A Novel Intramolecular Cyclopropanation Reaction of α -Keto Esters

Dan Yang,* Qiang Gao, Chi-Sing Lee, and Kung-Kai Cheung

*Department of Chemistry, The University of Hong Kong, Pokfulam Road
Hong Kong, P. R. China*

yangdan@hku.hk

Supporting Information

General procedure:

All reactions were performed in oven-dried flasks. Air and moisture-sensitive compounds were introduced *via* syringes through a rubber septum. THF and Et₂O were distilled from sodium metal-benzophenone ketyl before use. Dichloromethane and toluene were distilled over calcium hydride. Flash column chromatography was performed on E. Merck silica gel 60 (230–400 mesh ASTM) using ethyl acetate/*n*-hexane as eluting solvents.

Nuclear magnetic resonance spectra were recorded in deuteriochloroform (CDCl₃) unless otherwise indicated, with tetramethylsilane (TMS) as internal standard at ambient temperature on a Bruker Avance DPX 300 Transform Spectrometer operating at 300 MHz for ¹H and 75.47 MHz for ¹³C or a JEOL GSX 270 MHz Fourier Transform Spectrometer operating at 270 MHz for ¹H. Infrared absorption spectra were recorded as a solution in CH₂Cl₂ with a Bio-Rad FTS 165 Fourier Transform Spectrophotometer. Mass spectra were recorded with a Finnigan MAT 95 mass spectrometer for both low-resolution and high-resolution mass spectra. Melting points were determined by Axiolab ZEISS microscope apparatus and were uncorrected.

Olefinic α -keto esters **1a**–**1i** were prepared from methyl acetoacetate and corresponding unsaturated bromides.¹

Typical procedure for the cyclopropanation reactions: $\text{Mg}(\text{ClO}_4)_2$ (156 mg, 0.7 mmol) and **1a** (60 mg, 0.35 mmol) was dissolved in dry CH_2Cl_2 (8 mL) at rt. I_2 (356 mg, 1.4 mmol) was added to the solution in one portion, followed by Et_3N (0.121 mL, 0.875 mmol). The dark mixture was stirred for 12 h. The reaction was diluted with CH_2Cl_2 (50 mL), washed with aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution, water, and brine, then dried over MgSO_4 . After removal of the solvent, the crude product was purified by flash column chromatography to give **2a** (55.2 mg, 92 % yield).

2a: a colorless oil; analytical TLC (silic gel 60), *n*-Hexane:EtOAc = 3:1, R_f = 0.3; ^1H NMR (270 MHz) δ 3.72 (s, 3H), 2.36 (dt, J = 17.3, 6.3 Hz, 1H), 2.19 (ddd, J = 17.9, 12.4, 5.9 Hz, 1H), 2.05–1.92 (m, 3H), 1.85 (dd, J = 8.4, 5.1 Hz, 1H), 1.80–1.72 (m, 1H), 1.62–1.43 (m, 1H), 1.34 (t, J = 5.9 Hz, 1H); ^{13}C NMR (75 MHz) δ 200.2, 170.8, 51.8, 38.2, 35.4, 24.9, 21.0, 17.4, 15.2; IR (CH_2Cl_2) 2954, 1724, 1703 cm^{-1} ; LRMS (EI, 20 eV) m/z 168 (M^+ , 38), 136 (100), 108 (60); HRMS (EI) for $\text{C}_9\text{H}_{12}\text{O}_3$ (M^+): calcd 168.0786, found 168.0782.

2b: a colorless oil; analytical TLC (silic gel 60), *n*-Hexane:EtOAc = 2.5:1, R_f = 0.3; ^1H NMR (300 MHz) δ 3.72 (s, 3H), 2.37 (apparent d, J = 17.3 Hz, 1H), 2.11 (ddd, J = 18.9, 12.6, 6.7 Hz, 1H), 1.97 (dt, J = 14.3, 6.5 Hz, 1H), 1.84 (dd, J = 12.7, 7.0 Hz, 1H), 1.81–1.72 (m, 1H), 1.59–1.50 (m, 3H), 1.19 (s, 3H); ^{13}C NMR (75 MHz) δ 203.5, 169.2,

52.4, 44.5, 36.9, 29.3, 28.6, 20.9, 20.5, 17.7; IR (CH₂Cl₂) 2954, 1733, 1691 cm⁻¹; LRMS (EI, 20 eV) *m/z* 182 (M⁺, 16), 153 (87), 151 (100), 136 (58); HRMS (EI) for C₁₀H₁₄O₃ (M⁺): calcd 182.0943, found 182.0941.

2c: a colorless oil; analytical TLC (silic gel 60), *n*-Hexane:EtOAc = 2.5:1, *R_f* = 0.3; ¹H NMR (300 MHz) 3.69 (s, 3H), 2.47 (ddt, *J* = 17.7, 1.8, 4.7 Hz, 1H), 2.23–2.12 (m, 1H), 2.07 (dd, *J* = 3.8, 9.0 Hz, 1H), 2.03–1.92 (m, 2H), 1.85–1.76 (m, 2H), 1.52–1.26 (m, 3H), 0.99 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (75 MHz) 204.4, 171.6, 52.5, 39.9, 35.6, 34.6, 30.4, 23.1, 18.4, 18.3, 12.9; IR (CH₂Cl₂) 2935, 1730, 1702 cm⁻¹; LRMS (EI, 20 eV) *m/z* 196 (M⁺, 71), 164 (100), 136 (46); HRMS (EI) for C₁₁H₁₆O₃ (M⁺): calcd 196.1099, found 196.1079.

