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# A one-pot process for the microwave-assisted synthesis of 7-substituted pyrazolo[1,5-*a*]pyrimidine

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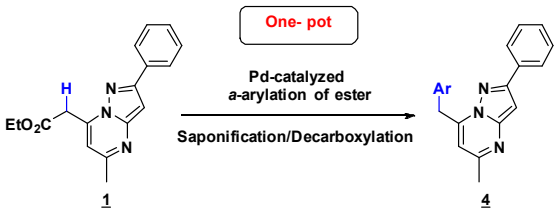
An efficient synthesis of 7-substituted pyrazolo[1,5-*a*]pyrimidines using a one-pot, two-step process via Pd-catalyzed direct CH-arylation followed by a saponification-decarboxylation reaction is reported. Compared to the classical method (Negishi coupling), this new procedure has the advantages of convenient manipulation, short reaction times, excellent yields and the use of commercially available and relatively non-toxic compounds.

## Introduction

Exploring chemical space is the key to discovering biologically active molecules.[1] Among the broad range of templates, heterocyclic scaffolds represent the most promising molecules as lead structures for the discovery of novel synthetic drugs.[2] Pyrazolopyrimidines and related heterocycles are found to possess a valuable and versatile pharmacophore, and are a privileged structure in medicinal chemistry. A literature survey shows that the pyrazolo[1,5-*a*]pyrimidine structural motif may be found in a large number of pharmaceutical agents with a diverse range of physiological activities, for example, angiotensin II receptor antagonists,[3] COX-2 selective inhibitors,[4] selective peripheral benzodiazepine receptor ligands,[5] corticotropin releasing factor 1 (CRF1) antagonists,[6] inhibitors of coxsackievirus B3 replication (CVB3),[7] estrogen receptor (ER) antagonists,[8] kinase inhibitors,[9] 5-HT$_6$ antagonists,[10] hepatitis C virus inhibitors,[11] HMG-CoA Reductase inhibitors,[12] inhibitors of Mitogen-Activated Protein Kinase-Activated Protein Kinase 2 (MAPKAP-K2),[13] as well as having antimicrobial activity.[14] Although there are a few reports describing the palladium-catalyzed synthesis of 7-substituted pyrazolo[1,5-*a*]pyrimidines, to the best of our knowledge, only Negishi[15,16] coupling has been reported for the preparation of these heterocycles in the Literature to date.

Our group therefore sought to develop new practical routes for the synthesis of functionalized pyrazolo[1,5-*a*]pyrimidines.[17,18] Recently, we disclosed methods for the regioselective palladium-catalyzed direct C-H arylation reaction of 5,7-dimethyl-2-phenylpyrazolo[1,5-*a*]pyrimidine with a variety of aryl and heteroaryl bromides.[18] As a continuation of our interest in the synthesis of this kind of heterocyclic ring, we report in this paper a novel and efficient protocol for the synthesis of a library of 7-substituted pyrazolo[1,5-*a*] pyrimidines **4** via palladium-catalyzed direct α-arylation of ester enolates followed by saponification-decarboxylation reactions in a one-pot procedure under microwave irradiation (**Scheme 1**).




**Scheme 1**: Sequential one-pot approach of **4**.

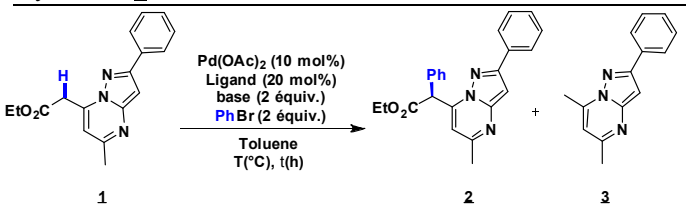
## Results and discussion

Over the past decade, the metal catalyzed α-arylation carbonyl compound has been broadly studied and is now explored on a large scale to synthesize pharmaceutical compounds. Driven by the pioneering work in the field by Hartwig[19], Buchwald[19], Miura[20], and Muratake[21], there are now many exploited examples of the palladium-catalyzed α-arylation of enolates derived from aryl methyl ketones, alkyl ketones, esters, amides, aldehydes, nitriles, β-difunctionalized compounds as well as several other carbonyl-like substrates with arylhalides.

We aimed at developing a method for the synthesis of 7-substituted pyrazolo[1,5-*a*]pyrimidines **4** *via* a one-pot procedure, the Pd-catalyzed direct C-H arylation of 7-ethoxycarbonylmethyl-

5-methyl-2-phenylpyrazolo[1,5-*a*]pyrimidine **1**[17] followed by saponification-decarboxylation of the product formed **(Scheme 1)**. Our initial study focused on the direct arylation of **1**, as the first step in the proposed sequence. We started our optimization with the use of the reaction conditions already described in our laboratory.[18] Compound **1** (1 equiv.) and bromobenzene (2 equiv.) were reacted in the presence of palladium (II) acetate (10 mol %), triphenylphosphine (20 mol %) and $Cs_2CO_3$ (2 equiv.) in toluene at 110 °C for 48 hours. Under these experimental conditions, the desired product was obtained in only 33% yield with a significant amount of starting material **1** being recovered **(Table 1, entry 1)**. In an effort to improve the yield, we decided to investigate the influence of some reaction parameters such as ligands, bases and temperature. Results are summarized in **Table 1**. For example, $Cs_2CO_3$ was found to be a suitable base, whereas NaH and LiHDMS lowered the yield to 17% and 4%, respectively **(Table 1, Entries 2-3)**. It was noticed that, when LiHDMS was used at room temperature, no product **2** was formed **(Table 1, entry 4)**. However, as noted in **Table 1**, **entry 5**, the use of 2-dicyclohexylphosphino-2′-(N,N-dimethylamino)biphenyl (DavePhos) instead of $PPh_3$ in presence of 10 mol % $Pd(OAc)_2$, bromobenzene (2 equiv.) and $Cs_2CO_3$ (2 equiv.) in toluene at 110 °C for 36h gave the desired product in 82% yield after total conversion.

