

Supporting information

Fine bubble technology for the green synthesis of fairy chemicals

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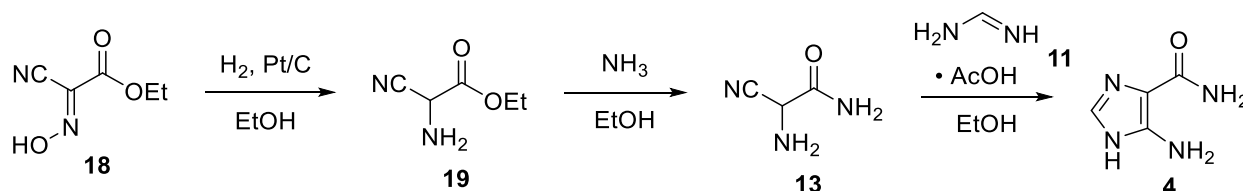
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Contents

Synthetic scheme from ester (18).....	3
Synthetic scheme by using NH ₃ in the final stage	4
Synthetic scheme using methyl 2-cyano acetate.....	4
Synthesis scheme by using 2-cyano acetamide as a starting material.....	5
Cascade-type one-pot reduction coupling using microporous-FB generator.....	5
Cascade-type one-pot reduction coupling using pressurized-depressurized FB generator.....	7
Cascade-type one-pot reduction coupling using spray-type FB generator	10
Cascade-type one-pot reduction coupling using MSE FB generator	12
Oxime conversion and AICA formation optimization using MSE FB generator	14
Catalyst amount optimization	14
Catalyst optimization	15
Reaction solvent optimization.....	15
Concentration optimization.....	16
Formamidine acetate equivalent optimization	16
Different types of formamidine salt.....	17
Mechanism of FB formation	18
FB Concentration measurement.....	18
Relation between MB and AICA yield	19
Calibration curve for AICA with internal standard (Benzimidazole).....	20
HPLC chromatogram for OPRCR	20
DICA stability determination.....	21
Mass spectra of intramolecular cyclisation reaction	22
References.....	23
Compound Data	24

Synthetic scheme from ester (18)

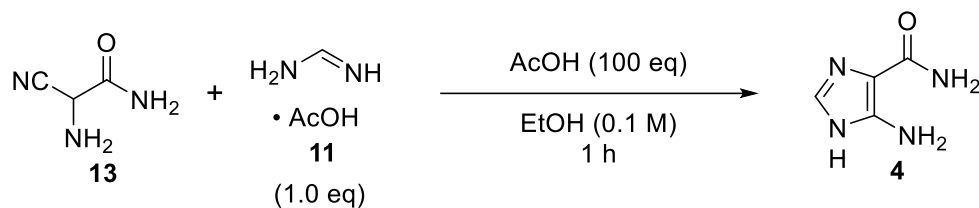
At first, we focused on synthesizing the active intermediate AICA from an ester. We have chosen ethyl cyano(hydroxyimino)acetate (**18**) as a starting material and the reduction reaction was done first to synthesize ethyl 2-amino-2-cyanoacetate (**19**) by using a spray-type FB generator. Then, the amidation reaction was done using ammonia gas to get 2-amino-2-cyanoacetamide (**13**) and finally the coupling reaction to get AICA (**4**).



Scheme S1. Starting material- ethyl 2-cyano-2-(hydroxyimino)acetate (**18**), reduction to ethyl 2-amino-2-cyanoacetate (**19**) amidation to 2-amino-2-cyanoacetamide (**13**), reductive coupling to AICA (**4**)

Both the reduction and amidation reaction was done by using spray type FB generator with a 78% yield. However low yield was found during the coupling reaction. We found that the previously used ammonia was affecting the coupling reaction, we added excess acetic acid from outside to activate the reaction, but the reactivity did not enhance. The reaction without ammonia and acetic acid is the preferred condition for the coupling reaction. However, it is not easy to remove ammonia from amino nitrile (**13**) for a plant batch, and it is not a suitable synthesis pathway from the green chemistry viewpoint. Then focused on using ammonia in the final stage by changing the reaction pathway.

Table S1. Effect of acid additive for the synthesis of AICA from ethyl ester

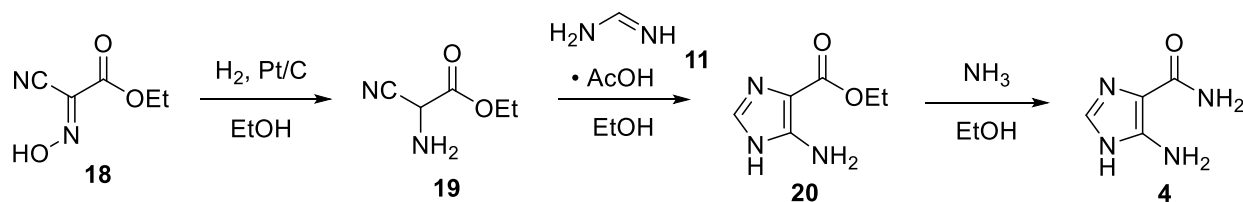


Entry	Solvent	Additives	Temperature (°C)	Yield (%) ^a
1	EtOH ^b	-	80	50
2	EtOH	AcOH	80	n.d. ^c
3	EtOH	-	120	28
4	EtOH	AcOH	120	n.d.
5	EtOH-NH ₃	-	80	20
6	EtOH-NH ₃	AcOH	80	n.d.
7	EtOH-NH ₃	-	120	32
8	EtOH-NH ₃	AcOH	120	n.d.

^aDetermined by ¹H NMR with dimethyl sulfone as an internal standard. ^bNH₃ was removed by concentration.

^cAICA was not detected.

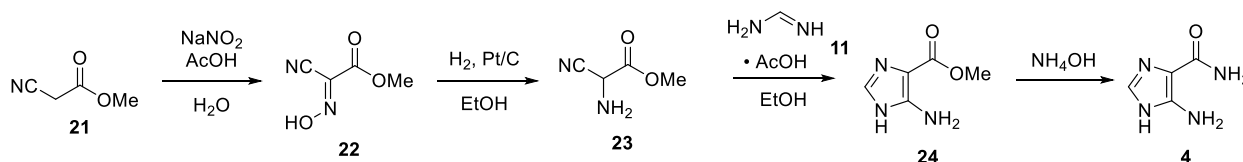
Synthetic scheme by using NH₃ in the final stage



Scheme S2. Starting material ethyl 2-cyano-2-(hydroxyimino)acetate (**18**), reduction to ethyl 2-amino-2-cyanoacetate (**19**), coupling reaction to ethyl 5-amino-1H-imidazole-4-carboxylate (**20**), finally amidation reaction to AICA (**4**)

After reducing oxime (**18**), a coupling reaction of ethyl 2-amino-2-cyanoacetate (**19**) and formamidine in batch condition was performed, yielding the ester (**20**) in 42% yield. Then, the amidation by ammonia which is the final stage was examined. First, the examination of ammonia FB by the spray-type FB generator was tried, but the amidation did not progress at one pass (30 °C, 11 mL/min). In addition, the circulatory system was tested. Still, as it circulated, the solvent absorbed ammonia, and it became difficult to pump the liquid according to the flow rate set by the pump (it is considered that it becomes negative pressure when sucking up the solution, and ammonia in the system becomes gas). Therefore, the amidation of ester **20** was performed at 0.3 MPa and 120 °C conditions in a pressure-resistant container. However, the progress of the reaction was not observed even after 2 hours.

Synthetic scheme using methyl 2-cyano acetate

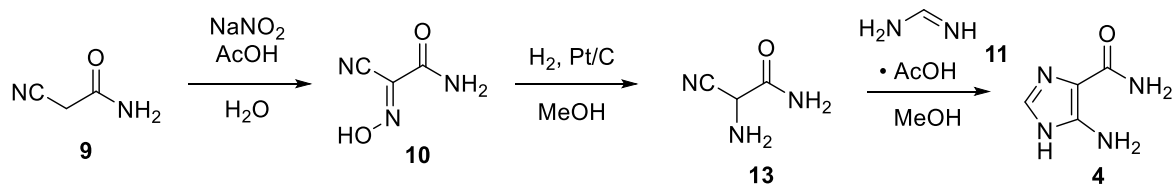


Scheme S3. Starting material methyl 2-cyano acetate (**21**), oximation to methyl 2-cyano-2-(hydroxyimino)acetate (**22**), reduction to methyl 2-amino-2-cyanoacetate (**23**), coupling reaction to methyl 5-amino-1H-imidazole-4-carboxylate (**24**) amidation in aqueous ammonia to AICA (**4**).

Next, we started with methyl ester (**21**) as the reactivity of methyl ester towards ammonolysis is higher than the ethyl ester.¹ Methyl 2-cyano-2-(hydroxyimino)acetate (**22**) was prepared using our usual method, yielding compound **24** in 52% yield (**21** to **24**). Amidation reaction was attempted using the pressure-resistant container described above for ethyl ester **20**, but the progress of the reaction was not confirmed. Therefore, decided to investigate the uniform liquid-phase reaction using aqueous ammonia, not just the gas-liquid phase reaction. After mixing the ester with aqueous ammonia, the vial was sealed at 100 °C. However, since the progress of the response could hardly be confirmed even after 3 hours had elapsed, it was judged to be difficult to put this scheme into practice.

Synthesis scheme by using 2-cyano acetamide as a starting material

The effect of the reaction using ammonia on the next stage, or the low activity of ammonia has been cited as a problem so far. Therefore, using 2-cyanoacetamide as the starting material, we designed a scheme for AICA synthesis that avoids ammonia.



Scheme S4. Starting material 2-cyano acetamide (**9**), oximation to 2-amino-N-hydroxy-2-oxoacetimidoyl cyanide (**10**), reduction to 2-amino-2-cyanoacetamide (**13**), coupling reaction to AICA (**4**)

After the synthesis of oxime **10**, the reduction of oxime by using spray type FB generator, the reduction yield was 91%. But there was a possibility of over reduction of **13**, and the stability of **13** was in concern. Again, the coupling reaction yield was 67%. So, we have planned to do a cascade-type one-pot reduction coupling reaction.

Cascade-type one-pot reduction coupling using microporous-FB generator

Micro porous FB generator is supplied by NORITAKE CO., LIMITED, Japan. This system injects pressurized gases through a tubular ceramic membrane with nanopores to create FBs. The reaction setup for a microporous FB method is composed of an HPLC pump, a hydrogen flow controller, a back pressure regulator, an MSE FB generator, a packed bed reactor for catalyst, a column oven (SHIMADZU), an SUS coil reactor, and a thermocouple.

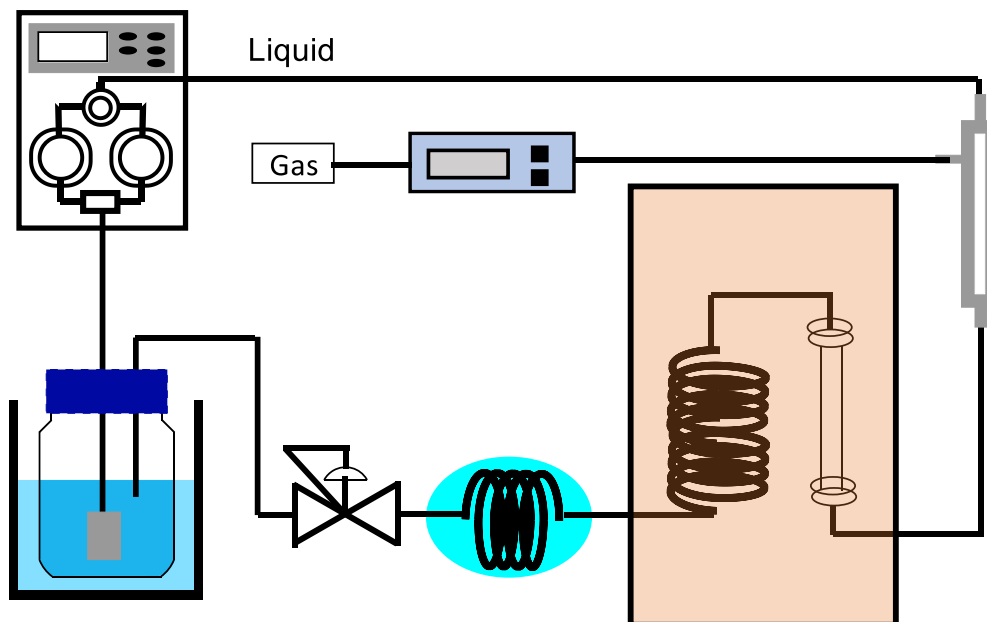


Figure S1. Schematic diagram for the microporous FB reaction

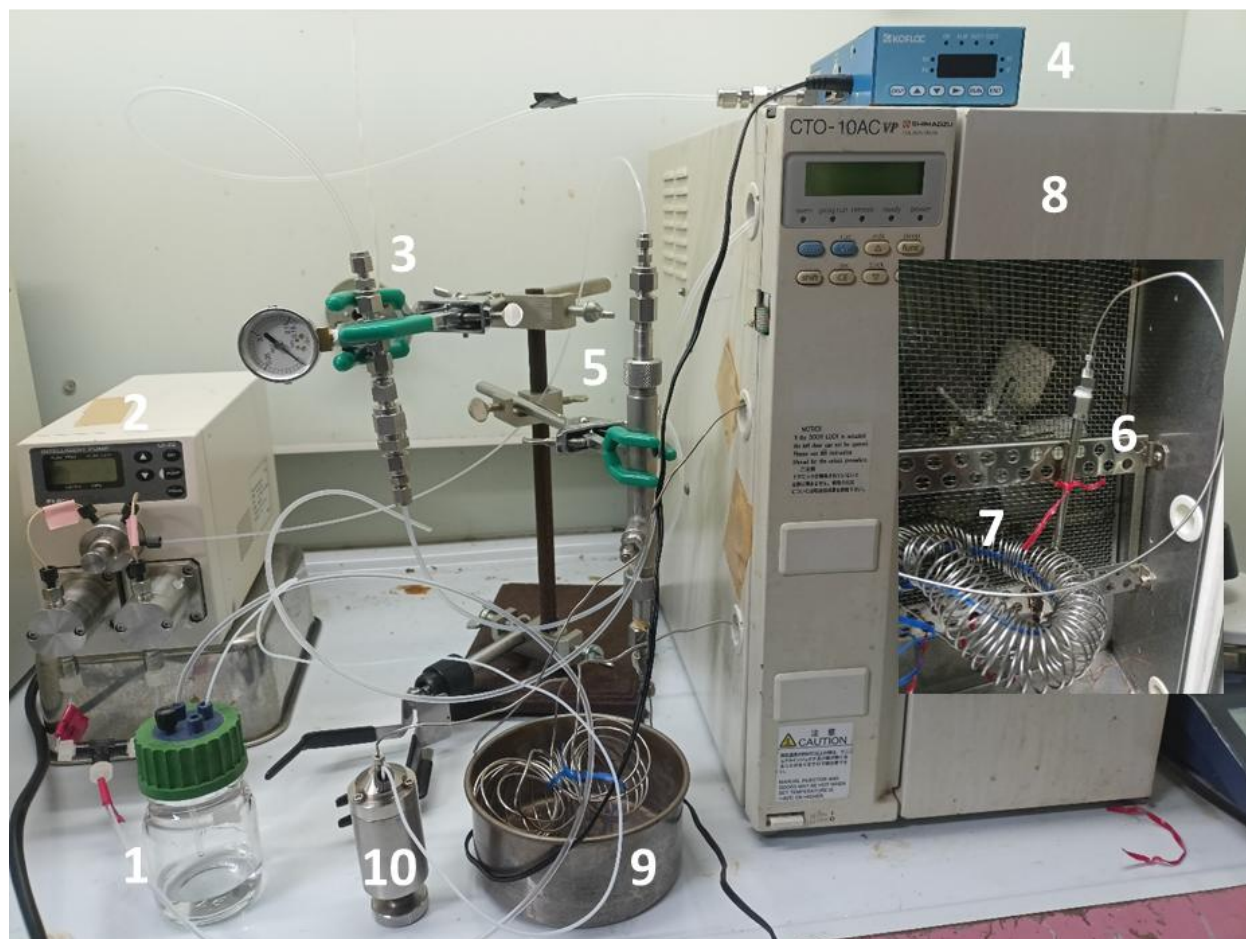


Figure S2. Picture of the reaction set up for microporous FB generator

Set-up explanation: using a glass beaker (1) to make the reaction solution, pump (2) is used to circulate the reaction solution from the glass beaker, microporous FB generator has (5), two connectors, the liquid flow from the up connector and gas flow from side connector. The hydrogen gas passes through a pressure gauge (3) and Mass flow controller (4) to find out the gas pressure and gas flow rate, respectively. Inside the generator, gases are passed through the microporous element and form FB by mixing with liquid. a column oven (8) to heat the reaction solution, a packed bed reactor placed inside the oven filled with catalyst (6) and up flow for the reduction of oxime, and a SUS coil reactor (7) inside the oven for the coupling reaction, another submerged coil reactor (9) to reduce the temperature by cooling, a back pressure regulator (10) to control the flow rate and a thermocouple to check to the temperature of reaction mass.

Temperature dependence on the synthesis of AICA and by-product:

The formation of AICA at different temperatures has been observed by using a microporous type of FB generator. Checked the AICA formation and by-product/AICA area ratio at 60 °C, 80 °C and 120 °C, respectively. other variables like formamidine acetate (1.2 equivalent), methanol (0.1 M), catalyst (3 mol%), and hydrogen gas flow keep constant. The obtained result indicates that the formation of AICA increases with increasing temperature. The ratio of by-product/AICA also increases with increasing temperature; it indicates that by-product formation also increases with increasing temperature.

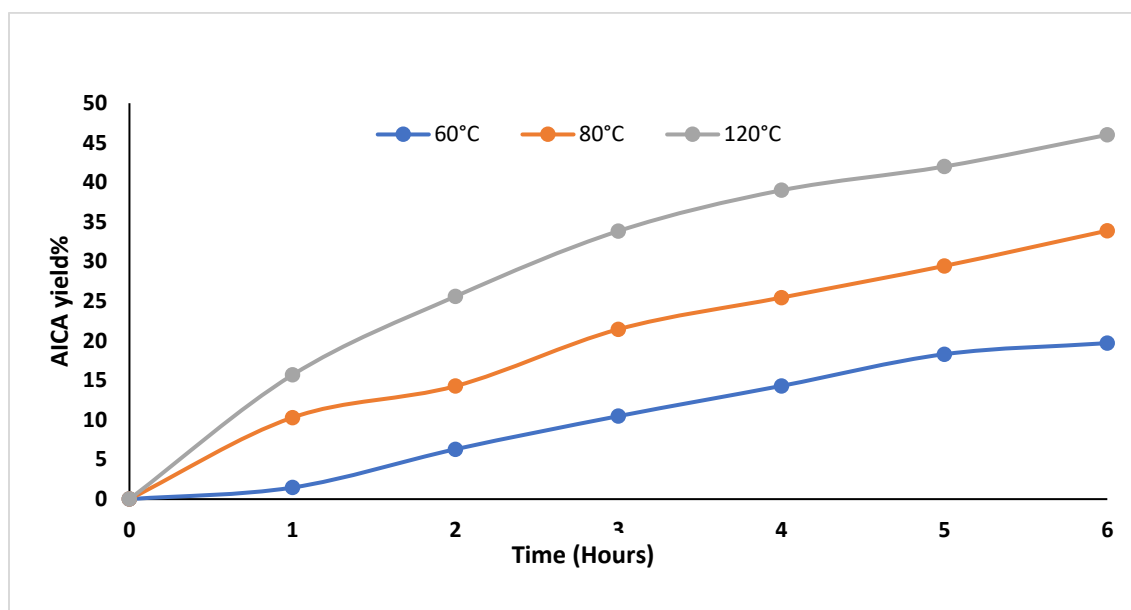
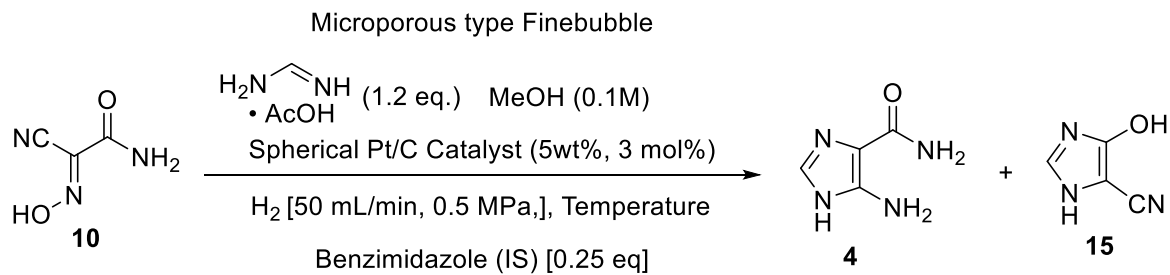


Figure S3. AICA formation at different temperatures

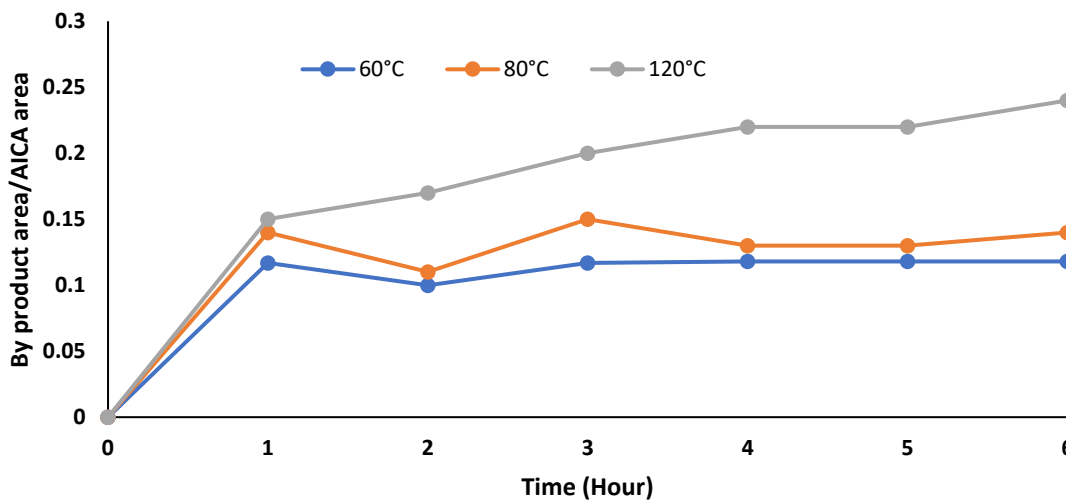


Figure S4. By-product/AICA area ratio at three different temperatures

Cascade-type one-pot reduction coupling using pressurized-depressurized FB generator.