2d: a colorless oil; analytical TLC (silic gel 60), *n*-Hexane:EtOAc = 2.5:1, *R_f* = 0.3; ¹H NMR (300 MHz) 3.75 (s, 3H), 2.33 (dt, *J* = 17.3, 9.6 Hz, 1H), 2.18 (ddd, *J* = 17.0, 10.5, 6.4 Hz, 1H), 2.05–1.97 (m, 3H), 1.80–1.58 (m, 4H), 1.38 (dt, *J* = 13.5, 7.0 Hz, 1H), 1.00 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (75 MHz) 202.7, 168.7, 52.2, 42.3, 37.8, 32.6, 30.4, 22.3, 21.4, 19.3, 13.3; IR (CH₂Cl₂) 2937, 1733, 1705 cm⁻¹; LRMS (EI, 20 eV) *m/z* 196 (M⁺, 30), 164 (99), 153 (100); HRMS (EI) for C₁₁H₁₆O₃ (M⁺): calcd 196.1099, found 196.1104.

2e: a colorless oil; analytical TLC (silic gel 60), *n*-Hexane:EtOAc = 2.5:1, *R_f* = 0.5; ¹H NMR (300 MHz) 3.74 (s, 3H), 2.88 (dt, *J* = 4.2, 8.5 Hz, 1H), 2.55 (dt, *J* = 3.2, 10.2 Hz,

1H), 2.45 (dt, $J = 9.9, 4.9$ Hz, 1H), 1.96–1.93 (m, 1H), 1.90–1.65 (m, 2H), 1.54 (dd, $J = 8.3, 3.7$ Hz, 1H), 1.48–1.31 (m, 2H), 1.72 (t, $J = 6.4$ Hz, 1H), 0.59 (dq, $J = 2.3, 11.5$ Hz, 1H); ^{13}C NMR (75 MHz) 205.2, 171.9, 52.4, 43.9, 39.6, 30.4, 26.2, 25.8, 25.3, 22.3; IR (CH_2Cl_2) 2937, 1733, 1705 cm^{-1} ; LRMS (EI, 20 eV) m/z 182 (M^+ , 6), 153 (100), 136 (74); HRMS (EI) for $\text{C}_{10}\text{H}_{14}\text{O}_3$ (M^+): calcd 182.0943, found 182.0942.

2f: a colorless oil; analytical TLC (silic gel 60), n -Hexane:EtOAc = 2.5:1, $R_f = 0.2$; ^1H NMR (300 MHz) 3.78 (s, 3H), 2.59 (br s, 2H), 2.32 (m, 1H), 2.14 (d, $J = 3.2$ Hz, 2H), 2.07 (ddt, $J = 13.5, 5.8, 0.8$ Hz, 2H), 1.81 (d, $J = 12.7$ Hz, 2H); ^{13}C NMR (75 MHz) 202.2, 169.3, 52.5, 44.9, 42.6, 32.1, 31.7, 27.9; IR (CH_2Cl_2), 1735, 1643 cm^{-1} ; LRMS (EI, 20 eV) m/z 180 (M^+ , 26), 153 (11), 137 (100); HRMS (EI) for $\text{C}_{10}\text{H}_{12}\text{O}_3$ (M^+): calcd 180.0786, found 180.0786.

2g: a colorless oil; analytical TLC (silic gel 60), n -Hexane:EtOAc = 2.5:1, $R_f = 0.3$; ^1H NMR (300 MHz) 3.76 (s, 3H), 2.38 (ddd, $J = 17.9, 4.8, 3.8$ Hz, 1H), 2.21–2.08 (m, 2H), 2.06–1.97 (m, 2H), 1.95–1.80 (m, 3H), 1.74–1.63 (m, 3H), 1.35–1.24 (m, 2H), 1.22–1.01 (m, 2H); ^{13}C NMR (75 MHz) 204.8, 168.3, 52.1, 47.3, 35.7, 30.9, 30.0, 28.5, 24.2, 21.2, 20.6, 19.4, 17.5; IR (CH_2Cl_2), 1740, 1625 cm^{-1} ; LRMS (EI, 20 eV) m/z 222 (M^+ , 5), 190 (100), 162 (27); HRMS (EI) for $\text{C}_{13}\text{H}_{18}\text{O}_3$ (M^+): calcd 222.1256, found 222.1252.

