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SYNTHESIS OF BROMINATED BISAMIDES AND THEIR APPLICATION TO THE SUZUKI COUPLING

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ABSTRACT

Two brominated bisamides were developed by this protocol. Compounds were synthesized either by 4-bromobenzoyl chloride and ethylenediamine or by ortho-phenylenediamine. The choice of the diamine led to the desired products, which were characterized by IR, ¹H NMR, ¹³C NMR and XRD techniques.

Compounds were applied to the Suzuki coupling. They were efficient for bromides with activating and deactivating substituent groups. In the reaction performed at low temperature and in short time, with yields over 95%, it was fundamental to choose the palladium source.

Keywords: Bisamide synthesis, palladium, Suzuki couplings, bisamide characterization

1 - INTRODUCTION

In the last decades, researchers have been studying new catalytic systems, such as the synthesis of catalysts and auxiliary ligands in the search for simpler processes with less waste generation and fewer pollutants. There has also been industrial interest in developing systems that apply to a wide variety of substrates [1,2,3].

The Suzuki coupling is an important reaction since it is applied to various areas in

Chemistry, such as the synthesis of natural polymeric pharmaceuticals [4-9]. In this coupling, palladium complexes, either with or without auxiliary ligands, are catalytic systems [10]. The class of compounds which acts with the palladium auxiliary ligand is broad; it comprises mainly phosphines, carbenes, guanidines, imines, iminophosphines, oximes and bisamides [11-18].

However, there has been need to develop new auxiliary ligands for the catalytic system to be applied to aryl halides with different substituents, with either aromatic ring activators or deactivators, as well as an efficient system for chlorides.

Bisamides are organic, peptidomimetic and biologically active compounds. This class of compounds has already been applied to catalysis as auxiliary ligands of palladium complexes [19,20]. However, they have been scarcely applied to coupling reactions, even though they proved to be very efficient in Suzuki reactions [21,22]. In the study carried out by Nobre et al., bisamides acted as ligands of palladium acetate in the coupling between aryl halides and arylboronic acids. The reaction occurred at room temperature in short time with no use of any inert atmosphere [21]. In this study, in addition to synthesizing and characterizing two new brominated bisamides, the evaluation of the influence of the bromine substituent and the nitrogen separating group on the bisamide molecule was carried out.

To extend the scope of use of these compounds as palladium auxiliary ligands applied to the Suzuki coupling, this protocol reports the synthesis and characterization of new bisamides, besides their application to the Suzuki coupling.

2 - EXPERIMENTAL

2.1 - Synthesis of bisamide 1,2-bis(4-bromobenzamide)benzene [21]

The synthesis of this compound was carried out by 4-bromobenzoyl chloride (5mmol, 1.1g) and triethylamine (5 mmol, 0.7 mL), together with ortho-phenylenediamine (2.5 mmol, 0.25g) and

Afterwards, the solvent was removed and the resulting solid was crystallized from dimethylsulfoxide. The purified product, whose melting point was 262 °C, was characterized by infrared spectroscopy, proton and carbon nuclear magnetic resonance and X-ray diffraction. Yield was 89%.

2.2 - Synthesis of bisamide 1,2-bis (4-bromobenzamide)ethane [21]

The synthesis of this compound was carried out by 4-bromobenzoyl chloride (5mmol; 1.1g) in 10 mL methylene chloride, together with ethylenediamine (2.5 mmol; 0.165 mL) and triethylamine (5 mmol; 0.7 mL). The system was maintained under magnetic stirring at 25 °C for 20 h. Afterwards, the solvent was removed and the resulting solid was crystallized from dimethylsulfoxide. The purified product, whose melting point was 210 °C, was characterized by infrared spectroscopy, proton and carbon nuclear magnetic resonance and X-ray diffraction. Yield was 90%.

2.3 – Catalytic Suzuki coupling reactions [21]

In this experiment, an oven-dried resealable Schlenk flask was filled with [Pd] (0.01 mmol), ligand (0.03 mmol), aryl halides (1.0 mmol), arylboronic acid (1.5 mmol), K₂CO₃ (2 mmol) and EtOH/H₂O (6 mL, 1:1) at 70°C. The reaction mixture was stirred at the desired temperature for 2h. After that, the solution was taken up in ether (30 mL), washed with aqueous NaOH (1 M, 2×5 mL) and brine (2 × 5 mL), and dried over MgSO₄. After purification by flash chromatography, the biphenyl product was characterized by ¹H and ¹³C NMR.

3 - RESULTS AND DISCUSSION TED MANUSCRIPT

This study aimed at contributing to the development of new catalytic systems by synthesizing two bisamide compounds which were applied to the Suzuki coupling after characterization.

