

Synthesis, characterisation and crystal structure of a co-crystal of two components: 1,2-bis(6-methylpyridin-2-yl)ethane-1,2-dione and 1-(pyridin-2-yl)-2-(6-methylpyridin-2-yl)ethane-1,2-dione

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A condensation reaction of an equimolar ratio of 2-pyridinecarboxaldehyde and (6-methylpyridin-2-yl)methanol without a catalyst in a solvent-free reaction at 140°C was expected to yield 2-hydroxy-[1,2-bis(6-methylpyridin-2-yl)]ethan-1-one. FT-IR spectroscopy of the yellow-brown solid reaction product indicated the presence of a –CO–COH– group. The solid compound was treated with cyclohexane and green crystals were produced. The crystals were characterised by FT-IR, ¹H NMR, EI mass spectrometry and single-crystal X-ray diffraction. The molecular and crystal structure determined by single-crystal X-ray diffraction resolved one crystal showing two molecular components [C₁₃H₁₀N₂O₂ and C₁₄H₁₂N₂O₂] at a ratio of 60.4:39.6 [C_{13.40}H_{10.79}N₂O₂]. Both compounds co-crystallise in the triclinic space group P-1, with *a* = 7.859(5), *b* = 8.021(14), *c* = 9.060(5) Å, α = 101.36(2)°, β = 90.06(3)°, γ = 90.92(3)°, *V* = 559.8(5) Å³, *Z* = 2. The compounds were 1,2-bis(6-methylpyridin-2-yl)ethane-1,2-dione and 1-(pyridin-2-yl)-2-(6-methylpyridin-2-yl)ethane-1,2-dione. These results are important because they confirm that condensation in a solvent- and catalyst-free reaction yielded precursors that were converted into α -diketone compounds by the action of solvent and oxygen.

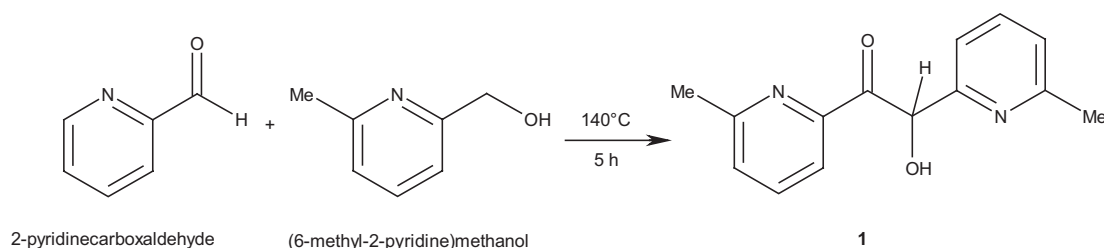
Keywords: 1,2-diketones, 2-hydroxy-[1,2-bis(6-methylpyridin-2-yl)]ethan-1-one, 1,2-bis(6-methylpyridin-2-yl)ethane-1,2-dione, 1-(pyridin-2-yl)-2-(6-methylpyridin-2-yl)ethane-1,2-dione, co-crystal structure

In organic chemistry, one of the oldest known reactions is the cyanide-catalysed benzoin condensation.¹ The remarkably specific cyanide ion catalysis of the reaction was first studied by Lapworth² in 1903. Benzoin condensation contains a –COCHOH– group and can be oxidised to the α -diketone (benzil) very efficiently by several reagents such as nitric acid³, Fehlings solution³ and thallium nitrate.^{4–7} It is also known that 2-pyridinecarboxaldehyde undergoes benzoin condensation,^{8–9} in the presence of KCN or glacial acetic acid as catalyst but yields *trans*-1,2-di-(2-pyridyl)-1,2-ethenediol instead of the benzoin derivative (α -pyridoin). On the other hand, it is known that weak forces, especially hydrogen bonding, considerably affect the structures of crystals and liquids.¹⁰ It has been suggested that α -pyridoin may be completely dominated by the enediol isomer because of intramolecular interactions taking place in the latter.¹¹ Butane-2,3-dione is in tautomeric equilibrium with but-1-en-2-ol-3-one and buta-1,3-diene-2,3-diol, which are expected to be stabilised by –OH...O=C< and –OH...OH– intramolecular hydrogen bonds. Osmialowski *et al.*¹¹ showed that in chloroform solution (1*Z*,3*Z*)-1,4-di(pyridin-2-yl)buta-1,3-diene-2,3-diol is in *ca* 9:1 equilibrium with (3*Z*)-3-hydroxy-1,4-di(pyridin-2-yl)but-3-en-2-one, while no 1,4-di(pyridin-2-yl)butane-2,3-dione was detected. Theoretical calculations showed that –CO–COH–, especially the highly

conjugated –HOC=COH– forms, are preferred in tautomeric mixtures in both vacuum and chloroform solution, due to one or two O–H...N interactions.

