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A CONVENIENT PROCEDURE FOR THE PREPARATION OF 5,6-DIHYDRO-6-NITRO-5-PHENYLFURO[2,3-d]PYRIMIDIN-4(3*H*)-ONES AND 5-PHENYLFURO[2,3-d]PYRIMIDIN-4(3*H*)-ONES

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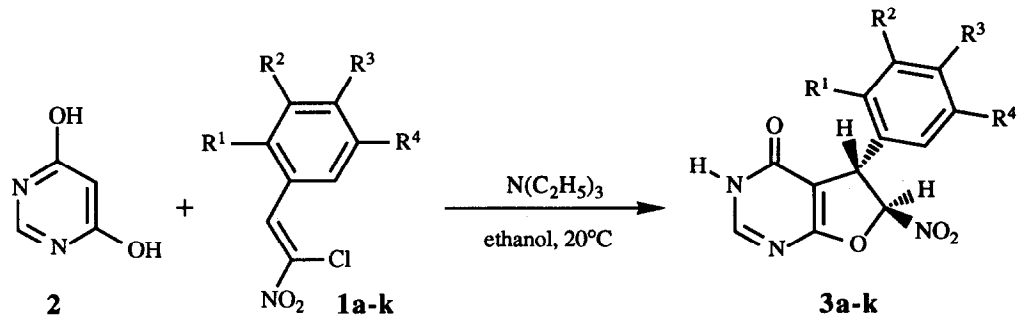
Abstract: The triethylamine-promoted condensation of *Z*-(2-chloro-2-nitroethenyl)benzenes with 4,6-dihydroxypyrimidine provides 5,6-dihydro-6-nitro-5-phenylfuro[2,3-d]pyrimidin-4(3*H*)-ones at room temperature. Involving the same starting materials, but using DBU in refluxing ethanol instead of triethylamine, the so far unknown 5-phenylfuro[2,3-d]pyrimidin-4(3*H*)-ones are obtained.

Pyrimidine fused heterocycles occupy an important place in biological and medicinal chemistry. In this context, the furo[2,3-d]pyrimidine ring has aroused considerable interest and a number of its derivatives have been synthesized, then tested in various fields. Thus, numerous products belonging to this class of compounds have been evaluated for their antiinflammatory,[1] antibacterial,[1,2] antitumoral,[2,3] antihypertensive,[4] antiulcer,[5] antiviral,[6] muscle relaxing,[7] radioprotective,[8] antimalarial,[9] trichomonacidal,[10] pesticidal,[11] insecticidal,[12] agrochemical,[13] or herbicidal[14] properties. Furthermore, two recent patents mention some furo[2,3-d]pyrimidine derivatives as agents for treating neuropathy.[15]

The chemistry of furo[2,3-d]pyrimidines has been reviewed a few years ago,[16] and most of the previously described routes to this heterocyclic structure are gathered in this publication, although some references have been omitted.[17] Moreover, several new syntheses appeared in more recent reports and deserve quotation.[18] This literature survey reveals that, to our knowledge, no preparation of the furo[2,3-d]pyrimidine ring has been achieved starting from 4,6-dihydroxypyrimidine, although this commercially available compound could be considered as a choice precursor for the synthetic approach of the furopyrimidin system. In view of this fact, and in continuation of our studies on the utilization of (2-chloro-2-nitroethenyl)benzenes in synthesis,[19] it appeared attractive to explore the possible use of these β-chloro-β-nitrostyrenes as building blocks to prepare furo[2,3-d]pyrimidine derivatives by condensation with 4,6-dihydroxypyrimidine.

