Supporting Information

**Palladium-catalyzed regioselective direct C-H Arylation of Pyrazolo [3,4-d]pyrimidines**



Mohamed El Hafi,a,b  Mohammed Naas,a,b, Mohammed Loubidi b, Jabrane Jouhab, Youssef Ramlic, , Joel T Mague,d El Mokhtar Essassi,a\* and Gérald Guillaumetb\*

*a Laboratoire de Chimie Organique Hétérocyclique URAC 21, Pôle de Compétences Pharmacochimie, Mohammed. V University in Rabat BP 1014, Avenue Ibn Batouta, Rabat, Morocco*

*b Institut de Chimie Organique et Analytique, Université d’Orléans, UMR CNRS 7311, BP 6759, 45067 Orléans Cedex 2, France*

*c Laboratoire de Chimie Thérapeutique, Faculté de Médecine et de Pharmacie, Mohammed. V University in Rabat BP 6203, Avenue Mohamed Belarbi El Alaoui, Rabat, Morocco.*

*d Departement of Chemistry, Tulane University, New Orleans, LA 70118, USA.*

[\*](mailto:*elhafi.mohamed1@gmail.com)emessassi@yahoo.fr, [\*](mailto:*elhafi.mohamed1@gmail.com)gerald.guillaumet@univ-orleans.fr

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6. **General Information:**

All reagents were purchased from commercial suppliers and were used without further purification. Microwave assisted reactions were carried out in a Biotage Initiator microwave synthesis instrument and temperatures were measured by an IR sensor. The reactions were monitored by thin-layer chromatography (TLC) analysis using silica gel (60 F254) plates. Compounds were visualized by UV irradiation Flash column chromatography was performed on silica gel 60 (230-400 mesh, 0.040 0.063 mm). Melting points (mp [°C]) were taken on samples in open capillary tubes and are uncorrected. 1H and 13C NMR spectra were recorded on a spectrometer at 250 MHz (13C, 62.9 MHz) or 400 MHz (13C, 100 MHz). Chemical shifts are given in parts per million from tetramethylsilane (TMS) as internal standard. The following abbreviations are used for the proton spectra multiplicities: s: singulet, d: doublet, t: triplet, q: quartet, qt: quintuplet, m: multiplet.. Coupling constants (*J*) are reported in Hertz (Hz). High-resolution mass spectra (HRMS) were performed on a Maxis Bruker 4G by the “Federation de Recherche” ICOA/CBM (FR2708) platform.

1. **Syntheses of starting materials:**

4-Chloro-1*H*-pyrazolo[3,4-*d*]pyrimidine **(2)**:

A mixture of allopurinol **1** (2.00 g, 14,69mmol) and N,N-dimethylaniline (2.1 mL, 16.52 mmol) was stirred in POCl3 (25 ml) at 80°C for 1h. Then the reaction mixture was diluted with water (35 ml), and extracted with ethyl acetate. The organic layer was washed with water and the organic phase was concentrated to dryness. A yellow solid (1.63 g, 10.60 mmol), 72% ; mp 154-156°C. (lit.1m.p 152−156 °C) used without further purification in the next step.

1-Methyl-4-chloro-1*H*-pyrazolo[3,4-d]pyrimidine **(3):**

Potassium hydroxide (0.45g, 7. 8 mmol) was added to compound **2** (1.2 g, 7.8 mmol) in acetone (20 mL) at 0°C, followed immediately by methyl iodide (0.5 mL, 7.8 mmol). The mixture was stirred for three hours. Potassium hydroxide was removed by filtration and the filter cake was washed with small amount of acetone. The filtrate and washings were concentrated and the reaction mixture was subjected to flash chromatography on silica gel (gradient elution 9:1 petroleum ether/ EtOAc) to afford (0.95g , 5.65 mmol), 73% of **3** as white powder; mp 97-99°C. (lit.2m.p 97−99 °C)

1-Methyl-4-phenyl-1*H*-pyrazolo [3,4-d]pyrimidine **(4):**

To a microwave vial was added **3** (50 mg, 0.3 mmol), phenylboronic acid (40.23 mg, 0.33 mmol), K2CO3 (124.38 mg, 0, 9 mmol) PdCl2(dppf) (22 mg, 0.03 mmol), THF (3ml), and H2O (10 µL). The reaction mixture was heated with stirring in microwave reactor at 170°C for 10 min. The crude reaction mixture was passed through a small silica gel plug eluting with EtOAc, and the crude material was purified by silica gel chromatography (0 to 10% EtOAc gradient in hexanes) to obtain (49 mg , 0.23 mmol), 80% of **4** as white powder ; mp 115-117°C.

