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Crystal structure of methyl 2-(4-(3-(2,4-difluorophenyl)pyrazolo[1,5-*a*]pyrimidin-6-yl)phenyl)acetate, C₂₁H₁₅F₂N₃O₂

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Table 1: Data collection and handling.

Crystal:	Yellow block
Size:	0.28 × 0.22 × 0.17 mm
Wavelength:	Mo K α radiation (0.71073 Å)
μ :	0.11 mm ⁻¹
Diffractometer, scan mode:	Bruker APEX-II, φ and ω
$\theta_{\max}$, completeness:	25.0°, 99%
$N(hkl)_{\text{measured}}$, $N(hkl)_{\text{unique}}$, R_{int} :	8606, 5888, 0.056
Criterion for I_{obs} , $N(hkl)_{\text{gt}}$:	$I_{\text{obs}} > 2 \sigma(I_{\text{obs}})$, 2400
$N(\text{param})_{\text{refined}}$:	506
Programs:	Bruker [1], SHELX [2, 3], Olex2 [4]

Abstract

C₂₁H₁₅F₂N₃O₂, triclinic, $P\bar{1}$ (no. 2), $a = 7.389(5)$ Å, $b = 14.011(9)$ Å, $c = 16.733(11)$ Å, $\alpha = 96.568(13)^\circ$, $\beta = 100.432(13)^\circ$, $\gamma = 94.589(13)^\circ$, $V = 1683.6(19)$ Å³, $Z = 4$, $R_{\text{gt}}(F) = 0.0589$, $wR_{\text{ref}}(F^2) = 0.1621$, $T = 296$ K.

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The molecular structure is shown in the figure. Table 1 contains crystallographic data and Table 2 contains the list of the atoms including atomic coordinates and displacement parameters.

Source of material

The solution of methyl 2-(4-(3-bromopyrazolo[1,5-*a*]pyrimidin-6-yl)phenyl)acetate (346.2 mg, 1 mmol), 2-(2,4-difluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (240.1 mg, 1 mmol), potassium carbonate (276.4 mg, 2 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium

(146.0 mg, 0.2 mmol) in dioxane (5 mL) and water (1 mL) was added in a 20 mL microwave vial, then degassed by nitrogen. The reaction solution was stirred at 25 °C for 1 h and heated under microwave irradiation at 120 °C for 0.5 h. The reaction mixture was washed with water and brine, and extracted with dichloromethane. The organic solution was dried over and concentrated. The crude product was purified by column chromatography over silica gel eluting with a gradient of methanol/dichloromethane (v/v, 0–3%) to afford the yellow solid. Yield, 284.6 mg, 74%. The title compound (100 mg, 0.26 mmol) was dissolved in dichloromethane, and the solvent was slowly evaporated at room temperature. After one week, light yellow crystals suitable for X-ray diffraction analysis were obtained.

Experimental details

Data reduction was carried out using the Bruker software APEX2 including SADABS [1]. The structure was determined by the intrinsic phasing routines in the SHELXT program [2] and refined by full-matrix least-squares methods in SHELXL [3] using Olex2 [4]. All of the H atoms were placed in the calculated positions and all the non-hydrogen atoms were refined anisotropically.

Comment

Heterocyclic building blocks represent useful scaffolds for applications in medicinal chemistry [5], catalytic chemistry, and materials chemistry [6]. Many pyrazole compounds have gotten extraordinary consideration for its organic and

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Table 2: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²).

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{iso} [*] / <i>U</i> _{eq}
F1	0.3785(3)	1.23461(16)	0.27958(12)	0.0726(8)
F2	0.1196(4)	0.92217(17)	0.27497(12)	0.0816(9)
F3	0.5260(4)	0.82840(18)	0.20690(13)	0.0966(10)
F4	0.2791(3)	0.51462(16)	0.20024(12)	0.0724(8)
N1	0.0436(5)	0.7917(2)	0.47141(18)	0.0625(11)
N2	0.1261(4)	0.8461(2)	0.54198(17)	0.0475(9)
N3	0.2876(4)	0.9985(2)	0.59424(17)	0.0504(9)
N4	0.1418(5)	0.3914(2)	0.39138(19)	0.0571(10)
N5	0.2012(4)	0.4497(2)	0.46301(17)	0.0462(9)
N6	0.3529(4)	0.6029(2)	0.51811(18)	0.0514(9)
O1	−0.0046(4)	0.8398(2)	1.06070(17)	0.0721(9)
O2	0.2165(5)	0.9593(3)	1.08059(17)	0.0898(12)
O3	0.2132(4)	0.3565(2)	1.04270(16)	0.0680(9)
O4	0.4003(6)	0.3456(3)	0.9570(2)	0.1278(17)
C1	0.3289(5)	1.1615(3)	0.3202(2)	0.0504(11)
C2	0.2484(6)	1.0766(3)	0.2761(2)	0.0562(12)
H2	0.227752	1.067324	0.219133	0.067*
C3	0.1992(5)	1.0052(3)	0.3198(2)	0.0515(11)
C4	0.2270(5)	1.0134(3)	0.4028(2)	0.0449(10)
C5	0.3103(5)	1.1027(3)	0.4443(2)	0.0522(11)
H5	0.331537	1.112275	0.501281	0.063*
C6	0.3618(5)	1.1768(3)	0.4034(2)	0.0560(12)
H6	0.417530	1.235870	0.431916	0.067*
C7	0.1707(5)	0.9359(3)	0.4467(2)	0.0460(11)
C8	0.0732(6)	0.8479(3)	0.4157(2)	0.0601(13)
H8	0.031138	0.829190	0.359809	0.072*
C9	0.2048(5)	0.9335(3)	0.5302(2)	0.0425(10)
C10	0.2906(5)	0.9726(3)	0.6664(2)	0.0533(12)
H10	0.345397	1.017493	0.711292	0.064*
C11	0.2178(5)	0.8820(3)	0.6825(2)	0.0425(10)
C12	0.1333(5)	0.8194(3)	0.6172(2)	0.0468(10)
H12	0.080838	0.758901	0.623761	0.056*
C13	0.2345(5)	0.8595(3)	0.7674(2)	0.0464(10)
C14	0.1143(5)	0.7904(3)	0.7878(2)	0.0539(11)
H14	0.022805	0.755646	0.747010	0.065*
C15	0.1271(6)	0.7718(3)	0.8674(2)	0.0585(12)
H15	0.045818	0.723664	0.879349	0.070*
C16	0.2568(5)	0.8227(3)	0.9290(2)	0.0495(11)
C17	0.3783(6)	0.8901(3)	0.9088(2)	0.0586(12)
H17	0.471425	0.923672	0.949580	0.070*
C18	0.3657(5)	0.9096(3)	0.8292(2)	0.0518(11)
H18	0.447713	0.957510	0.817466	0.062*
C19	0.2646(6)	0.8058(3)	1.0168(2)	0.0690(14)
H19A	0.210592	0.740924	1.018898	0.083*
H19B	0.392125	0.812668	1.045684	0.083*
C20	0.1596(7)	0.8779(4)	1.0563(2)	0.0595(13)
C21	−0.1260(7)	0.9039(4)	1.0905(3)	0.0925(17)
H21A	−0.242142	0.868267	1.091100	0.139*
H21B	−0.071220	0.933406	1.145067	0.139*
H21C	−0.146125	0.953111	1.055288	0.139*
C22	0.4648(6)	0.7575(3)	0.2472(2)	0.0611(13)
C23	0.4019(6)	0.6710(3)	0.2024(2)	0.0610(13)
H23	0.400575	0.659833	0.146450	0.073*
C24	0.3405(5)	0.6011(3)	0.2444(2)	0.0475(11)
C25	0.3409(5)	0.6128(3)	0.3267(2)	0.0446(10)

