

View Article Online View Journal

RSC Advances

This article can be cited before page numbers have been issued, to do this please use: J. aziz, J. D. BRION, M. Alami and A. hamze, *RSC Adv.*, 2015, DOI: 10.1039/C5RA14459K.



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. This Accepted Manuscript will be replaced by the edited, formatted and paginated article as soon as this is available.

You can find more information about *Accepted Manuscripts* in the **Information for Authors**.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard <u>Terms & Conditions</u> and the <u>Ethical guidelines</u> still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.



www.rsc.org/advances



Journal Name

SC Advances Accepted Manuscrip

RSCPublishina

ARTICLE

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012, Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

Synthesis of Benzofulvenes through Chemoselective Sonogashira, Barluenga Couplings of ortho Ethynyl-**N-Tosylhydrazones and Cycloisomerization**

Jessy Aziz,^a Jean-Daniel Brion,^a Mouad Alami^{*a} and Abdallah Hamze^{*a}

Chemoselective synthesis of ortho ethynylhydrazones 7, derived from 2-iodoacetophenone via a Sonogashira coupling is reported for the first time. In this challenging transformation, a siteselective coupling in the presence of a hydrazone function was developed. These compounds represent useful intermediates for the synthesis of benzofulvenes through a sequence of palladium-catalyzed cross-coupling and palladium-catalyzed 5-exo-dig cyclization.

Introduction

www.rsc.org/

Multi-functionalized building blocks have become an appealing tool in organic synthesis. In fact, they can be involved in cascade reactions, which became highly recommended for chemists due to their simple, inexpensive and time-saving character along with facile addition of complexity to the final structures. Among these new scaffolds, Ntosylhydrazones have emerged as precursors for the in-situ generation of non-stabilized diazo compounds.¹ When these compounds are properly functionalized, multiple C-C and C-heteroatom bonds are created in a one-pot fashion.²

One of the major research topics of our laboratory includes developing synthetic methods using N-tosylhydrazones as readily available starting materials for the C-C³ and C-N⁴ bonds formation. Recently, we disclosed an excellent approach to the synthesis of benzofulvenes 5 through a selective palladium-catalyzed 5-exo-dig cyclization of aromatic 1,5envnes 4.5 These latter were prepared from 2-iodoacetophenone 1 in a six steps sequence using as intermediate Ntosylhydrazone 2 having a trimethylsilylethynyl group at the C2 position (Scheme 1).



In our continuing attempts to discover new reactivity of Ntosylhydrazones, and to increase the interest of our synthetic approach in the formation of benzofulvenes 5, we decided to

improve two aspects of this sequence. First, we sought to shorten the synthetic scheme exploring the unprecedented site selective Sonogashira coupling of 2-iodo-N-tosylhydrazone 6 Published on 24 August 2015. Downloaded by University of Sussex on 24/08/2015 18:12:14.

with terminal aromatic alkynes while maintaining intact the hydrazone function.⁶ Second, because the Barluenga coupling of 7 and the 5-*exo-dig* cyclization of 4 both required the presence of a palladium catalyst and a base under heating, we tried to explore the ability of *N*-tosylhydrazone intermediates 7 to achieve the sequential Barluenga coupling and the aromatic 1,5-enynes cycloisomerization without prior isolation of compound 4. Each of these goals was met with success; herein we wish to disclose our full results that extended the scope of our earlier work.⁵ This strategy provides a convenient challenging and site selective approach to a variety of benzofulvenes, which are not readily available by other methods.

Results and discussion

As outlined in Scheme 2, 2-ethynylhydrazones 7 can be obtained according two routes starting from readily available 2-iodoacetophenone 1. The first one will involve a Sonogashira coupling with a terminal aryl alkyne, followed by the *N*-tosylhydrazones formation (compound 7, *path a*). The second one, more challenging, will consist in tosylhydrazone 6 formation from 1 and then its site selective Sonogashira coupling with an aryl alkyne under palladium-copper catalysis while keeping intact the hydrazine function (*path b*). In order to achieve this transformation selectively, fine-tuning of the palladium catalyst, the ligand and the base employed will be necessary to assure high reaction selectivity, thus avoiding the formation of indazole by-products as has been reported by Inamoto *et al.*⁷



Scheme 2.Synthesis of N'-(2-alkynylbenzilidene) hydrazides 7, derived from acetophenones.

According to *path a*, the Sonogashira coupling of 2iodoacetephenone **1** under standard conditions $(PdCl_2(PPh_3)_2$ (10 mol%), CuI (20 mol%), Et₃N (2equiv), THF, rt) took place with a good yield for the electron-rich alkyne (**8a**: R = *p*-OMe) but with a low yield for the electron-poor alkyne (**6b**: R = *p*-CN). The major drawback of this *path* is the condensation step with *p*-toluenesulfonylhydrazide because very low yields were obtained for hydrazone **7a** formation, and we never succeeded in isolating the hydrazone **7b** despite the use of many protocols by changing the solvent (MeOH, EtOH), the temperature (rt or reflux) and additives (MgSO₄, PTSA). In all cases, the ¹H NMR of the crude mixture was very complicated and separation was tedious. For these reasons, we turned our attention to the alternative synthetic route *path b* (Scheme 2). The first step consisting in the condensation of **1** with sulfonylhydrazide worked well, providing the *N*-tosylhydrazone **6** in an excellent yield (95%) as a mixture of *E*- and *Z*-isomers in a 75/25 ratio.⁸ The next step consists in installing an ethynyl group at position 2 by a Sonogashira reaction. To our knowledge, this site-selective coupling has never been described in the presence of a hydrazone function.

