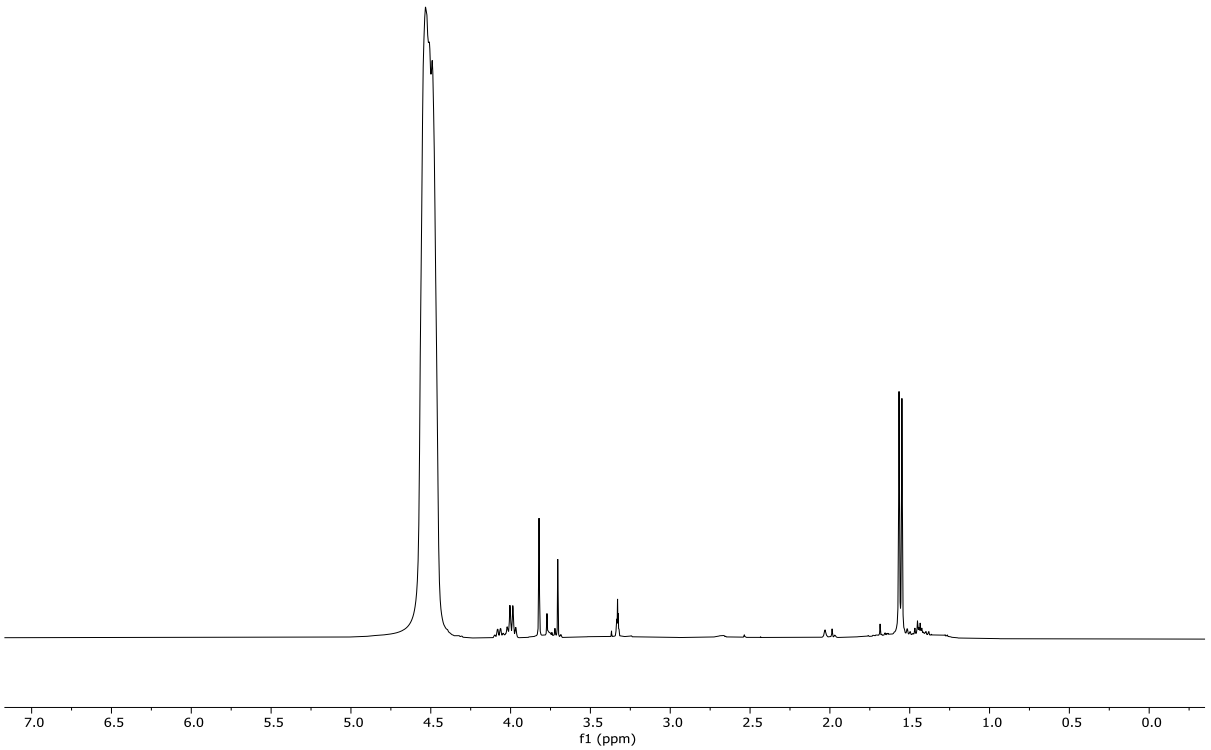


Figure S94 ^{1}H NMR of L-Crystine in H_2SO_4

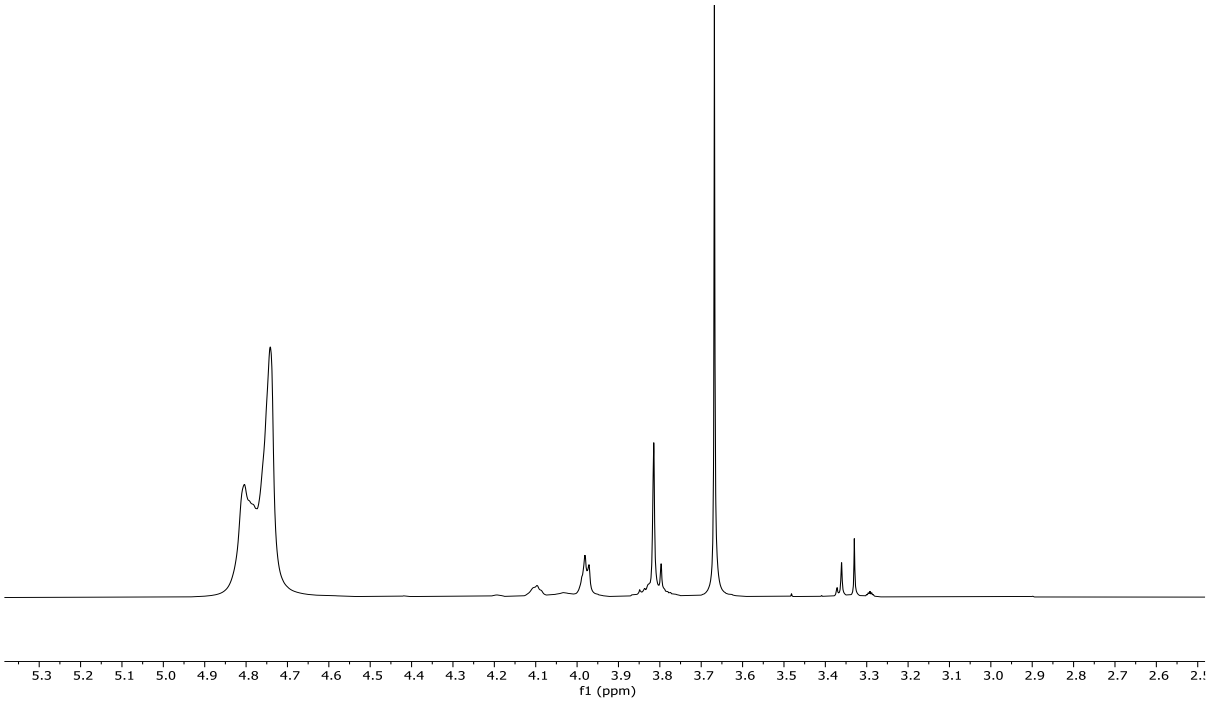


Figure S95 ^{1}H NMR of D-serine in H_2SO_4

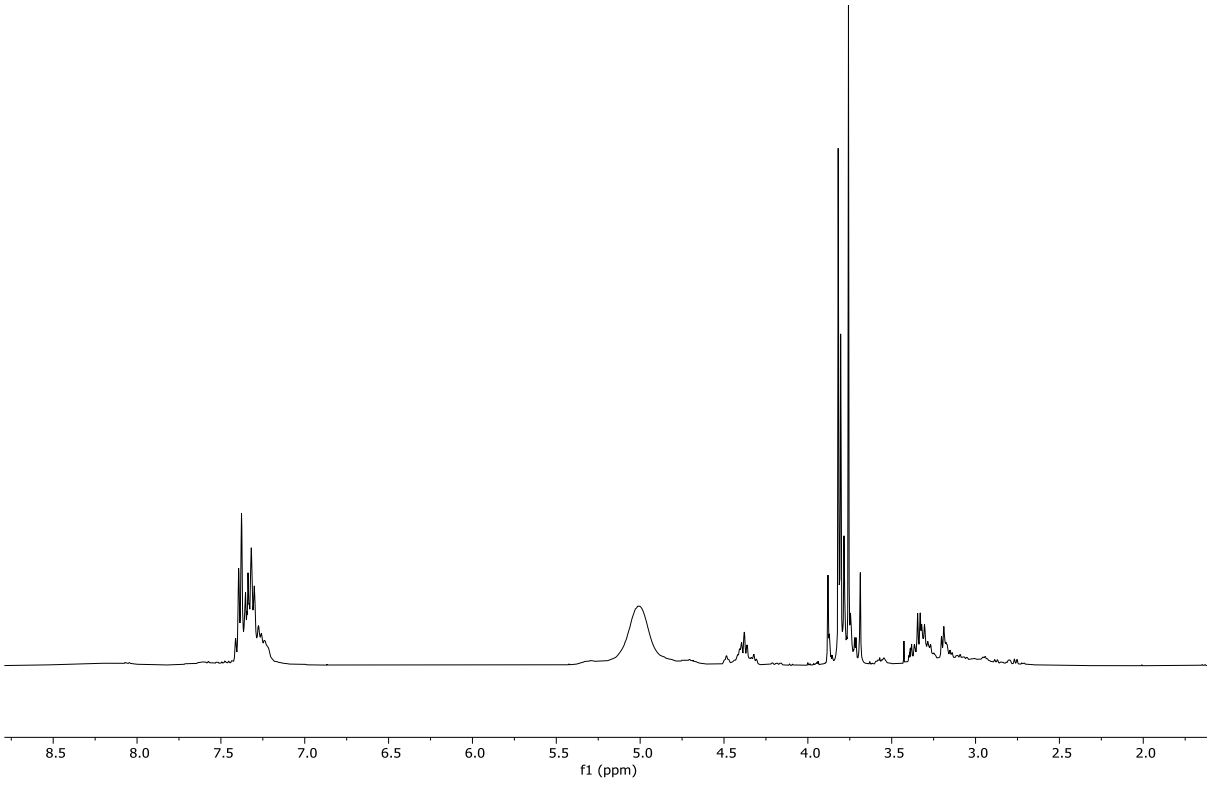


Figure S96 ^{1}H NMR of L-aspartame in H_2SO_4

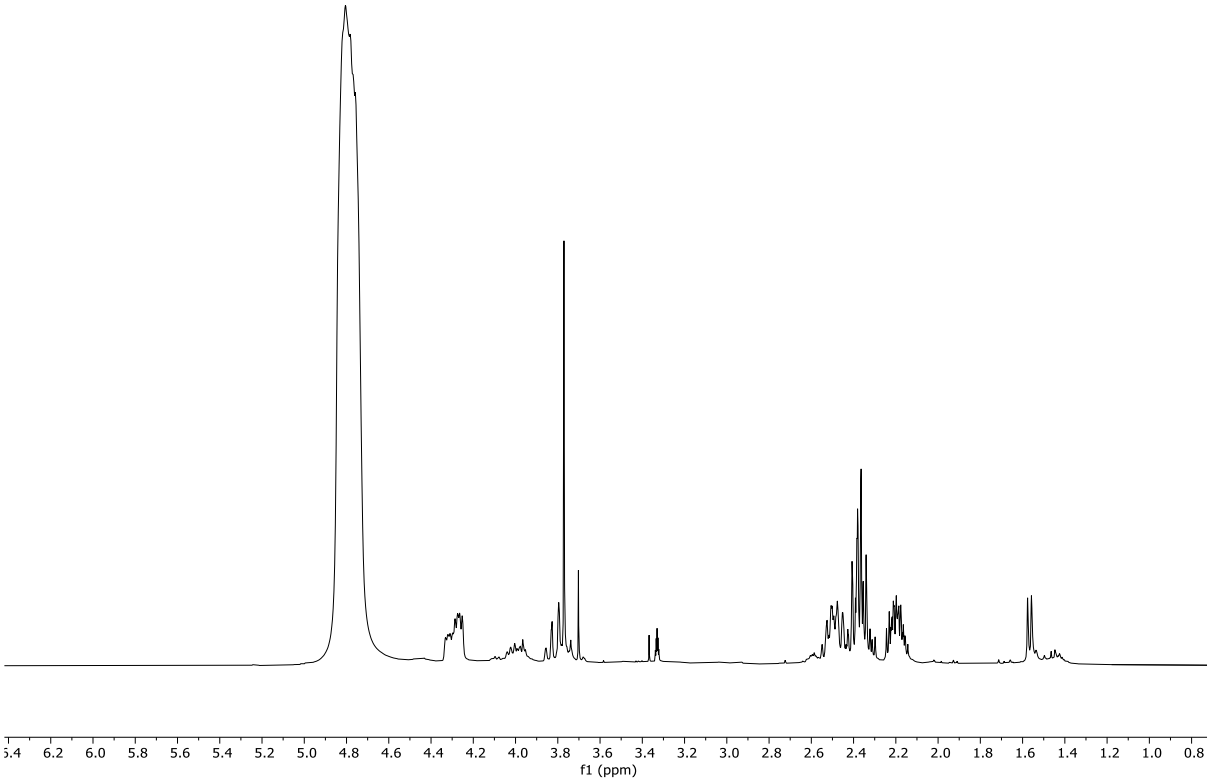


Figure S97 ^{1}H NMR of L-glutathione in H_2SO_4

