# *Articles*

## Efficient Pd(0)-Mediated Microwave-Assisted Arylation of 2-Substituted Imidazo[1,2-*a*]pyrimidines

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A short and practical synthesis of 2,3-substituted imidazo[1,2-*a*]pyrimidines, based on microwave-assisted Heck-type arylation of 2-substituted imidazo[1,2-*a*]pyrimidines, was developed. A 45-membered library of 2,3-substituted imidazo[1,2-*a*]pyrimidines was obtained with good yields and purities using this optimized protocol.

### Introduction

Many 2,3-substituted imidazo[1,2-*a*]pyrimidines **5** (Scheme 1) are found to be biologically active.[1] For example, 2,3-diaryl imidazo[1,2-*a*]pyrimidines possess inhibitory activity against cyclooxigenase-2 (COX-2) with high selectivity in relation to COX-1.[2,3] Therefore, they could be useful for the treatment of inflammation and diseases mediated by COX-2 with a reduced ulcerogenic potential. Moreover, these compounds have been shown recently to express anti-cancer activity.[4] In addition, several 2-carboxamidoimidazo[1,2-*a*]-pyrimidines **5** ($R_1$ = Ar, $R_2$ = $CONH_2$) display analgesic, antipyretic, and anti-inflammatory activity[5] and might serve as potent glutamate antagonists for the treatment of cancer.[6] Differently substituted 2-carboxamidoimidazo[1,2-*a*]pyrim-idines **5** were also reported to inhibit glycogen phosphorylase, making them useful in prophylactic and therapeutic treatment of diabetes, hyperglycemia, hypertension, and arteriosclerosis and as cardioprotectants.[7]

Within the framework of developing libraries of the aforementioned bioactive compounds, we are currently investigating the synthesis of various 2,3-substituted imidazo-[1,2-*a*]pyrimidines, bearing a phenyl, carboxamide, or car-boxylate function at the 2-position and an aromatic substit-uent at the 3-position of scaffold **5**. To our knowledge, there is no general methodology described in the literature for the synthesis of such compounds. The main approach (Scheme 1, pathway A) starts from a suitable 1,2-diaryl-2-bromoet-hanone (**2**) which is reacted with 2-aminopyrimidine (**1**).[4] Unfortunately, variation of the substituents $R_1$ and $R_2$ is restricted because of the limited availability of the starting 1,2-diaryl-2-bromoketones (**2**) and the low overall yields.[3]

### Scheme 1
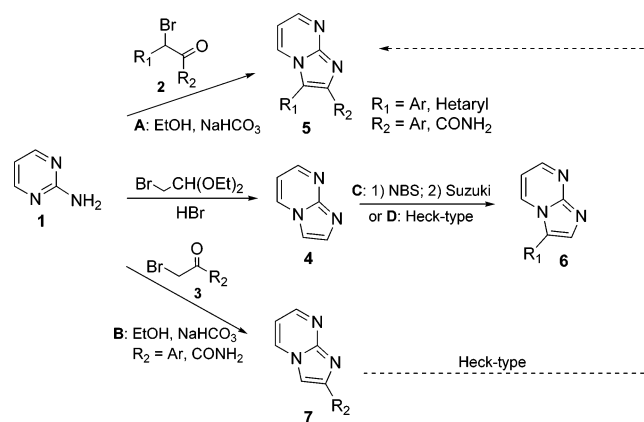


Only 3-monosubstituted compounds **6** are accessible via an alternative approach (Scheme 1, pathway C) involving bromination of the 3-position[7] of the unsubstituted imidazo-[1,2-*a*]pyrimidine (**4**), followed by Suzuki coupling with a suitable arylboronic acid.[8] Although this sequence was successful, an additional step for the activation of the 3-position is required. It was recently reported that the 2-unsubstituted imidazo[1,2-*a*]pyrimidine scaffold **4** could be selectively arylated at the 3-position via a Heck-type reaction, which applies arylbromides in the presence of base and a catalytic amount of palladium (Scheme 1, pathway D).[9] This method provided an efficient synthesis of mono-substituted 3-arylimidazo[1,2-*a*]pyrimidines **6**, using com-mercially available aryl and heteroaryl bromides.

However, our attempts to arylate the corresponding 2-substituted analogues, following the same Heck-type procedure, failed. To find proper arylation conditions, we started to investigate this reaction in more detail. Here, we report a hitherto unprecedented protocol for the arylation of the 3-position of 2-substituted imidazo[1,2-*a*]pyrimidines **7** using microwave irradiation (Scheme 1, pathway B).

