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THE PALLADIUM-CATALYZED CROSS-COUPLING REACTIONS OF 3-CHLORO-4-HALOGENO-1,2,5-THIADIAZOLES

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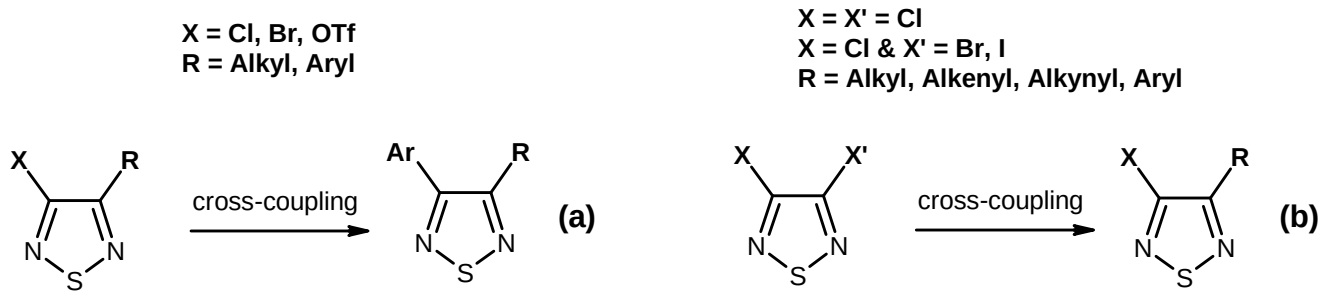
Abstract – 3,4-Dichloro- and 3-chloro-4-halogeno-1,2,5-thiadiazoles (halogeno-: bromo- and iodo-) are involved in Pd-catalyzed cross-coupling reactions under Stille and Suzuki conditions. As a result, by using the commercially available 3,4-dichloro-1,2,5-thiadiazole as substrate, several 3-alkyl-, 3-alkenyl-, 3-alkynyl- and 3-aryl-4-chloro-1,2,5-thiadiazoles can easily be prepared. However, these reactions through direct desymmetrization of the 3,4-dichloro-1,2,5-thiadiazole always occur with side-reactions resulting from the concurrent decomposition of the heterocyclic ring of the starting material. These problems are resolved by involving, in these Pd-catalyzed cross-coupling reactions, the more reactive and selective 3-bromo-4-chloro- and 3-chloro-4-iodo-1,2,5-thiadiazole. These new dihalogeno-1,2,5-thiadiazoles can easily be prepared, *via* diazotization reaction followed by halogen substitution, from the 3-amino-4-chloro-1,2,5-thiadiazole.

INTRODUCTION

Although highlighting the relevance of 1,2,5-thiadiazole derivatives in several areas such as polymer chemistry and material science, it is obvious that this typical heterocyclic moiety can be incorporated into the structure of compounds that display a wide range of biological activities.[1] In most cases, the active compounds correspond to unsymmetrical 3,4-disubtituted 1,2,5-thiadiazoles. In order to get access to all these derivatives the involvement of different synthetic approaches is required.[2] In addition, it is well-known that many of these synthetic methods use hazardous, corrosive and highly toxic reagents.[1,2] Recently, an innovative method for the synthesis of 3-alkyl-4-aryl- and unsymmetrical 3,4-diaryl-1,2,5-thiadiazoles, involving the Stille reaction, has been reported (Scheme 1a).[3] This type of Pd-catalyzed cross-coupling reaction, involving as substrates 3-alkyl- and 3-aryl-4-halogeno- (halogeno-: chloro- and bromo-) 1,2,5-thiadiazoles, and their corresponding 4-triflate analogues, has not so far been

applied on the more versatile substrates, i.e. the symmetrical and unsymmetrical 3,4-dihalogeno-1,2,5-thiadiazoles (Scheme 1b).[4]

Scheme 1



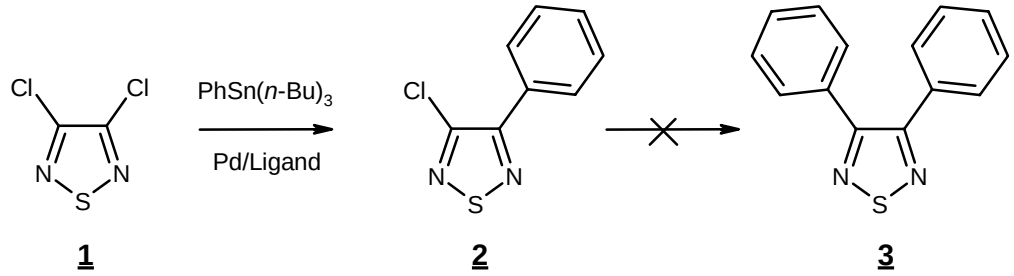
In this paper, we report the use of 3,4-dichloro-1,2,5-thiadiazole as substrate in both Stille and Suzuki reactions.[5,6] These methods make it possible to quickly prepare 3-alkyl-, 3-alkenyl-, 3-alkynyl- and 3-aryl-4-chloro-1,2,5-thiadiazole key intermediates. Additionally, in order to circumvent the problems resulting from the occurrence of a competitive degradation of the 3,4-dichloro-1,2,5-thiadiazole starting material, a more productive alternative using the new 3-chloro-4-halogeno-1,2,5-thiadiazoles (halogeno-: bromo- and iodo-) is proposed.[7]

The readily commercially available 3,4-dichloro-1,2,5-thiadiazole has been tentatively used as starting material in many nucleophilic substitution reactions. However, the intrinsic reactivity of this dichloro-substituted heterocycle (isoelectronic to the pyrazine heterocyclic nucleus) is suffering from major selectivity issues: susceptibility of the endocyclic sulfur atom to a nucleophilic attack and lack of control over the reactivity of the second chlorine atom. For example, under reaction of lithium and sodium amides or of lithium 2-(trimethylsilyl)acetylide, the only product still bearing the heterocyclic nucleus, corresponds to the symmetrical disubstituted 1,2,5-thiadiazole in very low yield (about 4%).[8] In these two reported cases, the authors claim that the main side-reaction, occurring by nucleophilic attack on the heterocyclic sulfur atom, leads by ring opening, essentially to degradation products. In contrast, a unique but very productive case is reported for the preparation of 3-chloro-4-(*N*-morpholino)-1,2,5-thiadiazole.[9] This key intermediate for the synthesis of the potent β-adrenergic blocking agent timolol, is prepared by reaction of morpholine on the 3,4-dichloro-1,2,5-thiadiazole with an almost quantitative yield (97%). These conflicting results might be explained by selectivity differences related to the multi-center reactivity of the 3,4-dichloro-1,2,5-thiadiazole heterocycle.

