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Short Note

2-(4-Methylpiperazin-1-yl)-4-phenyl-6-(thiophen-2-yl)-pyridine-3-carbonitrile

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Abstract: 2-(4-Methylpiperazin-1-yl)-4-phenyl-6-(thiophen-2-yl)-pyridine-3-carbonitrile (**4**) was synthesized via nucleophilic substitution reaction of 1-methylpiperazine with 2-bromo analogue **3**. The latter was obtained through bromination (Br_2/AcOH) of 2-[3-oxo-1-phenyl-3-(thiophen-2-yl)propyl]malononitrile (**2**).

Keywords: 2-propen-1-one; pyridine-3-carbonitrile; single crystal X-ray

Introduction

Pyridine-3-carbonitrile derivatives represent an important class of heterocyclic compounds characterized by promising biological properties. Recent publications describing pharmacological properties of pyridine-3-carbonitrile-containing analogues such as vasodilation activities are considered a driving force behind the present investigation [1]. Moreover, bioactivity and applications as pharmacological active agents and agricultural materials of pyridinecarbonitriles also prompted the present study [2,3]. Additionally, 4-aminopyridine-3-carbonitriles were reported as PKCθ inhibitors [4–6]. PKCθ, a novel isoform of protein kinase C (PKC), is crucial for the activation and survival of T cells [7]. Proof-of-concept studies with mice where the PKCθ gene was deleted or 'knocked out' validated that the inhibition of this kinase could have therapeutic utility in diseases such as multiple sclerosis [8] and arthritis [9]. 2-Alkoxypyridine-3-carbonitrile derivatives were reported to be active antimicrobial agents against Gram-positive, Gram-negative and acid fast bacteria and yeast [10]. Also, pyridine-3-carbonitriles with amino acid functions were reported to exhibit considerable antimicrobial properties [11]. 2-Amino-3-cyanopyridine derivatives were proved to have antitubercular activity against *Mycobaterium tuberculosis* H_{37} RV ATCC 27294, in BACTEC 12 B medium using the ALAMAR

radiometric system comparing with the standard drug rifampin [12]. 4-Aryl-6-(4-pyridyl)-2-oxo/ thioxo-1,2-dihydropyridine-3-carbonitriles and 2-amino-4-aryl-6-(4-pyridyl)-pyridine-3-carbonitriles were proved to exert cardiotonic activity comparable to that of milrinone using a spontanously beating atria model from reserpine-treated guinea pigs [13]. Pyridine-3-carbonitrile analogues were also reported as fluorescent materials useful as security markers for treatment of paper [14–16]. From all the above reports and in continuation with our previous work directing towards construction of various pyridine-3-carbonitrile containing-compounds [17–19], it is intended in the present work to investigate synthesis of 2-(4-methylpiperazin-1-yl)-4-phenyl-6-(thiophen-2-yl)-pyridine-3-carbonitrile.

Results and Discussion

Reaction of 3-phenyl-1-(thiophen-2-yl)-2-propen-1-one (**1**) with malononitrile in absolute ethanol in the presence of morpholine as a basic catalyst afforded 2-[3-oxo-1-phenyl-3-(thiophen-2-yl)propyl]-malononitrile (**2**) in good yield (90%). The isolated compound is similar to the product previously described [20,21] (Scheme 1). Single crystal X-ray studies of **2** provide conclusive support for its structure (Figures 1 and 2). Single crystal X-ray studies of **2** show that the atomic coordinates along with their esd's and equivalent isotropic thermal parameters for non-hydrogen atoms are those which are mentioned in Table 1. Selected intramolecular bond lengths and angles are listed in Table 2.

Scheme 1. Synthetic route towards the targeted 2-(4-methylpiperazin-1-yl)-4-phenyl-6-(thiophen-2-yl)-pyridine-3-carbonitrile (**4**).

