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Synthesis and Structure Determination of 2-Cyano-3-(1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)acrylamide

Benson M. Kariuki [1], Bakr F. Abdel-Wahab [2], Hanan A. Mohamed [2] and Gamal A. El-Hiti [3,*]

[1] School of Chemistry, Cardiff University, Main Building, Park Place, Cardiff CF10 3AT, UK; kariukib@cardiff.ac.uk
[2] Applied Organic Chemistry Department, Chemical Industries Research Institute, National Research Centre, Dokki, Giza 12622, Egypt; bf.fathy@nrc.sci.eg (B.F.A.-W.); hananmoh257@gmail.com (H.A.M.)
[3] Cornea Research Chair, Department of Optometry, College of Applied Medical Sciences, King Saud University, Riyadh 11433, Saudi Arabia
* Correspondence: gelhiti@ksu.edu.sa; Tel.: +966-11469-3778; Fax: +966-11469-3536

Abstract: 2-Cyano-3-(1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)acrylamide (**3**) was synthesized in 90% yield from condensation of equimolar equivalents of 1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazole-4-carbaldehyde (**1**) and 2-cyanoacetamide (**2**) in boiling ethanol under basic condition for 45 min. The structure of **3** was determined using NMR spectroscopy and single crystal X-ray diffraction.

Keywords: synthesis; X-ray crystal structure; heterocycles; pyrazole; thiophene

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1. Introduction

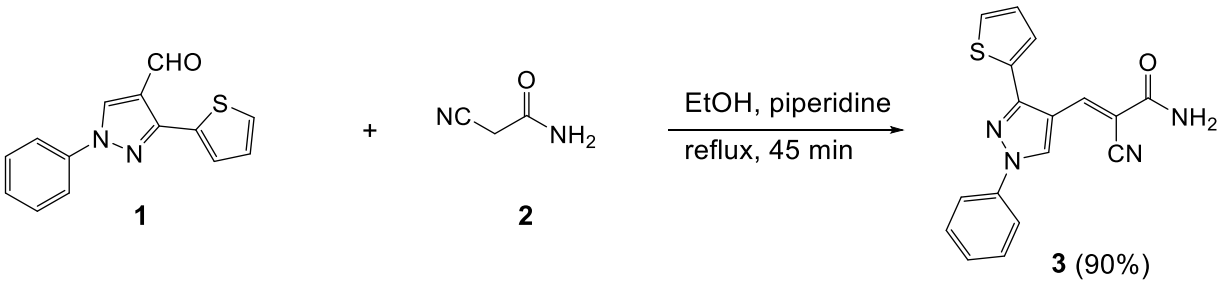
Compounds containing the acrylamide residue are potentially biologically active as well as acting as precursors in many organic syntheses [1–4]. Pyrazoles are also important heterocycles with promise for medicinal applications as a result of their wide range of biological activities [5,6]. In addition, heterocycles containing thiophene ring systems have many latent applications [7–9]. The synthesis of heterocycles containing both pyrazole and thiophene moieties is therefore an intriguing prospect.

The most recent synthetic procedures for the production of pyrazoles involve cycloaddition of *N*-isocyanoiminotriphenylphosphorane and terminal alkynes in the presence of a catalyst [10], one-pot condensation of carbonyl compounds and hydrazine monohydrochloride in the presence of oxygen [11], cyclization of β,γ-unsaturated hydrazones in the presence of oxygen and a copper catalyst [12], and the reaction of diarylhydrazones and vicinal diols in the presence of iron-containing catalyst [13]. In the case of thiophene derivatives, synthesis involves Paal–Knorr reaction [14,15], Gewald reaction [16–18], and reactions involving sulfuration and cyclization processes of alkynes [19–21]. It has been reported that 2-cyanoacrylamides can be used as an active ingredient in chemotherapy [22]. In this paper, we report the synthesis and characterization of 2-cyano-3-(1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)acrylamide (**3**). The structures of several related compounds that contain the pyrazole and thiophene ring systems have been reported [23–27].