RESULTS AND DISCUSSION

Despite these apparent contradictory results, we anticipate in the context of the Pd-catalyzed cross-coupling using as substrate the strong electron-deficient heterocycle 3,4-dichloro-1,2,5-thiadiazole, that the presence of two chlorine atoms will, *via* their synergistic electron withdrawing effects, enhance the reactivity of the first chlorine involved in the reaction. After this step, the reactivity of the second chlorine still present on the resulting product (**2**) is reduced to such a level that the consecutive cross-coupling reaction could be avoided (Scheme 2). In addition, involvement of highly selective reagents such as stannane or boronic acid derivatives should favor selectivity for the first chlorine and also decrease the probability of nucleophilic attack on the heterocyclic sulfur atom.

Scheme 2



1 **2** **3**

Preliminary trials have been performed by reaction of 3,4-dichloro-1,2,5-thiadiazole (**1)** with tributylphenyl stannane (**I**) in the presence of several Pd-catalysts and in various solvents.[10] Generally, the use of tetrakis(triphenylphosphine)palladium(0) as catalyst provides the best results (Table 1). When the reaction proceeds, its advancement is limited by some side-reactions, with formation of benzonitrile and triphenylphosphine sulfide as by-products (Scheme 3).

These data show that the 3,4-dichloro-1,2,5-thiadiazole (**1)** can be used as substrate in the Pd-catalyzed cross-coupling reaction with tributylphenyl stannane (**I**), by yielding the 3-chloro-4-phenyl-1,2,5-thiadiazole[11] (**2)** without occurrence of the consecutive reaction leading to 3,4-diphenyl-1,2,3-thiadiazole[12] (**3)**. Involvement of Pd-catalysts lacking phosphinic ligands (Runs *10*, *11*) does not allow the cross-coupling reaction to proceed. Involvement of Pd-catalysts bearing bidentate phospinic ligands (Runs *7*, *8*, *9*) and use of aprotic polar solvents (Run *4*) are ineffective. When using the readily available tetrakis(triphenylphosphine)palladium(0), it is possible, by portionwise addition of the catalyst, to get yields close to 50% (Runs *5*, *6*). Under these conditions, the unwanted 3,4-diphenyl-1,2,3-thiadiazole (**3)** could not be detected (< 1-2%). This is in accordance with the important difference

in reactivity between the 3-chloro- and 3-bromo-4-phenyl-1,2,5-thiadiazole used in the synthesis of the 3-(4-chlorophenyl)-4-phenyl-1,2,5-thiadiazole (7% and 89% yields respectively), as reported by Hanasaki.[3]

Table 1.

Trials using Stille approach in the cross-coupling on substrate (**1)** with reagent (**I)**.

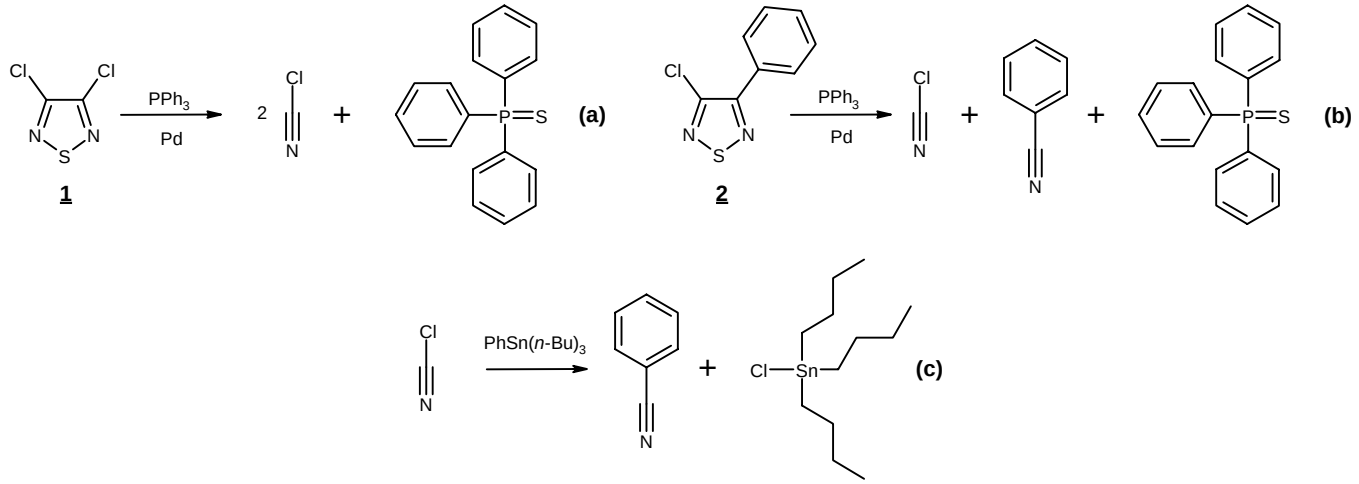
Run	Catalyst	mol %	Solvent[(a)]	**2**[(b)]	PhCN[(b)]	Ph_3PS[(b)]
1	$Pd(Ph_3P)_4$	5	Toluene	25	*nd*	*nd*
2	$Pd(Ph_3P)_4$	10	Toluene	35	*nd*	*nd*
3	$Pd(Ph_3P)_4$	5	Dioxane	28	*nd*	*nd*
4	$Pd(Ph_3P)_4$	5	DMF	14	*nd*	*nd*
5	$Pd(Ph_3P)_4$	8[(c)]	Dioxane	45	*nd*	*nd*
6	$Pd(Ph_3P)_4$	7.5[(d)]	Toluene	48	37.5	17.5
7	$Pd(dppe)Cl_2$	10	Dioxane	0	*nd*	*n/a*
8	$Pd(dppf)Cl_2$	10[(e)]	Toluene	19	17	*n/a*
9	Pd(dppf)	6.5[(f)]	Toluene	11	21	*n/a*
10	$Pd(CH_3CN)_2Cl_2$	10	Dioxane	0	0	*n/a*
11	$Pd_2(dba)_3$	2.5[(g)]	Toluene	0	3.5	*n/a*

[(a)] reflux under N_2 [(b)] HPLC assay (mol %) [(c)] 4% + 4% at 24 h [(d)] 5% + 2.7% at 8 h. [(e)] 5% + 5% at 6 h [(f)] $Pd(dppf)Cl_2$ + BuLi (–78°C) [(g)] corresponds to 5% Pd.

nd: not determined, *n/a*: non-applicable.

