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Technical Notes

A Preparative Route to Methyl 3-(Heteroaryl)acrylates Using Heck Methodology

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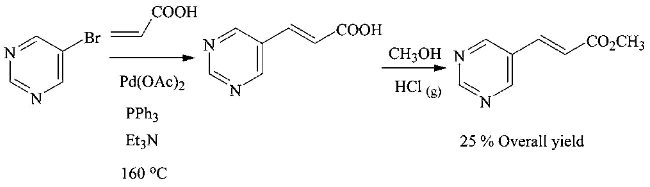
Abstract:

Methyl 3-(heteroaryl)acrylates were prepared using Heck coupling of heteroarene halides with methyl acrylate mediated by $Pd(OAc)_2/P(OCH_3)_3$. Reactions were highly efficient (reaction times between 60 and 120 min) and scalable to 100 g of heteroarene halide. The isolated yields are from 76 to 99%.

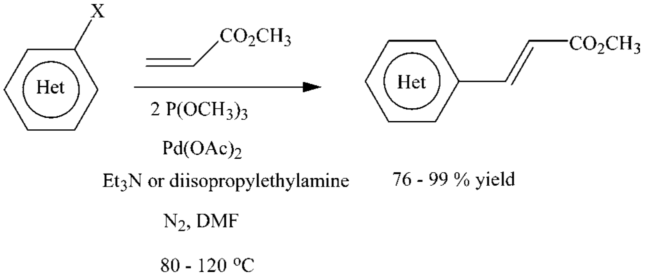
Palladium complexes have been extensively utilized in organic synthesis for the generation of carbon−carbon bonds.[1] A commonly used procedure is the arylation of alkenes using an "aryl palladium" reagent which can be generated in situ by several methods.[2] Regardless of the method used, all of these reactions are known as Heck reactions.[3] The reaction is generally carried out by combining an organic halide with a slight excess of the olefin, a slight excess of an amine base, and 1 mol % of palladium acetate and 2 mol % of a triarylphosphine (usually triphenyl- or tri-*o*-tolylphosphine).

We needed to prepare a number of methyl 3-(heteroaryl)-acrylates for use as intermediates for the production of pharmaceutical scaffolds. Surprisingly the reaction failed when run under the standard Heck conditions.[4] For example, the reaction of 5-bromopyrimidine with methyl acrylate using triphenylphosphine yielded none of the desired product.[4e] An alternate approach using acrylic acid in the place of methyl acrylate under standard Heck conditions at 160 °C followed by esterification of the crude product with methanol/HCl afforded the product in a disappointing 25% overall yield (Scheme 1). On a large preparative scale the high cost of the heteroarene halides would make this route prohibitively expensive.

Scheme 1



Scheme 2



Recent reports have indicated that bulky and electron-rich phosphorus ligands produce highly active catalysts; however, the examples described involved non-heteroarene chlorides and bromides.[5] Beller demonstrated that bulky phosphite compounds were good ligands for Heck reactions using chlorobenzene but did not study heteroarenes.[6] Phosphites have also been reported to enhance the reactivity of a variety of other processes mediated by transition metals.[7] We screened a number of different phosphorus-based ligands and found that trimethyl phosphite activated the palladium acetate-catalyzed coupling to give the desired methyl 3-(heteroaryl)acrylates in good yield (Scheme 2 and Table 1).

The reactions were effected by heating a 3-fold excess of methyl acrylate and the bromoheteroarene in DMF under

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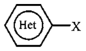
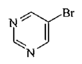
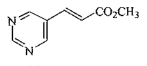
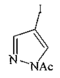
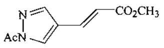
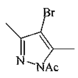
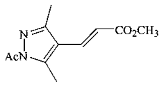
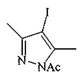
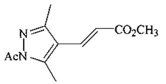
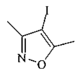
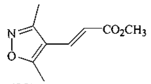
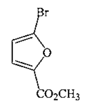
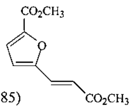
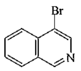
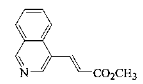
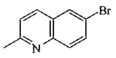
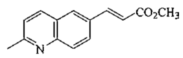
***Table 1.* Heteroarene Halides and Heck Reaction Products**

entry		mol %(Pd)	Time (min)	Temp (°C)	Base	Product (Yield %)[a]
1		2.5	60	110	DIPEA	 (89)
2		2	60	80	TEA	 (99)
3		2	120	130	DIPEA	 (17)[b]
4		1	60	90	TEA	 (99)
5		2	60	90	TEA	 (99)
6		1	120	100	TEA	 (85)
7		5	120	120	DIPEA	 (81)
8		5	120	120	DIPEA	 (76)