2. Results and Discussion

2.1. Synthesis of 3

The condensation of equimolar equivalents of 1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazole-4-carbaldehyde (**1**) and 2-cyanoacetamide (**2**) in boiling ethanol under basic conditions for 45 min gave 2-cyano-3-(1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)acrylamide (**3**) in 90% yield (Scheme 1). The structure of **3** was determined using NMR spectroscopy (See Section 3.2. for details) and confirmed by single crystal X-ray diffraction (Figure 1).



Scheme 1. Synthesis of **3**.

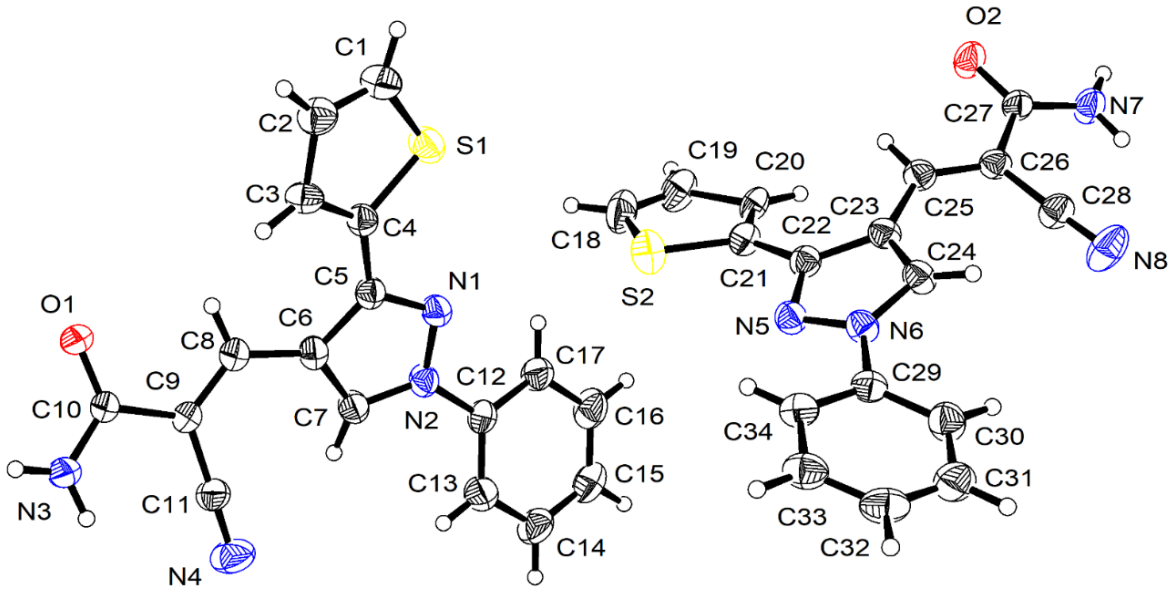


Figure 1. Ortep representation of the asymmetric unit of **3** showing 50% probability atomic displacement parameters.

2.2. NMR Spectroscopy

The ^{1}H NMR spectrum of **3** showed the presence of 12 protons with the NH_2 protons appearing as an exchangeable singlet at low field (δ = 9.11 ppm). The pyrazole proton appears as a singlet at 8.16 ppm. The ^{1}H NMR spectrum showed the presence of a doublet (two protons) and two triplets (one and two protons) corresponding to the five protons of the phenyl ring. The ^{13}C NMR spectrum of **3** showed the expected signals for all carbons with the carbonyl (C=O) and nitrile (C≡N) carbons appearing at 163.0 and 117.3 ppm, respectively. The NMR spectra for **3** are included in the supplementary materials.

2.3. X-ray Structure

The asymmetric unit of the crystal structure consists of two independent molecules. The molecules comprise thiophenyl ((A1: C1–C4, S1) and (A2: C18–C21, S2)), pyrazolyl ((B1: C5–C7, N1, N2) and (B2: C22–C24, N5, N6)), and phenyl ((D1: C12–C17) and (D2: C29–C34)) rings and cyanoacrylamide ((C1: C8–C11, N3, N4, O1) and (C2: C25–C28, N7, N8, O2)) groups.