Initially, *N*-tosylhydrazone **6** and 4-ethynylanisole were chosen as coupling partners to optimize the Sonogashira reaction. When conventional Sonogashira reaction conditions were applied $(PdCl_2(PPh_3)_2 (10 \text{ mol}\%), CuI (20 \text{ mol}\%), Et_3N (2equiv), THF, rt)$, the desired coupling product **7a** was formed with only a 33% isolated yield (Scheme 3).



Scheme 3.Chemoselectivity issue during the coupling of *N*-tosylhydrazone 6

As expected from Inamoto report,⁷ another product was formed simultaneously, the 3-methyl-1-tosyl-1*H*-indazole **9** in a 35% yield through an intramolecular Buchwald-Hartwig coupling of the hydrazone(*Z*)-**6** isomer.^{7, 9} It should be noticed that a possible E/Z isomerisation of hydrazone **6** can occur during storage or under the reaction conditions of the coupling; which explains the yield of indazole **9**.

As a consequence, the main challenge of this work is to determine chemoselective coupling conditions preserving the *N*-tosylhydrazone function, and favoring the intermolecular Sonogashira reaction over the intramolecular Buchwald-Hartwig coupling. The optimization assays for the Sonogashira coupling between *N*-tosylhydrazone **6** and 4-ethynylanisole are depicted in Table 1.¹⁰

We started screening different bases (entries 1-3), diisopropylamine gave the best result with a complete conversion of the hydrazone **6** and the formation of the desired product **7a** in a 45% yield (entry 3). Several solvents were also tested (entries 3-6) and dimethylsulfoxide permitted a full conversion of the starting material in just 8 hours, furnishing **7a** in a 55% yield (entry 6). It should be noticed that all the assays were conducted at room temperature. At higher temperatures, decomposition of the *N*-tosylhydrazone **6** occurred leading to the Bamford-Stevens product.¹¹Then, we turned our attention to the catalytic system. Different copper catalysts were tested (entries 6-9), however, no significant increase in the yield of **7a** was observed. Copper (I) iodide was maintained as the copper Published on 24 August 2015. Downloaded by University of Sussex on 24/08/2015 18:12:14.

source in this coupling. Changing the palladium source enabled the reduction of the reaction time to 3 hours (entries 10-12).

Table 1. Optimization assays for the Sonogashira coupling between *N*-tosylhydrazone 6 and 4-ethynylanisole^a



Among several palladium source examined, $Pd(OAc)_2$ afforded **7a** in the highest yield of 55% (entry 10). Finally, the ligands had the most notable effect on the yield of **7a** (entries 10 and 13-17). The chemoselectivity for the Sonogashira coupling was enhanced in the presence of a bidendate phosphine ligand (rac-Binap, entry 17), affording the desired product **7a** in a 76% yield and limiting the formation of indazole **9** to 19%.

Once the optimized conditions were established, the scope for the Sonogashira coupling between hydrazone **6** and different terminal alkynes was examined (Table 2). Electronenriched alkynes allow the coupling to proceed with good isolated yields ranging from 63 to 82% (compounds **7a-f**). *O*tolylacetylene gave also the desired coupling product **7c** with a good yield, indicating that there no influence of steric hindrance of the alkyne partner on the coupling.

This new protocol worked also well with electron-neutral alkynes, giving the desired products **7f** and **7g** in good yields.

Electron-deficient alkynes were also effective, albeit affording the coupling product **7h** with a slightly diminished yield.

Table 2. Synthesis of 7 from N-tosylhydrazone 6 and terminal arylalkynes^a



^aReaction conditions: *N*-tosylhydrazone**6** (0.48 mmol), alkyne (2 equiv), Pd(OAc)₂ (10 mol%), rac. Binap (20 mol%), CuI (20 mol%), iPr_2NH (3 equiv), DMSO (3 mL) at 20 °C for 3 hours, under argon inlet.

We were pleased to find that heterocyclic 3-thienylthiophene was successfully coupled with hydrazone **6** to access compound **7i** in a 60% yield. Unfortunately, our conditions were not compatible with aryl alkynes having electron-withdrawing substituents (CN, NO₂) on the aromatic nucleus as no coupling products were isolated. It should be noticed that all hydrazones **7** were obtained as a single (*E*)-isomer as determined by NOESY experiment.¹² This diastereoselectivity is in accordance with the above statement that only the *Z* isomer of hydrazone **6** gives indazole **9** *via* intramolecular amination while the *E* isomer reacts with the terminal alkyne and gives hydrazones **7**, with retention of the configuration, *via* a Sonogashira coupling.

Next, we tested the formation of enynes 4 through a palladiumcatalyzed cross-coupling reaction between *ortho*ethynylhydrazones 7a and aryl halides (Scheme 4). Thus, when using the following conditions: $PdCl_2(MeCN)_2$, dppp, Cs_2CO_3 , dioxane 90 °C, 4 h in a sealed tube,¹³ we noticed the formation of benzofulvenes 5a and 5b via in situ 5-exo-dig cyclisation alongside the expected enynes 4a and 4b. Enynes 4 and **RSC Advances**

benzofulvenes 5 were obtained as a mixture in a ratio of about 60/40 determined by ¹H NMR (Scheme 4).

In order to avoid any tedious separation of compounds 4 and 5, these results prompted us to consider the sequential synthesis of benzofulvenes 5 starting from *ortho*-ethynylhydrazones 7 and without prior isolation of 4.



Reaction conditions: N-tosylhydrazone **7a** (0.24 mmol), aryle iodide (1 equiv), $PdCl_2(MeCN)_2$ (10 mol%), Dppp (20 mol%), Cs_2CO_3 (3 equiv), Dioxane (3 mL) at 90 °C for 4 hours in a sealed tube. ^a Values between brackets refers to isolated yields.

Indeed, enynes **4**, formed *in situ* by a palladium-catalyzed coupling between hydrazones **7** and aryl iodides, ^{3b, 3c} were then subjected, without prior isolation, to a 5-*exo-dig* cyclization giving rise to benzofulvene derivatives **5**.

Table 3 shows unoptimized results for the sequential two steps synthesis of benzofulvenes 5^{10} We succeeded preparing a variety of benzofulvenes with electron-poor (5a) and electron-rich substituents (compounds 5b and 5c). Likewise, the reaction conditions were compatible with the thiophene moiety and benzofulvene 5e was formed in a 40% yield. Despite the moderate yields observed, this method represents a short approach for the synthesis of a variety of benzofulvene derivatives 5.





^{*a*} Reaction conditions for the palladium-catalyzed cross-coupling reaction: *N*-tosylhydrazone 7 (0.48 mmol), aryl iodide (0.80 eq), PdCl₂(MeCN)₂(10 mol%), XPhos (20 mol%), NaOtBu (3 eq), PhF (3 ml) at 100 °C for 3 hours, sealed tube. ^{*b*}*N*-tosylhydrazone 7 (0.48 mmol), aryl iodide (0.80 eq), PdCl₂(MeCN)₂(10 mol%), Dppp (20 mol%), Cs₂CO₃ (3 eq), dioxane (3 ml) at 100 °C for 3 hours, sealed tube.

Conclusions

In summary, a site-selective Sonogashira coupling was successfully performed on a *N*-tosylhydrazone **6** derived from 2-iodoacetophenone, leading to a variety of *ortho*-ethynylhydrazones **7**. These compounds were further used for the formation of aromatic 1,5-enynes and their *in situ* cyclisation to provide benzofulvene derivatives. This represents an original and practical synthetic method of benzofulvenes starting from functionalized *N*-tosylhydrazones.

Experimental section

General method

Melting points (mp) were recorded on a Büchi B-450 apparatus and were uncorrected. NMR spectra were performed on a Bruker AMX 200 (¹H, 200 MHz; ¹³C, 50 MHz), Bruker AVANCE 300 or Bruker AVANCE 400 (¹H, 400 MHz; ¹³C, 100 MHz). Solvent peaks were used as reference values: CDCl₃ at 7.26 ppm for ¹H NMR and 77.16 ppm for ¹³C NMR; DMSO at 2.50 ppm for ¹H NMR and 39.52 ppm for ¹³C NMR; Acetone at 2.05 ppm for ¹H NMR and 29.84 ppm for ¹³C NMR; MeOD at 3.31 ppm for ¹H NMR and 49.00 ppm for ¹³C NMR. Chemical shifts δ are given in ppm, and the following abbreviations are used: singlet (s), doublet (d), doublet of doublet (dd), triplet (t), quadruplet (q), multiplet (m) and broad singlet (bs). Infrared spectra (IR) were measured on a Bruker Vector 22 spectrophotometer and were recorded neat (neat, cm⁻ ¹). High resolution mass spectra were recorded on a MicrotofQBrukerDaltonics. Reaction courses and product mixtures were routinely monitored by TLC on silica gel (precoated F254 Merck plates), and compounds were visualized under a UVP Mineralight UVGL-58 lamp (254 nm) and with phosphomolybdic acid/ Δ . Flash chromatography was performed using silica gel 60 (40-63 mm, 230-400 mesh ASTM) at medium pressure (200 mbar). Dimethylsulfoxide was used as received, dioxane, cyclohexane and tetrahydrofuran were dried using the procedures described in D. Perrin Purification of Laboratory Chemicals.¹⁴N-Tosylhydrazones were prepared according to literature procedure described by Creary, X. et al.¹⁵ All products reported showed ¹H and ¹³C NMR spectra in agreement with the assigned structures.

Experimental procedure for the preparation of *N*-tosylhydrazone 6

To a rapidly stirred suspension of *p*-toluenesulfonylhydrazide (5.5 mmol) in dry methanol (10 mL) was added the carbonyl substrate (5 mmol) in portion wise. The reaction mixture was refluxed for 12 hours. The mixture was allowed to cool to room temperature and the tosylhydrazone began to precipitate. After approximately 30 min, the mixture was cooled to 0 °C and the product removed by filtration, washed with a small quantity of methanol and then dried under vacuum.

N'-(1-(2-iodophenyl)ethylidene)-4-methylbenzene-

sulfonohydrazide 6. Hydrazone (6) precipitated as a white solid (yield 95%) as a mixture of E and Z isomers (75/25); M =414.26 g.mol⁻¹; m.p.: 146-148 °C; R_{f} = 0.46 (Cyclohexane/EtOAc 70/30); IR (film, cm⁻¹): 3444, 3426, 3376, 3302, 3264, 3245, 3190, 3169, 3123, 3086, 3040, 3014, 2961, 2835, 2723, 2666, 2535, 2364, 2340, 2263, 2212, 2160, 2142, 2107, 1995, 1970, 1698, 1424, 1339, 1291, 1244, 1167, 1091, 1032, 1010; Major isomer: (E)-: ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.45 (s, 1H), 7.87 (d, J = 8.7 Hz, 2H), 7.74 (dd, J = 8.2, 1 Hz, 1H), 7.29 (d, J = 8.7 Hz, 2H), 7.27 (td, J = 8.2, 1 Hz, 1H), 7.07 (dd, J = 8.2, 1.7 Hz, 1H), 6.97 (td, J = 8.2, 1.7 Hz, 1H), 2.40 (s, 3H), 2.14 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 156.5 (C), 144.2 (C), 144.1 (C), 139.4 (CH), 135.7 (C), 130.0 (CH), 129.7 (2CH), 129.3 (CH), 128.2 (2CH), 128.1 (CH), 95.2 (C), 21.7 (CH₃), 18.1 (CH₃); Minor isomer: (Z)-: ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.84 (d, J = 8.7 Hz, 2H), 7.79 (dd, J =8.2, 1 Hz, 1H), 7.38 (td, J = 8.2, 1 Hz, 1H), 7.33 (s, 1H), 7.31 (d, J = 8.7, 2H), 7.05 (td, J = 8.2, 1.7 Hz, 1H), 6.92 (dd, J = 8.2, 1H), 6.92 (dd, J = 8.2, 1H), 6.92 (dd, J = 8.2, 1H), 6.1.7 Hz, 1H), 2.41 (s, 3H), 2.17 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 155.6 (C), 144.1 (C), 139.9 (CH), 139.6 (C), 135.5 (C), 131.2 (CH), 129.6 (2CH), 129.5 (CH), 128.1 (2CH), 127.7 (CH), 93.2 (C), 24.0 (CH₃), 21.7 (CH₃); HRMS (ESI) (M + H)⁺ calculated for C₁₅H₁₆IN₂O₂S 414.9959 found 414.9972.

Typical procedure for the Sonogashira coupling between hydrazone 6 and terminal alkynes

To 1 equivalent of *N*-tosylhydrazone (0.48 mmol) in 3 ml of anhydrous DMSO under argon inlet, 0.1 eq of $Pd(OAc)_2$ (0.048 mmol), 0.2 eq of rac-BINAP (0.097 mmol) and 0.2 eq of CuI (0.097 mmol) were respectively added. The reaction mixture was stirred at room temperature for 3 minutes. Then, 3 equivalents of the distilled base *i*Pr₂NH (1.45 mmol) were slowly added and the mixture stirred for about 1 minute before adding 2 equivalents of the terminal alkyne (0.97 mmol). The reaction mixture was stirred for 3 hours at 20 °C, than quenched with a saturated solution of NH₄Cl and washed with ethyl acetate. The organic layers were washed with a saturated solution of NaCl, dried with Na₂SO₄ and concentrated under pressure. Column chromatography (Cyclohexane/EtOAc 90/10) afforded the final products.

(*E*)-N'-(1-(2-((4-methoxyphenyl)ethynyl)phenyl)ethylidene)-4-methylbenzenesulfono- hydrazide 7a. Brown solid; Yield 76%; $M = 418.14 \text{ g.mol}^{-1}$; m.p.: 141-144 °C; $R_f = 0.36$ (Cyclohexane/EtOAc 70/30); IR (film, cm-1): 2214, 2168, 1605, 1511, 1340, 1307, 1288, 1248, 1165, 1080, 1051, 1030, 906; ¹H NMR (300 MHz, CDCl₃) δ (ppm) 8.02 (s, 1H), 7.90 (d, J = 8.3 Hz, 2H), 7.53 – 7.45 (m, 1H), 7.39 – 7.21 (m, 7H), 6.85 (d, J = 8.9 Hz, 2H), 3.81 (s, 3H), 2.37 (s, 3H), 2.33 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 160.0 (C), 155.4 (C), 144.2 (C), 141.2 (C), 135.6 (C), 133.0 (2CH), 132.8 (CH), 129.7 (2CH), 128.8 (CH), 128.7 (CH), 128.2 (2CH), 128.1 (CH), 121.8 (C), 115.1 (C), 114.2 (2CH), 94.6 (C), 86.9 (C), 55.5 (OCH₃), 21.7 (CH₃), 17.3 (CH₃); HRMS (ESI) (M + H)⁺ calculated for C₂₄H₂₃N₂O₃S 419.1418 found 419.1424.

(E)-4-methyl-N'-(1-(p-tolylethynyl)phenyl)ethylidene)-

benzenesulfonohydrazide 7b. Grey solid; Yield 82%; M= 402.14 $g.mol^{-1}$; m.p.: 142-144 °C; R_{f} = 0.33 (Cyclohexane/EtOAc 80/20); IR (film, cm⁻¹): 3459, 2214, 2040, 2006, 1971, 1950, 1597, 1511, 1405, 1341, 1309, 1166, 1081, 1052, 1019, 912; ¹H NMR (400 MHz, CDCl₃,) δ (ppm) 7.89 (d, J = 8.2 Hz, 2H), 7.82 (s, 1H), 7.51 (d, J = 7.3 Hz, 1H), 7.29 (m, 7H), 7.13 (d, J = 7.9 Hz, 2H), 2.37 (s, 3H), 2.37 (d, 3H), 2.32 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ (ppm) 155.1 (C), 144.2 (C), 141.3 (C), 139.0 (C), 135.6 (C), 133.0 (CH), 131.4 (2CH), 129.7 (2CH), 129.3 (2CH), 128.9 (CH), 128.8 (CH), 128.3 (CH), 128.2 (2CH), 121.7 (C), 120.0 (C), 94.7 (C), 87.6 (C), 21.7 (CH₃), 21.7 (CH₃), 17.2 (CH₃); HRMS (ESI) (M + H)⁺ calculated for C₂₄H₂₃N₂O₂S 403.1464 found 403.1475.

N'-(1-(o-tolylethynyl)phenyl)ethylidene)-(E)-4-methylbenzenesulfonohydrazide 7c. Green solid; Yield 65%; M = 402.14 g.mol⁻¹; m.p.: 78-80 °C; $R_f = 0.33$ (Cyclohexane/EtOAc 80/20); IR (film, cm⁻¹): 3060, 2212, 2196, 2155, 2118, 2045, 2001, 1597, 1492, 1455, 1403, 1381, 1341, 1308, 1266, 1166, 1081, 1049, 920, 913, 814; ¹H NMR (300 MHz, DMSO) δ (ppm) 10.63 (s, 1H), 7.75 (d, J = 8.2 Hz, 2H), 7.59 - 7.54 (m, 1H), 7.42 (d, J = 6.8 Hz, 2H), 7.40 – 7.37 (m, 1H), 7.28 (d, J = 8.2 Hz, 4H), 7.23 (dd, J = 6.8, 2.3 Hz, 2H), 2.35 (s, 3H), 2.31 (s, 3H), 2.28 (s, 3H);¹³C NMR (75 MHz, DMSO) δ 155.2 (C), 143.2 (C), 141.6 (C), 139.6 (C), 136.3 (C), 132.6 (CH), 131.6 (CH), 129.6 (CH), 129.3 (2CH), 128.9 (CH), 128.7 (CH), 128.7 (CH), 128.1 (CH), 127.3 (2CH), 125.8 (CH), 121.9 (C), 120.5 (C), 92.5 (C), 91.6 (C), 20.9 (CH₃), 20.2 (CH₃), 18.4 (CH₃); HRMS (ESI) $(M + H)^+$ calculated for C₂₄H₂₃N₂O₂S 403.1468 found 403.1475.

(*E*)-*N*²-(1-(2-((4-(dimethylamino)phenyl)ethynyl)phenyl)ethylidene)-4-methylbenzene- sulfonehydrazide 7d.

Green solid; Yield 63%; M = 431.17 g.mol⁻¹; m.p.: 148-150 °C; R_f = 0.19 (Cyclohexane/EtOAc 80/20); IR (film, cm⁻¹): 3259, 3235, 2855, 2206, 2192, 2158, 2098, 2044, 2011, 1987, 1913, 1605, 1524, 1444, 1402, 1365, 1340, 1309, 1265, 1166, 1084, 1052; ¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.95 (s, 1H), 7.91 (d, *J* = 8.3 Hz, 2H), 7.47 (d, *J* = 7.7 Hz, 1H), 7.36 – 7.17 (m, 7H), 6.62 (d, *J* = 8.9 Hz, 2H), 2.98 (s, 6H), 2.37 (s, 3H), 2.34 (s, 3H); ¹³C NMR (75 MHz, DMSO) δ (ppm) 155.9 (C), 150.3 (C), 143.2 (C), 141.2 (C), 136.3 (C), 132.3 (2CH), 131.9 (CH), 129.4 (2CH), 128.7 (CH), 128.1 (CH), 127.7 (CH), 127.4 (2CH), 121.3 (C), 111.8 (2CH), 108.2 (C), 95.6 (C), 85.9 (C), 39.7 (2CH₃), 21.0 (CH₃), 18.2 (CH₃); HRMS (ESI) (M + H)⁺ calculated for C₂₅H₂₆N₃O₂S 432.1732 found 432.1740. Published on 24 August 2015. Downloaded by University of Sussex on 24/08/2015 18:12:14.

(*E*)-*N*'-(1-(2-((6-methoxynaphtalen-2-yl)ethynyl)phenyl)ethylidene)-4-methylbenzene- sulfonohydrazide 7e.

Brown solid; Yield 82%; M = 468.15 g.mol⁻¹; m.p.: 152-154 ^oC; $R_f = 0.17$ (Cyclohexane/EtOAc 80/20); IR (film, cm⁻¹): 3368, 2214, 2199, 2038, 2017, 1985, 1627, 1601, 1499, 1477, 1437, 1390, 1339, 1309, 1261, 1211, 1165, 1121, 1094, 1080, 1052, 1030, 968, 909, 856, 814, 763, 733; ¹H NMR (300 MHz, DMSO) δ (ppm) 10.60 (s, 1H), 7.99 (s, 1H), 7.85 (d, J = 8.2Hz, 2H), 7.76 (d, J = 8.2 Hz, 2H), 7.62 – 7.55 (m, 1H), 7.50 – 7.34 (m, 4H), 7.24 (dd, J = 12.2, 5.6 Hz, 4H), 3.90 (s, 3H), 2.36 (s, 3H), 2.22 (s, 3H); ¹³C NMR (75 MHz, DMSO) δ (ppm) 158.2 (C), 155.6 (C), 143.1 (C), 141.7 (C), 136.3 (C), 134.1 (C), 132.4 (CH), 130.9 (CH), 129.3 (3CH), 128.8 (CH), 128.6 (CH), 128.3 (CH), 128.1 (CH), 127.9 (C), 127.3 (2CH), 127.1 (CH), 120.5 (C), 119.4 (CH), 116.9 (C), 106.1 (CH), 94.3 (C), 87.5 (C), 55.3 (OCH₃), 20.9 (CH₃), 18.3 (CH₃); HRMS (ESI) $(M + H)^{+}$ calculated for $C_{28}H_{25}N_2O_3S$ 469.1567 found 469.1580.

(*E*)-4-methyl- *N*⁻(1-(2-phenylethynyl)phenyl)ethylidene)benzenesulfonohydrazide 7f. Green solid; Yield 81%; M= 388.12 g.mol⁻¹;m.p.: 80-82 °C; $R_f = 0.33$ (Cyclohexane/EtOAc 80/20); IR (film, cm⁻¹): 3057, 2245, 2190, 2085, 2038, 2022, 1597, 1492, 1456, 1437, 1399, 1341, 1308, 1266, 1166, 1120, 1081, 1050, 1017, 916; ¹H NMR (300 MHz, MeOD) δ (ppm) 7.82 (d, *J* = 8.2 Hz, 2H), 7.54 – 7.45 (m, 1H), 7.33 (m, 7H), 7.25 (d, *J* = 8.0 Hz, 3H), 2.30 (s, 3H), 2.29 (s, 3H); ¹³C NMR (75 MHz, MeOD) δ (ppm) 157.5 (C), 145.2 (C), 143.4 (C), 137.5 (C), 133.6 (2CH), 132.4 (2CH), 130.4 (2CH), 129.7 (2CH), 129.5 (2CH), 129.3 (CH), 129.0 (2CH), 124.2 (C), 122.5 (C), 94.8 (C), 88.7 (C), 21.5 (CH₃), 18.3 (CH₃);HRMS (ESI) (M + H)⁺ calculated for C₂₃H₂₁N₂O₂S 389.1306 found 389.1318.

(*E*)-4-methyl- *N*'-(1-(2-(naphtalen-1-ylethynyl)phenyl)ethylidene)benzenesulfonohydrazide 7g.

Grey solid; Yield 68%; M = 438.14 g.mol⁻¹; m.p.: 134-136 °C; $R_f = 0.33$ (Cyclohexane/EtOAc 80/20); IR (film, cm⁻¹): 2836, 1603, 1583, 1498, 1484, 1466, 1453, 1414, 1394, 1336, 1311, 1225, 1204, 1161, 1124, 1081, 1051, 1037, 1007, 950; ¹H NMR $(300 \text{ MHz}, \text{CDCl}_3) \delta$ (ppm) 8.26 (d, J = 8.3 Hz, 1H), 8.18 (s, 1H), 7.89 (d, J = 8.3 Hz, 2H), 7.83 (d, J = 6.5 Hz, 1H), 7.68 – 7.59 (m, 3H), 7.57 - 7.53 (m, 1H), 7.53 - 7.48 (m, 1H), 7.44 (d, J = 7.3 Hz, 1H), 7.39 (dd, J = 4.8, 3.0 Hz, 1H), 7.35 (d, J = 1.0 Hz, 2H), 7.17 (d, J = 8.1 Hz, 2H), 2.39 (s, 3H), 2.26 (s, 3H); ¹³C NMR (75 MHz, MeOD)δ (ppm)157.2 (C), 145.0 (C), 143.4 (C), 137.4 (C), 134.6 (C), 134.2 (C), 133.7 (CH), 131.4 (CH), 130.3 (2CH), 130.1 (CH), 129.8 (CH), 129.6 (CH), 129.4 (CH), 129.3 (CH), 128.9 (2CH), 128.2 (CH), 127.6 (CH), 126.8 (CH), 126.3 (CH), 122.5 (C), 121.5 (C), 93.6 (C), 92.9 (C), 21.4 (CH_3) , 18.6 (CH_3) ; HRMS (ESI) $(M + H)^+$ calculated for C₂₇H₂₃N₂O₂S 439.1459 found 439.1475.

(*E*)-*N*'-(1-(2-((4-fluorophenyl)ethynyl)phenyl)ethylidene)-4methylbenzenesulfono- hydrazide 7h. Green solid; Yield 58%; $M = 406.11 \text{ g.mol}^{-1}$; m.p.: 134-136 °C; $R_f = 0.32$ (Cyclohexane/EtOAc 80/20); IR (film, cm⁻¹): 3470, 3380, 3364, 3196, 3130, 3100, 3071, 2209,2158, 2108, 2045, 1987, 1958, 1599, 1508, 1405, 1342, 1308, 1229, 1168, 1093, 1048, 920; ¹H NMR (300 MHz, DMSO) δ (ppm) 10.59 (s, 1H), 7.75 (d, J = 8.3 Hz, 2H), 7.59 – 7.46 (m, 3H), 7.44 – 7.34 (m, 2H), 7.34 – 7.15 (m, 5H), 2.30 (s, 3H), 2.28 (s, 3H); ¹³C NMR (75 MHz, DMSO) δ (ppm) 162.1 (C, ¹ $J_{C-F} = 234.0$ Hz), 155.4 (C), 143.2 (C), 141.8 (C), 136.3 (C), 133.6 (2CH, ³ $J_{C-F} = 8.6.0$ Hz), 132.5 (CH), 129.4 (2CH), 128.7 (2CH), 128.1 (CH), 127.4 (2CH), 120.2 (C), 118.6 (C, ⁴ $J_{C-F} = 3.0$ Hz), 115.9 (2CH, ² $J_{C-F} = 22.2$ Hz), 92.4 (C), 87.6 (C), 20.9 (CH₃), 18.2 (CH₃); ¹⁹F NMR (188 MHz, DMSO) δ (ppm) -108.42; HRMS (ESI) (M + H)⁺ calculated for C₂₃H₂₀FN₂O₂S 407.1230 found 407.1216.

(E)-N'-(1-(2-(thiophen-3-ylethynyl)phenyl)ethylidene)-4-

methylbenzenesulfonohydrazide 7i. yellow oil; Yield 60%; M = 394.51 g.mol⁻¹; R_f = 0.29 (Cyclohexane/EtOAc 80/20); IR (film, cm⁻¹): 3215, 1597, 1439, 1401, 1385, 1339, 1309, 1246, 1187, 1165, 1080, 1050, 1018; ¹H NMR (300 MHz, CDCl₃) δ (ppm)8.29 (bs, 1H), 7.89 (d, J = 8.3 Hz, 2H), 7.52 – 7.44 (m, 1H), 7.42 (dd, J = 3.0, 1.1 Hz, 1H), 7.25 (dd, J = 8.3, 6.3 Hz, 6H), 7.08 (dd, J = 5.0, 1.1 Hz, 1H), 7.25 (s, 3H), 2.31 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ (ppm)155.3 (C), 144.2 (C), 141.4 (C), 135.5 (C), 132.8 (CH), 129.7 (3CH), 128.9 (CH), 128.7 (CH), 128.7 (CH), 128.3 (CH), 128.1 (2CH), 125.6 (CH), 122.0 (C), 121.4 (C), 89.6 (C), 87.7 (C), 21.7 (CH₃), 17.34 (CH₃); HRMS (ESI) (M + H)⁺ calculated for C₂₁H₁₉N₂O₂S₂ 395.0888 found 395.0888.

General procedure for the sequential synthesis of benzofulvenes 5

Condition A: In sealed tube, N'-(2а alkynylbenzilidene)hydrazide (7) (0.48 mmol), PdCl₂(MeCN)₂ (0.05 mmol, 10 mol%), 2-dicyclohexylphosphino-2',4',6'triisopropylbiphenyl (XPhos) (0.1 mmol, 20 mol %), and 3 mL of fluorobenzene (PhF) were mixed under argon for 5 minutes at rt. NaOtBu (1.44 mmol, 3 eq) was then added, the reaction mixture is stirred for 1 minute and aryl halide (0.38 mmol, 0.80 eq) is added. The reaction vessel was then capped with a pressure screw cap and the reaction mixture was stirred at 100 °C for 3 h. After cooling to room temperature, EtOAc was added to the mixture, which was filtered through celite. The solvents were evaporated under reduced pressure. The crude residue was transferred in a sealed tube, where under argon inlet, PdI₂ (0.05)mmol, 10 mol%), 1,3-Bis(diphenylphosphino)propane (Dppp) (0.1 mmol, 20 mol%) and Cs_2CO_3 (0.48 mmol, 1 eq) were mixed in 3 mL of dioxane. The reaction vessel was then capped with a pressure screw cap and the reaction mixture was stirred at 150 °C for 12 hours. The crude reaction mixture was allowed to cool to room temperature. EtOAc was added to the mixture, which was filtered through celite. The solvents were evaporated under reduced pressure and the crude residue purified by flash chromatography on silica gel.

Condition B: In a sealed tube, $N^{-}(2-alkynylbenzilidene)hydrazide (7) (0.48 mmol), PdCl₂(MeCN)₂ (0.05 mmol, 10 mol%), 1,3-Bis(diphenylphosphino)propane (Dppp) (0.1 mmol, 20 mol%) and 3 mL of dioxane were mixed under argon for 5 minutes at rt. Cs₂CO₃ (1.44 mmol, 3 eq) was$

RSC Advances Accepted Manuscrip

then added, the reaction mixture is stirred for 1 minute and aryl halide (0.38 mmol, 0.80 eq) is added. The reaction vessel was then capped with a pressure screw cap and the reaction mixture was stirred at 100 °C for 3 h. After cooling to room temperature, EtOAc was added to the mixture, which was filtered through celite. The solvents were evaporated under reduced pressure. The crude residue was transferred in a sealed tube, where under argon inlet, PdI₂ (0.05 mmol, 10 mol%), 1,3-Bis(diphenylphosphino)propane (Dppp) (0.1 mmol, 20 mol%) and Cs_2CO_3 (0.48 mmol, 1 eq) were mixed in 3 mL of dioxane. The reaction vessel was then capped with a pressure screw cap and the reaction mixture was stirred at 150 °C for 15 hours. The crude reaction mixture was allowed to cool to room temperature. EtOAc was added to the mixture, which was filtered through celite. The solvents were evaporated under reduced pressure and the crude residue purified by flash chromatography on silica gel.

(*E*)-4-(1-(4-methoxybenzylidene)-1*H*-inden-3-yl)benzonitrile 5a.

Conditions A. For a complete description, see reference 5.

(*E*)-1-(4-methoxybenzylidene)-3-(*p*-tolyl)-1*H*-indene 5b. Condition A: Yellow oil; Yield 62%; M = 324.42 g.mol⁻¹; $R_f =$ 0.85 (Cyclohexane/EtOAc 70/30); IR (film, cm⁻¹): 3068, 2957, 2923, 2854, 2835, 1730, 1601, 1569, 1510, 1464, 1446, 1377, 1342, 1303, 1256, 1174, 1141, 1112, 1052; ¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.80 – 7.75 (m, 1H), 7.64 (m, 5H), 7.47 (s, 1H), 7.35 – 7.26 (m, 4H), 7.15 (s, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H), 2.44 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 160.1 (C), 146.9 (C), 140.7 (C), 139.3 (C), 138.1 (C), 137.5 (C), 133.2 (C), 131.9 (2CH), 130.1 (C), 129.5 (2CH), 127.9 (CH), 127.7 (2CH), 127.1 (CH), 125.4 (CH), 122.7 (CH), 120.4 (CH), 119.2 (CH), 114.5 (2CH), 55.5 (OCH₃), 21.5 (CH₃); HRMS (ESI) (M + H)⁺ calculated for C₂₄H₂₁O 325.1592 found 325.1596.