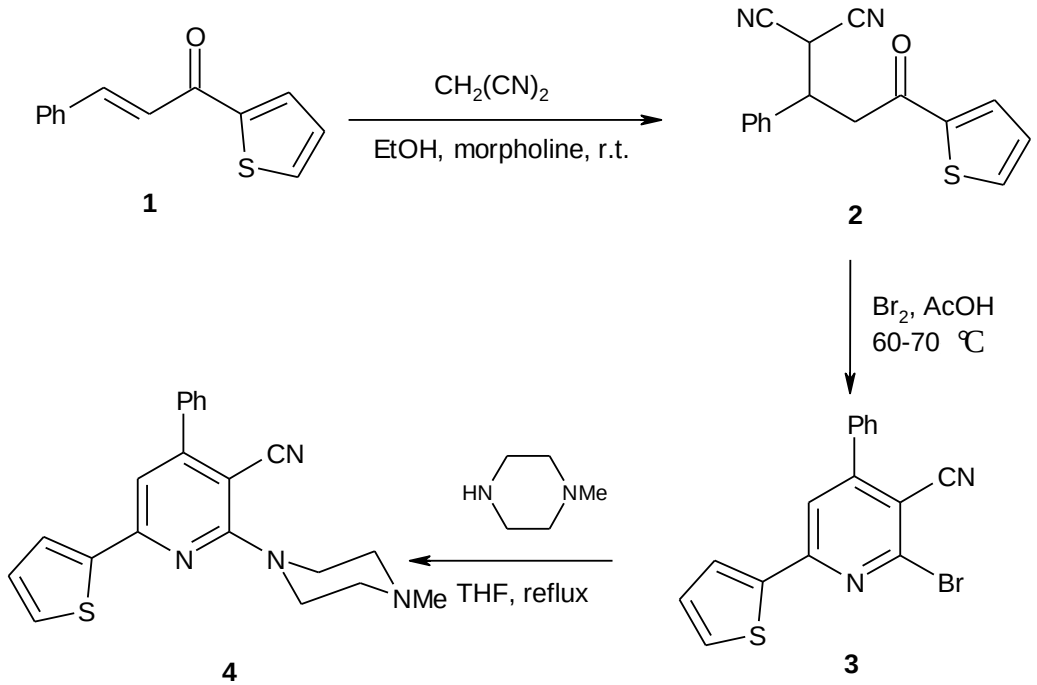

Figure 1. ORTEP projection of single crystal X-ray diffraction of **2**.

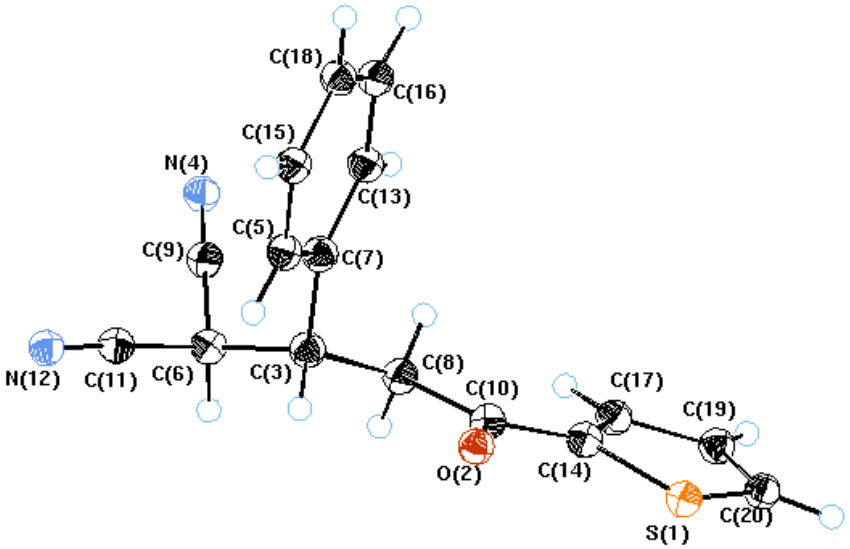

Figure 2. Packing preview of **2**, view along b-axis.