6: a colorless oil; analytical TLC (silic gel 60), *n*-Hexane:EtOAc = 4:1, R_f = 0.25; ^1H NMR (300 MHz) 5.32 (t, J = 1.7 Hz, 1H), 4.59 (m, 1H), 3.66 (s, 3H), 3.41–3.32 (m, 1H), 3.35 (dd, J = 4.8, 10.3 Hz, 1H), 3.26 (dd, J = 6.9, 10.3 Hz, 1H), 3.09–2.96 (m, 1H), 2.41–2.29 (m, 1H), 1.94–1.81 (m, 1H); ^{13}C NMR (75 MHz) 175.6, 168.7, 89.9, 82.3, 50.7, 30.2, 29.6, 6.8; LRMS (EI, 20 eV) m/z 282 (M^+ , 35), 155 (38), 101 (100)

7: a colorless oil; analytical TLC, (silic gel 60), *n*-Hexane:EtOAc = 2.5:1, R_f = 0.45; ^1H NMR (300 MHz, CD_2Cl_2) 4.30–4.10 (m, 2H), 3.16 (dd, J = 12.1, 2.8 Hz, 1H), 2.84 (t, J = 11.5 Hz, 1H), 2.82–2.75 (m, 1H), 2.48–2.43 (m, 2H), 2.21–2.13 (dq, J = 12.3, 3.7 Hz, 1H), 2.13–1.92 (m, 1H), 1.90–1.70 (m, 2H), 1.31 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz) 207.9, 172.0, 61.6, 61.5, 46.0, 37.9, 26.4, 22.7, 15.6, 14.1, 5.3; LRMS (EI, 20 eV) m/z 324 (M^+ , 3), 197 (74), 153 (100), 136 (61); HRMS (EI) for $\text{C}_{11}\text{H}_{17}\text{O}_3\text{I}$ (M^+): calcd 324.0222, found 324.0212. The stereochemistry of **7** was determined by 2D-NOESY analysis.

^1H - ^1H NOESY of **7**

Compound **3** was obtained by treating **1a** with Taguchi's protocol.²

3: A colorless oil; analytical TLC (silic gel 60), *n*-Hexane:EtOAc = 3:1, R_f = 0.30; ^1H NMR (300 MHz) 4.63 (t, J = 3.2 Hz, 1H), 3.77 (s, 3H), 2.42–2.31 (m, 1H), 2.04–1.94 (m, 2H), 1.88–1.78 (m, 2H), 1.55 (tdd, J = 16.2, 7.4, 3.3 Hz, 1H), 1.18 (dd, J = 5.7, 6.9 Hz, 1H); ^{13}C NMR (75 MHz) 195.2, 170.5, 52.8, 31.6, 29.5, 25.2, 24.0, 18.5, 15.5; LRMS (EI, 20 eV) m/z 294 (M^+ , 100), 262 (60), 167 (10), 135 (58).

Compound **8** was prepared by treating **1a** with $\text{Mg}(\text{ClO}_4)_2$ and NIS in EtOAc.³

8: A colorless oil; analytical TLC (silic gel 60), *n*-Hexane:EtOAc = 2.5:1, R_f = 0.70; ^1H NMR (300 MHz, CD_2Cl_2) 5.85–5.71 (m, 1H), 5.09 (s, 1H), 5.08–4.97 (m, 2H), 3.77 (s, 3H), 2.80 (t, J = 7.2 Hz, 2H), 2.07 (apparent q, J = 7.3 Hz, 2H), 1.71 (t, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz) 199.2, 167.0, 137.8, 115.1, 53.8, 38.2, 32.6, 25.6, 23.2; IR (CH_2Cl_2) 2950, 1727, 1695 cm^{-1} .

Preparation of **2**, 4-DNP derivatives **4** and **5**:

To a solution of **2c** (20 mg, 0.1 mmol) in 95% ethanol (1 mL) was added 2,4-dinitrophenylhydrazine solution (0.5 mL; freshly prepared from 1 g of 2,4-dinitrophenylhydrazine and 60 mL of H_2SO_4 in 250 mL of 70% ethanol). The mixture was stirred for 1.5 h, then diluted with Et_2O (30 mL) and washed with 5% aqueous NaHCO_3 , water, and brine subsequently. After being dried over Mg_2SO_4 and removal of the solvent, the crude product was purified by flash column chromatography to give **4** (34 mg, 90 % yield).

4: A yellow solid, mp: 112–115 °C (Et₂O/*n*-Hexane); analytical TLC (silic gel 60), *n*-Hexane:EtOAc = 2.5:1, *R_f* = 0.35; ¹H NMR (300 MHz) 11.22 (s, 1H), 9.13 (d, *J* = 2.5 Hz, 1H), 8.31 (dd, *J* = 9.6, 2.5 Hz, 1H), 7.97 (d, *J* = 9.6 Hz, 1H), 3.69 (s, 3H), 2.67 (ddt, *J* = 17.9, 5.5, 1.9 Hz, 1H), 2.17–2.01 (m, 4H), 1.97–1.88 (m, 1H), 1.72–1.58 (m, 1H), 1.33–1.24 (m, 1H), 1.14–0.96 (m, 2H), 1.01 (t, *J* = 6.9 Hz, 3H); ¹³C NMR (75 MHz) 173.5, 152.4, 144.9, 138.2, 130.1, 129.4, 123.4, 116.8, 52.5, 33.4, 29.7, 29.3, 26.5, 21.7, 18.9, 18.4, 12.7; IR (CH₂Cl₂) 3335, 2959, 1715, 1678 cm⁻¹; LRMS (EI, 20 eV) *m/z* 376 (*M*⁺, 100), 303 (32), 296 (24); HRMS (EI) for C₁₇H₂₀O₆N₄ (*M*⁺): calcd 376.1383, found 376.1363.

