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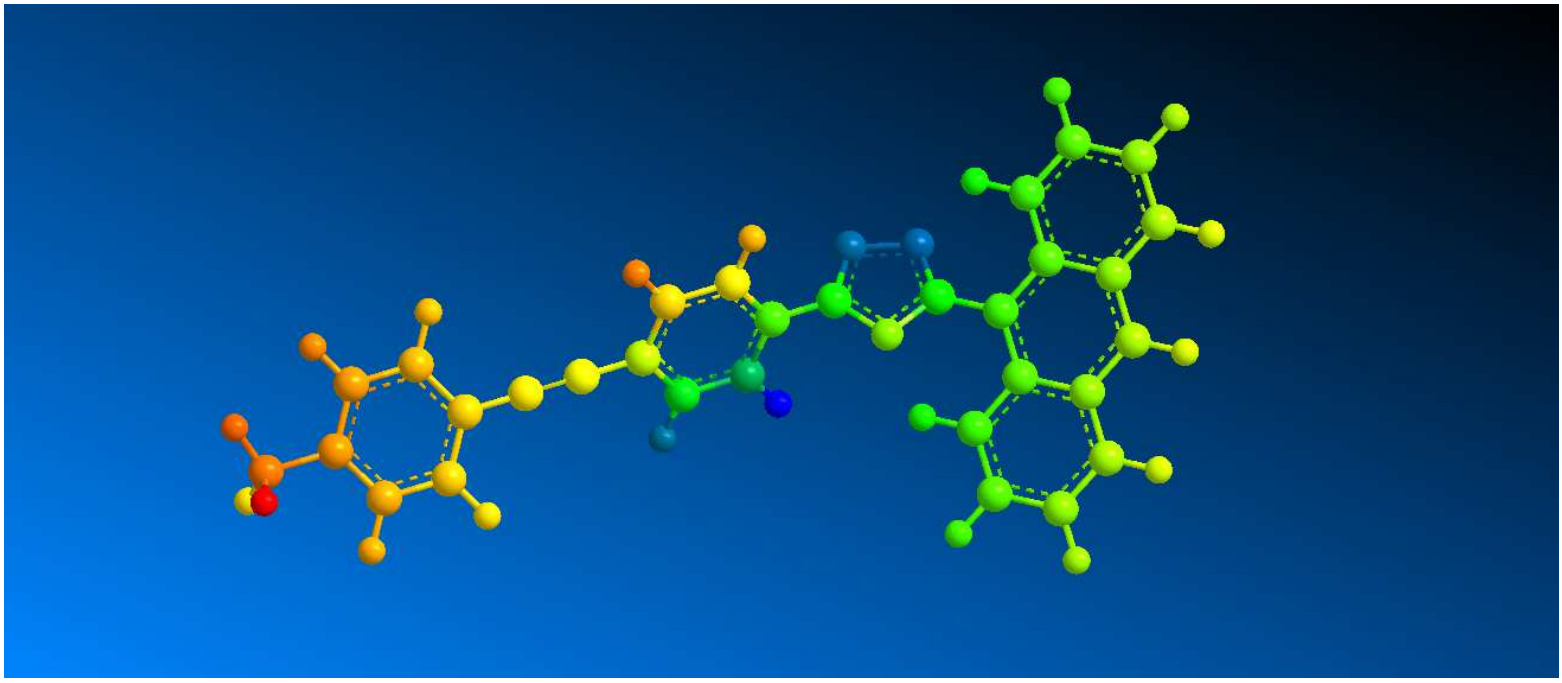

PhD THESIS

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PhD Supervisor:

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PhD THESIS

SYNTHESYS OF NEW HETEROAROMATIC COMPOUNDS BY SONOGASHIRA CROSS-COUPLING REACTION

A B S T R A C T

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2016

T A B L E O F C O N T E N T S

(*according to the PhD thesis*)

Introduction

Heteroaromatic derivatives are often the central core of various natural compounds such as vitamins and alkaloids, as well as a plethora of biologically active compounds and electroactive materials. Transition metal catalyzed cross-coupling reactions may provide an elegant, efficient and economical synthetic pathway of such heterocylic compounds and their derivatives.

In particular, the Sonogashira coupling reaction represents a useful tool for synthesis of heterocyclic compounds with interesting properties, bearing acetylene units directly connected to the heterocyclic motifs.

The latest challenges in this area are directed towards identifying new heteroaromatic functional groups able to act as convenient alternatives to halides, which are in many instances difficult to prepare. Their behavior to react efficiently and selectively in presence of halides is an advantage, providing thus molecular diversity to complex structural units.

Thioorganic derivatives are advantageous electrophilic substrates for a variety of cross-coupling reactions. The specific reactivity of the heterocyclic substrates, according to their structural and electronic features, justifies the individual study as substrates in the coupling reactions.

The thesis entitled „*Synthesis of new heteroaromatic compounds by Sonogashira cross-coupling reaction*" focuses on reactivity studies of some thioorganic and halogenated heterocyclic derivatives as electrophilic substrates in Sonogashira reaction. Thus, the thesis describes the investigation of metallo-catalysed coupling reactions of various substituted alkynes with thioorganic benzazole and oxadiazole derivatives, as well as with aryl halides bearing a π-deficient 1,3,4-oxadiazole core.

The thesis contains five chapters, the first one being dedicated to a critical survey of literature concerning the Sonogashira cross-coupling both in terms of mechanism, reaction conditions and applications. The other four chapters describe the analysis of the experimental results concerning the reactivity studies of thioorganic and halogenated heterocyclic substrates in the cross-coupling reaction.

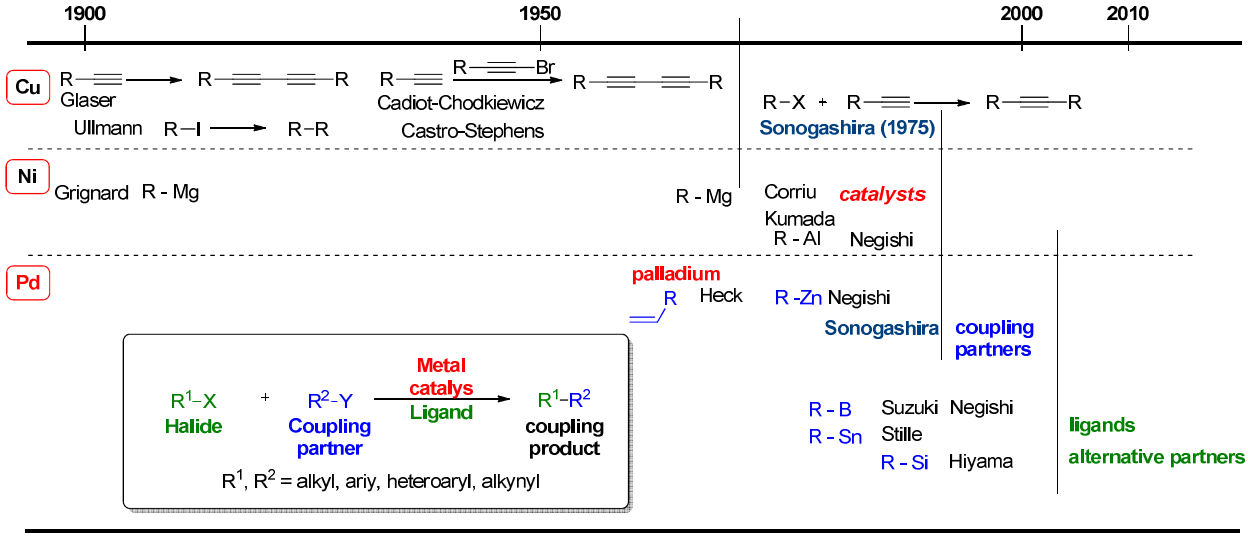
The outcome of this research aims to be a contribution to the development of the cross-coupling reaction field of benzazole and oxadiazole heterocycles, by studying their reactivity and by synthesis of new alkylated derivatives.

Chapter 1. Sonogashira cross-coupling reaction – useful tool in synthesis of alkynylated derivatives

Transition metal-catalyzed cross-coupling reactions are a powerful tool of organic chemistry for generating new C-C bonds under mild conditions. The development of this field involved the evolution of material, biological and organometallic chemistry, leading to the synthesis of new compounds with specific properties.

1.1. Cross-coupling reactions

The common traits of the cross-coupling reactions (**Scheme 1**) are *the electrophilic coupling partner* – a halide R^1X (or an analogue called pseudo-halide) and the presence in the reaction medium of transition metal complexes, as (pre)catalysts. *The nucleophilic coupling partner* varies and this may be an alkene or an organometallic compound R^2M (M belonging to the series B, Sn, Zn, Mg, Si, Cu).



Scheme 1 Evolution of cross-coupling reactions [1a]

The chemistry of the cross-coupling reactions has evolved over three successive waves [1a]:

1) the wave dedicated to identification and investigation of metal catalysts;

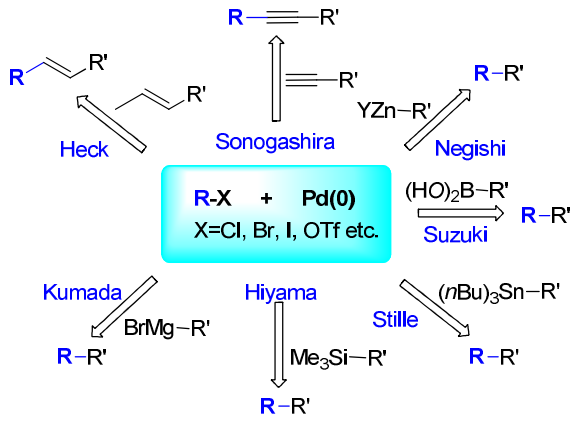
2) the wave dedicated to identification of the nucleophilic substrates able to react in this cross-coupling reactions (organometallic partners);

3) the wave dedicated to the development of new catalytically active species and the alternative electrophilic partners.

The beginning of the coupling reactions field was dominated by copper as catalyst. [1a] Both Glaser homocoupling of metal acetylides (1869) and Ullman homocoupling of aryl halides (1901) are examples which used copper in stoichiometric or supra-stoichiometric amounts.

Later, use of CuCl in catalytic amounts led to *selective* coupling reactions with high yields, as for example the Cadiot-Chodkiewicz coupling of alkynes with bromoalkynes.

The complexity of the coupling reactions has increased since the 1960s, concomitant with the development of nickel and palladium catalysts, thus opening new perspectives in organic chemistry. [1,2] The tolerance toward different functional groups, the mild reaction conditions and the high yields are just a few reasons for which the palladium catalyzed coupling reactions have become widely encountered in organic synthesis. Subsequent development of a wide range of ligands for the palladium complexes equally contributed. The most relevant palladium catalyzed cross-coupling reactions are depicted in **Scheme 2**: Heck [3], Suzuki [4], Negishi [5], Sonogashira [6], Stille [7], Hiyama [8] and Kumada [9].



Scheme 2 Palladium catalyzed cross-coupling reactions

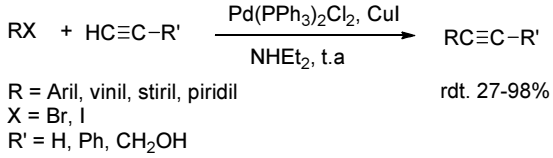
Suzuki-Miyaura cross-coupling reaction is the most efficient method for synthesis of diaryl derivatives. Heck and Sonogashira cross-couplings are also used in synthesis of interest. [10] Award of the Nobel Prize in 2010 for Suzuki, Heck and Negishi cross-coupling reactions provides an indisputable testimony of this field's importance.

One of the recent trends aims identification of new alternative partners which can act as electrophilic substrates in cross-couplings, particularly in the area of heteroaromatic compounds which exhibits specific reactivties.

1.2. Sonogashira cross-coupling reaction

The Sonogashira cross-coupling reaction [6, 11, 12] affords new C(sp^2)-C(sp) bonds between a vinyl or an aryl halide, as electrophilic partner, and a terminal alkyne, as nucleophilic partner (**Scheme 3**). The reaction occurs in presence of a palladium catalyst and a copper (I) co-catalyst, under basic medium.

The first reaction conditions [6, 11] (**Scheme 3**) involved a palladium complex, $Pd(PPh_3)_2Cl_2$, CuI as co-catalyst and inert atmosphere. The organic base, diethylamine, has a dual role, acting also as a solvent.



Scheme 3 Reaction conditions initially used to synthesize internal alkynes by Sonogashira cross-coupling

Later, the method was expanded to a wide range of vinyl, aryl and heteroaryl halides and triflates. The reaction conditions have been adjusted, according to the reactivity of the substrates, by varying the palladium catalysts precursors, Pd(II) or Pd(0) complexes with a plethora of ligands - usually phosphines, *N*-heterocyclic carbenes, or palladacycles (*vide infra*), by varying the solvent, the temperature and the base. [6]

The copper iodide, used as co-catalyst, leads to the *in situ* formation of copper acetylides. In the absence of a highly inert atmosphere, the competitive acetylenic Glaser homocoupling [13] gives rise to diynes, as main byproducts of the Sonogashira reaction.

