Synthesis of Bridgehead-Azacycles via Dual C-N/C-C Annulation of *α*-Amino Acids, Aminals and Maleimides

Nagender Thadem,[a,b] Manda Rajesh,[a] Harikrishna Balaboina,[a] and Saibal Das[a,b] *

[a]Department of Organic Synthesis & Process Chemistry, CSIR-Indian Institute of Chemical Technology (CSIR-IICT), Hyderabad 500007, India;
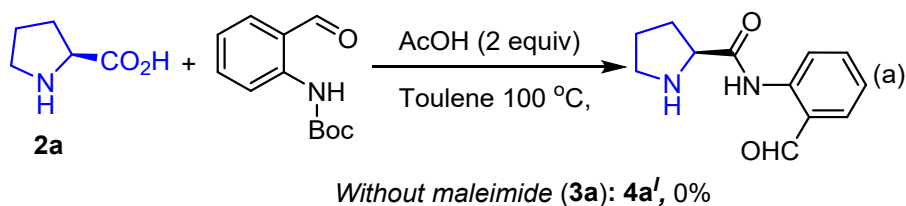
[b]Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India.

*Email: saibal@iict.res.in; Tel: +91 40 2719 1887

Table of Contents

I. Supporting Experiments


*Without maleimide (**3a**): **4a'**, 0%*

The reaction of L-proline with 2-amino benzaldehyde didn't give any intended peptide coupling adduct in absence of maleimide **3a** even in prolongation of reaction time up to 32 h. We therefore decided to analyze the intermediates from HRMS data. For that we conduct a reaction in presence of maleimide **3a**.
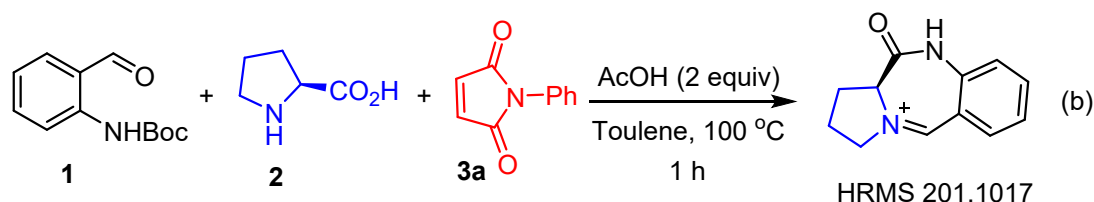
An oven dried 25 mL round bottom flask was added with a mixture of 2-amino benazldehyde (**1a**) (55 mg, 0.25 mmol), maleimide (**3a**) (64.5 mg, 0.375 mmol) and L-proline (35 mg, 0.3 mmol) in toluene (1 mL) was then added acetic acid (0.03 mL, 0.5 mmol) and stirred at 100 °C (preheated oil bath) for 1h. After this time crude reaction mixture was subjected for HRMS analysis. We found the cyclic intermediate in crude HRMS analysis: Formula: $C_{12}H_{13}N_2O^+$ $[M]^+$ 201.1022 found at 201.1017.
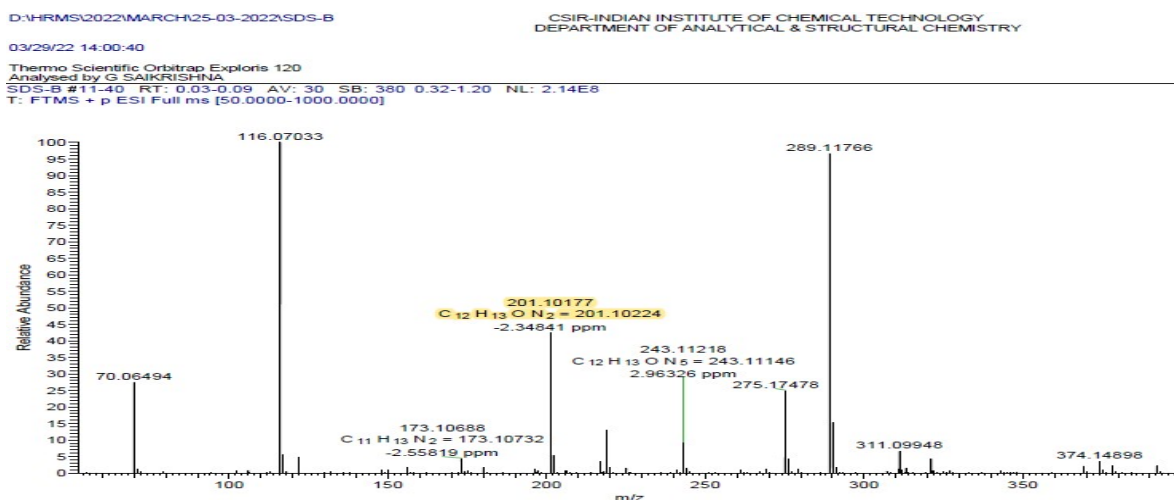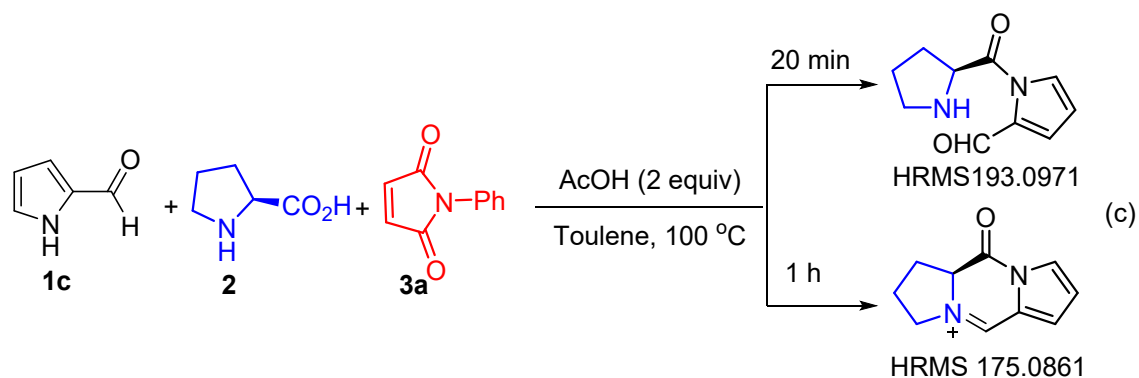
We found two deferent intermediate HRMS signals in two individual reaction time frames.

