

DIRECT SYNTHESIS OF HETEROARYLETHYNES VIA PALLADIUM-CATALYZED COUPLING OF HETEROARYL HALIDES WITH ETHYNYLZINC HALIDES. ITS APPLICATION TO AN EFFICIENT SYNTHESIS OF A THIOPHENELACTONE FROM CHAMAEMELUM NOBILE L[†]

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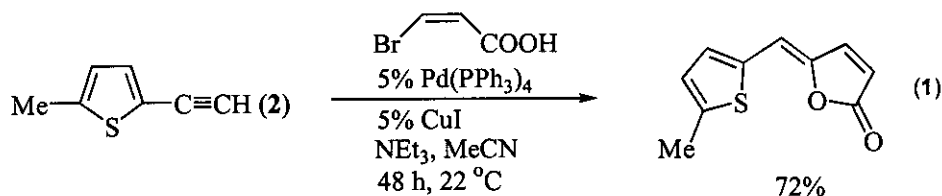
Abstract-A variety of terminal alkynes containing a heteroaryl group can be directly and selectively synthesized by the Pd-catalyzed coupling of heteroaryl iodides or bromides with ethynylzinc halides. Various compounds of this class containing furan, thiophene, and pyridine have been prepared, and the procedure has been applied to an efficient and selective synthesis of a thiophenelactone from *Chamaemelum nobile* L.

We have recently reported a direct synthesis of terminal alkynes *via* Pd-catalyzed coupling of aryl and alkenyl halides, in particular iodides, with ethynylmetals containing Mg and Zn¹ based on our earlier studies.²⁻⁴ Since the Sonagashira coupling⁵ does not permit direct cross coupling of acetylene itself in a selective manner, the Mg-Pd or Zn-Pd procedure offers a distinct advantage in the synthesis of terminal alkynes. We have also noted that direct ethynylation can be complicated by some difficulties which are not encountered in the synthesis of internal alkynes and that such difficulties are very much substrate dependent. In this paper, we report on its applicability to the synthesis of heteroarylethynes. We also describe an efficient and selective synthesis of a thiophenelactone from *Chamaemelum nobile* L. (1)⁶ involving the use of the procedure reported herein and a Pd-catalyzed method for the synthesis of (Z)- γ -alkylidenebutenolides we have recently developed⁷ based on a previously reported reaction⁸ (Scheme 1). In our recent study,¹ the merits and demerits of HC $\equiv$ CMgX and HC $\equiv$ CZnX, where X = Br or Cl, were discussed. In short, the Mg reagents are commercially and hence more readily available and more economical than the Zn reagents, which must be generated from ethynylmetals containing Mg, Na, or Li.

[†] We wish to dedicate this paper to the memory of Professor Shun-ichi Yamada.

On the other hand, the Mg reagents are less tolerant of heterofunctional groups, *e.g.*, carbonyl and nitro groups, and yet generally less reactive in the Pd-catalyzed cross coupling than the Zn reagents. In the direct synthesis of terminal alkynes *via* Pd-catalyzed coupling of aryl halides with ethynylmetals, the formation of diarylethynes has been identified as one of the potentially serious side reactions, and at least three factors listed below are considered to be significant: (i) slow cross coupling rate, (ii) formation of terminal alkynes that are more acidic than ethyne itself, and (iii) high ionicity of the ethynyl-metal bond. With respect to the items i and iii, the use of ethynylmagnesium halides has indeed been shown to be often problematical. Typically, the reaction of 2-iodo-5-methylthiophene with $\text{HC}\equiv\text{CMgCl}$ in the presence of 5 mol % of $\text{Pd}(\text{PPh}_3)_4$ gave the desired 2-ethynyl-5-methylthiophene (**2**) only in 35% yield along with a 24% yield (based on the starting iodide) of bis(5-methyl-2-thienyl)ethyne. On the other hand, the corresponding reaction of $\text{HC}\equiv\text{CZnBr}$ gave **2** in 87% yield (Scheme 2). Similar comparative results were obtained also with 2-iodofuran. Aryl halides containing an electron-rich aryl group are known to be less reactive in the Pd-catalyzed cross coupling than those containing an electron-withdrawing group due to slower rates of oxidative addition⁹ (factor i). This factor as well as the generally lower cross-coupling rates observed with Mg (factor i) and its expected high propensity to undergo H-Mg exchange (factor iii) must be largely responsible for the observed difficulty with Mg.