Copper-free procedures was recently considered in order to optimize the reaction [14] or development of methods which allow the room temperature coupling [15] even for deactivated substrates. [6b] The typically used solvents are, in general, polar solvents such as THF, [16] DMF, 1,4-dioxane, dimethoxyethan. The nonpolar solvents are also used, particularly for substrates with reduced polarity.

The bases can be used in stoichiometric or supra-stoichiometric amounts, frequently serving as (co)solvent. These may be organic bases (amines like diethylamine, di*iso*propylamine, triethylamine, piperidine, morpholine, *n*-butylamine, DABCO, etc.) or inorganic bases (Cs_2CO_3). Their roles are still a subject of debate, being considered as decisive, particularly in the copper-free approaches.

Recent studies [17] refer to the influence of amines nucleophilicity on the formation of palladium active intermediates rather than the influence of their Brönsted basicity on the deprotonating step of terminal alkynes in the copper catalytic cycle. Thus, the efficiency of the secondary cyclic amines in this coupling reaction may be due to their superior nucleophilicity. [18]

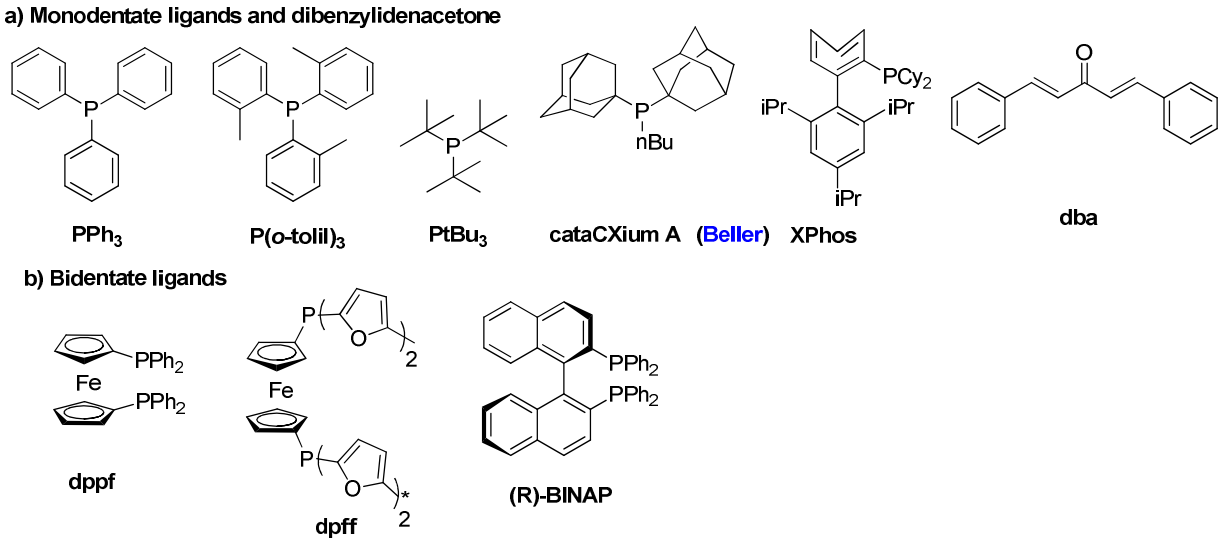
1.2.1. The ligand's influence on the palladium catalysts

The catalytically active species in Sonogashira reaction is a coordinated unsaturated complex of Pd(0), generated by Pd(II) or Pd(0) complexes with a large variety of ligands. The effect of ligands on the metal center is both of electronic and steric type. The ligands used in combination with palladium in Sonogashira reaction are in general: *monodentate phosphines*, *bidentate phosphines*, *N-heterocyclic carbenes*, or *palladacycles*. (**Scheme 4**).

The most frequently used ***monodentate phosphine*** is triphenylphosphine, usually as $Pd^{II}(PPh_3)_2Cl_2$ or $Pd^0(PPh_3)_4$.

The catalytically active species is $Pd^0(PPh_3)_2$, proving efficient both for (hetero)aryl and vinyl iodides and the bromides activated by electron withdrawing groups.

Palladium complexes with ***bidentate phoshine*** ligands (**Scheme 4b**) are more stable than those with monodentate ligands. A supplementary advantage of the bidentate ligands relates to the acceleration of the reductive elimination step, by forcing a *cis* geometry of moieties to be easily removed, and thus increasing the overall reaction rate. [19] Examples of such ligands in Sonogashira coupling of aryl halides, even deactivated ones, are BINAP [20] and ferrocen derivatives as dppf [21] and dpff [22].

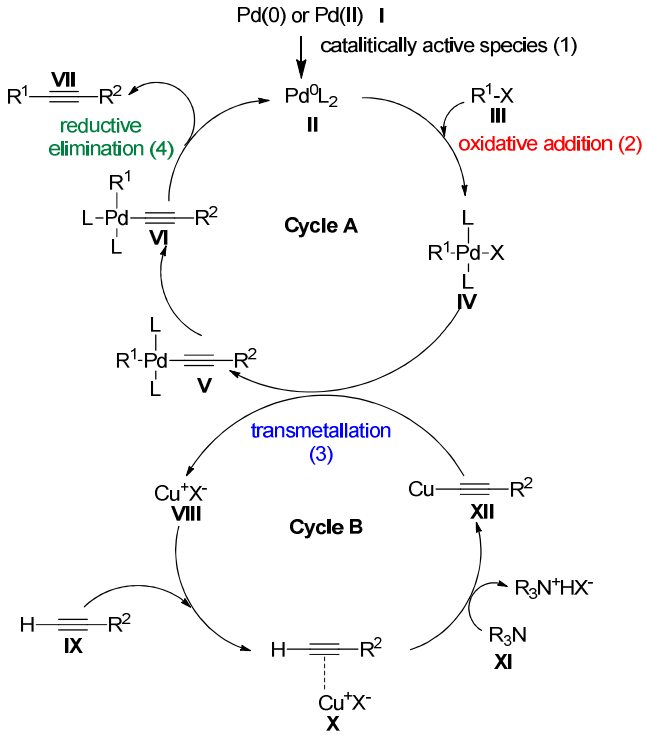


Scheme 4 Examples of palladium catalysts ligands used in Sonogashira cross-coupling reaction

N-heterocyclic carbenes (NHC) as well as ***palladacycles*** proved to be efficient in Sonogashira coupling reaction. The NHC ligands are mostly used for coupling of alkyl halides, while palladacycles are especially useful in coupling of hindered substrates. [6]

1.2.2. Mechanistic aspects

The combined action of palladium and copper (I) catalysts in Sonogashira cross-coupling reaction [5c, 6] refers, from a mechanistic point of view, to two independent catalytic cycles, according to the following four successive steps: (**Scheme 5)**:



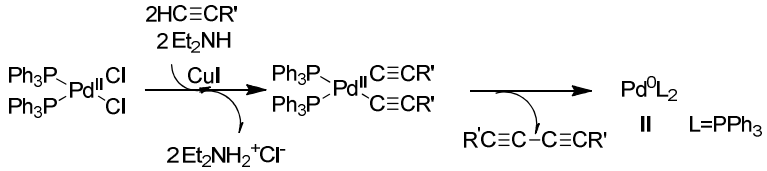
Scheme 5 Catalytic cycles of Sonogashira reaction co-catalysed by Cu

1. *Initiation of catalytic cycle by formation of the catalytically active species* Pd^0L_2 **II**;

2. *Oxidative addition of the substrate R^1-X* **III** *to the catalytically active species Pd^0L_2* **II***;*
3. *Transmetallation of the acetylenic units from Cu to organopalladic species* **IV***;*
4. *Reductive elimination occurring with the release of the reaction product* **VII** *followed by regeneration of the catalytically active species* **II** *for a new catalytic cycle.*

Catalytic cycle of palladium (cycle A)

The reaction mechanism proposed by Sonogashira *et al*. suggests as a result of the *initial step* the formation of the unsaturated active species Pd^0L_2, where L is a neutral ligand, as for example triphenylphosphine. The complex $[Pd(PPh_3)_2Cl_2]$ generates the catalytically active species $Pd^0(PPh_3)_2$ (**Scheme 6**) as follows: a) the copper acetylide formed in presence of the basic medium and CuI undergoes a double transmetallation to the metal center of the palladium (II) complex; b) reductive elimination of the corresponding diyne. [11]



Scheme 6 Generation of active species Pd^0L_2

The oxidative addition step (**Scheme 5**) may be the rate-determining step, depending on the aryl or vinyl halide used as **substrate**.

The reactivity of the electrophilic substrates in this step depends both on the nature of the *hydrocarbon unit* and the *moieties X* and lies on the dissociation energy of C-X bond. [23] The reactivity scale of the aryl and vinyl sp^2 species indicates: [24]

RCH=CH-I > RCH=CH-OTf > RCH=CH-Br > RCH=CH-Cl > Ar-I > Ar-OTf > Ar-Br >> Ar-Cl

The reactivity of less active halide substrates, namely the aryl bromides and chlorides is greatly influenced by the presence of different ***substituents grafted on the aromatic ring***. Thus, the ***electron withdrawing groups*** *activate* these substrates for the oxidative addition to the catalytically active species, by reducing the electron density on the aromatic ring, consequently leading to increased polarization of C-X bond. On the contrary, the ***electron donating groups*** increase the electron density on the aromatic ring and generate the deactivation of substrates for the oxidative addition.

The transmetallation step may be in certain cases the rate-determining step and corresponds to the attack of the nucleophilic copper(I) acetylide to the palladium complex resulted in the oxidative addition step. (**Scheme 5**).

The reductive elimination step, preceded by a *trans/cis* isomerization in the case of the monodentate phosphine ligands, leads to the coupling product concomitant with the release of the catalytically active species Pd^0L_2. One of the advantages of using bidentate ligands lies in the absence of the isomerization step. [19]

The catalytic cycle of copper (cycle B)

Generation of copper acetylide **XII** (**Scheme 5**) is assisted by the base from the reaction medium. In general, the amines are not basic enough to deprotonate the monosubstituted alkyne (pKa = 25). The prior generation of π Cu(I)-alkynyl complex **X** induces the increased acidity of acetylenic proton, subsequently captured by the organic or inorganic base **XI** from the reaction medium. [25]

The presence of copper in the reaction medium has a series of shortcomings, like the decrease of E factor (atom economy) and the requirement to work under inert atmosphere in order to avoid the diyne formation. [26]

These aspects led to sustained efforts for the development of copper-free procedures and/or under aerobic atmosphere, in order to increase the reaction efficiency. There are several mechanistic proposals for the copper-free coupling procedure, emphasizing the roles of the amines which exhibit important influence in this case. [17, 27-29] Studies regarding this aspect [17, 29] suggest the interference of amines in the reaction mechanism both as Brönsted base and as nucleophile.

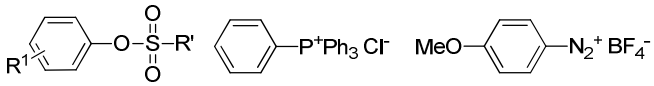
1.2.3 Electrophilic alternative partners in Sonogashira cross-coupling reaction

The great majority of the cross-coupling reactions uses as electrophilic substrates organic halides, iodides, bromides or activated aril chlorides. The large scale access to halides is often expensive and difficult. In order to expand the scope of these reactions, electrophilic compounds, generic called ***pseudohalides***, decorated with a variety of functional groups, other than halides, that can act as leaving groups, were investigated.

The field of the alternative electrophilic partners (pseudohalides) has been greatly developed lately, mainly in the case of heterocyclic substrates.

Vinyl and aryl triflates are the most acquainted pseudohalides. Their convenience is given by their facile synthesis from phenols or carbonyl derivatives. Their enhanced reactivity in cross-coupling reactions indicates them as feasible alternatives for halides. Their drawbacks reside in the instability at humidity and a high cost. [18]

Aryl, vinyl and imidazolyl sulfonates (**Scheme 7**) represent another class of alternative electrophilic partners in Sonogashira coupling reaction and even if their reactivity is lower than the corresponding triflates, they exhibit the advantage of higher stability. [30, 31]



Scheme 7 Exemples of alternative electrophilic partners in Sonogashira coupling

Tetraarylphosphonium chlorides [32]**,** ***aryldiazonium salts*** [33] and ***arylhydrazines*** [34] are other particular examples of pseudohalides used in Sonogashira reactions. ***(Hetero)aromatic thioderivatives*** are advantageous compounds in terms of stability and

synthetic availability. Such compounds studied as electrophilic partners are *sulfonyl chlorides* [35], *thioethers* [36] and *thiones* [37,38].

1.3. Conclusions

The Sonogashira cross-coupling reaction continues to be the most encountered method for the synthesis of simple or complex compounds bearing internal or terminal alkyne moieties. The triple bond induces structural rigidity– a desirable feature in order to design extended conjugated structures, which display specific optoelectronic properties.