An oven dried 25 mL round bottom flask was added with a mixture of 2-pyrrole aldehyde (**1c**) (22 mg, 0.25 mmol), maleimide (**3a**) (64.5 mg, 0.375 mmol) and L-proline (35 mg, 0.3 mmol) in toluene (1 mL) was then added acetic acid (0.03 mL, 0.5 mmol) and stirred at 100 °C (preheated oil bath) for 20 min or 1 h. After this time crude reaction mixture was subjected for HRMS analysis.

After 20 min: We found the peptide intermediate in crude HRMS analysis: Formula: $C_{10}H_{13}N_2O_2$ $[M+H]^+$ 193.0977 found at 193.0971.
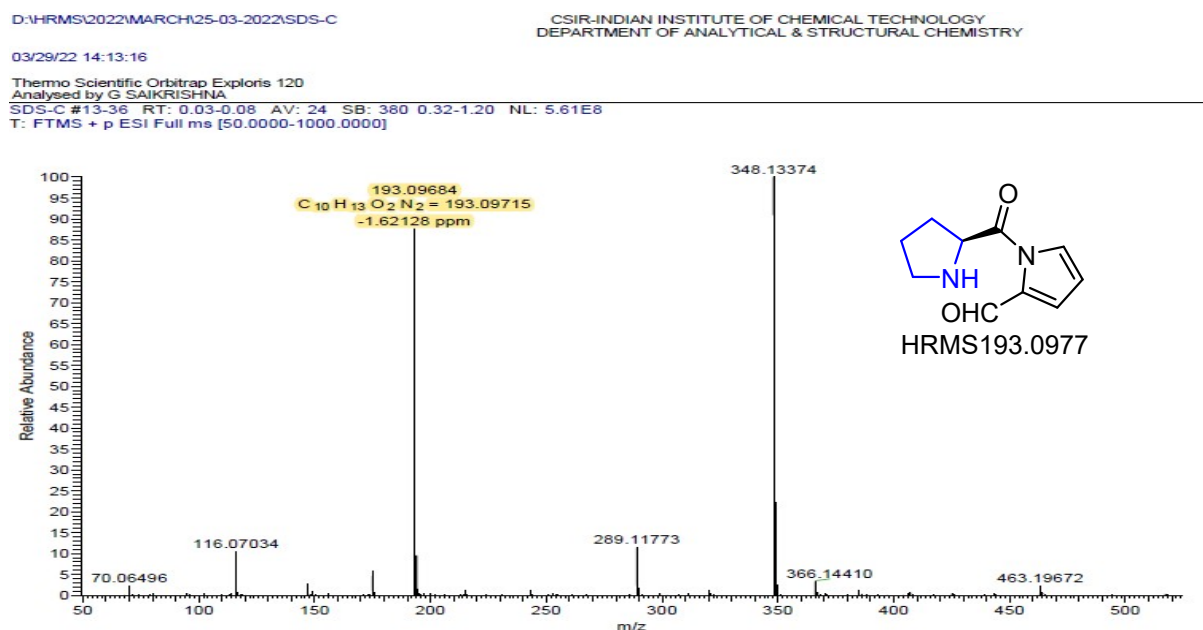
After 1 h: We found the cyclic intermediate in crude HRMS analysis: Formula: $C_{10}H_{11}N_2O^+$ $[M]^+$ 175.0866 found at 175.0861.

03/24/22 12:21:21
Thermo Scientific Orbitrap Exploris 120
Analysed by G SAIKRISHNA
SDS-A #11-38 RT: 0.03-0.09 AV: 28 SB: 382 0.32-1.20 NL: 2.13E7
T: FTMS + p APCI corona Full ms [50.0000-2000.0000]

