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A new synthetic approach to the imidazo[1,5-*a*]imidazol-2-one scaffold and effective functionalization through Suzuki-Miyaura cross coupling reactions

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We report herein a synthetic pathway to new 7-bromo-1-(4-methoxybenzyl)-5-methyl-imidazo[1,5-*a*]imidazol-2-one. The synthetic potential of this scaffold was demonstrated by displacing bromine by Suzuki–Miyaura cross-coupling reactions. A large panel of boronic acids (aryl, heteroaryl or vinyl) were easily introduced, giving access to a broad and diversified library of 1-(4-methoxybenzyl)-5-methyl-7-(substituted)-imidazo[1,5-*a*]imidazol-2-ones.

Introduction

In recent years, nitrogen-bridgehead heterocycles have received considerable attention from many different research teams in organic synthesis due to their interesting biological activities.[1] In addition, this family of compounds possesses a high reactivity for functionalization with new coupling methods.

Among nitrogen cycles, 5-5 bicycles have received particular attention due to their biologically interesting properties exploited in drug manufacture.[2] The imidazo[1,5-*a*]imidazole is a nitrogenous heterocycle with significant interest in drug synthesis and functionalization. It was reported that its oxoanalog imidazo[1,5-*a*]imidazolinone has also proved to be a structurally pertinent skeleton for the development of biologically active and pharmaceutically relevant compounds.[3]

Current strategies for preparing imidazo[1,5-*a*]imidazolinone derivatives generally consist in building the 5-5 fused ring with the desired substituents in appropriate position.[4] A careful literature survey revealed that no method for the functionalization of the heterocyclic moiety has yet been described. In this context, the overall goal of our research was to develop an efficient synthesis of imidazo[1,5-*a*]imidazol-2-one synthon that permits its subsequent functionalization, thereby enabling molecular diversity.
Based on the interest of our group in the synthesis of nitrogen-based heterocycles,[5] we disclose herein the access to a library of original 5-methyl-7-(hetero)arylated-imidazo[1,5-*a*]imidazol-2-one derivatives. Our synthetic strategy is based on an efficient four-step synthesis of the bicycle followed by palladium catalyzed Suzuki-Miyaura cross-coupling.[6] To the best of our knowledge, no example of palladium cross-coupling reaction on the imidazo[1,5-*a*]imidazolinone core has yet been reported.

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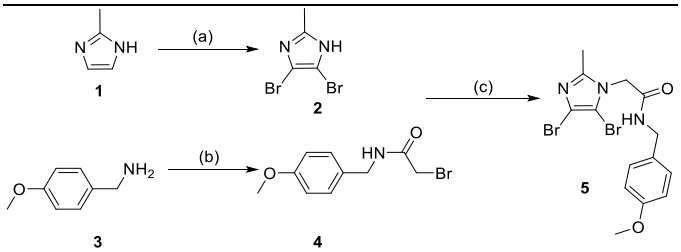
Results and discussion

The required starting compound for the Suzuki-Miyaura reaction was synthesized in four steps from the commercially available 2-methylimidazole **1**. After dibromation of **1**,[7] compound **2** was engaged in a *N*-alkylation with 2-bromo-*N*-(4-methoxybenzyl) acetamide **4** (obtained from a reaction between 4-methoxybenzylamine **3** and bromoacetyl bromide).[8]
The condensation reaction between **2** and **4** was performed in the presence of sodium hydride in dry tetrahydrofuran and afforded amide **5** in 90% yield. [9]



Scheme 1. Preparation of 2-(4,5-dibromo-2-methyl-1*H*-imidazol-1-yl)-*N*-(4-methoxybenzyl)acetamide **5**. (a) Br_2, $KHCO_3$, DMF, 0–100 °C, 2 h, 62 %; (b) bromoacetyl bromide, DIPEA, DCM, 0 °C to RT., 24 h, 95 %; (c) NaH, THF, 0 °C to RT., 24 h, 90 %.

Product **5** was engaged in an intramolecular cyclization. First, a Buchwald-type cyclization using palladium acetate, xantphos as ligand and cesium carbonate as base was tested[10] (Table 1, entries 1-4) but low conversion was observed. Replacing the catalyst by copper iodide[11] resulted in better conversion (Table 1, entry 5). The use of K_3PO_4 as base considerably improved the conversion rate to 89% in toluene and to 80% in *N*,*N*-dimethylformamide (Table 1, entries 6 and 7). The addition of a ligand such as *N*,*N*'-dimethylethylenediamine[12] did not improved the yield (Table 1, entries 8 and 9). We also carried out the reaction in different solvents (Table 1, entries 10-12). Finally, a total conversion was obtained in toluene at 160 °C during 4 hours (Table 1, entry 13). We also found that the heating system has a significant influence, since heating

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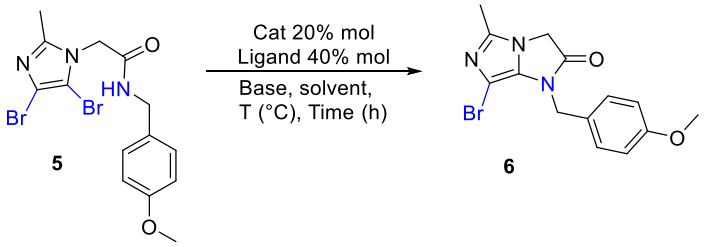
in a sealed tube for 20 hours also led to a conversion rate of 100%, and a yield after column chromatography of 81% (table1- entry 15). To complete the optimization, we evaluated the impact of the amount of base and CuI. Decreasing the quantity of K_3PO_4 to 2 equivalents did not maintain a coupling efficiency (Table 1, entry 16). On the other hand, the catalyst loading could be reduced to 10 mol% of CuI without impacting the yield of the reaction (Table 1, entry 17). However 5 mol% involved a partial conversion rate and a low yield (table 1, entry 18).

Table1. Optimisation of intramolecular cyclisation.