N-formylation of alanine. ^{1}H-NMR (CD_3OD+$CDCl_3$): 8.07 (s, 1H), 4.52-4.47 (q, 1H), 1.44-1.42 (d, 3H).

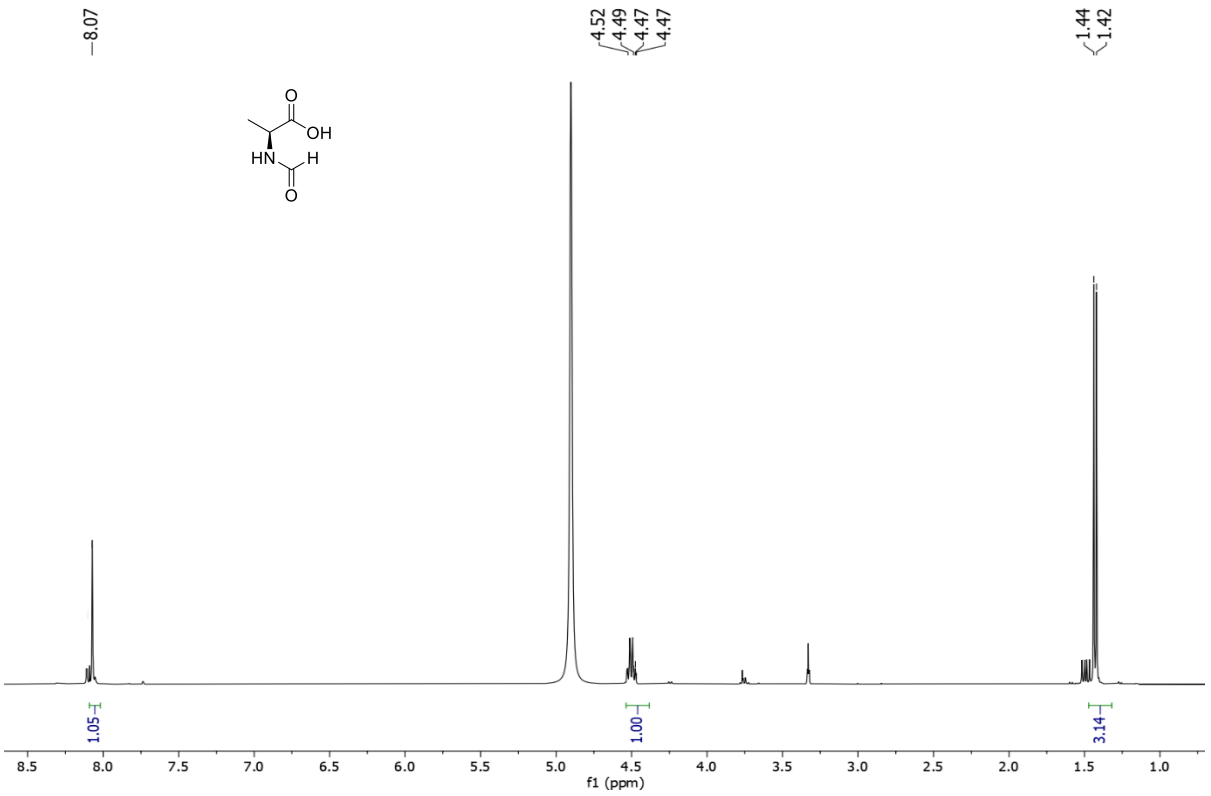


Figure S98. ^{1}H NMR of *N*-formylation of L-alanine in CD_3OD + $CDCl_3$

N-formylation of leucine. ^{1}H-NMR (CD_3OD+$CDCl_3$): 8.11 (s, 1H), 4.54 (brs, 1H), 1.68-1.61 (m, 2H), 0.95-0.91 (d, 6H)