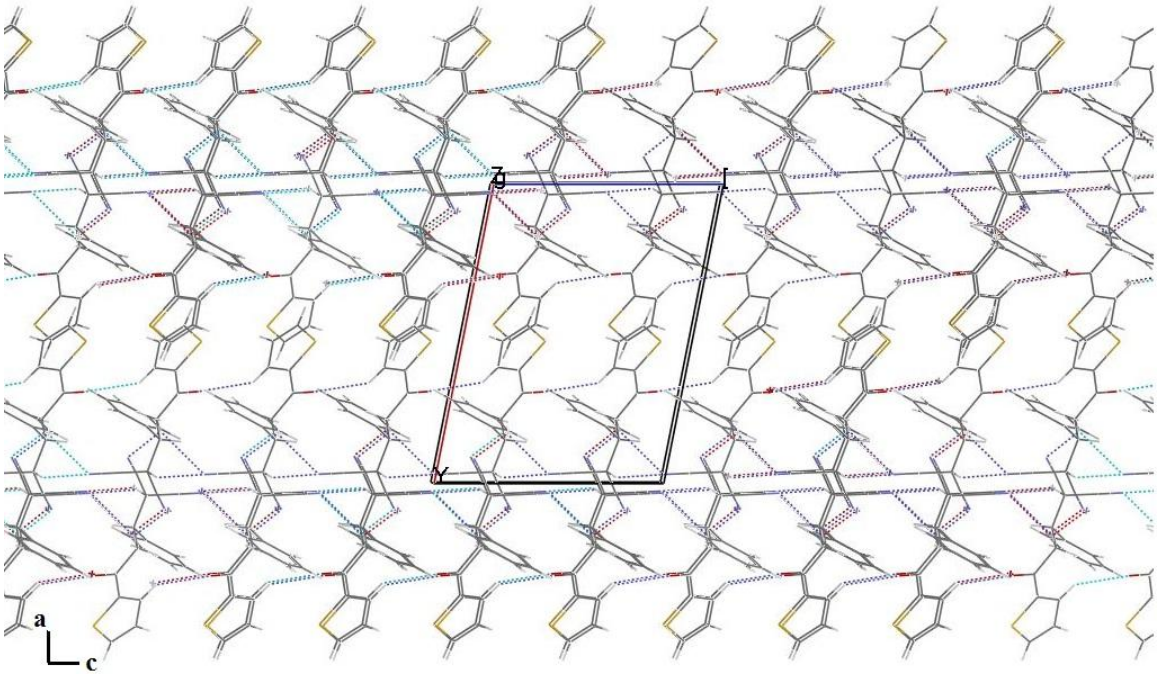

Table 1. Fractional atomic coordinates and equivalent isotropic thermal parameters (Å^2) of **2**, involving non-hydrogen atoms.

Entry	X	Y	z	U_{eq}	Occ
S1	0.52589(8)	0.32501(11)	0.36628(12)	0.0970(7)	1.00
O2	0.69418(18)	0.1481(2)	0.3989(2)	0.0734(15)	1.00
C3	0.8541(2)	0.1106(3)	0.2723(3)	0.0462(18)	1.00
N4	0.9703(2)	0.1684(3)	−0.0066(3)	0.082(2)	1.00
C5	0.8211(3)	−0.1158(4)	0.2735(3)	0.064(2)	1.00
C6	0.9616(2)	0.1392(3)	0.2462(3)	0.0486(17)	1.00
C7	0.8107(2)	−0.0058(3)	0.2039(3)	0.0495(18)	1.00