HRMS 175.0866
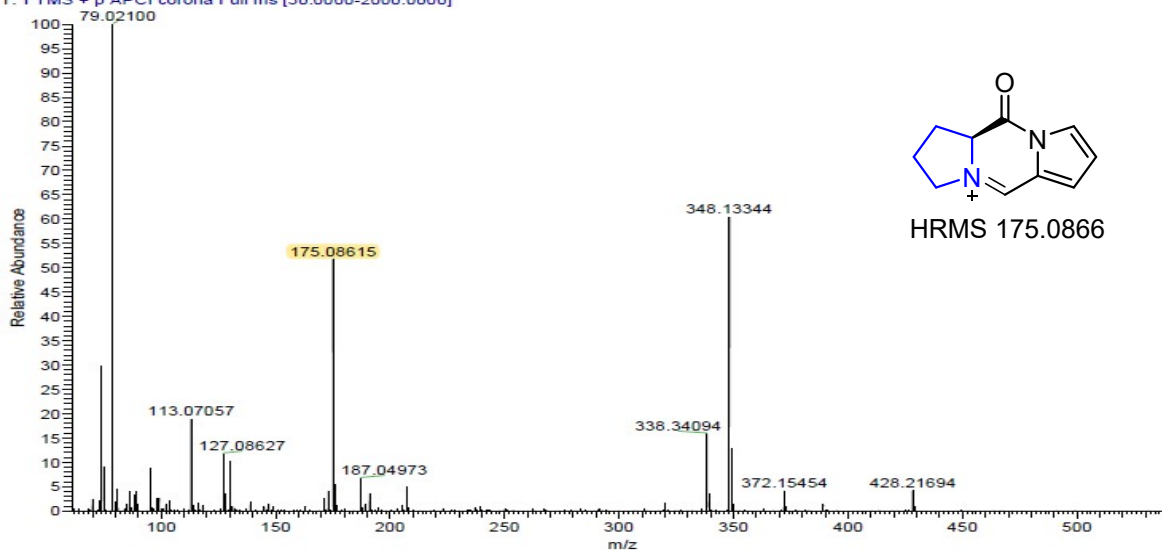
With these HRMS analysis results, we decided to synthesize the peptideic aldehyde **5a^I** through acid amine coupling procedure using Boc-L-proline.

The Synthesized intermediate **5a^I** was then subjected under standard condition which provides compound **5a** in 42% yield. This lower yield suggested that the *in situ* N-alkylation is more convenient than that of isolated one.
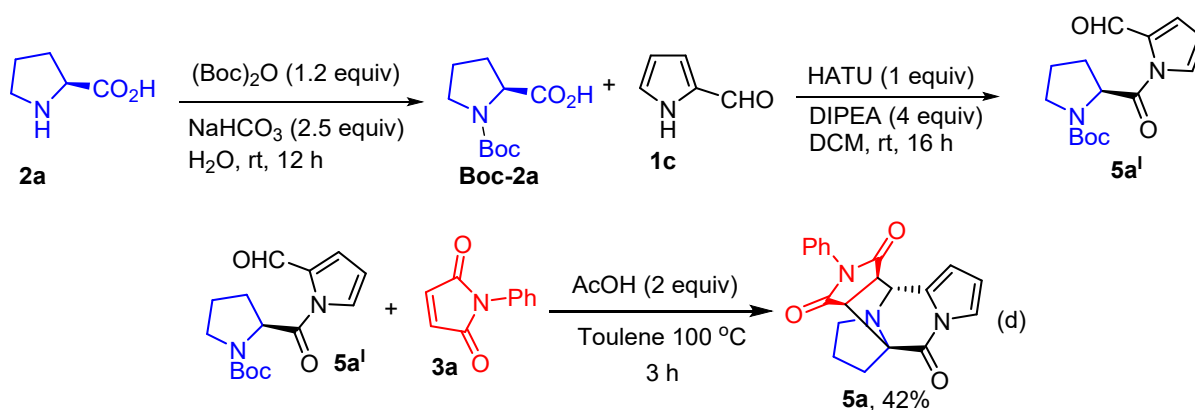
Synthesis of compound 5a^I: To 50 ml rbf was Pyrrole-2-carboxaldehyde (**1c**) (95 mg, 1 mmol, 1 equiv) in DCM (3 mL) was added HATU (384 mg, 1 mmol, 1 equiv), DIPEA (0.69 ml, 4 mmol, 4 equiv) and compound **Boc-2a** (215 mg, 1 mmol, 1 equiv), at 0 °C under N$_2$ atmosphere and the reaction mixture was stirred at RT for 16 h. Upon completion (monitored by TLC), reaction mixture was diluted with water and extracted with DCM (3x20 mL). The