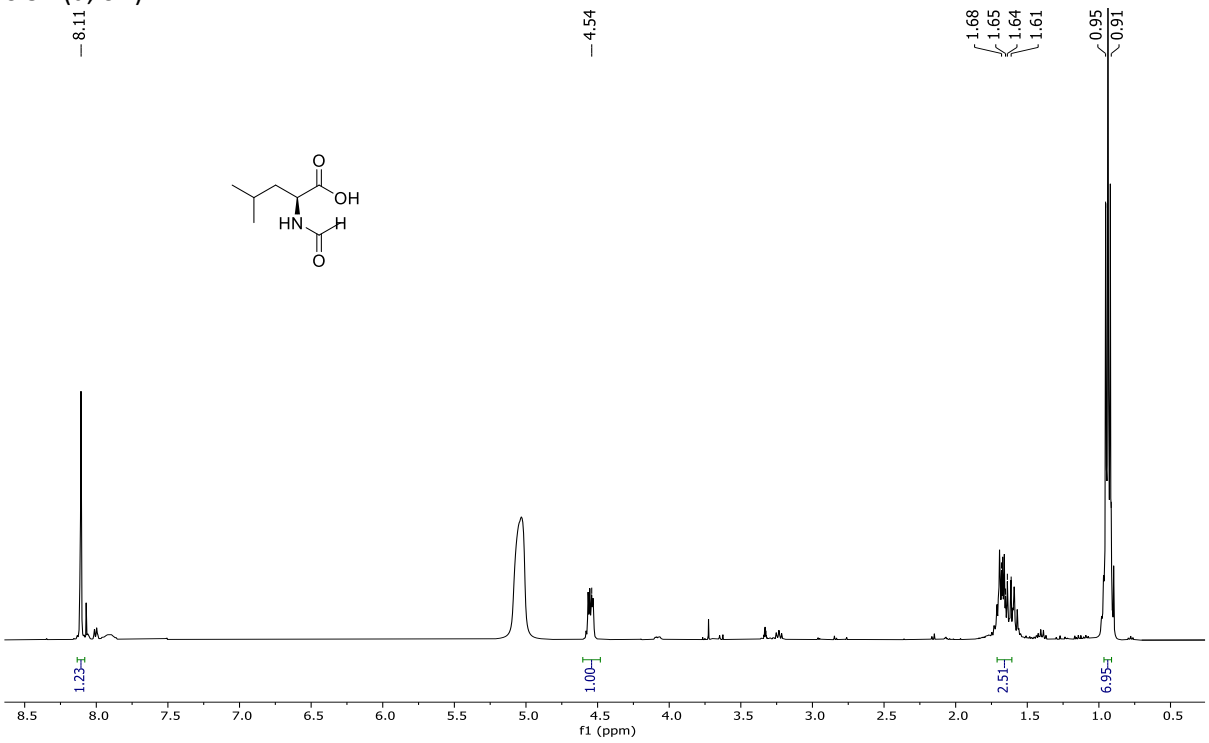


Figure S99. ^{1}H NMR of *N*-formylation of L-leucine in CD_3OD + $CDCl_3$

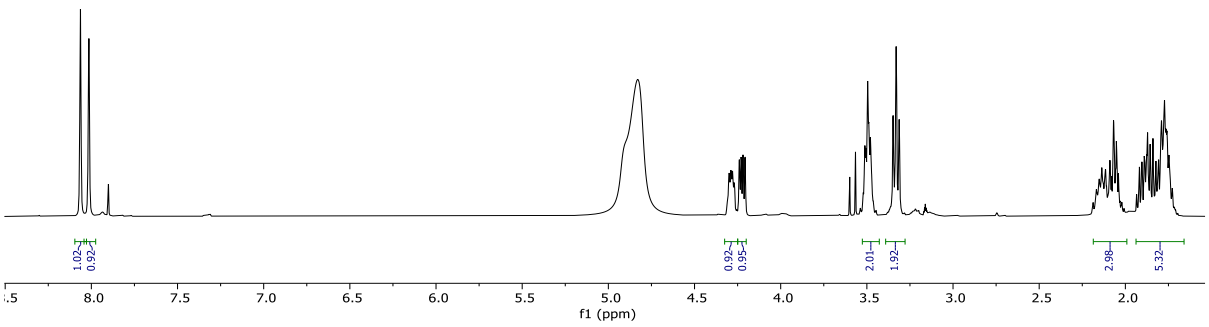


Figure S100. ^{1}H NMR of *N* L-proline in formic acid

N-formylation of glycine. ^{1}H-NMR (CD_3OD+$CDCl_3$): 8.14 (s, 1H), 3.98-3.97 (d, 2H); ^{13}C-NMR: δ 171.23, 162.55, 39.57.