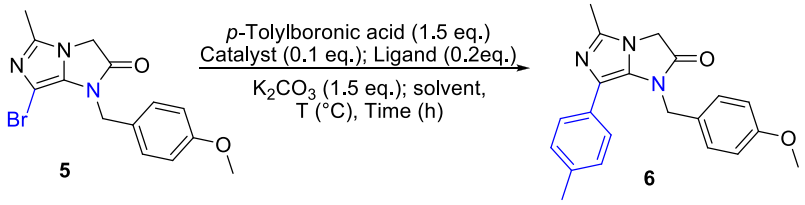
Entry	Catalyst	Ligand	Base	Solvent	Time (h)	T (°C)	Heating system	Conv. [a]	Yield[b]
1	$Pd(OAc)_2$	Xantphos	Cs_2CO_3 (2eq)	1,4-Dioxane	4	150°C	MW	0	-[c]
2	$Pd(OAc)_2$	Xantphos	Cs_2CO_3 (2eq)	tBuOH	4	150°C	MW	0	-[c]
3	$Pd(OAc)_2$	Xantphos	Cs_2CO_3 (2eq)	Toluene	4	150°C	MW	38	29
4	$Pd(OAc)_2$	Xantphos	Cs_2CO_3 (4eq)	Toluene	4	150°C	MW	46	37
5	CuI	-	Cs_2CO_3 (4eq)	Toluene	4	150°C	MW	72	55
6	CuI	-	K_3PO_4 (4eq)	Toluene	4	150°C	MW	89	74
7	CuI	-	K_3PO_4 (4eq)	DMF	4	150°C	MW	80	58
8	CuI	DMEDA	K_3PO_4 (4eq)	DMF	2	150°C	MW	55	42
9	CuI	DMEDA	Cs_2CO_3 (4eq)	DMF	2	150°C	MW	28	19
10	CuI	-	K_3PO_4 (4eq)	1,4-Dioxane	4	150°C	MW	0	-[c]
11	CuI	-	K_3PO_4 (4eq)	Toluene/DMF (4/1)	4	150°C	MW	57	44
12	CuI	-	K_3PO_4 (4eq)	Toluene/Ethanol (4/1)	4	150°C	MW	25	17
13	CuI	-	K_3PO_4 (4eq)	Toluene	4	160 °C	MW	100	80
14	CuI	-	K_3PO_4 (4eq)	Toluene	16	150°C	Sealed tube	87	68
15	CuI	-	K_3PO_4 (4eq)	Toluene	20	150°C	Sealed tube	100	81
16	CuI	-	K_3PO_4 (2eq)	Toluene	20	150°C	Sealed tube	57	46
17	CuI[d]	-	K_3PO_4 (4eq)	Toluene	20	150°C	Sealed tube	100	80
18	CuI[e]	-	K_3PO_4 (4eq)	Toluene	20	150°C	Sealed tube	78	64
19	-	-	K_3PO_4 (4eq)	Toluene	4	160 °C	MW	0	- [f]

(a) ^1H NMR ratio based on the integration of CH_3.
(b) Yield of isolated product after column chromatography.
(c) Degradation of the reaction mixture.
(d) With 10 mol % of copper iodide (CuI).
(e) With 5 mol % of copper iodide (CuI).
(f) 100% of starting material **5** is recovered.

These functionalizable intermediate **6** open the way to design a chemical library of imidazo[1,5-*a*]imidazolinone derivatives from the bromide in position 7.

Initial optimization trials of the Suzuki-Miyaura cross coupling reaction were performed on the imidazole skeleton **6** synthesized previously using *p*-tolylboronic acid. As a model, we began with the investigation using different palladium sources, (palladium (II) acetate, [1,1 bis(diphenylphosphino) ferrocene] dichloropalladium) complexed with dichloromethane $Pd(dppf)Cl_2.CH_2Cl_2$, or bis(dibenzylideneacetone)palladium(0)) as the catalyst, potassium carbonate as the base and a mixture of 1,4-dioxane/ethanol 2/1 as solvent. The coupling product **7** was obtained in the three tests with acceptable yields but with only a partial conversion rate (Table 2, entries 1-3).

Table 2: Screening Suzuki reaction conditions with 4-tolylboronic acid.



Entry	Catalyst	Ligand	Solvent	Time [min]	Heating system	Conv [%][(a)]	Yield [%][(b)]
1	$Pd(OAc)_2$	Xantphos	1,4-Dioxane/EtOH(2/1)	180	Reflux	82	61
2	$Pd(dppf)Cl_2.CH_2Cl_2$	-	1,4-Dioxane/EtOH(2/1)	90	Reflux	91	72
3	$Pd_2(dba)_3$	-	1,4-Dioxane/EtOH(2/1)	90	Reflux	71	44
4	$Pd(dppf)Cl_2.CH_2Cl_2$	-	1,4-Dioxane	90	Reflux	52	21
5	$Pd(OAc)_2$	Xantphos	Toluene/EtOH (2/1)	180	Reflux	90	67
6	**$Pd(dppf)Cl_2.CH_2Cl_2$**	**-**	**Toluene/EtOH (2/1)**	**90**	**Reflux**	**100**	**88**
7	$Pd_2(dba)_3$	-	Toluene/EtOH (2/1)	90	Reflux	79	51
8	$Pd(dppf)Cl_2.CH_2Cl_2$	-	Toluene/EtOH (2/1)	20	MW, 130 °C	100	73

(a) ^1H NMR ratio based on the integration of CH_3 or OCH_3.
(b) Yield of isolated product after column chromatography.

Without ethanol, even after 90 minutes of heating, only 52% of conversion was achieved (Table 2, entry 4), showing that a protic solvent is essential in this coupling process.

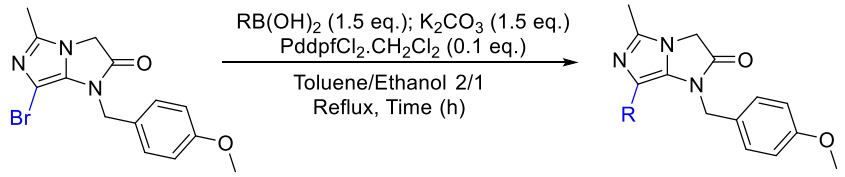
Replacing 1,4-dioxane by toluene led to a significant increase in conversion rate (Table, entries 5-7). The best conditions were found with a mixture of toluene/ethanol 2/1 as solvent. We next focused our attention on the influence of the catalyst. The use of palladium (0) instead a palladium (II) (i.e. Pd_2dba_3 in replacement of $Pd(OAc)_2$ or $Pd(dppf)Cl_2.CH_2Cl_2$), the yield significantly decreased (Table 2, entries 5-7). Finally, replacing conventional thermal heating by microwave irradiation produced no real improvement in terms of yield and time (Table 2, entry 8).