1H NMR (400 MHz, CDCl3-d) δ : 9.08 (s, 1H), 8.36 (s, 1H), 8.20 (dd, *J* = 6.7, 3.0 Hz, 2H), 7.62 – 7.56 (m, 3H), 4.18 (s, 3H). 13C NMR (101 MHz, CDCl3-d) δ : 160.9, 155.3 , 153.8 , 137.1 , 132.9 , 131.6 , 129.0 (2C) , 129.1 (2C) , 111.6 , 34.2. HRMS (ESI): calcd. for C12H11N4 [M + H]+ 211.0978 ; found 211.0979.

4-Methoxy-1-methyl-1*H*-pyrazolo [3, 4-d]pyrimidine **(14):**

To a conical vial was added **3** (100 mg, 0.59 mmol), MeOH (50 µL, 1.2 mmol), and THF (3 mL). The reaction mixture was allowed to stir, open to air, in an ice bath for 5 min, after which MeONa (65 mg, 1.2 mmol) was added. The reaction was allowed to r.t. and stirred for 6h. The crude reaction mixture was transferred to a separatory funnel, and CH2Cl2 (10 ml), sat. aq NH4Cl (10 mL) and brine (5 mL) were added. The layers were separated, and the aqueous layer was extracted with CH2Cl2. The combined organic layers were dried (Na2SO4), and the crude material was purified by silica gel chromatography (0 to 10% EtOAc gradient in petroleum ether) to obtain (80.05 mg, 0.49 mmol), 82% of **14** as white powder solid, m.p. 104-106°C. (lit.3m.p 105−106 °C).

1. **Copies of NMR Spectra:**

suzkiphenyl ME16 H tiffffff.tiff

ME16  Suzuki1 tiiiiiiiiif C.tiff

ME30B (2) tiiiiiif.tiff

ME30B (3) totale tiiiiiiif hhhhhhhhhhhh.tiff

Anisole 36B  1H tiiiiiif.tiff

ME36B(Anisole)  Totale tiiiiiiif .tiff

**ME35 (CF3) (H) 55555555555555.tiff**

**13C (CF3) (1).tiff**

**ME38 (3-iodotoluène) totale (1).tiff**

**ME38 (3-iodotoluène) totale (1).tiff**

**ME40 TOTALE.tiff**

ME40 TOTALE hhhhhhhhhhhhh.tiff

**ME39 (4-iodobenzonitrile) totale.tiff**

benzonitrile.tiff

ME42  1H RMN hhhhhhhh.tiff

CH3-COOCH3.tiff

1. X-Ray Structure of 7 (JTM717)

The X-ray intensity data were measured on a Bruker D8 VENTURE PHOTON 100 CMOS system equipped with a mirror monochromator and a Cu-Kα INCOATEC IμS micro--focus source (λ = 1.54178 Å)4.



Figure 1. Ortep diagram of 1-Methyl-4-phenyl-3-(p-tolyl)-1*H*-pyrazolo[3,4-d]pyrimidine **7** (The asymmetric unit with labeling scheme and 50% probability ellipsoids).

**Structure description**

The asymmetric unit consists of two independent molecules differing primarily in the orientations of the peripheral benzene rings. Thus for one molecule, the dihedral angles of the C7···C12 and C14···C19 rings, respectively, and the bicyclic core are 53.04(4) and 44.31(4)° while for the other the angles are 33.19(6) and 52.29(5)°, respectively, for the C26···C31 and C33···C38 rings. In the former molecule the bicyclic core is planar to within 0.0205(10)Å while in the second, the maximum deviation of the core from planarity is 0.0245(13)Å. The molecule containing N1–N4 forms stacks along the *b* direction in which slipped π-stacking interactions between adjacent heterobicyclic cores oriented head-to-tail (dihedral angle = 1.29(8)°, centroid of imidazole ring··· centroid of pyrimidine ring at 2 − *x*, −*y*, 2 − *z* is 3.533(1)Å) alternate with complementary C8—H8···π(ring) (ring is C1,C2,N1,C4,N2,C3 at 2 − *x*, 1 − *y*, 2 − *z* with centroid *Cg*2) interactions (Table 1 and Figs. 2 and 3). The molecules containing N5–N8 are positioned between the stacks and are bound to them *via* C22—H22···N4iii and C11—H11···π(ring) (symmetry code: (iii) *x*, 0.5 − *y*, −1/2 + *z*) interactions (Table 1 and Figs. 2 and 3).