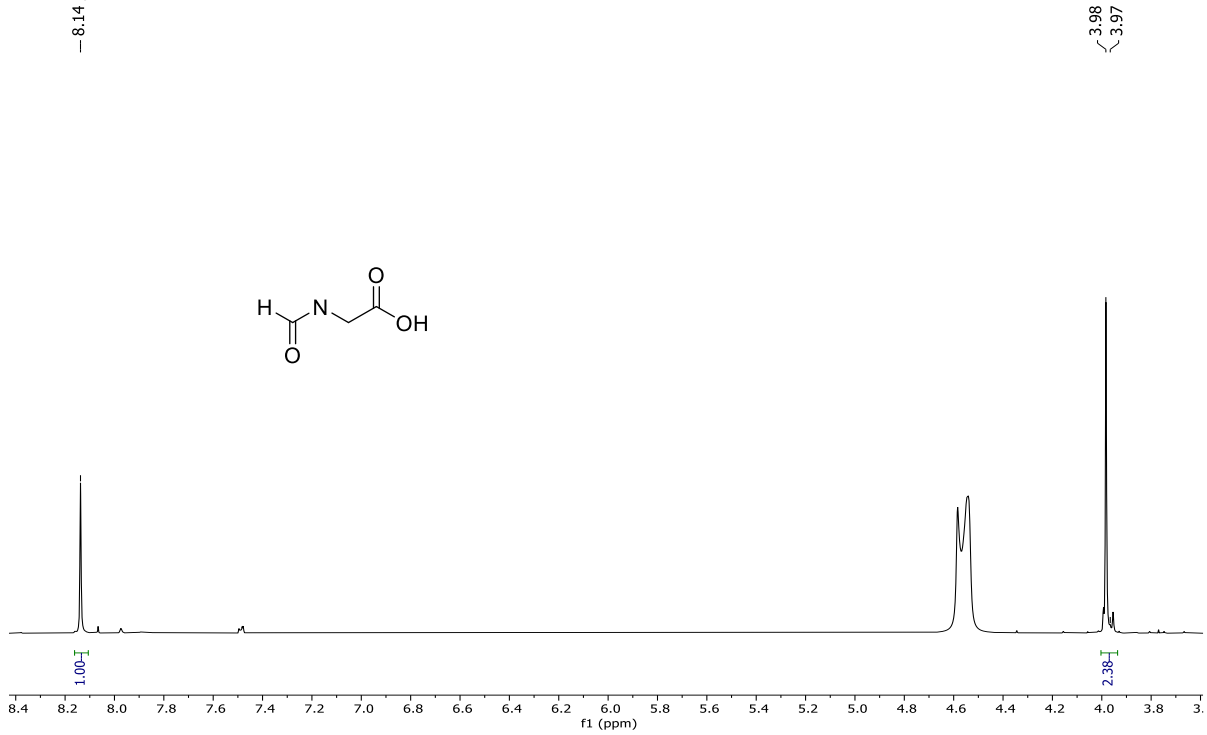


Figure S101. ^{1}H NMR of *N*-formylation of L-glycine in CD_3OD + $CDCl_3$

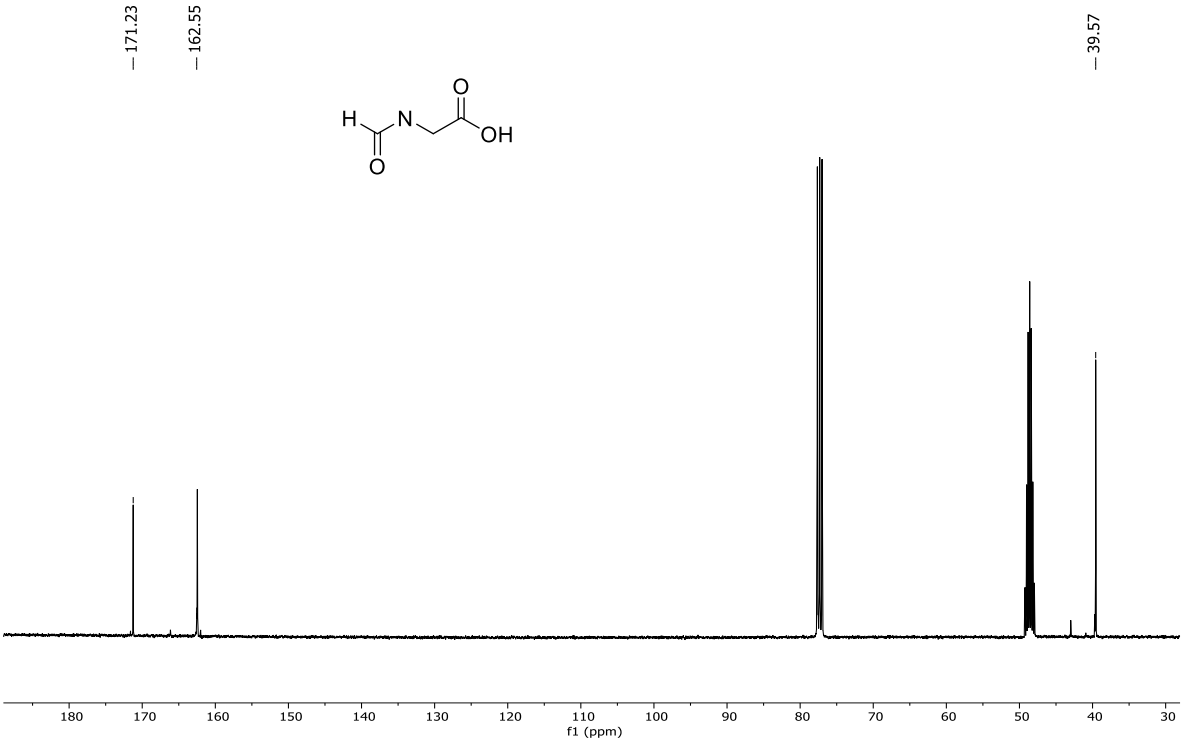


Figure S102. ^{13}C NMR of *N*-formylation of L-glycine in CD_3OD + $CDCl_3$

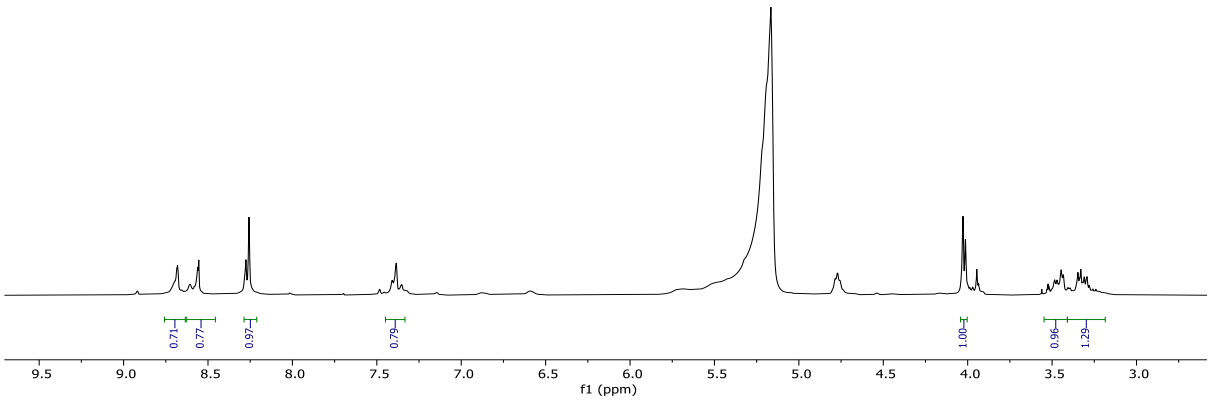


Figure S103. ^{1}H NMR of *N*-formylation of L-histidine in CD_3OD + $CDCl_3$

N-formylation of L-tyrosine. ^{1}H-NMR (CD_3OD+$CDCl_3$): 8.04 (s, 1H), 7.03-7.01 (d, 2H), 6.73-6.71 (d, 2H), 4.75-4.77 (t, 1H), 3.14-2.68 (m, 2H); ^{13}C-NMR: δ 173.03, 161.95, 155.79, 130.17, 127.07, 115.10, 52.39, 36.50.

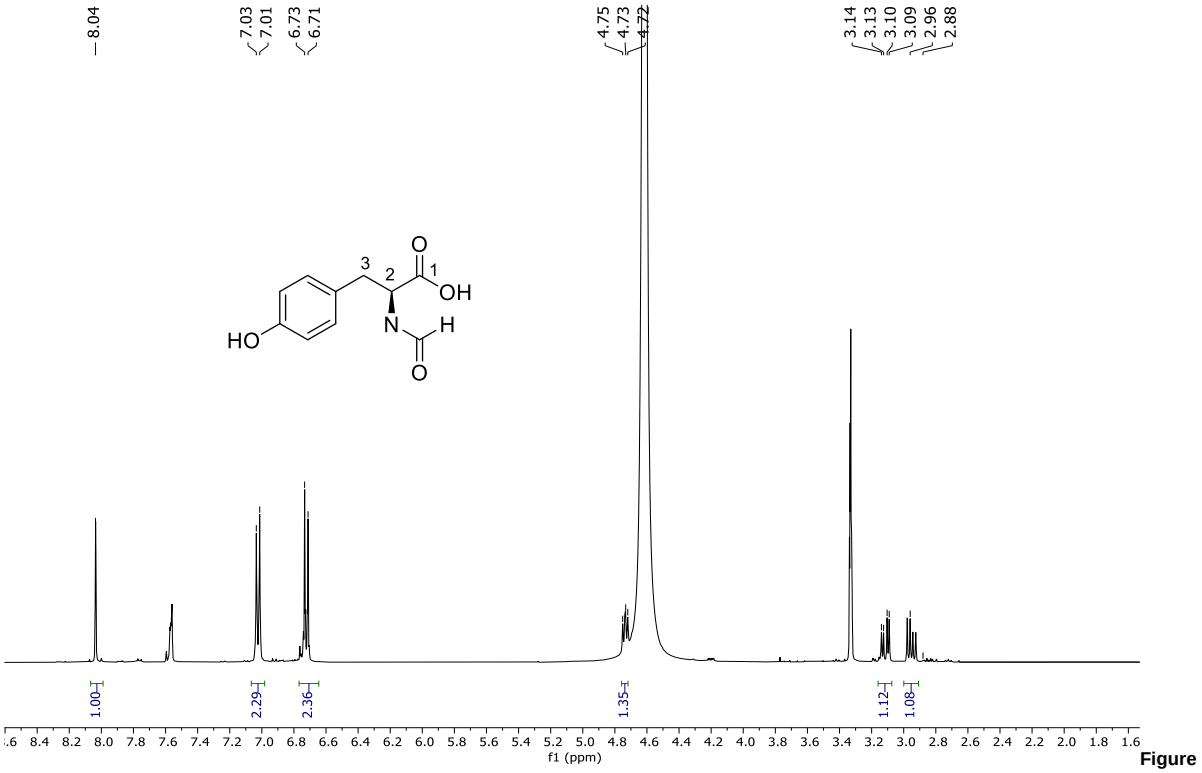
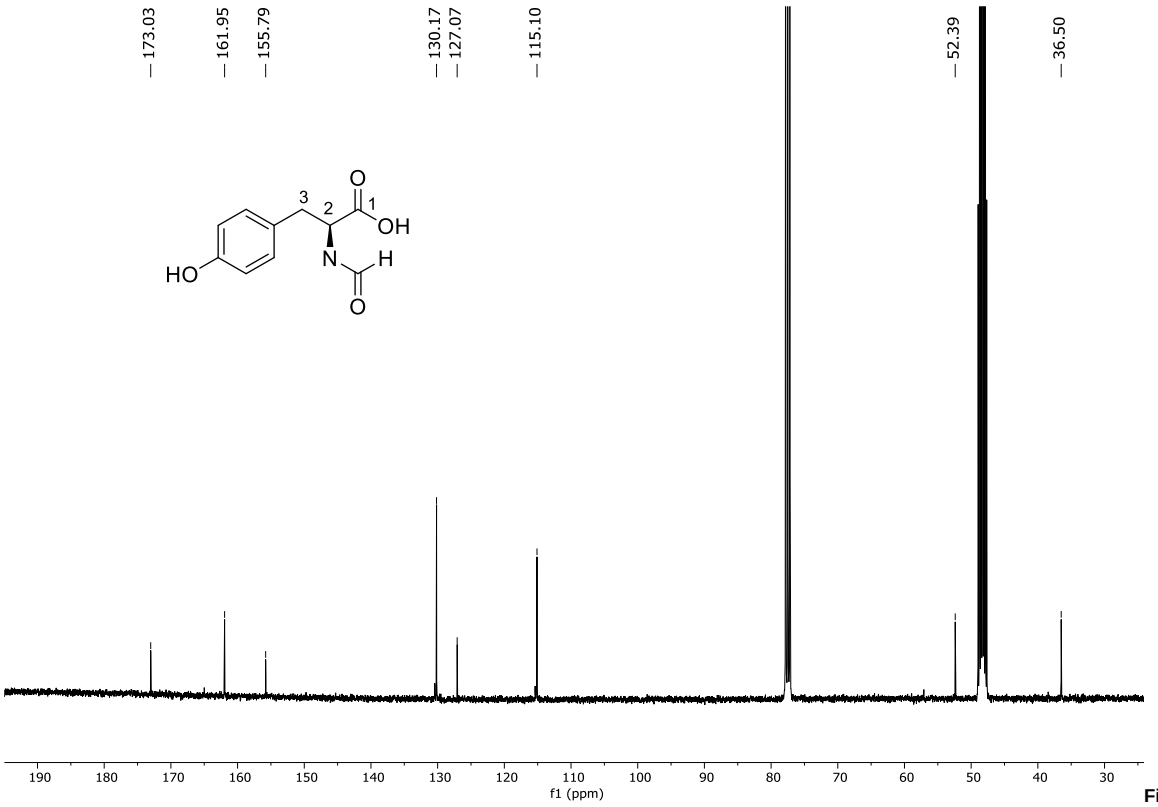


