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LETTERS

Iodoarenediazonium Salts : A New Class of Aromatic Substrates for Differential Palladium Catalyzed Reactions

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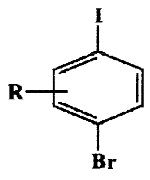
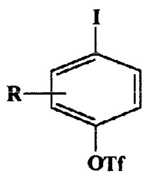
Abstract : By virtue of the superior reactivity of diazonium groups over the iodides in Pd-catalyzed rteactions,iodoarenediazonium salts have been investigated and established as a new class of substrates for differential Heck and cross coupling reactions.

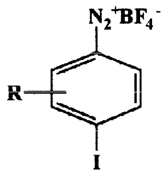
Palladium catalyzed vinylation (the Heck reaction)[1] and cross coupling reactions[2] of aryl halides (Br, I) and triflates continue to flourish as versatile synthetic methodologies in organic synthesis. It is been well known that by virtue of a significant rate difference between the iodides, triflates and bromides (I » OTf ⩾ Br),[3] differential Heck and cross coupling reactions can be carried out on bromoiodoarenes (**I**) and iodoaryltriflates (**II**). However, despite the synthetic potentials that these reactions had promised, differential Pd-catalyzed reactions with **I** and **II** have been sparsely studied and are limited to a few examples of differential Heck reactions on **I**[4] and differential Suzuki or organozinc cross couplings on **II**.[5] While such lack of activity may partly be attributed to the difficulties in preparing regioisomerically pure iodobromoarenes and to the high cost of preparing triflates, the immense potentials of differential Pd-catalyzed reactions in the synthesis of unsymmetrically substituted teraryls and oligioarylenevinylenes having medicinal and NLO properties can hardly be ignored. In course of our investigations on Pd-catalyzed reactions of arenediazonium salts, we had the opportunity to address these issues and with a view to broaden the scope of these reactions, we now introduce the iodoarenediazonium salts (**III**) as a new class of aromatic substrates for differential Heck and cross coupling reactions.



(I)



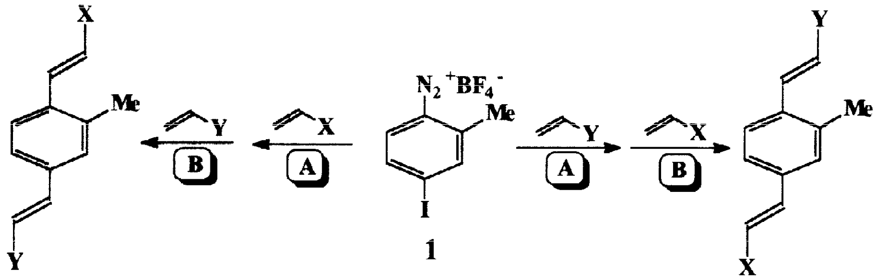
(II)



(III)

PII: S0040-4039(97)10643-8

We[6] and others[7] have already demonstrated the superior reactivity of the diazonium group over bromides in Pd-catalyzed reactions of bromoarenediazonium salts. Our recent results show that a similar trend exists even for iodoarenediazonium salts which prompted us to explore the latter as substrates for differential Pd-catalyzed reactions. Additional impetus was provided by the fact that, in contrast to **I** and **II**, regioisomerically pure iodoanilines (precursors to **III**) are readily available *via* simple iodination of anilines.



1

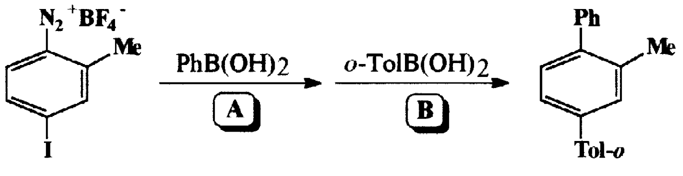
2a (55%)
2b (61%)

a: X = Ph, Y = CO_2Et ; **b**: X = CO_2Et, Y = CN

3a (47%)
3b (55%)

Scheme 1. A 2% Pd(OAc)$_2$, EtOH, 80°; B 2% Pd(OAc)$_2$, NaHCO$_3$, TBAC, DMF, 100°.

