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Ahlem Bouhlel, Christophe Curti, Omar Khoumeri, Patrice Vanelle. Efficient one-pot double Buchwald-Hartwig coupling reaction on 5-phenyl-4- phenylsulfonyl-2,3-dihydrofuran derivatives . Tetrahedron Letters, 2011, 52 (16), pp.1919-1923. 10.1016/j.tetlet.2011.02.049 . hal-01423396

HAL Id: hal-01423396

<https://hal.science/hal-01423396v1>

Submitted on 4 Jan 2017

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Efficient one-pot double Buchwald-Hartwig coupling reaction on 5-phenyl-4-phenylsulfonyl-2,3-dihydrofuran derivatives

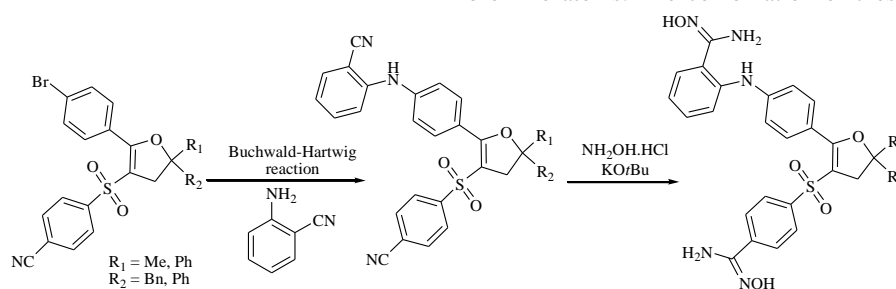
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ABSTRACT: We report a new and efficient method of conducting a one-pot double Buchwald-Hartwig coupling reaction on 2,3-dihydrofuran derivatives bearing two bromine atoms. This rapid and convenient synthesis allows us to access a great variety of original mixed dicoupled compounds. The strategy appears promising for combinatorial chemistry and pharmacomodulation studies.

Keywords: One-pot, Double Buchwald-Hartwig coupling, Manganese(III) acetate, Microwave

In view of our interest in anti-infectious drug discovery,¹ we have recently explored the antileishmaniasis potential of some diamidoximes. Several diamidoximes presenting a 2,3-dihydrofuran heterocyclic scaffold and obtained *via* a single Buchwald-Hartwig coupling reaction (Scheme 1) showed interesting antiparasitic activities.²



Scheme 1: Synthesis of amidoximes

These promising results encouraged us to synthesize a series of dicyano-derivatives using various aminobenzonitriles so as to perform a double Buchwald-Hartwig reaction. Our earlier results had shown that Buchwald-Hartwig amination realized on the sulfone moiety led to better yields.² Thus, we were able to use this difference in reactivity to carry out a one-pot double Buchwald-Hartwig reaction.

Since Buchwald-Hartwig's discovery, the amination reaction has successfully been applied to heteroaryl substrates, such as pyridines, quinolines, thiophenes, thiazoles, indoles, 1,3,5-triazines, or pyrimidines.³ Moreover, C-N cross-coupling reaction on dihalogenated compounds has been fairly thoroughly investigated, as reported in the literature.⁴

However, there have been few examples of efficiently modulating simple aryl scaffolds, particularly with products containing a sulfone moiety.⁵ To our knowledge, very few one-pot Buchwald-Hartwig coupling reactions have been conducted. One of these is reported as a tandem inter- and intramolecular Buchwald-

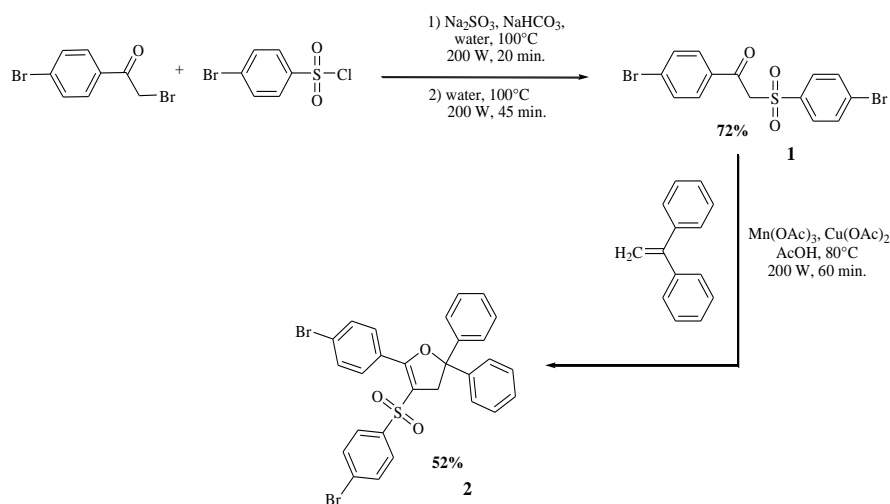
Hartwig amination;⁶ while others include an intramolecular domino process,⁷ or a double amination on the same aryl halide followed by an intermolecular Heck reaction.⁸

