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Highly regioselective palladium-catalyzed condensation of terminal acetylenes with 2,5-diiodobenzoic acid

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Abstract

Palladium-catalyzed coupling reactions between terminal alkynes and 2,5-diiodobenzoic acid have been shown to be highly regioselective, giving a rapid and efficient route for the synthesis of disymmetric 2,5-bis ethynyl benzoic acid derivatives. © 1999 Elsevier Science Ltd. All rights reserved.

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Over the last two decades, the palladium-catalyzed reactions of haloarenes with terminal alkenes or alkynes have been demonstrated to be efficient routes for the grafting of carbon chains on aromatic rings.[1,2] Only in some rare cases, regioselective condensation of alkynes with polyhaloarenes were observed. For example, 1,2,3,4-tetrabromobenzene has been regioselectively alkynylated at C1 and C4.[3] The selective monoalkenylation of dihaloarenes with the Heck reaction needs an aryl ring bearing two different halogenes. Iodoaryl are more reactive than bromoaryl which are also more reactive than chloroaryl derivatives, which let selective monoalkenylations of *o*- and *p*-bromoiodobenzene be reported.[4]

In this paper, we report a highly regioselective palladium-catalyzed monoalkynylation of the 2,5-diiodobenzoic acid at C5. When 2,5-diiodobenzoic acid **1** was treated with 1.1 equivalent of trimethylsilylacetylene (TMSA) using the conditions described by Sonogashira (dichlorobis(triphenylphosphine) palladium(II) as catalyst, copper iodide as co-catalyst, in a mixture of tetrahydrofuran (THF) and triethylamine (TEA) at room temperature), the compound **2** resulting from coupling of the *meta*-position was isolated in 73% yield after purification (Scheme 1). No trace of *ortho*-alkynylated product or dialkynylated product **3** was detected and the only other isolated compound was the starting material. Furthermore, **2** appeared to be unreactive towards another equivalent of TMSA in the same experimental conditions[†] (Scheme 1).

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[†] Experimental procedure: TMSA (1.2 equiv.) was added dropwise to a suspension of **1** (1 equiv.), dichloro-

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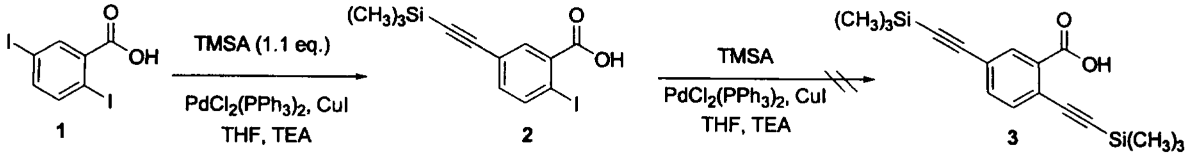
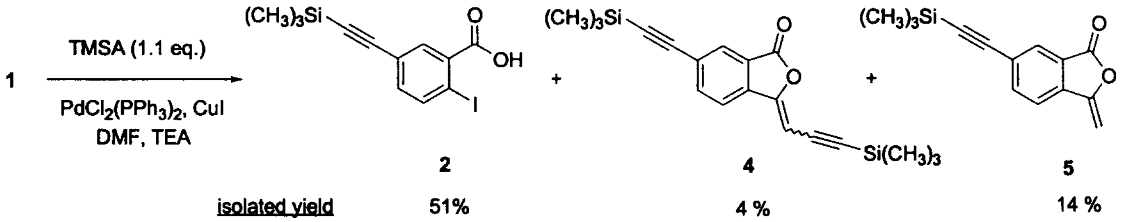


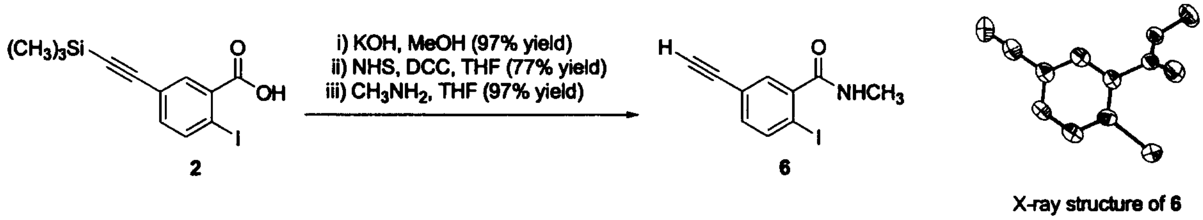
Scheme 1.

This latter result was surprising since it was previously reported that palladium-catalyzed alkynylation can be performed on *o*-iodobenzoic acid to lead to the formation of phtalides[5] or isocoumarins.[6] Pentaphenylethynylbenzoic acid has also been directly prepared through the coupling between phenylacetylene and pentaiodobenzoic acid.[7] However, all these palladium-catalyzed alkynylations were performed in DMSO, in DMF or in acetonitrile. This suggests that the THF/TEA mixture used in our experiments could be an important parameter for the regioselectivity of the condensation of terminal alkynes with 2,5-diiodobenzoic acid. In fact, when these reactions were performed in DMF, the alkynylation of 2,5-diiodobenzoic acid with TMSA was much less selective and we were able to isolate the corresponding phtalide derivatives **4** and **5** (Scheme 2).



