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Iodide Acceleration in the Pd-Catalyzed Coupling of Aromatic 1,2-Ditriflates with Alkynes: Synthesis of Enediynes

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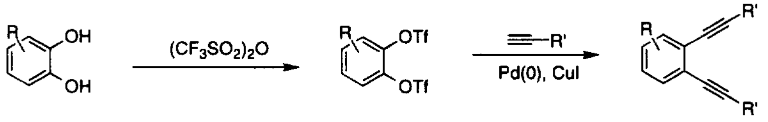
Key Words: aromatic ditriflates, aryl enediyne, alkyne, Hagihara reaction, Pd cross-coupling .

Abstract.: Aryl enediynes have been synthesized in a one-pot procedure by a Pd-catalyzed coupling of terminal alkynes and *ortho*-aryl ditriflates. A variety of substrates have been examined.

Enediynes have attracted attention as substrates for the Bergman cyclization,[1] and as a structural motif found in a variety of DNA cleaving antitumor antibiotics, such as dynemicin A and calicheamicin.[2] Aromatic enediynes have also found use as synthetic precursors to complex aromatic systems through tandem Bergman-radical cyclizations,[3] and in model enediyne antibiotics.[4,7] However, most aromatic enediynes have been synthesized from the corresponding 1,2-diiodo- or 1,2-dibromoarenes and a terminal alkyne by a Pd-catalyzed Hagihara reaction.[1,3,5,6d] Although superb coupling partners, aromatic 1,2-dihalides are often expensive and/or difficult to prepare. We were intrigued by the idea of using aromatic 1,2-ditriflates, which can be easily prepared from the less expensive and more readily available 1,2-dihydroxyarenes, as precursors to aromatic enediynes by the one-pot coupling of two alkynes (eq. 1). Aryl triflates have been shown to readily undergo Pd-catalyzed coupling reactions with alkynes.[6]



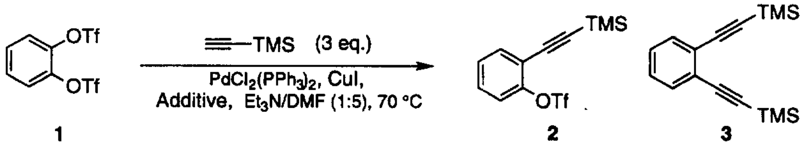
(1)

One report has been made of the use of an aromatic 1,2-ditriflate in a stepwise coupling of two different alkynes to prepare a dynemicin A model.[7] However, the reported procedure gave complex mixtures of starting material, monosubstituted and unidentified products when applied to our substrates. We describe a new synthetic method for the formation of aromatic enediynes from aromatic 1,2-ditriflates and alkynes.

The initial studies of enediyne formation with trimethylsilylacetylene and catechol ditriflate **1** are shown in Table 1. Coupling with $PdCl_2(PPh_3)_2$ under the Chen conditions[6a] gave a 29/71 ratio of **2**/**3** after 44 hr (entry 1), while other catalysts ($PdCl_2(CH_3CN)_2$ and $PdCl_2(PhCN)_2$) gave only starting material. Since it has been reported that the addition of halide salts often accelerates Pd-catalyzed reactions,[8] we examined the effect of addition of 300 mole% LiCl, but again saw only starting material (entry 2). The use of n-Bu_4NBr gave **2** in 38% yield (entry 3). Increasing the amount of Pd from 5 to

10 mole% and extending the reaction time (5 d) gave the desired enediyne **3** in 29% yield (entry 4). Increasing the amount of CuI to 25 mole% gave a marginal increase in yield of **3** (52%) and rate acceleration (18 h, entry 5). However, the use of 300 mole% n-Bu$_4$NI along with 30 mole% CuI gave **3** in 91% yield in only 3 h. Lesser amounts of n-Bu$_4$NI (100 and 30 mole%, entries 7 and 8 respectively) still gave a rate acceleration, but to a much lesser extent. Surprisingly, even KI was an effective halide source and rate accelerator, giving 91% of the dialkyne **3** in 4 hr (entry 9). The use of n-Bu$_4$NOTf accelerated the reaction but to a lesser extent. The difference in reactivity between the halides is quite interesting. The definitive rate increase with iodide suggests that the added halide is not simply increasing the ionic strength of the solvent, but instead is forming a more reactive Pd catalyst. Since more iodide is required than for simple complexation to the Pd catalyst (300 mole%), it is presumably stabilizing a hyperreactive Pd catalyst that undergoes oxidative addition to the triflate bond more readily, as suggested by Jutand in the case of chloride.[9] Aryl iodides are not intermediates.