Herein, we report a study allowing a convenient one-pot double Buchwald-Hartwig coupling reaction using three aminobenzonitriles differing from the cyano position (*ortho*, *meta*, or *para*) and a 2,3-dihydrofuran derivative bearing two bromine atoms. The combination of these aminobenzonitriles

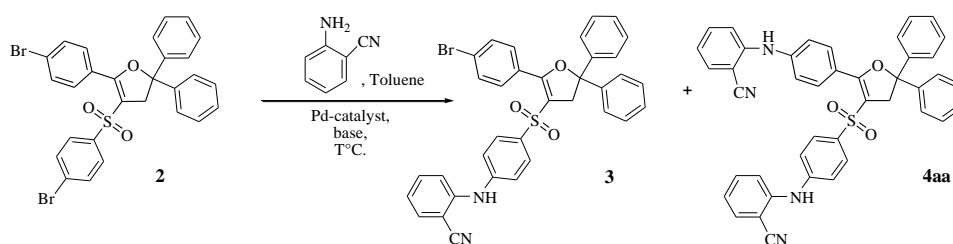
involved in C-N cross coupling reactions allowed us to access several dissymmetric dicoupled products.

The required starting material, 5-(4-bromophenyl)-4-(4-bromophenylsulfonyl)-2,2-diphenyl-2,3-dihydrofuran (**2**), was synthesized in two steps (see Scheme 2). Firstly, the β -ketosulfone **1** was obtained by using a previously reported microwave irradiated method.⁹ In the second step, the β -ketosulfone **1** was converted into the desired 2,3-dihydrofuran derivative **2** under microwave irradiation, *via* a manganese(III) acetate-based oxidative cyclization between compound **1** and 1,1-diphenylethene.¹⁰

Thus, we obtained our key-substrate, a double aryl halide (**2**), to be used in conducting the Buchwald-Hartwig coupling reaction. First of all, the reaction of 5-(4-bromophenyl)-4-(4-bromophenylsulfonyl)-2,2-diphenyl-2,3-dihydrofuran (**2**) with 2-aminobenzonitrile was conducted with only one equivalent of amine. We obtained a mixture of monocoupled **3**,¹¹ dicoupled **4aa**,¹¹ and unreacted **2** products (Scheme 3).



Scheme 2: Synthesis of 5-(4-bromophenyl)-4-(4-bromophenylsulfonyl)-2,2-diphenyl-2,3-dihydrofuran **2**



Scheme 3: Reaction of **2** in a Buchwald-Hartwig reaction with 2-aminobenzonitrile

The presence of one monocoupling product (**3**) revealed a difference in reactivity between the two brominated positions. This difference can be attributed to the electron-attracting effect of the sulfonyl group. Indeed, in the oxidative addition step, Pd(0) acts as a nucleophile and preferentially attacks the most electron-deficient position.¹² The position on which the first coupling reaction took place was confirmed by X-ray diffraction analysis of compound **3** (2-{4-[2-(4-bromophenyl)-5,5-diphenyl-4,5-dihydrofuran-3-ylsulfonyl]phenylamino}-benzonitrile, Fig. 1).¹³

In order to optimize the one-pot double Buchwald-Hartwig reaction, we started by investigating the conditions most likely to lead to a majority of monocoupled product in the first step. The study, realized with 2-aminobenzonitrile, examined various parameters (Table 1).

We began with two catalyst systems and different bases (Entries 1-6). We noted that the combined use of Pd(OAc)₂/BINAP and Cs₂CO₃ appeared to be the best reactive combination.¹⁴

Then, studies to optimize the temperature were undertaken (Entries 1, 7-10). We noted that yields of monocoupled product **3** increased from rt to 70°C, but decreased on reaching 100°C, favoring the dicoupled product.

Concerning the equivalent number of amine (Entries 1, 11, 14, 16), it appeared that 1.4 equivalent of amine led to the best yield of monocoupled product. Indeed, we observed some selectivity of monosubstituted product (41% of monocoupled vs 17% of dicoupled product). Moreover, as shown in Table 1, the use of three equivalents of amine led to complete consumption of the starting material, and we obtained, as expected, a majority of double-coupled product **4** (67%). This last result (Entry 16) is considered at the time when the second amine was added.