5: Prepared from **2d** following the same procedure for **4**. A yellow solid, mp: 108–110 °C (Et₂O/ *n*-Hexane); analytical TLC (silic gel 60), *n*-Hexane:EtOAc = 2.5:1, *R_f* = 0.35; ¹H NMR (300 MHz) 11.46 (s, 1H), 9.12 (t, *J* = 2.6 Hz, 1H), 8.29 (dd, *J* = 9.6, 2.5 Hz, 1H), 7.94 (d, *J* = 9.6 Hz, 1H), 3.74 (s, 3H), 2.51 (dt, *J* = 13.3, 3.6 Hz, 1H), 2.17 (dt, *J* = 3.8, 13.7 Hz, 1H), 2.09–1.84 (m, 5H), 1.82–1.72 (m, 1H), 1.42–1.28 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (75 MHz) 169.1, 157.1, 145.1, 137.7, 129.8, 129.2, 123.5, 116.6, 52.6, 36.0, 33.0, 30.1, 29.4, 22.1, 20.6, 20.5, 13.6; IR (CH₂Cl₂) 3690, 2957, 1742, 1618, 1589 cm⁻¹; LRMS (EI, 20 eV) *m/z* 376 (*M*⁺, 100), 303 (45), 256 (20); HRMS (EI) for C₁₇H₂₀O₆N₄ (*M*⁺): calcd 376.1383, found 376.1394.

References:

1. Sum, P. E., Weiler, L. *Can. J. Chem.* **1979**, *57*, 1475–1480.
2. Inoue, T.; Kitagawa, O.; Oda, Y.; Taguchi, T. *J. Org. Chem.* **1996**, *61*, 8256–8263.

3. Yang, D.; Yan, Y.-L.; Lui, B. *J. Org. Chem.*, in press.

X-ray structure of **4**

Experimental

Data Collection

An unknown unknown crystal of $C_{17}H_{20}N_4O_6$ having approximate dimensions of 0.00 x 0.00 x 0.00 mm was mounted on a glass fiber. All measurements were made on an unknown diffractometer with graphite monochromated Mo-K α radiation.

Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 0 carefully centered reflections in the range $0.00 < 2\theta < 0.00^\circ$ corresponded to a primitive triclinic cell with dimensions:

$$\begin{aligned}a &= 7.062(2) \text{ \AA} & \alpha &= 76.44(2)^\circ \\b &= 8.254(2) \text{ \AA} & \beta &= 85.19(2)^\circ \\c &= 16.228(3) \text{ \AA} & \gamma &= 78.2400(2)^\circ \\V &= 899.6(4) \text{ \AA}^3\end{aligned}$$

For $Z = 2$ and F.W. = 376.37, the calculated density is 1.39 g/cm³. Based on a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be:

$$P\bar{1} \text{ (\#2)}$$

The data were collected at a temperature of $0 \pm 1^\circ\text{C}$ using the ω scan technique to a maximum 2θ value of 51.1° . Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.00° with a take-off angle of 6.0° . Scans of $(0.00 + 0.00 \tan \theta)^\circ$ were made at a speed of $0.0^\circ/\text{min}$ (in omega).

Data Reduction

A total of 2710 reflections was collected. No decay correction was applied.

The linear absorption coefficient, μ , for Mo-K α radiation is 1.1 cm^{-1} . Azimuthal scans of several reflections indicated no need for an absorption correction. The data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement

The structure was solved by direct methods¹ and expanded using Fourier techniques². The non-hydrogen atoms were refined anisotropically. The final cycle of full-matrix least-squares refinement³ was based on 2004 observed reflections ($I > 3.00\sigma(I)$) and 247 variable parameters and converged (largest parameter shift was 0.03 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma ||Fo| - |Fc|| / \Sigma |Fo| = 0.059$$

$$R_w = \sqrt{(\Sigma w(|Fo| - |Fc|)^2 / \Sigma w Fo^2)} = 0.081$$

The standard deviation of an observation of unit weight⁴ was 2.09. The weighting scheme was based on counting statistics and included a factor ($p = 0.020$) to downweight the intense reflections. Plots of $\Sigma w(|Fo| - |Fc|)^2$ versus $|Fo|$, reflection order in data collection, $\sin \theta/\lambda$ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.29 and -0.34 $e^-/\text{\AA}^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber⁵. Anomalous dispersion effects were included in Fcalc⁶; the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley⁷. The values for the mass attenuation coefficients are those of Creagh and Hubbel⁸. All calculations were performed using the teXsan⁹ crystallographic software package of Molecular Structure Corporation.