Figure S104. ^{1}H NMR of *N*-formylation of L-tyrosine in CD_3OD + $CDCl_3$



Figure

Figure S105. ^{13}C NMR of *N*-formylation of L-tyrosine in CD_3OD + $CDCl_3$

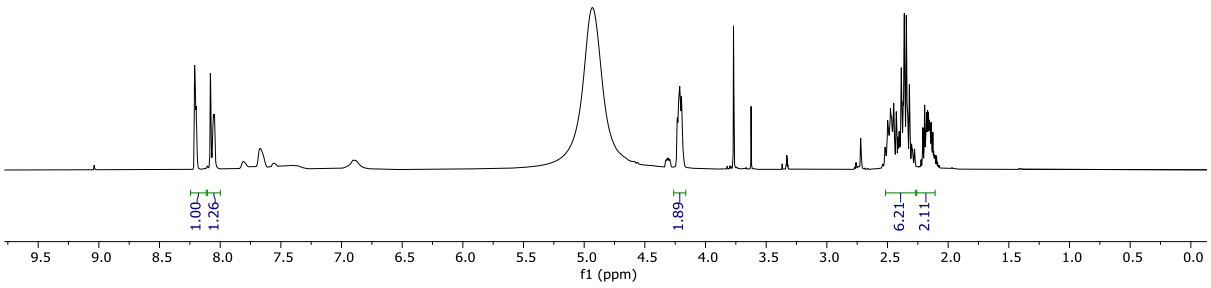


Figure S106. ^{1}H NMR of L-glutamine in formic acid

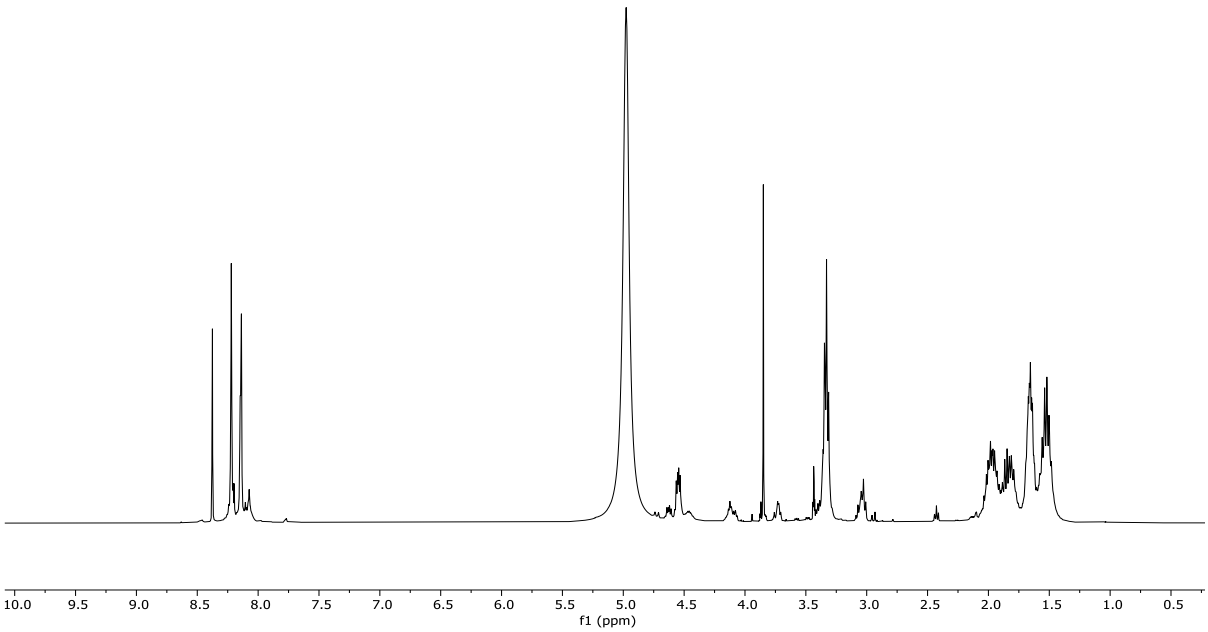


Figure S107. ^{1}H NMR of L-lysine in formic acid

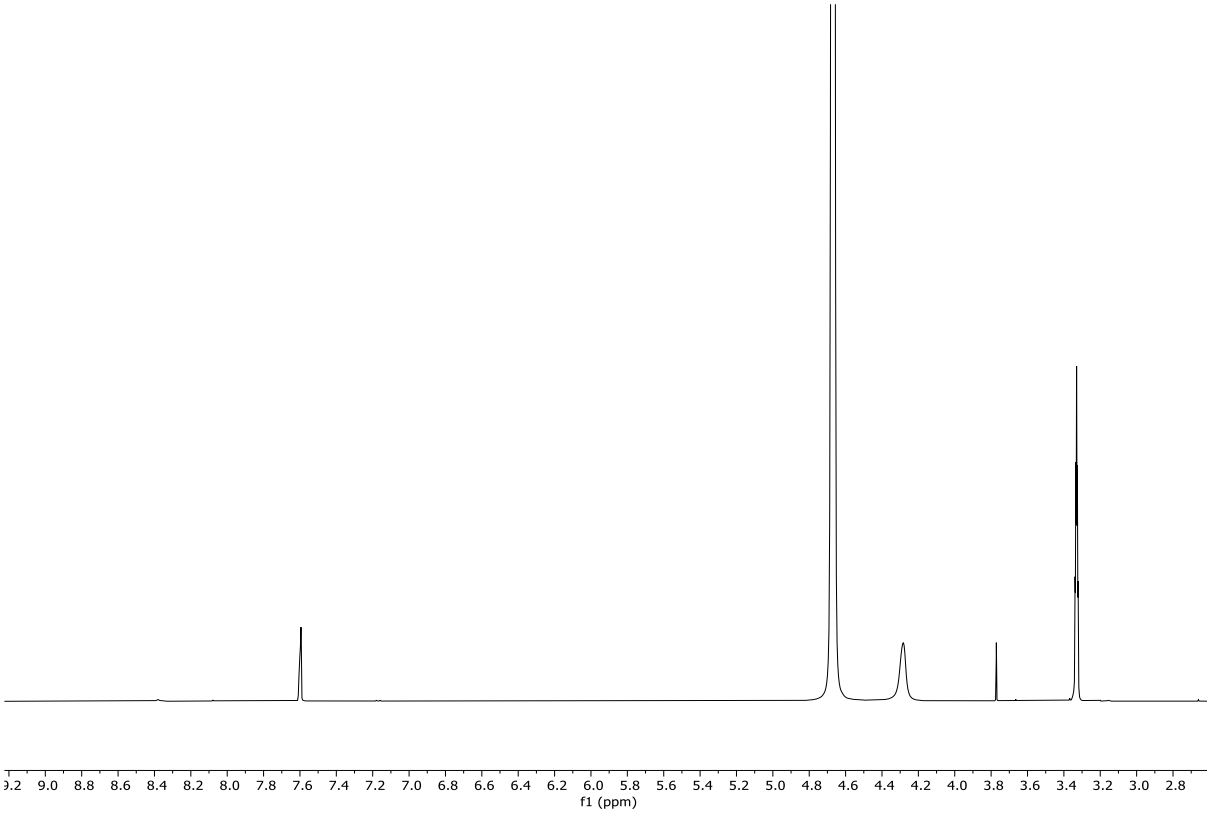


Figure S108. ^{1}H NMR of L-cystine in formic acid

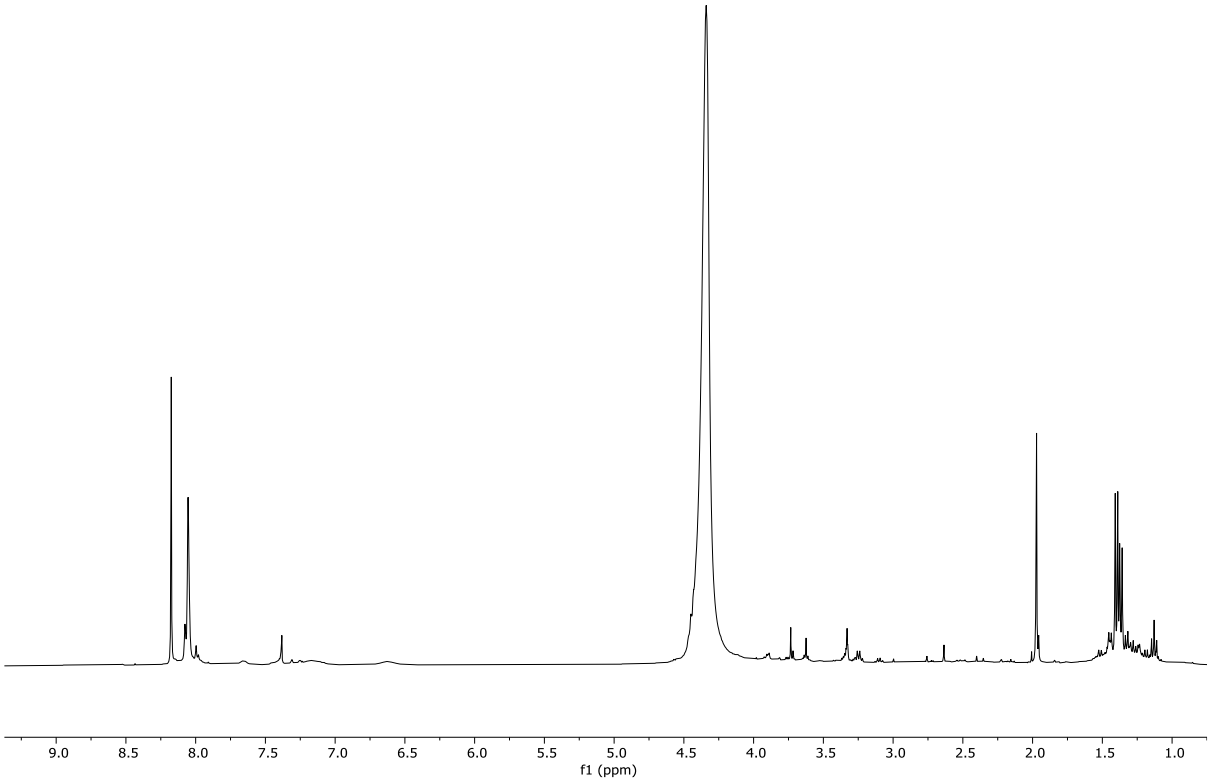


Figure S109. ^{1}H NMR of D-serine in formic acid

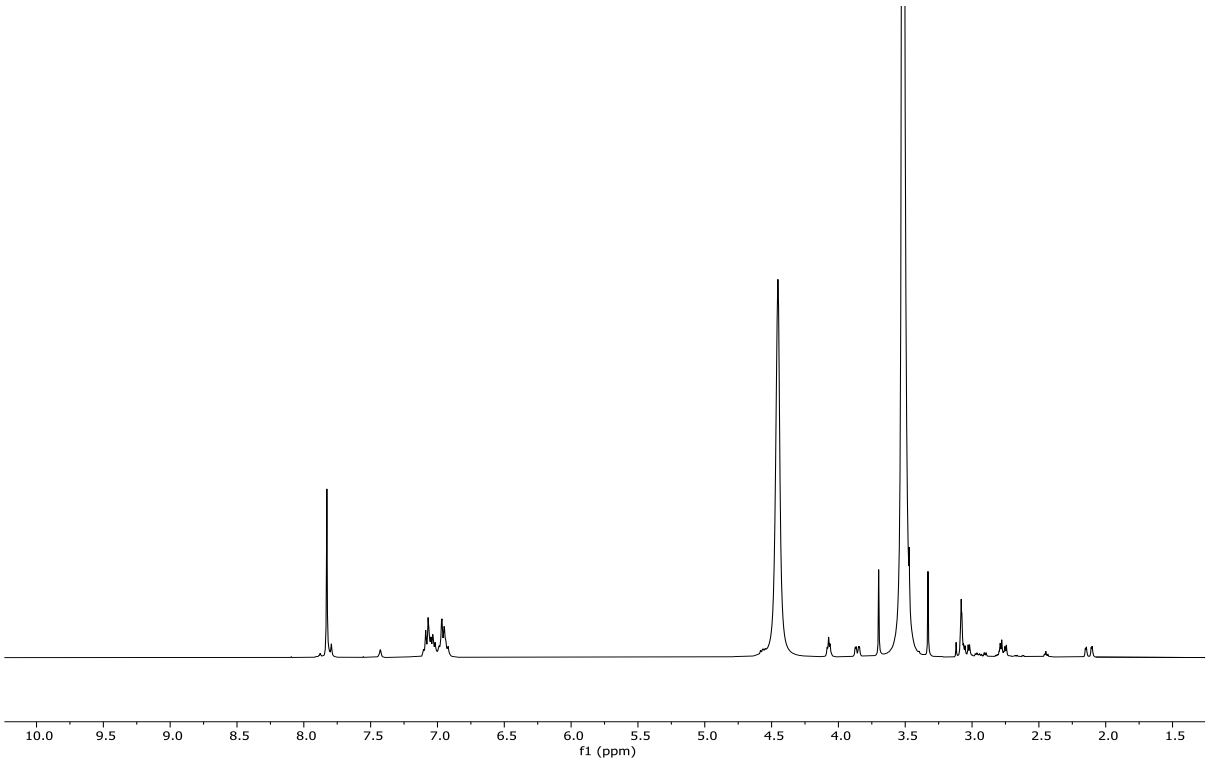


Figure S110. ^{1}H NMR of aspartame in formic acid

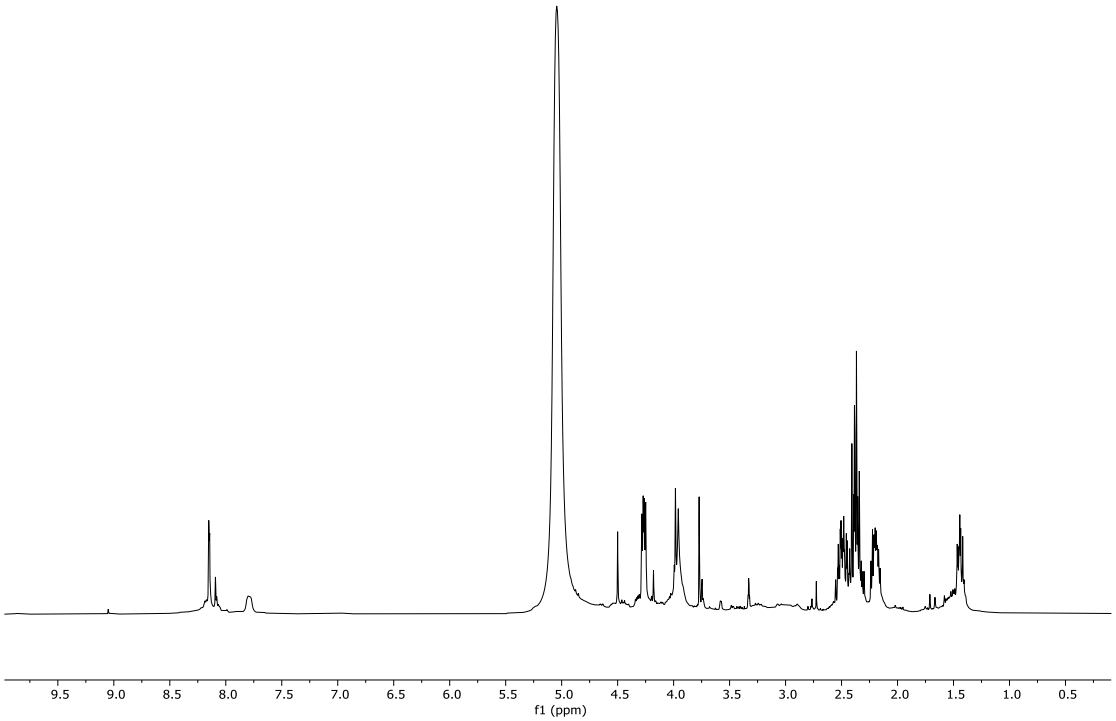


Figure S111. ^{1}H NMR of L-glutathione in formic acid

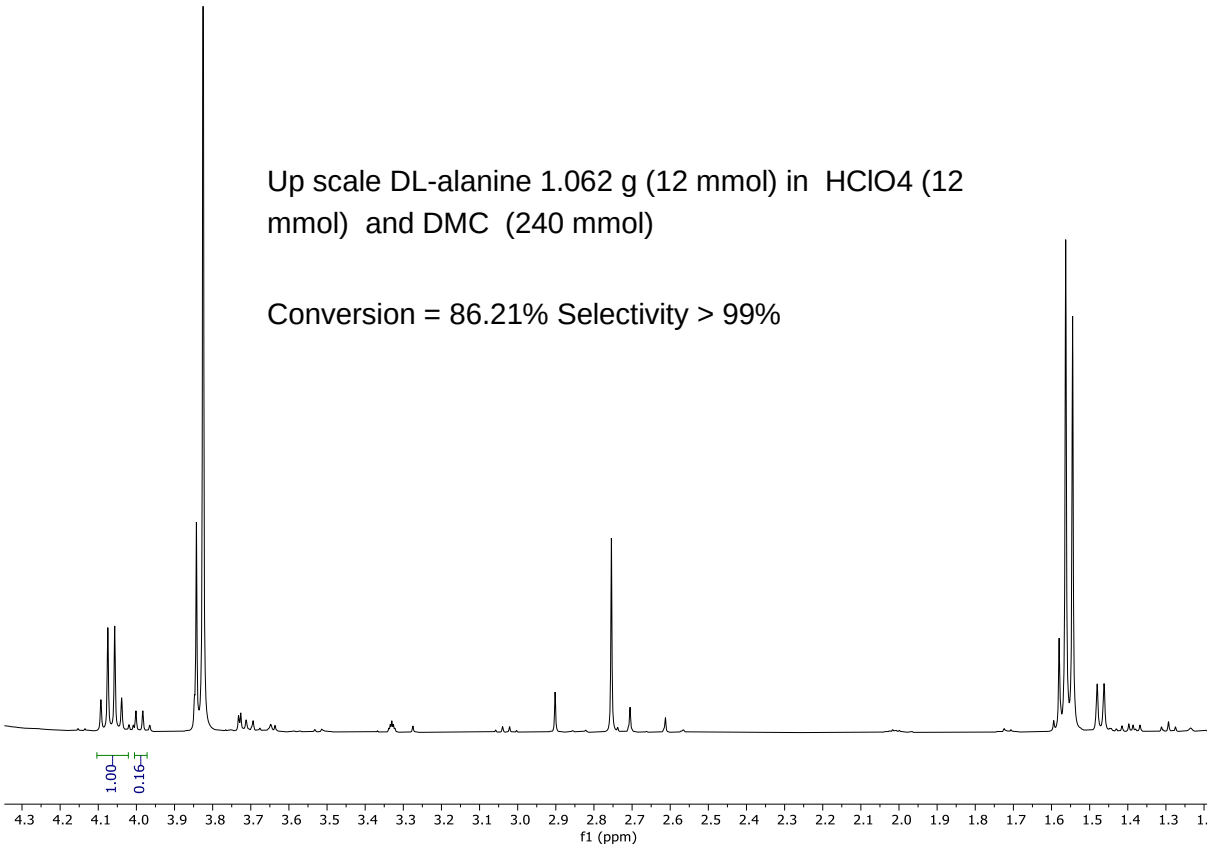
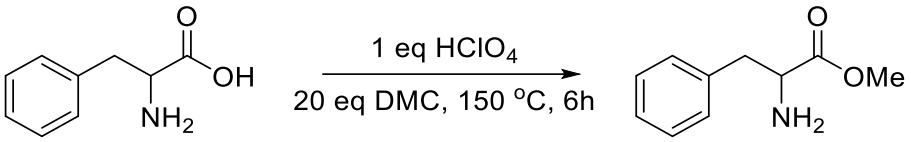


Figure S112. ^{1}H NMR of upscale 12 times alanine reaction with $HClO_4$

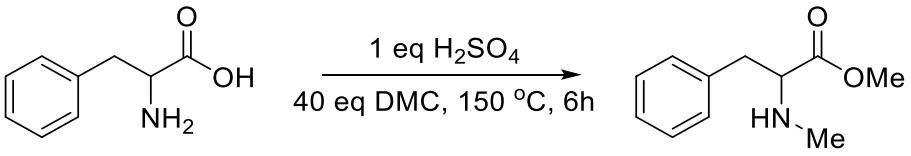
3. Green metrics calculations[4–6]

3.1 Current methods ($HClO_4$, H_2SO_4, and HCO_2H)

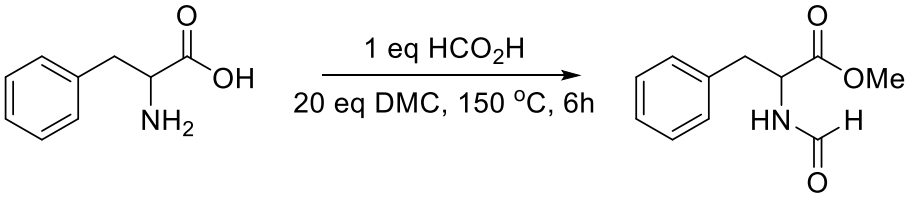
***O*-Methylation**



***N,O*-Dimethylation**



***N*-Formylation**



Role	Chemical	Mass (g)	Volume (mL)	Density (g/mL)
Reaction				
Reactant	Phenylalanine	0.165		
Reactant (1 eq)	DMC	0.09	0.084	1.07
Reactant (2 eq)	DMC	0.18	0.168	1.07
Reagent	$HClO_4$	0.10	0.06	1.664