We show here that the reaction of *Z*-(2-chloro-2-nitroethenyl)benzenes **1a-k** with 4,6-dihydroxypyrimidine **2** in anhydrous ethanol, at room temperature, in the presence of triethylamine, provides the 5,6-dihydro-6-nitro-5-phenylfuro[2,3-d]pyrimidin-4(3*H*)-ones (Table 1). In most of the considered examples, these hitherto unknown furopyrimidines are exclusively obtained in the *trans* configuration **3a-k** (Scheme 1). However, in certain cases, variable amounts of the *cis* isomer have been detected in the crude product of the reaction. This fact concerns the reactions carried out with compounds **1e**, **1g**, **1i**, **1j** or **1k** as starting materials. In these circumstances, the chromatographic separation of the pure *trans* derivative has been achieved for **3e** and **3g**, whereas the obtention of pure **3i**, **3j** or **3k** failed, since they were always contaminated with the *cis* isomer. Furthermore, with β-chloro-β-nitrostyrenes bearing a nitro group on the aromatic ring (**1i-k**), considerable amounts of 5,6-unsaturated compounds **4i-k** were formed, which markedly lowered the yields of 5,6-dihydro derivatives. In this context, it is worth pointing out that a condensation carried out starting from the 1-(2-chloro-2-nitroethenyl)-4-nitrobenzene **1k** in the presence of potassium fluoride (instead of triethylamine) enabled us to avoid the formation of the unsaturated compound **4k**, but provided the *trans* derivative **3k** still mixed with its *cis* isomer. We have also ascertained that the shortening of the reaction times did not remove these drawbacks and led to partial recovery of the starting materials.



1, 3, 4	R^1	R^2	R^3	R^4
a	H	H	H	H
b	Cl	H	H	H
c	H	Cl	H	H
d	H	H	Cl	H
e	OCH_3	H	H	H
f	H	OCH_3	H	H
g	H	H	OCH_3	H
h	H	OCH_3	OCH_3	OCH_3
i	NO_2	H	H	H
j	H	NO_2	H	H
k	H	H	NO_2	H

Scheme 1

Table1: Compounds **3a-h** prepared.[a]

Compound	Yield (%)	melting point (°C) (recrystallization solvent)	Molecular formula (molecular weight)	Analysis (%) Calculated / (found) C	H	N
3a	55	224-225 (benzene)	$C_{12}H_9N_3O_4$ (259.2)	55.60 (55.85)	3.50 (3.61)	16.21 (16.09)
3b	65	186-188 (benzene/acetonitrile)	$C_{12}H_8ClN_3O_4$ (293.7)	49.08 (48.90)	2.75 (2.83)	14.31 (14.42)
3c	57	239-240 (toluene)	$C_{12}H_8ClN_3O_4$ (293.7)	49.08 (49.33)	2.75 (2.84)	14.31 (14.20)
3d	68	230-232[b] (benzene/acetonitrile)	$C_{12}H_8ClN_3O_4$ (293.7)	49.08 (49.36)	2.75 (2.87)	14.31 (14.15)
3e	41	227-228 (benzene/cyclohexane)	$C_{13}H_{11}N_3O_5$ (289.2)	53.98 (54.17)	3.83 (3.93)	14.53 (14.35)
3f	51	175-177 (benzene/heptane)	$C_{13}H_{11}N_3O_5$ (289.2)	53.98 (54.22)	3.83 (3.90)	14.53 (14.65)
3g	60	221-222 (benzene/cyclohexane)	$C_{13}H_{11}N_3O_5$ (289.2)	53.98 (53.09)	3.83 (3.95)	14.53 (14.44)
3h	58	238-240 (2-propanol)	$C_{15}H_{15}N_3O_7$ (349.3)	51.58 (51.76)	4.33 (4.46)	12.03 (11.91)

[a] With regard to dinitro derivatives **3i-k**, pure products have not been isolated because they were always contaminated with their *cis* isomers. In these cases, the overall yields (*cis*+*trans*) were 40% starting from **1i**, 19% starting from **1j** and 31% starting from **1k**.

[b] Allotropic change at 140-142°C.

The spectral data for compounds **3a-h** are reported in Table 2. The low values (2.0-2.9 Hz) measured for the ^3J coupling constants between the protons H-5 and H-6 are indicative of a *trans* configuration. This stereochemistry has been confirmed by a single crystal X-ray analysis of the 5,6-dihydro-6-nitro-5-phenylfuro[2,3-d]pyrimidin-4(3*H*)-one (**3a**) selected as a representative of its class of products (Figure 1). The crystallographic study also reveals that this compound **3a** exists, in the solid state, in the pure 4(3*H*)-oxo form (to the exclusion of the 4-hydroxy form which could be present because of the possible prototropic tautomerism[20]). In this connection, the examination of the infrared spectra recorded for compounds **3a-h** (Table 2) shows characteristic strong absorptions (1667-1693 cm^{-1}) which indicate that the 4-oxo form is mainly present in all the considered cases.