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**Scheme 2**[a]
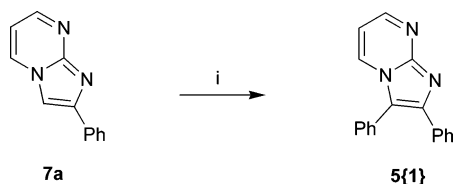


*a* Reaction conditions: (i) bromobenzene (1.35 equiv), Pd catalyst (8 mol %)/ligand (16 mol %), $Cs_2CO_3$ (1.1 equiv), 1,4-dioxane, and heating or MW-irradiation.

**Table 1.** Optimization of the Conditions for the Arylation of **7a** with Bromobenzene[a]

| entry | conditions | catalyst/ligand | temp (°C) | time (h) | yield (%) |
|---|---|---|---|---|---|
| 1 | Δ | $Pd(OAc)_2/Ph_3P$ | 100 | 72 | 24 |
| 2 | | $Pd(OAc)_2/Ph_3P$ | 120 | 72 | 42 |
| 3 | | $Pd(OAc)_2/Ph_3P$ | 145 | 72 | 56 |
| 4 | | $Pd(PPh_3)_2Cl_2/Ph_3P$ | 145 | 72 | 4 |
| 5 | | $Pd(PPh_3)_4$ | 145 | 72 | 15 |
| 6 | MW[b] | $Pd(OAc)_2/Ph_3P$ | 100 | 4 | 32 |
| 7 | | $Pd(OAc)_2/Ph_3P$ | 120 | 1 | 70 |
| 8 | | $Pd(OAc)_2/Ph_3P$ | 145 | 0.5 | 96 |
| 9 | | $Pd(PPh_3)_2Cl_2/Ph_3P$ | 145 | 0.5 | 0 |
| 10 | | $Pd(PPh_3)_4$ | 145 | 0.5 | 20 |

*a* All reactions were performed on a 0.5 mmol scale in 6 mL of 1,4-dioxane with 1.35 equiv of bromobenzene, 1.35 equiv of $Cs_2CO_3$, 8 mol % of the catalyst, and 16 mol % $PPh_3$ (if necessary). *b* All the MW experiments were performed at 150 W maximum power.

## Results and Discussion

We started to reinvestigate the arylation of 2-phenylimidazo[1,2-*a*]pyrimidine (**7a**) with bromobenzene by exploiting the previously described procedure[9] for 2-unsubstituted imidazo[1,2-*a*]pyrimidines (Scheme 2). However, with the literature conditions, even after 3 days of conventional heating at 100 °C in 1,4-dioxane and application of Pd-(AcO)$_2$/PPh$_3$ as the catalyst system and cesium carbonate as the base, a yield of only 24% was obtained for the desired arylated product **5{1}** (Table 1, entry 1). The best conditions were found when the temperature was increased to 145 °C, which resulted in a moderate yield of 56% (Table 1, entry 3). Increasing the temperature of the reaction up to 180 °C led to a number of unidentified side products and to decomposition of the catalyst in a few hours. Switching the catalyst system to Pd(PPh$_3$)$_2$Cl$_2$/PPh$_3$ (Table 1, entry 4) or Pd(PPh$_3$)$_4$ (Table 1, entry 5) seemed to be deleterious for the reaction. As we have previously demonstrated the beneficial effects of the application of microwave irradiation for transition metal-catalyzed reactions,[10,11] we decided to investigate the use of this technique for this arylation procedure.

The reaction of 2-phenylimidazo[1,2-*a*]pyrimidine (**7a**) was tested under microwave irradiation at 100 °C in 1,4-dioxane with Pd(OAc)$_2$/PPh$_3$ as the catalyst system and cesium carbonate as the base. However, after 4 h, the desired product **5{1}** was obtained in only a 32% yield (Table 1, entry 6). When the ceiling temperature was increased to 120 °C, the reaction time could be shortened to 1 h and a good yield of 70% was obtained (Table 1, entry 7). A further increase of the temperature to 145 °C produced the product

**Scheme 3**[a]
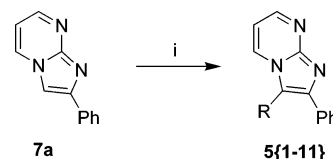


*a* Reaction conditions: (i) RBr (1.35 equiv), Pd(AcO)$_2$ (8 mol %), PPh$_3$ (16 mol %), $Cs_2CO_3$ (1.1 equiv), 1,4-dioxane, MW 150 W, 20−60 min, 145 °C.

