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Copper-free palladium-catalyzed Sonogashira and Hiyama cross-couplings using aryl imidazol-1-ylsulfonates

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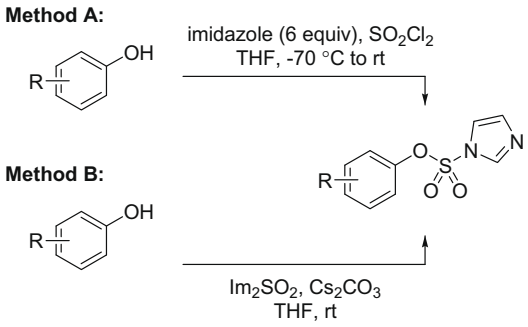
ABSTRACT

Aryl imidazylates are effective electrophilic partners in copper-free palladium-catalyzed Hiyama and Sonogashira cross-coupling reactions. The Sonogashira cross-coupling of estron-3-yl imidazylate afforded the corresponding phenylacetylene derivative in excellent yield.

Transition metal-catalyzed cross-coupling reactions have matured to the point where they now represent major cornerstones of organic synthesis. While halides are the most common electrophilic partners for these reactions, in recent years the use of various sulfonates such as mesylates,[1–3] tosylates[3–5], and fluoroalkylsulfonates (e.g., triflates,[5,6] nonaflates,[7] and tetraflates[8]) have been reported. These sulfonates have allowed the use of phenols as chemical feedstocks for cross-coupling reactions, however, mesylates and tosylates commonly suffer from poor reactivity.[1,9] Fluoroalkylsulfonates exhibit improved reactivity but suffer from a lack of stability and a higher cost of preparation.[8] Moreover, the byproducts obtained by the use of either halides or sulfonates are classified as genotoxic, dissuading from their use on scale.[9]

Imidazolyl-1-sulfonates (imidazylates) have been widely deployed as leaving groups for nucleophilic substitution reactions in the carbohydrate and nucleoside arenas.[10] Goddard-Borger and Stick reported the development of imidazolylsulfonylazide hydrochloride as a stable diazotransfer reagent.[11] More recently, Albaneze-Walker et al.[9] reported the first use of aryl imidazylates[12] in Suzuki-Miyaura and Negishi cross-coupling and carbonylation reactions. Aryl imidazylates, being electron-deficient aryl sulfamates, exhibit reactivity similar to triflates but are cheaper to prepare, especially on scale, and produce non-toxic leaving group derived byproducts, imidazole and sulfate.[9] More recently, aryl imidazylates have been used in the palladium-catalyzed formation of aryl phosphonates[13] and palladium-catalyzed arylation of oxazoles.[14]

The Sonogashira[15] and Hiyama[16] reactions are highly effective processes for the construction of sp–sp^2 and sp^2–sp^2 carbon–carbon bonds, respectively. The resulting products are highly valued in natural product and materials synthesis and in the pharmaceutical industry. Each of these reactions has the advantage of producing little waste from the 'nucleophilic' component. Only a proton is lost from the alkyne coupling partner in Sonogashira reactions. In Hiyama couplings a relatively benign silyl group is released and the use of HOMSi®† reagents (*o*-hydroxymethylphenyldimethylsilyl groups) allows for recycling of the resultant siloxane byproduct.[17] Protocols have been reported for Hiyama couplings of aryl and vinyl chlorides,[18] aryl arenesulfonates, and mesylates.[19] Herein, we report the development of protocols allowing the use of aryl imidazylates in Sonogashira and Hiyama reactions providing environmentally-benign syntheses of arylacetylenes and biaryls.



Scheme 1. Preparation of aryl imidazylates.

Several methods were investigated for the preparation of aryl imidazylates. While the procedure of Albaneze-Walker et al. (Scheme 1, Method B) was effective for electron-rich phenols,[9] no product was obtained for the electron-poor phenols, 4-nitrophenol and 4-acetylphenol. An alternative procedure using sulfuryl

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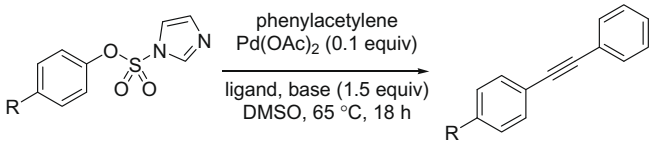
Table 1
Optimization of the Sonogashira reaction of aryl imidazylates



Entry	R	Ligand (equiv)	Base	Yield[a] (%)
1	4-NO_2	PPh_3 (0.1)	Et_2NH	60
2	4-NO_2	PPh_3 (0.1)	Et_3N	93
3	4-NO_2	PPh_3 (0.1)	DABCO	0
4	4-NO_2	PPh_3 (0.1)	DBU	0
5	4-NO_2	PPh_3 (0.1)	Cs_2CO_3	37
6	4-NO_2	PPh_3 (0.1)	K_3PO_4	78
7	4-Ac	PPh_3 (0.1)	Et_3N	73
8	4-Ac	PPh_3 (0.1)	K_3PO_4	81
9	4-MeO	PPh_3 (0.1)	K_3PO_4	23
10	4-MeO	SPhos (0.2)[b]	K_3PO_4	43
11	4-MeO	SPhos (0.2)[c]	K_3PO_4	72
12	4-MeO	XPhos (0.2)[c]	K_3PO_4	93

[a] Isolated yield.
[b] Water-mediated catalyst preactivation as described in Ref. 22.
[c] A catalyst stock solution was used as decribed in Ref. 20.