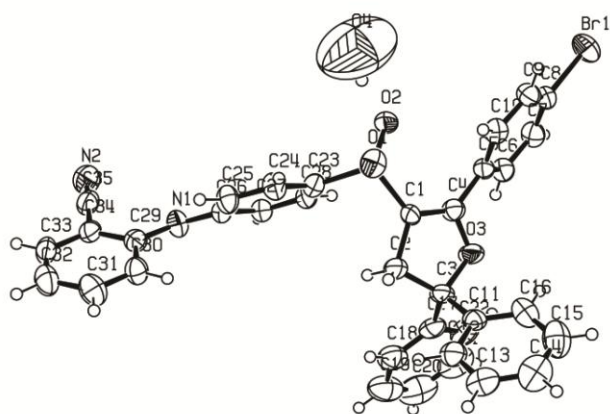


Figure 1: ORTEP view of compound 3

Table 1: Survey of Buchwald-Hartwig reaction conditions

Entry	Amine nbr equivalent	Catalyst ^a	Base ^b	Temperature	yield ^c 2 %	yield ^c 3 %	yield ^c 4aa %
1	0.8	Pd(OAc) ₂ / BINAP	Cs ₂ CO ₃	70	41	26	13
2	0.8	Pd(PPh ₃) ₄	Cs ₂ CO ₃	70	82	7	0
3	0.8	Pd(OAc) ₂ / BINAP	K ₂ CO ₃	70	100	0	0
4	0.8	Pd(OAc) ₂ / BINAP	Na ₂ CO ₃	70	100	0	0
5	0.8	Pd(OAc) ₂ / BINAP	K ₃ PO ₄	70	100	0	0
6	0.8	Pd(OAc) ₂ / BINAP	KOtBu	70	60	10	0
7	0.8	Pd(OAc) ₂ / BINAP	Cs ₂ CO ₃	r.t.	100	0	0
8	0.8	Pd(OAc) ₂ / BINAP	Cs ₂ CO ₃	40	83	8	8
9	0.8	Pd(OAc) ₂ / BINAP	Cs ₂ CO ₃	50	50	25	8
10	0.8	Pd(OAc) ₂ / BINAP	Cs ₂ CO ₃	100	10	32	19
11	1	Pd(OAc) ₂ / BINAP	Cs ₂ CO ₃	70	40	29	8
12 ^d	1	Pd(OAc) ₂ / BINAP	Cs ₂ CO ₃	70	35	23	12
13 ^e	1	Pd(OAc) ₂ / BINAP	Cs ₂ CO ₃	70	25	37	20
14	1.4	Pd(OAc) ₂ / BINAP	Cs ₂ CO ₃	70	28	41	17
15 ^e	1.4	Pd(OAc) ₂ / BINAP	Cs ₂ CO ₃	70	5	42	31
16	3	Pd(OAc) ₂ / BINAP	Cs ₂ CO ₃	70	5	18	67
17 ^e	3	Pd(OAc) ₂ / BINAP	Cs ₂ CO ₃	70	0	16	71

^a 4 mol% ^b 1.2 eq. base for 1 eq. amine ^c Reaction in dry toluene, under argon atmosphere, during 12h, yields for isolated products based on compound **2** ^d Crown ether in catalytic amount ^e Crown ether in stoichiometric amount.

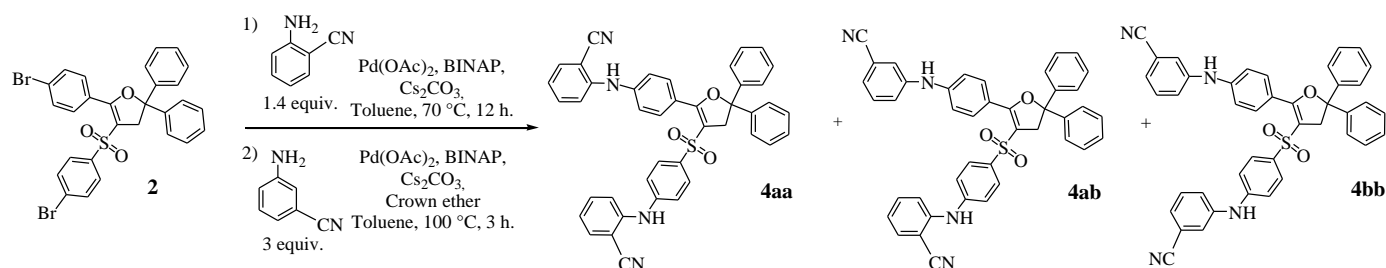
Next, we explored the compound produced by the sequential double Buchwald-Hartwig coupling reaction. First, we kept the same catalyst system and the same base, which were the most efficient. Then, in order to maximize double coupling product, we increased the amount of amine and the temperature. The first attempt was performed at 100°C, using 3 equivalents of the second aminobenzonitrile.

This second coupling reaction was improved by the use of crown ether. When we tested the influence of crown ether on coupling reactions with the optimized parameters, we observed a significant rate enhancement when stoichiometric amount 18-Crown-6 was added to the reaction mixture (Entries 13, 15, 17).