combined organic solvent was dried over Na$_2$SO$_4$ concentrated under reduced pressure. The crude material was washed with ether and the resulted off white solid material was used for further reaction.
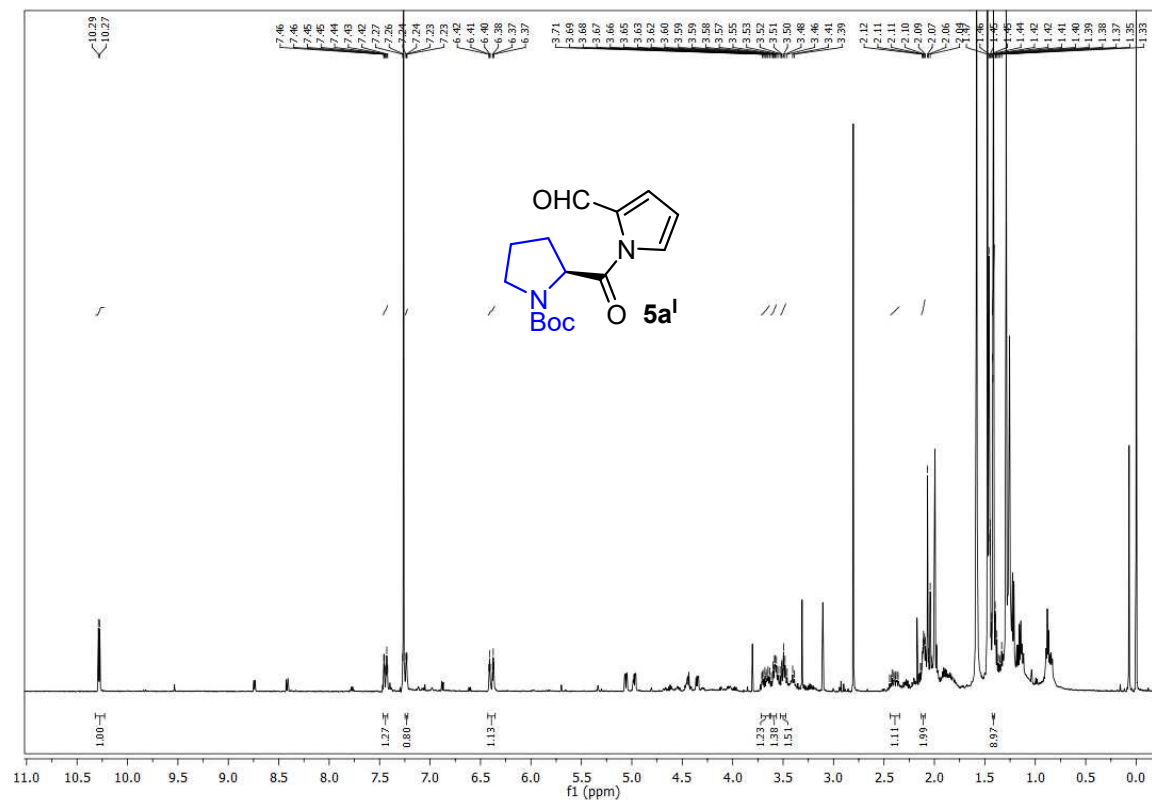
II. Procedure for gram scale synthesis of compound 4a
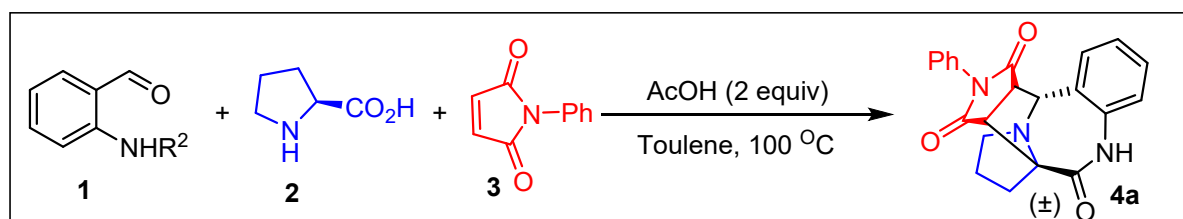
An oven dried 25 mL round bottom flask was added with a mixture of 2-amino benazldehyde (**1a**) (1 gm, 4.50 mmol), maleimide (**3a**) (1.16 gm, 6.75 mmol) and L-proline (621 mg, 5.4 mmol) in toluene (15 mL) was then added acetic acid (0.51 mL, 9 mmol) and stirred at 100 ºC (oil bath temperature) for 12 h. After completion of the reaction (monitored by TLC), the flask was cooled down to room temperature and neutralised with aq NaHCO$_3$ extracted with ethyl acetate (3x50 mL), the collected organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The resulted crude mixture was purified by column chromatography

with neutralised silica gel 100-200 mesh (ethyl acetate: hexane (6:4)) to afford the desired product **4a** as white solid (1.2 gm) 72% yield.

Procedure for gram scale synthesis of compound 5a

An oven dried 25 mL round bottom flask was added with a mixture of 2-pyrrole carbaldehyde (**1c**) (1 gm, 10.51 mmol), maleimide (**3a**) (2.72 gm, 15.77 mmol) and L-proline (1.45 gm, 12.61 mmol) in toluene (15 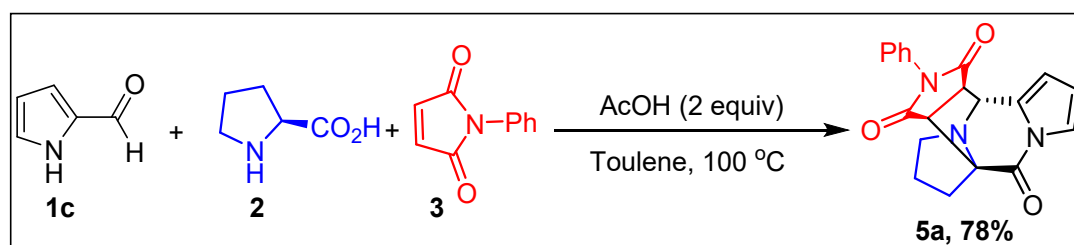mL) was then added acetic acid (1.2 mL, 21.02 mmol) and stirred at 100 °C (oil bath temperature) for 12 h. After completion of the reaction (monitored by TLC), the flask was cooled down to room temperature and neutralised with aq NaHCO$_3$ extracted with ethyl acetate (3x50 mL), the collected organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The resulted crude mixture was purified by column chromatography with neutralised silica gel 100-200 mesh (ethyl acetate: hexane (6:4)) to afford the desired product **5a** as white solid (1.85 gm) 78% yield.

III.   X-ray crystallography data

X-ray crystallography of 4b

X-ray data for the compound **4b** was collected at room temperature on a Bruker D8 QUEST instrument with an IµS Mo microsource (λ = 0.7107 A) and a PHOTON-100 detector. The raw data frames were reduced and corrected for absorption effects using the Bruker Apex 3 software suite programs [1]. The structure was solved using intrinsic phasing method [2] and further refined with the SHELXL [2] program and expanded using Fourier techniques. Anisotropic displacement parameters were included for all non-hydrogen atoms. The N-H atom as located in the difference Fourier map and its positions and isotropic displacement parameters were refined. All C bound H atoms were positioned geometrically and treated as riding on their parent C atoms [C-H = 0.93-0.97 Å, and Uiso(H) = 1.5Ueq(C) for methyl H or 1.2Ueq(C) for other H atoms].