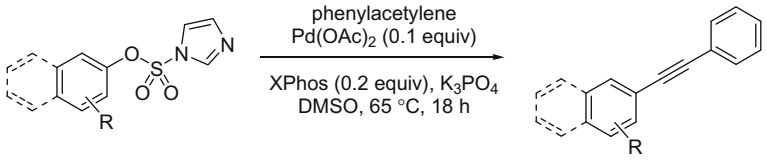
chloride and imidazole (Scheme 1, Method A) proved effective for the synthesis of imidazylates from these low pK_a phenols (67% from 4-nitrophenol; 52% from 4-acetylphenol).

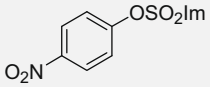
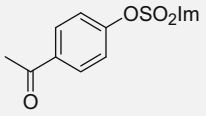
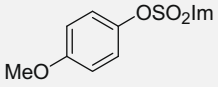
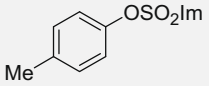
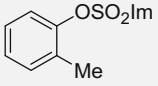
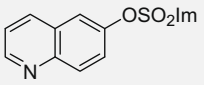
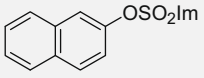
Our initial Sonogashira studies investigated the use of Ph_3P, $Pd(OAc)_2$ and Et_2NH with the activated 4-nitrophenyl substrate (Table 1). Using a THF/H_2O solvent system, no cross-coupled product was obtained owing to hydrolysis of the substrate. Gratifyingly, a 60% yield was obtained in dry DMSO (entry 1). Screening different bases led to an optimized yield of 93% using triethylamine (entries 1–6). When applied to 4-acetylphenyl imidazylate, a 73% yield was obtained (entry 7), however, an improved yield was obtained using K_3PO_4 (81%, entry 8). With the electron-rich substrate, 4-methoxyphenyl imidazylate, a dramatically reduced yield was obtained (23%, entry 9). Consequently, we next investigated the bulky biarylphosphine ligands SPhos and XPhos, which are known to promote the formation of highly reactive 12-electron monovalent Pd^0-complexes.[20,21] Comparison of protocols for water-mediated catalyst preactivation (entry 10)[22] versus a premixed catalyst preparation (entry 11)[20] revealed that the latter provided superior results. Finally, XPhos proved superior to SPhos (entries 11 and 12).

Next, the scope of the palladium-catalyzed reaction of a range of imidazylates was investigated under the optimized conditions.[23] As shown in Table 2, palladium-catalyzed Sonogashira couplings furnished the corresponding diarylacetylenes in generally good yields, with similar results seen for electron-rich, electron-poor, *ortho*-substituted, and bicyclic imidazylates. A poorer yield was obtained for the quinoline imidazylate (entry 6).

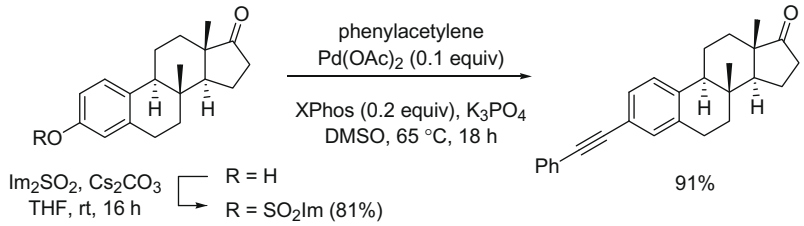
As a test case to illustrate the use of imidazylates of more complex phenols for which the corresponding halides are unavailable, we applied the optimized protocol to estron-3-yl imidazylate. As

Table 2
Palladium-catalyzed Sonogashira reactions of aryl imidazylates with phenylacetylene



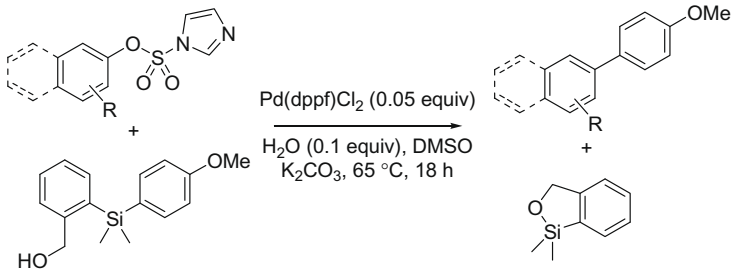
Entry	Substrate	Yield[a] (%)
1		89[b]
2		97
3		93
4		91
5		80
6		57[b]
7		87

[a] Isolated yield.
[b] Triethylamine as a base.



