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Exploratory Studies on the Reaction Between Iodoarenes and Acetylenes: One-pot, Pd-[Bmim][BF_4] Catalyzed Preparation of Trianisylethylene

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Abstract The reaction between iodoarenes and acetylenes mediated by palladium was studied, showing selectivity changes based on the nature of the substituent. A new, phosphine-, copper-, and amine-free methodology was developed, in which the synthesis of trianisylethylene from 4-iodoanisole and trimethylsilylacetylene was promoted presumably by an N-heterocyclic-carbene derived from an ionic liquid and a palladium salt, using ethanol as the hydrogen source.

Keywords Sonogashira reaction · Hydroarylation · SERM

1 Introduction

Substituted olefins are valuable building blocks in organic synthesis as they constitute the skeleton of oligoenes and enynes present in natural products [1, 2], which show interesting photochemical properties [3, 4]. In a medicinal context, the triarylyethylene pharmacophore possess biological activities in estrogen-dependent disorders like breast cancer, infertility, osteoporosis, CNS, cardiovascular or lipid malfunctions [5, 6].

Compounds of this class like tamoxifen, clomiphene and broparoestrol (Fig. 1) are called Selective Estrogen Receptor Modulators (SERMs). As they are neither estrogen nor hormones, they are considered to be potentially safer than hormone replacement therapy [7], and are now a strategy to prevent osteoporosis and reduce the risk of breast cancer in postmenopausal women [8, 9].

Current approaches to these substituted ethylenes include the hydroarylation reaction mediated by transition metals like copper [10], cobalt [11], iron [12], gold [13, 14], rhodium [15, 16], rhenium [17], platinum [18–20] or palladium [20–27], and metal-free protocols [28].

Our group has been involved in the reaction between haloarenes and acetylenes involving either Sonogashira coupling [29, 30] or tandem Sonogashira coupling-hydroarylation [31] to furnish trisubstituted olefins, and in that case, it was possible to direct the selectivity based on catalyst nature, ligand and solvent properties, also the phosphine-free and ionic liquid promoted reaction were tested (Scheme 1).

Here, we wish to disclose an expansion of our methodology using different halides and acetylenes. For this we have subjected alkynes and halides to our optimized conditions [31] for a tandem reaction involving a Sonogashira coupling followed by hydroarylation using $Pd(OAc)_2$, PPh_3, K_2CO_3 and EtOH as a suitable solvent and hydrogen transfer promoter [32].

2 Results and Discussion

First of all, we have evaluated the reaction between iodobenzene and several acetylenes (Scheme 2). The results are

This paper is dedicated to the memory of Professor Octavio Antunes and his family.

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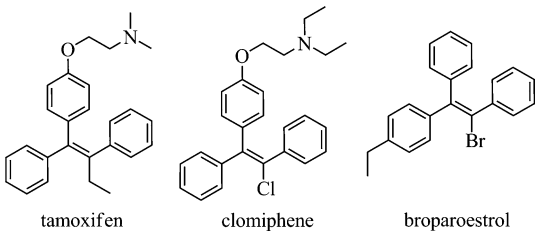
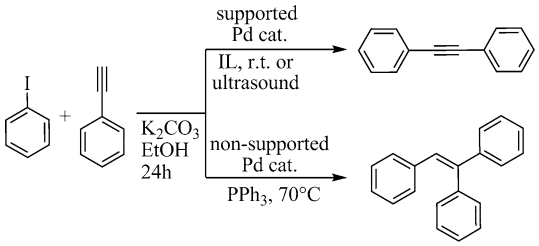
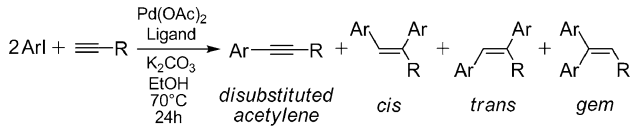


Fig. 1 Structure of SERMs



Scheme 1 Reaction between iodobenzene and phenylacetylene



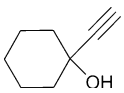
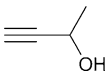
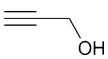
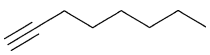
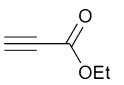
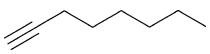
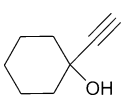
Scheme 2 Reaction between haloarenes and acetylenes

summarized in Table 1, where the three possible isomers of the products are shown.