However, our method is hampered by the desulfurization side-reactions of the 1,2,5-thiadiazole nucleus. This degradation might, in theory, affect either the starting material (**1)** (Scheme 3a) or its resultant product (**2)** (Scheme 3b).[13] Depending upon which mechanism or pathway is involved, either two or one equiv of cyanogen chloride is formed. However, since cyanogen chloride is then able to react in the next step (Scheme 2c) with tributylphenyl stannane (**I**), the overall balance of the reaction corresponds to two equiv. of benzonitrile for one equiv. of triphenylphosphine sulfide (Run *6*). In theory, it cannot be excluded that the first or second degradation pathway alone or both degradation pathways together can be involved. These side-reactions affect not only the stoichiometry of reactants and products, but by consuming both phosphine and palladium also block the catalytic cycle. It is therefore not surprising that the best results have been obtained by portionwise addition of the catalyst (Runs *5*, *6*).

Scheme 3



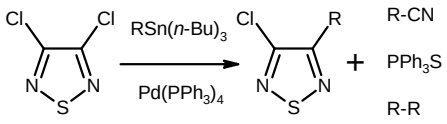
In this context some control experiments have been done. On one hand, the stability of the 3,4-dichloro-1,2,5-thiadiazole (**1)** was assessed, in the presence of either palladium or triphenylphosphine alone or in the presence of both catalytic components. On the other hand, the stability of the 3-chloro-4-phenyl-1,2,5-thiadiazole (**2)** was assessed in the presence of tetrakis(triphenylphosphine)palladium(0). These stability data show that the 3-chloro-4-phenyl-1,2,5-thiadiazole (**2)** is much more stable than the 3,4-dichloro analogue (**1)**. The 3,4-dichloro-1,2,5-thiadiazole (**1)** displays a relative instability against each catalytic component alone, but is far more unstable in the presence of both catalytic ingredients (Ph_3P < Pd <<< Pd/Ph_3P). As the decomposition pathway occurs competitively the overall yield in expected product reach about the 50%. The mass balance accounts in this case for 102-103%, when taking into account unreacted 3,4-dichloro-1,2,5-thiadiazole (**1**), 3-chloro-4-phenyl-1,2,5-thiadiazole (**2**) and either benzonitrile or triphenylphosphine sulfide taken either as 2 or 1 equiv. respectively (see Experimental : 3-chloro-4-phenyl-1,2,5-thiadiazole: 1st example).

This method was then generalized by using a series of commercially available stannane reagents [RSn(*n*-Bu)$_3$] permitting access to a family of 3-chloro-4-substituted 1,2,5-thiadiazoles as illustrated in Scheme 4. This family of 3-chloro-4-substituted 1,2,5-thiadiazoles[14] includes phenyl (**2**), pyrid-3-yl (**4**),[15,16] furan-2-yl (**5**), thiophen-2-yl (**6**), vinyl (**7**), 1-ethoxyvinyl (**8**), phenylethynyl (**9**) and allyl (**10**) 4-substituted derivatives (Scheme 4).

As shown in Table 2, the *in situ* yields vary from 35 to 60%. Here also, as in the example related to compound (**2**) (Scheme 3), similar side-reactions have been observed. In each case, occurrence of the corresponding nitrile (R-CN) has been demonstrated (by comparison with an authentic reference) or evaluated (unstable or volatile) on the basis of the degree of conversion. Accordingly, both the triphenylphosphine sulfide and the nitrile (1 equiv. Ph_3PS vs. 2 equiv. R-CN) were formed as expected.

However, in some cases significant amounts of stannane homo-coupling (R-R) by-products have also been observed. For example 3,3'-bipyridine and 1,4-diphenylbutadiyne homo-coupling by-products have been found in the synthesis of compounds (**4)** and (**9)**. Generally, as in the case of (**2)** (Scheme 2), no detectable amounts of the symmetrical 3,4-disubstituted 1,2,5-thiadiazole by-product could be observed. In this context, as an alternative to the Stille approach, the Suzuki cross-coupling using 3,4-dichloro-1,2,5-thiadiazole was tested for the synthesis of 3-chloro-4-phenyl-1,2,5-thiadiazole (**2)** and 3-chloro-4-(pyrid-3-yl)-1,2,5-thiadiazole (**4)**. For this purpose, phenylboronic acid (**II**) and diethyl(3-pyridyl)borane (**III**) or 3-pyridylboronic acid[17] (**IV**) were involved as reagents under different catalyst, base and solvent conditions.[18]

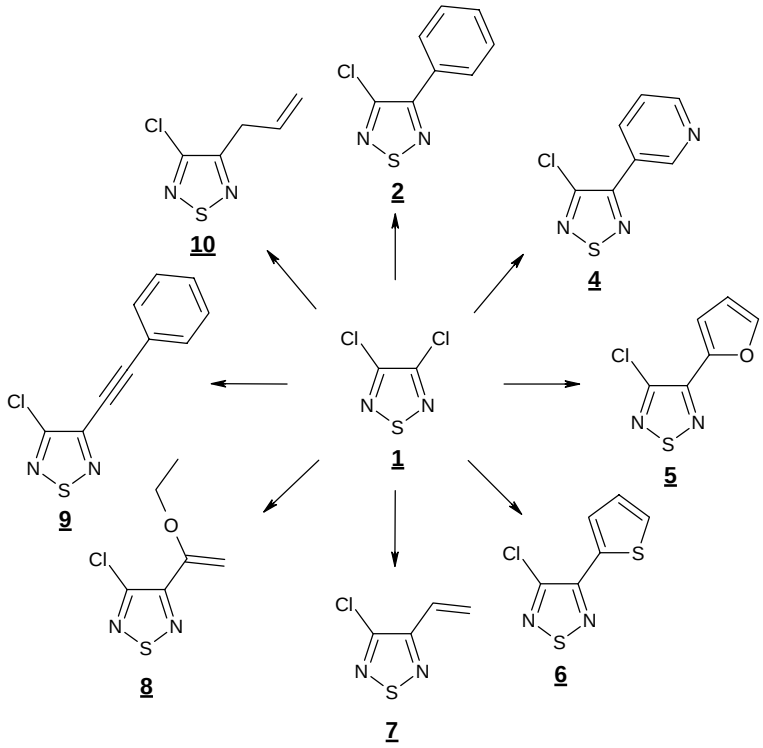
Scheme 4



3-Chloro-4-substituted 1,2,5-thiadiazoles

Run	Compd	Catalyst[(a)] mol %	Assay[(b)] mol %	Yield[(c)] %
1	**2**	5+2.5	48	-
2	**4**	7.5+4.5	38	-
3	**5**	5+1.6	60	*(51)*
4	**6**	5+1.6	54	*(47)*
5	**7**	5+2.2	35	*(31)*
6	**8**	5+2.5	55	*(42)*
7	**9**	5+2.5 +2.5	38	*(28.5)*
8	**10**	5+2.5+2.5	60	*(31)*