As reported in the literature, crown ether can facilitate the exchange of the halide with amine in the intermediate palladium complex, resulting in the overall reaction rate acceleration.¹⁵

These optimizations enabled us to carry out the one-pot double sequential Buchwald-Hartwig coupling reaction. We used a combination of three aminobenzonitriles on compound **2**, which permitted us to obtain several dissymmetric dicoupled products (**4ab**, **4ac**, **4ba**, **4bc**, **4ca**, **4cb**) (Scheme 4, Table 2).

Moreover, we were able here to synthesize three compounds per reaction at the same time. The method therefore offers great promise for future pharmacomodulation studies.



Scheme 4: Reaction of **2** in the one-pot double sequential Buchwald-Hartwig coupling reaction with 2-aminobenzonitrile and 3-aminobenzonitrile

Table 2: Synthesis of dicoupled products¹⁶

Entry ^a	First Amine	Second Amine	Total coupling yield %	Dicoupled of 1st Amine Product/ yield ^b (%)	Dissymmetric Product / Yield ^b (%)	Dicoupled of 2nd Amine Product/ yield ^b (%)
1			83	4aa (31)	4ab (35)	4bb (17)
2			86	4aa (20)	4ac (32)	4cc (34)
3			71	4bb (14)	4ba (36)	4aa (21)
4			47	4bb (11)	4bc (21)	4cc (15)
5			72	4cc (16)	4ca (21)	4aa (37)
6			47	4cc (7)	4cb (34)	4bb (6)

^a 4 mol% Pd(OAc)₂, 4 mol% BINAP, 2.86 mmol Cs₂CO₃, 2.35 mmol of first aminobenzonitrile in dry toluene under argon atmosphere at 70 °C for 12 h; then, 4 mol% Pd(OAc)₂, 4 mol% BINAP, 6.05 mmol Cs₂CO₃, 5.04 mmol of second aminobenzonitrile, 5.04 mmol crown ether are added at 100 °C ^b yields for isolated products based on compound **2**.

In summary, we have developed a novel and efficient method for a one-pot sequential double Buchwald-Hartwig coupling reaction on 2,3-dihydrofuran derivatives. We show that by controlling the amount of amine and the temperature, it is possible to synthesize dissymmetric dicoupled products with rather good global coupling yields.

This strategy can now be exploited with various amines, allowing access to a wide range of dihydrofuran derivatives. It should contribute to a combinatorial chemistry approach, of value in pharmacomodulation studies.

Acknowledgments

This work was supported by the Centre National de la Recherche Scientifique and the Université de la Méditerranée. We would like to express our thanks to Dr V. Remusat for RMN spectra recording.

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⁹ For procedure see: (a) Cohen, A.; Crozet, M. D.; Rathelot, P.; Vanelle, P. *Green Chem.* **2009**, *11*, 1736-1742; (b) Curti, C.; Laget, M.; Ortiz Carle, A.; Gellis, A.; Vanelle, P. *Eur. J. Med. Chem.* **2007**, *42*, 880-884. 1-(4-bromophenyl)-2-(4-bromophenylsulfonyl)ethanone (**1**) (with 200W, and 45 min. in the 2nd step): white solid, mp 162°C. ¹H NMR (DMSO-d₆, 200 MHz): δ 5.42 (s, 2H, CH₂), 7.74 (d, 2H, CH₂, *J* = 8.6 Hz), 7.84-7.91 (m, 6H, CH₂). ¹³C NMR (DMSO-d₆, 50 MHz): δ 62.3 (CH₂), 128.5 (C), 128.8 (C), 130.3 (2CH), 131.1 (2CH), 132.1 (2CH), 132.5 (2CH), 134.8 (C), 138.8 (C), 188.6 (C). Anal. Calcd for C₁₄H₁₀Br₂O₃S: C, 40.22; H, 2.41. Found: C, 40.45; H, 2.37.

¹⁰ For procedure see: Curti, C.; Crozet, M. D.; Vanelle, P. *Tetrahedron* **2009**, *65*, 200-205. 5-(4-bromophenyl)-4-(4-bromophenylsulfonyl)-2,2-diphenyl-2,3-dihydrofuran (**2**): white solid, mp 166°C. ¹H NMR (CDCl₃, 200 MHz): δ 3.76 (s, 2H, CH₂), 7.29 (s, 10H, 10CH), 7.50 (s, 4H, 4CH), 7.57 (d, 2H, CH₂, *J* = 8.7 Hz), 7.67 (d, 2H, CH₂, *J* = 8.7 Hz). ¹³C NMR (CDCl₃, 50 MHz): δ 45.3 (CH₂), 92.1 (C), 110.4 (C), 115.6 (C), 125.5 (4CH), 126.1 (C), 126.9 (C), 128.1 (2CH), 128.4 (2CH), 128.6 (4CH), 131.3 (4CH), 132.3 (2CH), 140.5 (C), 143.4 (2C), 161.7 (C). Anal. Calcd for C₂₈H₂₀Br₂O₃S: C, 56.39; H, 3.38. Found: C, 56.36; H, 3.43.