Pressurized-depressurized FB generator was supplied by PMT Inc., Japan, composed of an HPLC pump, a hydrogen flow controller, two back pressure regulators, a mixer, a Packed bed reactor for catalyst, a column oven (SHIMADZU), and a thermocouple.

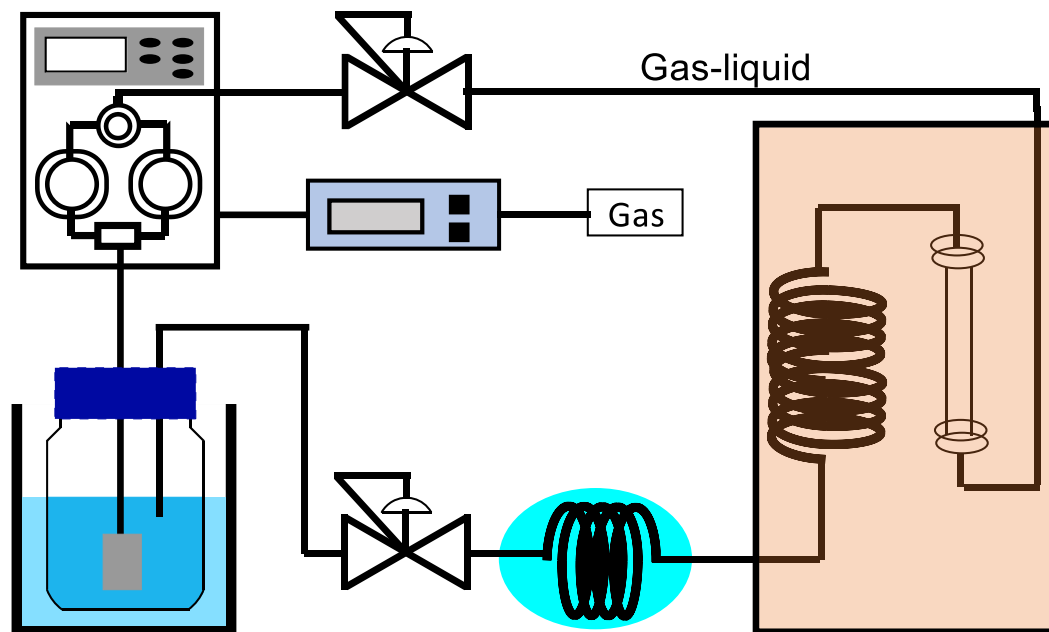


Figure S5. Schematic diagram for the pressurized-depressurized FB generator

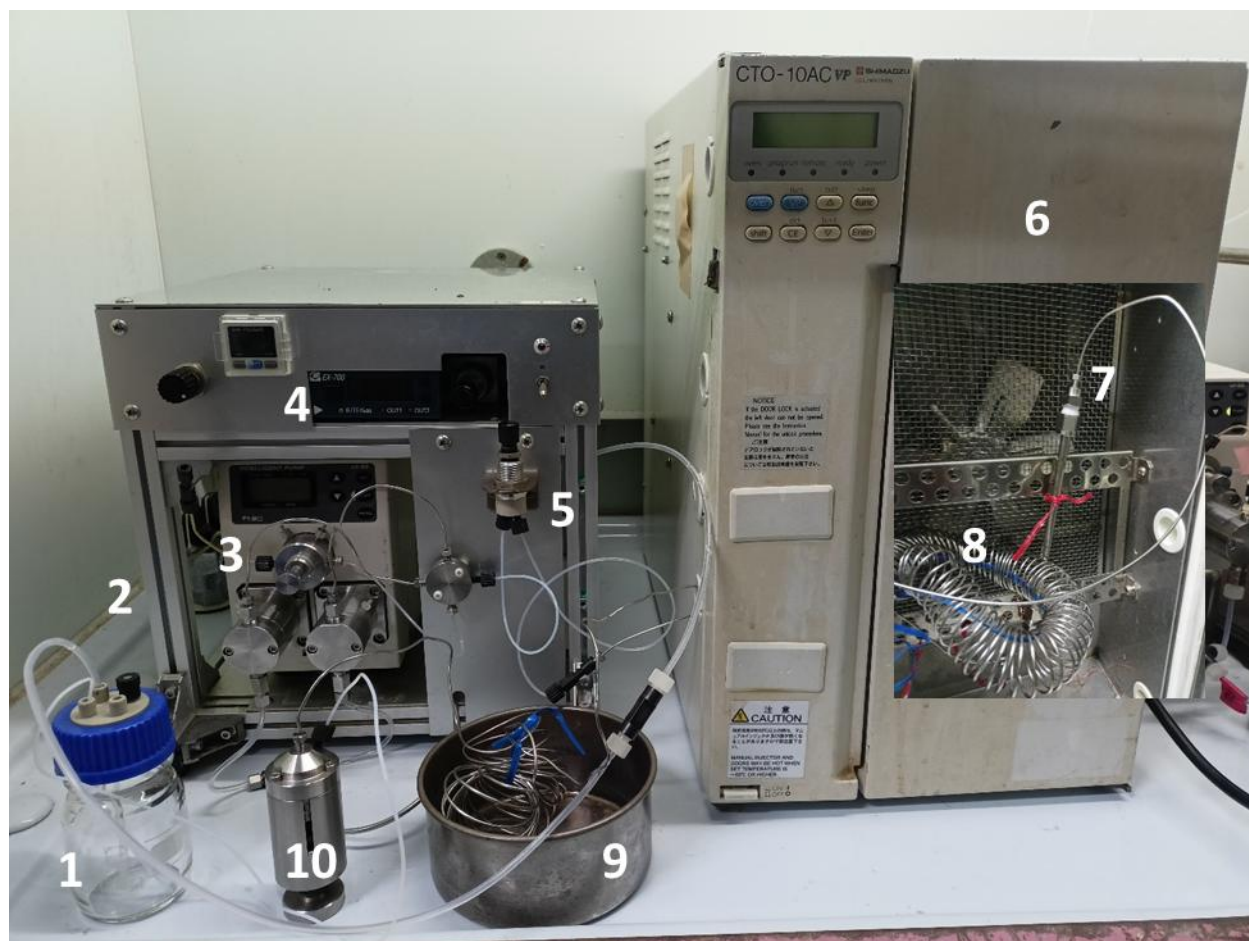
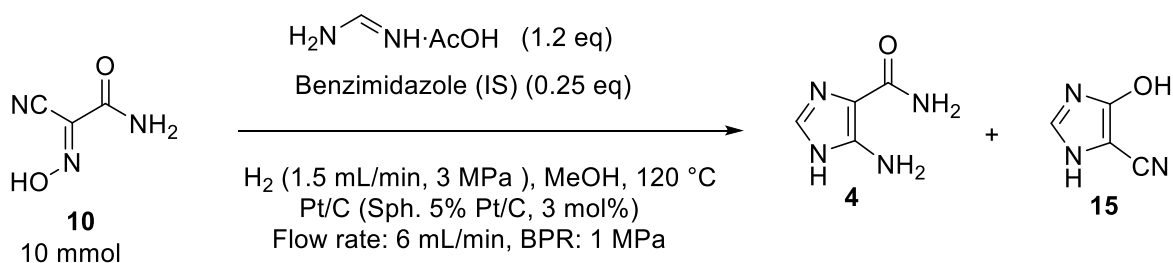


Figure S6. Picture of the reactor set up for pressurized-depressurized FB generator.

Reaction Set-up explanation: using a glass beaker (1) to make the reaction solution, a pressurized depressurized FB generator (2), which is made by combining a pump (3) is used to circulate the reaction solution from the glass beaker, a continuous hydrogen gas flow from a gas cylinder via mass flow controller (4), gas and liquid mix by the back pressure regulator (5) and used to make FB of the gas-liquid mixture, a column oven (6) to heat the reaction solution, a packed bed catalyst column (7) and a SUS coil reactor (8) inside the oven for the coupling reaction, another submerged coil reactor (9) to reduce the temperature after reaction, second back pressure regulator (10) to control the flow rate and a thermocouple to check to the temperature of reaction mass.



Scheme S5. Cascade-type one-pot reduction coupling using pressurized-depressurized FB generator.

Dissolved the oxime, formamidine acetate, and benzimidazole in methanol and placed the spherical Pt/C (5wt%) inside the column.). Placed a coil reactor (6.25 mL) with a catalyst column inside the oven (120 °C). Placed a water cooling before the second BPR to decrease the solution temperature. For this generator, the limitation is the flow rate. For this reaction, the liquid flow rate is 4.5 mL/min, and the hydrogen gas flow rate is 1.5 mL/min, applying the pressure of 3 MPa. The reaction was continued for 6 hours, but due to the limited gas supply and limited FB formation the AICA formation is not so high, it is around 34%.

Cascade-type one-pot reduction coupling using spray-type FB generator

Our laboratory developed its spray-type FB generator. Since FB is generated only by attaching a spray nozzle to the reaction tube supplying gas, this device can reduce the cost and experimental space by introducing the conventional FB generator. The reaction set up for the spray FB generator is composed of an HPLC pump, a spray nozzle, a SUS coil reactor, a hydrogen flow controller, a back pressure regulator, a steel reactor, a cylindrical filter, a column oven (SHIMADZU)

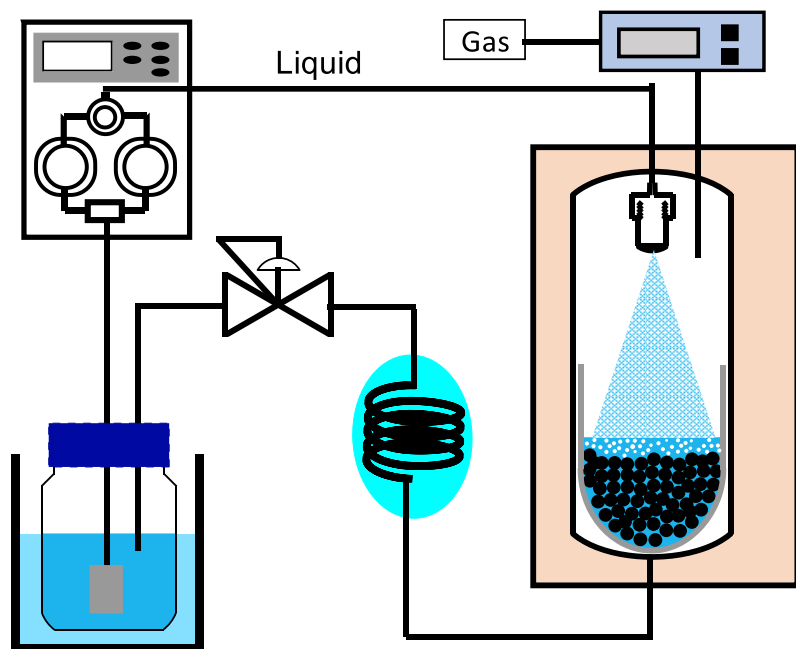


Figure S7. The schematic diagram for the spray FB generator

Set-up explanation: using a glass beaker (1) to make the reaction solution, pump (2) is used to circulate the reaction solution from the glass beaker, a continuous hydrogen gas flow from a gas cylinder and measure the gas flow rate by mass flow controller (3) and gas pressure by pressure gauge (4). a column oven (5) to heat the reaction solution, a steel reactor to create the FB (6) which has two connector, liquid flow as spray from upside and gas flow from side connector, FBs formed at the interface between the liquid and liquid spray at the presence of gas, a spray nozzle to convert the liquid into spray, a cylindrical filter to keep the catalyst inside the steel reactor, SUS coil for the coupling reaction (7) a submerged coil reactor (8) to reduce the temperature, a back pressure regulator (9) to control the flow rate and a thermocouple to check to the temperature of reaction mass.

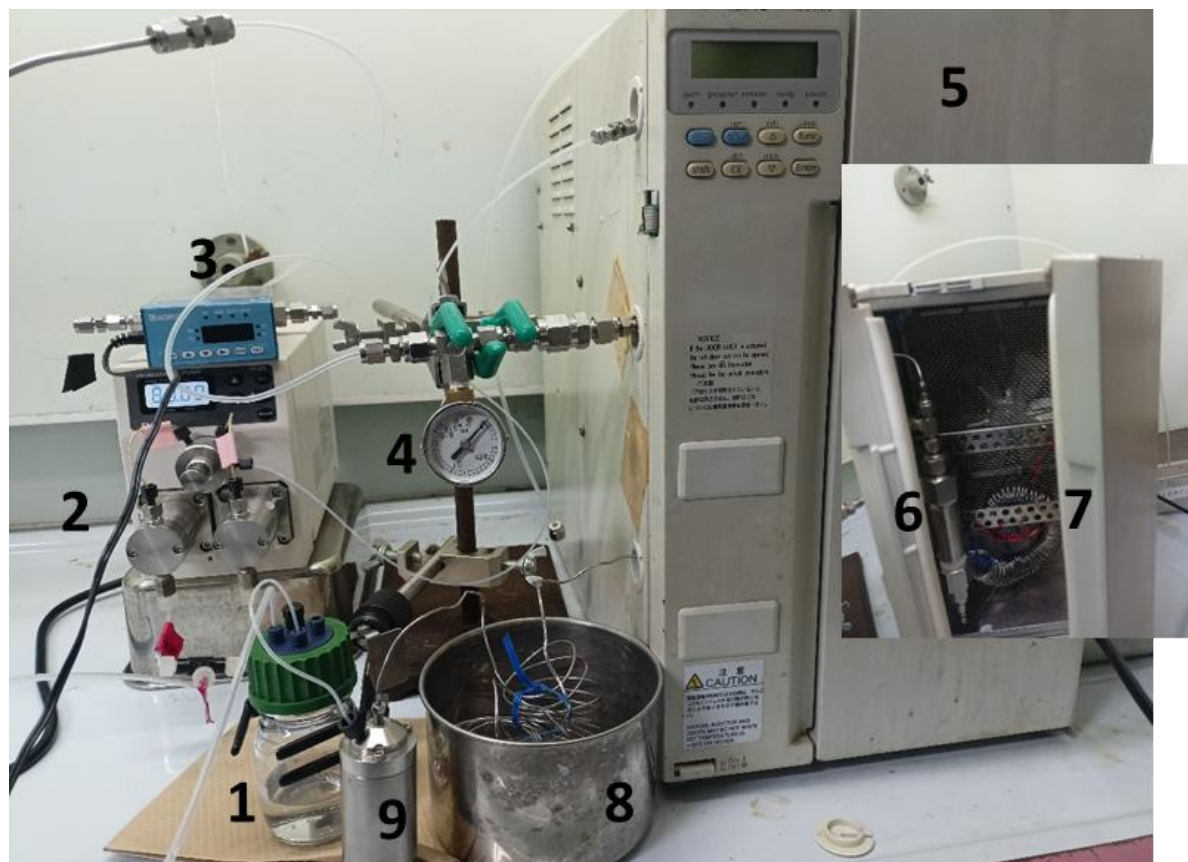
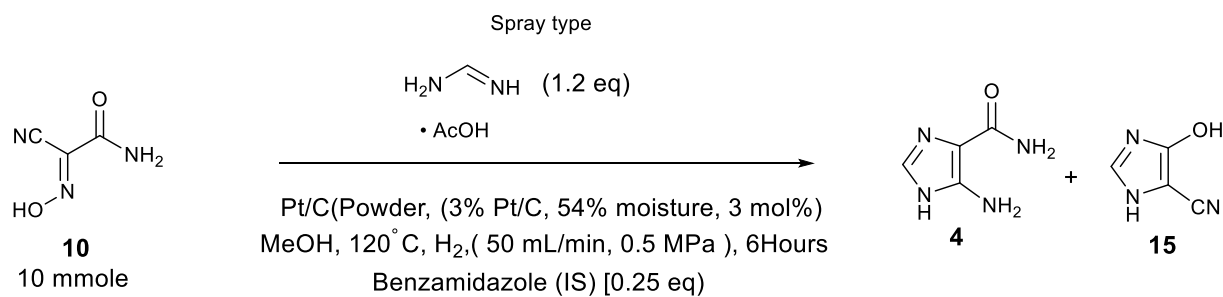


Figure S8. Picture of the reactor set up for spray FB generator



Scheme S6. Cascade-type one-pot reduction coupling using spray-type FB generator.

For this case, we have used a steel reactor and placed the powder Pt/C catalyst inside the reactor in a cylindrical filter paper. The pump flow rate was 10 mL/min, and the gas flow rate was 50-60 mL/min, under a constant pressure of 0.5 MPa. Placed a water bath for cooling after the oven. The reaction was continued for 6 hours at 120 °C. The AICA formation after 6 hours is also very low, around 7%.

Cascade-type one-pot reduction coupling using MSE FB generator

MSE FB generator is composed of a two-layer glass reactor, multi-stacked stirrer, mass flow controller, heating ribbons, condenser, and Thermocouple.