[(a)] 2 or 3 successive additions [(b)] HPLC [(c)] isolated



As shown in Table 3, the best conditions for the synthesis of 3-chloro-4-phenyl-1,2,5-thiadiazole (**2)** require the use of tetrakis(triphenylphosphine)palladium(0) as catalyst and potassium fluoride as base in a biphasic toluene-water mixture (Run *3*). The traditional Suzuki conditions using potassium carbonate as base were found to be less productive (Runs *1*, *2*). Other conditions using cesium fluoride as base do not bring any improvement (Runs *4*, *5*). Interestingly, the isolated 56% yield of compound (**2)** (Run 3) is even higher than that measured *in situ* under the best conditions in the Stille approach (Table 1, Run *6*). In contrast, similar conditions applied for the synthesis of 3-chloro-4-(pyrid-3-yl)-1,2,5-thiadiazole (**4)** with involvement of two different Suzuki reagents were found to be rather unproductive (Runs *6*, *7*, *8*). Finally, in addition to the lack of general conditions applicable with this cross-coupling method, side-reactions

similar to these observed in the previous approach (Scheme 3) could not be avoided in this alternative.

Table 3.

Trials using the Suzuki cross-coupling on substrate (**1)** with reagents (**II**, **III** and **IV)**.

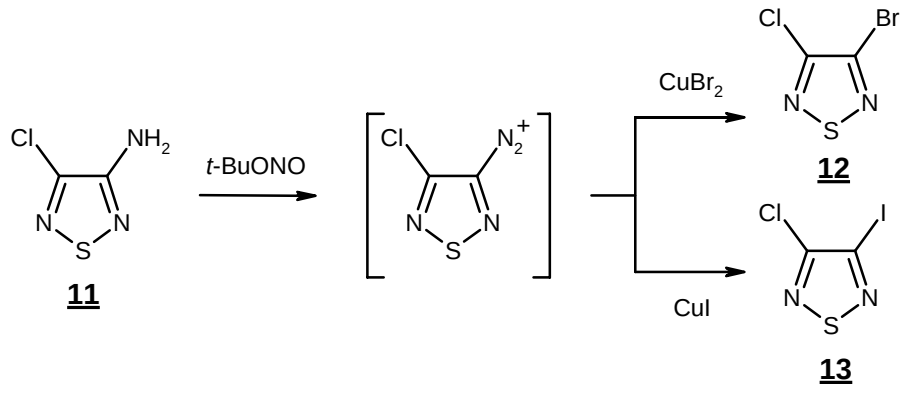
Run	Compd	Suzuki reagent[(a)]	Catalyst (mol %)	Base (equiv)	Solvent (v/v)	Yield[(b)]
1	2	II	$Pd(PPh_3)_4$ (5)	K_2CO_3 (2)	Toluene/EtOH/H_2O (4/2/1)	*(26)*
2	2	II	$Pd(dppb)Cl_2$ (10)	K_2CO_3 (2)	Toluene/EtOH/H_2O (4/2/1)	*(31)*
3	2	II	$Pd(PPh_3)_4$ (5)	KF (3)	Toluene/H_2O (1/1)	*(56)*
4	2	II	$Pd(PPh_3)_4$ (5)	CsF (3)	Dioxane/H_2O (4/1)	30
5	2	II	$Pd(PPh_3)_4$ (5)	CsF (3)	Dioxane	25
6	4	III	$Pd(PPh_3)_4$ (5)	K_2CO_3 (2)	Toluene/H_2O (2/1)	*(18)*
7	4	III	$Pd(PPh_3)_4$ (5)	KF (3)	Toluene/H_2O (1/1)	*(13)*
8	4	IV	$Pd(PPh_3)_4$ (5)	KF (3)	Toluene/H_2O (2/1)	5

[(a)] **II** = phenylboronic acid; **III** = diethyl(3-pyridyl)borane; **IV** = 3-pyridylboronic acid.

[(b)] By HPLC assay (mol %) or isolated (%) between brackets.

At this stage, it is obvious that the readily available 3,4-dichloro-1,2,5-thiadiazole can be involved as substrate in Pd-catalyzed cross-coupling reactions, using either Stille or Suzuki conditions. While this straightforward method does not achieve consistent yields in all cases, it makes it possible to quickly access a broad family of useful key intermediates. However, due to the competitive desulfurization side-reaction affecting the starting material, this approach cannot be considered as optimal.

Scheme 5



In order to avoid this major issue, the involvement of unsymmetrical 3,4-dihalogeno-1,2,5-thiadiazoles, such as the 3-bromo-4-chloro- and the 3-chloro-4-iodo-analogues has been proposed. These new

1,2,5-thiadiazole key intermediates (**12)** and (**13)** have been prepared from 3-amino-4-chloro-1,2,5-thiadiazole[19] (**11)** *via* a Sandmeyer-like reaction involving successively *tert*-butyl nitrite and either copper dibromide or copper iodide (Scheme 5) in anhydrous acetonitrile according to standard experimental conditions reported for the conversion of arylamines into their corresponding aryl bromide and iodide derivatives.[20,21]

Table 4.

Comparative trials on substrates **(1**, **12** and **13)** using Stille (**V**)[(a)] and Suzuki (**II**)[(b)] reagents.

Run	Substrate	Reagent	Product	Catalyst	Yield[(c)]
1	**1**	**V**	**4**	$Pd_2(dba)_3$	0
2	**1**	**V**	**4**	$Pd(2\text{-furyl}_3P)_4$	*(25)*
3	**12**	**V**	**4**	$Pd(2\text{-furyl}_3P)_4$	51
4	**13**	**V**	**4**	$Pd_2(dba)_3$	76
5	**1**	**II**	**2**	$Pd(Ph_3P)_4$	*(56)*
6	**12**	**II**	**2**	$Pd(Ph_3P)_4$	*(95)*
7	**13**	**II**	**2**	$Pd(Ph_3P)_4$	*(87)*

[(a)] **V** = tributyl-(3-pyridyl)stannane and 5 mol % catalyst in toluene.

[(b)] **II** = phenylboronic acid and 5 mol % catalyst + 3 equiv. KF in toluene-water.

[(c)] By HPLC assay (mol %) or isolated (%) between brackets.