Bisamides were synthesized by the reaction between 4-Bromobenzoyl chloride and the diamine which corresponded to the desired compound (Scheme 1). These reactions, whose solvent was dichloromethane and whose deprotonating agent was triethylamine, were carried out at room temperature.



Scheme 1: Synthesis of 1,2-bis(4-bromobenzamide)benzene (Bisamide 1) and 1,2-bis (4-bromobenzamide)ethane (Bisamide 2)

Initially, bisamides were characterized by infrared spectroscopy [23]. Compounds showed a strong band in the 3270 cm⁻¹ region. It was attributed to vNH; thus, it indicates the development of the bisamide. Amide carbonyl was also identified as a strong band around 1649 and 1633 cm⁻¹. These values are in agreement with the literature [23-25]. Table 1 shows the comparison among the

main bands obtained for the synthesized bisamides and bisamides found in the literature. (spectra in

the supplementary material)

	This study		Literature [21]			
Stretching	Bisamide 1	Bisamide 2	1,2 bis(benzamide)etane	1,2 bis(benzamide)benzene		
of groups	(cm ⁻¹)	(cm ⁻¹)	(cm ⁻¹)	(cm ⁻¹)		
NH	3270	3277	3392	3296		
С=О	1649	1633	1641	1632		
CaromH	3030	3069	3061	3062		
C _{alif.} -H	2984	2977	2955	2960		

Table 1. Comparison among the main bands found in the literature

The ¹H NMR spectrum of both compounds was obtained in DMSO-d₆ at 400 MHz. The spectrum of Bisamide *I* (Scheme 2a) had signals in the following regions: 6.12-6.14 ppm (d, H₁, J= 6 Hz), 6.45-6.46 ppm (d, H₂, 5.7 Hz), 6.54-6.56 ppm (dd, H₄, J = 8.56 and 3,5 Hz), 6.69-6.71 (dd, H₃, J = 8.56 and 3,5 Hz) and 8.92 (s, 2H - which referred to the amide NH). Bisamide *2* (Scheme 2b) had chemical shifts at 3.43 (m, H₁), 7.66-7.68 (d, H₃, J=8.56 Hz), 7.77-7.79 (d, H₂, J=8.56 Hz) and 8.67 ppm (s, 2H - which referred to the amide NH) (spectra can be found in the supplementary material). Results of both compounds are consistent with the ones of similar compounds found in the literature. [21]



Scheme 2: (a) Bisamide 1 with numbering in hydrogen atoms. (b) Bisamide 2 with numbering in hydrogen atoms.

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Structures were confirmed by the XRD analysis. Both compounds had a monoclinic crystalline system. Bisamide **1** belongs to the space group P 21/n, with final disagreement rates for the following data: $I > 2\sigma(I) R_1 = 0.0374$ and $wR_2 = 0.1082$, $R_1 = 0.0850$ and $wR_2 = 0.1357$, according to data collected by the analysis of 4067 independent reflections which were obtained by the refinement of 29434 total reflections (Figure 1 and Table 2).



Figure 1: Structural representation of the asymmetric unit of Bisamide 1

 Table 2. Data on intensity collection and refinement of crystalline/molecular structure of Bisamide 1

Empirical formula	$C_{20} H_{14} Br_2 N_2 O_2$		
Molecular weight	474,15 g/mol		
Name	1,2-bis(4-bromobenzamide)benzene		
Temperature	296 K		
Wavelength/radiation	0,71073 Å		
Crystal system	Monoclinic		
Space group	P 21/n		
Dimensions of unit cell	$a = 9,6534(5) \text{ Å} \qquad \alpha = 90^{\circ}$		
	$b = 19,7768(12) \text{ Å} \qquad \beta = 99,607(2)^{\circ}$		
	$c = 9,8465(5) \text{ Å} \qquad \gamma = 90^{\circ}$		
Volume	1853.46(18) Å ³		
Ζ	4		
Calculated density	1,699 Mg/m ³		
Absorption coefficient	4,390 mm ⁻¹		

F (000) ACCEPTED	936ANUSCRIPT
Dimensions of the glass	
Angular region of scanning for data	2,06 to 28,31°.
collection	
Region of indices	-12<=h<=12, -24<=k<=25, -9<=l<=12
Collected reflections	29434
Independent reflections	4067[R(int) = 0.0429]
Completeness to θ = 25.24	99,.9 %
Refinement method	Matrix of total least squares, including F^2
Final indices of discordance I> 2σ (I)	$R_1 = 0,0374, wR_2 = 0,1082$
Indices of discordance of all reflections	$R_1 = 0,0850, wR_2 = 0,1357$
Residual electronic density (max and min)	0,619 and -0,673 and Å ⁻³

In Bisamide 1, attachment distances (tables in the supplementary material) C(17)-O(1) correspond to a $Csp^2 = O$ double bond at 1.233 Å. Phenyl ring with bonding lengths are at 1.369 and 1.390 Å. The N(1) -C(21) bond is 1.353 Å long; these values are similar to those found in the literature [25,26]. For C(14) -Br(1) bonding, the single bond length between C-Br is 1.898 Å.

