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Regioselective Coupling Reactions Of Diiodophenol Derivatives

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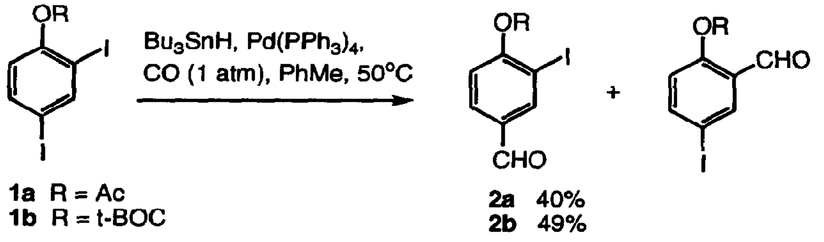
Abstract: The acetate and t-BOC derivatives of 2,4-diiodophenol undergo regioselective palladium catalyzed coupling reactions. The products are those of *para* substitution.

There are many naturally occurring phenols with *ortho* and *para* substituents.[1] The use of palladium catalyzed coupling reactions to attach the substituents is an attractive strategy due to the mild reaction conditions typically involved.[2] This, however, would require an element of selectivity. There are many examples of chemoselectivity: the palladium catalyzed coupling reactions of acid chlorides,[3] iodides[4] or triflates[5] are possible in the presence of bromides and chlorides.

For the synthesis of phenolic compounds, it is advantageous to use the more reactive iodo compounds, rather than the bromo compounds.[6,7] For this strategy to be applied, it was necessary to determine whether regioselective coupling of one iodide in the presence of another was possible. Regioselective palladium catalyzed reactions have been demonstrated for 2,5-dibromopyridine[8], one example of a diiodohistidine derivative[9] and for two kinds of alkenes.[10,11] Diihalopyrimidines can couple selectively depending on the substitution pattern.[12]

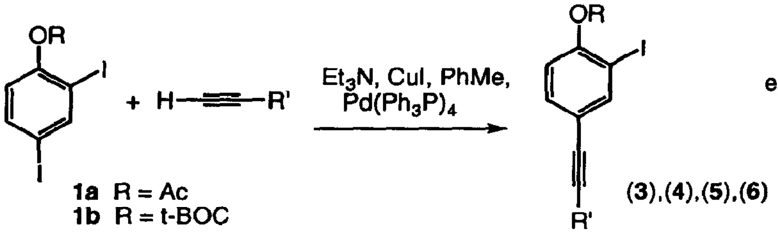
Our experiments involved the acetate of 2,4-diiodophenol (**1a**) [13] and the corresponding t-BOC derivative (**1b**), prepared from 2,4-diiodophenol by the method of Houlihan et al.[14]

Formylation of (**1a**) was carried out by with slow addition of a solution of tributyltin hydride in toluene (syringe pump over 24 hours) under one atmosphere of carbon monoxide in the presence of tetrakis(triphenylphosphine)palladium (0).[15] The major product was the aldehyde (**2a**) as a *ca* 10:1 mixture with its regioisomer in a combined yield of 40% (eq 1). The regiochemistry was determined by nOe experiments and by comparison to authentic material. The t-BOC protected phenol (**1b**) also reacted selectively. In this case, none of the other isomer was detected.



eq. 1

Coupling of either diiodide (**1a**) or (**1b**) with terminal alkynes in the presence of triethylamine and catalytic amounts of tetrakis(triphenylphosphine)palladium (5 mole%) and copper (I) iodide (20 mole%) at room temperature, overnight, proved very successful (eq 2), giving single regioisomers (**3**), (**4**), (**5**) and (**6**) in moderate to excellent yield (table 1). A number of functional groups on the alkyne were tolerated.

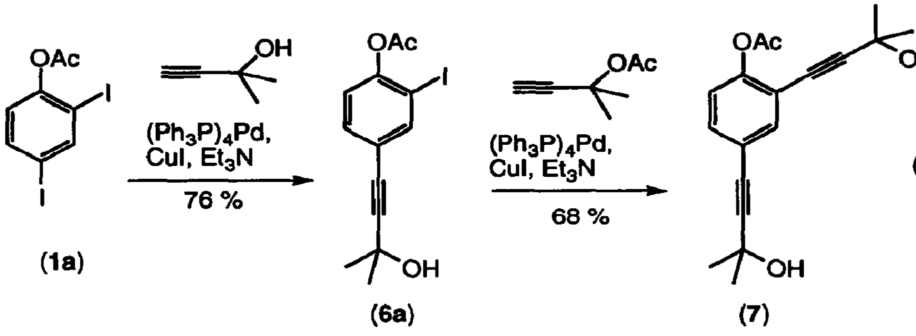


eq. 2

Table 1
Coupling of Diiodides with Terminal Alkynes

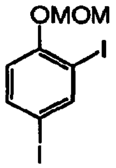
diiodide	R'	product	yield (%)
1a	n-Bu	**3a**	95
1b	n-Bu	**3b**	70
1a	Me_3Si	**4a**	80
1b	Me_3Si	**4b**	50
1a	$BnOCH^2$	**5a**	61
1b	$BnOCH_2$	**5b**	44
1a	$Me_2C(OH)$	**6a**	76

The remaining iodo group is not inert to further coupling reactions (eq. 3). Thus, use of two different alkynes in sequential reactions allows the synthesis of specific isomerically pure aryl diynes, such as (**7**).



(eq. 3)

The regioselectivity is not general for all protected phenols. The MOM phenol derivative (**1c**), to our surprise, underwent coupling with 1-hexyne with little selectivity. A mixture of three products was obtained. These were identified as the *ortho*, *para* and disubstituted products.



1c

Attempts to couple (**1a**) with phenyltrimethyltin, even using Cu(I) catalysis,[5] were unsuccessful. At best, only traces of product were detected. In addition, the Heck reaction of diiodide (**1a**) with methyl acrylate failed entirely. The corresponding 2-alkyl-4-iodo compounds, on the other hand, are known to react.[6]

While the reluctance of some Heck reactions has been attributed to the inhibition of oxidative addition of palladium (0) species to electron-rich aromatic halides,[16] this cannot be true in the present instance as all the reactions described are thought to involve oxidative-addition as the first step.[17] It seems likely that the aryl palladium (II) iodide intermediate does form, but is stabilized sufficiently by the electron donating ring to prevent alkene insertion and Sn/Pd transmetallation but not sufficiently to prevent the presumably more facile Cu/Pd transmetallation and CO insertion reactions. That alkene insertion is the rate determining step in the Heck reaction has been demonstrated by Cabri for the case of aryl triflates reacting with enol ethers.[18]

This work provides an additional example of regioselectivity in palladium catalysis. In addition the chemistry provides some insight into the mechanism of these reactions and allows a new strategy for the synthesis of polysubstituted arenes under very mild conditions.

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