Scheme 1



Scheme 2

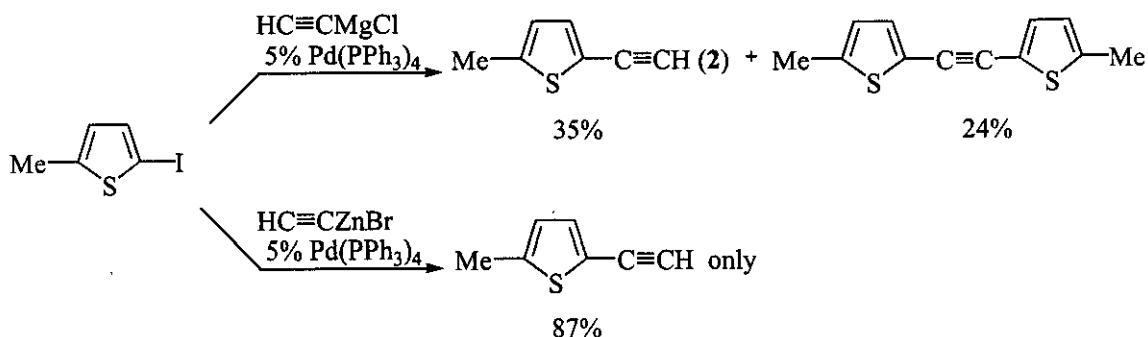
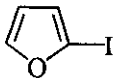
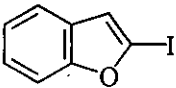
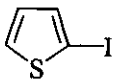
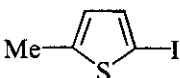
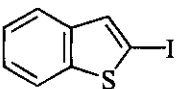
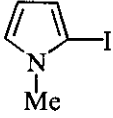


Table 1. Direct Synthesis of Heteroarylethynes Containing a Five-Membered Heteroaryl Group by Pd-Catalyzed Coupling of Heteroaryl Iodides with Ethynylzinc Bromide^a

Heteroaryl iodide	Time h	ArC≡CH % ^b
	1	92
	1	78(72)
	1	85(71)
	1	87(80)
	1	92(71)
	4	76

a) The reaction was carried out using 1.5 equiv. of $\text{HC}\equiv\text{CZnBr}$, generated *in situ* from $\text{HC}\equiv\text{CMgBr}$ and dry ZnBr_2 , and 5 mol% of $\text{Pd}(\text{PPh}_3)_4$ in THF at 22-23 °C. b) Determined by NMR or GLC. The numbers in parentheses are isolated yields.

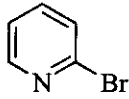
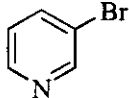
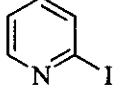
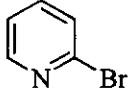
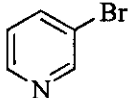
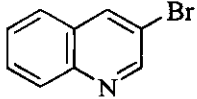
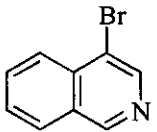
As summarized in Table 1, the use of $\text{HC}\equiv\text{CZnBr}$ has led to satisfactory results in the synthesis of arylethynes containing an electron-rich five-membered heteroaryl group. This procedure has been successfully applied to synthesis of a thiophenelactone from *Chamaemelum nobile* L.⁶ in two steps in 63% combined yield from 2-iodo-5-methylthiophene, prepared in 85% yield by HgI-promoted iodination¹⁰ of 2-methylthiophene, and (Z)-3-bromopropenoic acid,¹¹ obtained in 93% yield by the reaction of propynoic acid with LiBr in HOAc ¹² (Scheme 1). In principle, the two Pd-catalyzed steps involving $\text{Pd}(\text{PPh}_3)_4$ may be combined into one step. However, no such attempts have thus far been made. In general, heteroaryl bromides containing an electron-rich five-membered heteroaryl group are not sufficiently reactive in the Pd-catalyzed cross coupling. The preparation of **2** and its conversion with **1** are as follows, and the former is representative of the direct synthesis of heteroarylethynes reported herein.