The data in Table 4 show that the cross-coupling reaction is in all cases significantly improved by using as substrate, the 3-bromo-4-chloro- (**12**) or 3-chloro-4-iodo-1,2,5-thiadiazole (**13**), instead of the corresponding 3,4-dichloro analogue (**1**). In accordance with this increased productivity, no substantial levels of the by-products resulting from degradation of the heterocycle have been detected. Furthermore, involvement of the bromo and iodo analogues makes it possible to promote the reaction by catalysts that were found to be poorly active or inactive with 3,4-dichloro-1,2,5-thiadiazole. For example, under the Stille conditions the cross-coupling reaction works by using Pd-catalysts lacking phosphinic ligands such as tris(dibenzylideneacetone)dipalladium(0) (Run *4* vs. Run *1*). Finally, the involvement of 3-bromo-4-chloro- (**12**) and/or 3-chloro-4-iodo-1,2,5-thiadiazoles (**13**) are compatible with both Stille and Suzuki cross-coupling approaches.

CONCLUSIONS

The desymmetrization of 3,4-dichloro-1,2,5-thiadiazole *via* either the Stille or the Suzuki cross-coupling reaction is achievable. The reaction proceeds with formation of the 4-substituted 3-chloro-

1,2,5-thiadiazole without occurrence of the next consecutive reaction leading to the symmetrical 3,4-disubstituted analogue. This method using the commercially available 3,4-dichloro-1,2,5-thiadiazole makes it possible to prepare many different 4-substituted 3-chloro-1,2,5-thiadiazoles. Such a method might be appropriate by parallel syntheses to prepare series of key intermediates highly useful in medicinal chemistry. However, this cross-coupling reaction using as substrate 3,4-dichloro-1,2,5-thiadiazole suffers from a major selectivity issue due to a competitive side-reaction by degradation of the heterocyclic nucleus. Due to the intrinsic reactivity of the strong electron-deficient heterocycle 3,4-dichloro-1,2,5-thiadiazole, this unwanted desulfurization side-reaction by the Pd-catalyst cannot be avoided. Therefore, the productivity of this reaction remains limited and varies dramatically depending on the nature of the reagents and catalysts typically used in the Stille or Suzuki approaches.

Utilization of the unsymmetrical 3-bromo-4-chloro- and 3-chloro-4-iodo-1,2,5-thiadiazoles makes it possible to by-pass the major issue associated with 3,4-dichloro-1,2,5-thiadiazole. When using the new bromo-chloro- and chloro-iodo- unsymmetrical dihalogeno-substrates, the cross-coupling reaction occurs in all cases with much better yields. In accordance to that, involvement of these new substrates makes it possible to avoid the major competitive side-reaction(s) leading to degradation of the heterocyclic starting material. This improvement can easily been rationalized by the higher susceptibility of aryl bromides and iodides, relative to the corresponding chlorides, to be involved in the initial Pd-insertion rate-determining step of the overall cross-coupling reaction. In addition, the replacement of one chlorine of the 3,4-dichloro-1,2,5-thiadiazole, by a less electronegative halogen such as the bromine or iodine, should reduce the susceptibility of the endocyclic sulfur atom for a nucleophilic attack leading to degradation of the heterocycle. In this perspective, the use of these new unsymmetrical 3,4-dihalogeno-1,2,5-thiadiazoles opens the opportunity to develop and scale-up reactions that avoid the hazardous, corrosive and highly toxic reagents that are generally required in this type of chemistry. In this scope, the Suzuki approach involving boronic acid derivatives should be considered as the method of choice. In addition, our work is complementary to that developed earlier[3], by providing direct access to series of intermediates enabling the preparation of the 3-alkyl-4-aryl- and 3,4-diaryl-1,2,5-thiadiazoles (Scheme 1).

EXPERIMENTAL

Melting points were recorded on an Electrothermal Melting Point apparatus (according to Totolli) and are uncorrected. MS were recorded on a Nermag R3010 mass spectrometer. High-resolution MS were recorded on a VG AutoSpec (Fisons Intruments) mass spectrometer or a Q-TOF Ultima (Micromass). NMR spectra were performed on a Brücker 400 MHz spectrometer. Reactions are monitored by TLC (silica gel plates, Merck 60 F_{254}) and by HPLC in an isocratic mode using Zorbax-CN column with eluant

acetonitrile–water–trifluoroacetic acid mixture (5/95/0.1, v/v). Quantitative analyses are performed by HPLC using C18 Merck 60RP Select B column (25 cm × 4.6 mm) with eluant acetonitrile–water–trifluoroacetic acid (5/95/0.1 → 95/5/0.1, v/v) in a gradient mode for 25 min and at the end in isocratic mode for 10 min, injection 10 μL, concentration 20 mg/50 mL, detection 220 and 235 nm. Reference materials have been prepared, whether independently (**2**, **3**) or by extensive purification of an aliquot withdrawn from the reaction pool (**4** to **10**). 3,4-Dichloro-1,2,5-thiadiazole has been redistilled (155°C/760 mm Hg) before use. All solvents have been used after degassing under nitrogen or argon atmosphere. Purification by flash chromatography is performed using silica gel 60, 63-100 μm (Merck).

3-Chloro-4-phenyl-1,2,5-thiadiazole (2)

1st Example (Table 1, Run *6* or Table 2, Run *1*)

Tributylphenyl stannane (1.9 g, 5.17 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.29 g, 0.25 mmol) are added to a solution of 3,4-dichloro-1,2,5-thiadiazole (0.775 g, 5 mmol) in toluene (10 mL). This mixture is heated to reflux under nitrogen for 8 h. An additional amount of tetrakis (triphenylphosphine)palladium(0) (0.145 g, 0.125 mmol) is then added to the reaction mixture. At 24 h, the reaction medium is analyzed by quantitative HPLC: 472 mg (48%) *in situ* of **2**. *In process* monitoring against authentic reference samples shows also 280 mg (36%) of unreacted 3,4-dichloro-1,2,5-thiadiazole (**1**) starting material together with 193 mg (37.5%) of benzonitrile and 257 mg (17.5%) of triphenylphosphine sulfide degradation products.

2nd Example (Table 3, Run *3*)

Potassium fluoride (0.35 g, 6 mmol), phenylboronic acid (0.245 g, 2 mmol) and tetrakis-(triphenylphosphine)palladium(0) (0.115 g, 0.1 mmol) are added to a solution of 3,4-dichloro-1,2,5-thiadiazole (0.31 g, 2 mmol) in a biphasic mixture of toluene (5 mL) and water (5 mL). The reaction mixture is heated under vigorous stirring under nitrogen for 48 h. The organic layer is decanted off and the aqueous layer is re-extracted with ether. The combined organic phases are dried on magnesium sulfate, filtered and evaporated to dryness. The crude oily residue is purified by chromatography on a silica gel column eluted successively with cyclohexane and a mixture of cyclohexane – ether (98/2, v/v). The pooled fractions containing **2** are evaporated to dryness to give a colorless oil, which crystallizes on standing: 220 mg (56%) (mp 33°C, lit.,[2b] 31-33°C).