¹¹ General procedure for the first step optimization: Into a two-necked flask containing 25 mL of dry and degassed toluene, under inert atmosphere were added compound **2** (0.5 g, 0.84 mmol), 2-aminobenzonitrile (0.139 g, 1.18 mmol), palladium acetate (0.007 g, 0.03 mmol), BINAP (0.021 g, 0.03 mmol), and cesium carbonate (0.275 g, 1.43 mmol). The reaction mixture was stirred at 70°C from 12h, and monitored by TLC. Solvent evaporation gave a crude mixture which was solubilized in dichloromethane and filtered through Celite in order to remove inorganic salts. The mixture was purified by column chromatography (Chloroform/Petroleum Ether/DiethylEther: 5/4.5/0.5) and products obtained were recrystallized from isopropanol.

2-[4-[2-(4-bromophenyl)-5,5-diphenyl-4,5-dihydro-furan-3-ylsulfonyl]-phenylamino]benzotrile (**3**): white solid, mp 171°C. ¹H NMR (CDCl₃, 200 MHz): δ 3.81 (s, 2H, CH₂), 6.46 (bs, 1H, 1NH), 7.02-7.09 (m, 3H, 3CH), 7.21-7.35 (m, 10H, 10CH), 7.37 (s, 1H, CH), 7.47-7.51 (m, 1H, CH), 7.55-7.62 (m, 5H, 5CH), 7.67-7.71 (m, 2H, 2CH). ¹³C NMR (CDCl₃, 50 MHz): δ 45.6 (CH₂), 91.8 (C), 102.2 (C), 111.4 (C), 116.8 (C), 117.5 (CH), 117.7 (2CH), 122.2 (CH), 125.5 (4CH), 125.8 (C), 127.2 (C), 128.0 (2CH), 128.5 (4CH), 129.0 (2CH), 131.2 (2CH), 131.3 (2CH), 133.5 (CH), 134.0 (CH), 134.5 (C), 143.7 (2C), 144.2 (C), 145.2 (C), 160.5 (C). Anal. Calcd for C₃₅H₂₅BrN₂O₃S: C, 66.35; H, 3.98; N, 4.42. Found: C, 66.27; H, 4.16; N, 4.32.

2-[4-[2-[4-(2-cyanophenylamino)phenyl]-5,5-diphenyl-4,5-dihydrofuran-3-ylsulfonyl]phenyl-amino]benzotrile (**4aa**): white solid, mp 220°C. ¹H NMR (CDCl₃, 200 MHz): δ 3.82 (s, 2H, CH₂), 6.45 (bs, 1H, 1NH), 6.48 (bs, 1H, 1NH), 6.94-7.07 (m, 4H, 4CH), 7.18 (d, 2H, 2CH, *J* = 8.6 Hz), 7.29-7.37 (m, 10H, 10CH), 7.43-7.64 (m, 8H, 8CH), 7.86 (d, 2H, 2CH, *J* = 8.6 Hz). ¹³C NMR (CDCl₃, 50 MHz): δ 45.7 (CH₂), 91.2 (C), 100.7 (C), 102.0 (C), 109.4 (C), 116.4 (CH), 116.9 (C), 117.2 (C), 117.4 (CH), 117.7 (2CH), 118.1 (2CH), 121.0 (CH), 122.1 (CH), 122.5 (C), 125.6 (4CH), 127.9 (2CH), 128.5 (4CH), 128.9 (2CH), 131.5 (2CH), 133.3 (CH), 133.5 (CH), 133.9 (CH), 134.0 (CH), 134.8 (C), 143.2 (C), 143.9 (2C), 144.3 (C), 145.0 (C), 145.2 (C), 161.1 (C). HMRS (ESI): *m/z* calcd for C₄₂H₃₀N₄O₃S M+H⁺: 671.2111. Found: 671.2110.

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¹³ Crystal data for compound **3**: C₃₅H₂₇BrN₂O₃S, colourless prism (0.4x0.2x0.2 mm³), *M_w* = 651.56, orthorhombic, space group Pna21 (*T* = 293 K), *a* = 12.3746(2) Å, *b* = 9.9706(2) Å, *c* = 24.0578(5) Å, *α* = 90°, *β* = 90°, *γ* = 90°, *V* = 2968.30(10) Å³, *Z* = 4, *D_{calcd}* = 14.58 g.cm⁻³, *μ* = 1.499 mm⁻¹, *F*(000) = 1336, index ranges 0 ≤ *h* ≤ 15, 0 ≤ *k* ≤ 12, -30 ≤ *l* ≤ 0, *θ* range = 3.12-27.29°, 388 variables and 1 restraint, were refined for 2762 reflections with *R*₂σ_i to *R* = 0.05, GoF = 1.135.