**Table 2.** Arylation of 2-Phenylimidazo[1,2-*a*]pyrimidine (**7a**) with Various Aryl Bromides[a]

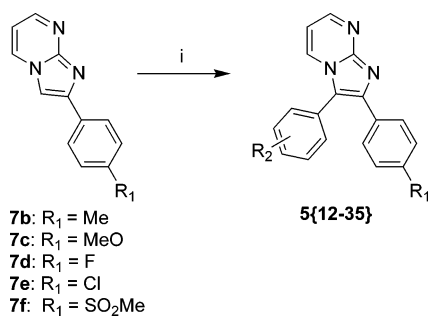| entry | product | R | time (min) | yield (%) |
|---|---|---|---|---|
| 1 | **5{1}** | phenyl | 30 | 96 |
| 2 | **5{2}** | 4'-fluorophenyl | 20 | 95 |
| 3 | **5{3}** | 4'-chlorophenyl | 35 | 82 |
| 4 | **5{4}** | 4'-trifluoromethylphenyl | 25 | 84 |
| 5 | **5{5}** | 2'-fluorophenyl | 60 | 86 |
| 6 | **5{6}** | 3',5'-difluorophenyl | 50 | 65 |
| 7 | **5{7}** | 4'-methoxyphenyl | 60 | 54 |
| 8 | **5{8}** | 4'-methanesulfonylphenyl | 25 | 80 |
| 9 | **5{9}** | isoquinol-4-yl | 60 | 67 |
| 10 | **5{10}** | pyridin-2-yl | 50 | 55 |
| 11 | **5{11}** | 4'-*tert*-butylphenyl | 55 | 46 |

*a* All reactions were performed on a 0.5 mmol scale in 6 mL of 1,4-dioxane with 1.35 equiv of aryl bromide, 1.35 equiv of $Cs_2CO_3$, 8 mol % Pd(OAc)$_2$, and 16 mol % PPh$_3$; all experiments were performed at 150 W maximum power and a ceiling temperature of 145 °C.

in an excellent 96% yield, and the irradiation time could be shortened to a mere 30 min (Table 1, entry 8). In all cases, a slight excess of bromobenzene (1.35 equiv) was used to drive the arylation to completion. The use of more than 1.5 equiv of bromobenzene resulted in the formation of a significant amount of unidentified side products.

To determine the scope and limitations of our microwave-assisted protocol, we investigated the arylation procedure with several aryl bromides (Scheme 3, Table 2). In agreement with the arylation mechanism proposed by Larsen et al.,[9] we noticed that in almost all cases the more-reactive electron-poor aryl bromides resulted in high yields (80−96%) (Table 2, entries 1−5 and 8). The less-reactive aryl bromides such as 4'-*tert*-butyl- (Table 2, entry 11) and 4'-methoxyphenyl bromide (Table 2, entry 7) resulted in lower yields. The procedure could also be applied successfully for hetaryl bromides (Table 2, entries 9 and 10), although lower yields were obtained.

Unexpectedly, 3',5'-difluorobromobenzene was quite unreactive despite the two electron-withdrawing groups (Table 2, entry 6). An increase of the temperature to 160 °C during microwave irradiation did not improve the yield and resulted in decomposition.

To further evaluate the applicability of our microwave-enhanced arylation procedure, we investigated different combinations of 2-arylimidazo[1,2-*a*]pyrimidines **7b**−**f**, which were prepared according to standard procedures,[12] with various arylbromides (Scheme 4, Table 3). To circumvent the problem of the poor solubility of several of the 2-arylimidazo[1,2-*a*]pyrimidines in 1,4-dioxane, the temperature was increased irradiation to 160 °C. The changeof 1,4-dioxane for DMF resulted in the formation of large amounts of

**Scheme 4**[a]



7b: R[1] = Me
7c: R[1] = MeO
7d: R[1] = F
7e: R[1] = Cl
7f: R[1] = SO[2]Me

5{12-35}

[a] Reaction conditions: (i) aryl bromide (1.35 equiv), Pd(AcO)[2] (8 mol %), PPh[3] (16 mol %), Cs[2]CO[3] (1.1 equiv), 1,4-dioxane, MW 150 W, 20–60 min, 160 °C.