The complex reaction medium, involving a couple of catalysts Pd/Cu, an organic or inorganic base, a polar solvent, and, in general, an inert atmosphere, has complicated the elucidation of the reaction mechanism and its generalization. Studies regarding the reaction conditions and the influence of palladium catalysts have accredited the utility of bulky phosphine ligands, featuring highly electron donor properties, whenever using deactivated or inert substrates (like aryl bromides and chlorides), along with the requirement to work at high temperatures.

However, the reported studies show an important particular character, specific to each substrate and to the reaction conditions, regarded as a set of interdependent factors. Taking into account each parameter influencing the reaction progress, and furthermore, influencing each other, it becomes difficult to establish some general reaction conditions for the Sonogashira cross-coupling, regardless the substrate type. In the light of the organic chemist, the above exposed reasons suggest the actuality of studies in this field.

R E F E R E N C E S (SELECTION)

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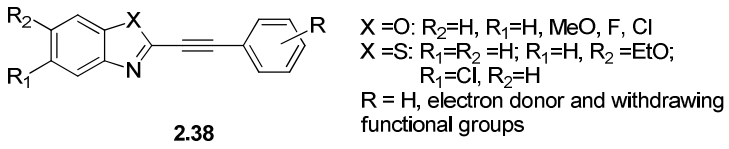
Chapter 2. Benzazole thioorganic derivatives – alternative electrophilic partners in Sonogashira cross-coupling reaction

Heteroaromatic thioorganic derivatives like: thioesters, thioethers, sulfonyl chlorides, thiones, sulfoxides, sulfinic acids, sulfinates or sulfonylhydrazides are viable electrophilic substrates, alternative to halides, in metal-catalyzed cross-coupling reactions. In recent years, thioorganic derivatives found a great aplicability in the the field of heterocyclic compounds.

The numerous examples of the benzazole derivatives in biological chemistry, as well as the limited number of systematic studies regarding the reactivity of such compounds as coupling partners in the cross-coupling reactions justifies the investigation of the reactivity of benzoazole thioorganic derivatives in the Sonogashira reaction.

This chapter describes the results obtained in this direction. The heterocyclic substrates that were used to couple with various alkynes, under aerobe conditions, using palladium and Cu(I) catalysis were benzoxazole and benzotiazole methylthioethers as well as their corresponding mercapto derivatives. A series of aliphatic and aromatic alkynes, bearing both electron withdrawing and donor functional groups were used as nucleophilic partners to yield 2-alkynyl-benazoles of type **2.38**. (**Scheme 8**).



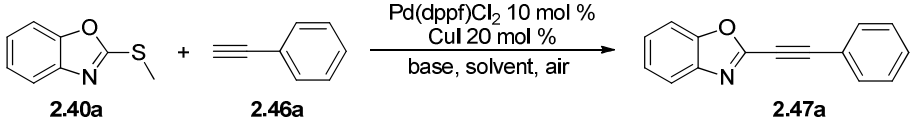
2.38

Scheme 8 Structure of the synthesized compounds

2.1. Optimization of the coupling reaction conditions

The 2-(methylthio)benzazol substrates were prepared starting from their corresponding 2-mercaptoderivatives, by an alkylation reaction of the sulfur atom with methyliodide under basic medium. [1]

Since benzazole thioethers have not been reported as electrophilic partners in the Sonogashira cross-coupling, this work began with an exploration of the reaction conditions using as model the coupling of 2-(methylthio)benzoxazole **2.40a** with phenylacetylene **2.46a,** in presence of copper(I) iodide and$Pd(dppf)Cl_2$ as the palladium source (**Scheme 9**).



2.40a **2.46a** **2.47a**

Scheme 9 Model reaction used for the optimization of the coupling reaction conditions of 2-(methylthio)benzoxazole **2.40a** with phenylacetylene **2.46a**

Election of this palladium complex was in line with previous reports which proved efficiency of this catalytic system with various heteroaromatics. [2]

In order to find the optimum reaction conditions for the preparation of compound **2.38a** we studied the influence of the following parameters: solvents, bases, alkyne equivalents as well as temperature and reaction times (**Table 1**).

Table 1 Optimization of the cross-coupling reaction conditions between 2-(methylthio)benzoxazole **2.40a** and phenylacetylene **2.46a**

Entry	Solvent	Temp. (°C)	Equivalents of 2.46a	Co-catalyst	Base	Reaction time (h)	η (%)
1[a]	THF	66	2	CuI	TEA	6	traces
2[a]	1,4-Dioxane	100	2	CuI	TEA	6	32
3	1,4-Dioxane	100	2	CuI	TEA	6	52
4	1,4-Dioxane	100	3	CuI	TEA	24	69
5[a]	Toluene	110	2	CuI	TEA	6	47
6	Toluene	110	2	CuI	TEA	6	67
7	**Toluene**	**110**	**3**	**CuI**	**TEA**	**24**	**72**
8	Toluene	110	3.5	CuI	TEA	24	70
9	DMF	130	3	CuI	TEA	24	traces
10	DMF	130	2	CuI	Cs_2CO_3	24	traces
11	-	106	2	-	piperidine	24	traces

[a] *Reaction performed under Ar*

The highest yield for the coupling reaction of 2-(methylthio)benzoxazole **2.40a** with phenylacetylene **2.46a** (***Table 1, entry 7***) was obtained when ***toluene was used as solvent, triethylamine as base, three equivalents of alkyne, aerobe atmosphere, rection time of 24 h and reflux temperature(120°C)***.

Expectedly, all reactions provided the homocoupling side-product, 1,4-diphenyl-1,3-butadiyne, as a combined result of the aerobic atmosphere [3] and the excess alkyne.

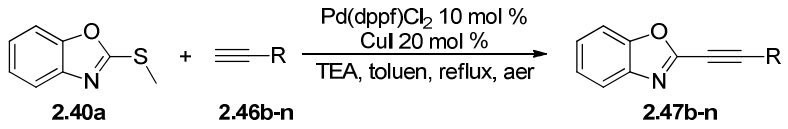
2.2. The reaction scope

With the optimized reaction conditions in hand, (**Table 1**, entry 7) the reaction scope was investigated (**Scheme 10**) by coupling between 2-(methylthioether)benzoxazole **2.40a** and a wide variety of substituted acetylenes (**Table 2**), taking into account both the reactivity of the alkynes and the optimum molar ratio substrate/alkyne. (**Table 2**)

The yields obtained in each case varied according to the nature of the alkyne partner. In the case of the aryl acetylenes with *electron-donor substituents* (**2.46b-g**), the yields differed according to the position of the substituent on the benzene ring. The *ortho*-substituted aryl acetylenes gave the highest yields (Table **2**, 92% for **2.38d** and 90% for **2.38g**). This was consistent with previous studies performed under classical Sonogashira cross-coupling reaction [4], which showed that bulky substituents in the *ortho* position of the aryl ring of the alkyne enhances the cross-coupling reaction rate.

Coupling of the aryl acetylenes with *electron-withdrawing substituents* led to overall yields significantly lower than those involving electron-rich alkynes (**Table 2**). However, using this protocol, we made possible the synthesis of new acetylene bridged benzoxazole compounds containing electron-withdrawing substituted aryl rings. Use of aliphatic alkynes in

the cross-coupling reaction led to very good yields using only 1.5 equivalents of the alkyne (**Table 2**, entries 12, 13). The literature data indicates that coupling reactions with aromatic alkynes are favored to the aliphatic alkynes. [5] The results obtained in this study show a higher reactivity of the aliphatic alkynes in the coupling reaction with the methylthioether **2.40a**. A possible reason for this behavior could be their lower reactivity in the homocoupling reaction, therefore having an implicit higher availability to participate in the cross-coupling reaction.



Scheme 10 The coupling reaction between the thioether derivative **2.40a** and the substituted alkynes **2.46b-n**

Table 2 Yields of the coupling reactions between 2-(methylthio)benzoxazole **2.40a** and substituted alkynes

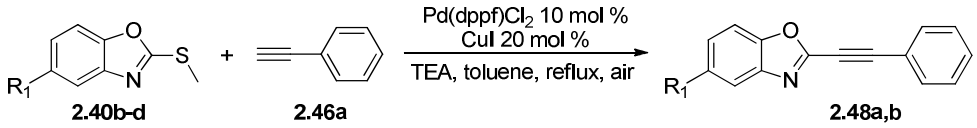
Entry	Alkyne	R	No. equiv. alkyne	Reaction time (h)	Product	η (%)
1	**2.46b**	4-Me-C_6H_4	1,5/2/3	24/24/24	**2.38b**	57/59/60
2	**2.46c**	3-Me-C_6H_4	1,5/2/3	24/48/24	**2.38c**	30/57/73
3	**2.46d**	2-Me-C_6H_4	1,5/3	24/24	**2.38d**	27/92
4	**2.46e**	4-MeO-C_6H_4	2/3	24/24	**2.38e**	47/52
5	**2.46f**	3-MeO-C_6H_4	3	24	**2.38f**	62
6	**2.46g**	2-MeO-C_6H_4	3	24	**2.38g**	90
7	**2.46h**	4-F-C_6H_4	3	24	**2.38h**	56
8	**2.46i**	3-F-C_6H_4	3	24	**2.38i**	45
9	**2.46j**	4-CN-C_6H_4	1,5/2/3	36/36/24	**2.38j**	14/17/29
10	**2.46k**	4-CF_3-C_6H_4	3	24	**2.38k**	19
11	**2.46l**	3-Cl-C_6H_4	1,5/2/3	36/36/24	**2.38l**	48/52/54
12	**2.46m**	C_5H_{11}	1.5	24	**2.38m**	62
13	**2.46n**	C_6H_{11}	1.5	24	**2.38n**	77

2.3. Sonogashira cross-coupling reactions of substituted 2-(methylthio)benzoxazoles

Table 3 displays the results of the coupling reactions of substituted methylthioethers **2.40b-d** with phenylacetylene **2.46a** (**Scheme 11**), using the reaction conditions described in **Table 1**, entry 7**.**

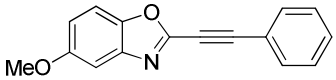
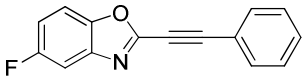
The reaction performed with the methoxy substituted benzoxazole thioether resulted in a slightly higher yield than that with the fluoro substituted derivative.

The coupling reaction of the bromoderivative **2.40e** under aerobe conditions did not selectively performed, yielding the dialkynylated compound **2.49** (**Scheme 12**).

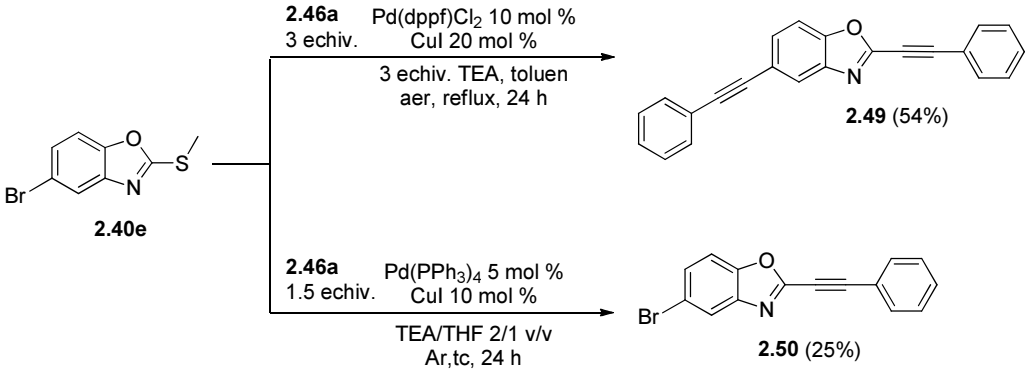


Scheme 11 The coupling reaction of substituted benzoxazole methylthioethers **2.40b-d** with phenylacetylene **2.46a**

Table 3 The yields of the coupling reactions between the derivatives **2.40b-d** with the alkyne **2.46a**

Entry	Reactant	R_1	No. equiv. alkyne	Reaction time (h)	Product	**η** (%)[a]
1	**2.40b**	MeO	3	24	 **2.48a**	75
2	**2.40c**	F	3	24	 **2.48b**	67
3	**2.40d**	Cl	3	24	-	-

The attempt to selectively perform the cross-coupling reaction of the compound **2.40e** with phenylacetylene *via* the classical Sonogashira protocol (under inert atmosphere, at room temperature), surprisingly yielded the 2-alkynylated product **2.50** (**Scheme 12**), with preservation of the bromine substituent. The molecular diversity of these substrates could be further increased through reactions of the C-Br bond.

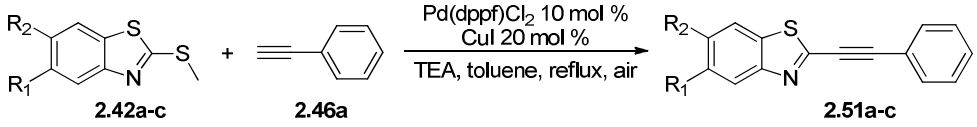


Scheme 12 Coupling reactions of the bromoderivative **2.40e** with phenylacetylene **2.46a**

2.4. Sonogashira cross-coupling reactions of benzothiazole methylthioethers

To further broaden the scope of the alkynylation procedure, we also examined the use of 2-(methylthio)benzothiazoles **2.42a-c** as substrates (**Table 4**) in the coupling reaction with phenylacetylene **2.46a** (**Scheme 13**).