Crystallographic data for the structure **3** have been deposited with the Cambridge Crystallographic Data Centre (CCDC) under number 798040.

Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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¹⁶ General procedure for one pot double sequential Buchwald-Hartwig coupling reaction: into a two-necked flask containing 50 mL of dry and degassed toluene, under inert atmosphere were added compound **2** (1 g, 1.68 mmol), corresponding first aminobenzonitrile (0.278 g, 2.35 mmol), palladium acetate (0.015 g, 0.07 mmol), BINAP (0.042 g, 0.07 mmol), and cesium carbonate (0.552 g, 2.86 mmol). The reaction mixture was stirred at 70°C from 12h. Then were added the second aminobenzonitrile (0.595 g, 5.04 mmol), crown ether (1.33 g, 5.04 mmol), palladium acetate (0.015 g, 0.07 mmol), BINAP (0.042 g, 0.07 mmol), and cesium carbonate (1.17 g, 6.05 mmol). The reaction mixture was stirred at 100°C from 3h, and monitored by TLC. Solvent evaporation gave a crude mixture which was solubilized in dichloromethane and filtered through Celite in order to remove inorganic salts. The mixture was purified by column chromatography (Dichloromethane/Petroleum Ether/DiethylEther: 6.5/3/0.5) and products obtained were recrystallized from isopropanol.

3-[4-[2-[4-(3-cyanophenylamino)phenyl]-5,5-diphenyl-4,5-dihydrofuran-3-ylsulfonyl]phenylamino]benzotrile (**4bb**): white solid, mp 188°C. ¹H NMR (DMSO-d₆, 200 MHz): δ 3.78 (s, 2H, CH₂), 7.10 (d, 2H, 2CH, *J* = 8.8 Hz), 7.20 (d, 2H, 2CH, *J* = 8.7 Hz), 7.27-7.40 (m, 9H, 9CH), 7.45-7.51 (m, 9H, 9CH), 7.58 (d, 2H, 2CH, *J* = 8.8 Hz), 7.82 (d, 2H, 2CH, *J* = 8.7 Hz), 9.04 (s, 1H, 1NH), 9.13 (s, 1H, 1NH). ¹³C NMR (DMSO-d₆, 50 MHz): δ 45.3 (CH₂), 90.2 (C), 108.7 (C), 112.2 (2C), 115.3 (3CH), 118.7 (C), 118.8 (C), 119.2 (C), 119.9 (CH), 120.9 (CH), 122.3 (CH), 123.2 (CH), 124.1 (CH), 125.0 (CH), 125.1 (4CH), 127.6 (2CH), 128.5 (5CH), 130.6 (2CH), 130.7 (2CH), 131.1 (2CH), 131.5 (C), 142.2 (C), 143.0 (C), 144.1 (2C), 145.1 (C), 146.8 (C), 159.7 (C). HMRS (ESI): *m/z* calcd for C₄₂H₃₀N₄O₃S M+H⁺: 671.2111. Found: 671.2113.

4-[4-[2-[4-(4-cyanophenylamino)phenyl]-5,5-diphenyl-4,5-dihydrofuran-3-ylsulfonyl]phenylamino]benzotrile (**4cc**): white solid, mp 209°C. ¹H NMR (DMSO-d₆, 200 MHz): δ 3.80 (s, 2H, CH₂), 7.12-7.32 (m, 10H, 10CH), 7.35-7.39 (m, 3H, 3CH), 7.44-7.48 (m, 4H, 4CH), 7.59-7.71 (m, 7H, 7CH), 7.80-7.84 (m, 2H, 2CH), 9.32 (s, 1H, 1NH), 9.39 (s, 1H, 1NH). ¹³C NMR (DMSO-d₆, 50 MHz): δ 45.3 (CH₂), 90.7 (C), 101.1 (C), 102.0 (C), 109.4 (C), 116.4 (2CH), 117.2 (2CH), 117.3 (4CH), 119.6 (C), 119.8 (C), 120.5 (C), 125.3 (4CH), 127.9 (2CH), 128.6 (2CH), 128.7 (4CH), 131.2 (2CH), 132.7 (C), 133.9 (4CH), 144.1 (C), 144.2 (2C), 145.9 (C), 146.1 (C), 146.9 (C), 160.0 (C). HMRS (ESI): *m/z* calcd for C₄₂H₃₀N₄O₃S M+H⁺: 671.2111. Found: 671.2111.