[a] The yields are based on isolated product after recrystallization. [b] Determined by GC (area %).

nitrogen with either triethylamine (TEA) or diisopropylethylamine (DIPEA) as the base. Trimethyl phosphite and palladium acetate were used in a 2:1 ratio with a catalyst loading of 1−5 mol %. Reaction temperature was 80−120 °C, depending on the particular heteroarene with reaction times of 60−120 min as determined by gas chromatography or thin-layer chromatography. Longer reaction times or a higher catalyst load had no effect on the yield. Workup involved removal of the DMF under reduced pressure and extraction of the residue with methylene chloride. The resulting suspension was filtered through a bed of silica and the methylene chloride solution washed with water. After drying and evaporation of the solvent, the crude product was purified by crystallization. The process was scaled to 100 g without any lowering of the yield.

Table 1 summarizes the yields obtained from various heteroarenes using this procedure. The yields were good for a variety of substrates except for *N*-acetyl-4-bromo-3,5-dimethylpyrazole (entry 3). It is unclear whether this was due to the electron-releasing character of the methyl groups or to steric hindrance, although the corresponding iodo compound gave a nearly quantitative yield (entry 4). In the case of 4-bromoisoquinoline (entry 7) and 3-bromo-7-methylisoquinoline (entry 8) the use of triethylamine required a longer reaction time and gave lower yields. Diisopropylethylamine gave improved reaction rates and higher yields. The use of DIPEA in place of TEA had no effect on the other reactions. The N−H group of the pyrazoles (entries 2−4) was protected by an acetyl group to prevent undesired coupling reactions. It was removed by hydrolysis with 2 M methanolic potassium hydroxide in quantitative yield. All products were characterized by mass spectrometry and ^{1}H NMR spectroscopy. The NMR spectra indicated the products were the expected E-olefins.

There are some practical aspects for using trimethyl phosphite as a ligand in the place of conventional phosphines. The highly volatile phosphite is readily separated during the removal of the DMF. Conventional triarylphosphines can remain in trace amounts after isolation of the product, and removal may require more rigorous and costly procedures to meet product purity specifications. Phosphines can also undergo oxidative cleavage forming undesirable cross-coupling products that can lead to catalyst deactivation.[8] No side-reaction products associated with the decomposition of trimethyl phosphite were detected in our reactions.

Experimental Section

General. The heteroarene halides were obtained from Aldrich or Alfa-Aesar. Palladium acetate was obtained from Strem Chemicals. Other reagents and anhydrous solvents were from Aldrich and were used as received. TLC was performed on Macherey−Nagel 40 mm × 80 mm silica gel plates with UV indicator (254 nm) using ethyl acetate−hexanes (1:2). ^{1}H NMR spectra were acquired on a Varian XL-300 spectrometer at 300 MHz. Mass spectra were recorded on a HP-5890 GC with a HP 5972 mass selective detector or by the Mass Spectral Services Unit, Department of Chemistry, CUNY Hunter College, New York, NY.

General Procedure for a Heck Coupling Using 5-Bromopyrimidine. A 5-L multineck flask was fitted with a mechanical stirrer, glycol-chilled (−10 °C) condenser, gas inlet adapter, and a thermometer. The system was purged with dry N_2 for a few minutes and then charged with 5-bromopyrimidine (100 g, 0.64 mol) dissolved in 1.5 L of DMF, methyl acrylate (165.2 g, 1.92 mol), diisopropylethylamine (120 mL), trimethyl phosphite (4.0 g, 32 mmol), and palladium acetate (3.6 g, 16 mmol). The mixture was warmed to 110°. The reaction was monitored by removing an aliquot under N_2 and analyzing by TLC. When the reaction was complete as determined by the disappearance of the 5-bromopyrimidine, the mixture was cooled to room temperature and the DMF removed under reduced pressure. The residue was stirred with 1.5 L of methylene chloride, and the suspension was filtered through a bed of silica gel. The filtrate was washed with 1 L of 3% hydrochloric acid, 1 L of water, and 1 L of saturated brine. The solution was dried over $MgSO_4$ and filtered; the solvent was removed under reduced pressure.

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The crude solid was crystallized from ethyl acetate−hexane to yield 93.4 g (89%) of the product.

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Supporting Information Available

^{1}H NMR chemical shifts and mass spectral data of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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