^{1}H-NMR ($CDCl_3$) δ 7.50 (3H, m), 7.92 (2H, dd); ^{13}C-NMR ($CDCl_3$) δ 128.6 (4C), 130.2, 130.7, 143.4, 157.9.

3rd Example (Table 4, Run *6*)

Tetrakis(triphenylphosphine)palladium(0) (0.055 g, 0.05 mmol) and 1M potassium fluoride aqueous solution (3 mL, 3 mmol) are added to a mixture of 3-bromo-4-chloro-1,2,5-thiadiazole (0.2 g, 1 mmol)

and phenylboronic acid (0.135 g, 1.1 mmol) in toluene (5 mL). The biphasic reaction mixture is heated under vigorous stirring under nitrogen for 26 h. The organic layer is decanted off and the aqueous layer is re-extracted twice with toluene (2 × 10 mL). The combined organic phases are dried on magnesium sulfate, filtered and evaporated to dryness. The crude oily residue is purified by chromatography on a silica gel column eluted successively with a mixture of *n*-hexane – ethyl acetate (99/1, v/v). The pooled fractions containing **2** are evaporated to dryness to give a colorless oil which crystallizes on standing: 180 mg (95%) (mp 33°C).

3-Chloro-4-(pyrid-3-yl)-1,2,5-thiadiazole (4)

1st Example (Table 2, Run *2*)

Tributyl(3-pyridyl)stannane (0.4 g, 1.1 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.086 g, 0.0745 mmol) are added to a solution of 3,4-dichloro-1,2,5-thiadiazole (0.16 g, 1 mmol) in toluene (2 mL). This mixture is heated to reflux under argon for 2 h. An additional amount of tetrakis (triphenylphosphine)palladium(0) (0.052 g, 0.045 mmol) is then added to the reaction mixture. At 24 h, the reaction medium is analyzed by quantitative HPLC (all the stannane is consumed): 75.2 mg (38%) *in situ* of **4**.

2nd Example: (Table 3, Run *6*)

Diethyl(3-pyridyl)borane (0.147 g, 1 mmol), 1M potassium carbonate aqueous solution (2 mL, 2 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.057 g, 0.05 mmol) are added to a solution of 3,4-dichloro-1,2,5-thiadiazole (0.155 g, 1 mmol) in toluene (4 mL). The reaction mixture is heated under stirring under nitrogen for 24 h. The organic phase is decanted and the aqueous phase is re-extracted with ether. The combined organic phases are dried over magnesium sulfate, filtered and concentrated to dryness. The crude oily residue is purified by chromatography on a silica gel column eluted successively with a mixture of cyclohexane – ethyl acetate (80/20, v/v). The pooled fractions containing **4** are evaporated to dryness give a colorless oil which slowly crystallizes on standing: 35 mg (18%) (mp 45°C, lit.,[16] 48-49°C).

^{1}H-NMR ($CDCl_3$) δ 7.46 (1H, m), 8.29 (1H, m), 8.74 (1H, dd, J = 5 Hz and 2 Hz); ^{13}C-NMR ($CDCl_3$) δ 123.3, 126.8, 135.6, 143.4, 149.3, 150.9, 155.0.

3rd Example: (Table 4, Run *4*)

Tributyl(3-pyridyl)stannane (0.092 g, 0.25 mmol) and tris(dibenzylideneacetone)dipalladium(0) (0.086 g, 0.0745 mmol) are added to a solution of 3-chloro-4-iodo-1,2,5-thiadiazole (0.062 g, 0.25 mmol) in toluene (1 mL). This mixture is heated to reflux under nitrogen for 2 h. The reaction medium is then analyzed by quantitative HPLC (no by-product detected): 38 mg (76%) *in situ* of **4**.

3-Chloro-4-(furan-2-yl)-1,2,5-thiadiazole (5) (Table 2, Run *3*)

2-(Tributylstannyl)furan (0.85 g, 2.38 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.12 g, 0.1 mmol) are added to a solution of 3,4-dichloro-1,2,5-thiadiazole (0.33 g, 2.13 mmol) in toluene (4 mL) and heated to reflux under nitrogen. After 3 and 6 h respectively, two supplementary amounts of tetrakis(triphenylphosphine)palladium(0) (2 × 0.04 g, 2 × 0.035 mmol) are added. After 24 h of reflux, quantitative HPLC shows that 60% of product is formed (all the stannane is consumed). The reaction medium is diluted with ethyl acetate (5 mL) and vigorously stirred with 1M aqueous solution of potassium fluoride (10 mL) for 2 h. After filtration through celite, the aqueous phase is re-extracted with ethyl acetate, the combined organic phases are dried over magnesium sulfate, filtered and concentrated. The resulting 0.86 g of a black oily material is triturated in a *n*-hexane – ethyl acetate mixture (97/3, v/v). The precipitate which consists primarily of triphenylphosphine sulfide is eliminated and the supernatant is purified by chromatography on silica gel (eluant: *n*-hexane – ethyl acetate, 99/1, v/v) to produce 0.2 g of a crude solid material. After crystallization in *n*-pentane, 0.14 g of **5** is isolated (36%) (mp 46°C).

^{1}H-NMR ($CDCl_3$) δ 6.59 (1H, dd, ^{2}J = 1.85 Hz, 3.58 Hz), 7.35 (1H, dd, ^{2}J = 3.58 Hz, ^{3}J = 0.62 Hz), 7.65 (1H, dd, ^{2}J = 1.85 Hz, ^{3}J = 0.62 Hz); ^{13}C-NMR ($CDCl_3$) δ 111.6, 112.5, 141.2, 144.9, 145.7, 148.5; HR-MS (DEI) *m/z*: Found: 185.964892 ($M^{+\cdot}$), Calcd for $C_6H_3N_2OClS$: 185.965462.

Anal. Calcd for $C_6H_3N_2OClS$: C, 38.62; H, 1.62; N, 15.01. Found: C, 37.42; H, 1.53; N, 15.03.