Scheme 2.

The regiochemistry of the monoalkynylation of 2,5-diiodobenzoic acid at the *meta* position has been confirmed through the preparation of **6** and the determination of its structure[‡] by single-crystal analysis. Compound **6** was prepared in three steps starting from 2-iodo-5-trimethylsilylethynylbenzoic acid **2** and isolated in 72% overall yield (Scheme 3).



Scheme 3.

The high selectivity observed for the monocondensation of TMSA on 2,5-diiodobenzoic acid only at C5 was specific for the presence of the carboxylic function. When 2,5-diiodo-*N*-methylbenzamide was treated with TMSA by using the Sonogashira conditions mentioned before, 2-iodo-5-trimethylsilanylethynyl-*N*-methylbenzamide and 2,5-bis-trimethylsilanylethynyl-*N*-methylbenzamide

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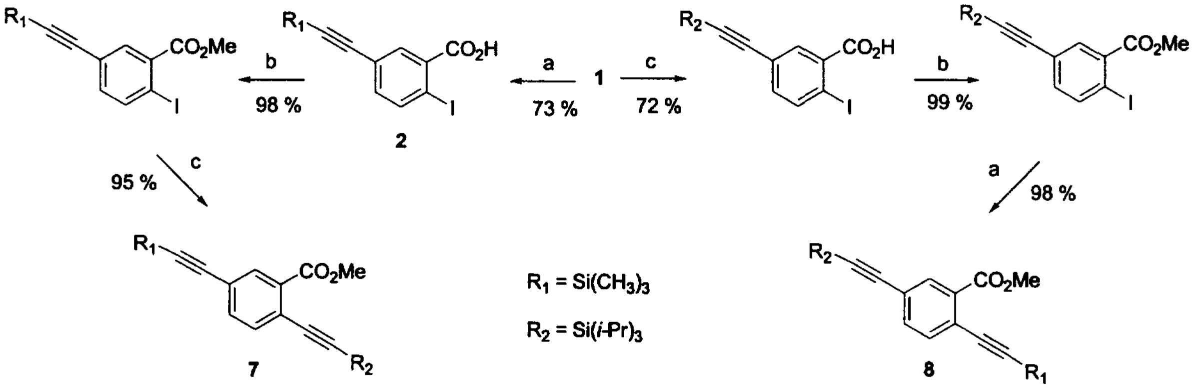
bis(triphenylphosphine) palladium(II) (0.1 equiv.) and copper iodide (0.1 equiv.) in a mixture of THF:TEA (2:1). The reaction was stirred overnight at room temperature then quenched with saturated aqueous NH_4Cl and finally extracted twice with EtOAc. The combined extracts were evaporated in vacuo and the residue purified by SiO_2 chromatography.

[‡] Crystal data for **6**: $C_{10}H_8NOI$, M=285.1, pale yellow crystals, 0.35×0.33×0.23 mm, monoclinic, space group C2/c, a=25.963(3), b=4.9718(5), c=16.363(3) Å, β=102.84(1)°, V=2059.3(5) $Å^3$, Z=8, Dc=1.839 g cm^{-3}, μ (Mo$k\alpha$)=30.36 cm^{-1}, F(000)=1082.

were isolated after purification in 61 and 21% yield, respectively. Similarly, the same reaction performed on 2,5-diiodomethylbenzoate gave a mixture of mono- and bis-alkynylated products. Thus, among all the benzoyl derivatives tested, alkynylation at the *ortho*-position appeared to be prevented only in the case of the 2,5-diiodobenzoic acid. In the THF/TEA mixture as solvent, the carboxylic group of 2,5-diiodobenzoic acid behaves as an intramolecular protective group which prevents palladium-catalyzed alkynylation of the *ortho*-position.

These results allowed the design of a rapid route for the synthesis of disymmetric 2,5-bis ethynyl benzoic acid derivatives.

Such compounds were easily prepared from 2,5-diiodobenzoic acid **1** through a three-step sequence: after a first palladium-catalyzed alkynylation at the *meta*-position (step 1), the esterification of the benzoic acid (step 2) was followed by a second alkynylation performed at the *ortho*-position (step 3). By using this sequential procedure the isomers **7** or **8** were prepared just by reversing the order of the two alkynylation steps (Scheme 4). When **1** was condensed in the first step with TMSA (step 1=conditions in a), **7** was isolated in 68% overall yield. Instead, when **1** was first alkynylated with triisopropylsilylacetylene (TIPSA) (step 1=conditions in c), **8** was obtained in 70% overall yield.



Scheme 4. *Conditions*: (a) TMSA (1.1 equiv.), $PdCl_2(PPh_3)_2$ (5%), CuI (15%), Et_3N, THF at rt for 15 h; (b) MeOH, EDC, HOBT, THF at rt for 15 h; (c) TIPSA (1.1 equiv.), $PdCl_2(PPh_3)_2$ (5%), CuI (15%), Et_3N, THF at rt for 15 h

In summary, palladium-catalyzed condensation of terminal alkynes with 2,5-diiodobenzoic acid only occurs at the *meta*-position (position 5) when reactions are performed in a mixture of THF and TEA. This result provides an efficient, rapid and regiocontrolled route for the preparation of iodophenylacetylene and disymmetric 2,5-bis ethynyl benzoic acid derivatives.

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