Table 1. *Cont.*

Entry	X	Y	z	Ueq	Occ
C8	0.7870(2)	0.2243(3)	0.2392(3)	0.0523(18)	1.00
C9	0.9662(2)	0.1547(3)	0.1028(4)	0.0549(18)	1.00
C10	0.6988(2)	0.2233(3)	0.3113(3)	0.0497(19)	1.00
C11	1.0333(3)	0.0438(3)	0.3056(3)	0.056(2)	1.00
N12	1.0872(2)	−0.0301(3)	0.3566(3)	0.082(2)	1.00
C13	0.7604(3)	−0.0079(4)	0.0702(3)	0.067(2)	1.00
C14	0.6229(2)	0.3184(3)	0.2777(3)	0.055(2)	1.00
C15	0.7835(3)	−0.2240(4)	0.2129(5)	0.084(3)	1.00
C16	0.7222(3)	−0.1158(6)	0.0096(4)	0.093(3)	1.00
C17	0.6139(3)	0.4093(4)	0.1841(4)	0.078(3)	1.00
C18	0.7343(3)	−0.2245(5)	0.0807(6)	0.095(3)	1.00
C19	0.5267(4)	0.4814(4)	0.1824(4)	0.105(3)	1.00
C20	0.4737(3)	0.4462(5)	0.2756(5)	0.107(3)	1.00

Table 2. Selected intramolecular geometrical parameters [bond lengths (Å); bond angles (°)] of **2**.

Geometrical parameters	Bond lengths (Å); Bond angles (°)
S(1)-C(14)	1.726(3)
S(1)-C(20)	1.682(4)
O(2)-C(10)	1.219(3)
C(3)-C(6)	1.556(3)
C(3)-C(7)	1.506(3)
C(3)-C(8)	1.532(3)
N(4)-C(9)	1.131(3)
C(5)-C(7)	1.383(3)
C(5)-C(15)	1.379(4)
C(6)-C(9)	1.475(4)
C(6)-C(11)	1.466(4)
C(7)-C(13)	1.392(3)
C(8)-C(10)	1.512(3)
C(10)-C(14)	1.449(3)
C(11)-N(12)	1.139(3)
C(13)-C(16)	1.379(4)
C(14)-C(17)	1.360(4)
C(15)-C(18)	1.373(5)
C(16)-C(18)	1.380(5)
C(17)-C(19)	1.411(4)
C(19)-C(20)	1.346(5)
C(3)-C(6)-C(9)	114.2(2)
C(9)-C(6)-C(11)	109.6(2)
C(3)-C(6)-C(11)	110.5(2)
C(14)-S(1)-C(20)	91.6(2)
N(4)-C(9)-C(6)	178.9(3)
C(6)-C(11)-N(12)	177.1(3)

Compound **2** crystallizes in a monoclinic unit cell and belongs to the space group $P2_1/c$ and has 4 molecules per each unit cell. The thienyl ring of compound **2** is nearly planer, with maximum and minimum deviation for C(17) = −0.011(4) Å and C(19) = 0.007(5) Å from the least square plane passing through the atoms S(1)/C(14)/C(17)/C(19)/C(20). The average values of the bond lengths and angles of the thienyl ring agree with that of identical rings in similar compounds [22,23]. The dihedral angle between the least square plane passing through the thienyl ring and that through the phenyl moiety is equal to 96.0(4) ° which indicates that the thienyl ring is nearly perpendicular to the phenyl ring, while the dihedral angle between the least square plane passing through the phenyl ring and the plane containing the two cyano groups is equal to 63.2(3) °. The methine carbon C(6) is a four coordinated in an asymmetric tetrahedral configuration forming angles in the range [105.5(2) °–114.2(2) °], *i.e.*, C(6) exists in asymmetric sp^3 hyperdization. The two cyano groups characterized by shortened triple bond C(9)-N(4) = 1.131(3) Å, C(11)-N(12) = 1.139(3) Å. Moreover the values of the bond angles C(6)-C(9)-N(4), C(6)-C(11)-N(12) are 178.9(3) ° and 177.1(3) °, respectively confirming the sp hybridization, consistent with other similar structures [24]. The dihedral angle between the least square plane through the butanedicarbonitrile moiety [O(2), C(3), N(4), C(6), C(8), C(9), C(10), C(11), N(12)] and that through the phenyl group [C(5), C(7), C(12), C(13), C(15), C(18)] is equal to 93.4(4) °, meaning thereby, that both the moieties are held almost perpendicular to each other.