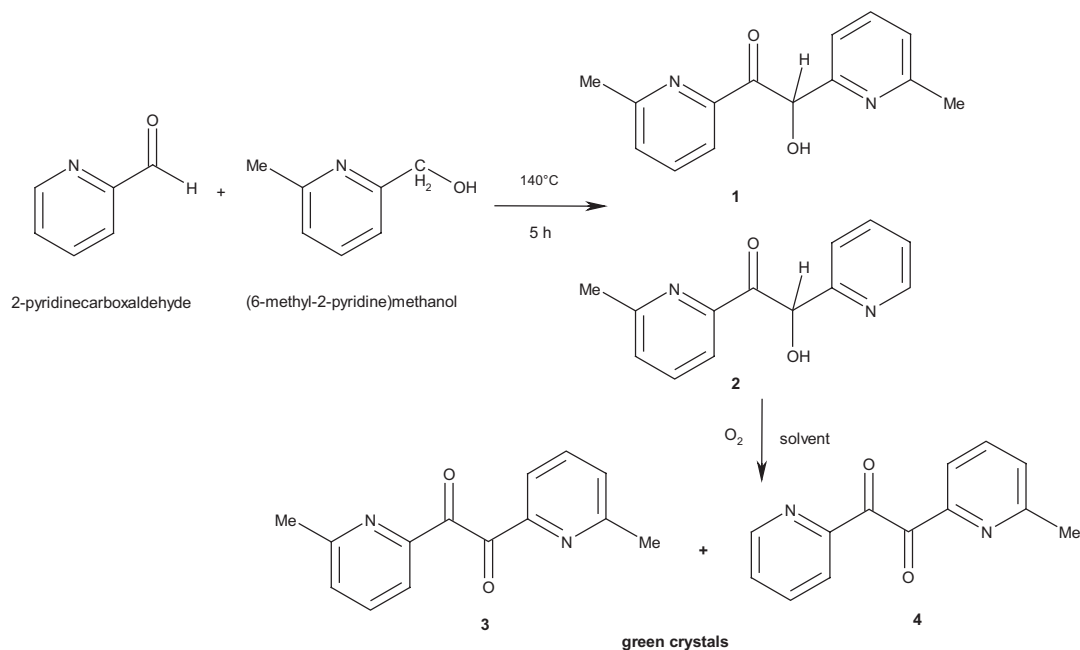
According to a recent study of condensation reactions without catalyst and solvent of different aldehydes and methylpyridines to obtain precursor or intermediary compounds,¹² it was proposed that the reaction of 2-pyridinecarboxaldehyde and 2-pyridinemethanol at 140°C without a catalyst or solvent yielded the compound 2-hydroxy-1,2-di(pyridin-2-yl)ethan-1-one.¹³ In addition, it has been reported that reaction of (6-methylpyridin-2-yl)methanol and 2-pyridinecarboxaldehyde without solvent and catalyst yielded the compound 1,2-bis(6-methylpyridin-2-yl)ethane-1,2-diol, with single-crystal X-ray diffraction showing that it is a symmetrical molecule with two intramolecular hydrogen bonds.¹⁴

As a result, it was proposed to isolate the precursor 2-hydroxy-[1,2-bis(6-methylpyridin-2-yl)]ethan-1-one (**1**) from the reaction of (6-methylpyridin-2-yl)methanol and 2-pyridinecarboxaldehyde according to Scheme 1 and justify the proposal that the compounds with a –CO–COH– group could be oxidised to –CO–CO– in solution in the presence of oxygen. However, the reaction results were more interesting, as proposed in Scheme 2. Crystal structure determination of the co-crystal is important because, to the best of our



Scheme 1

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knowledge, the synthesis conditions and crystal structure of the title compounds have not been reported.