Scheme 2. Sonogashira cross-coupling of estrone imidazylate and phenylacetylene.

Table 3
Hiyama cross-coupling reactions with 4-methoxyphenyl HOMSi reagent



Entry	Substrate	Yield[a] (%)
1	4-Nitrophenyl	76
2	4-Methoxyphenyl	72[b,c]
3	4-Acetylphenyl	76[b]
4	2-Methylphenyl	36
5	2-Naphthyl	99

[a] Isolated yield.
[b] Reaction run at 65 °C.
[c] 1 equiv of dppf added.

expected, the cross-coupled product was obtained in an excellent 91% yield (Scheme 2).

We next examined the use of aryl imidazylates in the Hiyama reaction. Nakao et al. have demonstrated that the use of HOMSi reagents allows the recovery of the released silicon auxiliary, as a cyclic silyl ether, and that this may be recycled for the preparation of new HOMSi reagents.[17] Again, we were unable to establish a cross-coupling protocol with aryl imidazylates under aqueous conditions. However, using $Pd(dppf)Cl_2$[24] as a source of palladium in dry DMSO, with K_2CO_3 as a base under copper-free[25] conditions afforded the expected products in good yields.[26] We obtained similar results for electron-rich, electron-poor, and bicyclic imidazylates, and a somewhat poorer yield with the *ortho*-substituted 2-methylphenyl imidazylate (Table 3).

In summary, aryl imidazylates have been shown to function as electrophiles in palladium-catalyzed Sonogashira and Hiyama cross-coupling reactions. The advantages of these protocols include excellent reactivity and broad scope. Together with the recently reported examples of aryl imidazylates as substrates for Suzuki–Miyaura, Negishi, and H-phosphonate couplings, these results point to the potential for aryl imidazylates to supplant aryl triflates as inexpensive, readily accessible, and stable electrophilic partners for palladium-catalyzed cross-couplings. This work is complementary to the recent reports of nickel-catalyzed cross-coupling reactions of other simple phenolic derivatives: aryl pivalates and acetates,[27] aryl *N*,*N*-dimethylsulfamates,[28] carbonates[28] and carbamates,[28,29] and diaryl sulfates.[30] As illustrated by the use of estrone imidazylate as a substrate, such cross-couplings allow the use of complex phenols as starting materials, which is of particular value when the corresponding halide is unavailable.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.03.110.

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23. *General procedure for the Pd-catalyzed Sonogashira coupling of aryl imidazylates*: A dry, screw-capped test tube containing $Pd(OAc)_2$ (0.10 equiv) and XPhos (0.20 equiv) was purged with nitrogen gas for 10 min. Dry DMSO (1.5 ml) was then added to the test tube and the catalyst-stock solution was stirred for 30 min at rt. Over this period the catalyst-stock solution changed color from bright orange to dark brown. Separately, a round-bottomed flask containing aryl imidazylate (1.0 equiv) and K_3PO_4 (1.7 equiv) or triethylamine (15 equiv) was purged with nitrogen for 30 min. Dry DMSO (5 ml/mmol) was added to the flask containing the aryl imidazylate and base, followed by the catalyst stock solution, which was transferred via syringe. The contents of the flask were sparged with nitrogen for 10 min at rt and then the flask was heated to 65 °C. Phenylacetylene (1.2 equiv) was added to the flask dropwise over 15 min and the mixture was stirred at 65 °C under nitrogen for 16 h. The reaction mixture was then allowed to cool to rt, diluted with EtOAc (20 ml), washed with H_2O (3×10 ml) and brine (3×5 ml). The organic phase was collected, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (EtOAc/petroleum spirit).
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26. *General procedure for the Pd-catalyzed Hiyama reaction of aryl imidazylates*: H_2O (0.1 equiv) and $Pd(dppf)Cl_2$ (0.05 equiv) were added to a nitrogen-sparged solution of aryl imidazylate (1.0 equiv), (2-[(4-methoxyphenyl)dimethylsilanyl]phenyl)methanol (1.25 equiv), and K_2CO_3 (2.0 equiv) in dry DMSO (15 ml/mmol). The reaction mixture was heated at 110 °C overnight, then diluted with EtOAc (30 ml) and filtered through a Celite plug. The plug was washed with H_2O (30 ml) and then with EtOAc (30 ml). The organic eluents were combined and washed with H_2O (30 ml), brine (30 ml), dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting crude product was purified by flash chromatography on silica gel (EtOAc/petroleum spirit).
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