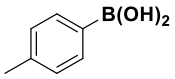
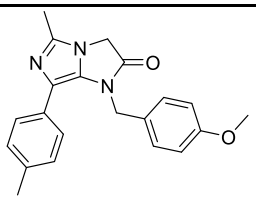
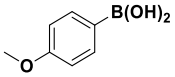
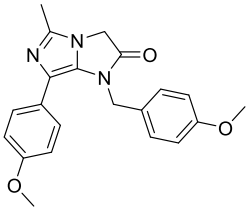
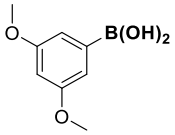
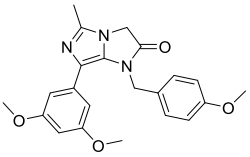
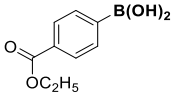
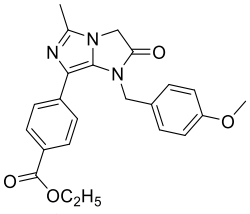
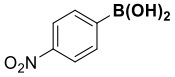
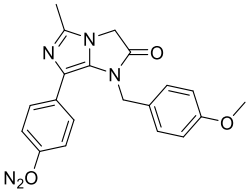
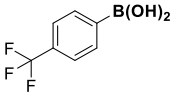
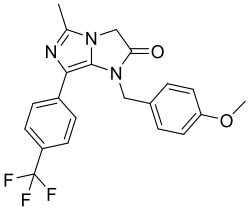
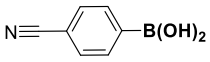
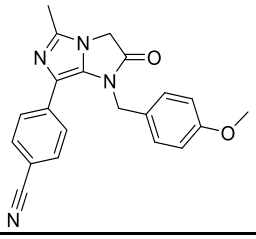
Optimum conditions were found to be boronic acid (1.5 equiv), $Pd(dppf)Cl_2.CH_2Cl_2$ (0.10 equiv), K_2CO_3 (1.5 equiv) in a mixture of toluene/ ethanol 2/1, refluxing for a short time of 1.5 hour.

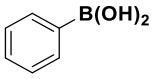
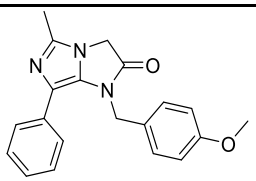
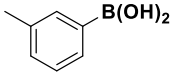
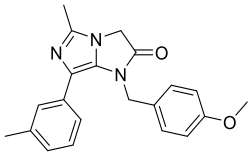
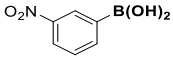
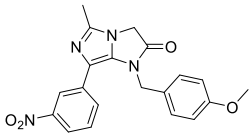
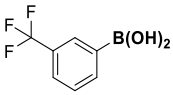
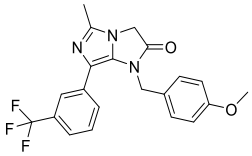
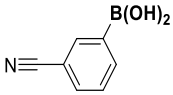
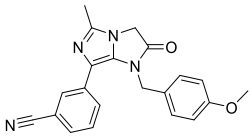
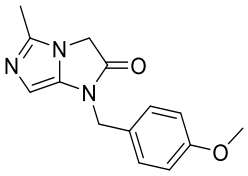
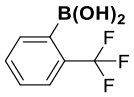
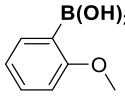
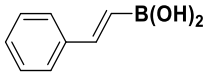
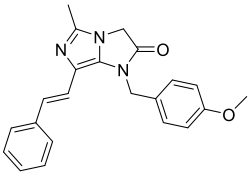
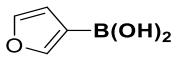
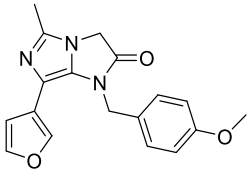
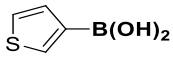
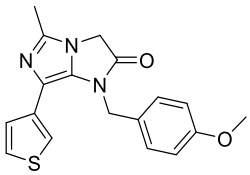
To explore the scope of the methodology, we applied these selected conditions using different boronic acids. Gratifyingly, the optimized conditions proved to be efficient with boronic acids containing a large variety of functional groups. More precisely, para-substituted phenylboronic acids bearing electron-rich (CH_3, OCH_3) or electron-poor (COOEt, NO_2, CF_3, CN) groups led to 7-aryl-1H-imidazo[1,5-*a*]imidazol-2-ones in good yields (Table 3, entries 1-7). Notably, meta-substitution did not disfavor the cross-coupling reaction. In fact, derivatives **15-18** were obtained in satisfactory yields (Table 3, entries 9-12). However, using ortho-sustituted phenylboronic acids provided only the dehalogenation product **19** (Table 3, entries 13-15). Steric hindrance could explain this result.

Finally, hererocycles such as 3-furane and 3-thiophene were introduced with moderate yields of 46% and 65% respectively (Table 3, entries 17 and 18). The strategy was also compatible with vinylboronic acid, since styryl derivative **20** was obtained in 67% yield (entry 16).

Table 3. Scope of Suzuki–Miyaura cross coupling of 6.



Entry	$RB(OH)_2$	Reaction time [h]	Product		Yield [%][a]
1		1.5		**7**	88
2		1,5		**8**	79
3		2		**9**	79
4		2		**10**	83
5		1.5		**11**	82
6		1.5		**12**	80
7		1.5		**13**	61

8		1.5		**14**	75
9		1.5		**15**	79
10		1.5		**16**	74
11		1.5		**17**	74
12		1.5		**18**	56
13		1.5		**19**	52
14		1.5			49
15		1.5			50
16		2		**20**	67
17		2		**21**	46
18		2		**22**	65

(a) Yield of isolated product after column chromatography.