Experimental

Materials and instruments

2-Pyridinecarboxaldehyde and (6-methylpyridin-2-yl)methanol were supplied by Aldrich Chemical Co. and were distilled before use. IR spectra of reaction products were recorded on a Vertex model 70 Bruker 750 FT-IR spectrophotometer by ATR. ^1H NMR spectra were obtained on a Varian 300-MHz NMR spectrometer in D_2O . Melting points were measured using an SEV (0–300°C) apparatus and are uncorrected. The crystal structure data were measured with a Bruker P4/Pc diffractometer with a graphite monochromator and $\text{Mo-K}\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$).

Synthesis of 2-hydroxy-[1,2-bis(6-methylpyridin-2-yl)]ethan-1-one (1) and 2-hydroxy-1-(pyridin-2-yl)-2-(6-methylpyridin-2-yl)ethan-1-one (2): Initially the reaction was expected to form only the compound 2-hydroxy-[1,2-bis(6-methylpyridin-2-yl)]ethan-1-one (1) (Scheme 1). A mixture of (6-methylpyridin-2-yl)methanol (0.008 mol) and 2-pyridinecarboxaldehyde (0.008 mol) was heated at 140°C with no solvent or catalyst. The reaction mixture was magnetically stirred for 5 h. The appearance of the mixture changed from colourless to a red-brown oily liquid. Immediately, without allowing it to cool, the mixture was precipitated by adding 2 M NaOH solution dropwise with agitation. After adding the required amount to obtain a precipitate (4.0 ml of NaOH solution), the yellow-brown powder was filtered using vacuum. The yield was 27% and the m.p. of the powder was 95–100°C.

Synthesis of a co-crystal of two components: 1,2-bis(6-methylpyridin-2-yl)ethane-1,2-dione (3) and 1-(pyridin-2-yl)-2-(6-methylpyridin-2-yl)ethane-1,2-dione (4): The powder obtained from the first procedure was dissolved in cyclohexane and filtered, producing a green-yellow solution that was poured into a precipitation vessel and kept at room temperature for a week. At the end of that time, small green crystals were formed, with m.p. 115–120°C, and a small portion of yellow powder on the glass wall, with m.p. 84–89°C. Both compounds were dissolved again in cyclohexane to obtain only green crystals with m.p. 120–123°C.

X-Ray experiments

The title mixture crystallises from cyclohexane as green prismatic crystals. A single crystal with approximate dimensions $0.50 \times 0.40 \times 0.30 \text{ mm}^3$ was selected for X-ray structure determination.

Three-dimensional room-temperature X-ray data were collected in the range $3.0^\circ < 2\theta < 50.0^\circ$ on a Bruker P4 diffractometer with a graphite monochromator and $\text{Mo-K}\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$) using

the ω -scan method. A total of 1968 independent reflections (out of 7836 measured) for which $|F|/\sigma(|F|) > 4.0$ were corrected for Lorentz and polarisation effects, but not for X-ray absorption. The structure was solved using direct methods and refined¹⁵ on F^2 by full-matrix least-squares analysis with anisotropic displacement parameters for the non-hydrogen atoms. Hydrogen atoms were placed in the calculated positions.

Results and discussion

The results from condensation reaction at an equimolar ratio of 2-pyridinecarboxaldehyde and (6-methylpyridin-2-yl)methanol at 140°C without catalyst or solvent were unexpected. Only the new compound 2-hydroxy-[1,2-bis(6-methylpyridin-2-yl)]ethan-1-one (1) was expected according to the recently reported conditions for the reaction of 2-pyridinecarboxaldehyde and (pyridin-2-yl)methanol.¹³

Figure 1 shows the IR spectrum for the yellow-brown powder from the condensation reaction of 2-pyridinecarboxaldehyde and (6-methylpyridin-2-yl)methanol. The spectrum shows an intense band at 1709 cm^{-1} assigned^{16,17} to $\text{C}=\text{O}$ stretching vibrations, which is weaker than in the starting material (2-pyridinecarboxaldehyde), and bands at 3472 and 1183 cm^{-1} assigned to $\nu\text{O-H}$ vibration stretching and $\nu\text{C-OH}$, respectively, indicating the presence of a $-\text{C}(\text{O})-\text{COH}-$ group, but the results did not indicate that it was a mixture of compounds. The green crystals obtained after the yellow-brown powder was treated with cyclohexane gave the IR spectrum in Fig. 2. It clearly shows two bands at 1710 and 1694 cm^{-1} due to the two $\text{C}=\text{O}$ groups characteristic of an α -diketone.