Reagent	H_2SO_4	0.098	0.053	1.84
Reagent	HCO_2H	0.046	0.038	1.22
Solvent (19 eq)	DMC	1.71	1.596	1.07
Solvent (38 eq)	DMC	3.42	3.276	1.07
	Reaction total ($HClO_4$)	2.065		
	Reaction total (H_2SO_4)	3.863		
	Reaction total (HCO_2H)	2.011		
Product				
Product	*O*-methylation ($HClO_4$)	0.179		
Product	*N,O*-dimethylation (H_2SO_4)	0.193		
Product	*N*-formylation (HCO_2H)	0.193		

***O*-methylation ($HClO_4$)**

$$\text{PMI (reaction)} = \frac{\text{Total mass in reaction}}{\text{Mass of product}} = \frac{2.065}{0.179} = 11.54$$

$$\text{E factor} = \frac{\text{Total mass of waste}}{\text{Mass of product}} = \frac{2.065 - 0.179}{0.179} = 10.54$$

$$\text{SI} = \frac{\text{Total mass of solvent}}{\text{Mass of product}} = \frac{1.71}{0.179} = 9.55$$

$$\text{WI} = \frac{\text{Total mass of water}}{\text{Mass of product}} = \frac{0}{0.179} = 0$$

***N,O*-dimethylation (H_2SO_4)**

$$\text{PMI (reaction)} = \frac{\text{Total mass in reaction}}{\text{Mass of product}} = \frac{3.863}{0.193} = 20.02$$

$$\text{E factor} = \frac{\text{Total mass of waste}}{\text{Mass of product}} = \frac{3.863 - 0.193}{0.193} = 19.02$$

$$\text{SI} = \frac{\text{Total mass of solvent}}{\text{Mass of product}} = \frac{3.42}{0.193} = 17.72$$

$$\text{WI} = \frac{\text{Total mass of water}}{\text{Mass of product}} = \frac{0}{0.193} = 0$$