Conclusion

In conclusion, we have reported here a new method to access the imidazo[1,5-*a*]imidazol-2-one core. We then developed the first C-7 pallado-catalyzed functionalization of this bicycle by Suzuki-Miyaura cross-coupling reactions. The methodology described is original and effective. Good yields were obtained for a wide range of (hetero)aryl boronic acids with both electron-poor and electron-rich substituents, giving access to a library of new 7-substituted-1-(4-methoxybenzyl)-5-methyl-1*H*-imidazo[1,5-*a*]imidazol-2-ones.

Experimental

General: All reagents were purchased from commercial suppliers and were used without further purification. The reactions were monitored by thin-layer chromatography (TLC) analysis by using silica gel (60 F254) plates. Compounds were visualized by UV irradiation at 256 or 365 nm. Flash column chromatography was performed on silica gel 60 (230–400 mesh, 0.040–0.063 mm). Melting points (m.p. [°C]) were taken on samples in open capillary tubes. Infrared spectra of compounds were recorded with a Thermo Scientific Nicolet iS10 instrument. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker spectrometer at 250 MHz (^{13}C, 61.5 MHz) or 400 MHz (^{13}C, 101 MHz). Chemical shifts are given in parts per million (ppm) from tetramethylsilane (TMS) as internal standard in $CDCl_3$, and the residual peak of DMSO in [D_6]DMSO. The following abbreviations are used for the ^{1}H NMR spectra multiplicities: br. s: broad singlet, s: singlet, d: doublet, t: triplet, q: quartet, qt: quintuplet, m: multiplet. Coupling constants (*J*) are reported in Hertz [Hz]. C_{IV} is the abbreviation for quaternary carbon atoms. High-resolution mass spectra (HRMS) were performed with a Maxis Bruker 4G instrument.

4,5-Dibromo-2-methyl-1*H*-imidazole (2)

Bromine (6.2 mL, 122 mmol) was added slowly to a solution of the 2-methyl-1*H*-imidazole **1** (5g, 61mmol) and potassium hydrogenocarbonate (12.19 g, 122 mmol) in dry DMF at 0 °C under argon, the reaction mixture was allowed to warm to room temperature for half an hour and heated at 100 °C for 3 hours. After cooling, the reaction mixture was poured into an aqueous saturated solution of $Na_2S_2O_3$ and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered off and concentrated under reduced pressure. The desired product **2** was obtained by precipitation in pentane (9.06 g, 62%).
White solid (9.06 g, 62%); M.p. 235–237 °C (ref.[13] 239-240 °C), IR (neat, cm^{-1}): 1397, 1556, 3122, 3216, 3490; ^{1}H NMR (400 MHz, DMSO-d_6): δ, 2.23 (s, 3H, CH_3); ^{13}C NMR (101 MHz, DMSO-d_6): δ 14.3, 105.95 (2C), 146.0 (C_{IV}); HRMS (ESI): calcd for $C_4H_5Br_2N_2$ 238.88140 [M+H]$^+$, 260.86334 [M+Na]$^+$ found 238.88134 [M+H]$^+$ 260.86327 [M+Na]$^+$.

2-Bromo-*N*-(4-methoxybenzyl)acetamide (4)

Bromoacetylbromide (3.2 mL, 36.4 mmol, 1.0 equiv.) was added slowly to a solution of 4-methoxybenzylamine **3** (5 g, 36.4 mmol, 1 equiv.) and diisoopropylethylamine (6.3 mL, 36.4 mmol, 1 equiv.) in 150 mL of DCM at 0 °C. The reaction mixture was allowed to warm up to room temperature and stirred for 24 hours before being quenched with an aqueous solution of HCl (1 M) and extracted with dichloromethane (3x75 mL). The combined organic layers were washed with brine (3x50 mL), dried over $MgSO_4$, filtered off and concentrated under reduced pressure and the resulting solid was filtered off, washed with water and pentane then dried to afford product **4** (8.9 g, 95 %).
White solid (8.9 g, 95 %); mp. 119–121 °C (ref.[14] 120–121 °C); IR (neat, cm^{-1}): 818, 1030, 1179, 1212, 1243, 1512, 1645, 3280; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.81 (s, 3 H), 3.92 (s, 2 H), 4.41 (d, *J* = 5.7 Hz, 2 H), 6.89 (d, *J* = 8.5 Hz, 2H), 6.70 (br. s, 1H), 7.22 (d, *J* =8.5 Hz,2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 29.5, 42.0, 55.1, 113.8 (2C), 128.7 (2C), 130.1, 158.3, 165.9; HRMS (ESI): calcd. for $C_{10}H_{13}BrNO_2$ 258.01242 [M+H]$^+$ 279.99436 [M+Na]$^+$ found 258.01227 [M+H]$^+$ 279.9944 [M+Na]$^+$.

2-(4,5-Dibromo-2-methyl-1*H*-imidazol-1-yl)-*N*-(4-methoxybenzyl) acetamide (5).

Sodium hydride (1.26 g, 31.5 mmol, 1.2 equiv.) was slowly added to a solution of the imidazole **2** (6.25 g, 26.3 mmol) in 130 mL of dry tetrahydrofuran under argon at 0 °C. After 15 minutes stirring, the acetamide **4** (6.80 g, 26.3 mmol, 1.0 equiv.) was added portion wise. The reaction mixture was allowed to warm up to room temperature and stirred for 24 hours before being quenched with water (100 mL). The tetrahydrofuran was then removed under reduced pressure and the resulting solid was filtered off, washed with water and pentane then dried to afford product **5** (9.90 g, 90%).
White solid (9.90 g, 90%); mp: 132-134 °C; IR (neat, cm^{-1}): 700, 846, 1017, 1245, 1462, 1504, 1600; ^{1}H NMR (250 MHz, DMSO-d_6): δ 2.28 (s, 3H), 3.73 (s, 3H), 4.25 (d, *J* = 5.7 Hz, 2H), 4.69 (s, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 7.20 (d, *J* = 8.7 Hz, 2H), 8.73 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 13.8, 42.1, 48.1, 55.3, 103.3 (2C), 114.0 (2C), 128.8 (2C), 130.8, 147.3, 158.5, 165.6; HRMS (ESI): calcd. for $C_{14}H_{16}Br_2N_3O_2$ 415.9606 [M+H]$^+$ found 415.9604 [M+1]$^+$.

7-Bromo-1-(4-methoxybenzyl)-5-methyl-1*H*-imidazo[1,5-*a*]imidazol-2(3H)-one (6).

A sealed tube containing a stirring bar was charged with the 2-(4,5-dibromo-2-methyl-1*H*-imidazol-1-yl)-*N*-(4-methoxybenzyl) acetamide **5** (500 mg, 1.2 mmol), and potassium phosphate tribasic (1.02 g, 4.82 mmol) in dry toluene (10 ml), copper iodide (46 mg, 0.24 mmol) was added and the mixture was heated at 150 °C for 20 hours. After cooling down to room temperature, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (petroleum ether`/ethyl acetate 70:30) to provide the desired product **6.**
White solid (328 mg, 81%); mp: 132-134 °C; IR (neat, cm^{-1}): 810, 1239, 1577, 1730, 2940; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 2.28 (s, 3H). 3.77 (s, 3H), 4.35 (s, 2H), 4.86 (s, 2H), 6.84 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 13.4, 43.7, 47.7, 55.4, 86.9, 114.2 (2C), 127.7, 129.9 (2C), 132.6, 138.3, 159.6, 169.8; HRMS (ESI): calcd. for $C_{14}H_{15}BrN_3O_2$ 336.03394 [M+H]$^+$ found 336.03421 [M+H]$^+$.

General procedure: Suzuki Coupling on imidazo[1,5-*a*]imidazoles 6. A flask containing a stirring bar was charged with the imidazole[1,2-*a*]imidazole **6** (100 mg), boronic acid (1.5 equiv.)

and potassium carbonate (1.5 equiv.) in a mixture of toluene/ ethanol (2/1 v/v). $Pd(dppf)Cl_2.CH_2Cl_2$ (0.1 equiv.) was added and the mixture was refluxed for the indicated time. After cooling down, solvents were removed under reduced pressure and the residue was purified by flash chromatography to provide the desired products **7**-**22**.

1-(4-Methoxybenzyl)-5-methyl-7-(*p*-tolyl)-1*H*-imidazo[1,5-*a*]imidazol-2(3*H*)-one (7).

Following the general procedure A with *p*-tolylboronic acid (61 mg, 0.45 mmol) the mixture was refluxed for 1.5 hours. The crude product was purified by flash chromatography on silica gel (75:25 dichloromethane / ethyl acetate).
Brown solid (88 mg; 85%); mp: 152-153 °C; IR (neat, cm^{-1}): 825, 1247, 1514, 1608, 1720, 2919; ^1H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 2.37 (s, 3H), 3.72 (s, 3H), 4.41 (s, 2H), 4.82 (s, 2H), 6.67 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 7.13 (d, *J* = 7.9 Hz, 2H), 7.27 (d, J = 7.9 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 13.0, 21.0, 44.1, 46.9, 55.3, 114.0 (2C), 118.0, 127.7, 128.6 (2C), 128.6 (2C), 129.9 (2C), 130.7, 131.4, 136.8, 137.7, 159.3, 170.9; HRMS (ESI): calcd. For $C_{21}H_{22}N_3O_2$ 348.17084 $[M+H]^+$ found 348.17065 $[M+H]^+$.

1-(4-Methoxybenzyl)-7-(4-methoxyphenyl)-5-methyl-1H-imidazo[1,5-*a*]imidazol-2(3H)-one. (8)

Following the general procedure with 4-methoxyphenylboronic acid (68 mg, 0.45 mmol),the mixture was refluxed for 1.5 hours. The crude product was purified by flash chromatography on silica gel (75:25 dichloromethane / ethyl acetate).
Brown solid (85 mg; 79%); mp: 175-177 °C; IR (neat, cm^{-1}): 811, 1029, 1184, 1230, 1525, 1572, 1730; ^1H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3H), 3.71 (s, 3H), 3.82 (s, 3H), 4.41 (s, 2H), 4.79 (s, 2H), 6.67 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 7.28 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 13.3, 44.0, 47.2, 55.3, 113.9 (2C), 114,0 (2C), 117.5, 126.2, 127.7, 129.2 (2C), 130.0 (2C), 131.1, 137.6, 158.9, 159.2, 170.8; HRMS (ESI): calcd. for $C_{21}H_{22}N_3O_3$ 364.16557 $[M+H]^+$ found 364.16579 $[M+H]^+$.

7-(3,5-Dimethoxyphenyl)-1-(4-methoxybenzyl)-5-methyl-1*H*-imidazo[1,5-*a*]imidazol-2(3*H*)-one (9).

Following the general procedure with 3,5-dimethoxyphenylboronic acid (81 mg, 0.45 mmol), the mixture was refluxed for 2 hours. The crude product was purified by flash chromatography on silica gel (75:25 dichloromethane / ethyl acetate).
White solid (93 mg; 79%); mp: 110-112 °C; IR (neat, cm^{-1}): 842, 1061, 1177, 1247, 1513, 1597, 1722; ^1H NMR (400 MHz, $CDCl_3$): δ 2.34 (s, 3H), 3.71 (s, 9H), 4.41 (s, 2H), 4.87 (s, 2H), 6.40 (s, 1H), 6.55 (s, 2H), 6.68 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 13.3, 44.2, 47.2, 55.3 (3C), 100.0, 106.7 (2C), 114.0 (2C), 118.0, 127.6, 129.1 (2C), 131.6, 135.6, 137.7, 159.8, 160.8 (2C), 170.9; HRMS (ESI): calcd. for $C_{22}H_{24}N_3O_4$ 394.17596 $[M+H]^+$ found 394.17613 $[M+H]^+$.

Ethyl 4-(1-(4-methoxybenzyl)-5-methyl-2-oxo-2,3-dihydro-1H-imidazo[1,5-*a*]imidazol-7-yl)benzoate (10).

