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Arylation of aryl chlorides, a convenient method for the synthesis of new potential triazolic fungicides

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ABSTRACT

We evaluated two alternative routes for the arylation of known chlorinated fungicides. The first pathway involved a $S_{RN}1$ substitution, followed by Stille reaction, while the second consisted in a one step reaction by the Suzuki coupling. Both methodologies were useful to obtain new products that could be potential fungicides.

1. Introduction

Triazoles have been widely used as fungicides in different countries, controlling fungi, such as *Septoria tritici* or *Gibberella zeae*.[1] The triazolic plant protection fungicides include 1-(4-clorofenoxi)-3,3-dimetil-1-(1*H*-1,2,4-triazol-1-il) butan-2-one (triadimefon®) (**1**) and 1-(4-chlorophenyl)-3-cyclopropyl-2-(1*H*-1,2,4-triazol-1-yl)butan-1-ol (cyproconazole®) (**2**). Triadimefon® and cyproconazole® are chlorinated triazolic analogs, relatively stable under natural conditions, which have become prominent pollutants for soils and aquatic systems. These azoles are systemic, having a broad antifungal spectrum. Systemic azoles inhibit cytochrome P-450 enzymatic system as well as fungal 1,4-α-demethylase, avoiding the synthesis of ergosterol and, thus, decreasing the viability of the fungal cell.[2] The inhibition of demethylase involves the bind of the heme iron atom, belonging to ferric cytochrome P450, to the nitrogen-4 of triazolic compounds, which constitutes the active site of the molecule. In order to produce new fungicides, less toxic to the environment, we decided to investigate two alternative routes for the arylation of triadimefon or cyproconazole, substituting the chloride atom but retaining the triazole ring and, thus, keeping potential bioactivity of new synthetic products.

Many cross-coupling reactions are palladium-catalyzed reactions, involving the formation of a new C–C bond, which are of great importance in organic chemistry.[3] The initiation step of these cross-coupling reactions involves the assembling of two molecules to the metal, via the formation of metal–carbon bonds. In the next step, these carbon atoms couple between them, leading to the formation of a new carbon–carbon single bond. These reactions are catalyzed by zerovalent palladium and can utilize an arylhalide (ArX) as the electrophilic coupling partner. The nucleophilic coupling partner can be an organometallic compound, namely Ar′M, where M is typically zinc, boron or tin (Eq. 1).

$$\overset{\text{electrophilic partner}}{ArX} \quad + \quad \overset{\text{nucleophilic partner}}{Ar'M} \xrightarrow{Pd(0)} Ar\text{-}Ar' \qquad (1)$$

M= zinc, *Negishi reaction*
M= boron, *Suzuki reaction*
M= tin, *Stille reaction*

These reactions begin generating an organopalladium complex ArPdX, arising from the reaction between the arylhalide and Pd(0). The insertion of palladium in a C–Cl bond requires high energy, which leads to slow initiation steps when aryl chlorides are used,[4] requiring special conditions to get good synthetic results.[5] Several advances have been reported to this respect. Buchwald studied inactive aryl chlorides (neutral or electron rich)[6] by Suzuki reactions for the first time. A study of Littke and Fu proposes a general method by the cross-coupling of aryl chlorides using Pd/$P(^{t}Bu)_3$. However, some aryl chlorides require the use of special

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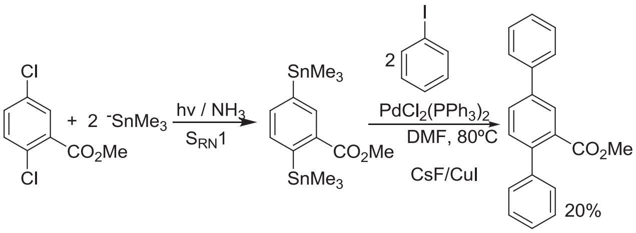
ligands for these reactions.[7] Moreover, electron deficient aryl chlorides react with arylboronic acids.[8] Also, non-active aryl chlorides require using sterically hindered phosphine ligands for these reactions.[3b,9]

One alternative way for substrates having non-reactive chlorides for the Stille reaction may be using stannyl derivatives, since stannyl compounds are good substrates in these reactions.[10] The reaction of $^{-}SnMe_3$ ions with aryl chlorides, by unimolecular Radical Nucleophilic Substitution ($S_{RN}1$),[11] is important to synthesize these stannyl intermediates. A sequence of $S_{RN}1$, followed by a cross-coupling reaction (Stille type) has been developed to obtain polyphenylated compounds as shown in Eq. 2.[12] It is also known that some organostannane compounds have also antifungal activities.[13]



(2)

Our main goal was to synthesize novel environmentally friendly fungicides. Therefore, we decided to investigate the dechlorination of chloro-fungicides in two different ways. In the first approach, we studied a sequence of $S_{RN}1$ followed by a Stille cross-coupling reaction, catalyzed by Pd(0). This methodology involves two steps, with the first providing a simple method for the preparation of compounds bearing trimethylstannyl groups. The second approach consists of a simple and efficient one step procedure for the Suzuki coupling of chloro-fungicides with organoboron compounds.