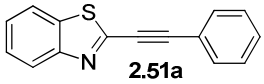
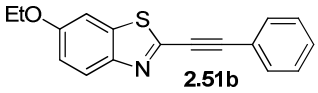
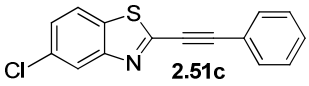
The yields of the cross-coupling reactions were similar to their corresponding benzoxazole derivatives for compounds **2.51a** (53%) and **2.51b** (60%), while the chlorine product **2.51c** was obtained in 40%, which was higher than its benzoxazole derivative which was not formed. The general reactivity of 2-(methylthio)benzothiazoles is slightly lower than both the benzoxazole thioethers and the mercaptobenzothiazole analogues (*vide infra*), except for the chlorosubstituted derivative.



2.42a-c 2.46a 2.51a-c

Scheme 13 Cross-coupling reaction between the benzothiazole methylthioethers **2.42a-c** and the phenylacetylene **2.46a**

Table 4 The coupling yields between the substituted benzothiazole methylthioethers **2.42a-c** and the phenylacetylene **2.46a**

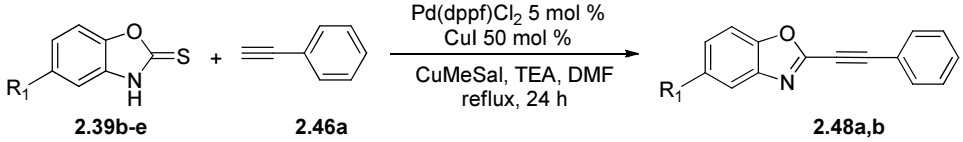
Entry	Reactant	R^1	R^2	No. equiv. alkyne	Reaction time (h)	Product	η (%)
1	**2.42a**	H	H	3	24	 **2.51a**	53
2	**2.42b**	H	EtO	3	24	 **2.51b**	60
3	**2.42c**	Cl	H	3	24	 **2.51c**	40

2.5. Sonogashira cross-coupling reactions of benzazole mercaptoderivatives

2.5.1. Sonogashira cross-coupling of 2-mercaptobenzoxazole derivatives

The coupling reactions between the substituted 2-mercaptobenzoxazole derivatives **2.39b-e** and the phenylacetylene **2.46a (Scheme 14)** were performed under the optimized reaction conditions that were foundfor the model coupling reaction between 2-mercaptobenzoxazole and phenylacetylene. The results are summarized in **Table 5**.

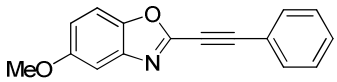
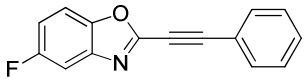
We observed that successful coupling was only achieved for the methoxy-substituted benzoxazole **2.39b** (**Table 5, entry 1**), proceeding in a modest yield (30%), while for the fluorine derivative **2.39c** (**Table 5, entry 2**) only traces of the product were observed by TLC. No coupling products were detected for the chlorine and bromine derivatives **2.39d** and **2.39e** (**Table 5, entries 3, 4**).



2.39b-e 2.46a 2.48a,b

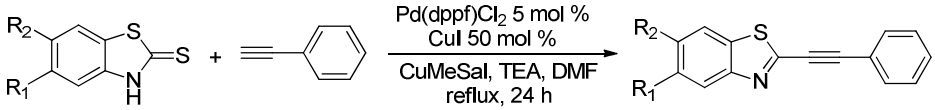
Scheme 14 The copuling reactions between compounds **2.39b-e** and phenylacetylene **2.46a**

Table 5 The coupling reaction yields between the substituted mercaptobenzoxazole derivatives **2.39b-e** and phenylacetylene **2.46a**

Entry	Compound	R_1	No. equiv. alkyne	Product	η (%)
1	**2.39b**	MeO	3	 **2.48a**	30
2	**2.39c**	F	3	 **2.48b**	traces
3	**2.39d**	Cl	3	-	-
4	**2.39e**	Br	3	-	-

2.5.2. The coupling reactions of 2-mercaptobenzothiazole derivatives

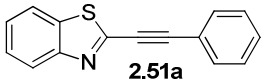
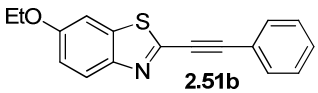
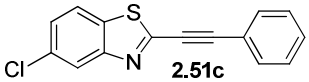
With the optimized reaction conditions in hand, the scope of the substrates was examined, by investigating the reactivity of 2-mercaptobenzothiazoles **2.41a-c** in the copupling reaction with phenylacetylene **2.46a** (**Scheme 15**) and the results are summarized in **Table 6**.



2.41a-c **2.46a** **2.51a-c**

Scheme 15 The coupling reactions between the mercaptobenzothiazole derivatives **2.41a-c** and the phenylacetylene **2.46a**

Table 6 The coupling reaction yields between the substituted mercaptobenzothiazole derivatives **2.41a-c** and the phenylacetylene **2.46a**

Entry	Compound	R_1	R_2	No. equiv. alkyne	Product	η (%)
1	**2.41a**	H	H	3	 **2.51a**	70
2	**2.41b**	H	EtO	3	 **2.51b**	75
4	**2.41c**	Cl	H	3	 **2.51c**	38

We observed an enhanced reactivity of the 2-mercapto-bezothiazole derivatives compared to all their 2-mercapto-benzoxazole derivatives as well as to their corresponding

thioethers in the case of compounds **2.51a** and **2.51b**. A possible explanation for this enhanced reactivity would be the higher aromaticity of the benzothiazole heterocycle, compared to benzoxazole. Consequently, the thione species prevails in the case of the benzothiazole derivative, which further allows the efficient coordination of CuMeSal, in agreement with Tatibouet mechanistic proposal [6]. This could influence both the oxidative addition step of the subatrate to the palladium catalytically active species, by activation of the C-S bond, as well as the transmetallation step of the copper acetylide, by activation of the Pd-S bond. Once again we noticed the enhanced reactivity of the substrate decorated with an electron-donating group **2.41b** than the chlorosubstituted compound **2.41c**.

Altogether, these results show that the 2-mercaptobenzothiazole derivatives are more efficient substrates in the Sonogashira desulfitative coupling reaction than their 2-mercaptobenzoxazole analogues.

2.6. Conclusions

In conclusion, we described a new C-C cross-coupling reaction of 2-methylthio-benzoxazole with terminal alkynes, using palladium and copper(I)-catalysis under aerobic conditions. The synthetic approach allowed preparation of 2-alkynyl benzoxazole derivatives containing aliphatic and substituted electron-donor and electron withdrawing aromatic moieties in moderate to good yields. In addition, the reaction proved to perform well when various benzothiazole methylthioethers, as well as mercapto benzothiazoles were used, providing coupling products in high yields. Our work showed that the reaction occurred better under aerobic conditions rather than an inert atmosphere. Use of 5-bromo-2-(methylthio)benzoxazole in our aerobic coupling conditions occurred with concomitant C-Br and C-S coupling of the alkyne. Surprisingly, the C-S cross-coupling reaction occurred selectively under an inert atmosphere, at room temperature, although in modest yield, allowing the possibility to further functionalize the benzoxazole core using the C-Br bond and therefore, extending the scope of the reaction.

R E F E R E N C E S (SELECTION)

[1]. L. Melzig, A. Metzger, P. Knochel, *J. Org. Chem.* **2010**, *75*, 2131.

[2]. B. C. Shook, D. Chakravarty, P. F. Jackson, *Tetrahedron Lett.* **2009**, *50*, 1013.

[3]. J. Tsuji, *Palladium Reagents and Catalysts—New Perspectives for the 21st Century*, John Wiley & Sons, New York, **2004**.

[4]. M. Schilz, H. Plenio, *J. Org. Chem.* **2012**, *77*, 2798.

[5]. L. Lu, H. Yan, P. Sun, Y. Zhu, H. Yang, D. Liu, G. Rong, J. Mao, *Eur. J. Org. Chem.* **2013**, 1644.

[6]. S. Silva, B. Sylla, F. Suzenet, A. Tatibouet, A. P. Rauter, P. Rollin, *Org. Lett.* **2008**, *10*, 853.

Chapter 3. Synthesis and behaviour of 1,3,4-oxadiazole thioderivatives in Sonogashira cross-coupling reaction

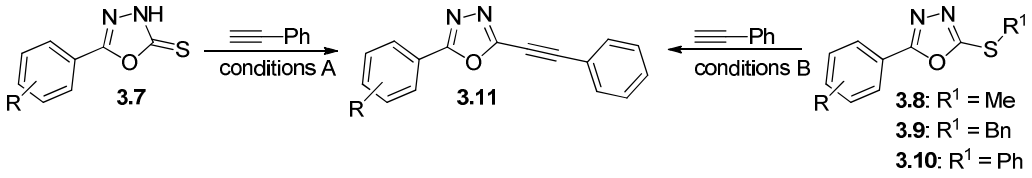
This chapter presents the results regarding behaviour of π-deficient 1,3,4-oxadiazole thioderivatives as electrophilic substrates in the Sonogashira cross-coupling reaction.

As an extension of our previous findings regarding the cross-coupling reactions of sulfur-heteroaromatics with terminal alkynes, we approached synthesis of the thiones, as well as their corresponding methyl, benzyl and phenyl thioethers and subsequent metal catalyzed cross-coupling of these compounds with phenylacetylene. Besides the synthetic effort aimed to obtain new (poly)alkynylated compounds containing one, two or three heterocyclic rings, our objective was to investigate how the substituent of each molecule as well as the thioether type influence the Pd-catalysed desulfitative alkynylation, considering that previous reports [1-5] did not indicate a significant influence of the oxadiazole aryl substituent onto the coupling reaction yields.

3.1. Investigation of the cross-coupling reaction between thione and thioether 1,3,4-oxadiazole substrates and phenylacetylene

The organosulfur heteroaromatics have recently gained attention as suitable alternative electrophilic partners in cross-coupling reaction, particularly because their stability and synthetic availability are more advantageous compared to the corresponding halides.

Due to their electron-deficient character, the oxadiazoles of type **3.7-3.10** (**Scheme 16**) meet the requirements of alternative electrophilic partners in the Sonogashira cross-coupling reaction.



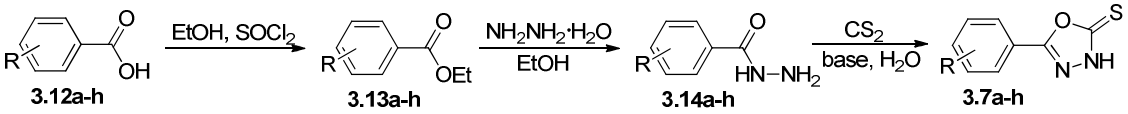
Scheme 16 General synthetic scheme for the cross-coupling reaction between phenylacetylene and compounds **3.7** (conditions A: CuI, Cu(I) 3-methylsalycilate, Pd(dppf)Cl_2, triethylamine, *N*,*N'*-dimethylformamide, reflux) and compounds **3.8**, **3.9** and **3.10**, respectively, (conditions B: CuI, Pd(dppf)Cl_2, triethylamine, toluene, reflux) to yield compounds **3.11**

The Sonogashira reactions of heteroaromatic thiones and thioethers, as electrophilic partners, were less exploited (Section 1.2.3). In particular, the heteroaromatic benzyl thioethers have not been reported so far in this cross-coupling reaction.

3.1.1. Synthesis of the substrates

The mercaptoderivatives **3.7** (**Schemes 17, 18)** and the methyl, benzyl and phenyl thioethers **3.8**, **3.9** and **3.10** respectively (**Scheme 20**) were synthesized in order to be further used in the coupling reactions with phenylacetylene.