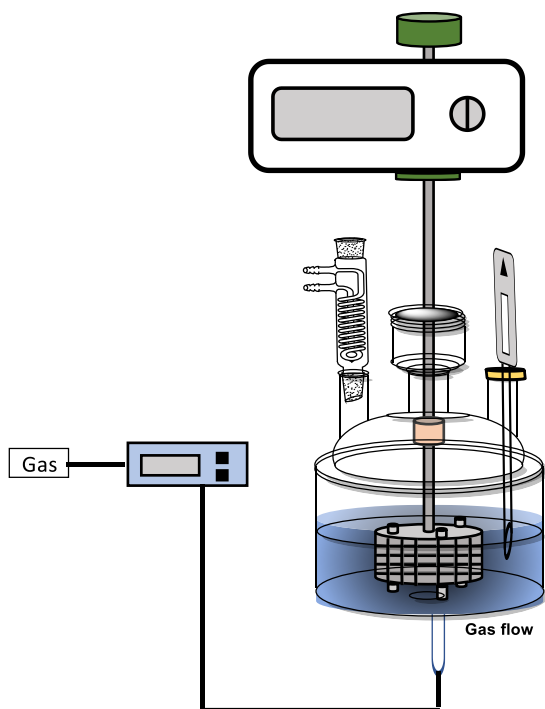
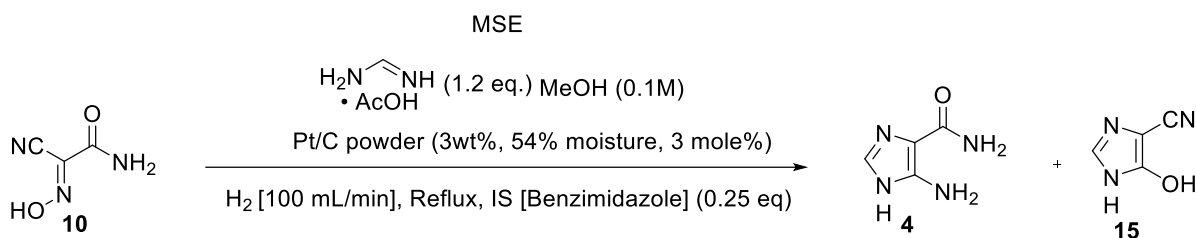


Figure S9. Schematic diagram for the MSE FB generator

In this case, the constant gas is supplied through a mass flow controller (1) to the reactor which is made of two separate glass reactors (4 and 5) via the connector (6). A multi-stack element stirrer (8) is connected to the upper glass and stirred by a stirrer (2). A reflux condenser (3) was used to cool down the vapour. The solution was heated by heating ribbons (7)



Scheme S7. Cascade-type one-pot reduction coupling using MSE FB generator.

At first, the gas flow was started (100 mL/min). A 100 mL solution of oxime (**10**, 10 mmol), and formamidine acetate (12 mmol) in methanol was added. the powder Pt/C catalyst (3 mol%) was added to the stirring reactor (carefully added, catalyst gets fire during addition due to the presence of hydrogen gas flow). Stirring speed 500 rpm. The reaction temperature increased by heating the ribbon and the reaction was continued under reflux conditions.



Figure S10. Picture of the reactor set up for MSE FB.

Oxime conversion and AICA formation optimization using MSE FB generator

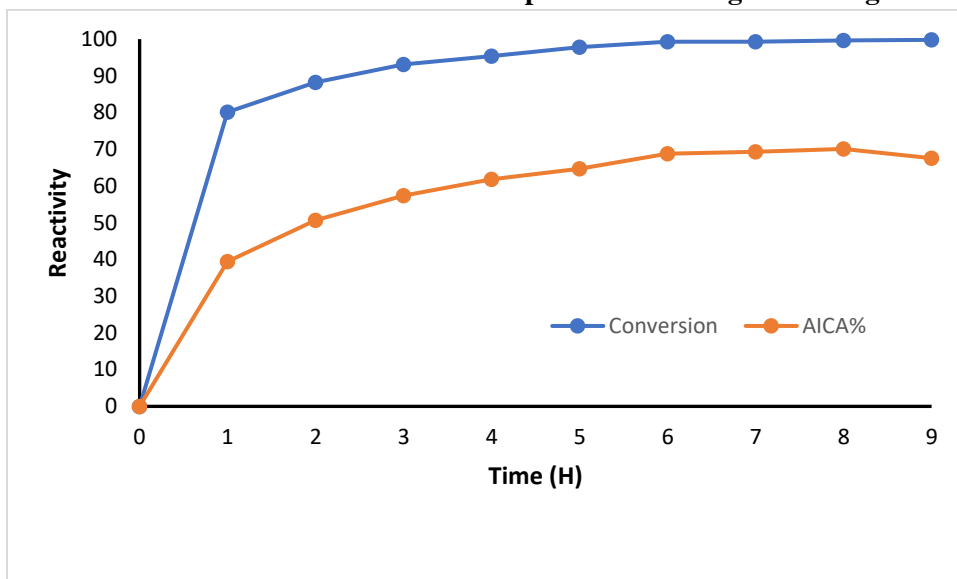


Figure S11. Reaction conversion and AICA yield% for MSE

Catalyst amount optimization

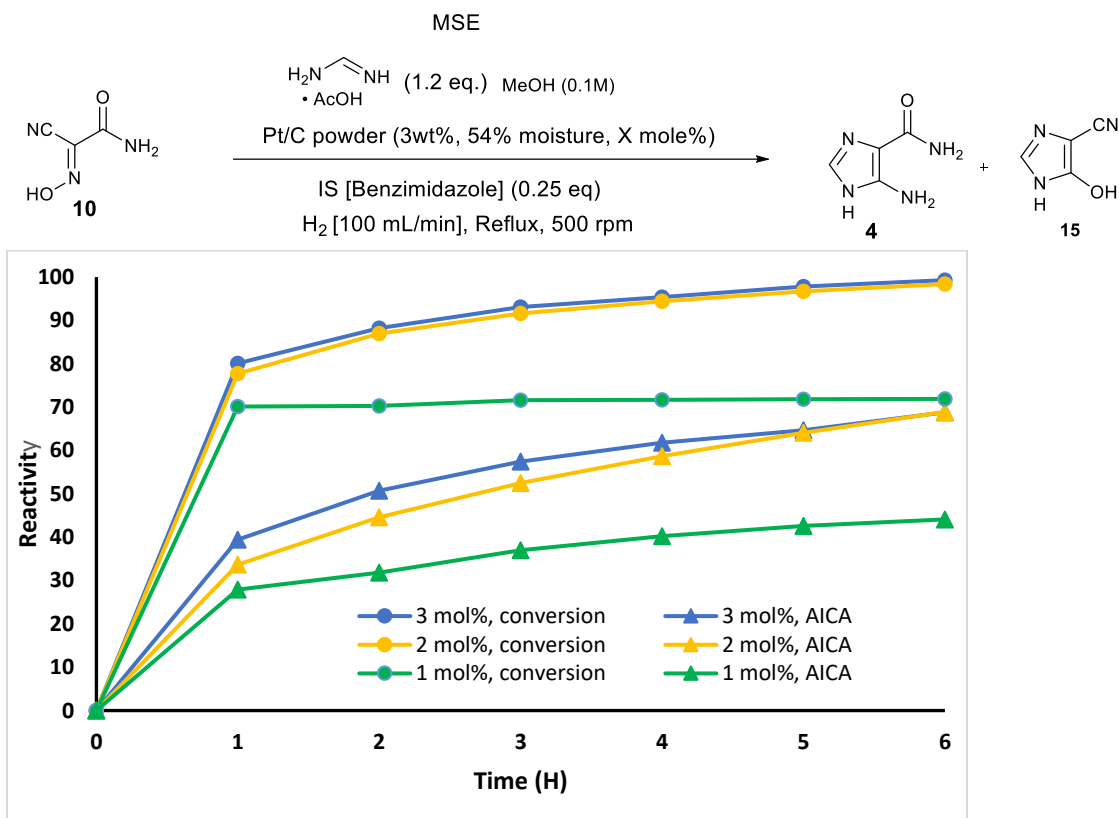


Figure S12. oxime conversion and AICA formation using different amount of Pt/C

Catalyst optimization

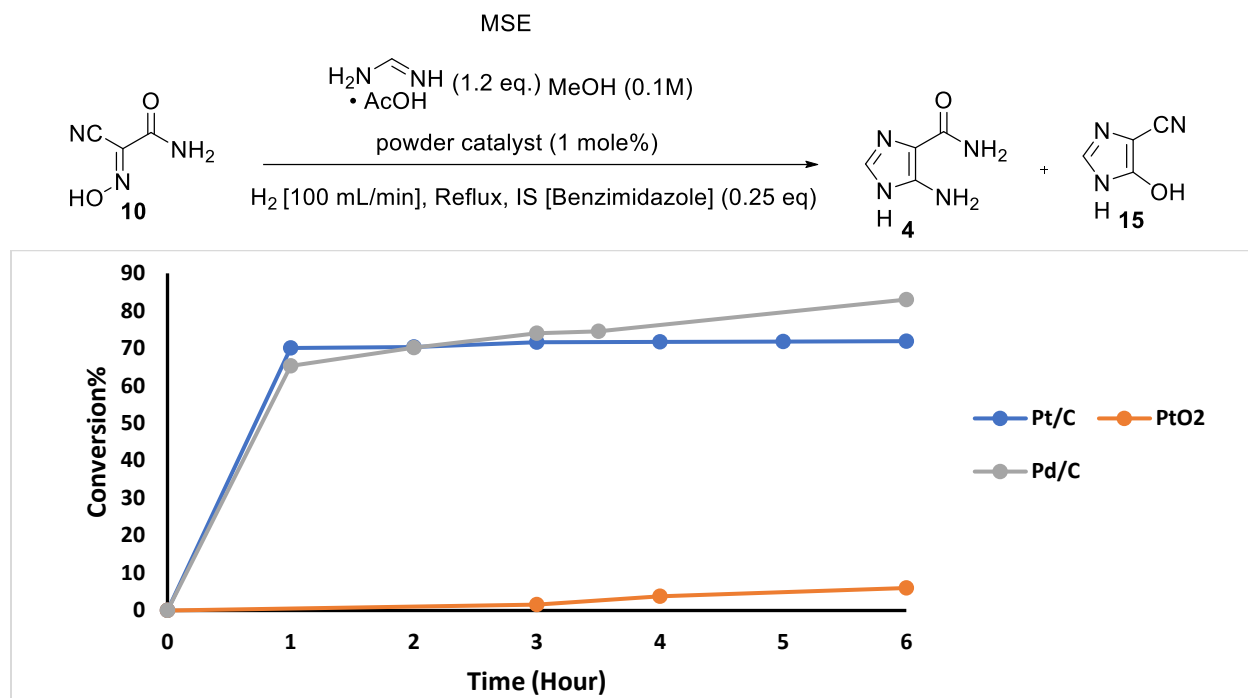


Figure S13. Oxime conversion of different catalyst

Reaction solvent optimization

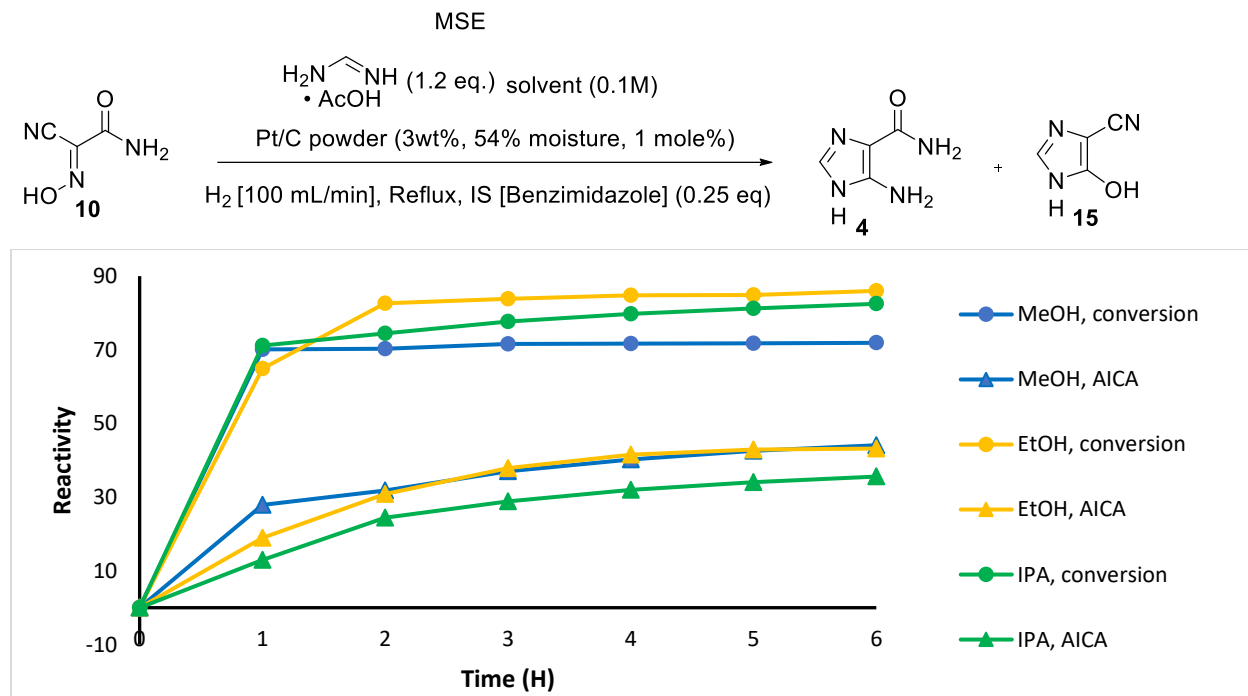


Figure S14. Oxime conversion and AICA formation using different solvent

Concentration optimization

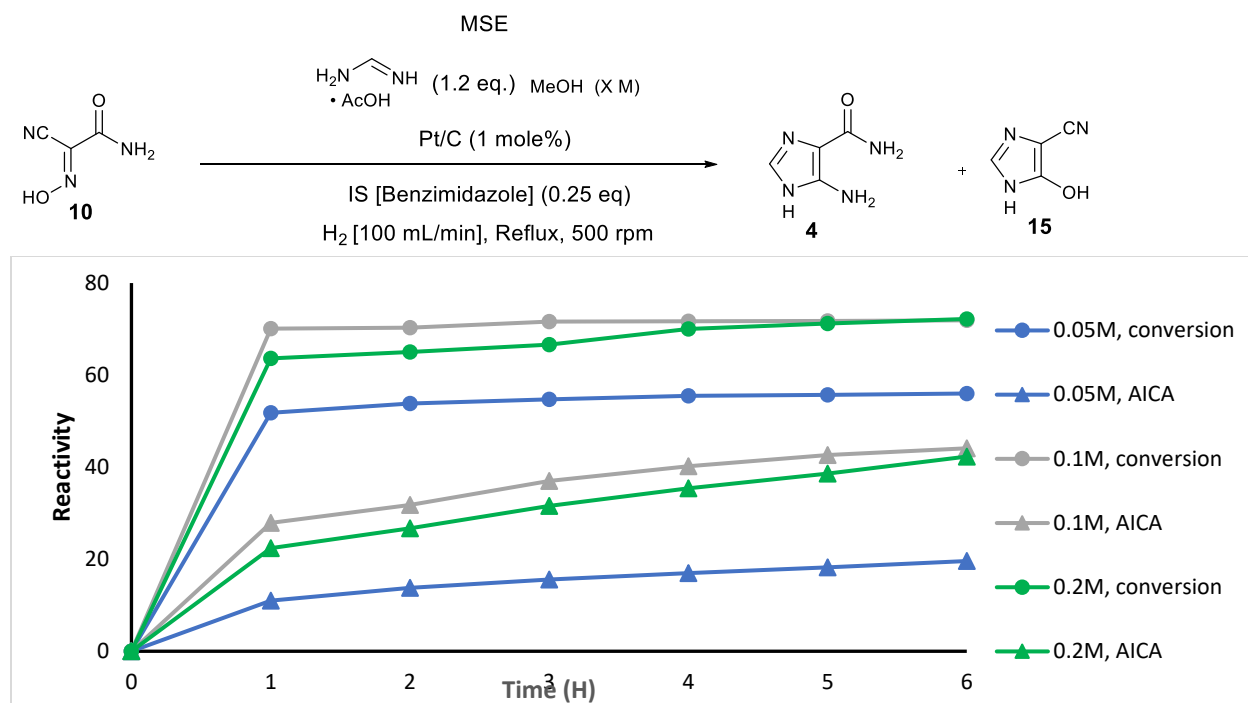


Figure S15. Oxime conversion and AICA formation using different concentration.

Formamidine acetate equivalent optimization

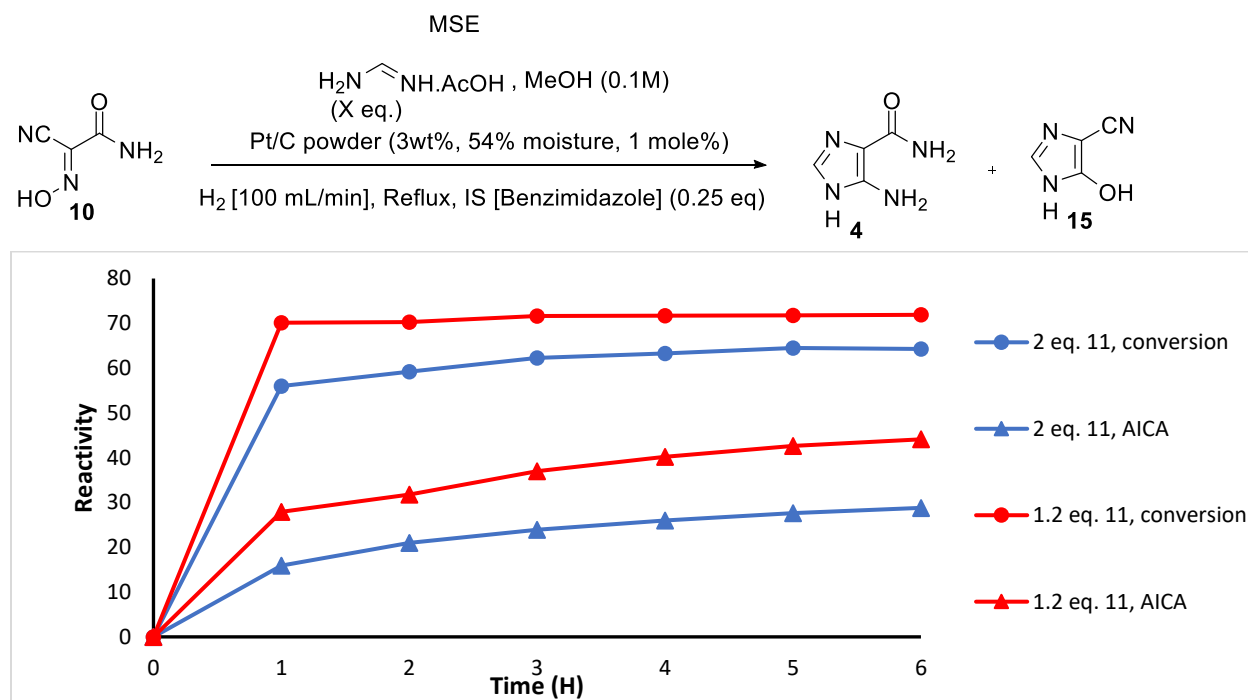


Figure S16. Oxime conversion and AICA formation using different amounts of formamidine acetate (11).

Different types of formamidine salt

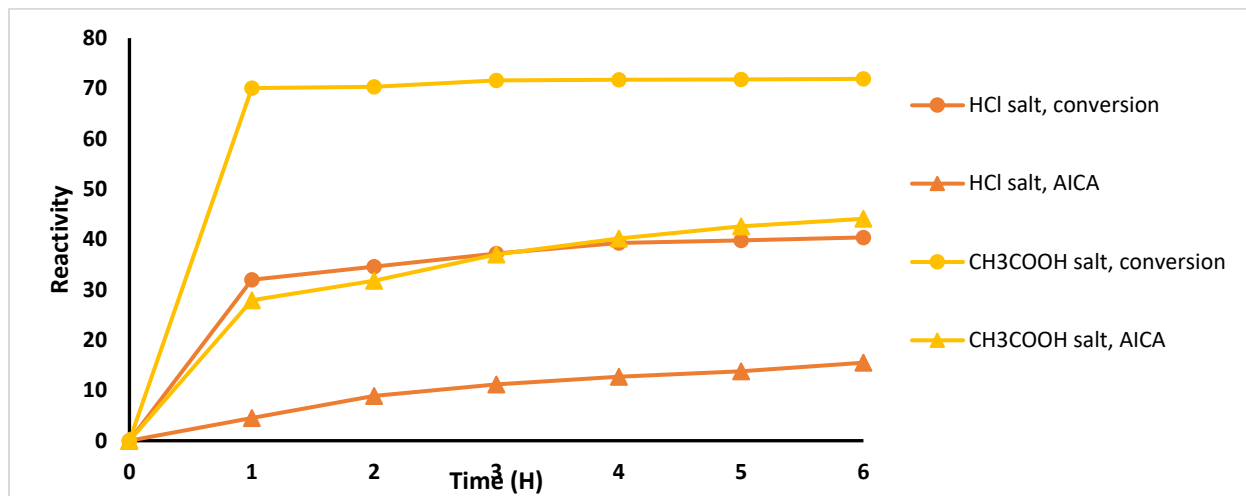
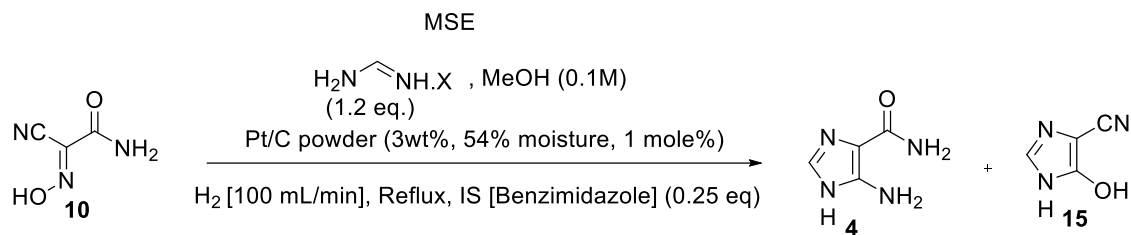


Figure S17. Oxime conversion and AICA formation using different formamidine salt.