Table 1 Initial Aromatic Enediyne Formation Studies

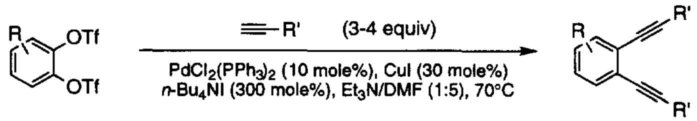


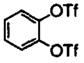
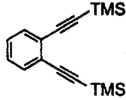
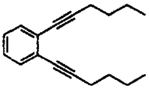
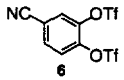
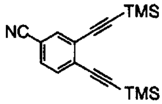
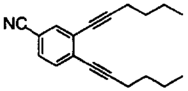
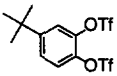
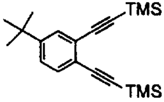
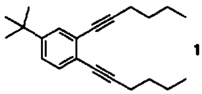
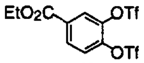
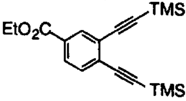
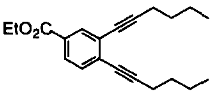
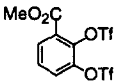
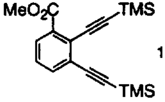
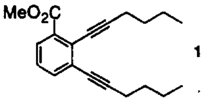
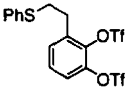
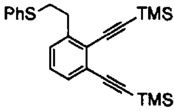
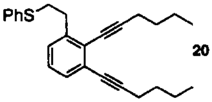
	PdCl$_2$(PPh$_3$)$_2$ (mole%)	CuI (mole%)	Time	Additive	Additive (mole%)	Product[a]
1	10	30	44 hr	none	none	**2/3** 29/71[b]
2	5	20	48 hr	LiCl	300	SM
3	5	20	20 hr	n-Bu$_4$NBr	300	**2** 38%
4	10	20	5 day	n-Bu$_4$NBr	300	**3** 29%
5	10	25	18 hr	n-Bu$_4$NBr	300	**3** 52%
6	10	30	3 hr	n-Bu$_4$NI	300	**3** 91%
7	10	30	5 hr	n-Bu$_4$NI	100	**2/3** 17/83[b]
8	10	30	19 hr	n-Bu$_4$NI	30	**2/3** 41/59[b]
9	10	30	4 hr	KI	300	**3** 91%
10	10	30	17 hr	n-Bu$_4$NOTf	300	**2** 47%, **3** 46%

[a] Yields shown are isolated yields. [b] GC ratio, no SM seen.

A variety of aromatic 1,2-ditriflates were examined under the optimized conditions with both TMS-acetylene and 1-hexyne as coupling partners (Table 2). All ditriflates were prepared from the corresponding catechols with the isolated yields shown,[6b] and are stable at room temperature for months. In all cases, the desired aromatic enediyne was synthesized in respectable yields. Lower yields were observed for 1,2-ditriflates with substituents at the 3-position, presumably due to steric hindrance (entries 5 and 6).[10] The use of KI in place of n-BuN$_4$I improved the yield in one problematic coupling (entry 2). This is not a general trend, however, as the use of KI in entry 5 gave a reduced yield.