References

(1) SIR92: Altomare, A., Burla, M.C., Camalli, M., Cascarano, M., Giacovazzo, C., Guagliardi, A., Polidori, G. (1994). J. Appl. Cryst., in preparation.

(2) DIRDIF94: Beurskens, P.T., Admiraal, G., Beurskens, G., Bosman, W.P., de Gelder, R., Israel, R. and Smits, J.M.M. (1994). The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

(3) Least-Squares:

Function minimized: $\Sigma w(|Fo| - |Fc|)^2$

where $w = \frac{1}{\sigma_c^2(Fo)} = [\sigma_c^2(Fo) + \frac{p^2}{4} Fo^2]^{-1}$

$\sigma_c(Fo)$ = e.s.d. based on counting statistics

p = p-factor

(4) Standard deviation of an observation of unit weight:

$$\sqrt{\Sigma w(|Fo| - |Fc|)^2 / (No - Nv)}$$

where: No = number of observations

Nv = number of variables

(5) Cromer, D. T. & Waber, J. T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

(6) Ibers, J. A. & Hamilton, W. C.; Acta Crystallogr., 17, 781 (1964).

(7) Creagh, D. C. & McAuley, W.J.; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.6.8, pages 219-222 (1992).

(8) Creagh, D. C. & Hubbell, J.H.; "International Tables for Crystallography", Vol C, (A.J.C. Wilson,

ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992).

(9) teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992).

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{17}H_{20}N_4O_6$
Formula Weight	376.37
Crystal Color, Habit	unknown, unknown
Crystal Dimensions	0.00 X 0.00 X 0.00 mm
Crystal System	triclinic
Lattice Type	Primitive
No. of Reflections Used for Unit	
Cell Determination (2θ range)	0 (0.0 - 0.0°)
Omega Scan Peak Width	
at Half-height	0.00°
Lattice Parameters	$a = 7.062(2) \text{ \AA}$ $b = 8.254(2) \text{ \AA}$ $c = 16.228(3) \text{ \AA}$ $\alpha = 76.44(2)^\circ$ $\beta = 85.19(2)^\circ$ $\gamma = 78.2400(2)^\circ$
	$V = 899.6(4) \text{ \AA}^3$
Space Group	$P\bar{1}$ (#2)
Z value	2
D_{calc}	1.389 g/cm ³
F_{000}	396.00
$\mu(\text{MoK}\alpha)$	1.07 cm ⁻¹

B. Intensity Measurements

Diffractometer	unknown
Radiation	MoK α ($\lambda = 0.71069 \text{ \AA}$) graphite monochromated
Take-off Angle	2.8°
Detector Aperture	2.0 - 2.5 mm horizontal 2.0 mm vertical
Crystal to Detector Distance	21 mm
Temperature	0.0°C
Scan Type	ω
Scan Rate	0.0°/min (in ω) (up to 0 scans)
Scan Width	$(0.00 + 0.00 \tan \theta)^\circ$
$2\theta_{max}$	51.1°
No. of Reflections Measured	Total: 2710
Corrections	Lorentz-polarization

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma w(Fo - Fc)^2$
Least Squares Weights	$w = \frac{1}{\sigma^2(Fo)} = [\sigma_c^2(Fo) + \frac{p^2}{4} Fo^2]^{-1}$
p-factor	0.0200
Anomalous Dispersion	All non-hydrogen atoms
No. Observations ($I > 3.00\sigma(I)$)	2004
No. Variables	247
Reflection/Parameter Ratio	8.11
Residuals: R; Rw	0.059 ; 0.081
Goodness of Fit Indicator	2.09

Maximum peak in Final Diff. Map	$0.29\ e^-/\text{\AA}^3$
Minimum peak in Final Diff. Map	$-0.34\ e^-/\text{\AA}^3$

atom	atom	distance	atom	atom	distance
O(1)	C(14)	1.332(4)	C(5)	C(6)	1.506(4)
O(1)	C(15)	1.432(4)	C(5)	H(6)	0.950
O(2)	C(14)	1.188(3)	C(5)	H(7)	0.948
O(3)	N(3)	1.233(3)	C(6)	C(7)	1.498(4)
O(4)	N(3)	1.211(3)	C(6)	H(8)	0.952
O(5)	N(4)	1.225(3)	C(6)	H(9)	0.950
O(6)	N(4)	1.229(3)	C(8)	C(9)	1.417(3)
N(1)	N(2)	1.387(3)	C(8)	C(13)	1.418(4)
N(1)	C(7)	1.288(3)	C(9)	C(10)	1.400(4)
N(2)	C(8)	1.351(3)	C(10)	C(11)	1.358(4)
N(2)	H(1)	0.93(4)	C(10)	H(10)	0.953
N(3)	C(9)	1.453(3)	C(11)	C(12)	1.398(4)
N(4)	C(11)	1.464(4)	C(12)	C(13)	1.364(4)
C(1)	C(2)	1.536(4)	C(12)	H(11)	0.951
C(1)	C(3)	1.535(4)	C(13)	H(12)	0.949
C(1)	C(7)	1.508(3)	C(15)	H(13)	0.953
C(1)	C(14)	1.480(4)	C(15)	H(14)	0.950
C(2)	C(3)	1.485(4)	C(15)	H(15)	0.949
C(2)	C(16)	1.487(5)	C(16)	C(17)	1.519(5)
C(2)	H(2)	0.948	C(16)	H(16)	0.947
C(3)	C(4)	1.508(5)	C(16)	H(17)	0.952
C(3)	H(3)	0.951	C(17)	H(18)	0.946
C(4)	C(5)	1.506(4)	C(17)	H(19)	0.949
C(4)	H(4)	0.952	C(17)	H(20)	0.954
C(4)	H(5)	0.951			