3-Chloro-4-(thiophen-2-yl)-1,2,5-thiadiazole (6) (Table 2, Run *4*)

2-(Tributylstannyl)thiophene (0.92 g, 2.46 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.12 g, 0.1 mmol) are added to a solution of 3,4-dichloro-1,2,5-thiadiazole (0.33 g, 2.13 mmol) in toluene (4 mL) and heated to reflux under nitrogen. After 3 and 6 h respectively, two supplementary amounts of tetrakis(triphenylphosphine)palladium(0) (2 × 0.04 g, 2 × 0.035 mmol) are added. After 24 h of reflux, quantitative HPLC shows that 54% of product is formed (all the stannane is consumed). The reaction medium is diluted with ethyl acetate (5 ml) and vigorously stirred with 1M aqueous solution of potassium fluoride (10 mL) for 2 h. After filtration through celite, the aqueous phase is re-extracted with ethyl acetate, the combined organic phases are dried over magnesium sulfate, filtered and concentrated. The resulting 0.77 g of a black oily material is triturated in a *n*-hexane – ethyl acetate mixture (97/3, v/v). The precipitate which consists primarily of triphenylphosphine sulfide is eliminated and the supernatant is purified by chromatography on silica gel (eluant: *n*-hexane) to produce 0.3 g of a crude solid material. After crystallization in *n*-pentane, 0.2 g of **6** is isolated (47%) (mp range 45-47°C). An analytical sample is prepared by further crystallization from methanol (mp 54-55°C).

^{1}H-NMR ($CDCl_3$) δ 7.175 (1H, dd, ^{2}J = 5.09 Hz, 3.58 Hz), 7.35 (1H, dd, ^{2}J = 5.09 Hz, ^{3}J = 1.23 Hz), 8.00 (1H, dd, ^{2}J = 3.85 Hz, ^{3}J = 1.23 Hz); ^{13}C-NMR ($CDCl_3$) δ 127.8, 128.5, 129.4, 133.1, 141.5, 152.1;

HR-MS (DEI) *m/z*: Found: 201.942459 ($M^{+\cdot}$), Calcd for $C_6H_3N_2ClS_2$: 201.942619.

Anal. Calcd for $C_6H_3N_2ClS_2$: C, 35.56; H, 1.49; N, 13.82; Cl, 17.49; S, 31.64. Found: C, 35.90; H, 1.62, N, 13.24; Cl, 17.64; S, 31.70.

3-Chloro-4-vinyl-1,2,5-thiadiazole (7) (Table 2, Run *5*)

2-Tributyl(vinyl)stannane (3.17 g, 10 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.56 g, 0.5 mmol) are added to a solution of 3,4-dichloro-1,2,5-thiadiazole (1.55 g, 10 mmol) in toluene (10 mL) and heated to reflux under nitrogen. After 8 h, a supplementary amount of tetrakis(triphenylphosphine)palladium(0) (0.28 g, 0.25 mmol) is added. After 24 h of reflux, quantitative HPLC shows that 35% of product was formed. The reaction medium is diluted with ethyl acetate (10 mL) and vigorously stirred with 1M aqueous solution of potassium fluoride (15 mL) for 2 h. After filtration through celite, the aqueous phase is re-extracted with ethyl acetate, the combined organic phases are dried over magnesium sulfate, filtered and concentrated. The resulting black oily material is triturated in a *n*-hexane – ethyl acetate mixture (97/3, v/v). The precipitate which consists primarily of triphenylphosphine sulfide is eliminated and the supernatant is purified by chromatography on silica gel (eluant: *n*-pentane) to produce **7** in the form of a colorless oil: 0.45 g (31%).

^{1}H-NMR ($CDCl_3$) δ 5.71 (1H, dd, J_{gem} = 1.30 Hz, J_{cis} 11.1 Hz), 6.38 (1H, dd, J_{gem} = 1.30 Hz, J_{trans} = 17.14 Hz), 6.91 (1H, dd, J_{cis} = 11.1 Hz, J_{trans} = 17.4 Hz); ^{13}C-NMR ($CDCl_3$) δ 122.9, 123.7, 142.9, 154.6; HR-MS (+ESI) *m/z*: Found: 146.9785 $(M+H)^+$, Calcd for $C_4H_4N_2ClS$: 146.9784.

3-Chloro-4-(1-ethoxyvinyl)-1,2,5-thiadiazole (8) (Table 2, Run *6*)

1-(Ethoxyvinyl)tributylstannane (1.805 g, 5 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.26 g, 0.225 mmol) are added to a solution of 3,4-dichloro-1,2,5-thiadiazole (0.775 g, 5 mmol) in toluene (6 mL) and heated to reflux under nitrogen. After 8 h, a supplementary amount of tetrakis(triphenylphosphine)palladium(0) (0.28 g, 0.25 mmol) is added. After 24 h of reflux, quantitative HPLC shows that 55% of product was formed. The reaction medium is diluted with ethyl acetate (10 mL) and vigorously stirred with 1M aqueous solution of potassium fluoride (15 mL) for 1 h. After filtration through celite, the aqueous phase is re-extracted with ethyl acetate, the combined organic phases are dried over magnesium sulfate, filtered and concentrated. The resulting black oily material is triturated in a *n*-hexane – ethyl acetate mixture (97/3, v/v). The precipitate which consists primarily of triphenylphosphine sulfide is eliminated and the supernatant is purified by chromatography on silica gel (eluant: *n*-pentane – diethyl ether, 99/1, v/v) to produce **8** in the form of a colorless oil: 0.45 g (42%).

^{1}H-NMR ($CDCl_3$) δ 1.40 (3H, t, J = 7.0 Hz), 3.93 (2H, q, J = 7.0 Hz), 4.60 (1H, d, J_{gem} = 3.2 Hz), 5.04 (1H, d, J_{gem} = 3.2 Hz); ^{13}C-NMR ($CDCl_3$) δ 13.9, 63.8, 90.1, 143.4, 152.0, 154.1; HR-MS (+ESI) *m/z*:

Found: 191.0043 $(M+H)^+$, Calcd for $C_6H_8N_2OClS$: 191.0046.

3-Chloro-4-phenylethynyl-1,2,5-thiadiazole (9) (Table 2, Run *7*)

Tributyl(phenylethynyl)stanne (2 g, 5 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.23 g, 0.2 mmol) are added to a solution of 3,4-dichloro-1,2,5-thiadiazole (0.62 g, 4 mmol) in toluene (8 mL) and heated to reflux under nitrogen. After 4 and 24 h respectively, two supplementary amounts of tetrakis(triphenylphosphine)palladium(0) (2 × 0.115 g, 2 × 0.1 mmol) are added. After 30 h of reflux, quantitative HPLC shows that 38% of product is formed. The reaction medium is diluted with ethyl acetate (10 mL) and vigorously stirred with 1M aqueous solution of potassium fluoride (15 mL) for 2 h. After filtration through celite, the aqueous phase is re-extracted with ethyl acetate, the combined organic phases are dried over magnesium sulfate, filtered and concentrated. The resulting 2.83 g of a black oily material is triturated in a *n*-hexane – ethyl acetate mixture (97/3, v/v). The precipitate which consists primarily of triphenylphosphine sulfide is eliminated and the supernatant is purified by chromatography on silica gel (eluant: *n*-hexane) to produce 0.34 g of a crude oily material which crystallizes slowly. After crystallization in *n*-hexane, **9** is isolated as a white solid: 0.25 g (28.5%) (mp 57°C).