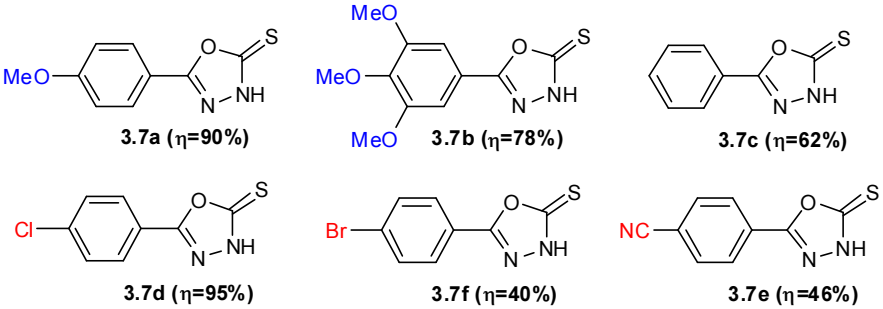
The 5-substituted-1,3,4-oxadiazole-2(3*H*)-thiones **3.7a-h** (**Scheme 17**) were readily accessible from the corresponding hydrazides (compound **6a-f**), in basic medium (aqueous sodium hydroxide) using carbon disulfide as sulfur source, in good to excellent yields. [6]



R: a=4-MeO, b=3,4,5-(MeO)$_3$, c=H, d=4-Cl, e=4-CN, f=4-Br, g=4-Me, h=3-NO$_2$

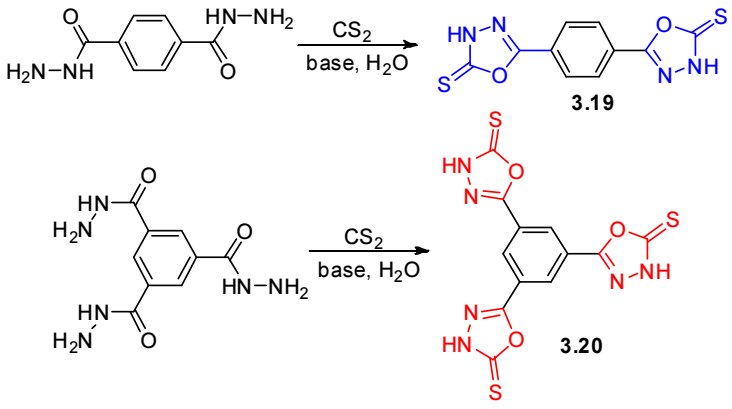
Scheme 17 Synthetic scheme for the preparation of hydrazides **3.14a-h** and, respectively, of thiones **3.7a-h**

We synthesized a variety of substrates containing either electron-donor or electron-withdrawing substituents on the phenyl ring (**Scheme 18**).



Scheme 18 The synthesis yields of thiones **3.7a-f**

Using the same protocol, bis- and tris-1,3,4-oxadiazole thiones **3.19** and **3.20** were synthesized in order to study their reactivity toward the Sonogahsira cross-coupling (**Scheme 19**).

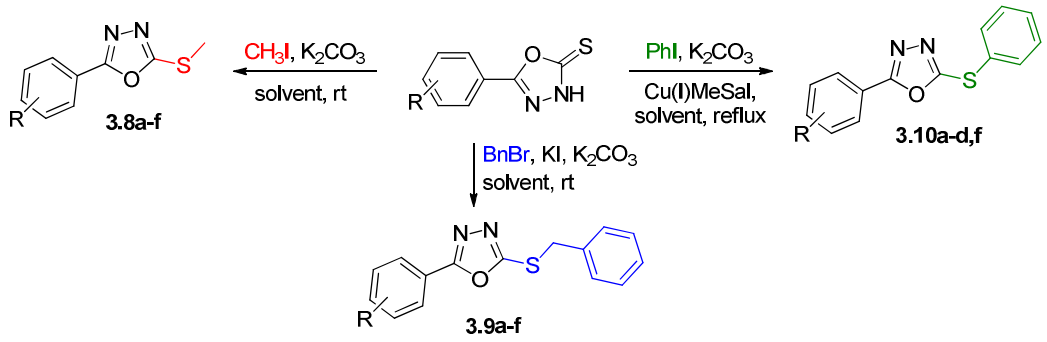


Scheme 19 Synthesis of bis-thione **3.19** and tris-thione **3.20**

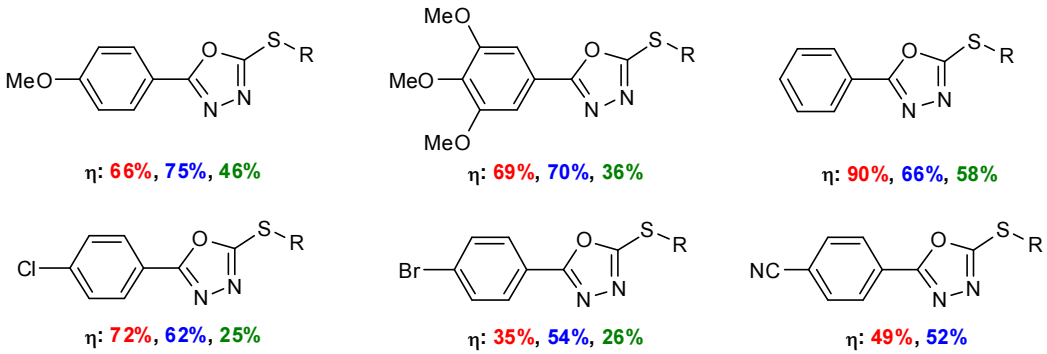
The methylthioethers **3.8a-f (Schemes 20, 21)** were synthesized in good to very good yields starting from the corresponding mercaptoderivatives through a simple alkylation of the thiol group with methyl iodide, using potassium carbonate as base and THF as solvent.

The benzylthioethers **3.9a-f** (**Schemes 20, 21**) were similarly obtained, using benzyl bromide and a stoichiometric amount of potassium iodide.

The phenylthioethers **3.10a-d,f** (**Schemes 20, 21**) were synthesized following a slightly modified previously described procedure, using copper(I) 3-methylsalicylate. [7]

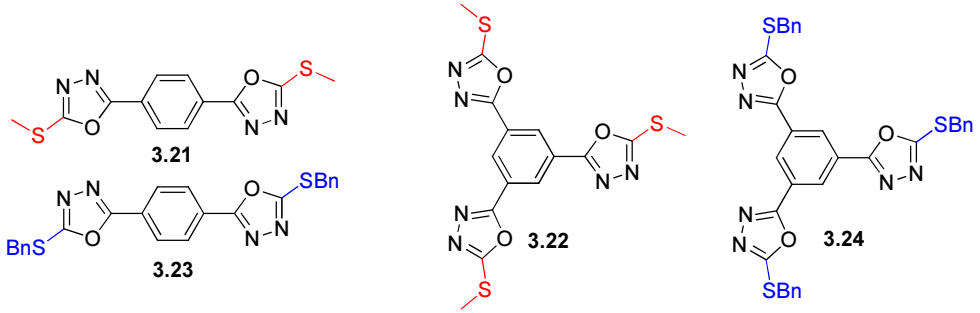


Scheme 20 General synthesis scheme for the preparation of methyl, benzyl and phenyl thioethers **3.8a-f, 3.9a-f** and **3.10a-d,f**



Scheme 21 The yields of the isolated compounds **3.8a-f**, **3.9a-f** and **3.10a-d,f**

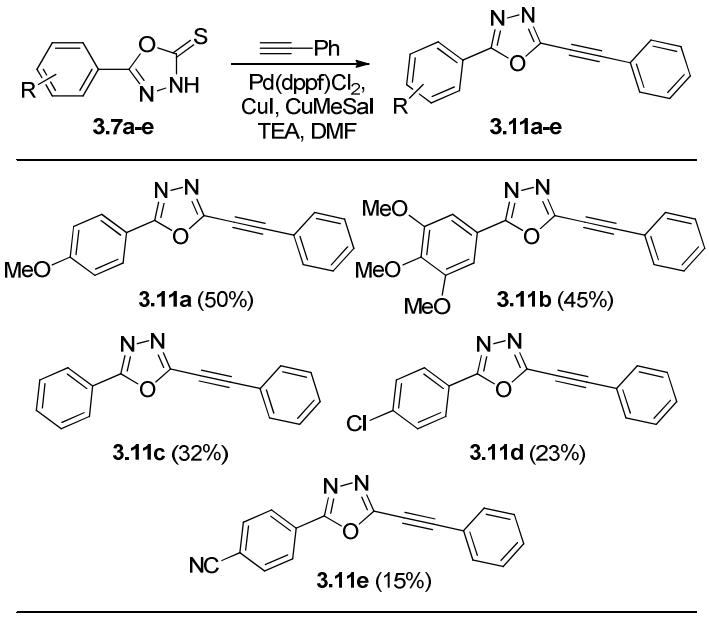
We also used bis- and tris- thiones **3.19** and **3.20** to synthesize the thioethers **3.21-3.24** (**Scheme 22**), in order to obtain new alkynylated compounds, otherwise more difficult to be achived.



Scheme 22 Structures of bis- and tris- methylthioethers **3.21** and **3.22** and bis- and tris-benzylthioethers **3.23** and **3.24**

3.1.2. Investigation of 1,3,4-oxadiazole thiones behaviour in Sonogashira cross-coupling reaction

Based on our previous findings, we approached the investigation of the reactivity of the 1,3,4-oxadiazole thiones **3.7a-e** in the Sonogashira cross-coupling reaction using the previously examined conditions. Thus, we used $Pd(dppf)Cl_2$ as palladium source (5 mol%), CuI (50 mol%) and Cu(I)MeSal (1 eq,) as copper sources, DMF as solvent and triethylamine as base and cosolvent. The yields of the isolated coupling products **3.11a-e** obtained for the reaction of the substrates **3.7a-e** with phenylacetylene varied between 10-44%, as shown in **Scheme 23**.



Scheme 23 The coupling reactions between the thiones **3.7a-e** with phenylacetylene (yields of isolated products)

Previous studies performed on the Sonogashira reaction using heteroaromatic or electron-deficient aromatic halides indicated that the reaction occurred better or site-selectively if the carbon atom bonded to the halogen had a high electrophilic character, which was favored by presence of strong electron-withdrawing substituents, or the proximity of electronegative heteroatoms. [8]

On the contrary, in the case of our alternative substrates, bearing a π-deficient character, one can note that the cross-coupling reaction occurred better for the substrates bearing electron-donor substituents on the aryl ring (compounds **3.7a** and **3.7b**), whereas the cyano-substituted compound **3.7e** proved to be the least reactive.

The same reactivity profile was also noticed in the case of the mercaptobenzoxazoles described in Chapter 2.

Examination of the reaction mechanism proposed by Tatibouet et al [9] for the oxazolinethione heterocycles, , suggests a similar reaction pathway for coupling of the thiones **3.7**. On the basis of the proposed mechanism, one can correlate the reactivity of the thiones substrates with the charge density onto the sulfur atom. This might indicate that substrates

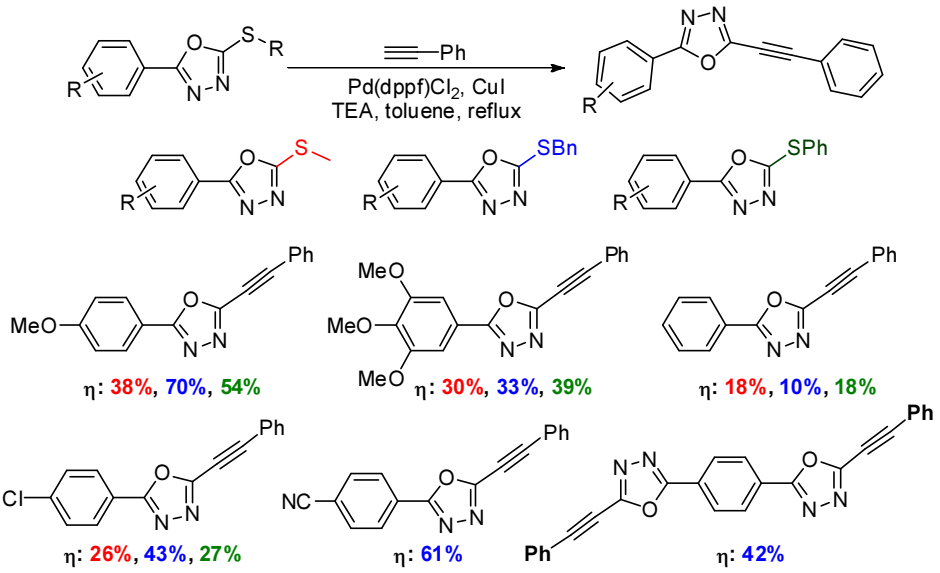
bearing a greater negative charge on the sulfur atom are prone to perform better in the coupling reaction. A greater electron density on the sulfur atom [10] acts as a favouring factor, interfering both in the oxidative addition and the transmetallation steps.

The thiones **3.19** and **3.20** were inert in the Sonogashira cross-coupling reaction with phenylacetylene. The low solubility of the thione **3.20** could be one of the factors which generated their low reactivity.

3.1.3. Investigation of 1,3,4-oxadiazole thioethers behaviour in Sonogashira cross-coupling reaction

We further investigated the cross-coupling reaction between thioethers **3.8-3.10** and phenylacetylene (**Scheme 24**), using the reaction conditions previously described: $Pd(dppf)Cl_2$ 10 mol%, CuI 20 mol%, triethylamine (2 equiv.), toluene as solvent, aerobe atmosphere and the reflux temperature of the solvent for 24h.

The results obtained for coupling of each oxadiazole thioether are depicted in **Scheme 24**. Overall, from a synthetic point of view, the benzylthioethers are a convenient choice both for the synthesis of 2-alkynyl-5-(substituted-aryl)-1,3,4-oxadiazoles **3.11**, and for synthesis of the alkynylated bis-oxadiazole coupling product.