Distances are in angstroms. Estimated standard deviations in the least significant figure are given in parentheses.

atom	atom	atom	angle	atom	atom	atom	angle
C(14)	O(1)	C(15)	116.6(3)	C(4)	C(5)	C(6)	111.6(3)
N(2)	N(1)	C(7)	114.1(2)	C(5)	C(6)	C(7)	114.8(2)
N(1)	N(2)	C(8)	119.7(2)	N(1)	C(7)	C(1)	115.2(2)
O(3)	N(3)	O(4)	122.7(2)	N(1)	C(7)	C(6)	125.5(2)
O(3)	N(3)	C(9)	118.4(2)	C(1)	C(7)	C(6)	119.3(2)
O(4)	N(3)	C(9)	118.8(2)	N(2)	C(8)	C(9)	122.7(2)
O(5)	N(4)	O(6)	123.9(2)	N(2)	C(8)	C(13)	120.7(2)
O(5)	N(4)	C(11)	118.1(2)	C(9)	C(8)	C(13)	116.6(2)
O(6)	N(4)	C(11)	118.0(3)	N(3)	C(9)	C(8)	122.5(2)
C(2)	C(1)	C(3)	57.9(2)	N(3)	C(9)	C(10)	116.1(2)
C(2)	C(1)	C(7)	117.9(2)	C(8)	C(9)	C(10)	121.4(2)
C(2)	C(1)	C(14)	116.0(2)	C(9)	C(10)	C(11)	118.9(2)
C(3)	C(1)	C(7)	115.3(2)	N(4)	C(11)	C(10)	118.3(2)
C(3)	C(1)	C(14)	115.0(2)	N(4)	C(11)	C(12)	119.8(2)
C(7)	C(1)	C(14)	119.7(2)	C(10)	C(11)	C(12)	121.9(2)
C(1)	C(2)	C(3)	61.0(2)	C(11)	C(12)	C(13)	119.3(2)
C(1)	C(2)	C(16)	120.9(2)	C(8)	C(13)	C(12)	121.8(2)
C(3)	C(2)	C(16)	124.4(3)	O(1)	C(14)	O(2)	123.2(3)
C(1)	C(3)	C(2)	61.1(2)	O(1)	C(14)	C(1)	112.7(2)
C(1)	C(3)	C(4)	116.5(2)	O(2)	C(14)	C(1)	124.1(3)
C(2)	C(3)	C(4)	124.9(3)	C(2)	C(16)	C(17)	112.3(3)
C(3)	C(4)	C(5)	111.1(3)				

Angles are in degrees. Estimated standard deviations in the least significant figure are given in parentheses.

X-ray structure of **5**

Crystal data. $[C_{17}H_{20}N_4O_6]$, formula weight = 376.37, Orthorhombic, space group $Pbcn$, $a = 27.345(6)$ Å, $b = 8.8890(18)$ Å, $c = 15.154(3)$ Å, $V = 3683.5(13)$ Å³, $Z = 8$, $D_c = 1.357$ gcm⁻³, $\mu(\text{Mo-K}\alpha) = 0.105$ mm⁻¹, $F(000) = 1584$, $T = 301$ K.

A colorless crystal of dimensions 0.40 x 0.35 x 0.20 mm mounted in a glass capillary was used for data collection at 28°C on a Rigaku AFC7R diffractometer with graphite monochromatized Mo-K α radiation ($\lambda = 0.71073$ Å) using ω -2 θ scans with ω -scan angle $(0.73 + 0.35 \tan \theta)^\circ$ at a scan speed of 8.0 deg min⁻¹ (up to 6 scans for reflection with $I < 15 \sigma(I)$). Unit-cell dimensions were determined based on the setting angles of 25 reflections in the 2 θ range of 39.7 to 41.6°. Intensity data (in the range of $2\theta_{\max} = 50.08^\circ$; h : 0 to 32; k : 0 to 10; l : 0 to 18 and 3 standard reflections measured after every 300 reflections showed no decay), were corrected for Lorentz and polarization effects, and empirical absorption corrections based on the ψ -scan of five strong reflections (minimum and maximum transmission factors 0.9594 and 0.9794). 3245 reflections were unique and $R_{\text{int}} = 0.0256$. The data was transformed to Shelx-Format using the software package *TeXsan*¹ on a Silicon Graphics Indy computer and processed with Shelxl-program package on PC.