All experiments involving iodobenzene and alkynes resulted in unreacted iodobenzene in the reaction mixtures. As reactions were conducted in a stoichiometric fashion (1 equivalent of alkynes and 2 equivalents of iodobenzene), the presence of unreacted iodobenzene in reactions like those in Table 1, entries 1, 6, and 7 indicates that conversions were not completed, so disubstituted acetylenes were found. But for the other reactions where no starting alkyne nor disubstituted acetylenes were found, it could indicate that some oligomerization of alkynes took place. Some selectivities did not reach 100% and it was not possible to identify all products formed in reaction mixtures.

As it can be drawn from Table 1, bulky alkynes resulted in better selectivities toward the trisubstituted olefins (entries 1,4,5 vs 2,3). The isomeric mixture of products from the reaction involving but-3-yn-2-ol (entry 2) also showed a fragment at *m/z* 222 revealing the presence of oxidized byproduct (ketone), and this side reaction was already reported elsewhere [33, 34]. But-3-yn-2-ol and 1-ethynylcyclohexanol have already been reported as acetylene surrogates [35], but under our conditions, diphenylacetylene was not detected in reaction mixtures. The reaction involving propargyl alcohol (entry 3) showed

Table 1 Selectivities in reaction between iodobenzene and acetylenes

Entry	Acetylene	Ligand	Selectivity[a] (%)	
			Trisubstituted alkenes	Disubstituted acetylene
1		PPh_3	1/2/67[b]	16
2		PPh_3	0/55/1[c]	–
3		PPh_3	0/13/3	–
4		PPh_3	23/76/1	–
5		PPh_3	1/39/22	–
6		[Bmim][BF_4]	4/22/0	41
7		[Bmim][BF_4]	–	45

[a] Ratios of the three possible isomers were determined by GC/MS

[b] Detection of [M-18] in GC/MS analysis

[c] The other 45% represents the oxidized product

only traces of coupled products together with homocoupling of the halide (1,1′-biphenyl).

In the trisubstituted olefin series, the isomer ratio (i.e.: *cis*, *trans* or *gem* in Tables 1 and 2) was assigned by NMR analysis of crude mixture for entry 2 in Table 1, and the assignment was based by comparison with literature data for the synthesized compounds [36–40]. This analysis revealed the *trans*-isomer (*Z*)-3,4-diphenylbut-3-en-2-ol as the major one, followed by the oxidized byproduct of the reaction (4,4-diphenylbut-3-en-2-one). The ratio *trans*:oxidized product was 1:0.6, which ultimately agreed with the ratio obtained by GC/MS analysis.

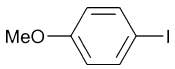
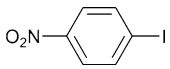
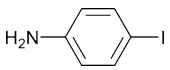
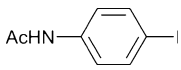
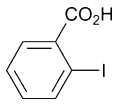
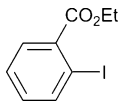
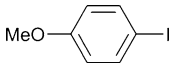
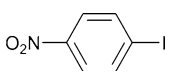
The use of [Bmim][BF_4] acting presumably as a *N*-heterocyclic carbene (NHC) precursor in place of triphenylphosphine (entries 6 and 7) resulted mainly in Sonogashira products. This corroborates our previous results of the role of ligands (PPh_3 vs NHC) in directing the selectivity to a Sonogashira reaction or an hydroarylation [31].