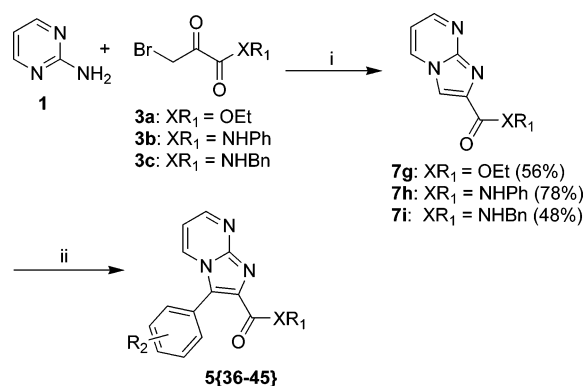**Table 3.** Arylation of 2-Arylimidazo[1,2-a]pyrimidines **7b-f**[a]

| entry | product | R[1] | R[2] | time (min) | yield (%) |
|---|---|---|---|---|---|
| 1 | **5{12}** | 4′-Me | H | 20 | 76 |
| 2 | **5{13}** | 4′-Me | 4′-F | 30 | 44 |
| 3 | **5{14}** | 4′-Me | 4′-MeSO[2] | 30 | 70 |
| 4 | **5{15}** | 4′-Me | 4′-CF[3] | 20 | 71 |
| 5 | **5{16}** | 4′-Me | Cl | 60 | 79 |
| 6 | **5{17}** | 4′-Me | 4′-MeO | 60 | 48 |
| 7 | **5{18}** | 4′-MeO | H | 30 | 65 |
| 8 | **5{19}** | 4′-MeO | 4′-F | 40 | 79 |
| 9 | **5{20}** | 4′-MeO | 4′-Cl | 30 | 70 |
| 10 | **5{21}** | 4′-MeO | 4′-CF[3] | 30 | 74 |
| 11 | **5{22}** | 4′-MeO | 2′-F | 60 | 55 |
| 12 | **5{23}** | 4′-MeO | 4′-MeSO[2] | 30 | 77 |
| 13 | **5{24}** | 4′-F | H | 20 | 90 |
| 14 | **5{25}** | 4′-F | 4′-F | 20 | 89 |
| 15 | **5{26}** | 4′-F | 4′-Cl | 20 | 94 |
| 16 | **5{27}** | 4′-F | 4′-CF[3] | 20 | 69 |
| 17 | **5{28}** | 4′-F | 4′-COMe | 40 | 35 |
| 18 | **5{29}** | 4′-F | 2′-F | 40 | 58 |
| 19 | **5{30}** | 4′-Cl | H | 20 | 86 |
| 20 | **5{31}** | 4′-Cl | 4′-F | 40 | 56 |
| 21 | **5{32}** | 4′-Cl | 4′-CF[3] | 40 | 72 |
| 22 | **5{33}** | 4′-Cl | 4′- MeSO[2] | 50 | 65 |
| 23 | **5{34}** | 4′- MeSO[2] | 4′-F | 30 | 84 |
| 24 | **5{35}** | 4′- MeSO[2] | biphenyl-4-yl | 40 | 67 |

[a] All reactions were performed on a 0.5 mmol scale in 6 mL of 1,4-dioxane with 1.35 equiv of aryl bromide, 1.35 equiv of Cs[2]CO[3], 8 mol % Pd(OAc)[2], and 16 mol % PPh[3]; all experiments were performed at 150 W maximum power and a ceiling temperature of 160 °C.

resinous material. Consistently, most activated aryl bromides bearing electron-withdrawing groups, gave good to excellent yields (Table 3, entries 3–5, 8–10, 12, 14–16, 21, and 23). Aryl bromides bearing electron-donating groups gave lower yields (Table 3, entry 6). The lower yields for 3-(2′-fluoro)-imidazo[1,2-α]pyrimidines **5{22}** and **5{29}** could probably be attributed to steric hindrance (Table 3, entries 11 and 18).

Although 2-(4′-methylsulfonylphenyl)imidazo[1,2-a]pyrimidine (**7f**) is hardly soluble in 1,4-dioxane, moderate to good yields were obtained at the elevated temperature of 160 °C (Table 3, entries 23 and 24).

Finally, we turned our attention to the arylation of imidazo-[1,2-a]pyrimidines bearing an ethyl carboxylate or carboxamide function at the 2-position (Scheme 5, Table 4).[13] The starting imidazo[1,2-a]pyrimidines[14,15] **7g–i** were prepared from commercially available ethyl 3-bromopyruvate **3a** and 3-bromopyruvamides[16,17] **3b** and **c**.

**Scheme 5**[a]



1

3a: XR[1] = OEt
3b: XR[1] = NHPh
3c: XR[1] = NHBn

7g: XR[1] = OEt (56%)
7h: XR[1] = NHPh (78%)
7i: XR[1] = NHBn (48%)

5{36-45}

[a] Reaction conditions: (i) (1) acetone, reflux, 45 min, (2) NaHCO[3] (4 equiv), EtOH/H[2]O (3:2), 65 °C, 1 h; (ii) aryl bromide (1.35 equiv), Pd(AcO)[2] (8 mol %), PPh[3] (16 mol %), Cs[2]CO[3] (1.1 equiv), 1,4-dioxane, MW 150 W, 25–40 min, 145 °C.