2-Ethynyl-5-methylthiophene (2). To a flame-dried 50-mL flask equipped with a magnetic stirring bar were sequentially added under argon atmosphere $\text{HC}\equiv\text{CZnBr}$, 2-iodo-5-methylthiophene (448 mg, 2 mmol), and $\text{Pd}(\text{PPh}_3)_4$ (115 mg, 0.1 mmol). A solution of $\text{HC}\equiv\text{CZnBr}$ was prepared *in situ* by the reaction of $\text{HC}\equiv\text{CMgCl}$ (3 mmol, 6 mL of 0.5 M solution in THF) and dry ZnBr_2 (675 mg, 3 mmol). The reaction was complete in 1 h at 22 °C, and analysis by GLC indicated that 2-ethynyl-5-methylthiophene was formed in 87% yield. Column chromatography on silica gel afforded the title product¹³ (190 mg, 80%): ^1H NMR (CDCl_3 , Me_4Si) δ 2.46 (s, 3 H), 3.29 (s, 1 H), 6.62 (m, 1 H), 7.09 (d, $J = 3.6$ Hz, 1 H) ppm; ^{13}C NMR (CDCl_3 , Me_4Si) δ 15.29, 77.34, 80.36, 119.46, 126.11, 133.28, 142.32 ppm.

(Z)-5-(5-Methyl-2-thienylidene)-5H-furan-2-one (1). To a solution of (Z)-3-bromopropenoic acid¹¹ (75 mg, 0.5 mmol) in MeCN (5 mL) were added 2-ethynyl-5-methylthiophene (122 mg, 1 mmol), $\text{Pd}(\text{PPh}_3)_4$ (29 mg, 25 μmol), CuI (5 mg, 25 μmol), and NEt_3 (202 mg, 2 mmol). After stirring at 23 °C for 48 h, the reaction mixture was concentrated *in vacuo*, treated with 3 N HCl, extracted with ether, dried over Na_2SO_4 , and concentrated. Column chromatography on silica gel (3/2 hexane/ Et_2O) afforded **1**⁶ (69 mg, 72%) as a yellow solid: mp 116 °C (lit.,⁶ mp 117 °C); ^1H NMR (200 MHz, CDCl_3) δ 2.51 (s, 3 H), 6.11 (d, $J = 5.3$ Hz, 1 H), 6.23 (s, 1 H), 6.73 (dq, $J = 3.7$ and 1 Hz, 1 H), 7.17 (d, $J = 3.7$ Hz, 1 H), 7.43 (d, $J = 5.3$ Hz, 1 H); ^{13}C NMR (50.3 MHz, CDCl_3) δ 15.63, 108.08, 117.29, 126.27, 131.85, 134.07, 143.66, 145.82, 146.64, 169.81; IR (CCl_4) 1782, 1752, 1642, 1102, 1062, 880 cm^{-1} .