In a second approach, several halides were reacted with phenylacetylene under our optimized conditions (Scheme 2) to afford substituted triphenyletylenes and the results are showed in Table 2.

The reaction of 4-iodoaniline (entry 3) with phenylacetylene resulted in an untreatable mixture of products. 2-Iodobenzoic acid as substate resulted in alkyne homocoupling (1,4-diphenylbuta-1,3-diyne) together with the Sonogashira coupling product. As a general tendency, electron withdrawing groups (EWG) in the haloarene moiety (entries 2 and 6) favoured Sonogahira coupling instead of hydroarylation. The reaction of 1-iodo-4-nitrodobenzene resulted in 11% of 4-nitrostilbene as a byproduct (entry 2).

The reactions employing [Bmim][BF_4] as ligand follow the same tendency described for PPh_3, which is haloarenes substituted with electron releasing groups (ERG) resulting in hydroarylation (entry 7) while EWG-substituted haloarenes furnished Sonogashira product (entry 8). Besides the fact that 4-iodoanisole and 1-iodo-4-nitrobenzene furnished different structural patterns—a triphenylethylene and a diphenylacetylene (Scheme 3)—it was worth to note that

Table 2 Selectivities in reaction between iodoarenes and phenylacetylene

Entry	Halide	Ligand	Selectivity[a] (%)	
			Trisubstituted alkenes	Disubstituted acetylene
1		PPh_3	16/20/47[b]	–
2		PPh_3	–	88[c]
3		PPh_3	–[d]	–
4		PPh_3	–[d]	–
5		PPh_3	–	25[e]
6		PPh_3	<1	9
7		[Bmim][BF_4]	9/38/52	–
8		[Bmim][BF_4]	–	95[f]

[a] Ratios of the three possible isomers were determined by GC/MS

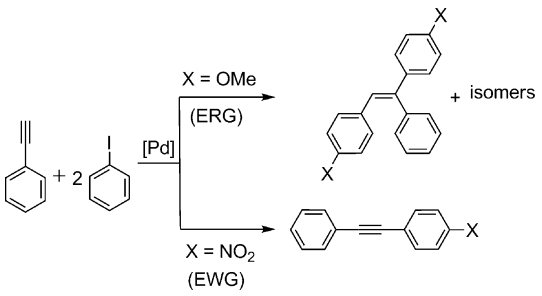
[b] Plus 4% of 4-methoxybenzophenone

[c] Plus 12% of 4-nitrostilbene

[d] Products not detected

[e] Plus 64% of alkyne homocoupling

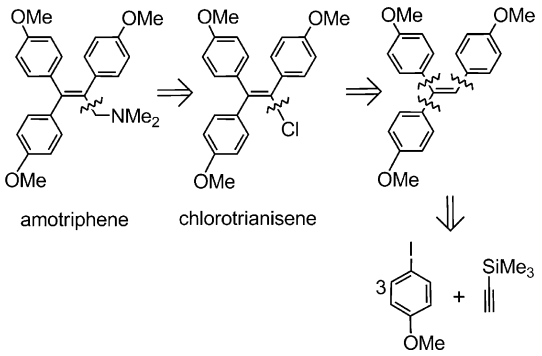
[f] Plus 3% of 4,4′-dinitrobiphenyl



Scheme 3 Reaction between phenylacetylene and ERG or EWG-substituted iodobenzenes

both methodologies under ionic liquid as ligand resulted in cleaner reactions as revealed by GC analysis. The hydroarylation of some hydroxylated internal acetylenes was already reported to proceed in presence of this ionic liquid, but in a system comprising amine and formic acid [34].

The role of [Bmim][BF_4] acting as a ligand in the reaction of 4-iodoanisole prompted us to attempt a new preparation of symmetrically trisubstituted ethylenes. These compounds could be employed in the preparation of chlorotrianisene (TACE®) and amotriphene (Myordil®) following a general retrosynthetic path (Scheme 4).