**Table 4.** Arylation of Imidazo[1,2-a]pyrimidine-2-carboxylic Acid Derivatives **7** g–i[a]

| entry | product | XR[1] | R[2] | time (min) | yield (%) |
|---|---|---|---|---|---|
| 1 | **5{36}** | OEt | 4′-CF[3] | 30 | 64 |
| 2 | **5{37}** | OEt | H | 45 | 47 |
| 3 | **5{38}** | NHPh | H | 25 | 80 |
| 4 | **5{39}** | NHPh | 4′-F | 25 | 67 |
| 5 | **5{40}** | NHPh | 4′-Cl | 30 | 86 |
| 6 | **5{41}** | NHPh | 4′-CF[3] | 45 | 67 |
| 7 | **5{42}** | NHPh | 3′,5′-diF | 60 | 54 |
| 8 | **5{43}** | NHBn | H | 20 | 92 |
| 9 | **5{44}** | NHBn | 4′-CF[3] | 20 | 86 |
| 10 | **5{45}** | NHBn | 4′-MeSO[2] | 30 | 55 |

[a] All reactions were performed on a 0.5 mmol scale in 6 mL of 1,4-dioxane with 1.35 equiv of aryl bromide, 1.35 equiv of Cs[2]CO[3], 8 mol % Pd(OAc)[2], and 16 mol % PPh[3]; all experiments were performed at 150 W maximum power and a ceiling temperature of 145 °C.

The reaction of ethyl imidazo[1,2-a]pyrimidine-2-carboxylate (**7g**) resulted in a considerable amount of decomposition products (Table 4, entries 1 and 2). The coupling of 1-bromo-4-(methylsulfonyl)benzene with **7i** unexpectedly resulted in the formation a lot of homo-coupled products, together with the desired compound (Table 4, entry 10). 1-Bromo-3′,5′-difluorobenzene appeared to be quite unreactive and required 1 h of microwave irradiation to give the arylated product **5{42}** in a 54% yield (Table 4, entry 7). In all other cases, the desired compounds were formed in good yields.

In conclusion, we have developed a short and efficient microwave-enhanced protocol for the Pd(0)-mediated arylation of 2-substituted imidazo[1,2-a]pyrimidines at their 3-position. The general applicability of this procedure was proven by the synthesis of a small combinatorial library of various 2,3-substituted imidazo[1,2-a]pyrimidines. Moreover, we have demonstrated that this procedure could be applied for the synthesis of difficult to obtain imidazo[1,2-a]-pyrimidines with 2-carboxamide or 2-carboxylate functions.

## Experimental Section

**General Methods.** Melting points were determined using a Reichert–Jung Thermovar apparatus or an Electrothermal 9200 digital melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker Avance 300

instrument using CDCl$_3$ as the solvent unless otherwise stated. The $^1$H and $^{13}$C chemical shifts are reported in parts per million relative to tetramethylsilane using the residual solvent signal as an internal reference. Mass spectra were recorded by using a Kratos MS50TC and a Kratos Mach III system. The ion source temperature was 150−250 °C, as required. High-resolution electrospray ionization mass spectra were performed with a resolution of 10 000. The low-resolution spectra were obtained with a HP5989A MS instrument. For thin-layer chromatography, analytical TLC plates (Alugram SIL G/UV$_{254}$) and 70−230 mesh silica gel (E. M. Merck) were used.

**Microwave Irradiation Experiments.** A monomode CEM-Discover microwave reactor (CEM Corporation, P.O. Box 200, Matthews, NC 28106) was used in the standard configuration as delivered, including proprietary software. All experiments were carried out in sealed microwave-process vials (10 mL) at the maximum power and temperature, as indicated in the tables. After completion of the reaction, the vial was cooled to 50 °C via air-jet cooling before it was opened.

**General Procedure for the Arylation of 2-Substituted Imidazo[1,2-a]pyrimidines.** Imidazo[1,2-a]pyrimidine (0.5 mmol), cesium carbonate (180 mg, 0.55 mmol, 1.1 equiv), palladium acetate (9 mg, 8 mol %), and triphenylphosphine (21 mg, 16 mol %) were placed in a 10 mL MW vial . Then 1,4-dioxane (6 mL) and arylbromide (0.68 mmol, 1.35 equiv) were added. The mixture was degassed by the bubbling of argon gas through it for 5 min. The vial was sealed and exposed to microwave irradiation at 150 W maximum power and a ceiling temperature as indicated. The reaction mixture was diluted with 200 mL of dichloromethane and washed with water (3 × 300 mL), and then the organic phase was dried over anhydrous Na$_2$SO$_4$. The solvent was evaporated in vacuo, and the crude mixture was purified by column chromatography on silica gel using ethyl acetate−methanol (9:1) as the eluent.

**2,3-Diphenylimidazo[1,2-a]pyrimidine 5{1}.** Yield: 138 mg (96%). mp: 147−149 °C. $^1$H NMR (CDCl$_3$): δ 8.55 (m, 1H), 8.23 (m, 1H), 7.78 (m, 2H), 7.53 (m, 5H), 7.28 (m, 3H), 6.82 (m, 1H). $^{13}$C NMR (CDCl$_3$): δ 150.2, 148.3, 144.2, 133.9, 131.1, 130.9 (×2), 130.2 (×2), 129.8, 129.2, 128.7 (×4), 128.4, 119.8, 109.0. HR-MS (EI): C$_{18}$H$_{13}$N$_3$ calcd 271.1109, found 271.1100.

**3-(4-Fluorophenyl)-2-phenylimidazo[1,2-a]pyrimidine 5{2}.** Yield: 145 mg (95%). mp: 174−176 °C. $^1$H NMR (CDCl$_3$): δ 8.58 (m, 1H), 8.19 (m, 1H), 7.73 (m, 2H), 7.45 (m, 3H), 7.29 (m, 4H), 6.83 (m, 1H). $^{13}$C NMR (CDCl$_3$): δ 165.2, 150.3, 148.3, 144.3, 133.9, 132.5, 130.9, 129.7 (×2), 128.8 (×2), 128.7 (×2), 128.6 (×2), 117.6, 109.2, 109.0. HR-MS (EI): C$_{18}$H$_{12}$FN$_3$ calcd 289.1015, found 289.1007.

**3-(4-Chlorophenyl)-2-phenylimidazo[1,2-a]pyrimidine 5{3}.** Yield: 132 mg (82%). mp: 178−180 °C. $^1$H NMR (CDCl$_3$): δ 8.57 (m, 1H), 8.22 (m, 1H), 7.75 (m, 2H), 7.53 (d, 2H, J = 7.3 Hz), 7.40 (d, 2H, J = 7.3 Hz), 7.30 (m, 3H), 6.83 (m, 1H). $^{13}$C NMR (CDCl$_3$): δ 150.4, 148.4, 144.5, 135.8, 132.5 (×2), 132.4, 132.3 (×2), 130.9 (×2), 130.5 (×2), 130.2, 128.6, 127.7, 118.5, 109.2. HR-MS (EI): C$_{18}$H$_{12}$N$_3$Cl calcd 305.0720, found 305.0711.

**3-[4-(Trifluoromethyl)phenyl]-2-phenylimidazo[1,2-a]-pyrimidine 5{4}.** Yield: 142 mg (84%). mp: 164−167 °C. $^1$H NMR (CDCl$_3$): δ 8.57 (m, 1H), 8.28 (m, 1H), 7.80 (d, 2H, J = 7.8 Hz), 7.67 (m, 2H), 7.60 (d, 2H, J = 7.7 Hz), 7.30 (m, 3H), 6.85 (m, 1H). $^{13}$C NMR (CDCl$_3$): δ 150.7, 148.6, 145.1, 133.4, 131.8 (×2), 131.3, 130.9, 130.9 (×2), 128.9, 128.8(×4), 128.7, 127.1, 118.2, 109.4. HR-MS (EI): C$_{19}$H$_{12}$N$_3$F$_3$ calcd 339.0983, found 339.0980.

**3-(2-Fluorophenyl)-2-phenylimidazo[1,2-a]pyrimidine 5{5}.** Yield: 121 mg (84%). mp: 177−179 °C. $^1$H NMR (CDCl$_3$): δ 8.60 (s, 1H), 8.08 (m, 1H), 7.77 (m, 2H), 7.58 (m, 1H), 7.36 (m, 6H), 6.87 (m, 1H). $^{13}$C NMR (CDCl$_3$): δ 162.3, 150.8, 148.3, 145.6, 144.9, 133.5, 132.8, 131.1, 128.5, 128.2 (×2), 128.5 (×2), 128.2, 117.4, 114.1, 109.9, 105.2. HR-MS (EI): C$_{18}$H$_{12}$N$_3$F calcd 289.1015, found 289.1014.

**3-(3,5-Difluorophenyl)-2-phenylimidazo[1,2-a]pyrimi-dine 5{6}.** Yield: 47 mg (65%). mp: 183−186 °C. $^1$H NMR (CDCl$_3$): δ 8.64 (m, 2H), 7.65 (m, 2H), 7.35 (m, 6H), 7.07 (m, 1H). $^{13}$C NMR (CDCl$_3$): δ 165.6, 162.5, 150.7, 148.5, 125.3, 144.9, 133.2, 132.3, 128.9, 128.9 (×2), 128.8 (×2), 117.2, 109.7, 105.7. HR-MS (EI): C$_{18}$H$_{11}$F$_2$N$_3$ calcd 307.0921, found 307.0910.

**3-(4-Methoxyphenyl)-2-phenylimidazo[1,2-a]pyrimi-dine 5{7}.** Yield: 81 mg (54%). mp: 181−183 °C. $^1$H NMR (CDCl$_3$): δ 8.53 (m, 1H), 8.19 (m, 1H), 7.75 (m, 2H), 7.54 (d, 2H, J = 7.3 Hz), 7.33 (m, 3H), 7.06 (d, 2H, J = 7.3 Hz), 6.79 (m, 3H), 3.91 (s, 3H). $^{13}$C NMR (CDCl$_3$): δ 160.4, 148.6, 143.5, 132.4, 132.0, 130.9, 128.9 (×2), 128.7 (×2), 127.7 (×2), 127.3 (×2), 126.1, 119.7, 114.6, 108.5, 55.9. HR-MS (EI): C$_{19}$H$_{15}$N$_3$O calcd 301.1215, found 301.1211.

**3-(4-Methanesulfonylphenyl)-2-phenylimidazo[1,2-a]-pyrimidine 5{8}.** Yield: 140 mg (80%). mp: 204−206 °C. $^1$H NMR (CDCl$_3$): δ 8.64 (s, 1H), 8.35 (d, 1H, J = 6.4 Hz), 8.12 (d, 2H, J = 8.2 Hz), 7.70 (m, 3H), 7.35 (m, 2H), 6.90 (m, 1H), 3.21 (s, 3H). $^{13}$C NMR (CDCl$_3$): δ 151.0, 148.7, 145.4, 141.1, 134.9, 133.2, 131.6 (×2), 131.1, 129.0 (×4), 128.9, 117.8, 109.7, 44.7. HR-MS (EI): C$_{19}$H$_{15}$N$_3$O$_2$S calcd 349.0885, found 349.0879.

**4-(2-Phenylimidazo[1,2-a]pyrimidin-3-yl)-isoquino-line 5{9}.** Yield: 108 mg (67%). mp: 202−205 °C. $^1$H NMR (CDCl$_3$): δ 9.47 (s, 1H), 8.66 (br, 1H), 8.19 (d, 1H, J = 8.0 Hz), 7.82 (d, 1H, J = 8.1 Hz), 7.70 (m, 3H), 7.42 (d, 1H, J = 7.8 Hz), 7.23 (m, 3H), 6.79 (m, 1H). $^{13}$C NMR (CDCl$_3$): δ 154.93, 150.74, 149.08, 146.48, 146.39, 133.16, 133.41, 132.47, 131.48, 129.13 (×2), 129.10 (×2), 128.84 (×2), 128.76 (×2), 128.27, 124.23, 114.32, 109.28. HR-MS (EI): C$_{21}$H$_{14}$N$_4$ calcd 322.1218, found 322.1218.

**2-Phenyl-3-(pyridin-2-yl)imidazo[1,2-a]pyrimidine 5{10}.** Yield: 75 mg (55%). mp: 156−158 °C. $^1$H NMR (CDCl$_3$): δ 8.50 (m, 2H), 8.42 (m, 1H), 8.02 (d, 2H, J = 7.3 Hz), 7.82 (m, 1H), 7.44 (m, 5H), 6.84 (m, 1H). $^{13}$C NMR (CDCl$_3$): δ 151.2, 150.2, 149.8, 147.4, 133.7, 133.5, 132.5, 132.4, 129.7 (×2), 129.1, 128.9, 128.8 (×2), 109.1, 106.8. HR-MS (EI): C$_{17}$H$_{12}$N$_4$ calcd 272.1062, found 272.1057.