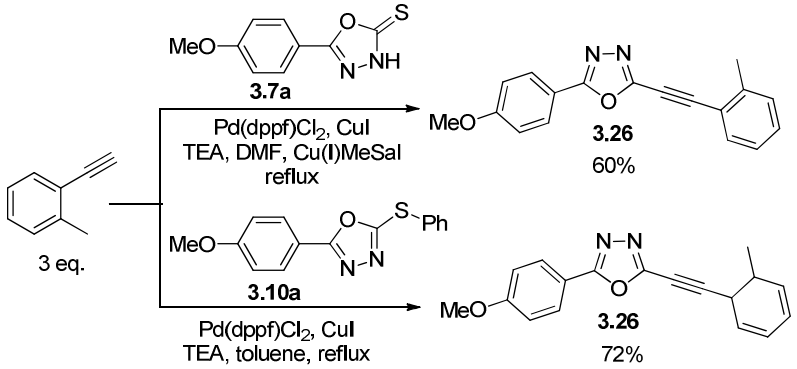


Scheme 24 The coupling reactions between the thioethers **3.8-3.10** and **3.23** and phenylacetylene and the yields of the isolated products

As far as the bis-and tris-thioethers **3.21-3.24**are concerned, one can note the following: the methyl thioether **3.21** was totally inactive in the cross-coupling reaction, while the benzylthioether **3.23** yielded the bis-alkynylated coupling product in 42% yield. No coupling product was detected between thioethers **3.22, 3.24** and phenylacetylene. The low coupling products yields obtained in some cases may be the result of each substrate electronic particularity in conjunction with the thioether type, in the sense there might be a random preference of the C-S bonds for the Pd-catalyst. [11]

3.1.4. The reaction scope

The reaction scope may be extended by variation of the nucleophilic partner. As an example, reaction between the thione **3.7a** and 2-ethynyltoluene (**Scheme 25**) provided product **3.26** in 60% yield. Similarly, the cross-coupling reaction between the phenylthioether **3.10a** and the same alkyne yielded product **3.26** in 72%. One can note the higher yields obtained when using 2-ethynyltoluene as nucleophilic partner than in the case of the phenylacetylene. This result proves that the coupling reaction mechanism is definitely influenced of a great number of factors. The steric factor imposed by the *ortho*-substituted alkyne interfere in the reductive elimination step while the electronic factor, linked to the higher nucleophilicity of the same alkyne has a positive effect in the transmetallation step.

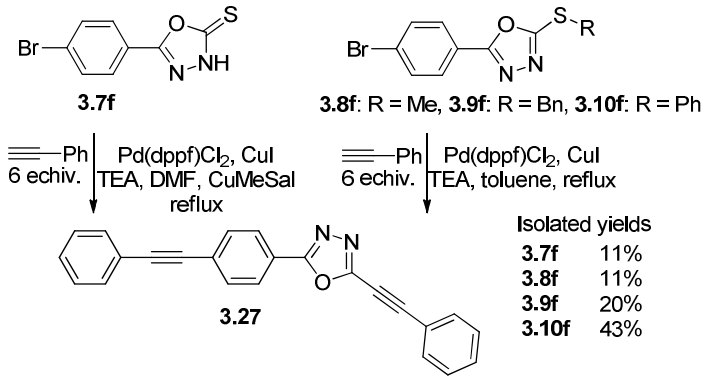


Scheme 25 The coupling reactions between 2-ethynyltoluene and the thione **3.7a**, respectively, the thioether **3.10a**

Therefore, each heterocyclic substrate may be used to design new alkynyl-1,3,4-oxadiazoles in combination with a wide variety of substituted-alkynes, allowing, thus, the possibility to achieve a large number of diverse structural compounds.

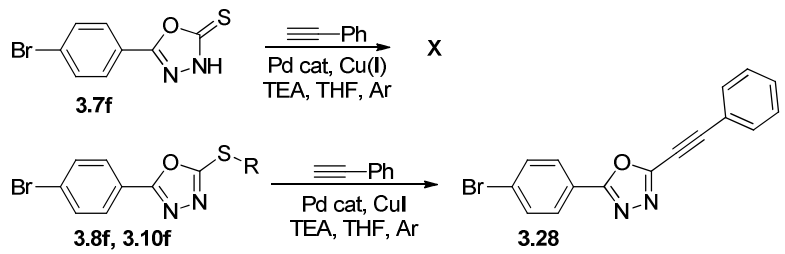
3.1.5. The chemoselective coupling reaction of substrates bearing two reaction centres

Any attempt to perform a selective cross-coupling of the C-S bond in presence of a bromine atom was not successful. Increase of the alkyne amount proceeded with double cross-coupling, providing compound **3.27** in all cases (the yields of isolated products are shown in **Scheme 26)**.



Scheme 26 The coupling reactions between the bromoderivatives **3.7f, 3.8f** and **3.9f** and, **3.10f** and the phenylacetylene

These results led to the attempt to realize a selective cross-coupling of the C-Br bond, using $Pd(PPh_3)_4$ (5 mol%) or $Pd(dppf)Cl_2$ (5 mol%) as palladium source and CuI (10 mol%) as copper source, THF as solvent and triethylamine as base and cosolvent, for 24h, under an inert atmosphere (**Scheme 27**). The bromothione **3.7f** was inert in this coupling reaction when working with $Pd(PPh_3)_4$, at room temperature. Changing the palladium cathalyst with $Pd(dppf)Cl_2$ led to the selective coupling of the C-S bond, providing the mono-alkynylated bromoderivative **3.28** in 13% yield when the bromo-methylthioether **3.8f** was used and 14% yield when the bromo-phenylthioether **3.10f** was used.



Scheme 27 Coupling reactions between the bromosubstrates **3.7f**, **3.8f** and **3.10f** and phenylacetylene under inert atmosphere

Overall, we can draw the following conclusions: *i)* the C-Br bond does not prove to be enough activated by the electron-withdrawing oxadiazole moiety, in order to react in the Sonogashira coupling under the investigated reaction conditions [12]; *ii)* the C-S bond in the oxadiazole thiones and thioethers requires the oxygene presence in the reaction medium along with increased temperatures in order to generate the alkynylated products.

3.2. Conclusions

In conclusion, we performed synthesis of a series of π-deficient heterocycles and used them as substrates in Sonogashira reaction, in order to accomplish an extensive screening of the C-C bond formation efficiency through C-S cleavage of 1,3,4-oxadiazole-2-thiones or 2-thioethers. Overall, the reactivity of the thiones and various thioethers (methyl, benzyl and phenyl) as alternative electrophiles in this reaction is moderate. The thione substrates containing electron-donor substituents on the phenyl ring in position 5 of the heterocylic ring provided higher coupling products yields, most probably due to an increased negative charge on the sulfur atom. The coupling reactions between the thioethers and phenylacetylene occurred irregularly in terms of yields. We could observe that the electron-donor substituted compounds (*p*-methoxyphenyl) were more reactive in all cases (thione, methyl, benzyl and phenyl thioethers). However, the 2-alkynyl-1,3,4-oxadiazole substituted with *p*-cyanophenyl could be prepared in a very good yield starting from the corresponding benzylthioether compound. Similarly, a good coupling product yield was achieved when 1,4-bis(5-(benzylthio)-1,3,4-oxadiazol-2-yl)benzene was used as substrate in reaction with phenylacetylene. The synthetic scope of 5-substituted-2-alkynylated-1,3,4-oxadiazoles may be extended by use of other alkynes as coupling partners.

R E F E R E N C E S (SELECTION)

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Chapter 4. Synthesis of new alkynyl-bridged 2,5-disubstituted-1,3,4-oxadiazoles by Sonogashira cross-coupling

The aim of this study was to design and prepare a series of organic compounds bearing π-extended conjugated structures that display enhanced photophysical properties and constitute proper candidates as OLEDs precursors.

Hence, the design of new ethylyne-bridged-1,3,4-oxadiazoles bearing various combinations of electron-donating or withdrawing functional groups, both on the alkyne and the oxadiazole core, is still challenging in order to obtain molecules with improved optoelectronic properties.

The synthetic approach used a convenient procedure and follows a three step pathway: the synthesis of *N*-acylhydrazones, their oxidative cyclisation and the Sonogashira cross-coupling of the 2-(*p*-bromophenyl)-5-aryl-1,3,4-oxadiazoles key intermediates with various alkynes.

The electron-transporting behaviour of the 1,3,4-oxadiazole core and its electron withdrawing ability have reasoned the utility of 2-(*p*-bromophenyl)-5-aryl-1,3,4-oxadiazoles as convenient electrophilic substrates in Sonogashira cross-coupling reaction.

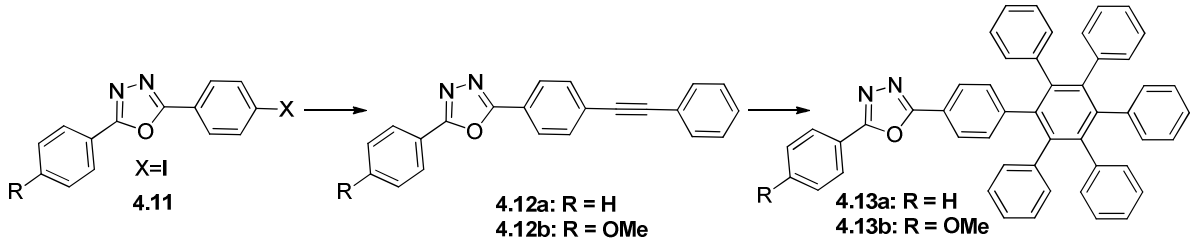
4.1. The relevance of alkynyl-bridged 2,5-disubstituted-1,3,4-oxadiazole derivatives

Organic compunds bearing π-conjugated structures are currently a topic of interest in materials chemistry, due to their photo- and electroluminescent properties. The utility of such systems is related to the synthesis of electroluminescent diodes [1] and photovoltaic cells [2].

The 2,5-disubstituted-1,3,4-oxadiazole derivatives are a class of heterocycles which features an electron deficient nature [3], high thermal stability and high quantum yields [4]. The electron mobility of the oxadiazole core recommends them as suitable moieties in the design of electron transporting materials for the preparation of *Organic Light Emitting Diodes - OLEDs*. [4]

The synthesys of alkynyl oxadiazole derivatives is justified both by the benefit of the oxadiazole core features and the extended conjugation, molecular rigidity and enhanced thermal stability induced by the alkynyl units. The alkynyl bond is a versatile structural unit, which can be further functionalised providing extended molecular diversity and fine tuning of the optoelectronic properties. Furthermore, the acetylenic unit can serve as a convenient bridge for the syntesis of donor-acceptor compounds. [5]

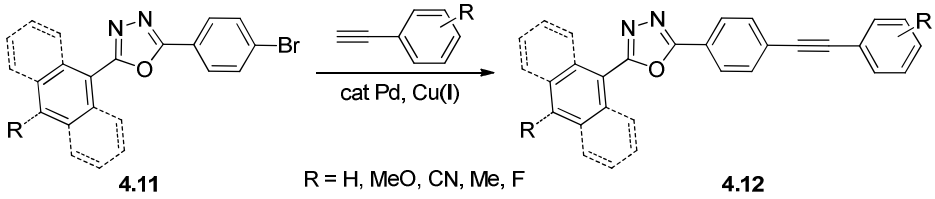
In addition, alkyne-substituted-1,3,4-oxadiazoles like **4.12** (**Scheme 28**) found use as building block for synthesis of further π-extended functional molecules. Notably, internal alkynes **4.12** were used in a Diels-Alder cycloaddition to generate compounds **4.13** that exhibit emissions in the UV region and very high fluorescence quantum yields (0.91 for **4.13a** and 0.85 for **4.13b** measured using quinine as reference). Blue electrophosphorescent devices with high efficiencies also resulted when used as host materials. [6]



Scheme 28 Synthesis of internal ethynyl-bridged-2,5-disubstituted-1,3,4-oxadiazoles precursors for compounds useful in OLEDs preparation

4.2 Synthesis of new alkynyl-bridged-2,5-disubstituted-1,3,4-oxadiazoles

The main purpose of this study aimed the design and synthesis of an extended series of alkynyl-bridged-2,5-diaryl-1,3,4-oxadiazoles **4.12** grafted with various substituents. The synthetic procedure involved the Sonogashira coupling of the key intermediates 2-(*p*-bromophenyl)-5-aryl-1,3,4-oxadiazoles **4.11** (**Scheme 29**).