The structure was solved by direct methods employing SHELXS-97 program². All atoms were found and the structure was refined and finalized by employing SHELXL-97³ program on PC. The final crystallographic data and report was made by employing WINGX program package⁴.

One crystallographic asymmetric unit consists of one formula unit. In the final stage of full-matrix least-squares refinements, all non-H atoms were refined anisotropically, and H atoms were added at calculated positions based on riding-on mode with thermal parameters equal to 1.2 times that of the attached C (or N) atoms and participate in the calculation of R-indices⁵.

Convergence ($\Delta/\sigma_{\max} = 0.001$, av. 0.001) for 244 variable parameters by full-matrix least-squares refinement on F^2 reaches to $R_1 = 0.0383$ and $wR_2 = 0.0978$ with a goodness-of-fit of 0.963, the parameters a and b for weighting scheme are 0.0607 and 0.0. The final difference Fourier map shows maximum rest peaks and holes of 0.143 and -0.211 eÅ⁻³ respectively.

Drawing: The ORTEP⁶ drawing of the molecule was made with thermal ellipsoids at the 30 % probability level. Screen drawing is provided for reference. The drawing with high quality can be provided upon request.

Tables: Table (1) of Crystallographic and refinement data, table (2) of atomic coordinates with thermal parameters, table (3) of full bond lengths and bond angles and this report are provided. The other supplementary materials, such as table of anisotropic displacement parameters, table of hydrogen coordinates and/or other tables and/or CIF, RES-files, can be provided under request by notifying the identification code.

¹ *TeXsan* : Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992), The Woodlands, Texas, U.S.A.

² SHELXS97, Sheldrick, G. M. (1997). SHELX97. Programs for Crystal Structure Analysis (Release 97-2). University of Goettingen, Germany.

³ SHELXL97, Sheldrick, G. M. (1997). SHELX97. Programs for Crystal Structure Analysis (Release 97-2). University of Goettingen, Germany.

⁴ An Integrated System of Windows Programs for the solution, Refinement and Analysis of Single Crystal X-ray Diffraction Data, Farrugia, L. J. (1999) J. Appl. Cryst., 32, 837-838.

⁵ Since the structure refinements are against F^2 , R-indices based on F^2 are larger than (more than double) those based on F . For comparison with older refinements based on F and an OMIT threshold, a conventional index R_1 based on observed F values larger than $4\sigma(F_o)$ is also given (corresponding to $\text{Intensity} \geq 2\sigma(I)$). $wR_2 = \{ \sum [w(F_o^2 - F_c^2)^2] / \sum [w(F_o^2)^2] \}^{1/2}$, $R_1 = \sum ||F_o| - |F_c|| / \sum |F_o|$. The Goodness of Fit is always based on F^2 : $\text{GooF} = S = \{ \sum [w(F_o^2 - F_c^2)^2] / (n - p) \}^{1/2}$, where n is the number of reflections and p is the total number of parameters refined. The weighting scheme is: $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$, where P is $[2F_c^2 + \text{Max}(F_o^2, 0)]/3$.

⁶ ORTEP3 for Windows - Farrugia, L. J. (1997) J. Appl. Cryst. 30, 565.

Table 1. Crystal data and structure refinement for afc1004.

Identification code	afc1004	
Empirical formula	C ₁₇ H ₂₀ N ₄ O ₆	
Formula weight	376.37	
Temperature	301(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P b c n	
Unit cell dimensions	a = 27.345(6) Å	α = 90°.
	b = 8.8890(18) Å	β = 90°.
	c = 15.154(3) Å	γ = 90°.
Volume	3683.5(13) Å ³	
Z	8	
Density (calculated)	1.357 Mg/m ³	
Absorption coefficient	0.105 mm ⁻¹	
F(000)	1584	
Crystal size	0.40 x 0.35 x 0.20 mm ³	
Theta range for data collection	2.41 to 25.00°.	
Index ranges	0 ≤ h ≤ 32, 0 ≤ k ≤ 10, 0 ≤ l ≤ 18	
Reflections collected	3245	
Independent reflections	3245 [R(int) = 0.0000]	
Completeness to theta = 25.00°	100.0 %	
Max. and min. transmission	0.9794 and 0.9594	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	3245 / 0 / 244	
Goodness-of-fit on F ²	0.963	
Final R indices [I > 2σ(I)]	R1 = 0.0383, wR2 = 0.0978	
R indices (all data)	R1 = 0.1772, wR2 = 0.1428	
Largest diff. peak and hole	0.143 and -0.211 e.Å ⁻³	