**3-(4-tert-Butylphenyl)-2-phenylimidazo[1,2-a]pyrimi-dine 5{11}.** Yield: 80 mg (49%). mp: 156−158 °C. $^1$H NMR (CDCl$_3$): δ 8.63 (s, 1H), 8.25 (m, 1H), 7.77 (m, 2H), 7.55 (d, 2H, J = 7.2 Hz), 7.36 (d, 2H, J = 7.2 Hz), 7.32 (m, 3H), 6.78 (m, 1H), 1.40 (s, 9H). $^{13}$C NMR (CDCl$_3$): δ 153.6,

149.8, 147.4, 139.1, 133.1, 130.2, 129.3 ($\times$2), 127.7 ($\times$2), 127.1 ($\times$2), 125.6 ($\times$2), 109.3, 107.8, 32.7, 30.3 ($\times$3). HR-MS (EI): $C_{22}H_{21}N_3$ calcd 327.1735, found 327.1732.

**Supporting Information Available.** Experimental procedures and spectroscopic data for compounds **5**{**12**−**35**}, **7g**−**i**, and **5**{**36**−**45**}. This material is available free of charge via the Internet at http://pubs.acs.org.

### References and Notes

(1) Casagrande, C.; Invernizzi, A.; Ferrari G. *Farmaco* **1968**, *23*, 1141−1145.

(2) Farrerons, G. C.; Miguel Bono, I. J.; Fernandez A. M.; Monserat, V. C.; Lagunas, A. C.; Gimenez, G. F.; Fernandez, G. A. Int. Patent WO 00/08024 A1, February 17, 2000.

(3) For the pyrimidine-based COX-2 inhibitors, see: (a) Almansa, A. F.; Cavalcanti, F. L.; Gomez, L. A.; Miralles, A.; Merlos, M.; Garcia-Rafanell, J.; Forn, J. *J. Med. Chem.* **2001**, *44*, 350−361. (b). Naylor, A.; Payne, J. J.; Pegg, N. A. Int. Patent WO 2002/096885 A1, May 12, 2002. (c). Weingarten, G.; Bravi, G. Int. Patent WO 2004018452 A1, April 3, 2004.

(4) Catena, R. J. L.; Farrerons, G. L.; Fernandez, S. A.; Serra, C. C.; Balsa, L. D.; Lagunas, A. C.; Salcedo, R. C.; Fernandez, G. A. Int. Patent WO 2005/014598 A1, July 29, 2004.

(5) Abignente, E.; Arena, F.; De Caprariis, P.; Montagnaro, G.; Rossi, F.; Lampa, E.; Giordano, L.; Vacca, C.; Marmo, E. *Farmaco* **1980**, *35*, 654−673.

(6) Ikonomidou, H. Eur. Patent EP 1002535 A1, 2000.

(7) Bradley, S. E.; Krulle, T. M.; Murray, P. J.; Rowley, R. J.; Sambrook Smith, C. P.; Thomas, G. H. Int. Patent WO 2004/104001 A2, December 2, 2004.

(8) Enguehard, C.; Renou, J.-L.; Collot, V.; Hervet, M.; Raults, S.; Gueiffier, A. *J. Org. Chem.* **2000**, *65*, 6572−6575.

(9) Wenjie, L.; Dorian, P. N.; Jensen, M. S.; Hoerner, R. S.; Javadi, G. J.; Cai, D.; Larsen, R. D. *Org. Lett.* **2003**, *5*, 4835−4837.

(10) Kaval, N.; Bisztray, K.; Dehaen, W.; Kappe, C. O.; Van der Eycken, E. *Mol. Diversity* **2003**, *7*, 125−133.

(11) Kaval, N.; Van der Eycken, J.; Caroen, J.; Kappe, O.; Dehaen, W.; Strohmeier, G. A.; Van der Eycken, E. *J. Comb. Chem.* **2003**, *5*, 560−568.

(12) Rival, Y.; Grassy, G.; Taudou, A.; Ecalle, R. *Eur. J. Med. Chem.* **1991**, *26* (1), 13−18.

(13) Abignente, E.; Sacchi, A.; Laneri, S.; Rossi, F.; D'Amico, M.; Berrino, L.; Calderaro, V.; Parrillo, C. *Eur. J. Med. Chem.* **1994**, *29*, 279−286.

(14) Liebeschuets, J. W. Int. Patent WO 00/76970 A2, December 21, 2000.

(15) Wang, G.-Z.; Mallat, T.; Baiker, A. *Tetrahedron: Asymmetry* **1997**, *8* (13), 2133−2140.

(16) Kluger, R.; Chow, J. F.; Croke, J. J. *J. Am. Chem. Soc.* **1984**, *106* (14), 4017−4020.

(17) Tully, W. R.; Gardner, C. R.; Gillespie, R. J.; Westwood, R. *J. Med. Chem.* **1991**, *34*, 2060−2067.