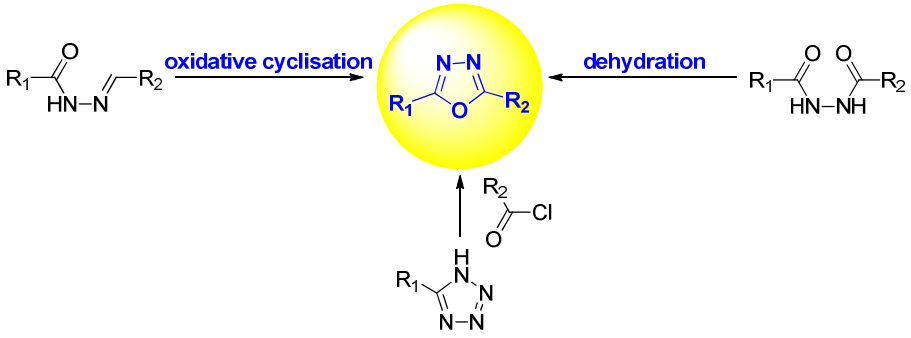


Scheme 29 The synthetic pathway of the alkynyl 2,5-diaril-1,3,4-oxadiazoles

The selection of the substituents grafted on the coupling partners was accomplished so that to provide coupling products substituted with functional groups with similar (MeO) or opposite (MeO and CN) electronic features, in order to study the influence of the structural particularities on the optoelectronic properties. Moreover, the naphtyl and anthranyl moieties were selected as a result of their recognised ability to induce good optoelectronic properties. [7]

4.2.1. Synthesis of bromo-oxadiazole substrates

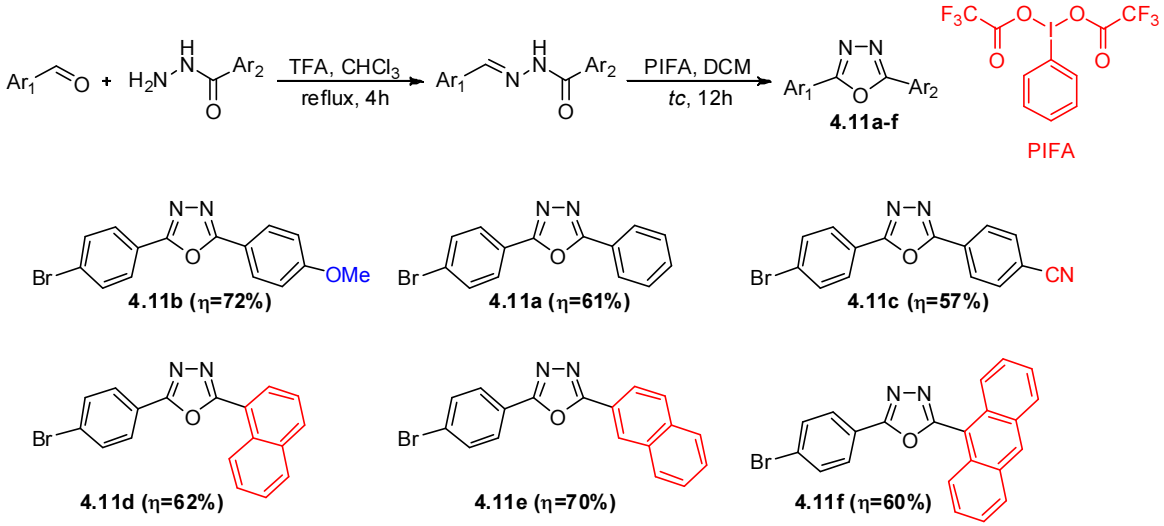
The oxadiazole heterocyclic ring may be usually obtained through the intramolecular dehydration of the *N,N'*-diacylhydrazines, the oxidative cyclisation of *N*-acylhydrazones or the Huisgen reaction of tetrazoles and acide chlorides. (**Scheme 30**). [8]



Scheme 30 General synthetic scheme of 2,5-disubstituted-1,3,4-oxadiazoles: dehydration of *N,N'*-diacylhydrazines, oxidative cyclisation of acylhydrazones and Huisgen reaction of tetrazoles and acide chlorides

Among the numerous methods described, we turned to the oxidative cyclisation using hypervalent iodine reagents due to the readily availability of the *N*-acylhydrazones from aldehydes and hydrazides, as well as the mild conditions required for the oxadiazole ring closure.

The 2,5-disubstituted-1,3,4-oxadiazole substrates **4.11** were synthesized following a two-step procedure (**Scheme 31**): condensation of the aldehydes with one of the corresponding hydrazides under acid catalysis (trifluoroacetic acid) and further treatment of the *N*-acylhydrazones with bis(trifluoroacetoxy) iodobenze (PIFA) at room temperature in dichloromethane, which led to the oxadiazoles **4.11a-f** in good to very good yields.



Scheme 31 Synthesis of the *N*-acylhydrazone precursors and the corresponding oxadiazoles **4.11a-f**

4.2.2. The Sonogashira coupling under inert atmosphere

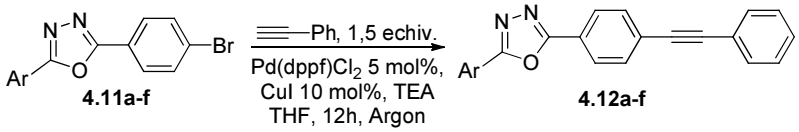
Once the substrates were synthesized, the cross-coupling reactions of **4.11a-f** derivatives with phenylacetylene (**Scheme 32**) were set up by modifying previously described procedures for Sonogashira couplings of aryl bromides. [9]

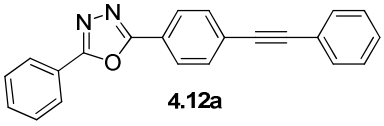
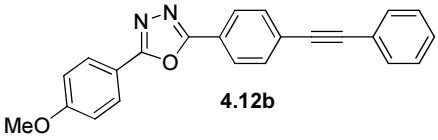
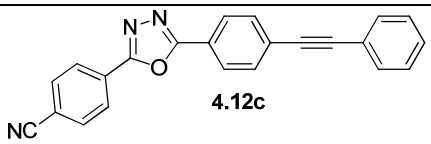
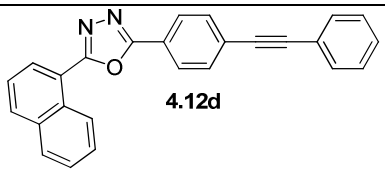
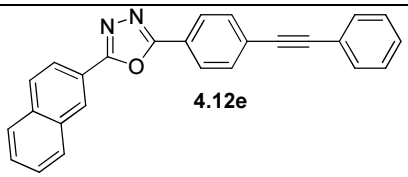
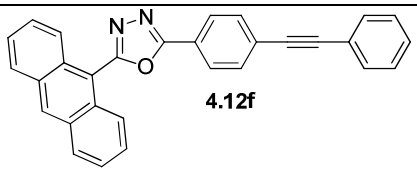
$Pd(dppf)Cl_2$ (5 mol%) was chosen as palladium source, considering the general advantages of a bulky diphosphine ligand for aryl bromides cross-couplings [10], mainly to better stabilize Pd(0) catalytic species over monodentate ligands (see Chapter 1).

Furthermore, we used CuI (10 mol%) as co-catalyst, tetrahydrofuran (THF) as polar aprotic solvent and triethylamine (TEA) as base. The reaction time was kept to 12h for all assays, under inert atmosphere, using 1.5 eq. of phenylacetylene.

Further, we successfully achieved synthesis of a diverse-substituted series of new alkynyl-bridged-1,3,4-oxadiazoles, using a variety of substituted arylacetylenes, as shown in **Scheme 33.**

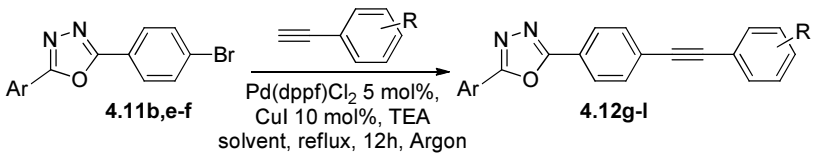
Generally, the coupling reactions proceeded in high yields. However, the 4-ethynylbenzonitrile proved to be less reactive than 4-ethynyltoluene and 2-ethynyltoluene, according to the decreasing order of the corresponding acetylides nucleophilicity.

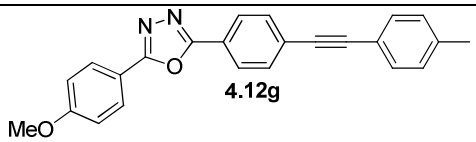


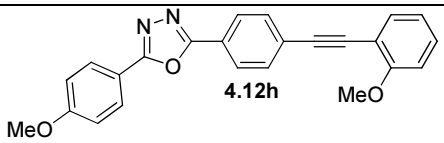
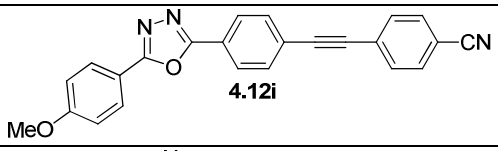
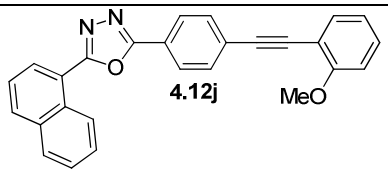
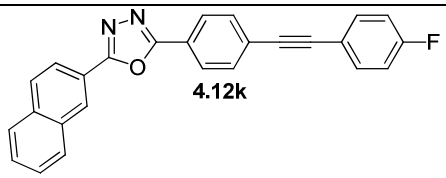
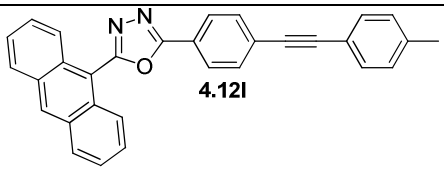
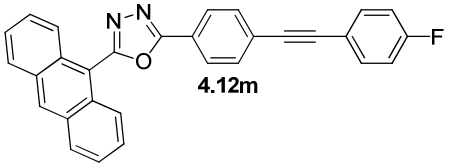
Entry	Compound 4.11	Ar	Temp. (°C)	Coupling product 4.12	η (%)
1	**4.11a**	Ph	25	 **4.12a**	-
2		Ph	63		70
3	**4.11b**	4-MeO-Ph	25	 **4.12b**	-
4		4-MeO-Ph	63		83
5	**4.11c**	4-CN-Ph	25	 **4.12c**	-
6		4-CN-Ph	63		75
7	**4.11d**	1-naphtyl	63	 **4.12d**	91
8	**4.11e**	2-naphtyl	63	 **4.12e**	80
9	**4.11f**	9-anthranyl	63	 **4.12f**	75

Scheme 32 The coupling yields and the structure of the reaction products **4.12a-f**

Furthermore, in the case of the anthranyl substituted compounds, one can note the decreasing order of the coupling yields depending upon the nucleofilicity order of the arylacetylides used as coupling partners (93% for **4.12l**, 75% for **4.12f** and 64% for **4.12m**).



Entry	Cmpn. 4.11	Ar	R	Solv.	Coupling product 4.12	η (%)
1	**4.11b**	4-MeO-Ph	4-Me	THF	 **4.12g**	95

2	**4.11b**	4-MeO-Ph	2-MeO	THF	 **4.12h**	85
3	**4.11b**	4-MeO-Ph	4-CN	THF	 **4.12i**	60
4	**4.11d**	1-naphtyl	2-MeO	THF	 **4.12j**	87
5	**4.11e**	2-naphtyl	4-F	DMF	 **4.12k**	78
6	**4.11f**	9-anthranyl	4-Me	THF	 **4.12l**	93
7	**4.11f**	9-anthranyl	4-F	THF	 **4.12m**	64

Scheme 33 Synthesis of a new series of substituted alkynyl-bridged-2,5-disubstituted-1,3,4-oxadiazoles, yields and structures of the coupling products **4.12g-l**

4.2.3. The Sonogashira coupling reaction under aerobic conditions

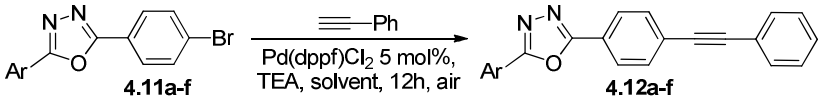
The interest in more simple experimental protocols of the Sonogashira cross-coupling, concomitant with preservation of high product yields, has led to reports showing experiments conducted under aerobic conditions and, consequently, copper-free procedures [11], in order to reduce formation of the homocoupling diyne side-product. [12]

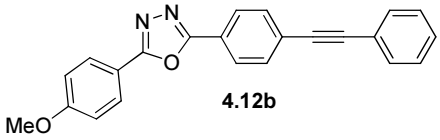
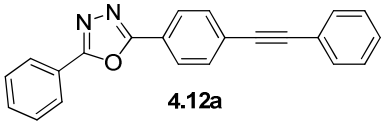
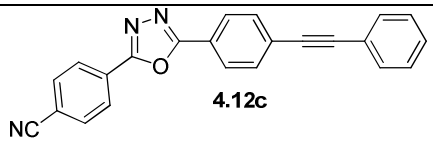
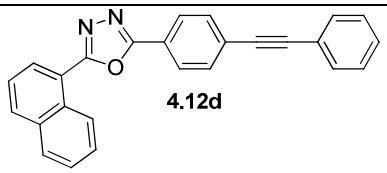
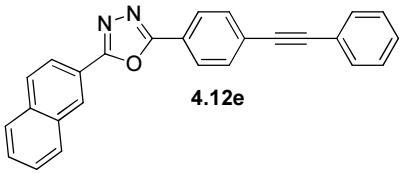
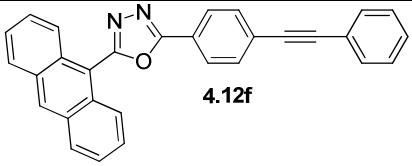
One can note that, overall, the coupling reactions of the 1,3,4-oxadiazole substrates with phenylacetylene also occur in aerobic conditions in moderate to very good yields, using an alkyne excess, along with the diyne side-product in considerable amounts (**Scheme 34**).