^1H NMR spectra clearly indicated that the green crystals are two compounds (Fig. 3), since the spectrum presented two signals at 2.41 and 1.56 ppm, which are due to two different $-\text{CH}_3$ groups. In addition, the signal at 8.59 ppm indicated that a proton is present in the *ortho*-position of the pyridine ring, which might be due to the co-compound 1-(pyridin-2-yl)-2-(6-methylpyridin-2-yl)ethane-1,2-dione, whereas the spectrum should only present signals for the compound 1,2-bis(6-methylpyridin-2-yl)ethane-1,2-dione. The signals between 8.59 and 7.24 ppm were assigned to aromatic protons.

The characterisation by EI mass fragmentation was decisive.¹⁸ The EI spectrum gave molecular ions at m/z 240

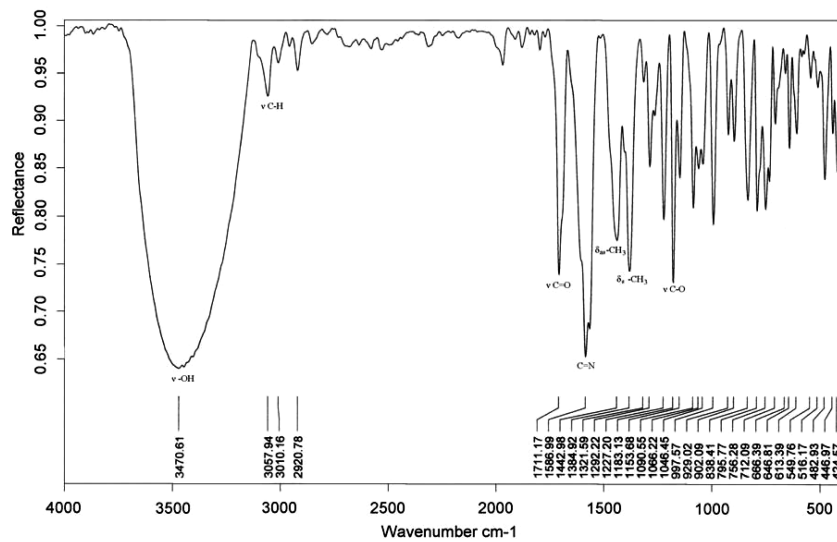


Fig. 1 IR spectrum of compounds 1 and 2.

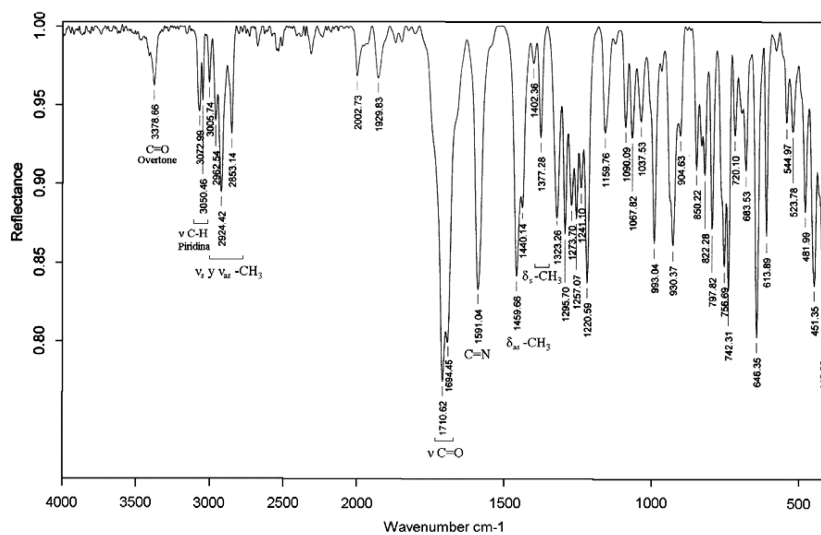


Fig. 2 IR spectrum of compounds 3 and 4.