Direct ethynylation of aryl halides containing electron-deficient six-membered heteroaryl group, such as pyridine, quinoline, and isoquinoline, can also be complicated by the formation of diarylethynes. In addition to the factors i and iii, the factor ii was expected to be significant. Typically, the Pd-catalyzed reaction of 2-bromopyridine with 1.5 equiv. of $\text{HC}\equiv\text{CMgBr}$ did not produce 2-ethynylpyridine in a detectable yield, the major product being bis(2-pyridyl)ethyne formed in 65% NMR yield based on 2-bromopyridine. Even with $\text{HC}\equiv\text{CZnBr}$ the yield of 2-ethynylpyridine was limited to 21% (NMR) due to the competitive formation of bis(2-pyridyl)ethyne in 44% (NMR). In contrast, the corresponding reaction of 2-iodopyridine cleanly produced 2-ethynylpyridine in 70% NMR yield without producing bis(2-pyridyl)ethyne in a detectable yield. Alternatively, a known indirect strategy involving the use of acetone-protected ethyne¹² may be adapted to the conversion of 2-bromopyridine by the Zn-Pd cross-coupling protocol. The required alkynylzinc reagent can be generated by treating commercially available 1,1-dimethyl-2-propyn-1-ol with 2 equiv. each of *n*-BuLi and ZnBr_2 . The experimental results of the synthesis of pyridine-containing heteroarylethynes are summarized in Table 2.

Table 2. Direct Synthesis of Heteroarylethynes Containing a Pyridine Ring by Pd-Catalyzed Cross Coupling^a

Heteroaryl halide	Organometallic reagent	Time h	ArC≡CZ % ^b	Z	ArC≡CAr % ^b
	$\left\{ \begin{array}{l} \text{HC}\equiv\text{CMgBr} \\ \text{HC}\equiv\text{CZnBr} \end{array} \right.$	24 24	<2 21	H H	65 44
	$\left\{ \begin{array}{l} \text{HC}\equiv\text{CMgBr} \\ \text{HC}\equiv\text{CZnBr} \end{array} \right.$	24 24	<2 30	H H	64 47
	$\text{HC}\equiv\text{CZnBr}^{\text{d}}$	5	70	H	<2
	$\text{BrZnOC}(\text{Me}_2)\text{C}\equiv\text{CZnBr}^{\text{e}}$	8	83(76)	CMe_2OH	c
	$\text{BrZnOC}(\text{Me}_2)\text{C}\equiv\text{CZnBr}^{\text{e}}$	8	(83)	CMe_2OH	c
	$\left\{ \begin{array}{l} \text{HC}\equiv\text{CMgBr} \\ \text{HC}\equiv\text{CZnBr} \end{array} \right.$	24 24	<2 (55)	H H	90 40
	$\text{HC}\equiv\text{CZnBr}$	24	62(58)	H	24

a) The reactions were carried out using 5 mol% of $\text{Pd}(\text{PPh}_3)_4$ in THF/DMF (1:1) at 50-55 °C. b) Determined by NMR or GLC. The numbers in parentheses are isolated yields. c) Not determined. d) The reaction was carried out in THF at 22 °C. e) The reaction was carried out in THF.

In summary, the Pd-catalyzed direct ethynylation of heteroaryl halides can be achieved using $\text{HC}\equiv\text{CZnBr}$ as a reagent. The use of the corresponding Mg reagents appears to be generally more problematical than in the reactions of more usual benzene ring-containing aryl iodides,¹ regardless of whether the heteroaryl group is electron-donating or electron-withdrawing. Satisfactory results have been obtained with all five-membered heteroaryl iodides reported in this study in their Pd-catalyzed reaction with $\text{HC}\equiv\text{CZnBr}$ (Table

1), which makes this protocol the method of choice. No difficulty was encountered in applying it to the synthesis of a naturally occurring thiophenelactone (1). The sufficiently high reactivity of heteroaryl bromides containing a pyridine ring makes it desirable to use them rather than the corresponding iodides in the Pd-catalyzed ethynylation. However, their use leads to generally modest yields of the ethynylated products. At least in a few cases, diarylation of ethyne has been shown to be the major side reaction. In such cases, the use of either iodo derivatives or acetone-protected ethyne may prove to be viable alternatives.

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