^{1}H-NMR ($CDCl_3$) δ 7.42 (3H, m), 7.62 (2H, dd); ^{13}C-NMR ($CDCl_3$) δ 79.5, 96.8, 121.2, 129.0 (2C), 130.5, 132.7 (2C); HR-MS (DEI) *m/z*: Found: 219.985638 ($M^{+\cdot}$), Calcd for $C_{10}H_5N_2ClS$: 219.986198.

Anal. Calcd for $C_{10}H_5N_2ClS$: C, 54.43; H, 2.28; N, 12.69; Cl, 16.07; S, 14.53. Found: C, 54.05; H, 2.43; N, 12.52; Cl, 16.05; S, 14.39.

3-Allyl-4-chloro-1,2,5-thiadiazole (10) (Table 2, Run *8*)

Tributyl(phenylethynyl)stannane (1.75 g, 5 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.23 g, 0.2 mmol) are added to a solution of 3,4-dichloro-1,2,5-thiadiazole (0.62 g, 4 mmol) in toluene (8 mL) and heated to reflux under nitrogen. After 4 and 24 h respectively, two supplementary amounts of tetrakis(triphenylphosphine)palladium(0) (2 × 0.115 g, 2 × 0.1 mmol) are added. After 30 h of reflux, quantitative HPLC shows that 60% of product was formed. The reaction medium is diluted with ethyl acetate (10 mL) and vigorously stirred with 1M aqueous solution of potassium fluoride (15 mL) for 2 h. After filtration through celite, the aqueous phase is re-extracted with ethyl acetate, the combined organic phases are dried over magnesium sulfate, filtered and concentrated. The resulting 1.6 g of a black oily material is triturated in a *n*-hexane – ethyl acetate mixture (97/3, v/v). The precipitate which consists primarily of triphenylphosphine sulfide is eliminated and the supernatant is purified by chromatography on silica gel (eluant: *n*-hexane) to produce **10** as an oil: 0.2 g (31%).

^{1}H-NMR ($CDCl_3$) δ 3.68 (2H, dd), 5.18 (1H, dd), 5.24 (1H), 6.01 (1H, m); ^{13}C-NMR ($CDCl_3$) δ 34.1, 118.8, 132.1, 144.9, 159.3; HR-MS (DEI) *m/z*: Found: 159.9860 ($M^{+\cdot}$), Calcd for $C_5H_5N_2ClS$: 159.9861.

3-Bromo-4-chloro-1,2,5-thiadiazole (12)

To a solution of copper(II) bromide (53 g, 0.2385 mol) in anhydrous acetonitrile (500 mL) under nitrogen is added *tert*-butyl nitrite (34 g, 0.3 mmol). The resulting mixture is heated to 60-70°C and a solution of 4-amino-3-chloro-1,2,5-thiadiazole (27 g, 0.2 mmol) in anhydrous acetonitrile (300 mL) is added dropwise. Heating is maintained for 30 min after the end of addition. After cooling to rt, water (400 mL) is added and acetonitrile is distilled off under reduced pressure. The resulting oily material is extracted with cyclohexane (2×400 mL). The combined organic layers are dried over magnesium sulfate, filtered and concentrated to a mass of 30 g. Distillation under reduced pressure (bp 58°C/5 mbar) affords 27.6 g of **12** (70%).

^{13}C-NMR ($CDCl_3$) δ 133.1, 147.2; GC-MS (EI) *m/z*: 198 ($M^{+\cdot}$); Anal. Calcd for C_2N_2BrClS : C, 12.04; N, 14.04; Br, 40.06; Cl, 17.77; S, 16.08. Found: C, 12.33; N, 13.92; Br, 39.80; Cl, 17.49; S, 15.79.

3-Chloro-4-iodo-1,2,5-thiadiazole (13)

To a solution of copper(I) iodide (22.83 g, 0.12 mol) in anhydrous acetonitrile (200 mL) under nitrogen is added *tert*-butyl nitrite (15 g, 0.146 mmol). The resulting mixture is heated to 60°C and a solution of 4-amino-3-chloro-1,2,5-thiadiazole (13.45 g, 0.1 mmol) in anhydrous acetonitrile (200 mL) is added dropwise whitin 30 min. Heating is maintained for 30 min after the end of addition. After cooling to rt, water (1 L) is added and acetonitrile is distilled off under reduced pressure. The resulting oily material is extracted with cyclohexane (2×500 mL). The combined organic layers are washed with water (2×200 mL), dried over magnesium sulfate, filtered and concentrated to a mass of 15 g. Distillation under reduced pressure (bp 50-51°C/0.2 mbar) affords 15 g of **13** (41%).

^{13}C-NMR ($CDCl_3$) δ 107.8, 152.7; GC-MS (EI) *m/z*: 246 ($M^{+\cdot}$); Anal. Calcd for C_2N_2ClIS : C, 9.75; N, 11.37; Cl, 14.39; I, 51.49; S, 13.01. Found: C, 10.34; N, 11.21; Cl, 14.33; I, 51.47; S, 13.17.

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13. Occurrence of minor degradations *via* pathway 2b is also suggested in reference 3.
14. According to the nomenclature the 3- and 4-position are ranked by alphabetic order. For example: 3-chloro-4-vinyl- vs. 3-allyl-4-chloro-1,2,5-thiadiazole.

15. In this case the cross-coupling reaction, involving 3,4-dichloro-1,2,5-thiadiazole as substrate and tributyl(3-pyridyl)stannane as Stille reagent, was screened with several other catalysts than $Pd(Ph_3P)_4$, *i.e.* $Pd(2\text{-furyl}_3P)_4$, $Pd[(C_6F_5)_3P]_4$, $Pd(o\text{-tolyl}_3P)_4$, $Pd(c\text{-hex}_3P)_4$, $Pd(Ph_3As)_4$, $Pd(Ph_3Sb)_4$, $Pd(dppe)Cl_2$, Pd(dppp), $Pd(dppp)_2$, Pd(dppb), $Pd(dppf)_2$, $Pd_2(dba)_3$ and $Pd(CH_3CN)_2Cl_2$. No any of these catalysts, except $Pd(2\text{-furyl}_3P)_4$ was found to be effective: see reference 10.
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