***N*-formylation (HCO_2H)**

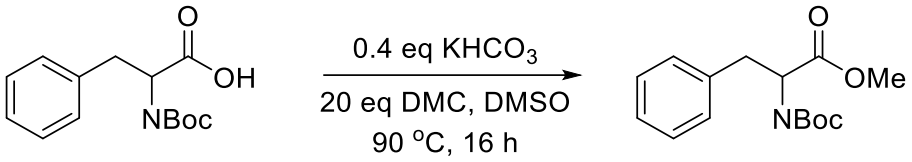
$$\text{PMI (reaction)} = \frac{\text{Total mass in reaction}}{\text{Mass of product}} = \frac{2.011}{0.193} = 10.42$$

$$\text{E factor} = \frac{\text{Total mass of waste}}{\text{Mass of product}} = \frac{2.011 - 0.193}{0.193} = 9.42$$

$$\text{SI} = \frac{\text{Total mass of solvent}}{\text{Mass of product}} = \frac{1.71}{0.193} = 6.07$$

$$\text{WI} = \frac{\text{Total mass of water}}{\text{Mass of product}} = \frac{0}{0.193} = 0$$

3.2 Previous method for *O*-methylation (DMC, $KHCO_3$)[7]



Experimental Procedures: To a 25 mL round-bottom flask equipped with magnetic stir bar, reflux condenser, and nitrogen inlet was added *N*-Boc phenylalanine (100 mg, 0.377 mmol), DMSO (0.2 M substrate concentration), and DMC (20 equiv). To the resulting solution was added potassium bicarbonate (15 mg, 0.15 mmol, 0.4 equiv) in one portion. The reaction mixture was magnetically stirred and heated to 90 °C for 16 h. After cooling to room temperature, the reaction was diluted with ethyl acetate (15 mL), washed with water (2 × 10 mL) and brine (1 × 10 mL), and dried with magnesium sulfate. After workup, the crude reaction mixture was further purified by column chromatography (19:1 hexanes/ethyl acetate eluent). *O*-methylation product was isolated as a white solid (72 mg, 68% yield).