2. Results and discussion

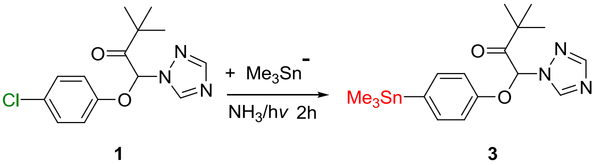
2.1. Tandem reactions: $S_{RN}1$ followed by Stille

Reactions of triadimefon (**1**) and cyproconazole (**2**) with Me_3Sn^{-} gave organostannanes as substitution products through the $S_{RN}1$ mechanism. These stannanes were used as intermediates in Stille reactions, providing arylated products. For instance, the photostimulated reaction of **1** with $^{-}SnMe_3$ ions afforded 36–77% yields of the substitution product (**3**), using liquid NH_3 as the solvent (Eq. 3) (Table 1 entries 1–3). This reaction was catalyzed by light and inhibited by inhibitors of $S_{RN}1$ reactions,[11] such as *p*-dinitrobenzene (*p*-DNB) (Table 1 entries 4 and 5).

Table 1
Reactions of triadimefon (**1**) and cyproconazole (**2**) with $^{-}SnMe_3$ ions in liquid ammonia

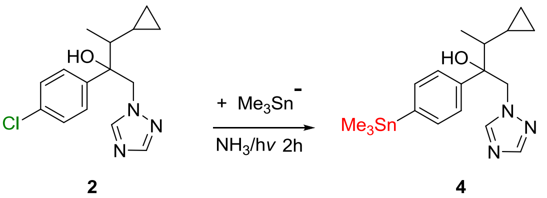
Entry	Substrate (10^{-3} M)	Nucleophile (10^{-3} M)	Conditions (min)	Cl^{-a} %	Yield of isolated product
1	**1** (2.0)	$^{-}SnMe_3$ (2.6)	$h\nu$ (60)	55	**3**, 36[b]
2	**1** (2.0)	$^{-}SnMe_3$ (6.0)	$h\nu$ (90)	100	**3**, 77[b]
3	**1** (2.0)	$^{-}SnMe_3$ (6.0)	$h\nu$ (180)	100	**3**, 77
4	**1** (2.0)	$^{-}SnMe_3$ (6.0)	Dark (180)	—	—[c]
5	**1** (2.0)	$^{-}SnMe_3$ (6.0)	$h\nu$[d] (90)	10	—[c]
6	**2** (2.0)	$^{-}SnMe_3$ (6.0)	$h\nu$ (90)	100	**4**, 98
7	**2** (2.0)	$^{-}SnMe_3$ (6.0)	Dark (90)	10	—[c]
8	**2** (2.0)	$^{-}SnMe_3$ (6.0)	$h\nu$[e] (90)	—	—[c]

[a] Chloride ions were determined by potentiometry.
[b] 5–10% chlorophenol was observed.
[c] Substrate was recovered.
[d] With 30% *p*-DNB added.
[e] With 20% *p*-DNB added.



(3)

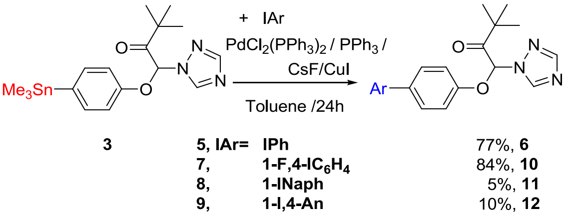
In the same way, the photostimulated reaction of **2** with $^{-}SnMe_3$ ions afforded 98% yields of the substitution product (**4**), using liquid NH_3 as the solvent (Eq. 4) (Table 1 entry 6). This reaction was also light catalyzed and inhibited with *p*-DNB (Table 1 entries 7 and 8).



(4)

The stannanes synthesized in Eqs. 3 and 4 are stable organometallic compounds in addition to good nucleophilic coupling partners through Stille reactions, using mild reaction conditions. The Stille reaction has been used as an alternative to the Negishi and Suzuki reactions for substrates with sensitive functional groups. However, the toxicity of organotin compounds has limited their industrial use.

The reaction of **3** with iodobenzene (**5**) and $PdCl_2(PPh_3)_2$ as catalyst in DMF did not occur, showing decomposition of **3** in this solvent (Table 2, entry 1). Nevertheless, using toluene, the coupling reaction was observed. Moreover, the reaction was increased using PPh_3 as ligand, providing 77% yield of **6** (Eq. 5) (Table 2, entries 2–4).



(5)

Table 2
Stille cross-couplings of **3** with iodobenzene catalyzed by $PdCl_2(PPh_3)_2$ during 48 h[a]

	Catalyst	Ligand	Additive	Solvent	Yield of **6** (%)
1	5 mol % $PdCl_2(PPh_3)_2$	—	CsF, CuI	DMF[b]	—[c]
2	10 mol % $PdCl_2(PPh_3)_2$	—	CsF, CuI	Toluene[d]	5%[e]
3	30 mol % $PdCl_2(PPh_3)_2$	—	CsF, CuI	Toluene[d]	7%[e]
4	10 mol % $PdCl_2(PPh_3)_2$	40 mol % PPh_3	CsF, CuI	Toluene[d]	77%[f]

[a] Concentrations of substrate and nucleophile were 6.0 10^{-2} M.
[b] The reaction was carried out at 80 °C.
[c] Only substrate decomposed.
[d] Reactions were carried out at 100–110 °C.
[e] Only product observed by GC trace with respect to substrate.
[f] Isolated yield.

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