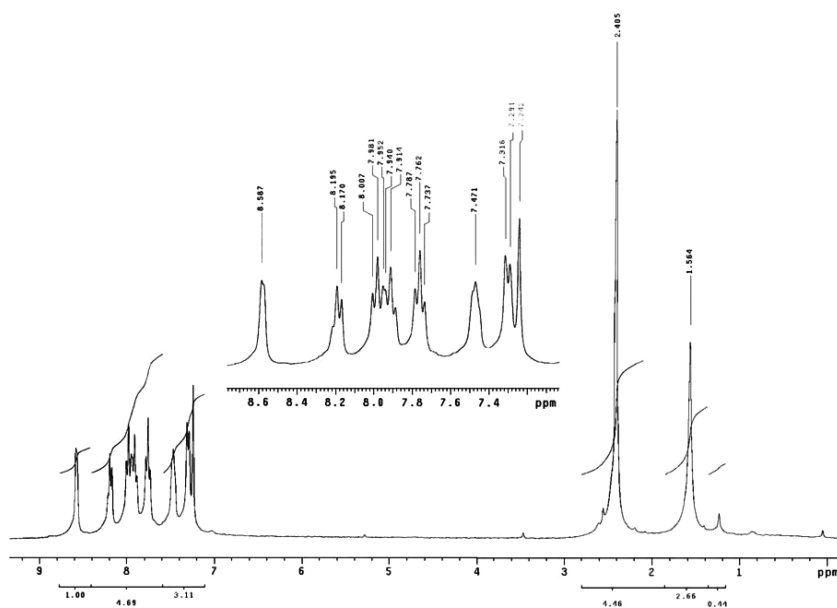


Fig. 3 ¹H NMR of the green crystals in CDCl₃.

for the 1,2-bis(6-methylpyridin-2-yl)ethane-1,2-dione (**3**) and m/z 226 for 1-(pyridin-2-yl)-2-(6-methylpyridin-2-yl) ethane-1,2-dione (**4**). Mass spectrometry confirmed the presence of both compounds based on molecular ions at m/z 240 and 226.

The spectroscopy data were corroborated by X-ray diffraction. The crystal data and pertinent details of the

Table 1 Crystal data and structure determination of the title compounds

Empirical formula	$C_{13.40}H_{10.79}N_2O_2$
Color, habit	Green, prismatic
Crystal size	$0.5 \times 0.4 \times 0.3 \text{ mm}^3$
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	$a = 7.859(5) \text{ \AA}$ $b = 8.021(4) \text{ \AA}$ $c = 9.060(5) \text{ \AA}$ $\alpha = 101.36(2)^\circ$ $\beta = 90.60(3)^\circ$ $\gamma = 90.92(3)^\circ$
Volume	$559.8(5) \text{ \AA}^3$
Z	2
Formula weight	231.77
Density (calc.)	1.375 g cm^{-3}
Absorption coefficient	0.095 mm^{-1}
$F(000)$	242
Diffractometer used	Bruker P4
System used	XSCAnS, ²¹ release 2.31
Radiation	Mo- K_α ($\lambda = 0.71073 \text{ \AA}$)
Voltage and tube current	50 kV, 25 mA
Temperature	297(2) K
Monochromator	Highly oriented graphite crystal
2θ range	$3.0\text{--}50.0^\circ$
Scan type	ω
Scan speed	Variable speed, $1.75\text{--}17.5^\circ \text{ min}^{-1}$ in ω
Scan range (ω)	1.86° + separation between the $K_{\alpha 1}$ and $K_{\alpha 2}$ positions
Background measurement	Stationary crystal and stationary counter at the beginning and end of a scan, each for 25% of the total scan time
Standard reflections	3 measured every 97 reflections: 1 0 2; 1 2 0; 2 0 1
Correction from standards	min 0.942, max 1.022
Index ranges	$-9 \leq h \leq 9$, $-9 \leq k \leq 9$, $-10 \leq l \leq 10$
Reflections collected	7836
Independent reflections	1968 ($R_{\text{int}} = 6.95\%$)
Completeness	99.2% to $2\theta = 50.0^\circ$
Reflections with $F_o > 4\sigma(F_o)$	1103
$\langle I/\sigma(I) \rangle$ (all data)	8.07
Absorption correction	None
System used ^{15,22}	SHELXTL 5.03 and SHELXL-Plus 5.10
Wilson's statistics	$\langle E^2 - 1 \rangle = 1.036$
Solution	Direct methods and difference Fourier maps
Refinement method	Full matrix least-squares
Quantity minimised	$\Sigma [w(F_o^2 - F_c^2)^2]$
Hydrogen atoms	Riding model, fixed isotropic U
Restraints, constraints	1, 0
Weighting scheme	$w = [\sigma^2(F_o^2) + (0.1283 P)^2 + 0.0584 P]^{-1}$, where $P = (\max[F_o^2, 0] + 2F_c^2)/3$ $R_1 = 6.60\%$, $wR_2 = 19.41\%$ $R_1 = 11.18\%$, $wR_2 = 23.26\%$ $S = 1.042$
Final R indices ($I > 2\sigma(I)$)	
Final R indices (all data)	
Goodness-of-fit	0.000, 0.000
Largest and mean Δ/σ	1968/166
Data-to-parameters ratio	0.223 e \AA^{-3}
Largest difference peak	$-0.275 \text{ e \AA}^{-3}$
Largest difference hole	