Scheme 4 Retrosynthetic analysis of amotriphene and chlorotrianisene

Inspired by Wu's results employing trimethylsilylacetylene (TMSA) as an acetylene surrogate [41], we have applied our catalytic system—$Pd(OAc)_2$, K_2CO_3, EtOH and stoichiometric halide—to this reaction in substitution of Wu catalytic system—$Pd(OAc)_2$ or $Pd(PPh_3)_4$ or $Pd_2(dba)_3$, sodium methoxide, dry methanol and five equivalents of halide. For the reaction between 4-iodoanisole and TMSA to furnish trianisylethylene, the conversions and selectivities were evaluated and the results are illustrated in Table 3.

Due to volatility of TMSA (b.p. 53 °C) the experiments were conducted in a sealed tube under argon atmosphere. Initially, we have screened the reaction in presence of triphenylphosphine, showing that 3 days resulted in better conversion than 1 day (entries 1 vs 2). However, as the current synthetic methodologies developed in our laboratory avoid toxic, expensive and moisture sensitive phopshines, we have tried both a ligand-free and a system containing [Bmim][BF_4] as pre-ligand, and the latter showed better conversion (entries 3 vs 4).

Based on our proposed mechanism of a tandem Sonogashira coupling-hydroarylation reaction, which would comprise at least three equivalents of added base, and together with Wu uses of five equivalents of CH_3ONa, we have screened the reaction employing 6 equivalents of base resulting in better conversions (entries 4 vs 5).

Lowering the Pd content from 5 to 1 mol% or the reaction time from 3 to 1 day resulted in lower selectivities (entries 5 vs 6 and 5 vs 7) with traces of the intermediate 1,2-bis(4-methoxyphenyl)ethyne (the Sonogashira product).

Attempts to use less expensives but-3-yn-2-ol or 1-ethynylcyclohexanol as acetylene surrogates [42] in substitution of TMSA did not succeed, only starting material being recovered, which was attributed to the lower reactivity of these acetylenes compared to the silylated one.

A mechanistic pathway for this kind of reaction was proposed by Wu [42] and by us [31] and comprised a

Table 3 Conversions and selectivities in reaction between 4-iodonisole and trimethylesilylacetylene

Entry	Ligand	Time (days)	Amount of base (eq.)	Amount of Pd cat. (mol%)	Conversion[a] (%)	Selectivity[a] (%)
1	PPh_3	1	2	5	89	97
2	PPh_3	3	2	5	>99	>99
3	–	3	2	5	17	74
4	[Bmim][BF_4]	3	2	5	52	>99
5	[Bmim][BF_4]	3	6	5	>99	>99
6	[Bmim][BF_4]	3	6	1	>99	92[b]
7	[Bmim][BF_4]	1	6	5	>99	98[c]

[a] Conversions and selectivities were determined by GC/MS

[b] Plus 7% of Sonogashira product 1,2-bis(4-methoxyphenyl)ethyne

[c] Plus 2% of Sonogashira product

Sonogashira coupling to furnish aryl-trimethylsilyl acetylene, a sila-Sonogashira coupling to furnish diarylacetylene, and finally an hydroarylation of the diarylacetylene with iodoarene to furnish triarylethylene. In this case EtOH serves as a source of hydrogen, and acetaldehyde is released.

Purification of trianisylethylene by flash chromatography using silica gel or preparative TLC using alumina resulted in considerable degree of degradation of the product.

3 Conclusion

We were able to prepare trianisylethylene in a one step procedure from 4-iodoanisole and trimethylsilylacetylene. To the best of our knowledge, this is the first one-step, copper-, phosphine- and amine-free, presumably NHC promoted preparation of trianisylethylene allowing a formal synthesis of chlorotrianisene and amotriphene. Also, our methodology uses readily available ethanol as a source of hydrogen for the hydroarylation, which is safer than the recently presented TFA mediated protocols [28, 42]. The functionalization of triarylethylenic core of antiestrogenic compounds will be subject of a forthcoming manuscript.

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