2-[4-[2-[4-(3-cyanophenylamino)phenyl]-5,5-diphenyl-4,5-dihydrofuran-3-ylsulfonyl]phenylamino]benzotrile (**4ab**): white solid, mp 220°C. ¹H NMR (DMSO-d₆, 200 MHz): δ 3.78 (s, 2H, CH₂), 7.03 (d, 2H, 2CH, *J* = 8.7 Hz), 7.17-7.22 (m, 3H, 3CH), 7.25-7.39 (m, 8H, 8CH), 7.44-7.51 (m, 8H, 8CH), 7.57 (d, 2H, 2CH, *J* = 8.8 Hz), 7.78-7.82 (m, 3H, 3CH), 9.04 (s, 1H, 1NH), 9.12 (s, 1H, 1NH). ¹³C NMR (DMSO-d₆, 50 MHz): δ 45.4 (CH₂), 90.4 (C), 105.0 (C), 108.9 (C), 112.3 (C), 115.5 (2CH), 115.7 (2CH), 117.4 (C), 109.0 (C), 119.4 (C), 120.1 (CH), 121.9 (CH), 122.5 (CH), 123.8 (CH), 124.3 (CH), 125.3 (4CH), 127.3 (CH), 127.8 (2CH), 128.5 (2CH), 128.7 (4CH), 130.8 (CH), 131.3 (2CH), 131.9 (C), 134.3 (CH), 143.1 (C), 144.2 (C), 144.3 (2C), 145.2 (C), 147.7 (C), 159.9 (C). HMRS (ESI): *m/z* calcd for C₄₂H₃₀N₄O₃S M+H⁺: 671.2111. Found: 671.2108.

2-[4-[2-[4-(4-cyanophenylamino)phenyl]-5,5-diphenyl-4,5-dihydrofuran-3-ylsulfonyl]phenylamino]benzotrile (**4ac**): yellow solid, mp 138°C. ¹H NMR (DMSO-d₆, 200 MHz): δ 3.79 (s, 2H, CH₂), 7.01-7.16 (m, 3H, 3CH), 7.20-7.39 (m, 10H, 10CH), 7.44-7.47 (m, 5H, 5CH), 7.55-7.71 (m, 5H, 5CH), 7.77-7.84 (m, 3H, 3CH), 9.12 (s, 1H, 1NH), 9.31 (s, 1H, 1NH). ¹³C NMR (DMSO-d₆, 50 MHz): δ 45.4 (CH₂), 90.6 (C), 101.0 (C), 105.0 (C), 109.6 (C), 115.7 (2CH), 115.9 (CH), 116.4 (2CH), 117.2 (2CH), 117.3 (2CH), 119.6 (C), 120.6 (C), 122.0 (CH), 123.8 (CH), 125.3 (4CH), 127.8 (2CH), 128.7 (4CH), 131.2 (2CH), 131.7 (C), 133.9 (2CH), 134.3 (C), 134.5 (CH), 144.1 (C), 144.2 (C), 144.3 (2C), 146.9 (C), 147.8 (C), 159.7 (C). HMRS (ESI): *m/z* calcd for C₄₂H₃₀N₄O₃S M+H⁺: 671.2111. Found: 671.2110.

2-[4-[3-[4-(3-cyanophenylamino)phenyl]-5,5-diphenyl-4,5-dihydrofuran-2-ylsulfo-nyl]phenylamino]benzotrile (**4ba**): yellow solid, mp 121°C. ¹H NMR (DMSO-d₆, 200 MHz): δ 3.78 (s, 2H, CH₂), 7.05-7.21 (m, 5H, 5CH), 7.27-7.59 (m, 18H, 18CH), 7.77-7.81 (m, 3H, 3CH), 8.98 (s, 1H,

1NH), 9.13 (s, 1H, 1NH). ¹³C NMR (DMSO-d₆, 50 MHz): δ 45.4 (CH₂), 90.4 (C), 103.8 (C), 109.1 (C), 112.4 (C), 115.5 (2CH), 115.7 (CH), 115.9 (2CH), 117.7 (C), 118.9 (C), 119.7 (CH), 120.8 (CH), 121.1 (CH), 122.9 (CH), 123.5 (CH), 125.3 (4CH), 127.8 (2CH), 128.7 (4CH), 130.9 (2CH), 131.1 (2CH), 131.3 (CH), 131.7 (C), 134.3 (CH), 134.5 (C), 142.4 (C), 144.3 (2C), 145.1 (C), 145.9 (C), 147.0 (C), 159.9 (C). HMRS (ESI): m/z calcd for C₄₂H₃₀N₄O₃S M+H⁺: 671.2111. Found: 671.2115.