The conformations of the two independent molecules are very similar in the crystal, as shown by the twist angles between adjacent groups. The angles between the groups are: A1/B1 = 18.9 (2)°, B1/C1 = 24.8 (2)°, and B1/D1 = 24.5 (2)° for the first molecule and A2/B2 = 23.6 (2)°, B2/C2 = 24.2 (2)°, and B2/D2 = 26.5 (2)° for the second molecule.

In the crystal structure (Figure 2), independent pairs of molecules are linked by two N–H···O hydrogen bonds (with geometry N3···O2 = 2.898 (4)Å, N3–H3B···O2 = 168.8° and N7···O1 = 2.886 (4)Å, N7–H7A···O1 = 167.9°) to form $R(8)^2_2$ rings. Additional bonds of type N–H···N (with geometry N3···N8 = 3.079 (5)Å, N3–H3C···N8 = 150.6°,

and N7···N4 = 3.107 (5)Å, N7–H7B···N4 = 149.4°) lead to the formation of molecular chains through the structure parallel to [100].

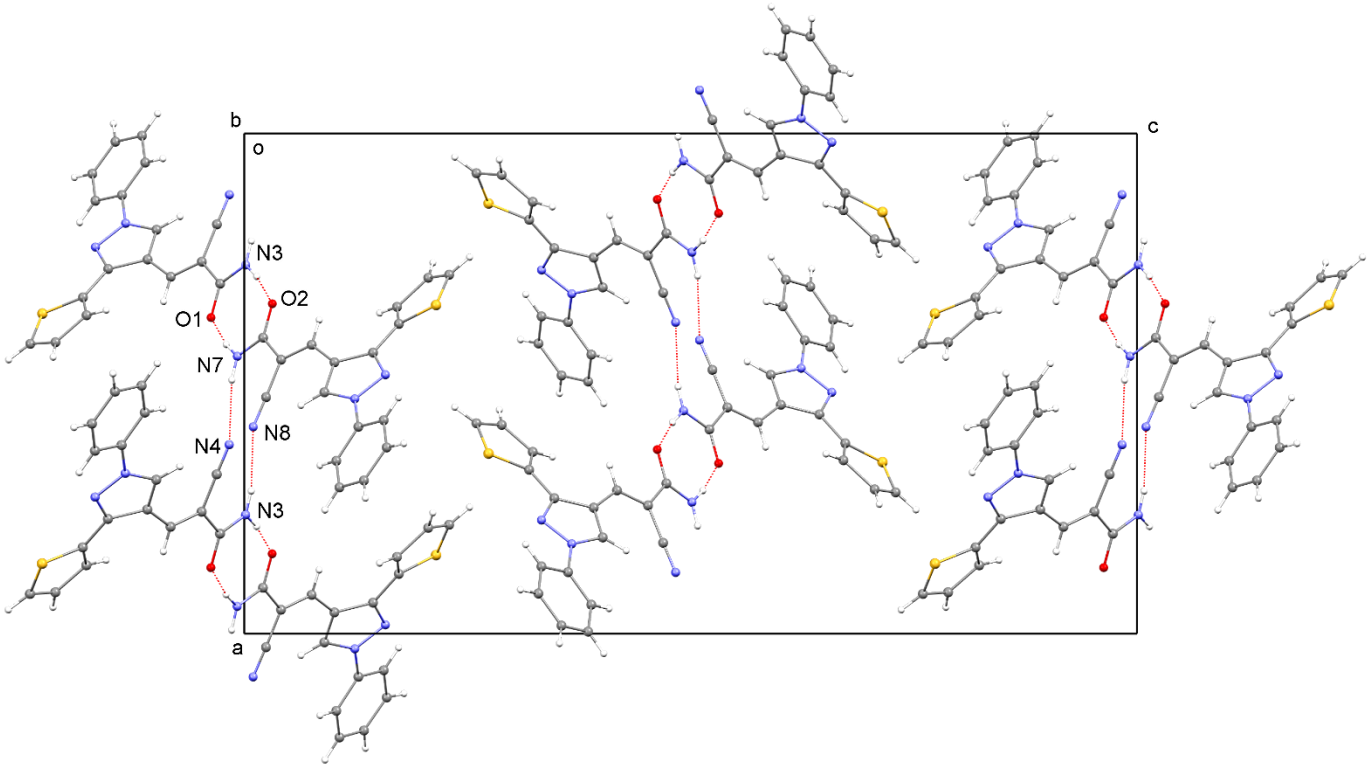


Figure 2. Crystal structure packing viewed down the *b* axis with hydrogen bonding contacts shown as red dashed lines.