Following the general procedure with 4-ethoxycarbonylphenylboronic acid (80 mg, 0.45mmol), the mixture was refluxed for 2 hours. The crude product was purified by flash chromatography on silica gel (75:25 dichloromethane / ethyl acetate).
Brown solid (100 mg; 83%); mp:173-175 °C; IR (neat, cm^{-1}): 990, 1175, 1248, 1510, 1607, 1722, 2835; ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (t, J = 7.1 Hz, 3H), 2.40 (s, 3H), 3.75 (s, 3H), 4.43 (q, *J* = 7.1 Hz, 2H), 4.49 (s, 2H), 4.90 (s, 2H), 6.72 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 8.1 Hz, 2H), 8.03 (d, *J* = 8.1 Hz, 2H).^{13}C NMR (101 MHz, $CDCl_3$) δ 13.4, 14.5, 44.4, 47.2, 55.4, 61.1, 114.2 (2C), 117.4, 127.2, 128.1 (2C), 128.9, 129.8 (2C), 130.0(2C), 132.7, 138.2, 138.5, 159.4, 166.7, 171.1; HRMS (ESI): calcd. for $C_{23}H_{24}N_3O_4$ 406.17607 $[M+H]^+$ found 406.17613 $[M+H]^+$.

1-(4-Methoxybenzyl)-5-methyl-7-(4-nitrophenyl)-1*H*-imidazo [1,5-*a*]imidazol-2(3*H*)-one (11).

Following the general procedure with 4-nitrophenylboronic acid (74 mg, 0.45 mmol), the mixture was refluxed for 1.5 hours. The crude product was purified by flash chromatography on silica gel (95:5 dichloromethane / ethyl acetate).
Brown solid (92 mg, 82%); mp: 169-171 °C; IR (neat, cm^{-1}): 814, 1048, 1097, 1249, 1318, 1509, 1723, 2923; ^1H NMR (400 MHz, $CDCl_3$): δ 2.39 (s, 3H), 3.74 (s, 3H), 4.52 (s, 2H), 4.91 (s, 2H), 6.74 (d, *J* = 8.0 Hz, 2H), 6.91 (d, *J* = 7.9 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), δ 8.15 (d, *J* = 7.9 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 13.3, 44.6, 47.2, 55.4, 114.4 (2C), 116.4, 123.9 (2C), 126.7, 128.3 (2C), 128.4 (2C), 133.6, 139.1, 140.4, 146.3, 159.5, 171.1; HRMS (ESI): calcd. for $C_{20}H_{19}N_4O_4$ 379.14009 $[M+H]^+$ found 379.14008 $[M+H]^+$.

1-(4-Methoxybenzyl)-5-methyl-7-(4-(trifluoromethyl)phenyl)-1*H*-imidazo[1,5-*a*]imidazol-2(3*H*)-one (12).

Following the general procedure with 4-(trifluoromethyl)phenylboronic acid (85 mg, 0.45mmol), the mixture was refluxed for 1.5 hours. The crude product was purified by flash chromatography on silica gel (75:25 dichloromethane / ethyl acetate).
White solid (96 mg; 80%); mp: 195-197 °C; IR (neat, cm^{-1}): 858, 1062, 1102, 1245, 1317, 1600, 1721, 2930; ^1H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H), 3.73 (s, 3H), 4.48 (s, 2H), 4.86 (s, 2H), 6.69 (d, *J* = 8.3 Hz, 2H), 6.84 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 13.3, 44.4, 47.2, 55.4, 114.2(2C), 116.9, 124.4 (q, $^1J_{C\text{-}F}$ = 273 Hz, CF_3), 125.36 (2C) (q, $^3J_{CHAr\text{-}F}$ = 3.8 Hz, CHAr), 127.0, 128.5 (2C), 128.6 (2C), 128.9 (q, $^2J_{CIV\text{-}F}$ = 32.4 Hz, CIV), 132.6, 137.3, 138.5, 159.4, 171.0; HRMS (ESI): calcd. for $C_{21}H_{19}F_3N_3O_2$ 402.14217 $[M+H]^+$ found 402.14239 $[M+H]^+$.

4-(1-(4-Methoxybenzyl)-5-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[1,5-*a*]imidazol-7-yl)benzonitrile (13).

Following the general procedure with 4-cyanophenylboronic acid (65 mg, 0.45 mmol), the mixture was refluxed for 1.5 hours. The crude product was purified by flash chromatography on silica gel (75:25 dichloromethane / ethyl acetate).
Brown solid (65 mg; 61%); mp: 137-139 °C; IR (neat, cm^{-1}): 844, 1296, 1509, 1605, 1720, 2215; ^1H NMR (400 MHz, $CDCl_3$): δ 2.38 (s, 3H), 3.75 (s, 3H), 4.51 (s, 2H), 4.88 (s, 2H), 6.73 (d, *J* = 8.1 Hz, 2H), 6.88 (d, *J* = 8.1 Hz, 2H), 7.46 (d, *J* = 7.7 Hz, 2H), 7.58 (d, *J* = 7.7 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$):δ 13.4, 44.5, 47.2, 55.4, 110.0, 114.3 (2C), 116.7, 119.2, 126.8, 128.5 (2C), 128.4 (2C), 132.2 (2C), 133.0, 138.4, 138.8, 159.5, 171.1; HRMS

(ESI): calcd. for $C_{21}H_{18}N_4O_2$ 359.15007 $[M+H]^+$ found 359.15025 $[M+H]^+$.

1-(4-Methoxybenzyl)-5-methyl-7-phenyl-1*H*-imidazo[1,5-*a*]imidazol-2(3*H*)-one (14).

Following the general procedure with phenylboronic acid (54 mg, 0.45 mmol), the mixture was refluxed for 1.5 hours .The crude product was purified by flash chromatography on silica gel (95:5 dichloromethane / ethyl acetate).
Brown solid (74 mg; 75%); mp: 126-128 °C; IR (neat, cm^{-1}): 769, 1031, 1252, 1332, 1615, 1700; ^1H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 3H), 3.71 (s, 3H), 4.42 (s, 2H), 4.83 (s, 2H), 6.66 (d, *J* = 8.8 Hz, 2H), 6.8 (d, *J* = 8.8 Hz, 2H), 7.25 – 7.32 (m, 1H), 7.36 (q, *J* = 7.7 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 13.3, 44.1, 47.2, 55.3, 114.0 (2C), 118.0, 127.1, 127.6 (2C), 128.4 (2C), 128.7 (2C), 129.2, 131.6, 133.7, 137.8, 159.2, 170.9. HRMS (ESI): calcd. for $C_{20}H_{20}N_3O_2$ 334.15488 $[M+H]^+$; found 334.15500 $[M+H]^+$.

1-(4-Methoxybenzyl)-5-methyl-7-(*m*-tolyl)-1*H*-imidazo[1,5-*a*]imidazol-2(3*H*)-one (15).

Following the general procedure A with *m*-tolylboronic acid (61 mg, 0.45 mmol), the mixture was refluxed for 1.5 hours. The crude product was purified by flash chromatography on silica gel (75:25 dichloromethane / ethyl acetate).
Brown solid (82 mg; 79%); mp: 142-143 °C; IR (neat, cm^{-1}): 825, 1246, 1513, 1637, 1721, 2920; ^1H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 2.35 (s, 3H), 3.72 (s, 3H), 4.43 (s, 2H), 4.84 (s, 2H), 6.68 (d, *J* = 8.0 Hz, 2H), 6.54 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 7.4 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.20 (s, 1H), 7.21 – 7.25 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 13.3, 21.5, 44.2, 47.20, 55.3, 114.01 (2C), 118.1, 125.8, 127.6, 127.9, 128.27, 129.0 (2C), 129.3, 131.5, 133.5, 137.8, 138.07, 159.3, 170.9; HRMS (ESI): calcd. For $C_{21}H_{22}N_3O_2$ 348.17050 $[M+H]^+$ found 348.17065 $[M+H]^+$.

1-(4-Methoxybenzyl)-5-methyl-7-(3-nitrophenyl)-1*H*-imidazo[1,5-*a*]imidazol-2(3*H*)-one (16).

Following the general procedure with 3-nitrophenylboronic acid (74 mg, 0.45 mmol), the mixture was refluxed for 1.5 hours. The crude product was purified by flash chromatography on silica gel (95:5 dichloromethane / ethyl acetate).Brown solid (83 mg, 74%); mp: 178-180 °C; IR (neat, cm^{-1}) 810, 1033, 1112, 1245, 1329, 1512, 1727, 2925; ^1H NMR (400 MHz, $CDCl_3$): δ 2.39 (s, 3H), 3.71 (s, 3H), 4.54 (s, 2H), 4.91 (s, 2H), 6.6 (d, *J* = 8.0 Hz, 2H), 6.8 (d, *J* = 8.0 Hz, 2H), 7.4 (t, *J* = 8.0 Hz, 1H), 7.7 (d, *J* = 8.0 Hz, 1H), 7.9 (dd, *J* = 8.0, 2.0 Hz, 1H), 8.2 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 13.3, 44.4, 47.2, 55.4, 114.2 (2C), 116.1, 121.6, 122.9, 126.6, 128.3 (2C), 129.3, 132.7, 134.1, 135.5, 138.7, 148.3, 159.4, 170.9; HRMS (ESI): calcd. for $C_{20}H_{19}N_4O_4$ 379.14010 $[M+H]^+$ found 379.14008 $[M+H]^+$.

1-(4-Methoxybenzyl)-5-methyl-7-(3-(trifluoromethyl)phenyl)-1*H*-imidazo[1,5-*a*]imidazol-2(3*H*)-one (17).

Following the general procedure with 3-(trifluoromethyl)phenylboronic acid (85 mg, 0.45 mmol), the mixture was refluxed for 1.5 hours. The crude product was purified by flash chromatography on silica gel (75:25 dichloromethane / ethyl acetate).
White solid (88 mg; 74%); mp: 156-158 °C; IR (neat, cm^{-1}): 804, 1034, 1103, 1175, 1266, 1305, 1512, 1729, 2928; ^1H NMR (400 MHz, $CDCl_3$): δ 2.38 (s, 3H), 3.74 (s, 3H), 4.51 (s, 2H), 4.83 (s, 2H), 6.65 (d, *J* = 8.5 Hz, 2H), 6.77 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.51 – 7.44 (m, 2H), 7.63 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 13.3, 44.2, 47.2, 55.3, 113.8 (2C), 116.5, 123.4 (q, J_{C-F} = 3.7 Hz), 123.9 (q, J_{C-F} = 273 Hz, CF_3), 125.0 (q, J_{C-F} = 3.7 Hz), 126.6, 128.3 (2C), 128.5, 130.5 (q, *J* = 32.2 Hz), 131.5, 132.3, 134.6, 138.3, 159.4, 170.9; HRMS (ESI): calcd. for $C_{21}H_{19}F_3N_3O_2$ 402.14226 $[M+H]^+$ found 402.14239 $[M+H]^+$.

3-(1-(4-Methoxybenzyl)-5-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[1,5-*a*]imidazol-7-yl)benzonitrile (18).

Following the general procedure with 3-cyanophenylboronic acid (65 mg, 0.45 mmol), the mixture was refluxed for 1.5 hours,the crude product was purified by flash chromatography on silica gel (75:25 dichloromethane / ethyl acetate).
Brown solid (60 mg; 56%); mp: 147-149 °C; IR (neat, cm^{-1}): 805, 1242, 1512, 1605, 1726, 2224; ^1H NMR (400 MHz, $CDCl_3$): δ 2.38 (s, 3H), 3.74 (s, 3H), 4.51 (s, 2H), 4.85 (s, 2H), 6.73 (d, *J* = 8.2 Hz, 2H), 6.86 (d, *J* = 8.2 Hz, 2H), 7.40 (t, J = 7.6, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.58 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 13.3, 44.4, 47.2, 55.4, 112.6, 114.37 (2C), 116.0, 118.8, 126.7, 128.4 (2C), 129.2, 130.4, 131.6, 132.5, 132.6, 135.0, 138.6, 159.3, 170.8; HRMS (ESI): calcd. for $C_{21}H_{19}N_4O_2$ 359.15012 $[M+H]^+$ found 359.15025 $[M+H]^+$.

1-(4-Methoxybenzyl)-5-methyl-1*H*-imidazo[1,5-*a*]imidazol-2(3*H*)-one (19).