**Table 1**: Optimization of reaction conditions for the direct C-H arylation of **1** with bromobenzene



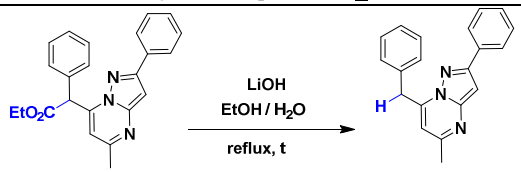

**1** **2** **3**

[a] Isolated yield. [b] Under microwave irradiation. [c] Under microwave irradiation using Toluene/EtOH (2/1) as solvent.

To reduce the reaction time, we decided to optimize the reaction conditions under microwave irradiation. It was found that the use of microwave irradiation at 158°C for 0.5 h afforded the desired compound in 81% yield **(Table 1, entry 6)**. Moreover, when the reactions were carried out in a mixture of toluene/ethanol (2/1), no desired product was found; only product **3**, resulting from decarboxylation, was isolated in 68% with a significant amount of starting material **1** being recovered **(Table 1, entry 7)**. After a suitable method for the synthesis of precursor **2** had been established, we searched for efficient conditions for the saponification/decarboxylation of **2**. To reach our goal, we first tested the reaction conditions already described in the literature.[22] Compound **2** (1 equiv.) was treated with LiOH (1.2 equiv.) in refluxing EtOH/$H_2O$ (20/1) for 4.5 h. Under these experimental conditions, the desired product **4** was isolated in 69% yield with a significant amount of starting material **2** being recovered **(Table 2, entry 1)**. Increasing the quantity of LiOH from 1.2 to 2.3 equiv., under the same reaction conditions, gave **4** in 87% yields **(Table 2, Entry 2)**. However, microwave irradiation **(Table 2, entry 3)** provided compound **4** in good yield with the greatest efficiency.

| Entry | Ligand | Base | T(°C) | t(*h*) | Yield[a]; **1/2/3 (%)** |
|---|---|---|---|---|---|
| 1 | $PPh_3$ | $Cs_2CO_3$ | 110 | 48 | 39/33/_ |
| 2 | $PPh_3$ | NaH | 110 | 48 | 30/17/22 |
| 3 | $PPh_3$ | LiHMDS | 110 | 48 | 77/4/7 |
| 4 | $PPh_3$ | LiHMDS | T.A | 72 | 97/_/_ |
| 5 | DavePhos | $Cs_2CO_3$ | 110 | 36 | _/82/_ |
| **6** | **DavePhos** | **$Cs_2CO_3$** | **158[b]** | **0.5** | **_/81/_** |
| 7 | DavePhos | $Cs_2CO_3$ | 158[c] | 0.5 | 22/_/68 |

**Table 2:** Optimization of reaction conditions for the saponification/decarboxylation of precursor **2**.




**2** **4**

| Entry | LiOH (eq) | t(*h*) | Yield; [a] **2/4 (%)** |
|---|---|---|---|
| 1 | 1.2 | 4.5 | 11/69 |
| 2 | 2.3 | 3.5 | -/87 |
| 3 | 2.3 | 20 min | **-/87[b]** |

[a] Isolated yield. [b]Under microwave irradiation.

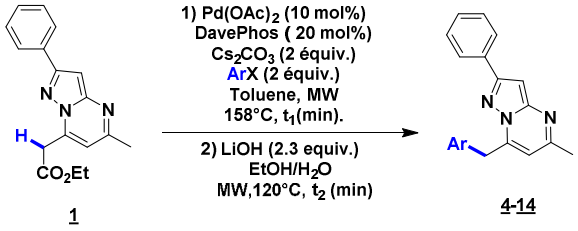
We were encouraged to attempt a one-pot two-step protocol for the formation of product **4** based on our results described in **Tables 1** and **2**.

The sequential one-pot process proved to work successfully, as the desired product **4** was isolated in 81% yield **(Table 3, entry 1)**. It is worth mentioning that the presence of toluene in the solvent mixture, although in lower amounts, affected the outcome of the second step and afforded compound **4** in poor yield. The reaction mixture was therefore evaporated to dryness before the saponification/decarboxylation reaction.

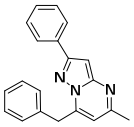
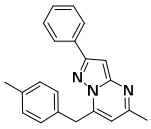
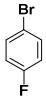
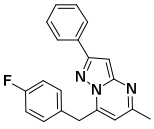
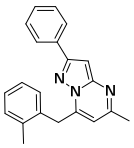
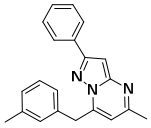
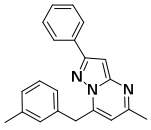
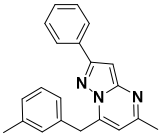
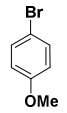
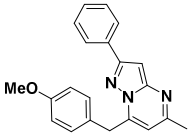
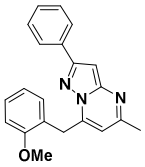
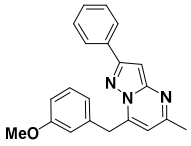
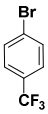
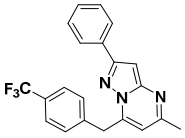
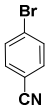
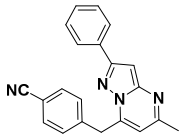
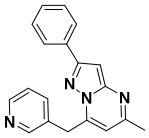
These interesting results stimulated us to investigate the generality of the present one-pot reaction. The results are summarized in **Table 3**, **entries 2-13**. It was found this method is quite general, as various aryl halides, possessing electron-rich (Me, MeO) and electron-poor (F, $CF_3$, CN) groups in *ortho*-, *meta*- and *para*-positions, were well tolerated under the reaction conditions to give the desired products **5-13** in good yields of 48-80% **(Table 3, entries 2-12)** although the ortho-substituents lead to more moderate yields caused by steric

hindrance. In fact, the methoxylated compounds **9**-**11** were obtained in good yields by employing double the amount of lithium hydroxide **(Table 3, entries 8-10)**. Thus, using 3-bromopyridine as substrate in the one-pot reaction gave the desired product **14** in high yield (84%) **(Table 3, entry 13)**.

**Table 3:** Scope of the one-pot microwave-assisted synthesis

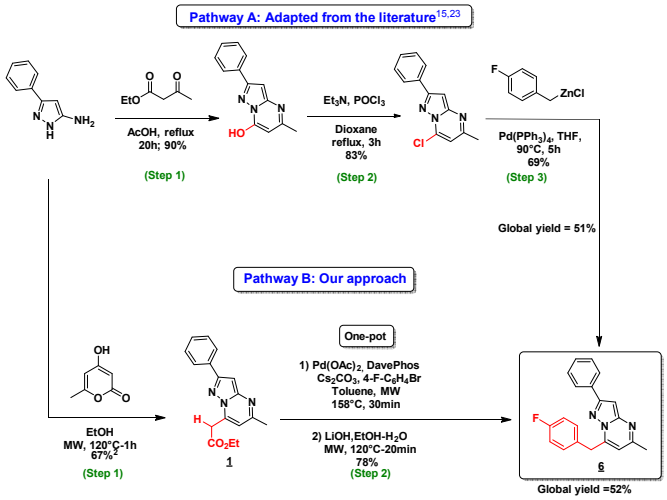



1 4-14

| Entry | Ar-Br | $t_1$(min) | $t_2$(min) | Product | Yield[a](%) |
|---|---|---|---|---|---|
| 1 |  | 30 | 20 |  | 4: 78 |
| 2 |  | 30 | 20 |  | 5: 78 |
| 3 |  | 30 | 20 |  | 6: 78 |
| 4 |  | 40 | 35 |  | 7:65 |
| 5 |  | 30 | 30 |  | 8: 64 |
| 6 |  | 30 | 30 |  | 8: 52 |
| 7 |  | 35 | 30 |  | 8: 60 |
| 8 |  | 30 | 40 |  | 9: 73 [b] |
| 9 |  | 120 | 30 |  | 10: 49 [b] |
| 10 |  | 45 | 30 |  | 11: 52 [b] |
| 11 |  | 60 | 30 |  | 12 : 80 |
| 12 |  | 30 | 20 |  | 13: 62 |
| 13 |  | 180 | 20 |  | 14: 84 |

[a] Isolated yield. [b] Using 4.6 equiv. of LiOH.

To compare our method to that described in the literature, [15, 23] we elected to prepare compound **6** **(Scheme 2)**.




**Scheme 2:** Comparison between the literature method and our synthesis.

Using the literature conditions, product **6** was obtained after three steps with a global yield of 51% **(Pathway A, Scheme 2)**. However, by applying our method, **6** were isolated rapidly, in just two steps, with a global yield of 52%. The sequence begins with the development of product **1**, which, prepared by the condensation reaction recently reported by our group,[17] and subjected to the "one-pot" reaction, leads to the desired derivative **6** with a global time of 1h50min **(pathway B, Scheme 2)**.

On comparing these results, we were pleased to find that our approach gave a similar yield, but a great improvement in terms of time and number of reaction steps involving the economy of some reagents such as zinc derivatives and phosphoryl oxychloride **(Scheme 2)**. The present method would allow rapid access, in two steps, to a library of pyrazolo[1,5-*a*]pyrimidines functionalized at position 7 by benzylic entities.

## Conclusion

In summary, we have developed a one-pot synthesis of 7-substituted pyrazolo[1,5-*a*]pyrimidines *via* Pd-catalyzed direct CH-arylation followed by saponification-decarboxylation. Compared to the classical method (Negishi coupling), this new method consistently has several advantages: good yields, shorter times, a reduced number of steps and the use of commercially available and relatively non-toxic compounds.

## Experimental section

### General information

All reagents were purchased from commercial suppliers and were used without further purification. Microwave assisted reactions were carried out with a microwave synthesis instrument and temperatures were measured by an IR sensor. The reactions were monitored by thin-layer chromatography (TLC) analysis. 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. $^{1}$H and $^{13}$C NMR spectra were recorded on a spectrometer at 250 MHz ($^{13}$C, 62.9 MHz) or 400 MHz ($^{13}$C, 100 MHz). Chemical shifts ($\delta$) are given in parts per million from tetramethylsilane (TMS) as internal standard. The following abbreviations are used for the proton spectra multiplicities: s: singlet, dd: double doublet, ddd: double double doublet, d: doublet, t: triplet, dt: double triplet, m: multiplet. Coupling constants (*J*) are reported in Hertz (Hz). High-resolution mass spectra (HRMS) were performed on a Q-TOF mass spectrometer.

**Procedure for synthesis of 7-ethoxycarbonylmethyl-5-methyl-2-phenylpyrazolo [1, 5-*a*] pyrimidine 1** .

Prepared by condensation reaction recently reported by our group.[17] White solid, mp 116-117°C. $^{1}$H NMR (400 MHz, $CDCl_3$): 7.98 (d, 2H, *J*= 6.8 Hz), 7.45 (t, 2H, *J*= 7.4 Hz), 7.38 (t, 1H, *J*= 7.3 Hz), 6.87 (s, 1H), 6.69 (s, 1H), 4.24 (t, 2H, *J*= 7.1 Hz), 4.18 (s, 2H), 2, 60 (s, 3H) 1.27 (t, 3H, *J*= 7.1 Hz). $^{13}$C NMR (100.62 MHz, $CDCl_3$): 167.9, 158.4, 155.5, 149.6, 140.9, 133.0, 128.8, 128.7, 126.5, 109.0, 92.8, 61.6, 36.2, 24.8, 14.1. HRMS: m/z $[M+Na]^+$ calcd for $C_{17}H_{17}N_3O_2Na$: 318.1215; found: 318.1218.

**One-Pot two-step microwave-assisted synthesis of 7-substituted pyrazolo[1,5-*a*]pyrimidines. General procedure.**

Under argon, a mixture of 7-ethoxycarbonylmethyl-5-methyl-2-phenylpyrazolo[1,5-*a*] pyrimidine **1** (0.1 g, 0.34 mmol), an aryl or heteroaryl bromide (0.68 mmol, 2 equiv.), $Cs_2CO_3$ (0.68 mmol, 2 equiv. ), 2-dicyclohexylphosphino-2'-(N,N-dimethylamino) biphenyl (DavPhos) (0.068 mmol, 0.2 equiv.) and $Pd(OAc)_2$ (0.034 mmol, 0.1 equiv.) in toluene (2 mL) was heated at 150 °C for 30 minutes under microwave irradiation. After cooling to room temperature, the reaction mixture was evaporated under reduced pressure. Then, the lithium hydroxide monohydrate (0.78 mmol) and 0.2 ml of water were added to the residue dissolved in 4 mL of ethanol, and the mixture was heated at 120°C for 20 minutes under microwave irradiation. After the reaction was complete, the mixture was cooled, washed with water and extracted with ethyl acetate (3x 15 mL). The combined organic layers were dried with anhydrous MgSO4. The solvent was evaporated and the crude product was purified by column chromatography on silica gel to give compounds **4-14.**

**7-Benzyl-5-methyl-2-phenylpyrazolo[1,5-*a*]pyrimidine 4.** Column chromatography (EtOAc: Petroleum ether (1/9)), Yellow solid, (81% yield), mp 115-116 °C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, 2H, *J* = 7.6 Hz), 7.47 (t, 2H, *J* = 7.6 Hz), 7.40 (d, 2H, *J* = 3.6 Hz), 7.41-7.31 (m, 4H), 6.87 (s, 1H), 6.23 (s, 1H), 4.53 (s, 2H), 2.50 (s, 3H). $^{13}$C NMR (100.62 MHz, $CDCl_3$) δ 158.7, 155.6, 149.8, 148.2, 13.2, 133.4, 130.0, 129.0, 128.9, 128.8, 127.5, 126.7, 107.7, 92.8, 36.4, 24.9. HRMS: *m/z* $[M+H]^+$ calcd for $C_{20}H_{18}N_3$ : 300.14952; found: 300.14995.

**5-Methyl-7-(4-methylbenzyl)-2-phenylpyrazolo[1,5-*a*]pyrimidine 5.** Column chromatography (EtOAc: Petroleum ether (1/9)), White solid, (78% yield), mp 142-143 °C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ

8.03 (d, 2H, *J* = 7.2 Hz), 7.43 (ddd, 3H, *J* = 7.2, 7.6, 32.4 Hz), 7.28 (d, 2H, *J* = 8.0 Hz), 7.20 (d, 2H, *J* = 8.0 Hz), 6.86 (s, 1H), 6.23 (s, 1H), 4.48 (s, 2H), 2.49 (s, 3H), 2.37 (s, 3H). $^{13}$C NMR (100.62 MHz, $CDCl_3$) δ 158.7, 155.6, 149.8, 148.5, 137.2, 133.4, 132.1, 129.9, 129.7, 128.9, 128.8, 126.7, 107.6, 92.7, 36.0, 24.9, 21.3. HRMS: *m/z* [M +H] $^+$ calcd for $C_{21}H_{20}N_3$ : 314.16517; found: 314.16558.

**7-(4-Fluorobenzyl)-5-methyl-2-phenylpyrazolo[1,5-*a*]pyrimidine 6.** Column chromatography (EtOAc: Petroleum ether (1/9)), Yellow solid, (78% yield), mp 139-140°C. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, 2H, *J* = 7.2 Hz), 7.50-7.40 (m, 2H), 7.37 (dd, 2H, $J_{H,H}$ = 8.4, $^4J_{H,F}$ = 5.6 Hz), 7.07 (t, 2H, $J_{H,H}$ = $^3J_{H,F}$ = 8.4 Hz), 6.87 (s, 1H), 6.23 (s, 1H), 4.49 (s, 2H), 2.51 (s, 3H). $^{13}$C NMR (100.62 MHz, $CDCl_3$) δ 157.2 (d, $^1J_{CF}$ = 300.0 Hz), 149.9, 147.8, 133.3, 131.5 (d, $^3J_{CF}$ = 7.9 Hz), 130.9 (d, $^4J_{CF}$ = 3.4 Hz), 129.0, 128.9, 126.7, 115.9 (d, $^2J_{CF}$ = 21.4 Hz), 107.6, 92.9, 35.6, 24.9. HRMS: *m/z* [M +H] $^+$ calcd for $C_{20}H_{17}N_3F$: 318.14010; found: 318.14041.

**5-Methyl-7-(2-methylbenzyl)-2-phenylpyrazolo[1,5-*a*]pyrimidine 7.** Column chromatography (EtOAc: Petroleum ether (1/9)), White solid, (65% yield), mp 210-211 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, 2H, *J* = 7.2 Hz), 7.48 (t, 2H, *J*= 7.4 Hz), 7.24 (t, 1H, *J*= 7.4 Hz), 7.24-7.30 (m, 4H), 6.89 (s, 1H), 6.00 (s, 1H), 4.53 (s, 2H, *J*= 0.4 Hz), 2.46 (s, 3H), 2.29 (s, 3H). $^{13}$C NMR (100.62 MHz, $CDCl_3$) δ 158.7, 155.7, 149.8, 147.6, 137.5, 133.4, 133.3, 131.0, 130.8, 129.0, 128.9, 127.9, 126.7,126.6, 107.1, 92.8, 34.0, 24.9, 19.6. HRMS: *m/z* [M +H] $^+$ calcd for $C_{21}H_{20}N_3$ : 314.165174; found: 314.165632.

**5-Methyl-7-(3-methylbenzyl)-2-phenylpyrazolo[1,5-*a*]pyrimidine 8.** Column chromatography (EtOAc: Petroleum ether (1/9)), Yellow solid, (64% yield for X= Br, 52% yield for X= Cl et 60% yield for X= I), mp 118-119 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, 2H, *J* = 7.2 Hz), 7.42-7.37 (m, 3H), 7.30-7.14 (m, 3H), 7.20 (s, 1H), 6.87 (s, 1H), 6.23 (s, 1H), 4.48 (s, 2H), 2.50 (s, 3H), 2.37 (s, 3H, $CH_3$). $^{13}$C NMR (100.62 MHz, $CDCl_3$) δ 158.7, 155.6, 149.8, 148.3, 138.6, 135.1, 133.4, 130.8, 128.9, 128.8, 128.3, 127.1, 126.7, 107.7, 92.8, 36.3, 24.9, 21.6. HRMS: *m/z* [M +H] $^+$ calcd for $C_{21}H_{20}N_3$ : 314.16517; found: 314.16560.

**7-(4-Methoxybenzyl)-5-methyl-2-phenylpyrazolo[1,5-*a*]pyrimidine 9.** Column chromatography (EtOAc: Petroleum ether (1.5/8.5)), Yellow solid, (73% yield), mp 133-134°C. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, 2H, *J* = 7.2 Hz), 7.43 (ddd, 3H, *J* = 7.2, 7.6, 32.4 Hz), 7.31 (d, 2H, *J* = 8.4 Hz), 6.92 (d, 2H, *J* = 8.8 Hz), 6.86 (s, 1H), 6.22 (s, 1H), 4.46 (s, 2H), 3.82 (s, 3H), 2.50 (s, 3H). $^{13}$C NMR (100.62 MHz, $CDCl_3$) δ 159.0, 158.7, 155.6, 149.9, 148.6, 133.4, 131.1, 128.9, 128.8, 127.1, 126.7, 114.4, 107.5, 92.7, 55.5, 35.5, 24.9. HRMS: *m/z* [M +H] $^+$ calcd for $C_{21}H_{20}N_3O$: 330.16009; found: 330.16042.

**7-(2-Methoxybenzyl)-5-methyl-2-phenylpyrazolo[1,5-*a*]pyrimidine 10.** Column chromatography (EtOAc: Petroleum ether: Dichloromethane (0.4/5/5)), Yellow solid, (49% yield), mp 113-114°C. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, 2H, *J* = 8.0 Hz), 7.47 (t, 2H, *J* = 7.8 Hz), 7.41-7.32 (m, 3H), 6.98 (dd, 2H, *J* = 7.6, 13.4 Hz), 6.86 (s, 1H), 6.14 (s, 1H), 4.54 (s, 2H), 3.80 (s, 3H), 2.47 (s, 3H). $^{13}$C NMR (100.62 MHz, $CDCl_3$) δ 158.6, 158.1, 155.5, 149.9, 148.0, 133.5, 131.9, 129.1, 128.8, 126.7, 123.5, 120.9, 110.9, 107.2, 92.6, 55.5, 30.8, 24.9. HRMS: *m/z* [M +H] $^+$ calcd for $C_{21}H_{20}N_3O$: 330.16009; found: 330.16042.

**7-(3-Methoxybenzyl)-5-methyl-2-phenylpyrazolo[1,5-*a*]pyrimidine 11.** Column chromatography (EtOAc: Petroleum ether (1/9)), White solid, (52% yield), mp 218-219°C. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, 2H, *J* = 7.2 Hz), 7.47 (t, 2H, *J* = 7.4 Hz), 7.39 (t, 1H, *J* = 7.4 Hz), 7.31 (t, 1H, *J* = 8.0 Hz), 6.88-6.69 (m, 3H), 6.87 (s, 1H), 6.25 (s, 1H), 4.50 (s, 2H), 3.81 (s, 3H), 2.50 (s, 3H). $^{13}$C NMR (100.62 MHz, $CDCl_3$) δ 160.1, 158.7, 155.6, 149.9, 148.0, 136.7, 133.4, 130.0, 128.9, 128.8, 126.7, 122.4, 115.8, 112.8, 107.6, 92.8, 55.4, 36.4, 24.9. HRMS: *m/z* [M +H] $^+$ calcd for $C_{21}H_{20}N_3O$: 330.160089; found: 330.160571.

**5-Methyl-2-phenyl-7-(4-(trifluoromethyl)-benzyl)-pyrazolo[1,5-*a*]pyrimidine 12.** Column chromatography (Dichloromethane), Yellow solid, (80% yield). mp 148-149 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, 2H, *J* = 7.2 Hz), 7.64 (d, 2H, *J* = 8.0 Hz), 7.53 (d, 2H, *J* = 7.6 Hz), 7.43 (dt, 3H, *J* = 7.2 Hz), 6.88 (s, 1H), 6.26 (s, 1H), 4.57 (s, 2H), 2.52 (s, 3H). $^{13}$C NMR (100.62 MHz, $CDCl_3$) δ 158.7, 155.8, 149.9, 146.8, 139.4, 133.2, 130.3, 129.9 (d, $^2J_{CF}$ = 32.6 Hz), 129.1, 128.9, 126.7, 125.9 (q, $^4J_{CF}$ = 3.8 Hz), 107.7, 93.0, 36.2, 24.9. HRMS: *m/z* [M +H] $^+$ calcd for $C_{21}H_{17}N_3F_3$: 368.13691; found: 368.13745.

**4-((5-Methyl-2-phenyl-pyrazolo[1,5-*a*]pyrimidin-7-yl)-methyl)benzonitrile 13.** Column chromatography (Dichloromethane), Yellow solid, (62% yield), mp 162-163 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, 2H, *J* = 7.2 Hz), 7.66 (d, 2H, *J* = 8.0 Hz), 7.54 (d, 2H, *J* = 8.4 Hz), 7.43 (ddd, 3H, *J* = 7.2, 7.6, 28.4 Hz), 6.88 (s, 1H), 6.30 (s, 1H), 4.56 (s, 2H), 2.54 (s, 3H). $^{13}$C NMR (100.62 MHz, $CDCl_3$) δ 158.7, 155.9, 149.8, 146.1, 140.9, 133.1, 132.7, 130.6, 129.1, 128.9, 126.6, 118.7, 111.6,107.8, 93.1, 36.5, 24.9. HRMS: *m/z* [M +H] $^+$ calcd for $C_{21}H_{17}N_4$: 325.14477; found: 325.14522.

**5-Methyl-2-phenyl-7-(pyridin-3-yl-methyl)-pyrazolo[1,5-*a*]pyrimidine 14.** Column chromatography (EtOAc: Petroleum ether (2/8)), Yellow solid, (84% yield), mp 159-160 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.57 (d, 1H, *J* = 4.0 Hz), 8.01 (d, 2H, *J* = 7.6 Hz), 7.74 (d, 1H, *J* = 8.0 Hz), 7.43 (ddd, 3H, *J* = 7.2, 7.6, 30.0 Hz), 7.30 (dd, 1H, *J* = 4.8, 7.6 Hz), 6.88 (s, 1H), 6.31 (s, 1H), 4.52 (s, 2H), 2.53(s, 3H). $^{13}$C NMR (100.62 MHz, $CDCl_3$) δ 158.7, 155.8, 151.0, 149.8, 148.9, 146.6, 137.3, 133.2, 131.1, 129.0, 12.9, 126.6, 123.8, 107.7, 93.0, 33.8, 24.9. HRMS: *m/z* [M +H] $^+$ calcd for $C_{19}H_{17}N_4$: 301.14477; found: 301.14511.

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## Notes and references

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1. Reymond, JL., Deursen, RV., Blum, L C., Ruddigkeit, L. *Med. Chem. Comm.,* **2010**, 1, 30.
2. **(a)** Jr, D. J. S. J., Fotsch, C. *J. Med. Chem*. **2012**, 55, 6002. **(b)** Taylor, R. D., MacCoss, M., Lawson, A. D. G. *J. Med. Chem*. **2014**, 57, 5845.
3. Shiota, T.;Yamamori,T.; Sakai, K.; Kiyokawa, M.; Honma, T., Ogawa, M.; Hayashi, K.; Ishizuka, N.; Matsumura, K.; Hara, M., Fujimoto, M.; Kawabata,T.; Nakajima, S. *Chem. Pharm. Bull.,***1999**, 47,928.
4. Al-Mansa, C., Arriba, A.F., Cavalcanti, F.L., Gomez, L.A., Miralles, A., Forn J. *J. Med. Chem*., **2001**, 44, 350.
5. **(a)** Selleri, S.; Bruni, F.; Costagli, C.; Costanzo, A.; Guerrini, G.; Ciciani, G.; Costa, B.; Martini, C. *Bioorg. Med. Chem*. **2001**, 9, 2661. **(b)** Selleri, S.; Gratteri, P.; Costagli, C.; Bonaccini, C.; Costanzo, A.; Melani, F.; Guerrini, G.; Ciciani, G.; Costa,B.; Spinetti, F.; Martini, C.; Bruni, F. *Bioorg. Med. Chem.* **2005**, 13, 4821.
6. **(a)** Wustrow, D. J.; Capiris, T.; Rubin, R.; Knobelsdorf, J. A.; Akunne, H.; Davis, M. D.; MacKenzie, R.; Pugsley, T. A.; Zoski, K. T.; Heffner, T. G.; Wise, L. D. *Bioorg. Med. Chem. Lett*. **1998**, 8, 2067. **(b)** Gilligan, P.J.; Baldauf,C.; Cocuzza, A.; Chidester, D.; Zaczek, R.; Fitzgerald, L.W.; McElroy, J.; Smith, M.A.; Shen, H.-S. L.; Saye, J. A.; Christ, D.; Trainor, G.; Robertson, D. W.; Hartig, P. *Bioorg. Med. Chem*., **2000**, 8, 181. **(c)** Chen, C.; Wilcoxen, K.M.; Huang, C. Q.; McCarthy, J. R.; Chen, T.; Grigoriadis, D.E. *Bioorg. Med. Chem. Lett*., **2004**, 14, 3669.
7. Makarov, V. A.; Riabova, O. B.; Granik, V. G.; Dahse, H. M.; Stelzner, A.; Wutzlerc, P.; Schmidtkec, M. *Bioorg. Med. Chem. Lett*., **2005**, 15, 37.
8. **(a)** Compton, D. R.; Carlson, K. E.; Katzenellenbogen, J. A. *Bioorg. Med. Chem. Lett*. **2004**, 14, 5681. **(b)** Compton, D. R.; Sheng, S.; Carlson, K. E.; Rebacz, N. A.; Lee, I. Y.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *J. Med. Chem*. **2004**, 47, 5872. **(c)** Zhou, H. B.; Sheng, S.; Compton, D. R.; Kim, Y.; Joachimiak, A.; Sharma, S.; Carlson, K. E.; Katzenellenbogen, B. S.; Nettles, K. W.; Greene, G. L.; Katzenellenbogen, J. A. *J. Med. Chem*. **2007**, 50, 399. **(d)** Dwyer, M. P., Paruch, K., Alvarez, C., Doll, R. J., Keertikar, K., Duca, J., Fischmann, T. O., Hruza, A., Madison, V., Lees, E., Parry, D., Seghezzi, W., Sgambellone, N., Shanahan, F., Wiswell, D., Guzi, T. J. *Bioorg. Med. Chem. Lett*. **2007**, 17, 6216. **(e)** Gopalsamy, A., Ciszewski, G., Hu, Y., Lee, F., Feldberg, L., Frommer, E., Kim, S., Collins, K., Wojciechowicz, D., Mallon, R. *Bioorg. Med. Chem. Lett*. **2009**, 19, 2735. **(f)** Gopalsamy, A., Ciszewski, G., Shi, M., Berger, D., Hu, Y., Lee, F., Feldberg, L., Frommer, E., Kim, S., Collins, K., Wojciechowicz, D., Mallon, R. *Bioorg. Med. Chem. Lett*. **2009**, 24, 6890.
9. **(a)** Fraley, M. E.; Hoffman, W. F.; Rubino, R. S.; Hungate, R. W.; Tebben, A. J.; Rutledge, R. Z.; McFall, R. C.; Huckle, W. R.; Kendall, R. L.; Coll, K. E.; Thomas, K. A. *Bioorg. Med. Chem. Lett*. **2002**, 12, 2767. **(b)** Frey, R. R.; Curtin, M. L.; Albert, D. H.; Glaser, K. B.; Pease, L. J.; Soni, N. B.; Bouska, J. J.; Reuter, D.; Stewart, K. D.; Marcotte, P.; Bukofzer, G.; Li, J.; Davidson, S. K.; Michaelides, M. R. *J. Med. Chem*. **2008**, 51, 3777. **(c)** Heathcote, D. A.; Patel, H.; Kroll, S. H. B.; Hazel, P.; Periyasamy, M.; Alikian, M.; Kanneganti, S. K.; Jogalekar, A. S.; Scheiper, B.; Barbazanges, M.; Blum, A.; Brackow, M.; Siwicka, A.; Pace, R. D. M.; Fuchter, M. J.; Snyder, J. P.; Liotta, D. C.; Freemont, P. S.; Aboagye, E. O.; Coombes, C.; Barrett, A. G. M.;Ali, S. *J. Med. Chem.* **2010**, 53, 8508.
10. **(a)** Ivachtchenko, A V., Golovina, ES., Kadieva, M G., Kysil, V M., Mitkin, O D., Tkachenko, S E., Okun, I M. *J. Med. Chem*., **2011**, 54, 8161. **(b)** Ivachtchenko, A V., Golovina, ES., Kadieva, M G., Kysil, V M., Mitkin, O D., Tkachenko, S E., Okun, I M. *Eur. J. Med. Chem*., **2011**, 46, 1189. **(c)** Ivachtchenko, A V., Golovina, ES., Kadieva, M G., Kysil, V M., Mitkin, O D., Tkachenko, S E., Okun, I M. *Bioorg. Med. Chem*., **2011**, 19, 1482.
11. **(a)** Deng Y., Shippr G.W. Jr., Wang T., PopoviciMuller J., Rosner K.E., Siddiqui M.A., Duca J., Cooper A. B., Cable M., *Bioorg. Med. Chem. Lett.*, **2009**, 19, 5363. **(b)** Hwang, J. Y., Windisch, M. P., Jo, S., Kim,K., Kong, S., Kim, H. C., Kim, S., Kim, H., Lee, M. E., Kim, Y., Choi, J., Park, D-S., Park, E., Kwon, J., Nam, J., Ahn, S., Cechetto, J., Kim, J., Liuzzi,M., No,Z., Lee, J. *Bioorg. Med. Chem. Lett.*, **2012**, 22, 7297.
12. Suzuki, M.; Iwasaki, H.; Fujikawa, Y.; Sakashita, M.; Kitahara, M.; Sakoda, R. *Bioorg. Med. Chem. Lett*. **2001**, 11, 1285.
13. Kosugi, T., Mitchell, D R., Fujino, A., Imai, M., Kambe, M., Kobayashi, S., Makino,H., Matsueda, Y., Oue,Y., Komatsu, K., Imaizumi, K., Sakai, Y., Sugiura, S., Takenouchi, O.,Unoki, G., Yamakoshi, Y., Cunliffe, V., Frearson, J., Gordon, R., Harris, C J., Kalloo-Hosein, H., Le, J., Patel, G., Simpson, D J., Sherborne, B., Thomas, P S., Suzuki, N.,Takimoto-Kamimura, M., Kataoka, K I. *J. Med. Chem.,* **2012,** 55, 6700.
14. Shaikh, B. M.; Konda, S. G.; Chobe, S. S.; Mandawad, G. G.; Yemul, O. S.; Dawane, B. S. *J. Chem. Pharm. Res.,* **2011**, 3, 435.
15. Luo, Z., Slee, D., Tellew, J. E., Williams, J., Zhang, X. *PCT Int. Appl. 2005, WO 063755; Chem Abstr.* **2005**, 86, 612293.
16. Shiota T, Yamamori T, *J. Org. Chem*. **1999**, 64.453.
17. I. Bassoude, S. Berteina-Raboin, J. M. Leger, C. Jarry, E. M. Essassi, G. Guillaumet. *Tetrahedron*, **2011**, 67, 2279.
18. I. Bassoude, S. Berteina-Raboin, S. Massip, J. M. Leger, C. Jarry, E.M. Essassi, G. Guillaumet. *Eur. J. Org. Chem*, **2011**, 2572.
19. See for exemple: **(a)** Palucki,M.; Buchwald, S. *J. Am. Chem. Soc.,* **1997**, 119, 11108. **(b)** Hamann, B.; Hartwig, J. *J. Am. Chem. Soc*., **1997**, 119, 1238. **(c)** Shaugnessy, K.; Hamann, B.; Hartwig, J. *J. Og. Chem*. **1998** , 63, 6546. **(d)** Moradi, W.; Buchwald, S. *J. Am. Chem. Soc.* **2001**, 123, 7996. **(e)** Lee, S.; Beare, N.; Hartwig, J. *J. Am. Chem. Soc*. **2001**, 123, 8410. **(f)** Stauffer, S.; Beae, N.; Stambuli, J.; Hartwig, J. *J. Am. Chem. Soc*. **2001**, 123, 4641. **(g)** Hamada, T.; Chieffi, A.; Åhman, J.; Buchwald, S. *J. Am. Chem. Soc*. **2002**, 124, 1261. **(h)** Vogl, E.; Buchwald, S. *J. Org. Chem*. **2002**, 67, 106. **(i)** Culkin, D.A.; Hartwig, J. F. *Acc. Chem. Res.*, **2003**, 36, 234.**(j)** Chae, J.; Yun, J.; Buchwald, S. L. *Org. Lett*. **2004**, 6, 4809. **(k)** Liao, X.; Weng, Z.; Hartwig, J. F. *J. Am. Chem. Soc*. **2008**, 130, 195. **(l)** Hyde, A. M.; Buchwald, S. L. *Angew. Chem. Int. Ed*. **2008**, 47, 177.
20. See for exemple: **(a)** Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem. Int. Ed*. **1997**, 36, 1740. **(b)** Terao, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett*. **1998**, 39, 6203. **(c)** Terao, Y.; Fukuoka, Y.; Satoh, T.; Miura, T.; Nomura, M. *Tetrahedron Lett*. **2002**, 43, 101.

 

21. See for exemple: **(a)** Muratake, H., Natsume, M. *Tetrahedron Lett*, **1997**, 38, 7577. **(b)** Muratake, H.; Natsume, M. *Tetrahedron Lett*. **2002**, 43, 2913.
22. Putey, A.; Joucla, L.; Picot, L.; Besson, T.; Joseph, B. *Tetrahedron.* **2007**, 63, 867.
23. Senga, K.; Navinson, T.; Wilson, H, R. *J. Med. Chem*. **1981**, 24, 610-613.