Figure caption: ORTEP diagram of **4b** compound with the atom-numbering. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radius.

Crystal structure determination of 4b

   Crystal Data for $C_{45}H_{38}N_6O_6F_2Cl_2$ (M =867.71 g/mol): orthorhombic, space group Aea2 (no. 41), a = 22.524(2) Å, b = 24.034(7) Å, c = 7.426(6) Å, V = 4020(3) Å^3, Z = 4, T = 294.15 K, μ(MoKα) = 0.230 mm^{-1}, $Dcalc$ = 1.434 g/cm^3, 32846 reflections measured (4.958° $\leq$ 2Θ $\leq$ 61.044°), 6106 unique (R_{int} = 0.0376, R_{sigma} = 0.0348) which were used in all calculations. The final R_1 was 0.0407 (I > 2σ(I)) and wR_2 was 0.0991 (all data).**CCDC-2154455** deposition numbers contains the supplementary crystallographic data for this paper which can be obtained free of charge at https://www.ccdc.cam.ac.uk/structures/

1. Bruker (2016). APEX3, SAINT and SADABS. Bruker AXS, Inc., Madison, Wisconsin, USA.
2. Sheldrick G. M. (2015).ActaCrystallogr C71: 3-8.

X-ray Crystallography of 4o.

X-ray data for the compound **4o** was collected at room temperature on a Bruker D8 QUEST instrument with an IμS Mo micro source (λ = 0.7107 A) and a PHOTON-100 detector. The raw data frames were reduced and corrected for absorption effects using the Bruker Apex 3 software suite programs [1]. The structure was solved using intrinsic phasing method [2] and further refined with the SHELXL [2] program and expanded using Fourier techniques. Anisotropic displacement parameters were included for all non-hydrogen atoms. The N-H atom as located in the difference Fourier map and its positions and isotropic displacement parameters were refined. All C bound H atoms were positioned geometrically and treated as riding on their parent C atoms [C-H = 0.93-0.97 Å, and Uiso(H) = 1.5Ueq(C) for methyl H or 1.2Ueq(C) for other H atoms].
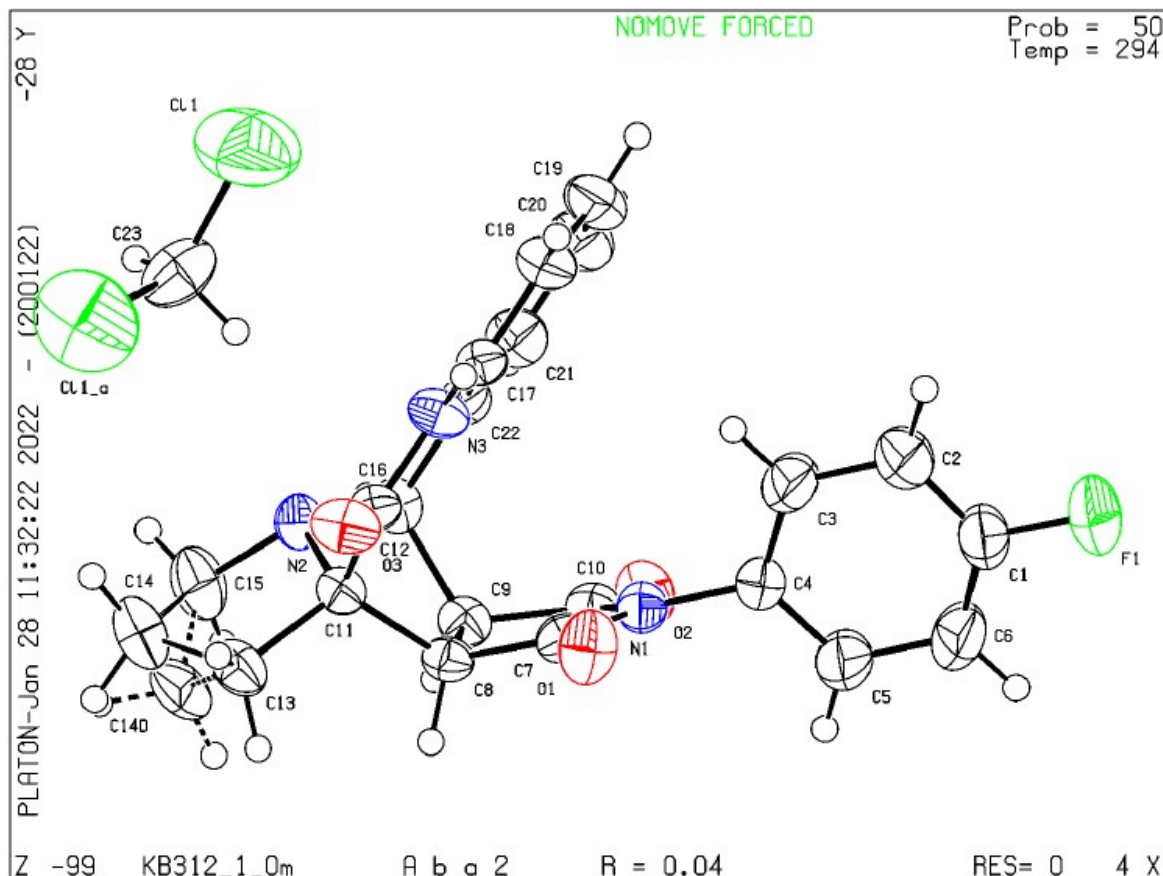
Crystal structure determination of 4o

  Crystal Data for $C_{19}H_{21}N_3O_3$ (M =339.39 g/mol): monoclinic, space group P2$_1$/c (no. 14), $a =$ 10.6245(10) Å, $b =$ 11.4523(17) Å, $c =$ 14.3907(19) Å, $\beta =$ 93.884(4)°, $V =$ 1747.0(4) Å^3, $Z =$ 4, $T =$ 294.15 K, μ(MoKα) = 0.089 mm^{-1}, $Dcalc =$ 1.290 g/cm^3, 32522 reflections measured (4.55° ≤ 2Θ ≤ 61.046°), 5272 unique (R_{int} = 0.0433, R$_{sigma}$ = 0.0298) which were used in all calculations. The final R_1 was 0.0540 (I > 2σ(I)) and wR_2 was 0.1532 (all data).**CCDC-2154458** deposition numbers contains the supplementary crystallographic data for this paper which can be obtained free of charge at https://www.ccdc.cam.ac.uk/structures/

1. Bruker (2016). APEX3, SAINT and SADABS. Bruker AXS, Inc., Madison, Wisconsin, USA.
2. Sheldrick G. M. (2015).ActaCrystallogr C71: 3-8.
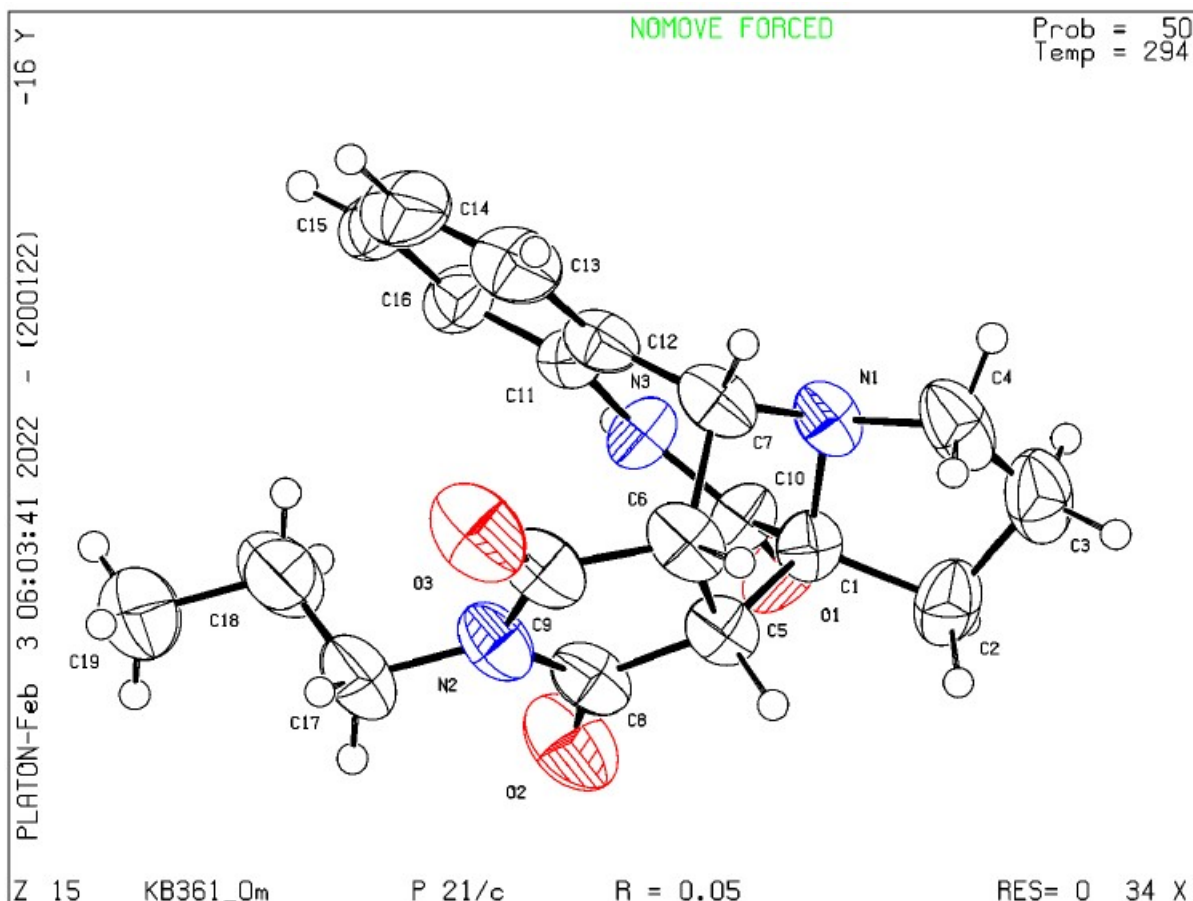
Figure caption: ORTEP diagram of **4o** compound with the atom-numbering. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radius.

X-ray Crystallography of 5u.

X-ray data for the compound **5u** was collected at room temperature on a Bruker D8 QUEST instrument with an IμS Mo microsource (λ = 0.7107 A) and a PHOTON-100 detector. The raw data frames were reduced and corrected for absorption effects using the Bruker Apex 3 software suite programs [1]. The structure was solved using intrinsic phasing method [2] and further refined with the SHELXL [2] program and expanded using Fourier techniques. Anisotropic displacement parameters were included for all non-hydrogen atoms. All C bound H atoms were positioned geometrically and treated as riding on their parent C atoms [C-H = 0.93-0.97 Å, and Uiso(H) = 1.5Ueq(C) for methyl H or 1.2Ueq(C) for other H atoms].

Crystal structure determination of 5u

Crystal Data for C16H17N3O3 (M =299.32 g/mol): monoclinic, space group P21/n (no. 14), a = 6.7220(3) Å, b = 19.1925(7) Å, c = 11.3024(5) Å, β = 103.638(2)°, V = 1417.03(10) Å3,

Z = 4, T = 294.15 K, μ(MoKα) = 0.099 mm-1, Dcalc = 1.403 g/cm3, 18455 reflections measured (5.638° ≤ 2Θ ≤ 54.996°), 3250 unique (Rint = 0.0343, Rsigma = 0.0251) which were used in all calculations. The final R1 was 0.0464 (I >2σ(I)) and wR2 was 0.1194 (all data). CCDC-**2154454** deposition numberscontains the supplementary crystallographic data for this paper which can be obtained free of charge at https://www.ccdc.cam.ac.uk/structures/

1. Bruker (2016). APEX3, SAINT and SADABS. Bruker AXS, Inc., Madison, Wisconsin, USA.
2. Sheldrick G. M. (2015).ActaCrystallogr C71: 3-8.
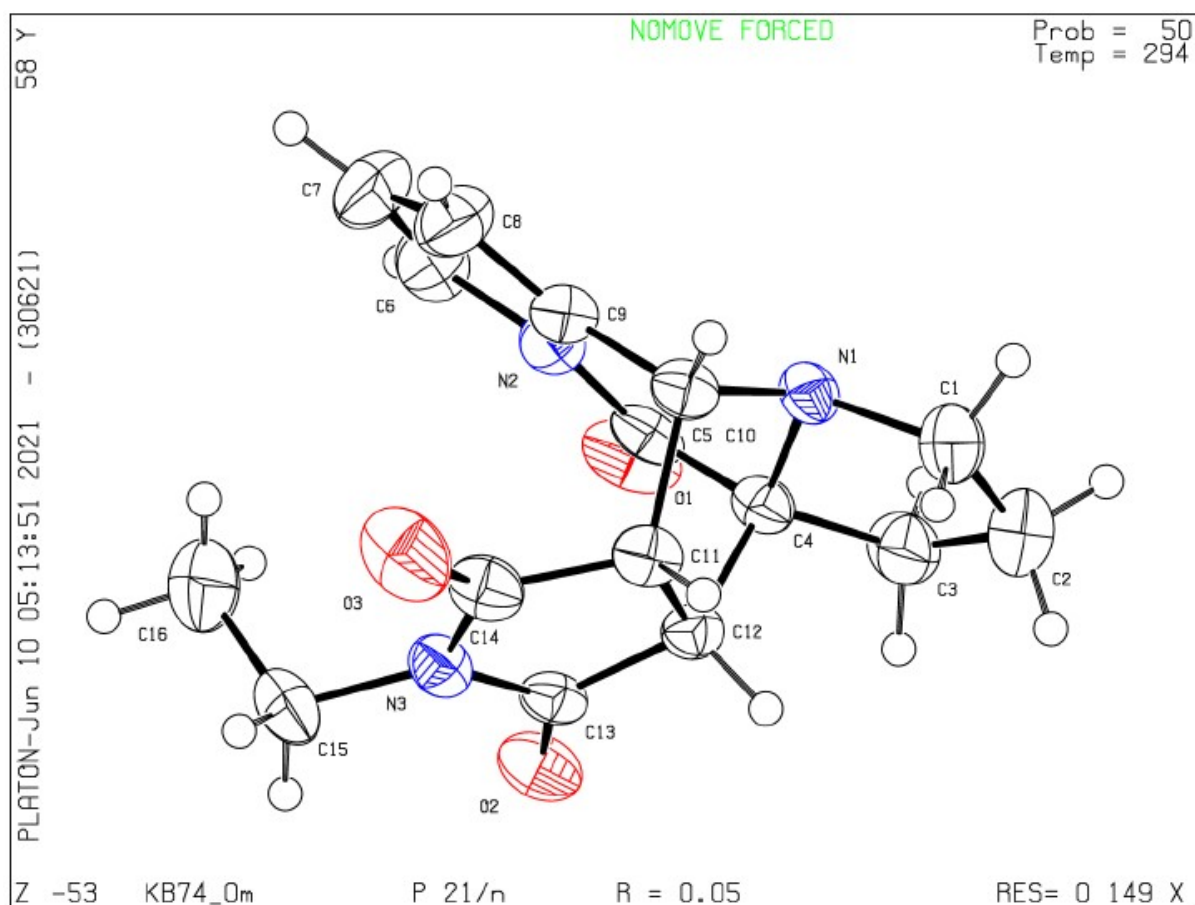
Figure caption: ORTEP diagram of **5u** with the atom-numbering. Displacement ellipsoids are drawn at the 35% probability level and H atoms are shown as small spheres of arbitrary radius.

IV. Copies of ¹H, ¹³C and ¹⁹F NMR data of **4a-u**, **5a-5bb**, **6a-6m**, **7, 8** and **9**:

4a, 79%

4a, 79%

4b, 73%

4b, 73%

4e, 66%

4e, 66%

¹H NMR peaks (labeled): 7.75, 7.57, 7.56, 7.55, 7.54, 7.26, 7.17, 7.16, 7.15, 7.12, 7.10, 7.03, 7.01, 6.79, 6.78, 6.63, 6.62, 5.63, 5.61, 4.96, 4.94, 4.22, 4.20, 4.18, 3.71, 3.69, 3.47, 3.45, 3.44, 3.25, 3.24, 2.98, 2.96, 2.24, 2.21, 2.19, 2.18, 2.17, 2.16, 2.14, 1.99, 1.97, 1.96, 1.95, 1.94

Integrations: 0.79, 0.90, 1.34, 1.04, 1.90, 1.00, 1.01, 0.90, 1.00, 0.96, 1.01, 1.06, 1.13, 1.22, 1.38, 2.38

f1 (ppm)

4f, 69%

¹³C NMR peaks (labeled): 172.91, 172.25, 171.32, 135.73, 133.25, 131.31, 130.88, 129.22, 129.17, 128.23, 123.70, 123.24, 122.22, 119.72, 78.67, 71.59, 60.42, 54.85, 38.04, 25.45

f1 (ppm)

4f, 69%

S16

4g, 61%

4g, 61%

4h, 69%

4h, 69%

-62.87

4i, 61%

4j, 52%

4j, 52%

4k, 56%

4k, 56%

4m, 66%

4m, 66%

4n, 64%

4n, 64%

4o, 68%

4o, 68%

4p, 59%

4p, 59%

4q, 61%

4q, 61%

1H NMR peaks: 7.35, 7.34, 7.34, 7.31, 7.30, 7.26, 6.74, 6.72, 6.71, 6.28, 6.27, 6.26, 6.15, 6.14, 6.13, 5.04, 5.03, 4.23, 4.20, 4.19, 3.73, 3.70, 3.31, 3.30, 3.28, 3.27, 2.83, 2.79, 2.70, 2.68, 2.46, 2.16, 2.14, 2.12, 2.10, 2.08

Integrations: 1.26, 0.88, 2.11, 2.02, 1.00, 1.00, 0.90, 1.02, 0.97, 1.03, 1.09, 1.06, 1.08, 2.19

5a, 82%

13C NMR peaks: 173.39, 173.27, 165.88, 131.43, 131.07, 129.05, 128.82, 126.67, 116.56, 113.40, 109.95, 79.20, 62.13, 55.36, 50.51, 50.17, 30.13, 29.73, 23.31

5a, 82%

5b, 71%

5b, 71%

1H NMR peak labels: 7.32, 7.31, 7.31, 7.30, 6.85, 6.79, 6.22, 6.21, 6.18, 6.18, 6.17, 5.00, 4.98, 4.32, 4.30, 4.29, 4.27, 3.83, 3.81, 3.30, 3.29, 3.29, 3.28, 3.26, 2.75, 2.72, 2.70, 2.53, 2.52, 2.15, 2.14, 2.13, 2.12, 1.96, 1.35

Integrals: 1.00, 2.16, 1.96, 1.06, 1.10, 1.15, 1.11, 2.12, 0.99, 2.94, 2.25, 3.10, 3.07

5c, 77%

f1 (ppm)

13C NMR peak labels: 173.18, 172.68, 166.08, 139.39, 136.08, 134.65, 131.54, 129.24, 129.11, 127.20, 117.19, 113.45, 110.25, 78.29, 77.35, 77.24, 77.04, 76.72, 60.78, 54.63, 49.99, 49.79, 30.26, 23.08, 21.01, 17.86, 17.27

5c, 77%

f1 (ppm)

5e, 81%

5e, 81%

5f, 74%

5f, 74%

5g, 71%

5g, 71%

5h, 69%

5h, 69%

5i, 73%

5i, 73%

5j, 70%

5j, 70%

5k, 78%

5k, 78%

5l, 67%

5l, 67%

5l, 67%

5m , 69%

5m , 69%

5n , 71%

5n , 71%

5o , 73%

5o , 73%

5p , 62%

5p , 62%

5q, 73%

5s, 71%

5s, 71%

5t, 67%

5t, 67%

5v, 71%

7.24, 7.24, 7.23, 7.23
6.18, 6.17, 6.16, 6.07, 6.06, 6.05
4.93, 4.91
4.06, 4.04, 4.03, 4.02
3.55, 3.52
3.23, 3.07, 3.05, 3.03, 2.73, 2.65, 2.63, 2.42
2.11, 2.10, 2.09, 2.09, 2.08
1.03, 1.02, 1.01, 1.00, 0.99, 0.98, 0.96, 0.73, 0.72, 0.70

0.86
0.94, 0.91
1.00
1.04
1.05, 1.04, 2.06
1.07, 1.11, 1.08
2.13
2.15, 3.08

f1 (ppm)

5v, 71%

174.14
166.03
131.38
116.28, 113.13, 109.69
78.62
61.54
55.02, 50.34, 50.01
40.37
30.05
23.21, 20.99
11.31

f1 (ppm)

S55

5w, 70%

5w, 70%

5x, 76%

5y, 68%

5y, 68%

5z, 80%

5z, 80%

6a, 81

6a, 81

6b, 74%

6b, 74%

6c, 70%

6c, 70%

1H NMR spectrum of 6d

13C NMR spectrum of 6d

S65

6e, 73%

6e, 73%

6f, 66%

6f, 66%

6g, 63%

6g, 63%

6h, 78%

6h, 78%

6j, 67%

6j, 67%

6k, 69%

6k, 69%

6l, 71%

6l, 71%

6m, 74%

6m, 74%

8, 68%

8, 68%

9, 73%

9, 73%