Mechanism of FB formation

Pressurized-depressurized FB generator generates FB by applying pressure and depressure respectively in a gas-liquid mixture (Figure A). The microporous FB method contains a microporous body that forms FB by passing the gas through the micropores in the presence of shear liquid force. For spray, first, when the droplet collides with the liquid surface at low speed, a hemispherical gas phase occurs between the droplet and the liquid surface. Next, a perforation is caused on the side of the air phase, and the end is combined as it spreads. Then, bubbles are generated in the form of necklaces. Eventually, they become FB by repeating spontaneous rupture (C, 1-4). For MSE up flow gas is supplied to form milli bubble by mixing with solvent. The FB is formed by high stirring of a multi stack element.

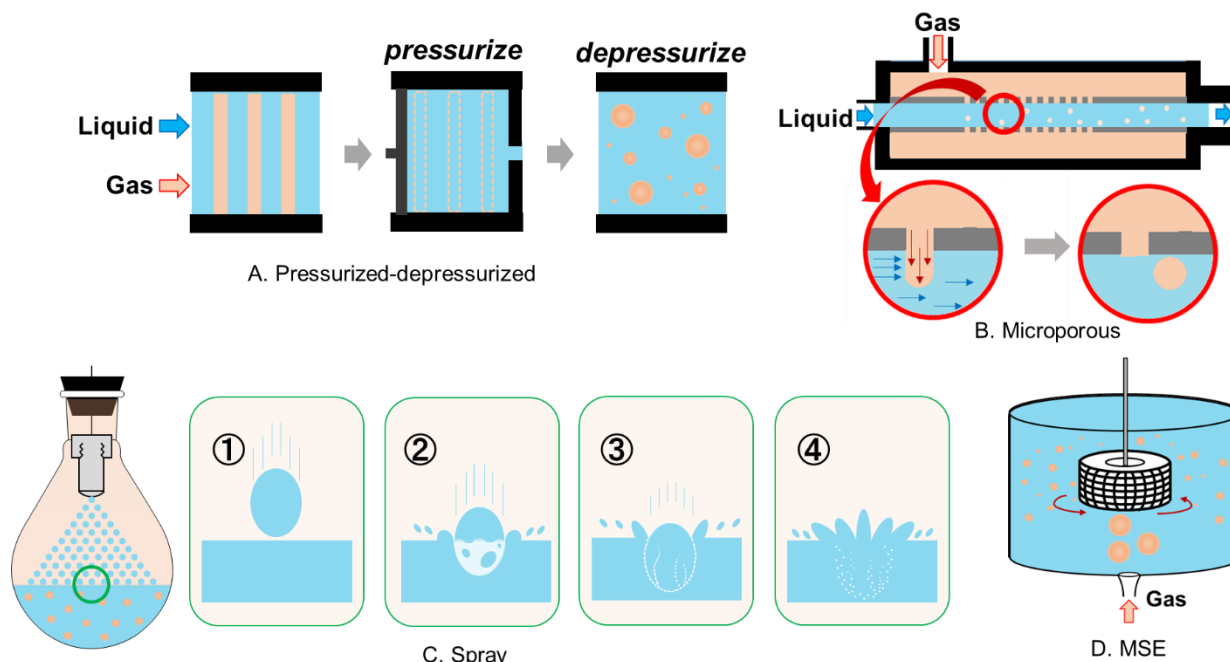


Figure S18. Mechanism for the formation of FB from different FB generator.

FB Concentration measurement

NanoSight LM10 (Malvern Panalytical, UK) was used for UFB measurements, and PartAn SI (MicrotracBEL Corp., Japan) for MB measurements. The basic setup of the measurement equipment followed our previous experimental approach.² The operating times were assumed to be until the FB concentration reached a steady state.

Generation method	Gas flow rate (mL/min)	Liquid flow rate (mL/min)	Total liquid volume (mL)	Operation time (h)
Microporous	20	80	100	4
Pressurized-depressurized ^a	25	25	200	4
MSE ^b	50	—	450	2
Spray	—	50	200	6

^aBPR was for the maintenance of system pressure (4 MPa). ^bStirring speed was 300 rpm.

Relation between MB and AICA yield

To confirm the yield of AICA synthesised using different FB generators, we measured the concentration and size of the FBs. We used Nanosight (LM10, Malvern Panalytical, UK) and PartAn SI (MicrotracBEL Corp., Japan) to quantify the concentration and size of UFBs and MBs, respectively. The concentration of UFBs obtained using the spray-type FB generator was the highest (165×10^7 particle/mL), followed by that obtained using the microporous- (106×10^7 particle/mL), MSE- (79×10^7 particle/mL), and pressurized-depressurized (40×10^7 particle/mL) FB generators using Nanosight (Table 2). This finding indicates the reactivity order of the FB generators as spray > microporous > MSE > pressurised-depressurised. In our previous study, we confirmed that higher MB concentrations led to lower catalytic activity because larger MBs were adsorbed on the catalyst surface, reducing the available area for the reaction.² Therefore, we determined the MB concentration using PartAn SI, with the following results: spray (1635 particle/mL) > pressurised-depressurised (763 particle/mL) > microporous (103 particle/mL) > MSE (23 particle/mL). This finding indicates that the order of the FB generators for the catalytic activity is MSE > microporous > pressurised-depressurised > spray. Greater MB concentration reduces the catalytic activity.

Table S2. Concentration and size of UFBs and MBs measured using different FB generation methods

FB generation method	UFB concentration ($\times 10^7$ particle/mL) ^a	UFB size (nm) ^a	MB concentration (particle/mL) ^b	MB size (μm) ^b
Spray	165 \pm 1.95	114 \pm 1	1635 \pm 15	34.8 \pm 0
Pressurised-depressurised	39.7 \pm 2.0	113 \pm 1	763 \pm 17	66.7 \pm 0.6
Microporous	106 \pm 1.5	103 \pm 2	429 \pm 98	36.9 \pm 2.6
MSE	79.3 \pm 12.3	91 \pm 3	23 \pm 0	10.6 \pm 0

^aDetermined by Nanosight. ^bDetermined by PartAn SI

Calibration curve for AICA with internal standard (Benzimidazole)

Hilic column (250 × 4.6 mm I.D. S-5 μm, 12 nm) has been used for the quantification of AICA. Acetonitrile and 50 mM NH₄HCO₂ aqueous solution are used as an eluent with a gradient manner acetonitrile-50 mM NH₄HCO₂ aq with a liner gradient of 95:5 to 40:60 over 15 minutes and then isocratic flow of 40:60 for 5 minutes at a flow rate of 1 mL/min at a detection wavelength of 265 nm. Benzimidazole was used as an internal standard.

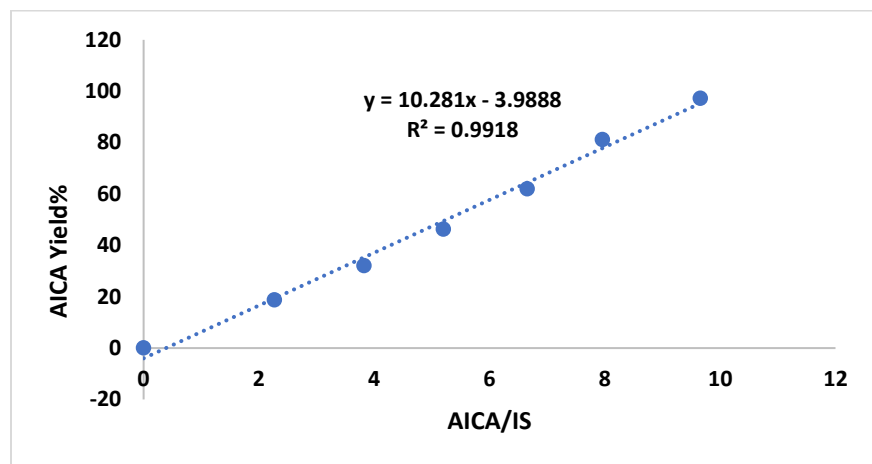


Figure S19. Calibration curve for AICA and internal standard (benzimidazole)

HPLC chromatogram for OPRCR

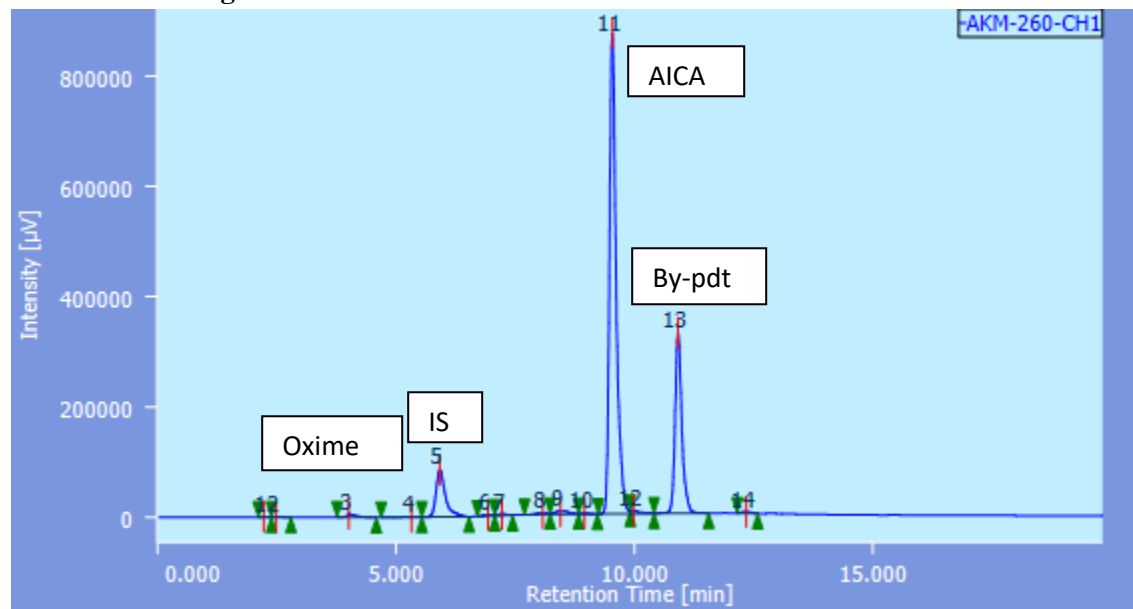
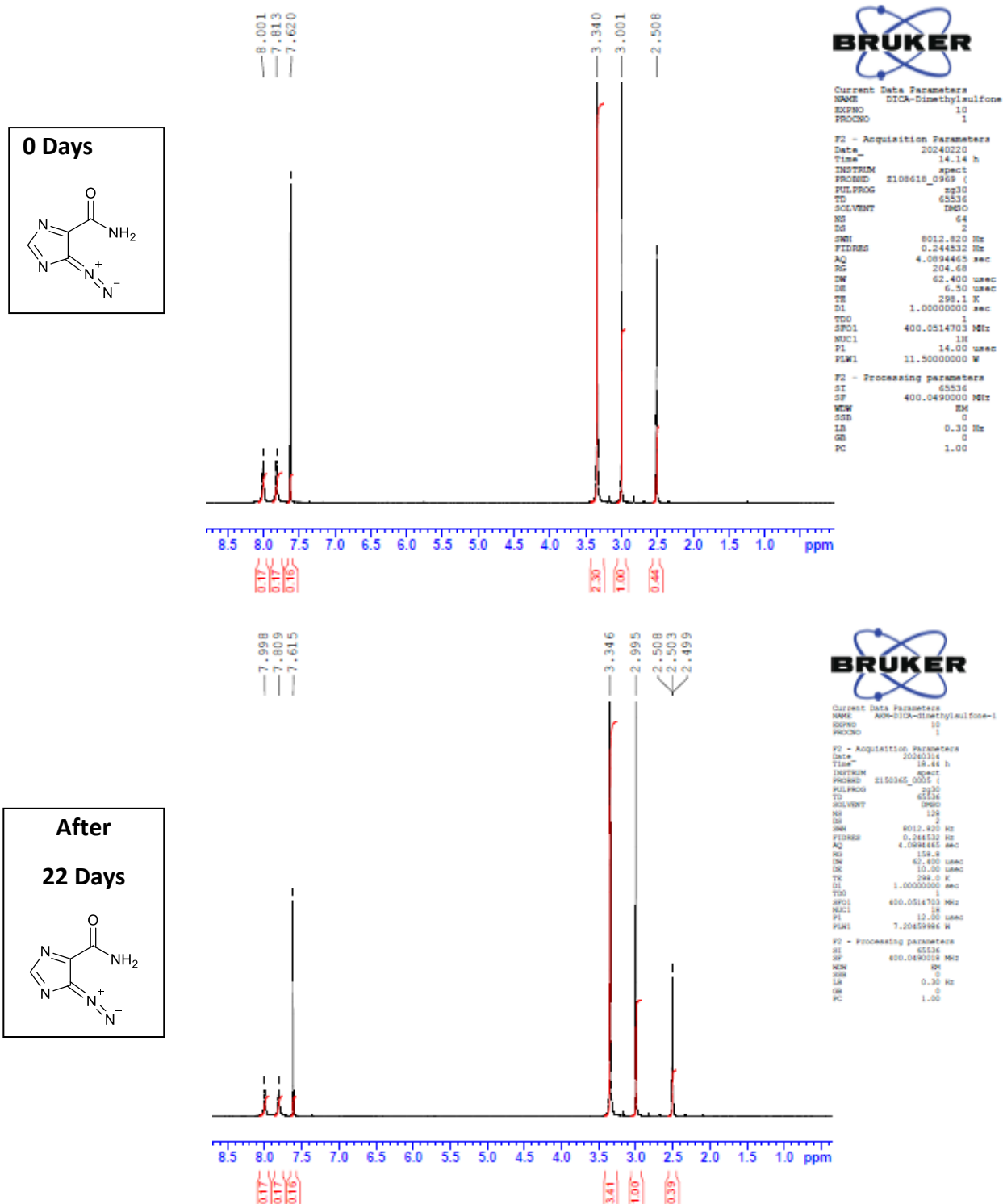


Figure S20. HPLC chromatogram of COPRC

DICA stability determination

DICA stability was determined by ^1H NMR, using a similar amount of DICA (0.017 mmol) and dimethyl sulfone (IS, 0.016 mmol). Here, the data for 0 days and after 22 days were shown. The ratio of the integrated area of DICA/dimethyl sulfone remained the same at 0.16 after 22 days. It indicates that DICA is stable at 4 °C for a long period.



Mass spectra of intramolecular cyclisation reaction

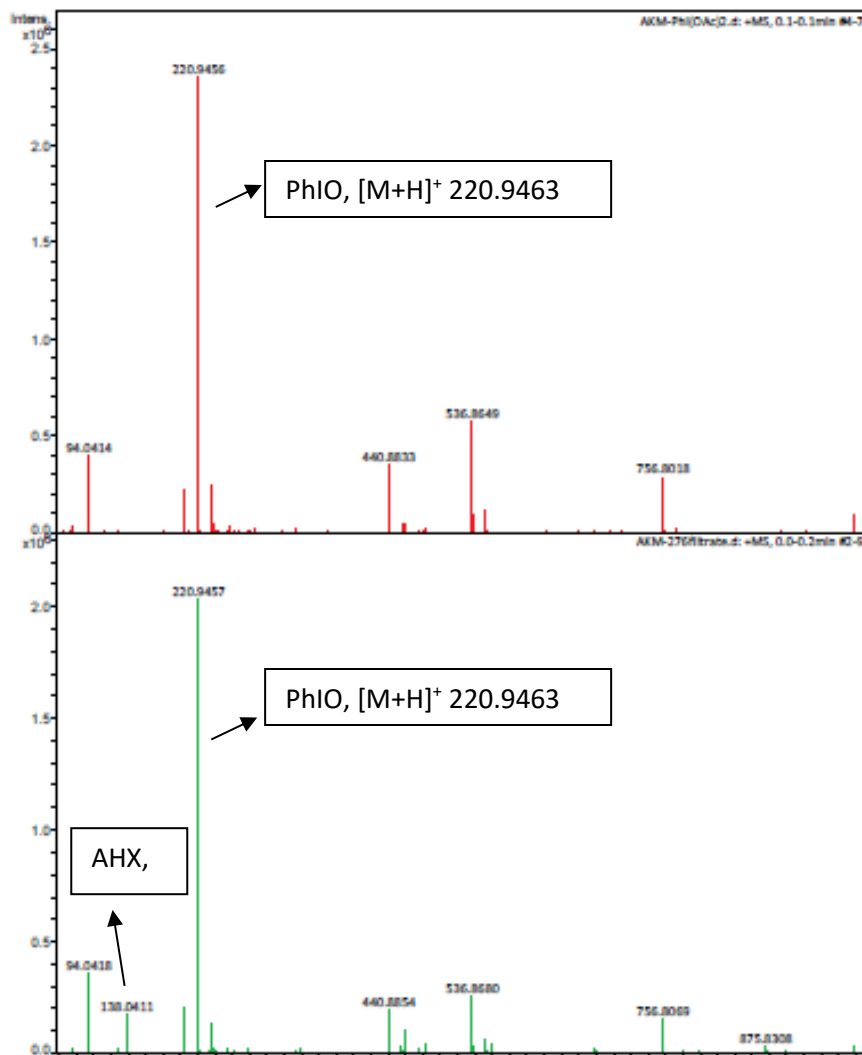


Figure S21. (a) Mass spectrum of PhI(OAc)₂ in water. (b) Mass spectrum of reaction mass

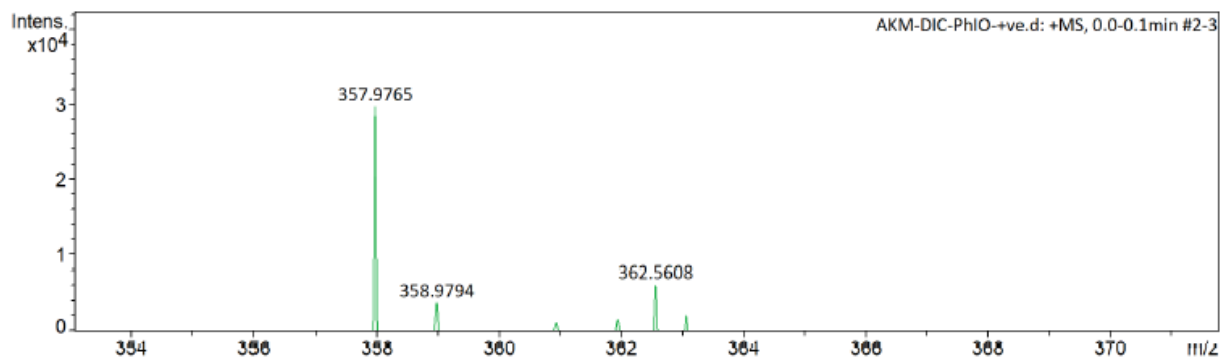


Figure S22. Mass spectra peaks for complex A/B.

References

- 1 M. Gordon, J. G. Miller, A. R. Day. *J. Am. Chem. Soc.* 1948, **70**, 5, 1946–1953
2. T. Kozuka, T. Iio, S. Suzuki, K. Kakiuchi, G. Tadano, K. Sato, T. Narumi and N. Mase, *Bull. Chem. Soc. Jpn.*, 2023, **96**, 752–758

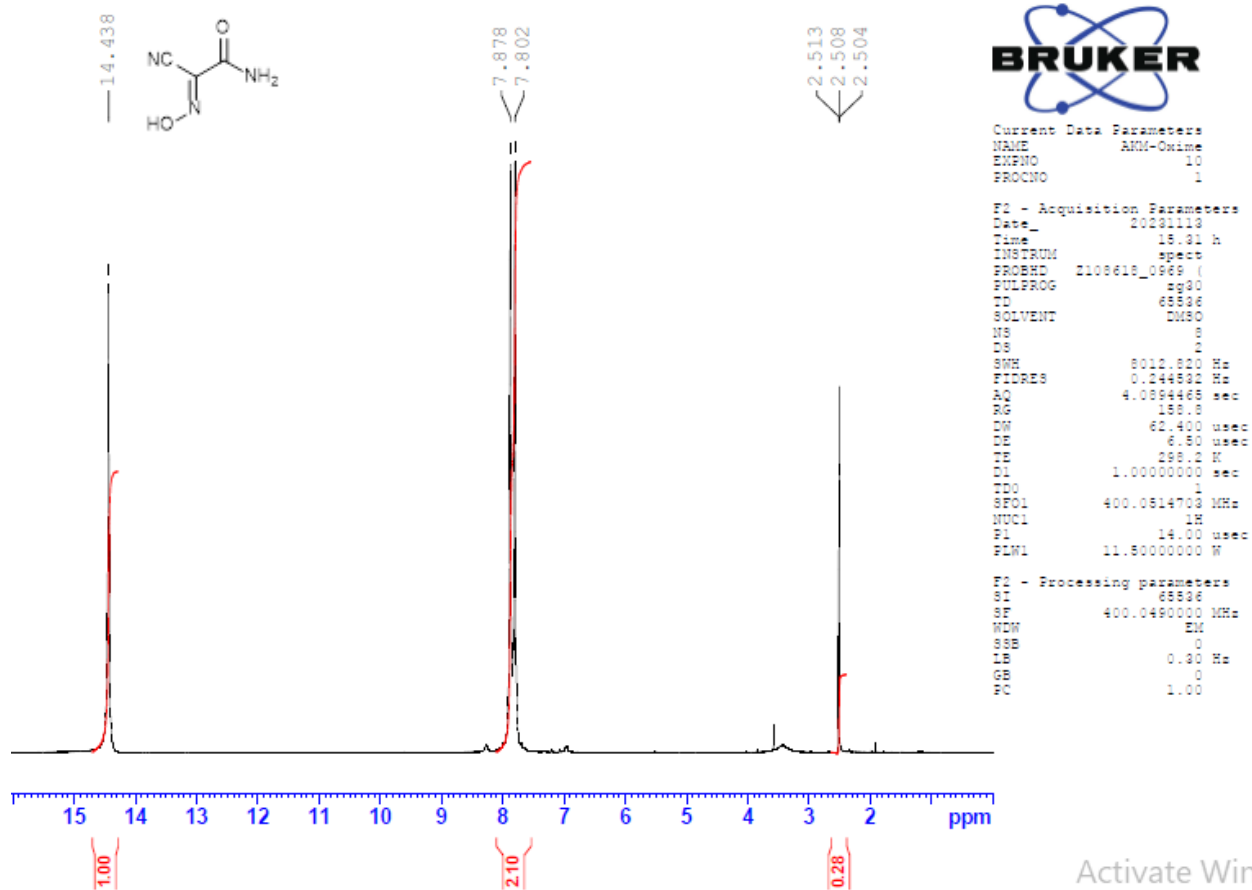
Compound Data

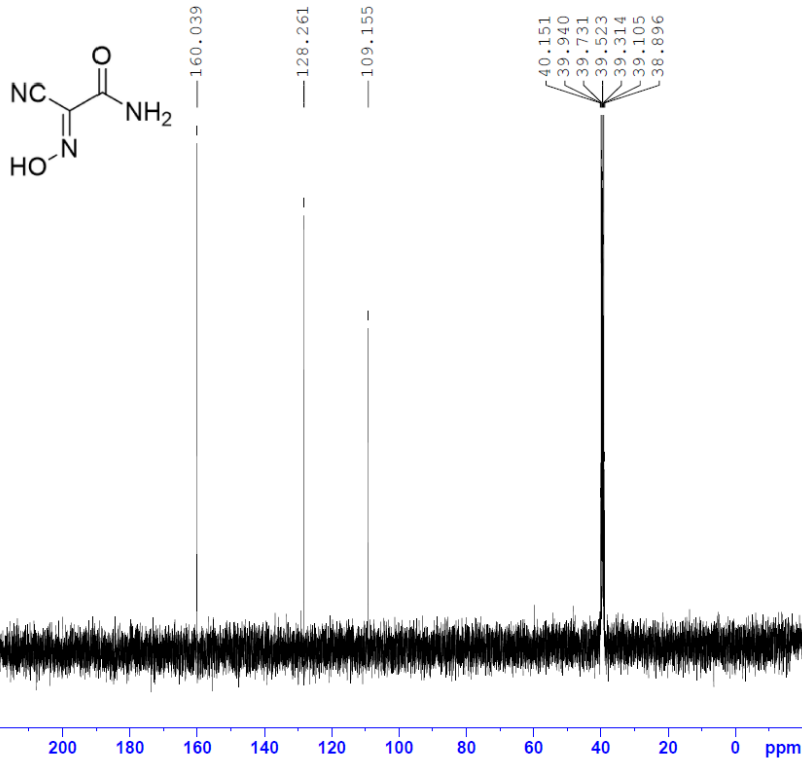
2-Amino-N-hydroxy-2-oxoacetimidoyl cyanide (10)

Chemical Formula: $C_3H_3N_3O_2$,

1H NMR (DMSO- d_6 , 400 MHz) δ 7.88 (s, 1H, -NH $_2$), 7.80 (s, 1H, -NH $_2$), 14.4 (-OH)

^{13}C NMR (DMSO- d_6 100 MHz) δ 109.2 (CN), 128.3 (C), 160.0 (CO)





Current Data Parameters
 NAME DM344
 EXPNO 11
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20210115
 Time_ 17.14 h
 INSTRUM spect
 PROBHD z150365_0005 ()
 PULPROG zgpg30
 TD 65536
 SOLVENT DMSO
 NS 512
 DS 4
 SMH 24938.461 Hz
 FIDRES 0.733596 Hz
 AQ 1.3631498 sec
 RG 204.68
 DW 20.800 usec
 DE 18.00 usec
 TE 299.2 K
 DL 2.00000000 sec
 D11 0.03000000 sec
 TD0 1
 SF01 100.6228298 MHz
 NUC1 13C
 P1 10.50 usec
 PLW1 36.68799973 W
 SF02 400.1316005 MHz
 NUC2 1H
 CPDPRG2 waltz16
 PCPD2 80.00 usec
 PLW2 7.25239992 W
 PLW12 0.16317999 W
 PLW13 0.08194900 W

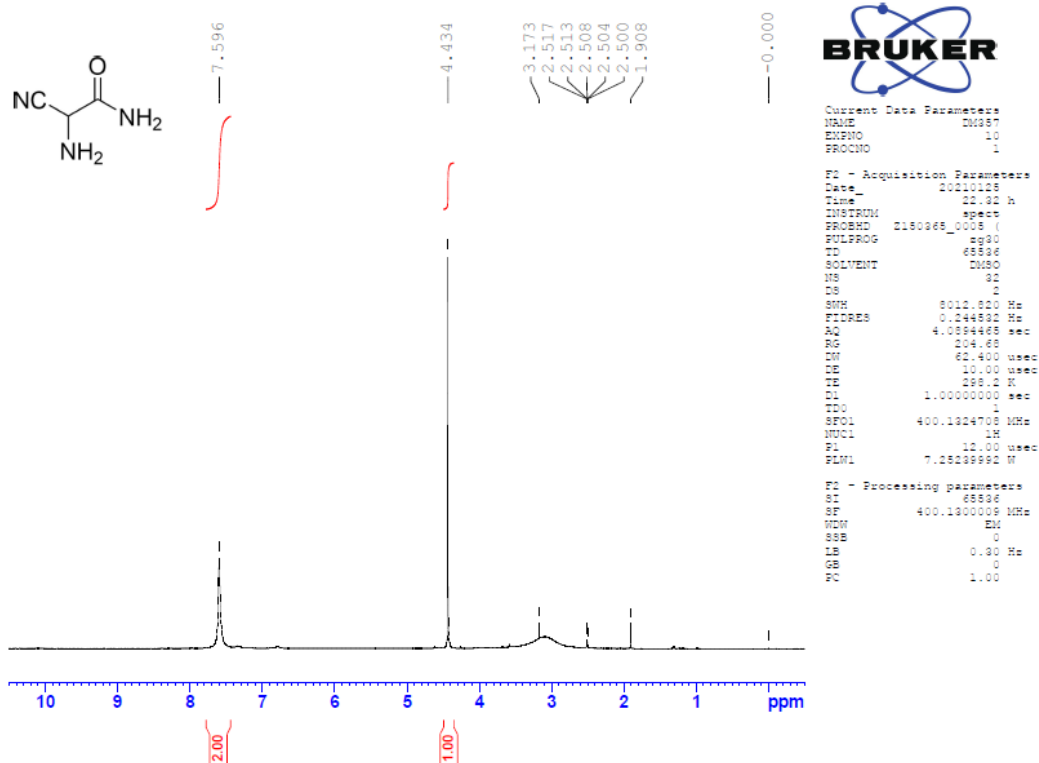
F2 - Processing parameters
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 SF 100.6127685 MHz
 WDW EM
 SSB 0
 LB 1.00 Hz
 GB 0
 PC 1.40

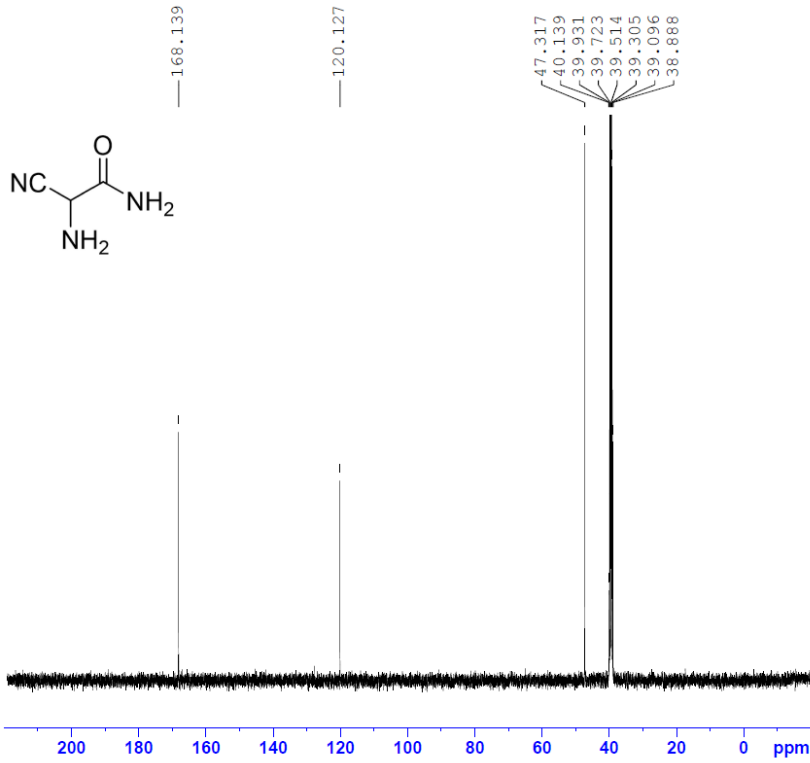
2-Amino-2-cyanoacetamide (13)

Chemical Formula: $C_3H_5N_3O$

1H NMR (DMSO- d_6 , 400 MHz,) δ 4.43 (s, 1H, -CH-), 7.60 (br, 2H, -CONH $_2$)

^{13}C NMR (DMSO- d_6 100 MHz) δ 47.3 (CH), 120.1 (CN), 168.1 (CO)





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Current Data Parameters
NAME      DM357
EXPNO    11
PROCNO    1

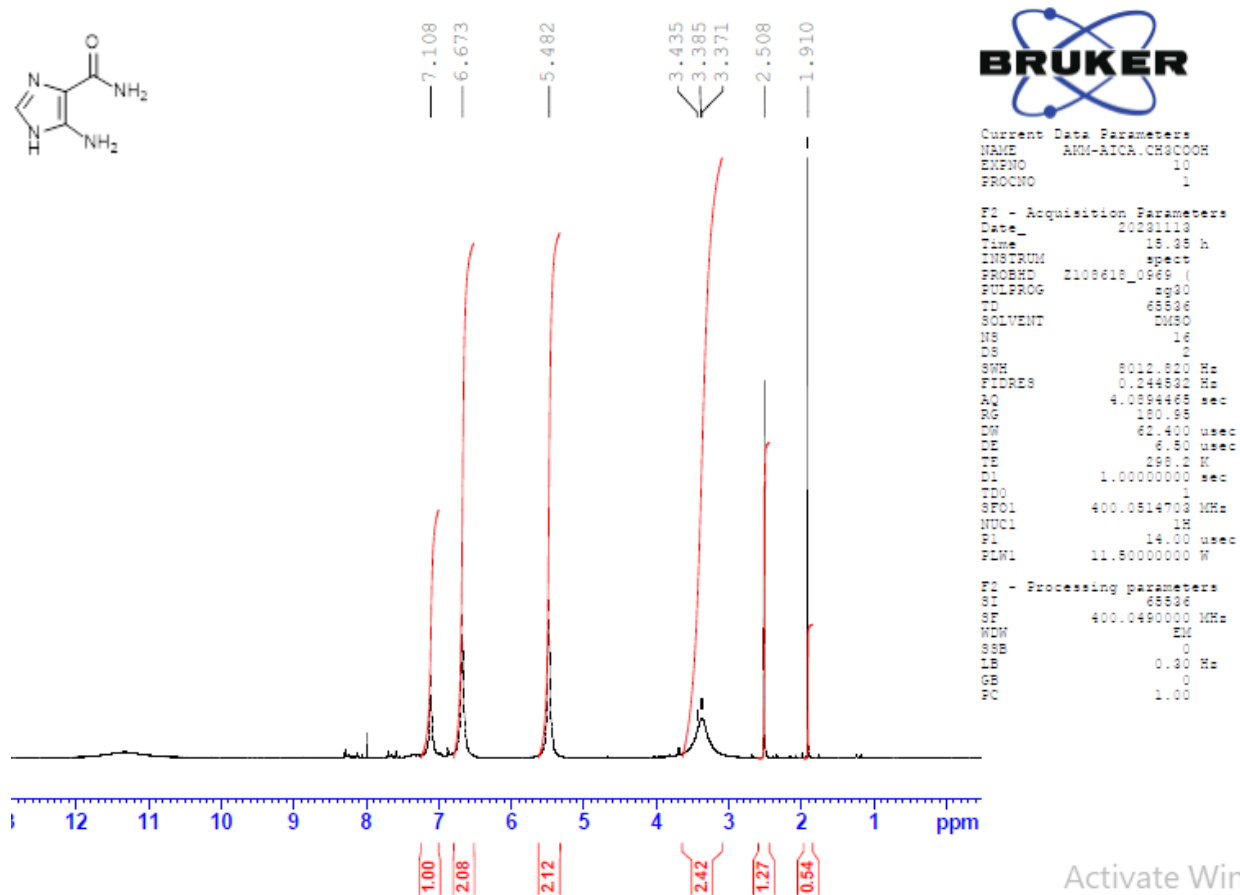
F2 - Acquisition Parameters
Date_    20210126
Time     0.31 h
INSTRUM  spect
PROBHD   Z150365_0005 (
PULPROG  zgpg30
TD       65536
SOLVENT  DMSO
NS       2048
DS       4
SWH      24038.461 Hz
FIDRES   0.733586 Hz
AQ       1.3631488 sec
RG       204.68
DW       20.800 usec
DE       18.00 usec
TE       299.1 K
DL       2.00000000 sec
D11      0.03000000 sec
TD0      1
SFO1     100.6228298 MHz
NUC1     13C
PI       10.50 usec
PLW1     36.68799973 W
SFO2     400.1316005 MHz
NUC2     1H
CPDPRG2  waltz16
PCPD2    80.00 usec
PLW2     7.25239982 W
PLW12    0.16317999 W
PLW13    0.08194900 W

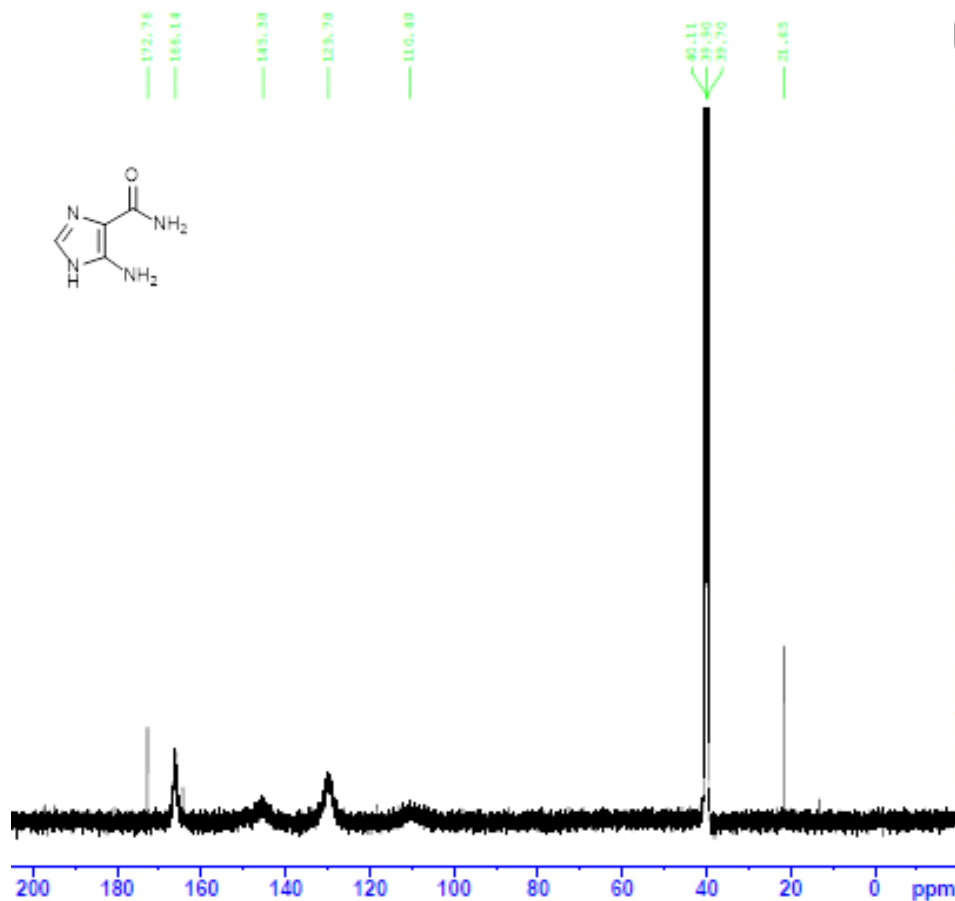
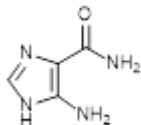
F2 - Processing parameters
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SF       100.6128110 MHz
WDW      EM
SSB      0
LB       1.00 Hz
GB       0
PC       1.40
  
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5-Amino-1H-imidazole-4-carboxamide (AICA, 4)

Chemical Formula: C₄H₆N₄O

¹H-NMR (400 MHz, DMSO-d₆), δ_H: 5.48 (2H, br, -NH₂), 6.67 (2H, br, -CONH₂), 7.10 (1H, s, Ar-H), and 11.48 (br, -NH). ¹³C-NMR (100 MHz, DMSO-d₆), δ_C: 110.5 (C), 129.7 (C), 145.3 (CH), 166.1 (CO).





Current Data Parameters
 NAME AJ04-AICA-CH3COOH-con
 EXPNO 20
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20231130
 Time_ 22.00 h
 INSTRUM spect
 PROBRD 2108618_0969 ()
 PULPROG zgpg30
 TD 65536
 SOLVENT DMSO
 NS 4096
 DS 4
 SWH 24038.461 Hz
 FIDRES 0.733596 Hz
 AQ 1.3631488 sec
 RG 158.8
 DW 20.800 usec
 DE 6.50 usec
 TE 298.2 K
 D1 2.0000000 sec
 D11 0.0300000 sec
 TDO 1
 SFO1 100.6024603 MHz
 NUC1 13C
 P1 10.00 usec
 PLW1 57.0000000 W
 SFO2 400.0506002 MHz
 NUC2 1H
 CPOPRG[2] waltz16
 PCPD2 80.00 usec
 PLW2 11.5000000 W
 PLW12 0.27827001 W
 PLW13 0.13997000 W

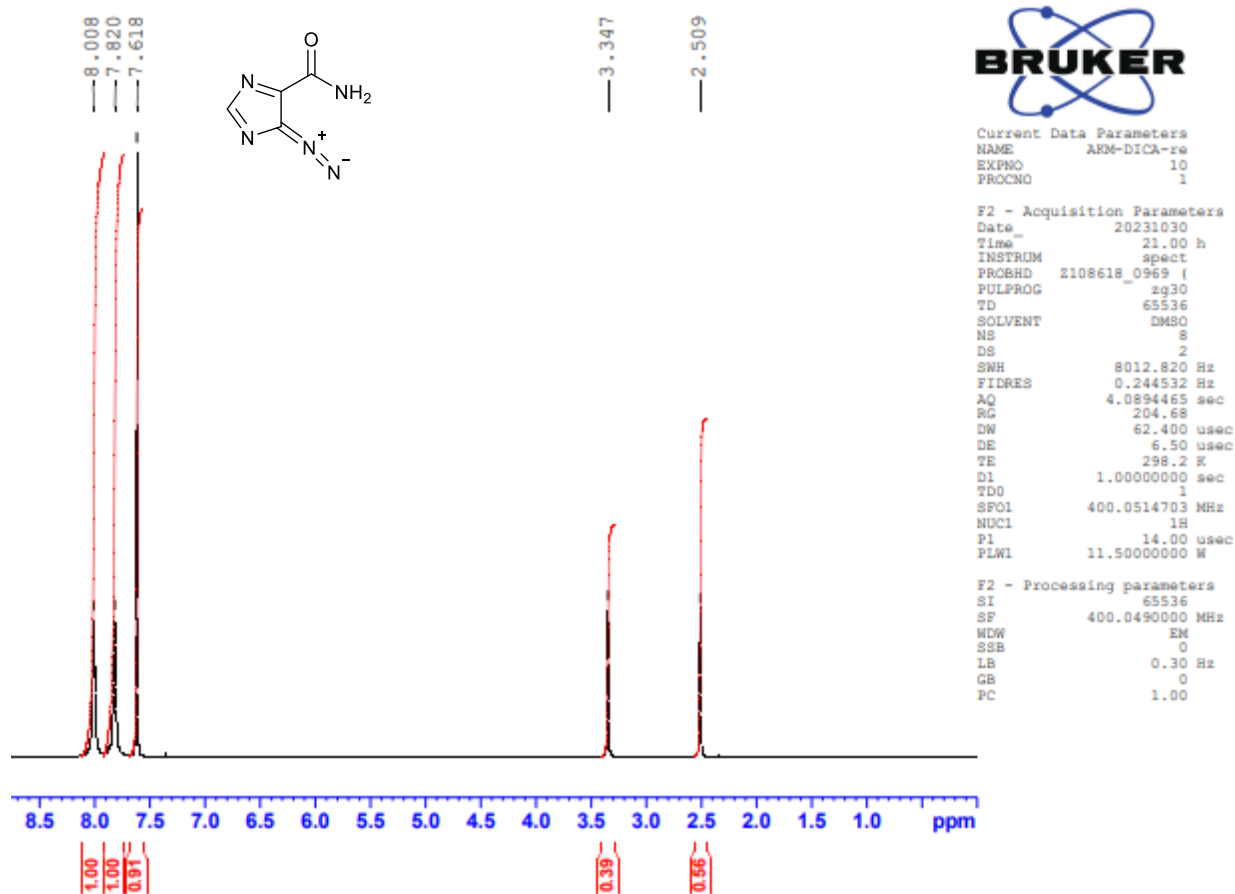
F2 - Processing parameters
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 SF 100.5924011 MHz
 MW EM
 SSB 0
 LB 1.00 Hz
 GB 0
 PC 1.40

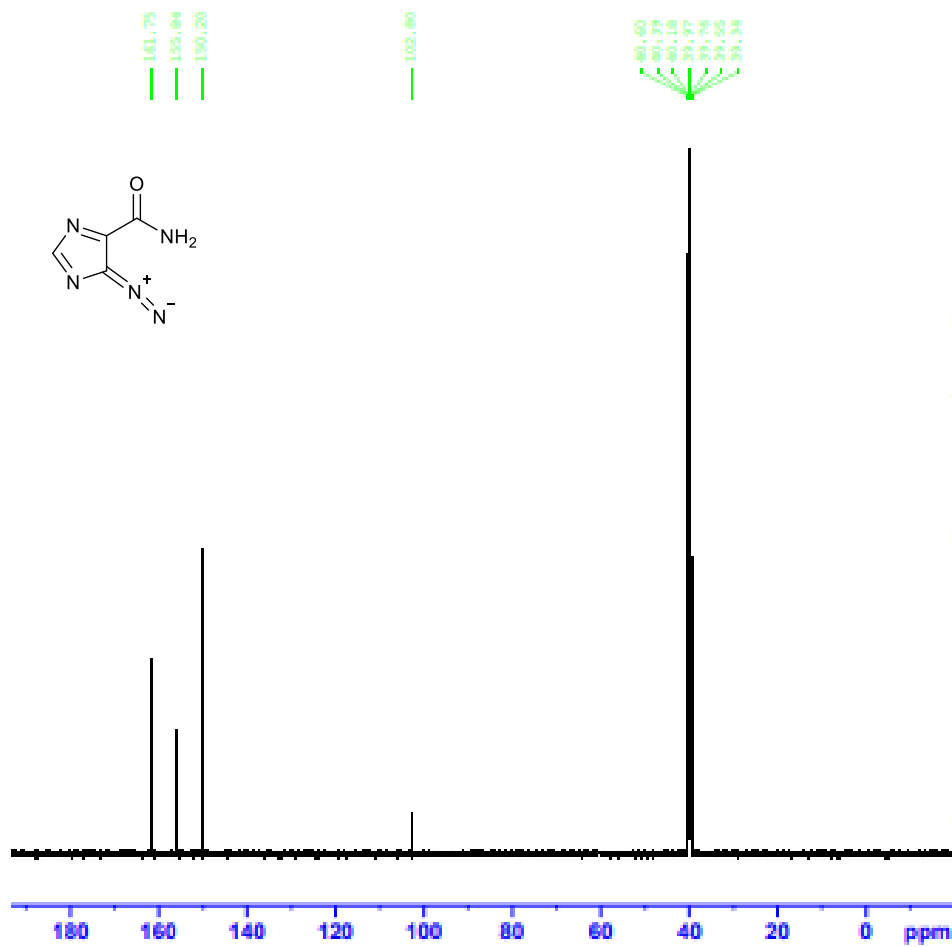
4-Diazo-4H-imidazole-5-carboxamide (DICA, 5)

Chemical Formula: C₄H₃N₅O

¹H NMR (DMSO-d₆, 400 MHz) δ 7.61 (s, 1H, -CH-), 7.82 (s, 1H, -CONH₂), 8.0 (s, 1H, -CONH₂)

¹³C NMR (DMSO-d₆ 100 MHz) δ 102.8 (C-N=N), 150.2 (C-CO), 155.8 (CH), 161.8 (CO)





Current Data Parameters
 NAME AM-01CA-re
 EXPNO 11
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20231010
 Time_ 21.17 h
 INSTRUM spect
 PROBHD Z100C10 0909 (4
 PULPROG _zgpg30
 TD 65536
 SOLVENT H2O
 NS 256
 DS 4
 SWH 34038.441 Hz
 FIDRES 0.733596 Hz
 AQ 1.3631489 sec
 RG 90.35
 DW 20.800 usec
 DE 6.50 usec
 TE 298.2 K
 D1 2.00000000 sec
 D11 0.03000000 sec
 TDD 1
 SFO1 100.624603 MHz
 NUC1 13C
 P1 18.00 usec
 PLN1 37.00000000 W
 SFO2 400.0506002 MHz
 NUC2 1H
 CPDPRG2 waltz16
 PCPD0 90.00 usec
 PLN2 11.50000000 W
 PLN3 0.27827001 W
 PLN4 0.13997000 W

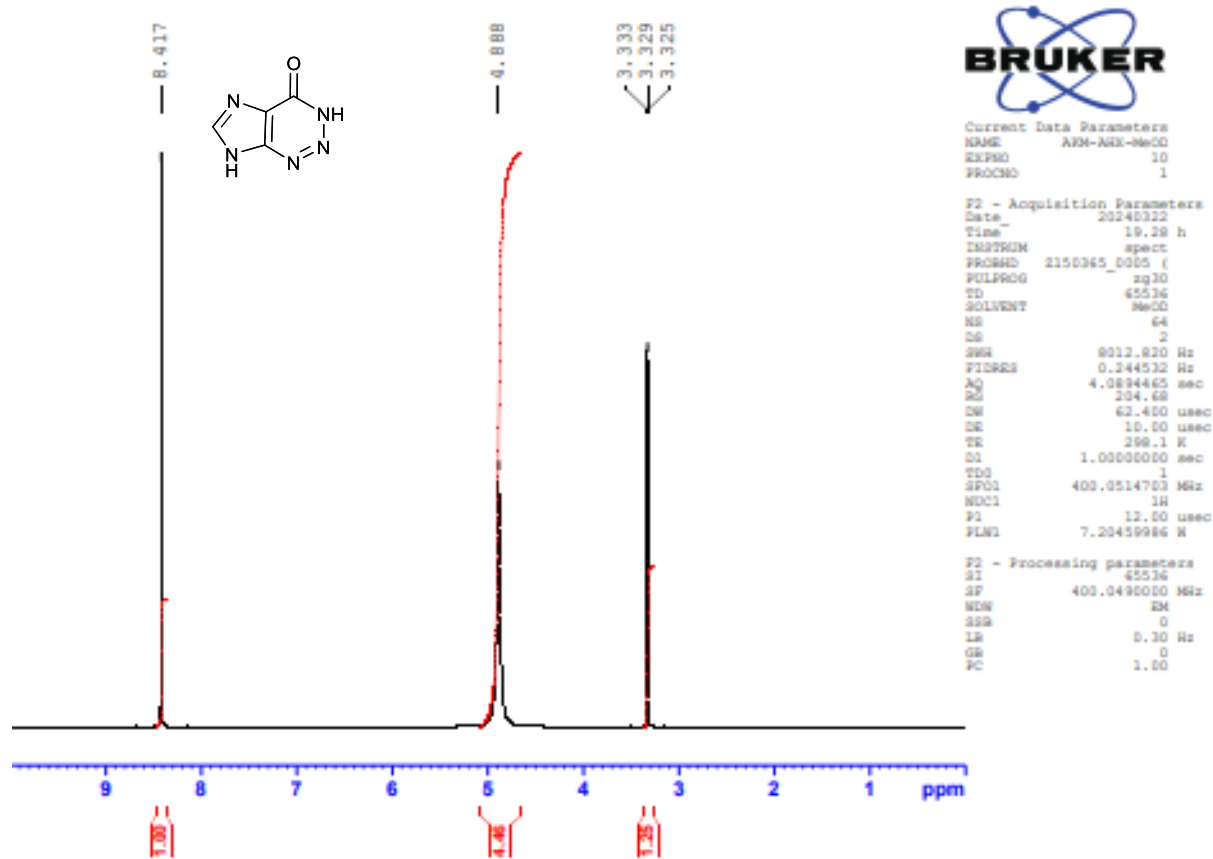
F2 - Processing parameters
 SI 32768
 SF 100.5924011 MHz
 NDN 0
 ZS 0
 LB 1.00 Hz
 GB 0
 PC 1.40

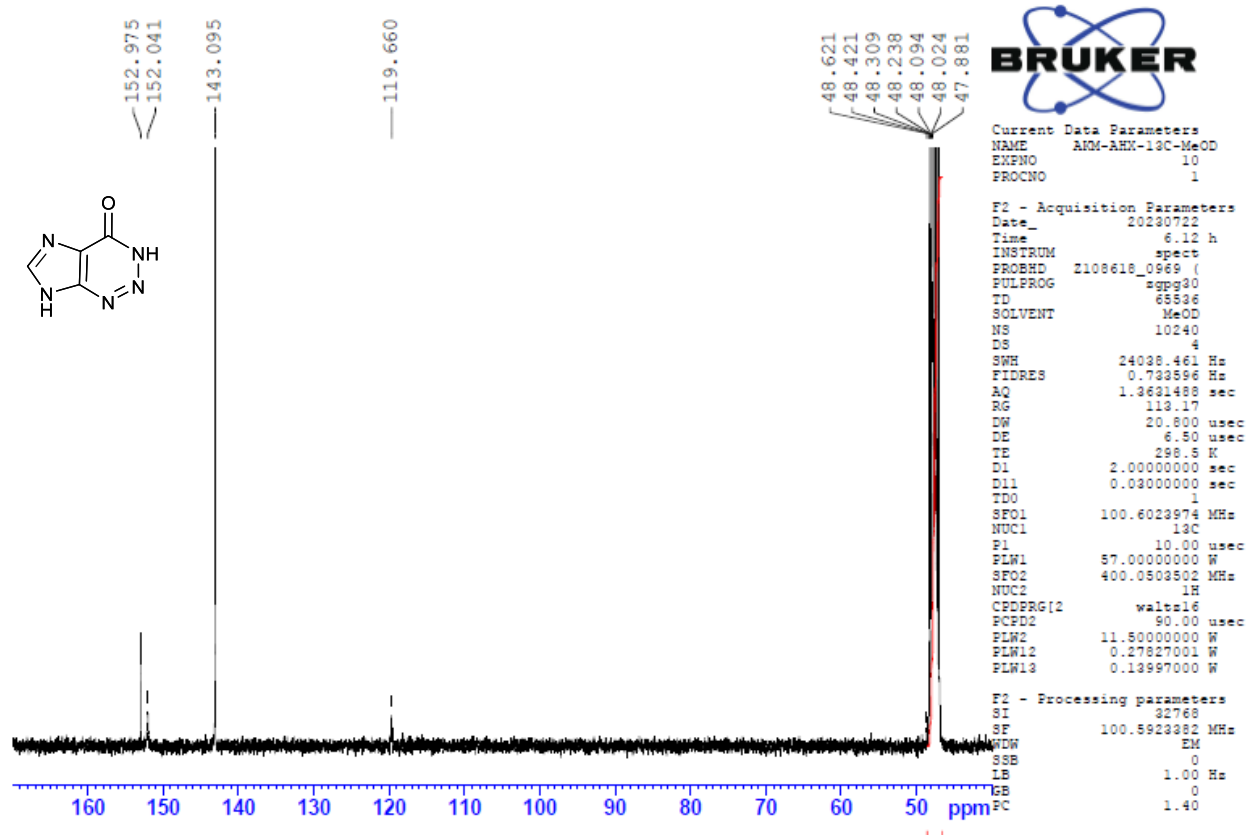
AHX (6)

Chemical Formula: C₄H₃N₅O,

¹H NMR (CD₃OD, 400 MHz) δ 8.41 (s, 1H, -CH-)

¹³C-NMR (100 MHz, CD₃OD), δ_C: 119.7, 143.1, 152.0, 153.0





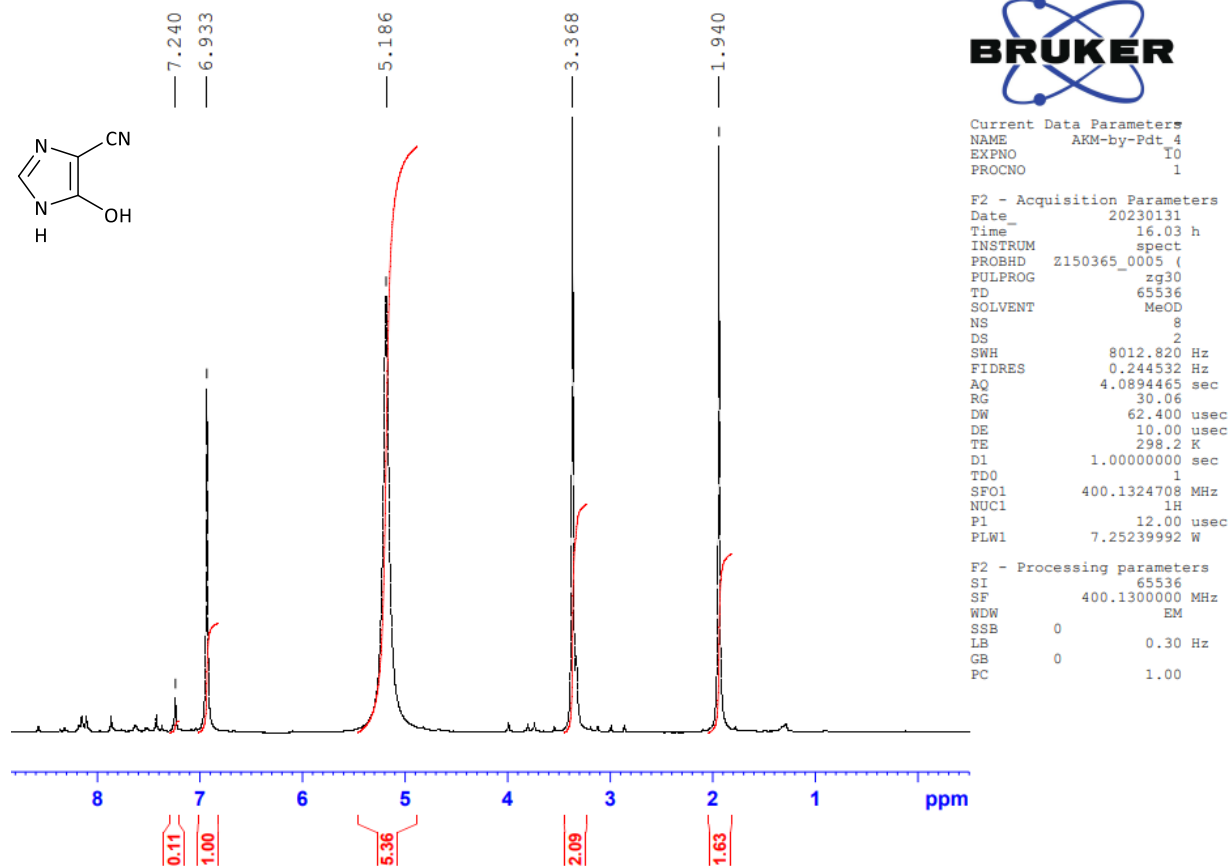
By-product: 5-Hydroxy-1H-imidazole-4-carbonitrile (15)

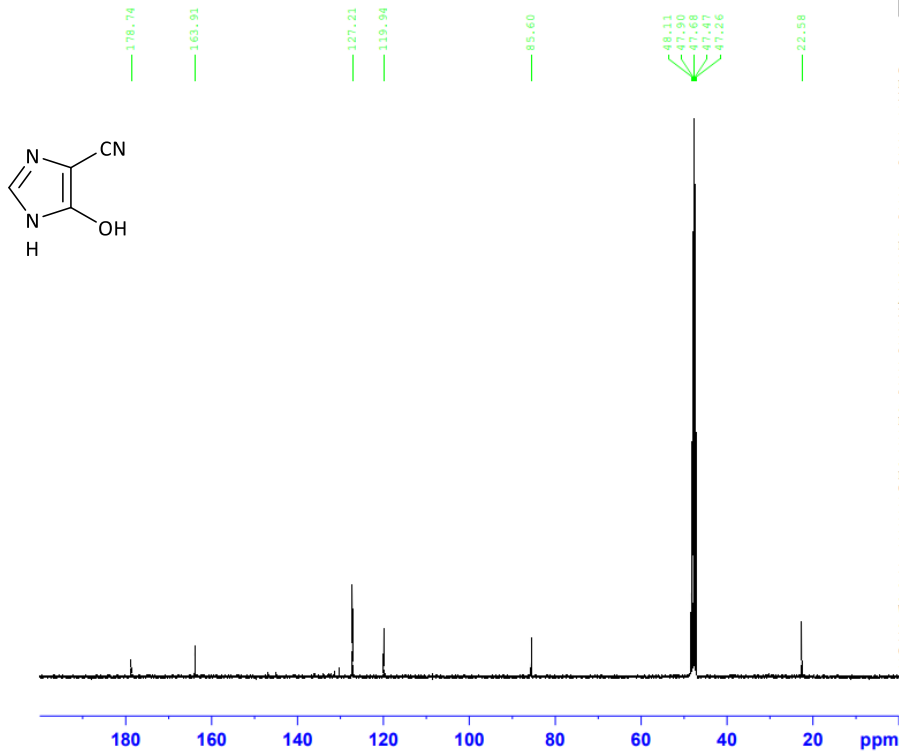
Chemical formula: C₄N₃H₄O,

¹H NMR (CD₃OD, 400 MHz): δ 6.933 (s, 1H, -CH-)

¹³C NMR (CD₃OD, 100 MHz) δ 22.6, 85.6, 119.9, 127.2, 163.9, 178.7

DEPT 135(CD₃OD, 100 MHz) δ 22.6, 127.2, DEPT 90 (CD₃OD, 100 MHz) δ 127.2

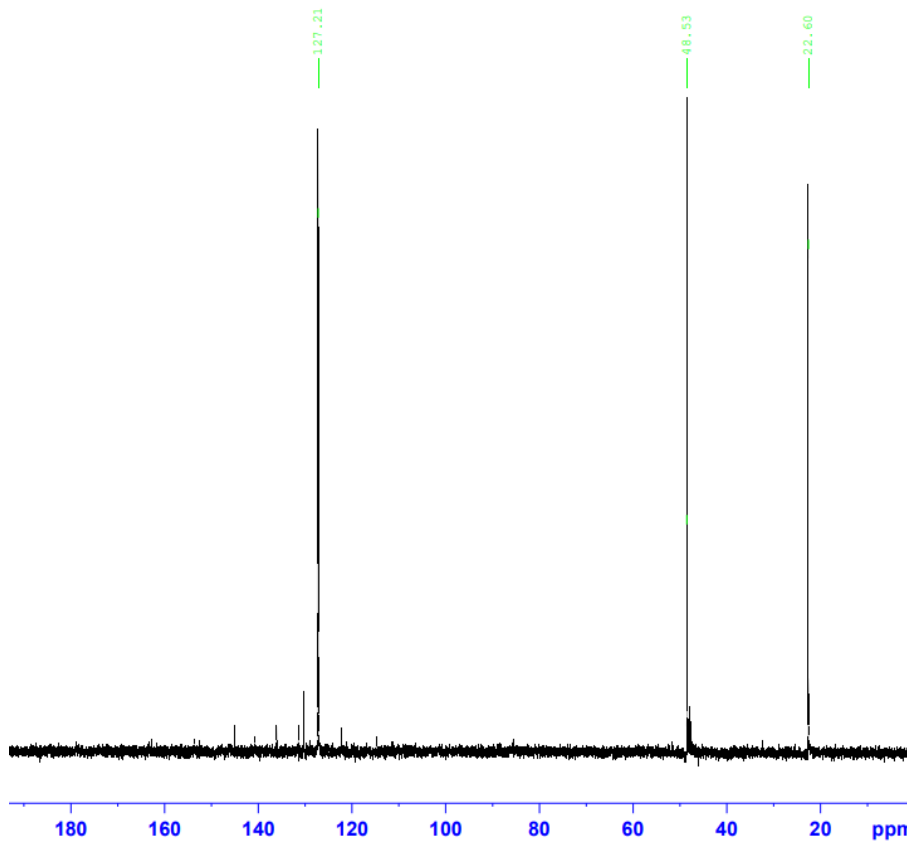




Current Data Parameters
 NAME AKM-By-Pdt
 EXPNO 31
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20230130
 Time_ 17.53 h
 INSTRUM spect
 PROBHD Z150365_0005 (
 PULPROG zgpg30
 TD 65536
 SOLVENT MeOD
 NS 64
 DS 4
 SWH 24038.461 Hz
 FIDRES 0.733596 Hz
 AQ 1.3631488 sec
 RG 49.46
 DW 20.800 usec
 DE 18.00 usec
 TE 298.1 K
 D1 2.00000000 sec
 D11 0.03000000 sec
 TD0 1
 SFO1 100.6228298 MHz
 NUC1 13C
 P1 10.50 usec
 PLW1 36.68799973 W
 SFO2 400.1316005 MHz
 NUC2 1H
 CPDPRG2 waltz16
 PCPD2 80.00 usec
 PLW2 7.25239992 W
 PLW12 0.16317999 W
 PLW13 0.08194900 W

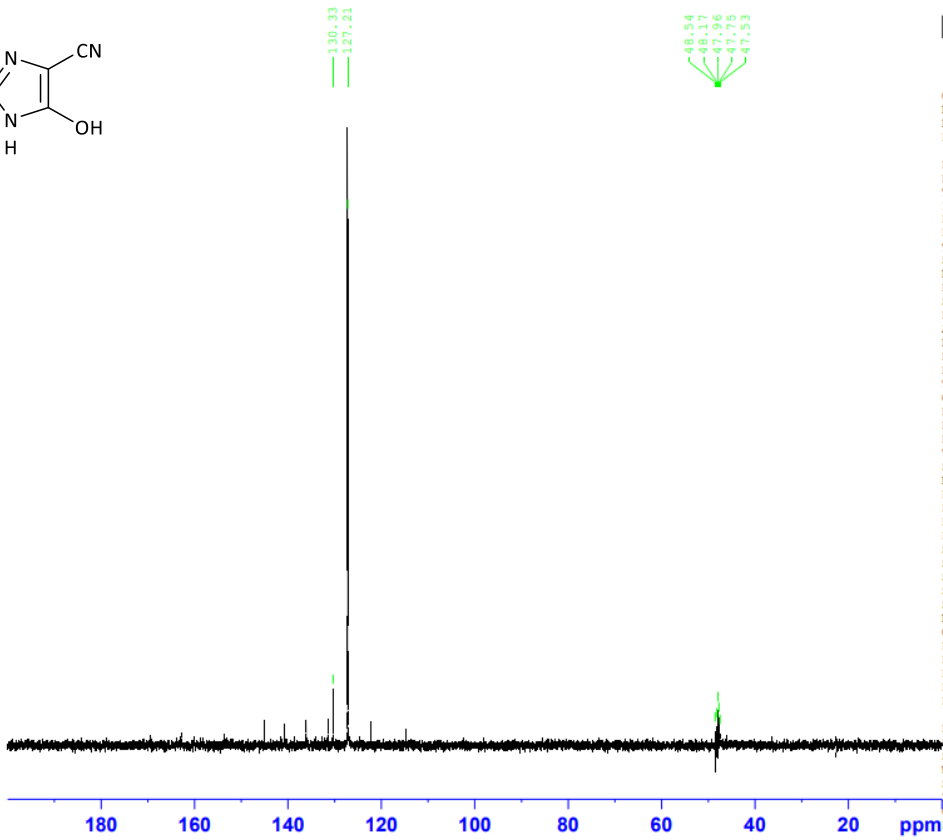
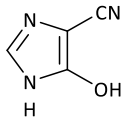
F2 - Processing parameters
 SI 32768
 SF 100.6127685 MHz
 WDW EM
 SSB 0
 LB 1.00 Hz
 GB 0
 PC 1.40



Current Data Parameters
 NAME AKM-by-Pdt_2
 EXPNO 10
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20230131
 Time_ 15.34 h
 INSTRUM spect
 PROBHD Z150365_0005 (
 PULPROG deptsp135
 TD 65536
 SOLVENT MeOD
 NS 128
 DS 8
 SWH 24038.461 Hz
 FIDRES 0.733596 Hz
 AQ 1.3631488 sec
 RG 204.68
 DW 20.800 usec
 DE 18.00 usec
 TE 298.1 K
 CNST2 145.0000000
 D1 2.00000000 sec
 D2 0.00344828 sec
 D12 0.00002000 sec
 TD0 1
 SFO1 100.6228298 MHz
 NUC1 13C
 P1 10.50 usec
 P13 2000.00 usec
 PLM0 0 W
 PLW1 36.68799973 W
 SPNAM[5] Crp60comp.4
 SPOAL5 0.500
 SPOFFS5 0 Hz
 SFW5 6.18020010 W
 SFO2 400.1316005 MHz
 NUC2 1H
 CPDPRG2 waltz16
 P3 12.00 usec
 P4 24.00 usec
 PCPD2 80.00 usec
 PLW2 7.25239992 W
 PLW12 0.16317999 W

F2 - Processing parameters
 SI 32768
 SF 100.6127685 MHz
 WDW EM
 SSB 0
 LB 1.00 Hz
 GB 0
 PC 1.40



```

Current Data Parameters
NAME          AKM-By-Pdt
EXPNO        11
PROCNO       1

F2 - Acquisition Parameters
Date_        20230131
Time         15.42 h
INSTRUM      spect
PROBHD       z150365_0005 (
PULPROG      dEptsp90
TD           65536
SOLVENT      MeOD
NS           128
DS           8
SWH          24038.461 Hz
FIDRES       0.733596 Hz
AQ           1.3631488 sec
RG           35.06
DW           20.800 usec
DE           18.00 usec
TE           298.1 K
CNST2        145.0000000
D1           2.00000000 sec
D2           0.00344828 sec
D12          0.00002000 sec
TD0          1
SFO1         100.6228298 MHz
NUC1         13C
P1           10.50 usec
P13         2000.00 usec
PLW0         0 W
PLW1         36.68799973 W
SPNAM[5]    Crp60comp.4
SPOALS       0.500
SPOFFS5      0 Hz
SPW5         6.18020010 W
SFO2         400.1316005 MHz
NUC2         1H
CPDPRG[2]   waltz16
P3           12.00 usec
P4           24.00 usec
PCPD2       80.00 usec
PLW2         7.25239992 W
PLW12        0.16317999 W

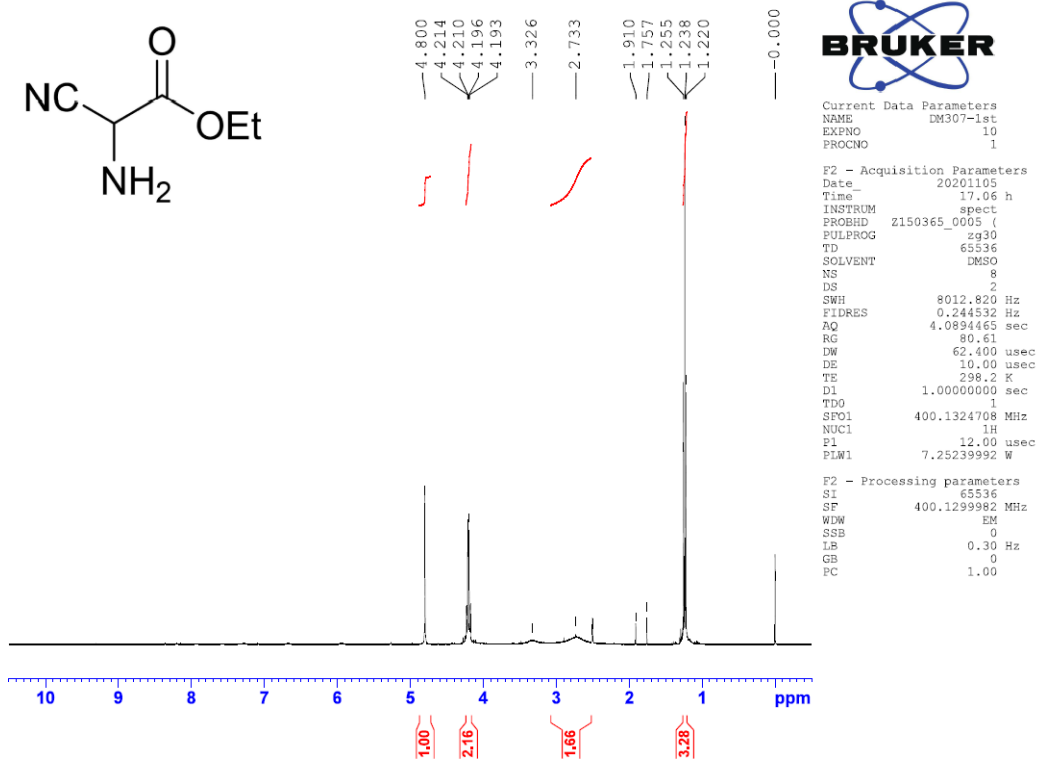
F2 - Processing parameters
SI           32768
SF           100.6127685 MHz
WDW          EM
SSB          0
LB           1.00 Hz
GB          0
PC           1.40
  
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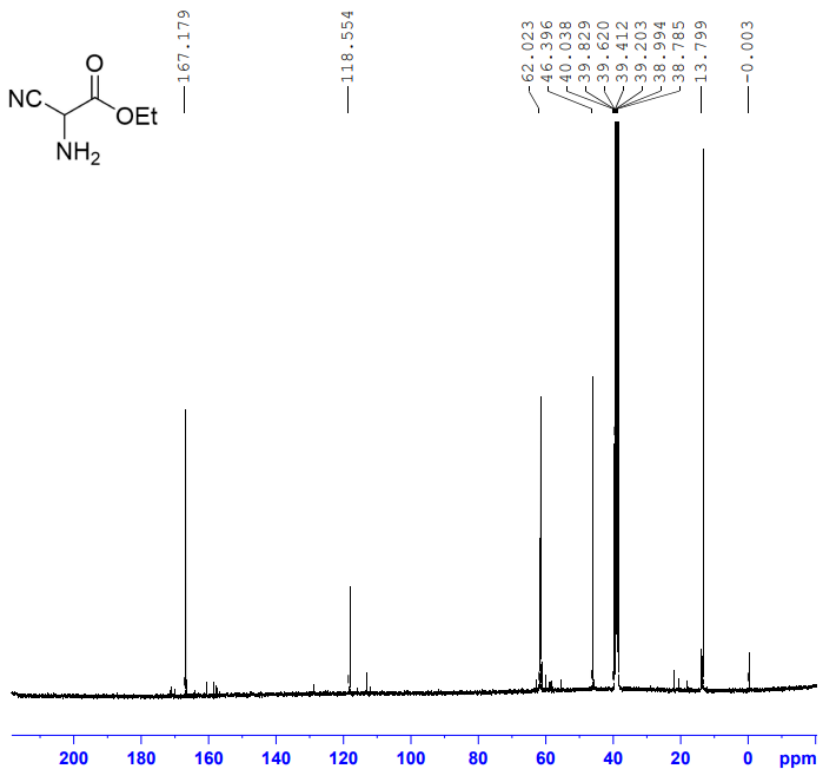
Ethyl 2-amino-2-cyanoacetate (19)

Chemical Formula: $C_5H_8N_2O_2$,

1H NMR (400 MHz, DMSO- d_6) δ 1.23 (t, 3H), 4.20 (q, 2H)

^{13}C NMR (DMSO- d_6 100 MHz) δ 13.8 (CH_3), 46.4 (CH_2), 62.0 (CH), 118.6 (CN), 167.2 (CO)





Current Data Parameters
 NAME DM307-1st
 EXPNO 11
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20201110
 Time 10.28 h
 INSTRUM spect
 PROBHD z150365_0005 ()
 PULPROG zgpg30
 TD 65536
 SOLVENT DMSO
 NS 1024
 DS 4
 SWH 24038.461 Hz
 FIDRES 0.733596 Hz
 AQ 1.3631488 sec
 RG 35.06
 DW 20.800 usec
 DE 18.00 usec
 TE 298.2 K
 D1 2.0000000 sec
 D11 0.0300000 sec
 TDO 1
 SFO1 100.6228298 MHz
 NUC1 13C
 P1 10.50 usec
 PLW1 36.68799973 W
 SFO2 400.1316005 MHz
 NUC2 1H
 CPDPRG[2] waltz16
 PCPD2 80.00 usec
 PLW2 7.25239992 W
 PLW12 0.16317999 W
 PLW13 0.08194900 W

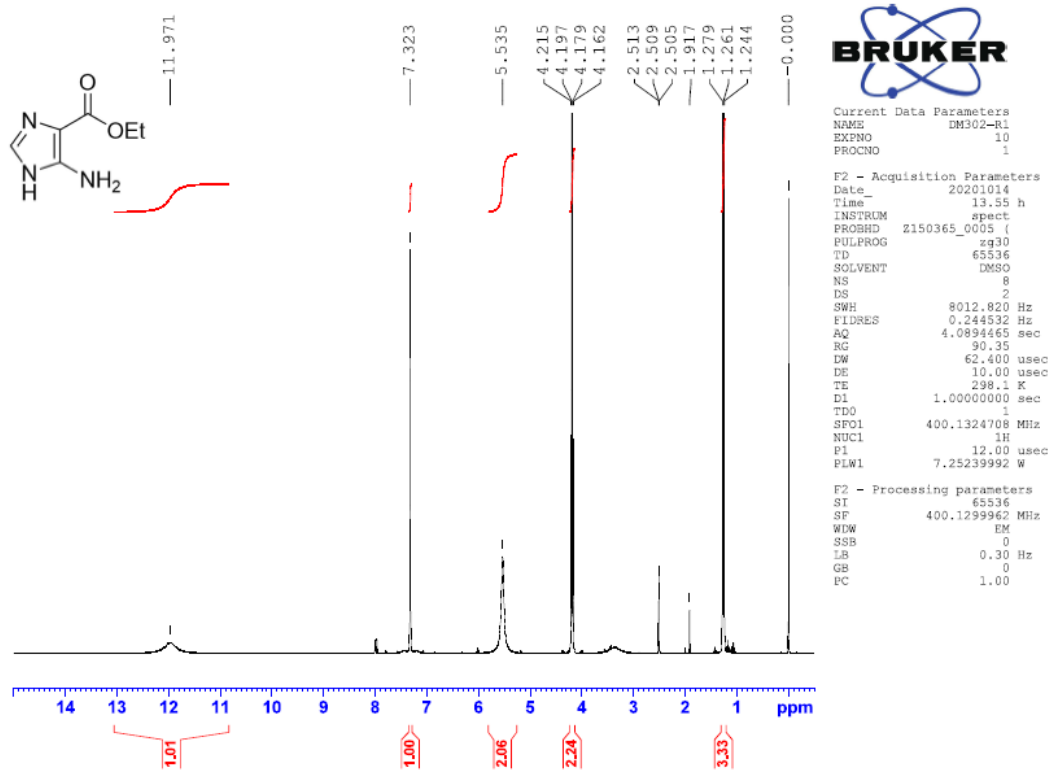
F2 - Processing parameters
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 SF 100.6128745 MHz
 WDW EM
 SSB 0
 LB 1.00 Hz
 GB 0
 PC 1.40

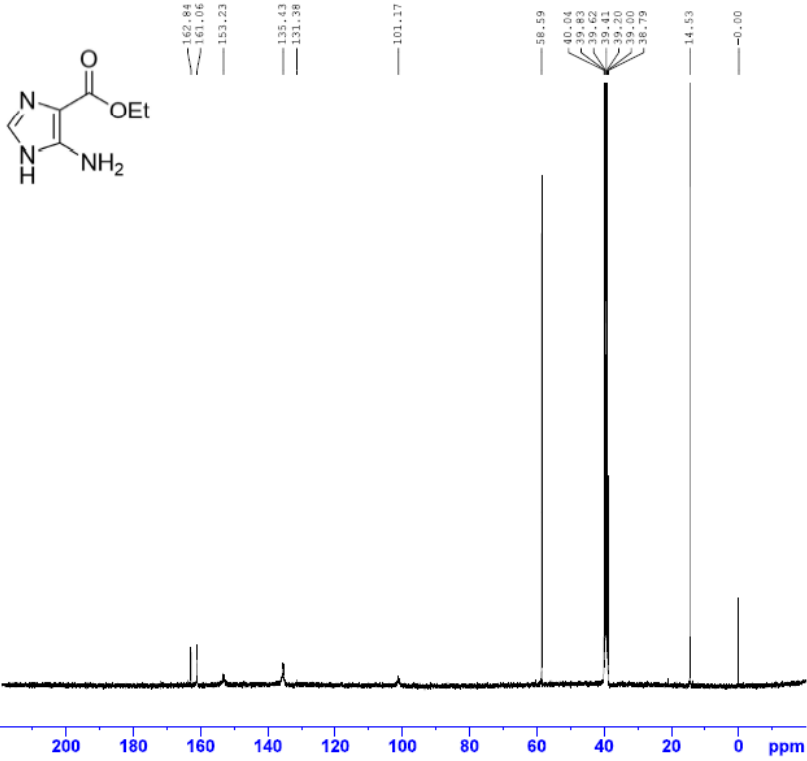
Ethyl 5-aminoimidazole-4-carboxylate (20)

Chemical Formula: $C_6H_9N_3O_2$, $R_f = 0.50$ (AcOEt : MeOH = 90 : 10)

1H NMR (DMSO- d_6 , 400 MHz) δ 1.26 (t, $J = 7.2$, 3H, $-CH_3$), 4.20 (q, $J = 7.2$, 2H, $-CH_2-$), 5.54 (br, 2H, $-NH_2$), 7.32 (s, 1H, Ar-H), 11.97 (br, 1H, $-NH-$)

^{13}C NMR (DMSO- d_6 100 MHz) δ 161.1, 162.84 (C=O), 153.2 (N=C-N), 135.4 (N-C-N), 101.2 (C-CO), 58.6 ($-CH_2-$), 14.5 ($-CH_3$)





Current Data Parameters
 NAME DM302-R1
 EXPNO 11
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20201014
 Time_ 14.26 h
 INSTRUM spect
 PROBHD z150365_0005 (zppg30
 PULPROG zgpg30
 TD 65536
 SOLVENT DMSO
 NS 512
 DS 4
 SWH 24038.461 Hz
 FIDRES 0.733596 Hz
 AQ 1.3631488 sec
 RG 43.17
 LW 20.800 usec
 DE 18.00 usec
 TE 298.1 K
 D1 2.0000000 sec
 D11 0.0300000 sec
 TD0 1
 SFO1 100.6228298 MHz
 NUC1 13C
 P1 10.50 usec
 PLW1 36.68799973 W
 SFO2 400.1316005 MHz
 NUC2 1H
 CFP2PRG2 waltz16
 PCPD2 80.00 usec
 PLW2 7.25239992 W
 PLW12 0.16317999 W
 PLW13 0.08194900 W

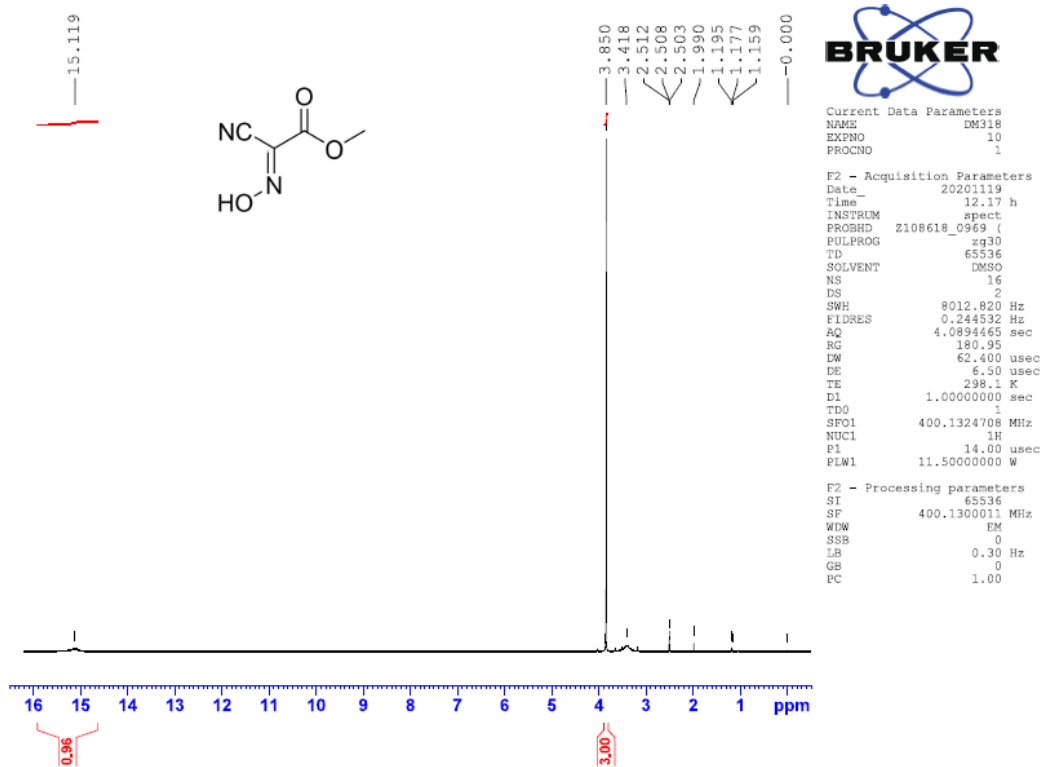
F2 - Processing parameters
 SI 32768
 SF 100.6128228 MHz
 WDW EM
 SSB 0
 LB 1.00 Hz
 GB 0
 PC 1.40

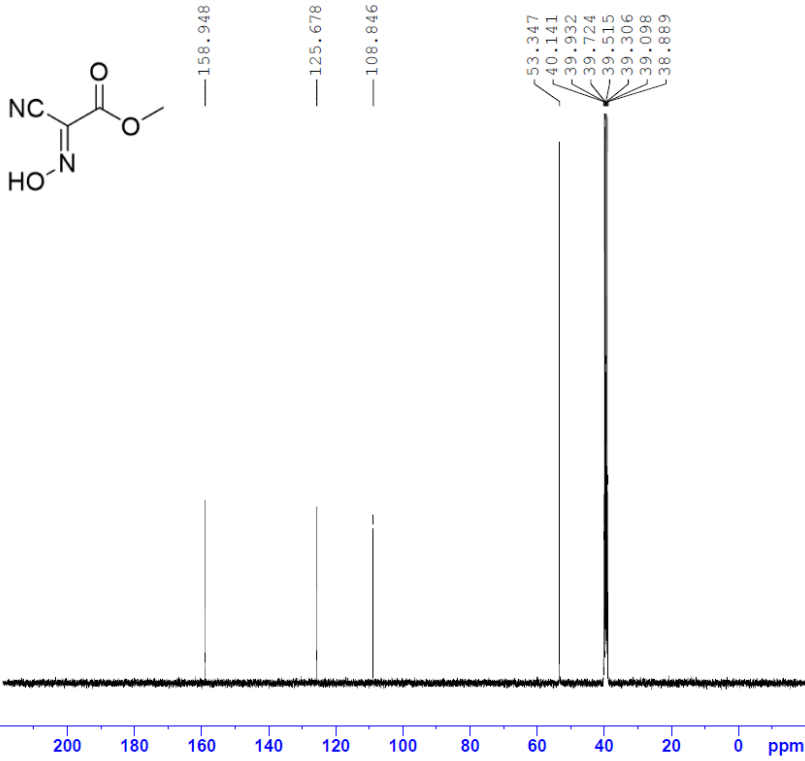
Methyl 2-cyano-2-(hydroxyimino)acetate (22)

Chemical Formula: C₄H₄N₂O₃,

¹H NMR (DMSO-d₆, 400 MHz) δ 3.85 (s, 3H, -CH₃), 15.12 (br, 1H, -OH)

¹³C NMR (DMSO-d₆ 100 MHz) δ 53.4 (CH₃), 108.9 (CN), 125.7 (C), 159.0 (CO)





Current Data Parameters
 NAME DM318
 EXPNO 11
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20201119
 Time 12.48 h
 INSTRUM spect
 PROBEID Z108618_0969 ()
 PULPROG zgpg30
 TD 65536
 SOLVENT DMSO
 NS 512
 DS 4
 SWH 24038.461 Hz
 FIDRES 0.733596 Hz
 AQ 1.3631488 sec
 RG 113.17
 EW 20.800 usec
 DE 6.50 usec
 TE 298.2 K
 D1 2.00000000 sec
 D11 0.03000000 sec
 ID0 1
 SFO1 100.6228298 MHz
 NUC1 13C
 P1 10.00 usec
 PLW1 57.00000000 W
 SFO2 400.1316005 MHz
 NUC2 1H
 CDPFRG(2) waltz16
 PCPD2 90.00 usec
 PLW2 11.50000000 W
 PLW12 0.27827001 W
 PLW13 0.13997000 W

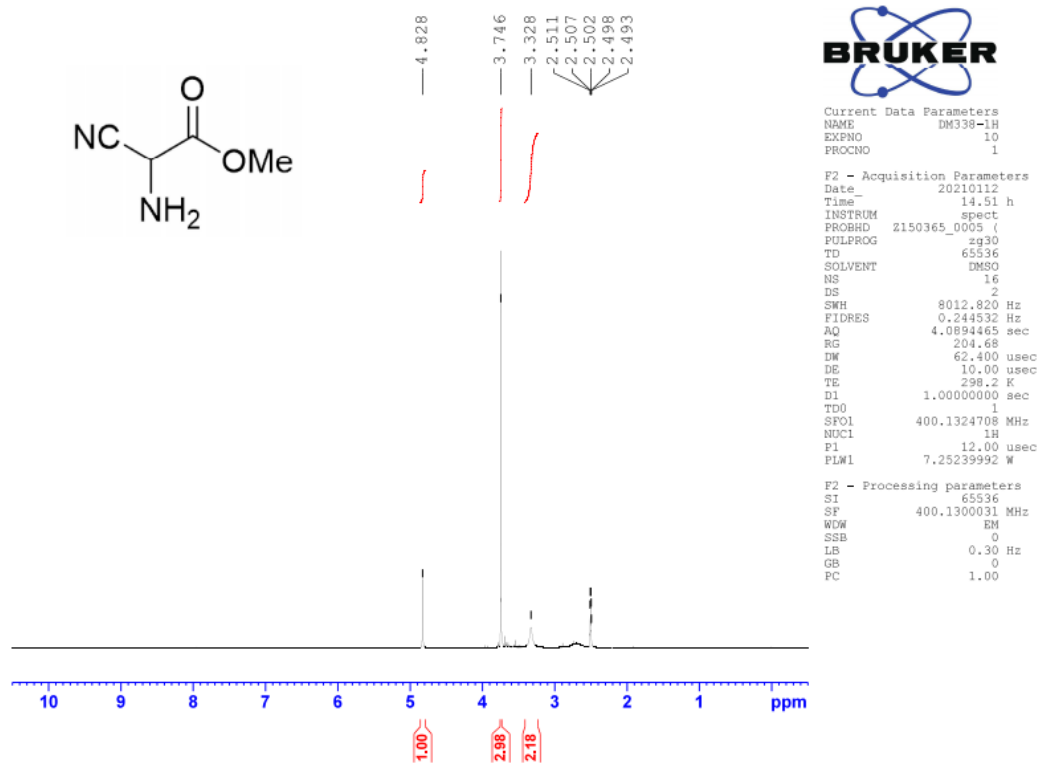
F2 - Processing parameters
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 SF 100.6128132 MHz
 WDW EM
 SSB 0
 LB 1.00 Hz
 GB 0
 PC 1.40

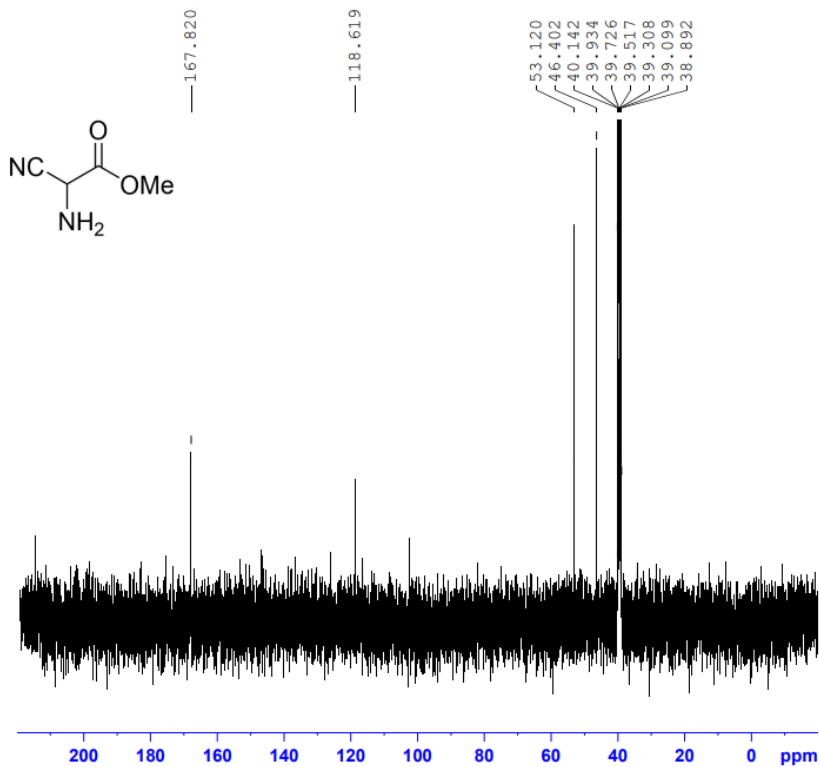
Methyl 2-amino-2-cyanoacetate (23)

Chemical Formula: $C_4H_6N_2O_2$,

1H NMR (DMSO- d_6 , 400 MHz) δ 3.33 (br, 2H, $-NH_2$), 3.75 (s, 3H, $-OMe$), 4.83 (s, 1H, $-CH-$)

^{13}C NMR (DMSO- d_6 100 MHz) δ 46.4 (CH $_3$), 53.1 (CH), 118.6 (CN), 167.8 (CO)





Current Data Parameters
 NAME DM338-13C
 EXPNO 10
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20210112
 Time_ 19.49 h
 INSTRUM spect
 PROBHD z150365_0005 ()
 PULPROG zgpg30
 TD 65536
 SOLVENT DMSO
 NS 1024
 DS 4
 SWH 24038.461 Hz
 FIDRES 0.733596 Hz
 AQ 1.3631488 sec
 RG 204.68
 DW 20.800 usec
 DE 18.00 usec
 TE 298.2 K
 D1 2.0000000 sec
 D11 0.03000000 sec
 TD0 1
 SFO1 100.6228298 MHz
 NUC1 13C
 P1 10.50 usec
 PLW1 36.68799973 W
 SFO2 400.1316005 MHz
 NUC2 1H
 CPDPRG2 walzr16
 PCPD2 80.00 usec
 PLW2 7.25239992 W
 PLW12 0.16317999 W
 PLW13 0.08194900 W

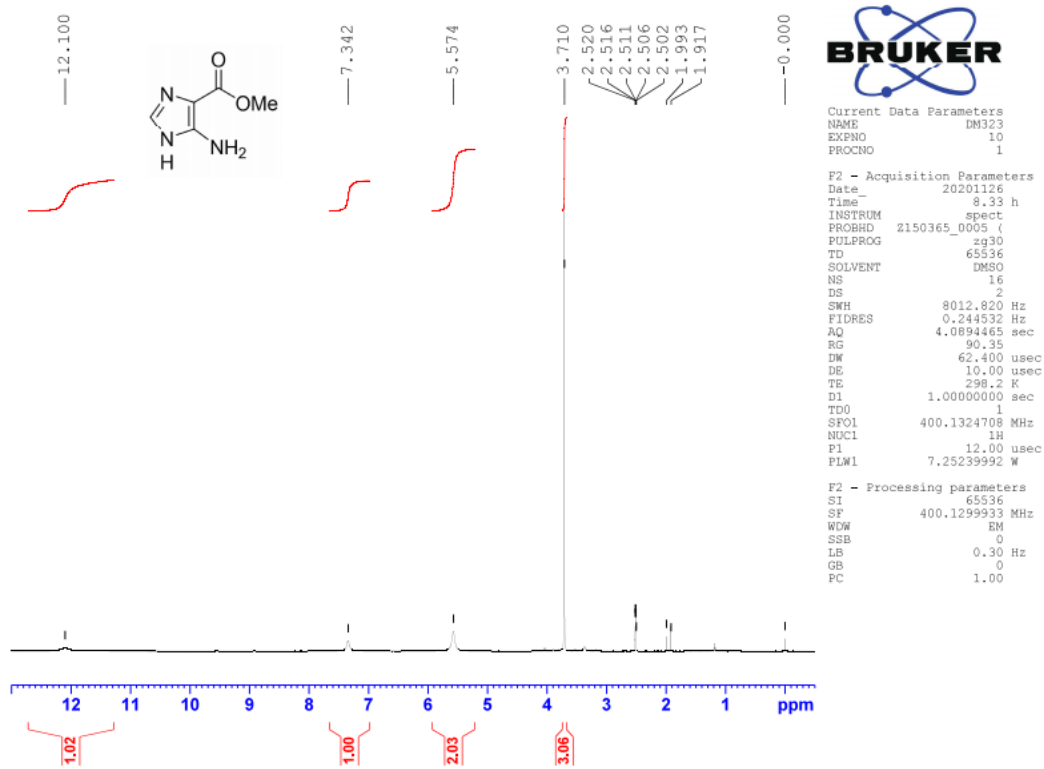
F2 - Processing parameters
 SI 32768
 SF 100.6127685 MHz
 WDW EM
 SSB 0
 LB 1.00 Hz
 GB 0
 PC 1.40

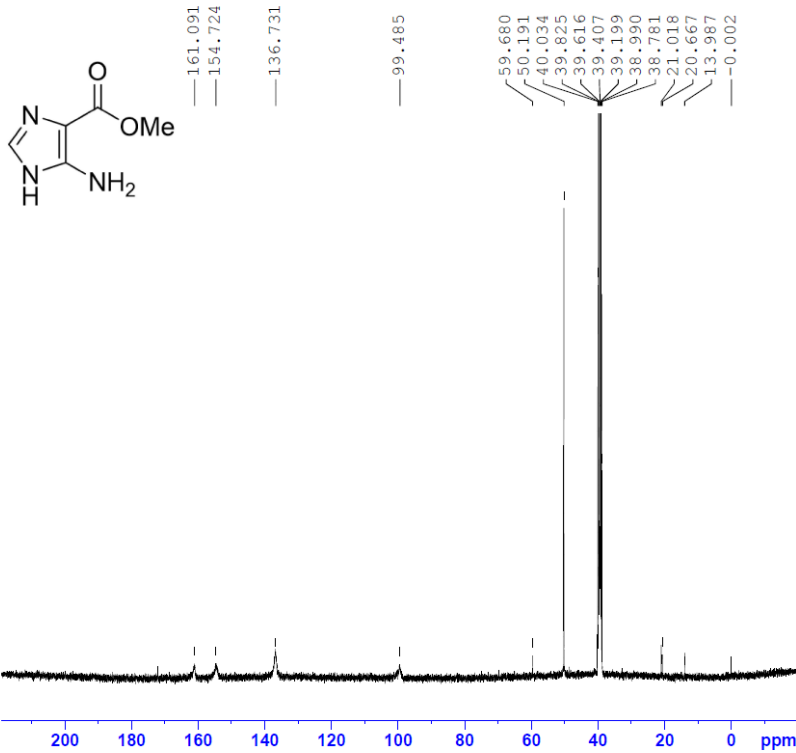
Methyl 5-amino-1H-imidazole-4-carboxylate (24)

Chemical Formula: $C_5H_7N_3O_2$, $R_f = 0.50$ (AcOEt : Methanol = 90 : 10)

1H NMR (DMSO- d_6 , 400 MHz) δ 3.71 (s, 3H, -OCH $_3$), 5.57 (br, 2H, -NH $_2$), 7.34 (s, 1H, Ar-H), 12.10 (br, 1H, -NH-)

^{13}C NMR (DMSO- d_6 100 MHz,) δ 50.2 (CH $_3$), 99.5 (C), 136.7 (C), 154.7 (CH), 161.1 (CO)





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Current Data Parameters
NAME          DM323
EXPNO         11
PROCNO        1

F2 - Acquisition Parameters
Date_         20201126
Time          9.03 h
INSTRUM       spect
PROBHD        Z150365.0005 (
PULPROG       zgpg30
TD            65536
SOLVENT       DMSO
NS            512
DS            4
SMH           24038.461 Hz
FIDRES        0.733596 Hz
AQ            1.3631488 sec
RG            37.79
DW            20.800 usec
DE            18.00 usec
TE            298.2 K
D1            2.00000000 sec
D11           0.03000000 sec
TDO           1
SFO1          100.6228298 MHz
NUC1          13C
P1            10.50 usec
PLW1          36.68799973 W
SFO2          400.1316005 MHz
NUC2          1H
CPDPRG[2]     waltz16
PCPD2         80.00 usec
PLW2          7.25239992 W
PLW12         0.16317999 W
PLW13         0.08194900 W

F2 - Processing parameters
SI            32768
SF            100.6128220 MHz
WDW           EM
SSB           0
LB            1.00 Hz
GB            0
PC            1.40
  
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