Role	Chemical	Mass (g)	Volume (mL)	Density (g/mL)
Reaction				
Reactant	*N*-Boc phenylalanine	0.100		
Reactant	DMC	0.679	0.635	1.07
Reagent	$KHCO_3$	0.015	0.635	1.664
Solvent	DMSO	2.074	1.885	1.10
	Reaction total	2.868		
Work-up				
Extraction solvent	Ethyl acetate	13.53	15	0.902
Washing solvent	Water	20	20	1.0
Washing solution	Brine	12	10	1.2
CC	Silica-gel column	50		
Solvent	Ethyl acetate	4.51	5	0.902
Solvent	Hexane	62.80	95	0.661
	Work-up total	162.84		
	Reaction and work-up total	165.71		
Product				
Product	*O*-methylation	0.072		

$$\text{PMI (reaction)} = \frac{\text{Total mass in reaction}}{\text{Mass of product}} = \frac{2.868}{0.072} = 39.83$$

$$\text{PMI (workup)} = \frac{\text{Total mass used for workup}}{\text{Mass of product}} = \frac{162.84}{0.072} = 2{,}261.67$$

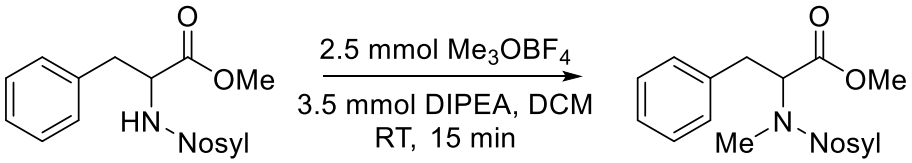
$$\text{PMI (total)} = \frac{\text{Total mass process}}{\text{Mass of product}} = \frac{165.71}{0.072} = 2{,}301.53$$

$$E = \frac{\text{Total mass of waste}}{\text{Mass of product}} = \frac{165.71 - 0.072}{0.072} = 2{,}300.53$$

$$SI = \frac{\text{Total mass of solvent}}{\text{Mass of product}} = \frac{2.074 + 13.53 + 20 + 12 + 4.51 + 62.80}{0.072} = 1{,}596.03$$

$$WI = \frac{\text{Total mass of water}}{\text{Mass of product}} = \frac{20 + 12}{0.072} = 444.44$$

3.3 Previous method for *N*-methylation (Me_3OBF_4)[8]



Experimental Procedures: To a solution of *N*-nosylphenylalanine methyl ester (1 mmol), in DCM (20 mL) were added DIPEA (3.5 mmol) and solid trimethyloxonium tetrafluoroborate (2.5 mmol). The reaction mixture was stirred for 15 min at room temperature and under an inert atmosphere. The mixture was then quenched with 1 N aqueous HCl until pH 2 and extracted with DCM (3x10 mL). The organic layer was washed with 1 N aqueous NaOH (3x10 mL) and then brine (10 mL). The combined organic layers were dried with Na_2SO_4 and evaporated to dryness under reduced pressure conditions to give the respective *N*-methylation product as colorless oils in quantitative yields.

Role	Chemical	Mass (g)	Volume (mL)	Density (g/mL)
Reaction				
Reactant	*N*-nosyl phenylalanine methyl ester	0.100		
Reactant	Me_3OBF_4	0.099		
Reagent	DIPEA	0.124	0.167	0.742
Solvent	Dichloromethane	26.6	20	1.33
	Reaction total	26.923		
Work-up				
Quenched solution	1 N HCl	30.6	30	1.02
Extraction solvent	Dichloromethane	39.9	30	1.33
Washing solution	1 N NaOH	31.2	30	1.04
Washing solution	Brine	12	10	1.2
	Work-up total	113.7		
	Reaction and work-up total	140.623		
Product				
Product	*N*-methylation	0.103		

$$\text{PMI (reaction)} = \frac{\text{Total mass in reaction}}{\text{Mass of product}} = \frac{26.923}{0.103} = 261.39$$

$$\text{PMI (workup)} = \frac{\text{Total mass used for workup}}{\text{Mass of product}} = \frac{113.7}{0.103} = 1{,}103.88$$

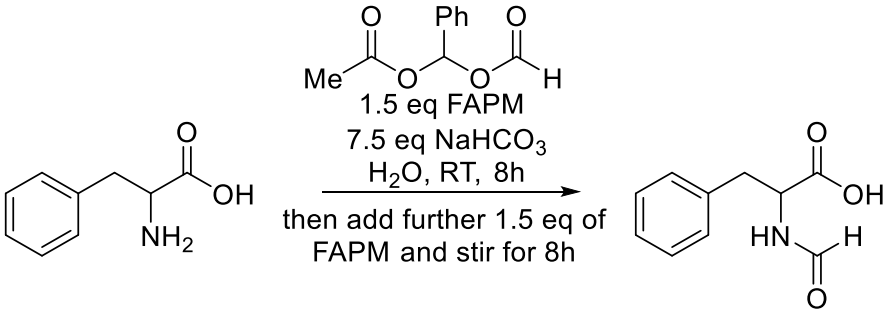
$$\text{PMI (total)} = \frac{\text{Total mass process}}{\text{Mass of product}} = \frac{140.623}{0.103} = 1{,}365.27$$

$$\text{E} = \frac{\text{Total mass of waste}}{\text{Mass of product}} = \frac{140.623 - 0.103}{0.103} = 1{,}364.27$$

$$\text{SI} = \frac{\text{Total mass of solvent}}{\text{Mass of product}} = \frac{26.6 + 30.6 + 39.9 + 31.2 + 12}{0.103} = 1{,}362.14$$

$$\text{WI} = \frac{\text{Total mass of water}}{\text{Mass of product}} = \frac{30.6 + 31.2 + 12}{0.103} = 716.50$$

3.4 Previous method for *N*-formylation (FAPM)[9]



Experimental Procedures: (Formyloxy)(phenyl)methyl acetate (FAPM) (0.291 g, 1.5 mmol) was added to a solution of phenylalanine (1.0 mmol) and $NaHCO_3$ (0.630g, 7.5 mmol) in H_2O (4 mL) and the reaction mixture stirred at room temperature for 8 h. A second portion of FAPM (1.5 mmol, 0.291 g) was then added and the reaction mixture stirred for a further 8 h. The reaction mixture was acidified (1 M HCl), extracted with CH_2Cl_2 (10 mL x 3), the organic layers combined, dried ($MgSO_4$) and concentrated in vacuo. The crude residue was then purified via recrystallization from EtOAc/petrol to afford the desired *N*-formylation product (0.166 g, 0.86 mmol).

Role	Chemical	Mass (g)	Volume (mL)	Density (g/mL)
Reaction				
Reactant	phenylalanine	0.33		
Reactant	FAPM	0.582		
Reagent	$NaHCO_3$	0.63		
Solvent	Water	4	4	1.0
	Reaction total	5.542		
Work-up				

Quenched solution	1 M HCl	30.6	30	1.02
Extraction solvent	Dichloromethane	39.9	30	1.33
Solvent	Ethyl acetate	9.02	10	0.902
Solvent	Petroleum ether	6.53	10	0.653
	Work-up total	86.05		
	Reaction and work-up total	91.592		
Product				
Product	*N*-formylation	0.166		

$$\text{PMI (reaction)} = \frac{\text{Total mass in reaction}}{\text{Mass of product}} = \frac{5.542}{0.166} = 33.39$$

$$\text{PMI (workup)} = \frac{\text{Total mass used for workup}}{\text{Mass of product}} = \frac{86.05}{0.166} = 518.37$$

$$\text{PMI (total)} = \frac{\text{Total mass process}}{\text{Mass of product}} = \frac{91.592}{0.166} = 551.76$$

$$\text{E} = \frac{\text{Total mass of waste}}{\text{Mass of product}} = \frac{91.592 - 0.166}{0.166} = 550.76$$

$$\text{SI} = \frac{\text{Total mass of solvent}}{\text{Mass of product}} = \frac{4 + 30.6 + 39.9 + 9.02 + 6.53}{0.166} = 542.47$$

$$\text{WI} = \frac{\text{Total mass of water}}{\text{Mass of product}} = \frac{4 + 30.6}{0.166} = 208.43$$

References

1 R. J. Ouellette and J. D. Rawn, in *Principles of Organic Chemistry*, eds. R. J. Ouellette and J. D. Rawn, Elsevier, Boston, 2015, pp. 371–396.
2 J. Trygg, P. Trivedi and P. Fardim, *Cellul. Chem. Technol.*, 2016, **50**, 557–567.
3 T. P. Silverstein and S. T. Heller, *J. Chem. Educ.*, 2017, **94**, 690–695.
4 D. Prat, A. Wells, J. Hayler, H. Sneddon, C. R. McElroy, S. Abou-Shehada and P. J. Dunn, *Green Chem.*, 2015, **18**, 288–296.
5 R. A. Sheldon, *ACS Sustainable Chem. Eng.*, 2018, **6**, 32–48.
6 S. Michałek, L. Gurba-Bryśkiewicz, W. Maruszak, M. Zagozda, A. M. Maj, Z. Ochal, K. Dubiel and M. Wieczorek, *RSC Adv.*, 2022, **12**, 33605–33611.
7 Y. Ji, J. Sweeney, J. Zoglio and D. J. Gorin, *J. Org. Chem.*, 2013, **78**, 11606–11611.
8 R. De Marco, M. L. Di Gioia, A. Liguori, F. Perri, C. Siciliano and M. Spinella, *Tetrahedron*, 2011, **67**, 9708–9714.
9 R. S. L. Chapman, R. Lawrence, J. M. J. Williams and S. D. Bull, *Org. Lett.*, 2017, **19**, 4908–4911.