Table 2 Examples of Pd-Coupling of Aromatic 1,2-Ditriflates with Alkynes



	Substrate	Yield of Triflate	TMS-acetylene[a] Yield (Rxn Time)	1-Hexyne[a] Yield (Rxn Time)
1	 1	96 %	 3 91% (3 h)	 5 78 % (4 h)
2	 6	83 %	 7 59% (8 h) 80% (3.5 h)[b]	 8 74% (3 h)
3	 9	91 %	 10 77% (8.5 h)	 11 54% (5 h)[c]
4	 12	86 %	 13 67% (8 h)	 14 87% (18 h)
5	 15	88 %	 16 34% (7 h) 13% (17 h)[b]	 17 66% (3 h)
6	 18	81 %	 19 35% (12 h)	 20 23% (12 h)

[a] Yields are isolated yields. All compounds characterized by ^{1}H and ^{13}C NMR, FT-IR, HRMS and/or elemental analysis. [b] KI (300 mole%) was used in place of *n*-Bu$_4$NI. [c] 11% of the 2 possible monocoupled products was also isolated.

Sample Experimental Procedure: A flame-dried screw-cap test tube was charged under Ar with 199 mg (0.447 mmole) ethyl 1,2-(((trifluoromethyl)sulfonyl)oxy)-4-benzoate **12**, 495 mg (1.34 mmole) *n*-Bu$_4$NI, 31 mg (0.0447 mmole) PdCl$_2$(PPh$_3$)$_2$, 26 mg (0.134 mmole) CuI, and 2.5 ml of 1/5 solution of Et$_3$N /DMF that had been degassed by freeze/pump/thaw techniques. After stirring at 25 °C for 5 min, 0.211 mL (1.836 mmole) 1-hexyne was added and the test tube sealed. The yellow solution was stirred in a 70 °C oil bath for 3 hr. After dilution with 50% CH$_2$Cl$_2$/hexanes, the organic layers were washed with 2X deionized H_2O, 1N HCl, brine, and dried over $MgSO_4$. Concentration under reduced pressure and purification by flash chromatography (SiO_2, 30% CH_2Cl_2/hexanes) gave 120 mg (87%) of **14**[11] as a brown oil.

In conclusion, we have developed a new method for the synthesis of aromatic enediynes from aromatic 1,2-ditriflates and alkynes. Iodide salts (300 mole% of either KI or *n*-Bu_4NI) greatly accelerate the Pd-catalyzed coupling reaction. Bromide, chloride, or triflate salts do not show the same rate enhancement.

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10 Best results were achieved by a sequential addition of reagents: Ditriflate, *n*-Bu_4NI, solvent, and $PdCl_2(PPh_3)_2$ were stirred under Ar at rt for 10 min. Then, CuI was added, and the dark brown solution was stirred for another 10 min. Finally, alkyne was added, and the yellow solution was heated in 70 °C oil bath.

11 Characterization data for **14**. R_f 0.50 (10% EtOAc/hexanes); FT-IR 2958, 2933, 2871, 2230, 1722, 1600, 1553, 1464, 1411, 1367, 1297, 1266, 1229, 1103, 1025, 767 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, J = 1.3 MHz, 1 H), 7.82 (dd, J = 1.6, 8.1 Hz, 1 H), 7.41 (d, J = 8.1 Hz, 1 H), 4.36 (q, J = 7.1 Hz, 4 H), 2.48 (t, J = 6.8 Hz, 2 H), 2.47 (t, J = 6.8 Hz, 2 H), 1.62 (quintet, J = 7.4 Hz, 4 H), 1.53 (sextet, J = 7.2 Hz, 4 H), 1.38 (t, J = 7.2 Hz, 3 H), 0.95 (t, J = 7.2 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7, 132.8, 131.7, 130.6, 128.9, 127.9, 126.5, 97.4, 94.9, 79.3, 78.9, 61.1, 30.7, 30.6, 21.9, 19.4, 19.3, 19.2, 14.3, 13.6 (2). HRMS (CI/isobutane) calcd for $[C_{21}H_{26}O_2]^+$ 310.1933, found 310.1942. Anal calcd for $C_{21}H_{26}O_2$: C, 81.24; H, 8.45. Found: C, 80.89; H, 8.32.

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