In the case of Bisamide 1, lengths of the axes which define the unit cell of the monoclinic system are, respectively, a = 9,654 (5) Å, b = 19.7768 (12) Å and 9.8465 (5) Å, perpendicular, resulting in a unit cell with four units (Figure 2) [25,26].



Figure 2: Projection of the structure of Bisamide 1 in the elemental cell

Bisamide 2 belongs to the space group P 21/c, with final disagreement rates for the following data: $I > 2\sigma(I) R_1 = 0.0336$ and $wR_2 = 0.0824$, $R_1 = 0.0459$ and $wR_2 = 0.0871$, according to data collected by the analysis of 1669 independent reflections which were obtained by the refinement of 9726 total reflections (Figure 3 and Table 3).



Figure 3: Structural representation of the asymmetric unit of Bisamide 2

Table	3 :	Data	on	intensity	collection	and	refinement	of	crystalline/molecular	structure	of
		Bisan	nide	2							

Empirical formula	$C_{16}H_{14}Br_2N_2O_2$				
Molecular weight	426,11 g/mol				
Name	1,2-Bis (4-bromobenzamide)ethane				
Temperature	100 K				
Wavelength/radiation	0,56086 Å				
Crystal system	Monoclinic				
Space group	P 21/c				
Dimensions of unit cell	a = 8,4725(7)Å	$\Box = 90^{\circ}$			
R	b = 9,3594(7)Å	$\Box = 95,127(2)^{\circ}$			
	c = 9,8577(8)Å	$\Box = 90^{\circ}$			
Volume	1853.46(18) Å ³				
Z	2				
Calculated density	1,818 Mg/m ³				
Absorption coefficient	2,797 mm ⁻¹				
F (000)	420				
Dimensions of the glass	0,33 x 0,22 x 0,18 mm	1			

collection

Region of indices	-10<=h<=10, -11<=k<=11, -12<=l<=12		
reflections Collected	9726		
Independent reflections	1669 [R(int) = 0,0475]		
Completeness to θ = 25.24	99,9 %		
Refinement method	Matrix of total least squares, including F^2		
Final indices of discordance I> 2σ (I)	$R_1 = 0,0336, wR_2 = 0,0824$		
Indices of discordance of all reflections	$R_1 = 0,0459, wR_2 = 0,0871$		
Residual electronic density (max and min)	0,064 and -0,427 and.Å ⁻³		

In the case of Compound 2, the bond length between NC (2) and C (2) -O was, respectively, 1333 Å and 1238 Å. Bond length for C (1) -C (1 °) for the methylene groups was 1.528 Å. Attachment lengths of the aromatic ring carbons were 1.379 and 1.385. C (6) -Br binding the single bond length is 1,902Å. These values are consistent with a similar bisamide derivative, but they did not agree with data found in the literature [25,26].

Regarding Bisamide 2, the length of the axes defining the unit cell of the monoclinic system are, respectively, a = 8,4725(7) Å, b = 9,3594(7) Å e c = 9,8577(8) Å, perpendicular, resulting in a unit cell with four units (Figure 4).



Figure 4: Projection of the structure of Bisamide 2 in the elemental cell

These bisamides have different space structure. Bisamide 2 has an ethane group between the nitrogen atoms of the amide moiety whereas Bisamide 1 has a more rigid structure among the nitrogen atoms. These compounds were tested as auxiliary ligands of palladium in the Suzuki cross coupling. The objective was to evaluate the influence of the separating group on the Suzuki reaction and to deepen the study of this class of binders in the catalysis.

Firstly, different bases (K_2CO_3 , Na_2CO_3 and EtONa), solvents (MeOH, EtOH, EtOH; H_2O (1:1), H_2O, MeOH:H_2O (1:1), DMF), reaction time (0.5, 1, 2, 4 and 8h) and temperature (70, 100 and 130 °C) were used. These reactions were followed by gas chromatographic analysis with internal standard (undecane). Reaction tests showed excellent results at 70 °C with K_2CO_3 as the basis and ethanol/water (1:1) as the solvent. Different sources of palladium were evaluated with both synthesized bisamides. Besides, for this Pd-ligand system, the reaction time was also evaluated (Table 4).