Table 2 Selected bond lengths/ \AA

O(1)–C(7)	1.196(4)	C(8)–C(9)	1.465(4)
O(2)–C(8)	1.188(4)	C(1)–C(2)	1.464(5)
C(6)–C(7)	1.449(5)	C(13)–C(14)	1.481(5)
C(7)–C(8)	1.524(5)		

experimental crystal data, structure determination and refinement are shown in Table 1. Selected bond lengths are given in Table 2. The solid sample is a co-crystal formed by two molecules present in different proportions: $C_{13}H_{10}N_2O_2$ (Fig. 4A) with 60.4% occupancy and $C_{14}H_{12}N_2O_2$ (Fig. 4B) with 39.6% occupancy. These molecules are present in solution and crystallised together.

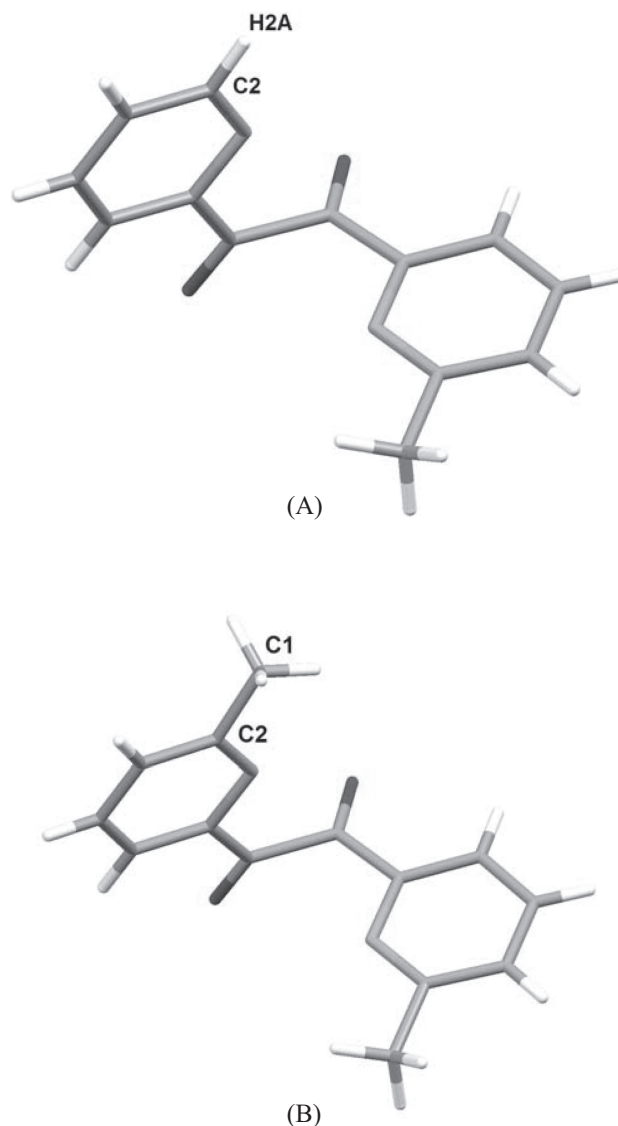


Fig. 4 (A) Molecule A, $C_{13}H_{10}N_2O_2$ with 60.42% occupancy in the co-crystal. (B) Molecule B, $C_{14}H_{12}N_2O_2$ with 39.58% occupancy in the co-crystal.