The packing diagram of the compound (Figure 2) highlights the intermolecular contacts through the hydrogen bonding. The important function of these intermolecular bonds is to stabilize the molecules in the crystallographic sites of their space group. The most important intermolecular contacts are listed in Table 3. For example, carbon atom C(6) is hydrogen bonded to the nitrogen atom N(4) of the nitrile group of the neighbouring molecule with symmetry code x, 0.5−y, 0.5+z. Also Figure 2 reveals that the molecules are arranged in a layer manner and the direction of these molecules in different layers is opposite to each other.

Table 3. Hydrogen bonding geometry of **2**.

D-H….A	D-H (Å)	H…A (Å)	D….A (Å)	D-H….A °
C6-H6-N4	0960(2)	2.431(2)	3.251(3)	143.19(20)
C8-H8A-N12	0.960(3)	2.658(2)	3.409(4)	135.39(20)
C17-H17-O2	0.960(3)	2.547(2)	3.336(3)	139.58(24)

x, 0.5−y, 0.5+z; 2−x, 0.5+y, 0.5−z; X, 0.5−y, 0.5+z.

Bromination of **2** (Br_2/AcOH) afforded 2-bromo-4-phenyl-6-(thiophen-2-yl)-pyridene-3-carbonitrile (**3**) [20]. The latter, upon reaction with 1-methylpiperazine in tetrahydrofuran, underwent aromatic nucleophiic substitution giving 2-(4-methylpiperazin-1-yl)-4-phenyl-6-(thiophen-2-yl)-pyridine-3-carbonitrile (**4**) in good (80%) yield. The IR spectrum of **4** exhibits a strong nitrile stretching vibration band at ν = 2203 cm^{-1}. ^{1}H-NMR spectrum reveals the methyl group of the piperazinyl moiety as a singlet at δ = 2.41 ppm, while, the piperazinyl methylene protons appear as triplets at δ = 2.63 and 3.83 ppm. The ^{13}C-NMR spectrum of **4** exhibits the pyridinyl *C*-3 and *C*-5 at δ = 91.89 and 110.24 ppm, respectively. The piperazinyl carbons appear at δ = 48.66 and 55.00 ppm, while the nitrile carbon appears at δ = 118.09 ppm. The mass spectrum (EI) of **4** exhibits the parent ion peak with a considerable relative intensity value.

Experimental

Melting points were recorded on a Stuart SMP3 melting point apparatus. IR spectra (KBr) was recorded on a Shimadzu 8400S FT-IR spectrophotometer. NMR spectra were recorded on a JEOL AS 500 (^{1}H: 500 MHz, ^{13}C: 125 MHz) spectrometer. MS spectra was recorded on a Shimadzu QP-2010 plus (EI, 70 eV) spectrometer. The starting compounds **1** [25], **2** and **3** [20,21] were prepared according to the previously reported procedures.

Synthesis of 2-(4-methylpiperazin-1-yl)-4-phenyl-6-(thiophen-2-yl)-pyridine-3-carbonitrile (**4**)

A solution of **3** (1.7 g, 5 mmol) and 1-methylpiperazine (1.5 mL, 10 mmol) in tetrahydrofuran (30 mL) was refluxed for 5 h. The solid separated while refluxing was collected and identified as the corresponding 1-methylpiperazine hydrobromide (soluble in water). The clear reaction mixture was evaporated till dryness, methanol (5 mL) was added, the separated solid was collected, washed with water and crystallized from methanol to give **4** as straw-yellow needles, m.p. 144–146 ℃, yield (1.3 g, 80%). IR: ν_{max}/cm^{-1} 2923, 2845, 2795 (CH aliphatic), 2203 (C≡N), 1569, 1539 (C=N, C=C). ^{1}H-NMR ($CDCl_3$): δ 2.41 (s, 3H, NCH_3), 2.63 (t, 4H, 2 piperazinyl CH_2, J = 4.6 Hz), 3.83 (t, 4H, 2 piperazinyl CH_2, J = 4.6 Hz),7.12 (d, 1H, thienyl *H*-3, J = 5.35 Hz), 7.14 (s, 1H, pyridinyl *H*-5), 7.46 (d, 1H, thienyl *H*-4, J = 5.35 Hz), 7.49–7.52 (m, 3H, Ar H's), 7.56–7.58 (m, 2H, Ar H's), 7.65 (d, 1H, thienyl *H*-5, J = 5.30 Hz). ^{13}C-NMR ($CDCl_3$): δ 46.18 (N*C*H$_3$), 48.66 (piperazinyl N*C*H$_2$), 55.00 (piperazinyl N*C*H$_2$), 91.89 (pyridinyl *C*-3), 110.24 (pyridinyl *C*-5), 118.09 (*C*≡N), 126.69, 128.41, 128.65, 128.90, 129.73, 129.82, 137.28, 144.24, 153.20, 157.36, 162.25 (arom. *C*). MS: *m/z* (%) 360 (M, 16), 362 [(M+2), 4]. Anal. Calcd. for $C_{21}H_{20}N_4S$ (360.48): C, 69.97; H, 5.59; N, 15.54. Found: C, 69.72; H, 5.48; N, 15.33.

Single Crystal X-Ray Crystallographic Data of **2**

A colorless needle single crystal recrystallized from ethanol of dimensions 0.09 × 0.07 × 0.13 mm was selected and mounted on a thin glass fiber. X-ray diffraction data were collected at room temperature (T = 298 K) on Enraf Nonius Kappa CCD single crystal diffractometer with graphite monochromatic MoKα (λ = 0.71073 Å) radiation; the crystal to detector distance was 35 mm. Crystals were indexed from the first ten frames using the DENZO package and positional data were refined along with diffractometer constants to give unit cell parameters suitable for integration and scaling (DENZO, Scalepack) [26]. With φ-ω scan mode, 6291 measured reflections, 3985 independent reflections out of them 1324 reflections with I ≥ 3σ(I) were used for structure analysis. The crystal structure was solved by direct method using SIR92 program [27], which revealed the positions of all non-hydrogen atoms and refined by the full matrix least squares based on F^2 using maXus package [28]. The anisotropic displacement parameters of all non-hydrogen atoms were refined, then the hydrogen atoms were introduced as a riding model with C–H = 0.96Å and refined isotropically. The maximum and the minimum heights in the final difference Fourier map were found to be, 0.64 e/Å^3 and −0.68 e/Å^3. The Molecular graphics were prepared using ORTEP program [29]. Chemical formula $C_{16}H_{12}N_2OS$, M_r = 280.349, monoclinic, crystallizes in space group $P2_1/c$, Cell lengths "a = 13.4825(6), b = 10.8934(4), c = 10.1309(4) Å", Cell angles "α = 90.00, β = 101.2682(13), γ = 90.00°", V =

1459.25(10) Å^3, Z = 4, D_c = 1.276 g/m^3, θ values 2.910–27.485 °, absorption coefficient μ (Mo-K$_\alpha$) = 0.22 mm^{-1}, F(000) = 584. Convergence for 181 variable parameters by least-squares refinement on F^2 with $w = 1/[\sigma^2(F_o^2) + 0.10000\ F_o^2]$. The final agreement factors were R = 0.044 and wR = 0.073 with a goodness-of-fit of 1.376. Full crystallographic details, excluding structure factors have been deposited at Cambridge Crystallographic Data Centre (CCDC) as supplementary publication number CCDC 873576 which can be obtained free of charge (www.ccdc.cam.ac.uk/data request/cif).

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