Table 2 (continued)

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{iso} [*] / <i>U</i> _{eq}
C26	0.4076(6)	0.7038(3)	0.3673(2)	0.0603(13)
H26	0.410888	0.715747	0.423437	0.072*
C27	0.4693(6)	0.7771(3)	0.3281(2)	0.0673(14)
H27	0.512556	0.838037	0.356387	0.081*
C28	0.2760(5)	0.5366(3)	0.3696(2)	0.0446(10)
C29	0.1876(5)	0.4448(3)	0.3368(2)	0.0523(11)
H29	0.163186	0.423104	0.280895	0.063*
C30	0.2837(5)	0.5370(3)	0.4522(2)	0.0431(10)
C31	0.3351(5)	0.5788(3)	0.5891(2)	0.0511(11)
H31	0.384521	0.623768	0.634720	0.061*
C32	0.2490(5)	0.4917(3)	0.6038(2)	0.0449(10)
C33	0.1826(5)	0.4263(3)	0.5375(2)	0.0488(11)
H33	0.125320	0.366380	0.542809	0.059*
C34	0.2288(5)	0.4711(3)	0.6869(2)	0.0456(10)
C35	0.2677(6)	0.5414(3)	0.7534(2)	0.0652(13)
H35	0.315054	0.603049	0.747209	0.078*
C36	0.2379(7)	0.5224(3)	0.8292(2)	0.0763(15)
H36	0.268416	0.571097	0.873460	0.092*
C37	0.1659(6)	0.4352(3)	0.8406(2)	0.0594(12)
C38	0.1294(6)	0.3644(3)	0.7757(3)	0.0692(14)
H38	0.083669	0.302752	0.782697	0.083*
C39	0.1590(6)	0.3825(3)	0.7000(2)	0.0656(13)
H39	0.130590	0.332856	0.656355	0.079*
C40	0.1233(7)	0.4187(4)	0.9219(2)	0.0744(14)
H40A	0.109835	0.480587	0.951580	0.089*
H40B	0.005191	0.379678	0.913100	0.089*
C41	0.2628(7)	0.3709(4)	0.9737(3)	0.0688(14)
C42	0.3301(6)	0.3076(4)	1.0975(2)	0.0861(17)
H42A	0.277986	0.301853	1.145459	0.129*
H42B	0.341293	0.244418	1.071074	0.129*
H42C	0.450081	0.343455	1.112938	0.129*

biological significance for instance as inhibitors of anti-cancer, pesticides, fungicides, and antihypertensive, also they are valuable starting materials for many heterocyclic systems [7, 8]. Pyrazolo[1,5-*a*]pyrimidine is an important aromatic fused heterocycle widely present in synthetic drugs and related intermediates [8].

In this work, we prepared methyl 2-(4-(3-(2,4-difluorophenyl)pyrazolo[1,5-*a*]pyrimidin-6-yl)phenyl)acetate in good yield using a coupling reaction of methyl 2-(4-(3-bromopyrazolo[1,5-*a*]pyrimidin-6-yl)phenyl)acetate with 2-(2,4-difluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. This compound will be used for the development of novel AMPK inhibitors. One of two crystallographically independent molecules of the crystal structure is shown in the figure. The NMR results are consistent with the proposed structure. The asymmetric unit of the title compound contains two molecules. The bond lengths and angles in both crystallographically independent molecules are in the normal ranges [9]. In conclusion, we have developed a facile microwave-assisted process for the synthesis of the title compound using

a one-pot procedure. This facile procedure can be readily used to synthesize a diverse range of compounds for high throughput screening in AMPK inhibitors.

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