**Figure 2** : Detail of the intermolecular interactions (slipped π- stacking, orange dotted lines; C—H···π(ring), purple dotted lines; C—H···N, black dotted lines. Symmetry codes: (i) 2 − *x*, 1 − *y*, 2 − *z*; (ii) 2 − *x*, −*y*, 2 − *z*; (iii) *x*, 0.5 − *y*, −1/2 + *z*).



**Figure 3 :** Packing viewed along b (color code as in Fig. 2)

**Table 1**. Crystal data of **7** (JTM717)

|  |  |
| --- | --- |
| Crystal data | |
| Chemical formula | [C19H16N4](JTM717_0m%20_chemical_formula_moiety) |
| *M*r | [300.36](JTM717_0m%20_chemical_formula_weight) |
| Crystal system, space group | [Monoclinic](JTM717_0m%20_space_group_crystal_system), [*P*21/*c*](JTM717_0m%20_space_group_name_H-M_alt) |
| Temperature (K) | [150](JTM717_0m%20_cell_measurement_temperature) |
| *a*, *b*, *c* (Å) | [19.2902 (4)](JTM717_0m%20_cell_length_a), [8.6738 (2)](JTM717_0m%20_cell_length_b), [19.7059 (3)](JTM717_0m%20_cell_length_c) |
| β (°) | [110.213 (1)](JTM717_0m%20_cell_angle_beta) |
| *V* (Å3) | [3094.12 (11)](JTM717_0m%20_cell_volume) |
| *Z* | [8](JTM717_0m%20_cell_formula_units_Z) |
| Radiation type | [Cu *K*α](JTM717_0m%20_diffrn_radiation_type) |
| µ (mm−1) | [0.62](JTM717_0m%20_exptl_absorpt_coefficient_mu) |
| Crystal size (mm) | [0.29](JTM717_0m%20_exptl_crystal_size_max) × [0.20](JTM717_0m%20_exptl_crystal_size_mid) × [0.06](JTM717_0m%20_exptl_crystal_size_min) |
|  | |
| Data collection | |
| Diffractometer | [Bruker D8 VENTURE PHOTON 100 CMOS](JTM717_0m%20_diffrn_measurement_device_type) |
| Absorption correction | [Multi-scan](JTM717_0m%20_exptl_absorpt_correction_type)  [*SADABS* (Bruker, 2016)](JTM717_0m%20_exptl_absorpt_process_details) |
| *T*min, *T*max | [0.87](JTM717_0m%20_exptl_absorpt_correction_T_min), [0.96](JTM717_0m%20_exptl_absorpt_correction_T_max) |
| No. of measured, independent and observed [[*I* > 2σ(*I*)](JTM717_0m%20_reflns_threshold_expression)] reflections | [23506](JTM717_0m%20_diffrn_reflns_number), [6021](JTM717_0m%20_reflns_number_total), [4905](JTM717_0m%20_reflns_number_gt) |
| *R*int | [0.042](JTM717_0m%20_diffrn_reflns_av_R_equivalents) |
| (sin θ/λ)max (Å−1) | 0.618 |
|  | |
| Refinement | |
| *R*[*F*2 > 2σ(*F*2)], *wR*(*F*2), *S* | [0.040](JTM717_0m%20_refine_ls_R_factor_gt), [0.102](JTM717_0m%20_refine_ls_wR_factor_ref), [1.04](JTM717_0m%20_refine_ls_goodness_of_fit_ref) |
| No. of reflections | [6021](JTM717_0m%20_refine_ls_number_reflns) |
| No. of parameters | [533](JTM717_0m%20_refine_ls_number_parameters) |
| H-atom treatment | [H atoms treated by a mixture of independent and constrained refinement](JTM717_0m%20_refine_ls_hydrogen_treatment) |
| Δρmax, Δρmin (e Å−3) | [0.24](JTM717_0m%20_refine_diff_density_max), [−0.25](JTM717_0m%20_refine_diff_density_min) |

1. **References:**

[1] Y. Li, T. T. Cao, S. Guo, Q. Zhong, C. H. Li, Y. Li, L. Dong, S. Zheng, G. Wang, S. F. Yin, *Molecules*. **2016**, *21*, 771. [2] R. E. Bacon, T. Bailey, N. C. Becknell, E. D. Gingrich, G. Hostetler, L. R. Hudkins, S. K. Learn, C. J. Wanger, *Chem. Abstr*. **2007**,*37*, 281949. [3] C. C. Cheng, R. K. Robins, *J. Org. Chem.* **1956**, *21*, 1241-1256. [4] Bruker **2016**. APEX3, SAINT, SADABS & SHELXTL, Bruker AXS, Inc., Madison, WI.