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for afc1004. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U(\text{eq})$
O(1)	1555(1)	585(2)	8216(2)	66(1)
O(2)	2268(1)	1645(3)	7881(2)	94(1)
O(3)	1532(1)	-965(3)	5996(2)	88(1)
O(4)	1333(1)	-2767(4)	5134(2)	115(1)
O(5)	-312(1)	-3961(3)	4476(2)	100(1)
O(6)	-891(1)	-2966(4)	5240(2)	111(1)
N(1)	677(1)	1902(3)	7222(2)	52(1)
N(2)	867(1)	740(3)	6717(2)	53(1)
N(3)	1222(1)	-1744(3)	5617(2)	68(1)
N(4)	-462(1)	-3093(4)	5042(2)	79(1)
C(1)	985(1)	2838(3)	7554(2)	49(1)
C(2)	1527(1)	2821(3)	7415(2)	50(1)
C(3)	1770(1)	4347(3)	7311(2)	64(1)
C(4)	1492(1)	5749(4)	7554(2)	79(1)
C(5)	938(1)	5577(4)	7521(2)	74(1)
C(6)	777(1)	4168(3)	8017(2)	67(1)
C(7)	1685(1)	3453(4)	6510(2)	61(1)
C(8)	2092(1)	2783(4)	5961(2)	84(1)
C(9)	2226(2)	3781(5)	5197(3)	116(2)
C(10)	1832(1)	1645(4)	7848(2)	59(1)
C(11)	1819(1)	-605(4)	8658(3)	86(1)
C(12)	559(1)	-206(3)	6302(2)	45(1)
C(13)	711(1)	-1421(3)	5773(2)	49(1)
C(14)	376(1)	-2357(3)	5367(2)	58(1)
C(15)	-112(1)	-2120(4)	5485(2)	57(1)
C(16)	-278(1)	-939(4)	5999(2)	57(1)
C(17)	47(1)	1(4)	6395(2)	53(1)

Table 3. Bond lengths [Å] and angles [°] for afc1004.

O(1)-C(10)	1.331(4)	O(4)-N(3)-C(13)	119.4(3)
O(1)-C(11)	1.447(3)	O(3)-N(3)-C(13)	118.3(3)
O(2)-C(10)	1.194(3)	O(6)-N(4)-O(5)	123.8(3)
O(3)-N(3)	1.235(3)	O(6)-N(4)-C(15)	117.7(4)
O(4)-N(3)	1.205(3)	O(5)-N(4)-C(15)	118.5(4)
O(5)-N(4)	1.224(4)	N(1)-C(1)-C(6)	116.7(3)
O(6)-N(4)	1.216(4)	N(1)-C(1)-C(2)	125.9(3)
N(1)-C(1)	1.286(3)	C(6)-C(1)-C(2)	116.9(3)
N(1)-N(2)	1.386(3)	C(10)-C(2)-C(1)	120.0(3)
N(2)-C(12)	1.347(3)	C(10)-C(2)-C(3)	115.3(3)
N(3)-C(13)	1.448(4)	C(1)-C(2)-C(3)	116.0(3)
N(4)-C(15)	1.454(4)	C(10)-C(2)-C(7)	119.3(3)
C(1)-C(6)	1.487(4)	C(1)-C(2)-C(7)	113.5(2)
C(1)-C(2)	1.497(4)	C(3)-C(2)-C(7)	57.35(19)
C(2)-C(10)	1.489(4)	C(7)-C(3)-C(4)	124.7(3)
C(2)-C(3)	1.519(4)	C(7)-C(3)-C(2)	62.19(19)
C(2)-C(7)	1.545(4)	C(4)-C(3)-C(2)	119.5(3)
C(3)-C(7)	1.470(4)	C(3)-C(4)-C(5)	114.3(3)
C(3)-C(4)	1.505(4)	C(4)-C(5)-C(6)	110.6(3)
C(4)-C(5)	1.524(5)	C(1)-C(6)-C(5)	108.1(3)
C(5)-C(6)	1.526(4)	C(3)-C(7)-C(8)	123.4(3)
C(7)-C(8)	1.511(4)	C(3)-C(7)-C(2)	60.46(19)
C(8)-C(9)	1.504(5)	C(8)-C(7)-C(2)	123.5(3)
C(12)-C(13)	1.408(4)	C(9)-C(8)-C(7)	111.8(3)
C(12)-C(17)	1.420(4)	O(2)-C(10)-O(1)	123.5(3)
C(13)-C(14)	1.381(4)	O(2)-C(10)-C(2)	125.3(3)
C(14)-C(15)	1.363(4)	O(1)-C(10)-C(2)	111.2(3)
C(15)-C(16)	1.383(4)	N(2)-C(12)-C(13)	124.1(3)
C(16)-C(17)	1.359(4)	N(2)-C(12)-C(17)	119.3(3)
		C(13)-C(12)-C(17)	116.6(3)
C(10)-O(1)-C(11)	115.2(3)	C(14)-C(13)-C(12)	121.3(3)
C(1)-N(1)-N(2)	117.0(2)	C(14)-C(13)-N(3)	116.6(3)
C(12)-N(2)-N(1)	119.3(2)	C(12)-C(13)-N(3)	122.1(3)
O(4)-N(3)-O(3)	122.3(3)	C(15)-C(14)-C(13)	119.9(3)

C(14)-C(15)-C(16)	120.7(3)	C(17)-C(16)-C(15)	120.1(3)
C(14)-C(15)-N(4)	119.5(3)	C(16)-C(17)-C(12)	121.4(3)
C(16)-C(15)-N(4)	119.8(3)		

Symmetry transformations used to generate equivalent atoms: