An Expeditious Synthesis of 2,4-Disubstituted 2-Imidazolin-5-ones

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Abstract: 2-Thiomethylimidazolin-5-one undergoes efficient palladium-catalyzed cross-coupling with boronic acids and organostannanes mediated by copper(I) thiophene-2-carboxylate.

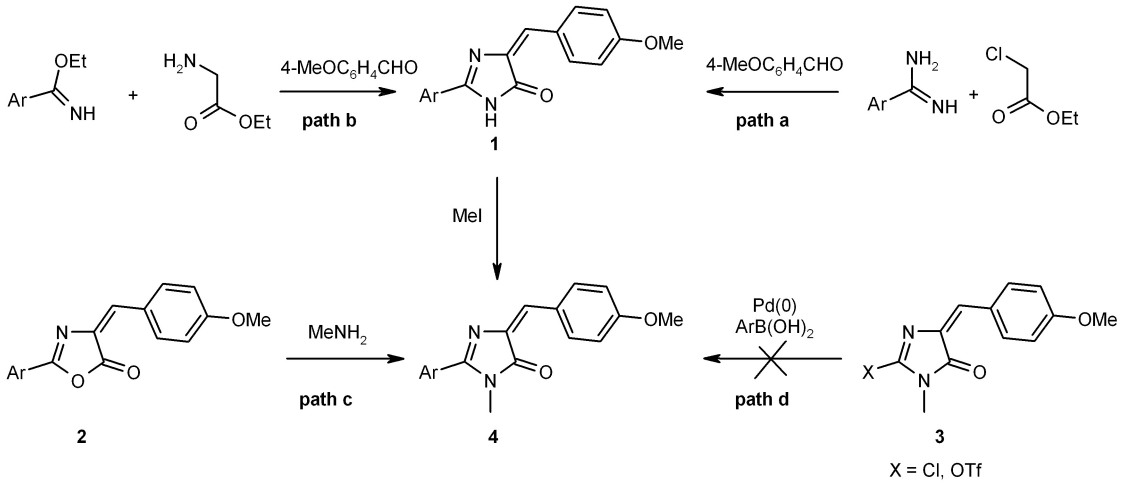
Key words: imidazolones, palladium, boronic acids, organostannanes, copper(I) thiophene carboxylate

2,4-Disubstituted 2-imidazolin-5-ones constitute an important class of heterocyclic compounds, as they may present original fluorescent properties.[1] Classical methods dealing with the synthesis of substituted imidazolin-5-ones **4** result either from the reaction of a benzamidine with ethyl chloroacetate and an aromatic aldehyde (path **a**),[2,3] or a phenyliminoether with methyl glycinate and an aldehyde (path **b**),[4,5] or the treatment of an oxazolone intermediate **2** with an alkylamine (path **c**, Scheme 1).[6] However these classical methods give poor to moderate and erratic yields. The present work describes a new strategy for the synthesis of 2-arylimidazolin-5-ones based on palladium cross-coupling reactions.

In a first attempt, we explored the possibility to prepare 2-arylimidazolinones using 2-chloroimidazolinones or 2-*O*-triflate imidazolinones **3** for our purposes (path **d**, Scheme 1). However these two intermediates could not be prepared due to their high instability. Thus, an alternative method based on cross-coupling strategy between boronic acids and the readily available and more stable 2-methylthioimidazolone **7** was performed. Liebeskind et al[7] have already described the functionalization of various heterocycles via cross-coupling reactions between boronic acids and heteroaromatic thioethers in the presence of copper(I) thiophene-2-carboxylate (CuTC), tris(2-furyl)phosphine and palladium complex. This method was used by Kappe[8] for the cross-coupling of 3,4-dihydropyrimidine-2-thiones and boronic acids. We applied the scope of this approach to our heteroaromatic system.

The thioimidazolone **5**, obtained from the reaction of ethyl glycinate and methylisothiocyanate,[9] was reacted with 4-methoxybenzaldehyde to afford the corresponding benzylidene intermediate **6** in 70% yield. Methylation[10,11] of **6** with methyl iodide took place at the sulfur atom to give **7** in 75% yield (Scheme 2).

Five different aryl boronic acids were chosen in order to explore the scope and limitation of the method. In addition, the catalyst used by Liebeskind was first attempted for this purpose. The results are summarized in Table 1. No reaction was observed with 4-cyanophenylboronic acid in the presence of $Pd_2(dba)_3$ in refluxing THF condi-



Scheme 1 Access to various 2-substituted unsaturated imidazolin-5-ones

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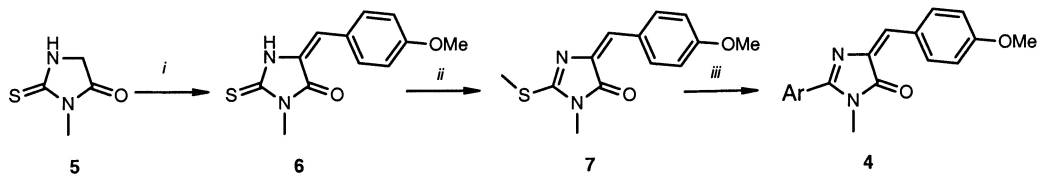
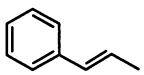
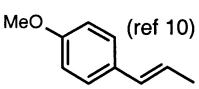


Scheme 2 *Reagents and conditions*: *i*. *p*-$MeOC_6H_4CHO$, AcOH, NaOAc, reflux; *ii*. NaOMe, MeI; *iii*. $ArB(OH)_2$, $Pd(Ph_3P)_4$, CuTC, DMF, microwave.

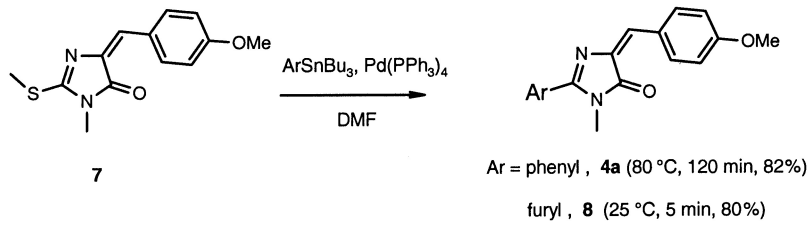
tion, even after 48 hours (entry 9). Using the same conditions in a microwave (300 W) led to only 10% of transformation after 15 minutes (entry 10). $Pd(Ph_3P)_4$ gave better results, when the reaction was performed in refluxing DMF (entry 11). However, about 70% (see experimental) of transformation was observed, when the reaction was carried out in a sealed tube, or under microwave (300 W) (entries 12, 13). As expected, 2-methylthioimidazolone **7** reacted more rapidly with electron-rich boronic acids. This method was also successfully applied to vinylboronic acids to give **4d** and **4e** in good yields.

Recently Liebeskind[12] and Guillaumet[13] described the formation of C–C bonds in a heteroaromatic thioether-organostannane cross coupling reaction. Thus commercially available aryl stannanes were reacted with the imidazolone **7**. CuTC was used as a source of Cu(I), and $Pd(PPh_3)_4$ as the catalyst. 2-Methylthioimidazolone **7** reacted rapidly with 2-furylstannane to afford **8** in good yield. With a less reactive stannane (phenyl derivative), the reaction was complete only after heating in DMF for two hours (82% yield) (Scheme 3).

Table 1 CuTC-Mediated Cross-Coupling of 2-Thiomethylimidazolin-5-ones with Arylboronic Acids

Entry	Product	Ar	Experimental Conditions	Reaction Time (h)	Yield (%)
1	**4a**	Ph	–[a]	18	31
2		'	–[b]	0.25	40
3		'	–[f]	0.25	65
4	**4b**	4-$MeOC_6H_4$	–[a]	20	40
5		'	–[b]	0.25	50
6		'	–[c]	18	54
7		'	–[e]	0.25	68
8		'	–[f]	0.25	70
9	**4c**	4-NCC_6H_4	–[a]	48	0
10		'	–[b]	0.25	10
11		'	–[d]	0.25	38
12		'	–[e]	0.25	66
13		'	–[f]	0.25	68
14	**4d**		–[f]	0.25	75
15[g]	**4e**		–[f]	0.25	80

[a] Pd_2dba_3 (4%)-TFP (16%), CuTC (1.3 equiv), THF, reflux.
[b] Pd_2dba_3 (4%)-TFP (16%), CuTC (1.3 equiv), THF, microwave.
[c] $Pd(Ph_3P)_4$ (5%), CuTC (1.3 equiv), THF, reflux.
[d] $Pd(Ph_3P)_4$ (5%), CuTC (1.3 equiv), DMF, reflux.
[e] $Pd(Ph_3P)_4$ (5%), CuTC (1.3 equiv), DMF, sealed tube, 130 °C (external temperature).
[f] $Pd(Ph_3P)_4$ (5%), CuTC (1.3 equiv), DMF, microwave.
[g] See also Ref.[10]



Scheme 3

In conclusion, the Liebeskind–Srogl coupling reaction was performed with success in neutral conditions with 2-methylthioimidazolin-5-one using tetrakis(triphenylphosphine)palladium as a catalyst, copper(I) thiophene-2-carboxylate as a mediation agent in a sealed tube, or under microwave irradiation. It is noteworthy that the reaction of compound **7** with organostannanes occurred at lower temperature and in good yields. In addition it constitutes another illustration of the use of thiomethyl group as a leaving group in palladium coupling reactions, when the heteroaromatic halide or corresponding *O*-triflate are not available.

The microwave reactor used was a multimods NORMATRON® 112 (reference 41500 from NORMALAB ANALYSIS S.A.).

4-{4-[(*E*)-(4-Methoxyphenyl)methylidene]-1-methyl-5-oxo-4,5-dihydro-1*H*-imidazol-2-yl}benzonitrile (4c); Typical Procedure

Compound **7** (120 mg, 0.458 mmol), $Pd(Ph_3P)_4$ (26 mg, 0.022 mmol), CuTC (114 mg, 0.595 mmol), *p*-cyanophenylboronic acid (90 mg, 0.504 mmol) were placed in a sealed tube and anhyd DMF (3 mL) was added. This suspension was stirred and submitted to microwave irradiation (300 W) for 15 min. The solution was evaporated to dryness under reduced pressure and diluted with sat. aq solution of $NaHCO_3$. The aqueous solution was extracted with CH_2Cl_2 (3 ×). The dried organic layer was evaporated in vacuo and the resulting oil was purified by flash chromatography on silica gel (EtOAc-hexane, 1:3) to afford the desired product **4c** (101 mg, 70%) as an orange powder; mp 156–158 °C.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 8.1 (d, *J* = 8.7 Hz, 2 H, ArH), 8.0 (d, *J* = 8.2 Hz, 2 H, ArH), 7.8 (d, *J* = 8.2 Hz, 2 H, ArH), 7.3 (s, 1 H, =CH), 6.9 (d, *J* = 8.7 Hz, 2 H, ArH), 3.8 (s, 3 H, OCH_3), 3.3 (s, 3 H, NCH_3).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 171.5, 162.3, 159.4, 137.1, 135.2, 134.0, 132.9, 131.1, 129.5, 127.4, 118.4, 115.0, 114.8, 70.7, 55.8, 29.4.

Anal. Calcd for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24. Found: C, 71.63; H, 4.97, N, 12.79.

2-(2-Furyl)-5-[(*E*)-(4-methoxymethyl)methylidene]-3-methyl-3,5-dihydro-4*H*-imidazol-4-one (8); Typical Procedure

2-(Tributylstannyl)furane (65.7 μL, 0.21 mmol) was added to a solution of CuTC (79 mg, 0.41 mmol), $Pd(Ph_3P)_4$ (11 mg, 5 mol%) and compound **7** (50 mg, 0.19 mmol) in DMF (4 mL). The reaction mixture was stirred at r.t. for 5 min, then aq sat. solution of $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, and dried (Na_2SO_4). Purification by flash chromatography on silica gel (EtOAc-hexane, 1:3) gave the desired product (48 mg, 80%) as a yellow powder; mp 128–130 °C.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 8.2 (d, *J* = 8 Hz, 2 H, ArH), 7.7 (m, 1 H, H_{furyl}), 7.4 (d, *J* = 4 Hz, 1 H_{furyl}), 7.2 (s, 1 H, =CH), 7.0 (d, *J* = 8 Hz, 2 H, ArH), 6.7 (dd, *J* = 4, 1.7 Hz, 1 H_{furyl}), 3.9 (s, 3 H, OCH_3), 3.5 (s, 3 H, NCH_3).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 171.2, 161.8, 151.8, 146.1, 145.6, 137.4, 134.8, 128.7, 127.5, 116.2, 114.7, 112.9, 55.7, 28.9.

Anal. Calcd for $C_{16}H_{14}N_2O{\cdot}0.5H_2O$: C, 65.97; H, 5.19; N, 9.62. Found: C, 65.95; H, 5.12, N, 9.89.

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