The iodoarenediazonium salt **1**, readily derived from *p*-iodo-*o*-toluidine, was chosen as a model substrate for **III**. In the event, differential Heck reaction on **1**, first at the diazonium end (with CH_2=CHX) followed by reaction at the iodide end (with CH_2=CHY) smoothly gave rise to the unsymmetrical *p*-phenylene distyryl derivatives **2a** (55%) and **2b** (61%) in good overall yields.[8] The diagonal regioisomers **3a** (47%) and **3b** (55%) could also be prepared from **1** in good yields, simply by switching the order of the olefins added (**Scheme 1**). Interestingly, both these sequences i.e. **1**→**2** or **1**→**3** can be carried out in "one-pot" in ethanol without any significant loss of overall yields.

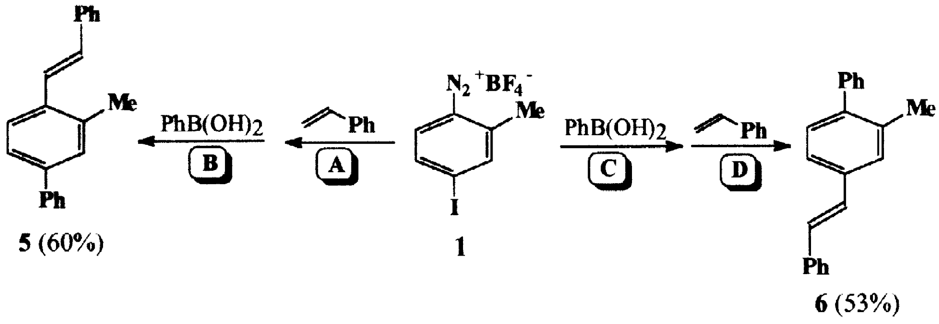


1

4 (40%)

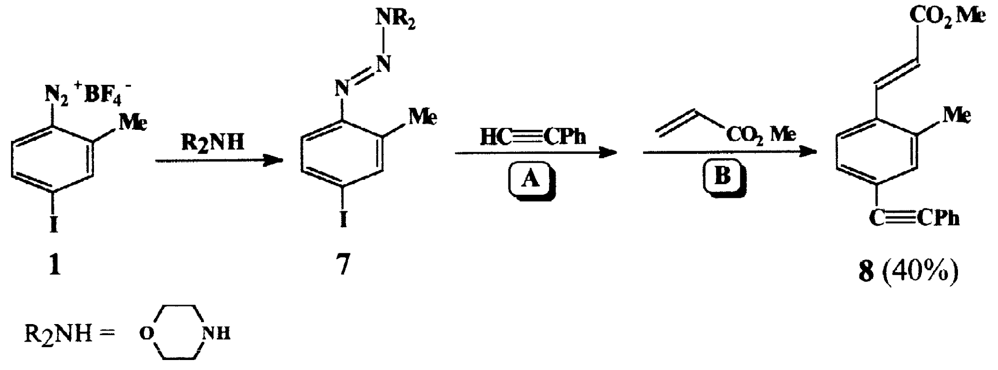
Scheme 2. A 10% Pd(OAc)$_2$, MeOH, 60°; B 5% Pd(OAc)$_2$ Ba(OH)$_2$, EtOH, RT.

Differential cross coupling on **1** with arylboronic acids was carried out as shown in **Scheme 2**. Thus reaction of **1**, first at the diazonium end with PhB(OH)$_2$ followed by coupling at the iodide end with *o*-TolB(OH)$_2$ gave rise to the unsymmetrical teraryl **4** in 40% overall yield. However, problems were encountered in the reverse sequence where steric effects severely affected the yield (15%) of the initial cross coupling of **1** with *o*-TolB(OH)$_2$. Nevertheless, this steric problem stands to be remedied by using $ArBF_3K$ instead of ArB(OH)$_2$ according to a recent Genet-protocol[7b] and hence should in no way undermine the potentials of iodoarenediazonium salts in differential cross coupling reactions.