Table 2: Spectral data of compounds **3a-h**.

Compound	IR $\nu_{C=O}$ (cm^{-1})	^{1}H-NMR[a] δ, J (Hz)
3a	1667	4.93 (br d, 1H, J = 2.1); 6.60 (d, 1H, J = 2.1); 7.13-7.50 (m, 5Harom); 8.27 (s, 1H); 11.00-14.00 (sh, 1H, exchangeable with D_2O)
3b	1682	5.23 (br d, 1H, J = 2.3); 6.57 (d, 1H, J = 2.3); 6.96-7.13 (m,1Harom); 7.20-7.65 (m, 3Harom); 8.27 (s, 1H); 12.50-13.75 (sh, 1H, exchangeable with D_2O)
3c	1672	4.81 (d, 1H, J = 2.3); 6.18 (d, 1H, J = 2.3); 7.05-7.40 (m, 4Harom); 8.06 (s, 1H); 11.00-12.50 (sh, 1H, exchangeable with D_2O)
3d	1675	4.82 (br d, 1H, J = 2.0); 6.20 (d, 1H, J = 2.0); 7.18 and 7.37 (AA'BB' system, 4Harom); 8.06 (s, 1H); 12.50-13.50 (sh, 1H, exchangeable with D_2O)
3e	1672	3.87 (s, 3H); 5.12 (d, 1H, J = 2.9); 6.08 (d, 1H, J = 2.9); 6.90-7.08 (m, 3Harom); 7.23-7.50 (m, 1Harom); 8.03 (s,1H); 12.70-13.20 (sh, 1H, exchangeable with D_2O)
3f	1684	3.76 (s, 3H); 4.88 (d, 1H, J = 2.1); 6.60 (d, 1H, J = 2.1); 6.70-7.00 (m, 3Harom); 7.16-7.40 (m, 1Harom); 8.28 (s, 1H); 12.50-13.60 (sh, 1H, exchangeable with D_2O)
3g	1668	3.80 (s, 3H); 4.78 (br d, 1H, J = 2,1); 6.08 (d, 1H, J = 2.1); 6.86 and 7.16 (AA'BB'system, 4Harom); 8.06 (s, 1H); 12.70-13.10 (sh, 1H, exchangeable with D_2O)
3h	1693	3.67 (s, 3H); 3.77 (s, 6H); 4.87 (d, 1H, J = 2.1); 6.52 (s, 2Harom); 6.60 (d, 1H, J = 2.1); 8.28 (s, 1H); 11.70-13.20 (sh, 1H, exchangeable with D_2O)

[a] Performed in DMSO - d_6 for **3a**, **3b**,**3f** and **3h**, in $CDCl_3$ for **3e**, or in the mixture $CDCl_3$ / DMSO - d_6 8:2 for **3c**, **3d**, and **3g**.

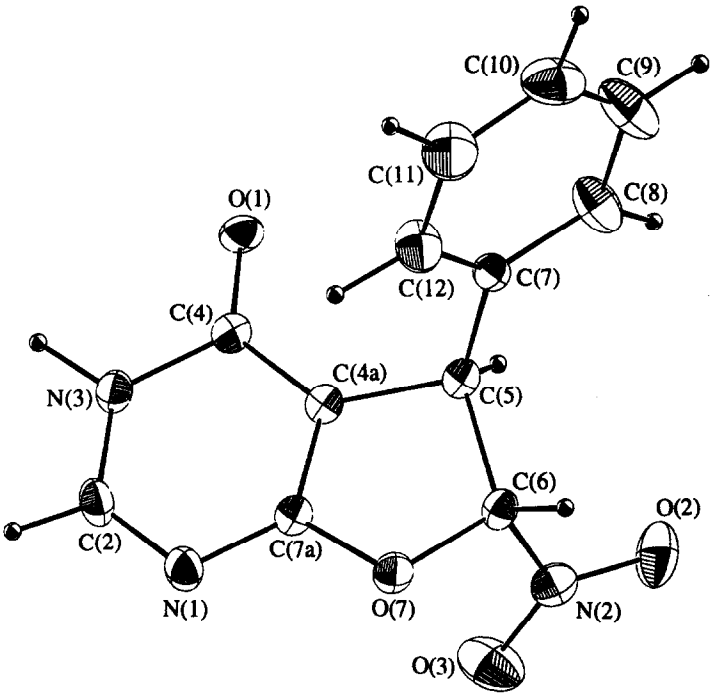
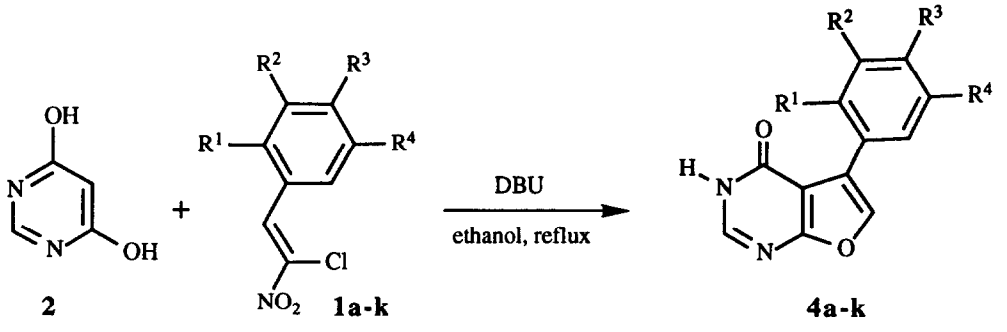


Figure 1. An ORTEP drawing of **3a.**
The thermal ellipsoids are drawn at a 30% probability level

When the above condensation is carried out in refluxing ethanol, involving 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) instead of triethylamine as a base, a complete loss of nitrous acid occurs *in situ* to afford the novel 5-phenylfuro[2,3-d]pyrimidines-4(3*H*)-ones **4a-k** according to Scheme 2 (Table 3).



Scheme 2

The spectral data relevant to furopyrimidines **4a-k** are reported in Table 4. As for the 6-nitro derivatives **3a-k**, the intense absorptions observed between 1662 and 1691 cm^{-1} in the infrared spectra of compounds **4a-k** clearly indicate that the 4-oxo tautomeric form strongly dominates.

Table3: Compounds **4a-k** prepared.

Compound	Reaction time (h)	Yield (%)	melting point (°C) (recrystallization solvent)	Molecular formula (molecular weight)	Analysis (%) Calculated / (found) C	H	N
4a	24	60	216-218 (benzene/cyclohexane)	$C_{12}H_8N_2O_2$ (212.2)	67.92 (68.14)	3.80 (3.91)	13.20 (13.38)
4b	24	58	213-215 (benzene/cyclohexane)	$C_{12}H_7ClN_2O_2$ (246.7)	58.44 (58.33)	2.86 (2.93)	11.36 (11.19)
4c	24	41	233-235 (benzene)	$C_{12}H_7ClN_2O_2$ (246.7)	58.44 (58.65)	2.86 (2.97)	11.36 (11.16)
4d	24	63	>260 (benzene/acetonitrile)	$C_{12}H_7ClN_2O_2$ (246.7)	58.44 (58.69)	2.86 (2.98)	11.36 (11.47)
4e	32	66	186-188 (benzene)	$C_{13}H_{10}N_2O_3$ (242.2)	64.46 (64.66)	4.16 (4.27)	11.56 (11.59)
4f	32	60	189-191 (benzene)	$C_{13}H_{10}N_2O_3$ (242.2)	64.46 (64.71)	4.16 (4.21)	11.56 (11.49)
4g	32	61	254-256 (benzene/acetonitrile)	$C_{13}H_{10}N_2O_3$ (242.2)	64.46 (64.57)	4.16 (4.09)	11.56 (11.41)
4h	32	56	223-225 (benzene/cyclohexane)	$C_{15}H_{14}N_2O_5$ (302.3)	59.60 (59.75)	4.67 (4.76)	9.27 (9.17)
4i	10	40	215-217 (benzene/acetonitrile)	$C_{12}H_7N_3O_4$ (257.2)	56.04 (56.13)	2.74 (2.84)	16.34 (16.16)
4j	16	51	259-260 (butanone)	$C_{12}H_7N_3O_4$ (257.2)	56.04 (56.33)	2.74 (2.86)	16.34 (16.20)
4k	8	65	>260 (butanone)	$C_{12}H_7N_3O_4$ (257.2)	56.04 (56.10)	2.74 (2.79)	16.34 (16.40)

Table 4: Spectral data of compound **4a-k**.

Compound	IR $\nu_{C=O}$ (cm^{-1})	^{1}H-NMR[a] δ, J (Hz)
4a	1686	7.23-7.50 (m, 3Harom); 7.73 (s, 1H); 7.83-8.05 (m, 2Harom); 8.11 (s, 1H); 8.17 (s, 1H); 12.45-12.85 (br s, exchangeable with D_2O)
4b	1682	7.28-7.65 (m, 4Harom); 7.93 (s, 1H); 8.10 (s, 1H); 12.35-12.85 (br s, exchangeable with D_2O)
4c	1691	7.20-7,56 (m, 2Harom); 7.85-8.05 (m, 1Harom); 8.13 (s, 2H); 8.28 (s, 1H); 12.45-13.15 (br s, exchangeable with D_2O)
4d	1686	7.40 and 8.05 (AA'BB'system, 4Harom); 8.12 (s, 1H); 8.22 (s, 1H); 12.60-13.20 (br s, exchangeable with D_2O)
4e	1672	3.80 (s, 3H); 6.83-7.43 (m, 3Harom); 7.83-7.90 (dd, 1Harom, J=1.8, 7.5); 8.00 (s, 1H); 8.10 (s, 1H);12.00-12.70 (br s, exchangeable with D_2O)
4f	1662	3.78 (s, 3H); 6.76-6.96 (m, 1Harom); 7.16-7.36 (dd, 1Harom, J=7.8, 8.1); 7.43-7.59 (m, 1Harom); 7.65-7.75 (m, 1Harom); 8.10 (s, 1H); 8.19 (s, 1H); 12.00-13.15 (sh, exchangeable with D_2O)
4g	1666	3.80 (s, 3H); 6.93 and 7.90 (AA'BB'system, 4Harom); 8.05 (s, 1H); 8.09 (s, 1H); 12.10-13.00 (sh, exchangeable with D_2O)
4h	1690	3.70 (s, 3H); 3.83 (s, 6H); 7.43 (s, 2Harom); 8.11 (s, 1H); 8.24 (s, 1H); 12.00-13.25 (sh, exchangeable with D_2O)
4i	1676	7.50-7.85 (m, 3H arom); 8.01 (s, 1H); 8.09 (br s, 1H); 8.07- 8.25 (m, 1Harom); 12.10-12.80 (br s, exchangeable with D_2O)
4j	1690	7.66 (t, 1Harom J=8.1); 8.05-8.20 (m, 1H arom); 8.12 (s, 1H); 8.38 (s, 1H); 8.33-8.46 (m, 1Harom); 8.93-9.05 (m, 1Harom); 10.30-12.30 (sh, exchangeable with D_2O)
4k	1685	8.16 (s, 1H); 8.25-8.35 (AA'BB'system, 4Harom); 8.44 (s,1H); 12.10-12.80 (br s, exchangeable with D_2O)

[a]Performed in DMSO - d_6.