The coupling reactions of the substrates **4.11d-f** with phenlacetylene, performed under aerobic conditions, led to moderate yields (**Scheme 34,** entries 8-11), no matter the solvent used in some cases.

Basically, under aerobic conditions, which favour the competitive alkyne homocoupling, one can notice a decrease in the rectivity of the oxadiazole substrates in the oxidative addition as follows: the ones substituted with electron-donor groups (**4.11b**, 87%) are more reactive than the oxadiazole substrates substituted with electron-withdrawing groups. (**4.11c**, 47% and **4.11f**, 35%, for exemple). This behaviour is in disagreement with the

general reactivity of aryl halides, well-known to display a higher reactivity when electron-withdrawing groups are present on the halide skeleton.



Entry	Cmpn. 4.11	Solv.	Co-cat. (10 mol%)	Temp. (°C)	Equiv. alkyne	Coupling product 4.12	η (%)
1	4.11b	DMF	-	25	1.5	 4.12b	-[b]
2		DMF	-	63	3		26[c]
3		THF	CuI	63	3		87
4	4.11a	THF	CuI	63	1.5	 4.12a	36
5		THF	CuI	63	3		60
6	4.11c	THF	CuI	63	3	 4.12c	-
7		DMF	CuI	130	3		47
8	4.11d	THF	CuI	63	3	 4.12d	55
9	4.11e	THF	CuI	63	3	 4.12e	42
10		DMF	CuI	130	3		51
11	4.11f	THF	CuI	63	3	 4.12f	35

Scheme 34 Sonogashira coupling reactions between substrates **4.11a-f** and phenylacetylene under aerobic conditions; [a]yields of isolated products after purification on column chromatography; [b] the yield of the isolated diyne was 79%, no coupling product detected; [c]yield calculated from the ^{1}H RMN spectrum performed on unseparable mixture of the starting material and the coupling product

4.3 Photophysical properties of the synthesized compounds

Preliminary studies of the absorption and emission properties of compounds **4.12a-m** indicate various profiles of the optoelectronic features. For example, Figure 1 shows the spectra profile of some selected compounds **4.12** having a different substitution pattern (**4.12c,f,i,k,l**).

In general, compounds **4.12** have similar absorption profiles, with the excitation maxima between 320-340 nm, except for compounds bearing the anthranyl moiety, for which the most intense maxima vary between 260-280 nm.

The emission spectra indicate high luminescence intensities at low concentrations, in the nanomolar range, with emission maxima near the blue region, ranging between 360 and 396 nm. One can note the different behaviour of the anthranyl derivatives **4.12l** and **4.12m**, which emit in the late blue-near green region and have $\lambda_{em,\ max}$=478 nm. The Stokes shifts are moderate for all compounds except for the anthranyl derivatives, which have very large values (218 nm for **4.12l** and 198 nm for **4.12m**). Another interesting observation would be that the moderate Stokes shifts are, however, accompanied by high luminescence intensities.

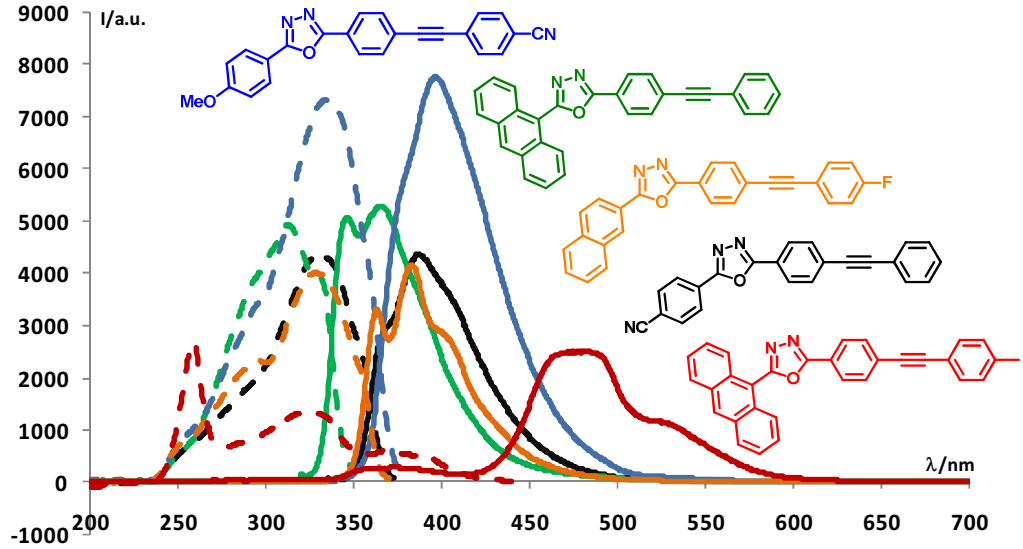


Figura 1 Excitation (dotted lines) and emission (plain lines) spectra of selected compunds **4.12** (performed in $CHCl_3$ at 1 x 10^{-7}M)

4.4 Solid state structural analysis of compound 4.12d

The single crystal X-ray diffraction confirmed the structure of compound **4.12d** (**Figura 2**). The oxadiazole ring and the aromatic units directly bonded to it adopt a planar arrangement. The dihedral angle between the average planes of the oxadiazole ring and the naphthalene ring is 7.6°, while the dihedral angle between the average planes of the oxadiazole and benzene (bonded to C12 atom) rings is 8.3°. On the contrary, the dihedral angle between the average planes of benzene rings bonded to the carbon atoms within the acetylene unit (C19 and C20) is 82.7°.

These suggest that in solid state there is a π extended conjugation between the ox diazole ring and the aromatic moieties bonded to it and there is a π hindered conjugation between the phenylacetylene fragment and the rest of the molecule.

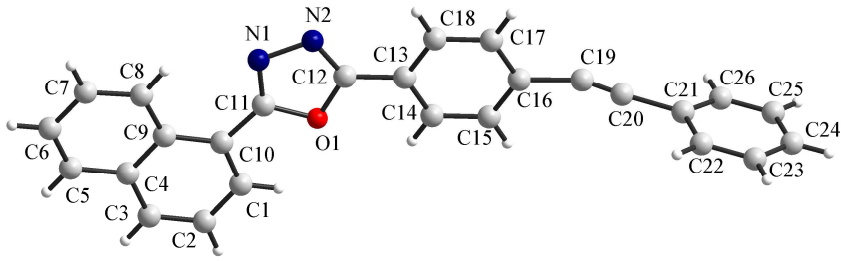


Figura 2 Molecular structure of compound **4.12d**, showing the atom numbering scheme

4.5. Conclusions

The target compounds were designed and synthesized to contain various electron-donating or withdrawing functional groups. The alkynylation approach followed the Sonogashira coupling procedure between bromo-phenyl-1,3,4-oxadiazole derivatives and various substituted arylacetylenes, bearing activating or deactivating functional groups. The coupling reactions occurred in good to excellent yields, indicating a convenient strategy to synthesize new decorated 2,5-disubstituted-1,3,4-oxadiazoles as potential OLEDs precursors. The coupling reactions of the 1,3,4-oxadiazole substrates with phenylacetylene also occur in aerobic conditions in moderate to very good yields, using an alkyne excess. Preliminary studies indicate that the target internal oxadiazole alkynes are compounds that bear luminescent properties in the near-blue or blue region. In addition, such compounds may also be used as building blocks in the synthesis of new small molecules more complex from a structural point of view in the attempt to generate enhanced optoelectronic properties.

R E F E R E N C E S (SELECTION)

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General conclusions

The Ph.D thesis entilted „*Synthesis of new heteroaromatic compounds by Sonogashira cross-coupling reaction*" was directed toward the investigation of thioorganic and halogenated heterocyclic compounds as electrophilic coupling partners in Sonogashira cross-coupling. The benzoxazole and oxadiazole structural motifs are often encountered in simple and complex molecules relevant in biological and materials chemistry. Consequently, both the synthesis of such compounds and the studies regarding their behaviour and properties are still subjects of interest. Furthermore, the cross-coupling reactions are efficient and elegant strategies to access new diverse molecules, allowing in the same time the development of studies regarding the structural particularities correlated to the specific reactivity of the target precursors.

The first chapter covers the critical survey and analysis of the literature data concerning the Sonogashira cross-coupling reaction.

The second chapter comprises the results achieved by using the thioorganic benzazole derivatives as alternative electrophilic coupling partners in the Sonogashira reaction. Therefore, the studies focused investigation of the reactivities of both bezoxazole and bezothiazole methylthioethers and their corresponding mercaptobenzazoles in the coupling reaction with a series of terminal alkynes bearing various substituents. The approached synthetic strategy led to alkynyl-benzazols substituted both on the heteroaromatic ring and the phenylacetylene moiety. By this procedure we synthesized 2-alkynyl benzazol derivatives in yields ranging between 30-95%, according to the heterocycles and acetylenes substituents (aliphatic and aromatic structural units decorated with electron-donor and electron-withdrawing groups). The studies regarding the optimum reaction conditions proved that the cross-coupling reactions performed efficiently under aerobe atmosphere.

The attempt to perform a selective cross-coupling reaction on substrates bearing two reactivity centers: C-S and C-Br respectively succeded with the synthesis of the dilakynylated product when working under aerobic conditions and with the selective desulfitative coupling when the inert atmosphere was used. Preservation of the C-Br bond allows the possibility to further functionalize the benzoxazole core and therefore, to extend the scope of the reaction.

The third chapter describes the results of the studies concerning the reactivity of a new class of π-deficient heterocyles in the Sonogashira reaction, namely the 1,3,4-oxadiazole thioorganic derivatives. The main objective was to develop a new alternative synthetic method of the 2-alkynyl-5-aryl-1,3,4-oxadiazoles. In this context, 1,3,4-oxadiazole thiones and methyl, benzyl and phenyl thioethers were synthesized and further used as electrophilic substrates in the Sonogashira cross-coupling reactions. The results indicate an irregular behaviour of these substrates under the performed reaction conditions. However, the 1,3,4-oxadiazole thiones bearing electron donor substituents were more reactive than the thiones bearing electron-withdrawing groups, contrary to the behaviour of the corresponding aryl halides. These suggest a reaction mechanism that correlates the charge density on the sulfur

atom to the availability of the oxadiazole thioderivatives for the oxidative addition and the transmetallation steps. A reactivity profile of the thioether according to their type (methyl, benzyl or phenyl) could not be achieved. Similar to the thiones behaviour, the thioethers bearing electron-donor groups (*p*-methoxyphenyl) led to higher coupling products yields. A particular case is represented by the *p*-cyanophenyl coupling product which could be obtained in good yield starting from the corresponding benzyl thioether. Similarly, the benzyl thioether of the bis-oxadiazole substrates is an efficient coupling partner for the synthesis of the dialkynylated product, otherwise difficult to obtain.

The fourth chapter describes the results obtained in the synthesis of a series of compounds with extended conjugation, namely alkynylated oxadiazole derivatives bearing donor and acceptor functional groups. The structure of the target compounds was designed so that to prepare molecules with interesting photophysical properties. Thus, the synthetic strategy focused on *i)* synthesis of donor-acceptor structures linked through an acetylene bridge: *ii)* achievement of extended conjugated and rigid structures induced by the triple bond. In addition, we took into consideration the possibility to further functionalize the target structures through reactions of the acetylene unit. Thus, the Sonogashira cross-coupling reactions of the brominated 2,5-diaryl-1,3,4-oxadiazoles provided in very good to excellent yields the coupling products that constitute promissing materials for preparation of OLEDs. Notably, the synthesis was also performed under aerobic conditions, providing the target coupling products in moderate to good yields when an alkyne excess was used. Study of the absorption and emission properties of the alkynylated compounds indicated a large spectral range which may be tuned through proper selection of the substituents both on the oxadiazole and the alkyne moieties. Furthermore, these compounds may serve as precursors in the synthesis of more complex structural units, displaying enhanced optoelectronic properties.

All synthesized compounds were characterised by physical and spectral methods (Nuclear Magnetic Resonance spectroscopy, High Resolution Mass Spectrometry, Ultraviolet and Visible molecular absorption spectroscopy, Fluorescence spectroscopy) in order to confirm purity, structure and the photophysical properties.

In conclusion, the results of the PhD thesis complement the studies regarding the Sonogashira cross-coupling reaction, through an extension of the heterocyclic substrates either thioorganics or halides as electrophilic coupling partners. Hence, the results presented herein open new perspectives for investigation of the parameters that essentially influence the efficiency of the C-C bond formation, with important applications, mainly, in organic synthesis.

P U B L I C A T I O N S

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