Scheme 3. A 2% Pd(OAc)$_2$, EtOH, 80°; B 5% Pd(OAc)$_2$, Ba(OH)$_2$, EtOH, RT C 10% Pd(OAc)$_2$, MeOH, 60°; D 2% Pd(OAc)$_2$, NaHCO$_3$, TBAC, DMF, 100°.

Differential Pd-catalyzed reactions on **1** using mixed Heck - cross coupling sequences were also studied. Thus, initial Heck reaction (with styrene) at the diazonium end of **1** followed by cross coupling with PhB(OH)$_2$ at the iodide end produced the *p*-phenylstilbene derivative **5** in 60% yield whereas the reverse sequence yielded the corresponding regioisomer **6** in 53% yield over the two steps (**Scheme 3**).



Scheme 4. A 3% Pd(OAc)$_2$, cat. CuI, Et$_3$N, RT; B 42% HBF$_4$ (2 equivs.), 2% Pd(OAc)$_2$, MeOH, 60° (**ref. 6a**).

A limitation of the synthon **III** arises from the fact that arenediazonium salts do not participate in Sonogashira-type couplings with terminal acetylenes. However, mixed Sonogashira coupling - Heck reaction sequences may be carried out on the iodoaryltriazene **7**,[9] using the iodide trigger, to produce the *p*-vinylated tolan derivative **8** in 40% yield (**Scheme 4**).[10]

In summary, we have shown the synthetic prospects of iodoarenediazonium salts **III** as a new substrate for differential Heck and cross coupling reactions. Moreover, **III** can be attached to a solid support *via* formation of a resin-bound triazene[11] thus providing a new platform for solid-phase synthesis towards building combinatorial libraries of unsymmetrically substituted aromatics. Such options are not available with iodobromoarenes and iodoaryl triflates.

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8. All new compounds gave satisfactory spectral data (IR, NMR) in accordance to the proposed structures.
9. Sonogashira-couplings were found to be more efficient with iodoaryltriazenes than with the corresponding iodoanilines.
10. $Pd(OAc)_2$ (12 mg) was added to a mixture of the triazene **7** (0.40 g, 1.20 mmol), phenyl acetylene (0.15 ml, 1.32 mmol) and CuI (12 mg) in Et_3N (6 ml) and stirred overnight at RT. The reaction mixture was then diluted with CH_2Cl_2 (10 ml) and filtered (Celite). The filtrate was washed thoroughly with water, concentrated and the product (0.305 g) precipitated with pet. ether. The latter, without further purification, was dissolved in MeOH (7 ml) and 42% HBF_4 (0.30 ml, 1.96 mmol) was added to it at 0^o. After 5 min, methyl acrylate (0.2 ml, 1.86 mmol) and $Pd(OAc)_2$ (9 mg) were added and the whole heated under reflux for 45 min. It was then cooled, filtered (Celite) and the filtrate diluted with water and extracted with CH_2Cl_2. Removal of the solvent followed by preparative TLC (10% EtOAc in pet. ether) gave **8** (0.10 g, 40% from **7**); IR: 1710, 1660, 1600, 1310, 1170 cm^{-1}; ^1H NMR (200 MHz): 2.47 (3H, s), 4.29 (3H, s), 6.42 (1H, d, J = 16 Hz), 7.36-7.50 (5H, m), 7.52-7.80 (3H, m), 7.96 (1H, d, J = 16 Hz).
11. See (a) Jones, L., II; Schumm, J. S.; Tour, J. M. *J. Org. Chem.* **1997**, *62*, 1388; (b) Nelson, J. C.; Young, J. K.; Moore, J. S. *ibid* **1996**, *61*, 8160.