Following the general procedure with 2-tolylboronic acid, 2-methoxyphenylboronic acid or 2-(trifluoromethyl) phenylboronic acid (1.5 eq, 0.45 mmol), the mixture was refluxed for 1.5 hours. The crude product was purified by flash chromatography on silica gel (75:25 dichloromethane / ethyl acetate).
White solid; (yield See table N°3 above). mp: 98-100 °C; IR (neat, cm^{-1}): 845, 1027, 1176, 1243, 1512, 1609, 1719, 2927; ^1H NMR (400 MHz, $CDCl_3$): δ 2.32 (s, 3H), 3.81 (s, 3H), 4.41 (s, 2H), 4.75 (s, 2H), 6.06 (s, 1H), 6.86 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 13.6, 45.2, 47.6, 55.4, 103.2, 114.4 (2C), 126.6, 130.0 (2C), 136.5, 138.1, 160.0, 170.0; HRMS (ESI): calcd. for $C_{14}H_{16}N_3O_2$ 258.12369 $[M+H]^+$ found 258.12370 $[M+H]^+$.

(*E*)-1-(4-Methoxybenzyl)-5-methyl-7-styryl-1*H*-imidazo[1,5-*a*]imidazol-2(3*H*)-one (20).

Following the general procedure with trans-2-phenylvinylboronic acid (62 mg, 0.45 mmol), the mixture was refluxed for 2 hours. The crude product was purified by flash chromatography on silica gel (75:25 dichloromethane / ethyl acetate).
Brown solid (72 mg; 67%); mp: 192–194 °C; IR (neat, cm^{-1}): 918, 1176, 1246, 1511, 1614, 1729; ^1H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H), 3.78 (s, 3H), 4.43 (s, 2H), 4.98 (s, 2H), 6.65 (d, *J* = 15,8Hz, 1H), 6.92 (d, *J* = 8,3Hz, 2H), 7.13 (d, *J* = 15,8Hz, 1H), 7.18-7.27 (m, 1H), 7.28 – 7.32 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$):δ 13.4, 44.3, 47.3, 55.4, 114.5 (2C), 116.3, 117.5, 125.2, 126.0 (2C), 126.8, 127.2, 128.5 (2C), 128.6 (2C), 133.0, 138.0, 138.8, 159.6, 170.5; HRMS (ESI): calcd. for $C_{22}H_{22}N_3O_2$ 360.17047 $[M+H]^+$ found 360.17065 $[M+H]^+$.

7-(Furan-3-yl)-1-(4-methoxybenzyl)-5-methyl-1*H*-imidazo[1,5-*a*]imidazol-2(3*H*)-one (21).

Following the general procedure with 3-furanylboronic acid (50 mg, 0.45 mmol),the mixture was refluxed for 2 hours. The crude product was purified by flash chromatography on silica gel (75:25 dichloromethane / ethyl acetate).
Brown solid (44 mg; 46%); mp: 167-169 °C; IR (neat, cm-1); 1021, 1176, 1246, 1513, 1581, 1724; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.34 (s, 3H), 3.75 (s, 3H), 4.43 (s, 2H), 4.84 (s, 2H), 6.47 (s, 1H), 6.77 (d, *J* = 7.8 Hz, 2H), 7.01 (d, *J* = 7.8 Hz, 2H), 7.40 (d, *J* = 5.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 13.3, 44.0, 47.3, 55.4, 108.8, 111.3, 114.2 (2C), 118.3, 127.4, 128.8 (2C), 132.0, 138.1, 140.0, 143.2, 159.4, 170.4; HRMS (ESI): calcd. for $C_{18}H_{18}N_3O_3$ 324.13425 $[M+H]^+$ found 324.13426 $[M+H]^+$.

1-(4-Methoxybenzyl)-5-methyl-7-(thiophen-3-yl)-1*H*-imidazo[1,5-*a*]imidazol-2(3*H*)-one (22).

Following the general procedure with 3-thienylboronic acid (57 mg, 0.45 mmol), the mixture was refluxed for 2 hours. The crude product was purified by flash chromatography on silica gel (75:25 dichloromethane / ethyl acetate).
White solid (70 mg; 65%); mp:161-163 °C; IR (neat, cm^{-1}): 863, 1031, 1175, 1248, 1513, 1632, 1723; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.33 (s, 3H), 3.72 (s, 3H), 4.42 (s, 2H), 4.83 (s, 2H), 6.71 (d, *J* = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 7.14 (d, *J* = 3.7 Hz, 2H), 7.33 – 7.29 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 13.3, 44.0, 47.2, 55.3, 113.1, 114.1 (2C), 122.2, 125.7, 127.6, 128.5, 129.0 (2C), 131.7, 134.2, 137.6, 159.3, 170.6; HRMS (ESI): calcd. for $C_{18}H_{18}N_3O_2S$ 340.11139 $[M+H]^+$ found 340.11142 $[M+H]^+$.

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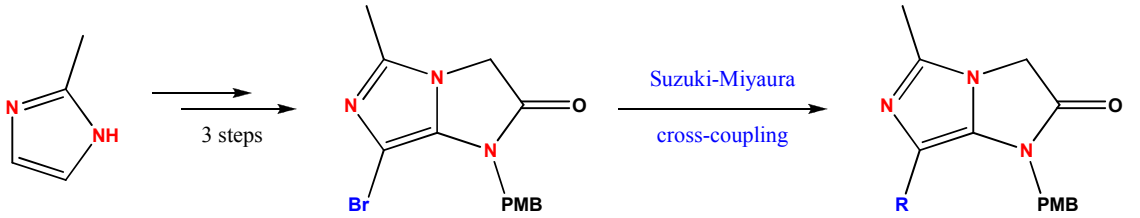
A pathway to new 7-bromo-1-(4-methoxybenzyl)-5-methyl-imidazo[1,5-*a*]imidazol-2-one was reported. The synthetic potential of this scaffold was demonstrated by displacing bromine by Suzuki–Miyaura cross-coupling reactions. A large panel of boronic acids (aryl, heteroaryl or vinyl) were easily introduced, giving access to a broad and diversified library of 1-(4-methoxybenzyl)-5-methyl-7-(substituted)-imidazo[1,5-*a*]imidazol-2-ones.



R = aryl, heteroaryl or vinyl
18 examples
49-88%