3-(4-{2-[4-(4-cyanophenylamino)phenyl]-5,5-diphenyl-4,5-dihydrofuran-3-ylsulfonyl}phenylamino)benzotrile (**4bc**): yellow solid, mp 211°C. ¹H NMR (DMSO-d₆, 200 MHz): δ 3.79 (s, 2H, CH₂), 7.10 (d, 2H, 2CH, *J* = 8.7 Hz), 7.22-7.41 (m, 11H, 11CH), 7.45-7.49 (m, 7H, 7CH), 7.58 (d, 2H, 2CH, *J* = 8.7Hz), 7.67 (d, 2H, 2CH, *J* = 8.7 Hz), 7.82 (d, 2H, 2CH, *J* = 8.7Hz), 9.14 (s, 1H, 1NH), 9.32 (s, 1H, 1NH). ¹³C NMR (DMSO-d₆, 50 MHz): δ 45.4 (CH₂), 90.6 (C), 101.0 (C), 109.5 (C), 112.4 (C), 115.5 (CH), 116.4 (2CH), 117.2 (2CH), 117.3 (2CH), 117.9 (CH), 118.9 (C), 120.6 (C), 121.1 (CH), 123.5 (C), 125.3 (4CH), 127.3 (CH), 127.9 (2CH), 128.7 (4CH), 130.9 (2CH), 131.2 (2CH), 131.5 (C), 133.9 (2CH), 142.4 (C), 144.1 (C), 144.3 (2C), 145.8 (C), 146.9 (C), 159.7 (C).). HMRS (ESI): m/z calcd for C₄₂H₃₀N₄O₃S M+H⁺: 671.2111. Found: 671.2114.

2-(4-{3-[4-(4-cyanophenylamino)phenyl]-5,5-diphenyl-4,5-dihydrofuran-2-ylsulfonyl}phenylamino)benzotrile (**4ca**): yellow solid, mp 140°C. ¹H NMR (DMSO-d₆, 200 MHz): δ 3.79 (s, 2H, CH₂), 7.01-7.05 (m, 1H, 1CH), 7.12-7.16 (m, 2H, 2CH), 7.20-7.27 (m, 5H, 5CH), 7.29-7.38 (m, 6H, 6CH), 7.44-7.47 (m, 5H, 5CH), 7.55-7.71 (m, 5H, 5CH), 7.76-7.84 (m, 2H, 2CH), 8.98 (s, 1H, 1NH), 9.39 (s, 1H, 1NH). ¹³C NMR (DMSO-d₆, 50 MHz): δ 45.4 (CH₂), 90.6 (C), 102.0 (C), 103.9 (C), 109.0 (C), 115.7 (CH), 115.9 (2CH), 116.4 (CH), 117.2 (2CH), 117.3 (2CH), 119.7 (C), 120.8 (C), 122.9 (C), 125.3 (4CH), 127.9 (2CH), 128.6 (2CH), 128.7 (4CH), 131.2 (2CH), 132.9 (C), 133.9 (2CH), 134.3 (CH), 134.5 (CH), 144.3 (2C), 145.0 (C), 145.8 (C), 146.0 (C), 146.2 (C), 160.2 (C). HMRS (ESI): m/z calcd for C₄₂H₃₀N₄O₃S M+H⁺: 671.2111. Found: 671.2108.

3-(4-{3-[4-(4-cyanophenylamino)phenyl]-5,5-diphenyl-4,5-dihydrofuran-2-ylsulfonyl}phenylamino)benzotrile (**4cb**): yellow solid, mp 139°C. ¹H NMR (DMSO-d₆, 200 MHz): δ 3.79 (s, 2H, CH₂), 7.08-7.28 (m, 6H, 6CH), 7.32-7.39 (m, 6H, 6CH), 7.44-7.49 (m, 8H, 8CH), 7.55-7.71 (m, 4H, 4CH), 7.79-7.83 (m, 2H, 2CH), 9.13 (s, 1H, 1NH), 9.39 (s, 1H, 1NH). ¹³C NMR (DMSO-d₆, 50 MHz): δ 45.4 (CH₂), 90.5 (C), 102.0 (C), 108.7 (C), 112.4 (C), 115.5 (2CH), 116.4 (CH), 117.2 (2CH), 119.0 (C), 120.1 (CH), 121.1 (C), 122.5 (C), 123.4 (CH), 124.3 (CH), 125.3 (4CH), 127.8 (2CH), 128.7 (4CH), 130.8 (2CH), 131.2 (2CH), 131.3 (2CH), 132.9 (C), 133.9 (2CH), 142.4 (C), 143.1 (C), 144.3 (2C), 145.3 (C), 146.2 (C), 160.1 (C). HMRS (ESI): m/z calcd for C₄₂H₃₀N₄O₃S M+H⁺: 671.2111. Found: 671.2114.