Table 4: Bisamide effect, source of palladium and time

	Br +	$\rightarrow B(OH)_2 \xrightarrow{[Pd], b}{base, s}$	isamide 1 or 2 olvent ie		
Entry	Bisamide	[Pd]	(h)	Conv. (%)	Yield (%)
1	1	PdCl ₂	4	99	95
2	1	Pd(OAc) ₂	4	62	61
3	1	Pd(Acac) ₂	4	57	55
4	1	PdCl ₂	2	100	96
5	1	Pd(OAc) ₂	2	62	60
6		Pd(Acac) ₂	2	50	45
7^{a}	1	PdCl ₂	2	85	80
8	1		4	0	0

9		A (PdCl2 TED)	MAN4USCRIPT	98	86
10	2 2	Pd(OAc) ₂	4	54	52
11	2	Pd(Acac) ₂	4	43	42
12	2	PdCl ₂	2	98	95
13	2	Pd(OAc) ₂	2	53	49
14	2	Pd(Acac) ₂	2	41	39
15 ^a	2	PdCl ₂	2	60	58
16	2		4	0	0
17		PdCl ₂	2	66	63

Condition: aryl halides (1.0 mmol), arylboronic acid (1.5 mmol), K₂CO₃ (2 mmol), [Pd] (0.01 mmol), ligand (0.03 mmol), EtOH/H₂O (6 mL, 1:1), 70°C. ^a [Pd] (0.005 mmol)

Table 4 shows that the catalytic activity is mainly related to the palladium source. However, the presence of bisamide as an auxiliary ligand is important because it facilitates its coordination to the metal, making the oxidative addition step more efficient [3,27,28]. Test 16 shows that the reaction does not occur without the palladium source whereas Test 17 shows that the reaction shows low conversion and yields without an auxiliary binder.

After establishing that palladium chloride was the best catalytic source, the required amounts of catalyst precursor and binder were analyzed (0.5, 1, 1.1 and 1.5 mol). Results obtained by chromatographic analysis showed that, to enable the reaction under study to occur with total conversion, 1 mol% PdCl₂ and 1.1 mol ligand were needed.

The last stage of this study was to test different substrates (Table 5) in order to evaluate the

effect of substituents.

Table 5: Results of the study of different substrates



Condition: aryl halides (1.0 mmol), arylboronic acid (1.5 mmol), K₂CO₃ (2 mmol), PdCl₂ (0.01 mmol), ligand (0.03 mmol), EtOH/H₂O (6 mL, 1:1), 70°C, 2 h.* 4-chlorotolueno.

This study showed excellent results of the Suzuki coupling for aryl bromides and aryl boronic acid with either activating or deactivating substituents in the ring with high yield (entry 18-22). Results of both bisamides were similar, an evidence of the fact that the source of palladium is determinant in the reaction. This bisamide-palladium system was evaluated in the reaction between chlorotoluene and phenylboronic acid. Even though results were modest, the one shown by entry 23 is promising, by comparison with other systems applied to aryl chlorides [29].

4 - CONCLUSION

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This study synthesized and characterized two different brominated bisamides and concluded that they are excellent auxiliary ligands when coordinated to PdCl₂. Bisamides were characterized by different techniques, such as X-ray diffraction. After characterization, these compounds were tested in the Suzuki reaction, in which good palladium auxiliary ligands were shown. It may be concluded that, in the proposed system, it was fundamental to choose the source of palladium, having PdCl₂ as the best catalytic precursor. Besides, the separation group between nitrogen atoms did not interfere in the catalytic result

Finally, the PdCl₂-bisamide system was found to be quite efficient in reactions between aryl bromides and arylboronic acids, both with aromatic and deactivating groups of the aromatic ring.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary synthesis and data on NMR, IR and X-ray diffraction of bisamides and biphenlys

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Scheme 1: Synthesis of 1,2-bis(4-bromobenzamide)benzene (Bisamide 1) and 1,2-bis (4-bromobenzamide)ethane (Bisamide 2)

Scheme 2: (a) Bisamide 1 with numbering in hydrogen atoms. (b) Bisamide 2 with numbering in hydrogen atoms

Figure 1: Structural representation of the asymmetric unit of Bisamide 1

Figure 2: Projection of the structure of Bisamide 1 in the elemental cell

Figure 3: Structural representation of the asymmetric unit of Bisamide 2

Figure 4: Projection of the structure of Bisamide 2 in the elemental cell

- Table 1. Comparison among the main bands found in the literature
- Table 2. Data on intensity collection and refinement of crystalline/molecular structure of Bisamide 1
- Table 3: Data on intensity collection and refinement of crystalline/molecular structure of Bisamide 2
- **Table 4**: Bisamide effect, source of palladium and time
- Table 5: Results of the study of different substrates

- Synthesis brominated bisamides,
- Bisamides in Suzuki,
- Choice of the best catalyst.