3. Materials and Methods

3.1. General

The melting point of **3** was determined using an Electrothermal melting point apparatus. The IR spectrum of **3** was recorded on a JASCO FT/IR-4600 spectrometer. The NMR spectra of **3** were measured on a JEOLNMR 500 MHz spectrometer at 500 MHz for the ^{1}H and 125 MHz for the ^{13}C NMR. The coupling constant (*J*) and the chemical shift (δ) are reported in Hz and ppm, respectively. Compound **1** was prepared based on a literature procedure [28].

3.2. Synthesis of **3**

A mixture of **1** (0.51 g, 2.0 mmol) and **2** (0.17 g, 2.0 mmol) in ethanol (10 mL) containing piperidine (0.17 g, 2.0 mmol) was refluxed for 45 min. The mixture was cooled to room temperature and the solid formed was filtered, washed with ethanol, and dried. The crude product was recrystallized from dimethylformamide to give pale yellow crystals of **3**. Yield: 90%, Mp: 248–250 °C. IR (KBr): 3599 (NH_2), 3375 (NH_2), 3143 (CH), 2796 (CH), 2225 3 (C≡N), 1697 (C=O), 1589 (C=N), 1381 (C–C), 1227 (C–O) cm^{-1}. ^{1}H NMR (DMSO-d_6): 7.24 (t, *J* = 7.7 Hz, 1H, Ph), 7.42–7.46 (m, 2H, thienyl), 7.57 (t, *J* = 7.7 Hz, 2H, Ph), 7.74 (br, 1H, thienyl), 7.87 (d, *J* = 7.7 Hz, 2H, Ph), 7.95 (s, 1H, olefin), 8.16 (s, 1H, pyrazolyl), 9.11 (s, exch., 2H, NH_2). ^{13}C NMR (DMSO-d_6): 105.7 (*C*–C≡N), 114.7 (C4 of pyrazolyl), 117.3 (C≡N), 120.0 (C2/C6 of Ph), 128.6 (C4 of thienyl), 128.66 (C4 of thienyl), 128.69 (C4 of Ph), 128.9 (C5 of thienyl), 129.9 (C5 of pyrazolyl), 130.4 (C3/C5 of Ph), 132.7 (C3 of pyrazolyl), 138.9 (C1 of Ph), 141.4 (C2 of thienyl), 148.9 (CH), 163.0 (C=O).

3.3. Data Collection and Refinement Details

An Agilent SuperNova Dual Atlas diffractometer using mirror monochromated CuKα radiation (λ = 1.54184 Å) was used to collect single crystal diffraction data. The structure of **3** was solved by direct methods using SHELXS [29] and refined by full-matrix least-squares methods on F^2 with SHELXL-2014 [30]. Crystal Data: $C_{17}H_{12}N_4OS$ (M = 320.37 g/mol), Orthorhombic, space group $Pca2_1$, 0.32 × 0.14 × 0.04 mm, a = 17.2514 (3) Å, b = 5.8392 (1) Å, c = 30.8194 (6) Å, V = 3104.57 (10) $Å^3$, Z = 8, T = 296 K, μ(Cu Kα) = 1.93 mm^{-1}, D_{calc} = 1.371 Mg m^{-3}, 10,454 reflections measured (θ = 5.1–72.6°), 5046 unique, R_{int} = 0.024, R1 = 0.0432, wR2 = 0.1209 for I > 2σ(I)] and R1 = 0.0451, wR2 = 0.1242 for all data. The X-ray crystallographic data for compound **3** have been deposited in the Cambridge Crystallographic Data Center with CCDC reference number 2169792.

4. Conclusions

2-Cyano-3-(1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)acrylamide was synthesized in excellent yield using a simple procedure and its structure was established based on the data NMR spectroscopy and single crystal X-ray diffraction analysis.

Supplementary Materials: The following are available online, IR, ^1H, and ^{13}C NMR spectra, CIFs and check if reports for the title compound.

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