EXPERIMENTAL

Melting points were determined with a Köfler hot stage apparatus and are uncorrected. ^{1}H NMR spectra were recorded using a Varian EM390 (90 MHz) instrument with tetramethylsilane as an internal standard. Infrared spectra were recorded on a Perkin-Elmer 1710 spectrometer as KBr pellets. Microanalyses were

carried out by the "Service d'Analyse du C.N.R.S., Vernaison". Silica gel Merck (230-400 Mesh ASTM) was used for column chromatography. Starting *Z*-(2-chloro-2-nitroethenyl)benzenes **1a-k** were synthesized following a previously described procedure.[19c] Absolute ethanol was obtained according to classical methods.[21] Commercially available reagents (Janssen Chimica) were used without further purification.

***General Procedure for the preparation of 5,6-dihydro-6-nitro-5-phenylfuro[2,3-d]pyrimidin-4(3H)-ones* 3a-k:**

A mixture of the appropriate (2-chloro-2-nitroethenyl)benzene(**1a-k**, 5 mmol), 4,6-dihydroxypyrimidine (**2**, 0.62 g, 5.5. mmol) and absolute ethanol (20 mL) was placed in a dried, two-necked, 50-mL round-bottomed flask fitted with a septum inlet. This suspension was stirred for 5 minutes with a magnetic bar under argon atmosphere, before anhydrous triethylamine (0.55 g, 0.76 mL, 5.5. mmol) was added with a syringe. An efficient stirring was continued for 24 hours, and the volatile materials were evaporated under reduced pressure. The crude product obtained was then flash-chromatographed over a silica gel column (150 g, eluting with a dichloromethane / methanol mixture 96:4). Removal of the solvents *in vacuo* gave the pure compounds **3a-h** which were recrystallized in the appropriate solvent (Table 1). With regard to derivatives bearing a nitro substituent on the aromatic ring, the expected products **3i-k** were always contaminated with variable amounts of the *cis* isomer in spite of numerous attempted chromatographies involving either larger quantities of silica gel or /and the use of other eluting systems.

***General Procedure for the preparation of 5-phenylfuro[2,3-d]pyrimidin-4(3H)-ones* 4a-k:**

A mixture of the appropriate (2-chloro-2-nitroethenyl)benzene (**1a-k**, 5 mmol), 4,6-dihydroxypyrimidine (**2**, 0.62 g, 5.5. mmol) and absolute ethanol (20 mL) was placed in a dried, two-necked, 50-mL round-bottomed flask equipped with a septum inlet and a water condenser. This suspension was stirred with a magnetic bar, then gently refluxed under inert atmosphere using a thermostated oil bath. Five minutes later, when the starting 2-chloro(2-nitroethenyl)benzene **1a-k** was completely dissolved, DBU (1.67 g, 1.64 mL, 11 mmol) was carefully added with a syringe maintaining a moderate boiling. The progress of the reaction was monitored by thin layer chromatography (eluent dichloromethane / methanol 96:4). When the starting (2-chloro-2-nitroethenyl)benzene **1a-k** had completely disappeared (Table 3), the reaction mixture was allowed to cool to room temperature, then filtered by suction using a sintered funnel. In most cases, the isolated solid (after thorough rinsing with several portions of dichloromethane and methanol) did not contain any furopyrimidine **4**. The combined filtrates were then evaporated under reduced pressure to leave a crude residue which was flash-chromatographed on a silica gel column (150 g, eluent dichloromethane / methanol 96:4). Evaporation of the solvents under reduced pressure provided pure **4a-k** (Table 3) which were subsequently recrystallized.

In the case of the nitro derivatives **4j** and **4k** which are scarcely soluble, a part of the product remained in the precipitate filtered out from the reaction mixture (even after several washings with methanol). In such cases, the solid was taken up in the appropriate recrystallizating solvent (Table 3), the suspension was refluxed with stirring, then filtered whilst hot. Cooling of the filtrate afforded a crop of the wanted compound (**4j** or **4k**) which was combined with the chromatographed product to calculate the yields reported in Table 3.

X-Ray Crystallographic Analysis of 3a:

Crystal data, collection and refinement parameters:

molecular formula: $C_{12}H_9N_3O_4$; molecular weight: 259.2; crystal system: monoclinic; space group: $P2_1/c$; crystal size: 0.70 x 0.50 x 0.45 mm; a = 13.241(5) Å; b = 13.789(6) Å; c = 6.483(3) Å; β = 104.22(3) deg.; V = 1147(2) Å^3; Z = 4; ρ calc.= 1.50 g.cm^{-3}; F (000): 536; μ = 1.1 cm^{-1}; number of reflections for lattice parameters: 25; range 15-16; scan type: ω-2θ; scan width: 1.2 + 0.34 tan θ; θ range: 1-25 deg.; standard reflections: two, measured every two hours; number of measured reflections: 2004; number of reflections used [$I \geq 3\ \sigma(I)$]: 1163; minimum and maximum height in final $\Delta\rho$: -0.2 and 0.2 e.Å^{-3}; number of refined parameters: 174; $R = [\ \Sigma|\Delta F| / \Sigma\ |F_o|\ ] = 0.051$; $R_w = [\ \Sigma w(\Delta F)^2 / \Sigma w F_o^2\ ]^{1/2} = 0.050$ (w = 1).

The data were collected at 18°C on a Philips PW1100 diffractometer using graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å). The structure was solved by direct methods and subsequent Fourier maps. Refinements were carried out by least squares methods in three blocks. Non-hydrogen atoms were anisotropically refined. All hydrogen atoms were found on difference maps, their coordinates were not refined, and they were given an overall isotropic parameter. Neither absorption correction, nor extinction correction was necessary. Interatomic bond lengths and bond angles are listed in Tables 5 and 6, respectively.[22]

Table 5: Bond Lenghts (Å) for compound **3a**.

N (1)	C (2)	1.311(5)	N (1)	C (7a)	1.338(5)
N (2)	O (2)	1.211(4)	N (2)	O (3)	1.205(4)
N (2)	C (6)	1.533(5)	N (3)	C (2)	1.341(5)
N (3)	C (4)	1.412(5)	O (1)	C (4)	1.231(5)
O (7)	C (6)	1.404(4)	O (7)	C (7a)	1.374(5)
C (4)	C (4a)	1.420(5)	C (4a)	C (5)	1.499(5)
C (4a)	C (7a)	1.353(5)	C (5)	C (6)	1.555(5)
C (5)	C (7)	1.528(5)	C (7)	C (8)	1.373(6)
C (7)	C (12)	1.366(6)	C (8)	C (9)	1.394(7)
C (9)	C (10)	1.374(7)	C (10)	C (11)	1.351(8)
C (11)	C (12)	1.391(7)			

Table 6: Bond Angles (deg.) for compound **3a**.

C (7a)	N (1)	C (2)	111.3(3)	O (3)	N (2)	O (2)	125.9(4)
C (6)	N (2)	O (2)	115.5(3)	C (6)	N (2)	O (3)	118.5(4)
C (4)	N (3)	C (2)	123.7(3)	C (7a)	O (7)	C (6)	106.3(3)
N (3)	C (2)	N (1)	125.8(4)	O (1)	C (4)	N (3)	120.2(4)
C (4a)	C (4)	N (3)	111.1(3)	C (4a)	C (4)	O (1)	128.7(4)
C (5)	C (4a)	C (4)	131.1(3)	C (7a)	C (4a)	C (4)	118.9(4)
C (7a)	C (4a)	C (5)	110.0(3)	C (6)	C (5)	C (4a)	98.5(3)
C (7)	C (5)	C (4a)	114.5(3)	C (7)	C (5)	C (6)	112.2(3)
O (7)	C (6)	N (2)	108.1(3)	C (5)	C (6)	N (2)	108.2(3)
C (5)	C (6)	O (7)	108.7(3)	C (8)	C (7)	C (5)	119.0(4)
C (12)	C (7)	C (5)	122.2(4)	C (12)	C (7)	C (8)	118.8(4)
O (7)	C (7a)	N (1)	117.9(3)	C (4a)	C (7a)	N (1)	129.2(4)
C (4a)	C (7a)	O (7)	112.9(3)	C (9)	C (8)	C (7)	119.9(5)
C (10)	C (9)	C (8)	120.5(5)	C (11)	C (10)	C (9)	119.5(5)
C (12)	C (11)	C (10)	120.2(5)	C (11)	C (12)	C (7)	121.0(5)

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