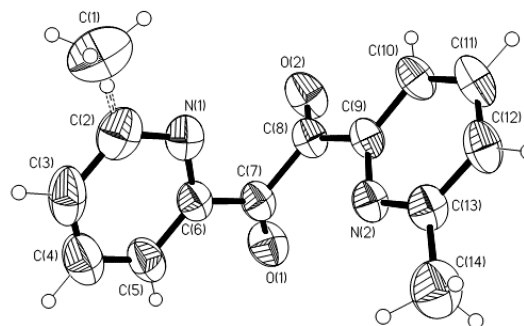


Fig. 5 Molecular representation of the composite title compound, $C_{13.40}H_{10.79}N_2O_2$, with the atom labelling scheme shown; thermal ellipsoids are at the 30% probability level.

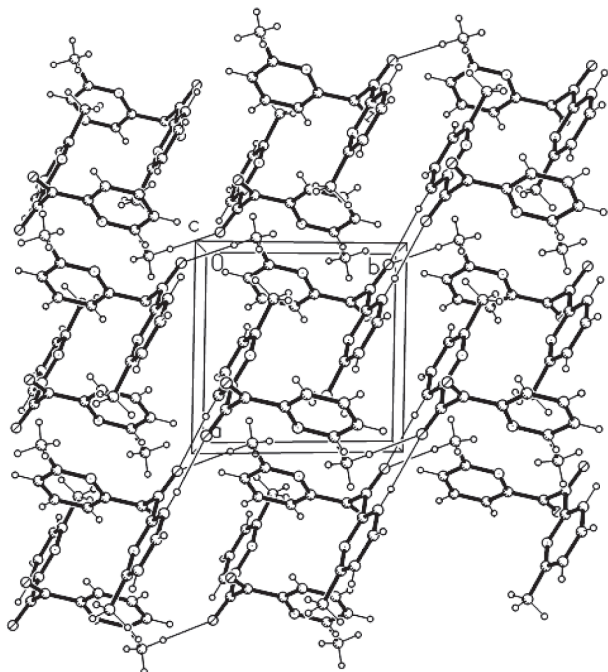


Fig. 6 View of the molecular packing structure of $C_{13.40}H_{10.79}N_2O_2$, showing H-bonding and $\pi\cdots\pi$ interaction at 3.673 Å between equivalent symmetry related pyridine rings [N1, C2 to C6; symmetry code: $1-x, 1-y, 1-z$].

All atoms occupy general positions in the unit cell and a representation of the composition of the two molecules in the crystal is given in Fig. 5. The pyridine rings in the title compound are nearly perpendicular to each other, with a dihedral angle of 85.9° . Related compounds show similar dihedral geometry: 1,2-di-2-pyridylethanedione¹⁹ with 82.1° and 1-(6-methylpyridin-2-yl)-2-phenylethanedione²⁰ with 86.1° . The torsion angle for the dione moiety, $O=C-C=O$, is 73.5° for the title compound, and -78.6° and 75.8° for the related compounds mentioned above. The C7–C8 distance of 1.524(5) Å is significantly longer than the value of 1.48 Å expected for a $C\ sp^2-C\ sp^2$ bond. Elongation of the corresponding bond in the related compounds is also evident, which could be due to repulsion between the two ketonic oxygen atoms.

The crystal packing presents intermolecular H-bonding contacts between one of the O atoms [O2] and two hydrogens, H1B of the CH_3 group of a symmetry related molecule (B) [O2...H1B, 2.199 Å; C1–H1B...O2, 173.93°] and H10A of the other ring of the same molecule [O2...H10A, 2.512

Å; C10–H10A...O2, 165.98°]. There is a $\pi\cdots\pi$ interaction between equivalent symmetry related pyridine rings [N1, C2 to C6; symmetry code: $1-x, 1-y, 1-z$], with a separation of 3.673 Å (3.35 Å in graphite);²¹ these interactions stabilise the solid structure (Fig. 6). The results open the opportunity to obtain precursor compounds that could then yield novel compounds without a catalyst in a solvent-free reaction.

CCDC 644649 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request.cif.

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