(*E*)-1-(4-methoxybenzylidene)-3-(4-methoxyphenyl)-1*H*-indene 5c.

Condition B: Yellow oil; Yield 55%; M = 340.41 g.mol⁻¹; $R_f = 0.8$ (Cyclohexane/EtOAc 70/30); IR (film, cm⁻¹): 3000, 2958, 2835, 1731, 1599, 1569, 1510, 1498, 1462, 1441, 1418, 1378, 1342, 1302, 1284, 1246, 1172, 1111, 1052, 1028; ¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.81 – 7.73 (m, 1H), 7.70 – 7.57 (m, 5H), 7.45 (s, 1H), 7.33 – 7.27 (m, 2H), 7.11 (s, 1H), 7.00 (dd, J = 9.9, 8.9 Hz, 4H), 3.88 (s, 3H), 3.87 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 160.0 (C), 159.7 (C), 146.5 (C), 140.7 (C), 139.4 (C), 137.5 (C), 131.9 (2CH), 130.1 (C), 129.0 (2CH), 128.6 (C), 127.6 (CH), 127.1 (CH), 125.4 (CH), 122.1 (CH), 120.4 (CH), 119.2 (CH), 114.5 (2CH), 114.2 (2CH), 55.5 (2OCH₃); HRMS (ESI) (M + H)⁺ calculated for C₂₄H₂₁O₂ 341.1542 found 341.1537.

(E)-1-benzylidene-3-(4-methoxyphenyl)-1H-indene 5d.

Condition B: Yellow oil; Yield 60%; $M = 310.39 \text{ g.mol}^{-1}$; $R_f = 0.67$ (Cyclohexane/EtOAc 80/20); IR (film, cm⁻¹): 2956, 2923, 2852, 1732, 1606, 1502, 1465, 1453, 1438, 1343, 1303, 1286, 1249, 1177, 1157; ¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.82 – 7.74 (m, 1H), 7.71 – 7.64 (m, 4H), 7.63 – 7.57 (m, 1H), 7.47 (dd, J = 14.7, 7.5 Hz, 3H), 7.37 (dd, J = 5.0, 3.7 Hz, 1H), 7.35 –

7.29 (m, 2H), 7.10 (s, 1H), 7.05 – 6.98 (m, 2H), 3.88 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 159.8 (C), 147.2 (C), 141.1 (C), 139.4 (C), 137.4 (C), 136.0 (C), 130.3 (2CH), 129.0 (2CH), 128.9 (2CH), 128.4 (C), 128.3 (CH), 127.60 (CH), 125.6 (CH), 124.9 (CH), 122.2 (CH), 120.5 (CH), 119.4 (CH), 114.2 (2CH), 55.5 (OCH₃); HRMS (ESI) (M + H)⁺ calculated for C₂₃H₁₉O 311.1436 found 311.1432.

E)-3-((3-(4-methoxyphenyl)-1H-inden-1-ylidene)methyl)thiophene 5e.

Condition B: Yellow oil; Yield 40%; M = 316.42 g.mol⁻¹; $R_f = 0.67$ (Cyclohexane/EtOAc 80/20); IR (film, cm⁻¹): 2958, 2927, 2834, 1621, 1606, 1501, 1448, 1415, 1361, 1330, 1303, 1286, 1250, 1177, 1033; ¹H NMR (300 MHz, CDCl₃) δ (ppm)7.78 – 7.70 (m, 1H), 7.67 (d, J = 8.8 Hz, 2H), 7.62 – 7.55 (m, 2H), 7.49 (dd, J = 5.0, 1.2 Hz, 1H), 7.43 (s, 1H), 7.41 (dd, J = 5.0, 2.9 Hz, 1H), 7.32 – 7.27 (m, 2H), 7.09 (s, 1H), 7.02 (d, J = 8.8 Hz, 2H), 3.88 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ (ppm)159.8 (C), 146.6 (C), 141.0 (C), 139.3 (C), 139.1 (C), 138.0 (C), 129.0 (2CH), 128.7 (CH), 128.4 (C), 127.2 (CH), 127.0 (CH), 126.6 (CH), 125.5 (CH), 122.0 (CH), 121.2 (CH), 120.6 (CH), 119.3 (CH), 114.3 (2CH), 55.5 (OCH₃); HRMS (ESI) (M + H)⁺ calculated for C₂₁H₁₇OS 317.1000 found 317.1002.

Acknowledgements

We gratefully acknowledge the support of this project by CNRS, University Paris Sud, and by La Ligue Contre le Cancer throughout an Equipe Labellisee 2014 grant. The BioCIS UMR 8076 laboratory is a member of the Laboratory of Excellence LERMIT supported by a grant from ANR (ANR-10-LABX-33).

Notes and references

2.

^aUniv Paris Sud, CNRS, BioCIS-UMR 8076, Laboratoire de Chimie Thérapeutique, Equipe Labellisée Ligue Contre le Cancer, LabEx LERMIT, Faculté de Pharmacie, 5 rue J-B Clément, Châtenay-Malabry, F-92296, France, E-mail: <u>mouad.alami@u-psud.fr</u>, <u>abdallah.hamze@upsud.fr</u>, Phone: (+33)-1-4683-5498; Fax: (+33)-1-46835498

†Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

- Citations here in the format A. Name, B. Name and C. Name, Journal Title, 2000, 35, 3523; A. Name, B. Name and C. Name, Journal Title, 2000, 35, 3523.
- For reviews, see (a) J. Barluenga and C. Valdés, Angew. Chem. Int. Ed., 2011, 50, 7486;(b) Z. Liu and J. Wang, J. Org. Chem., 2013, 78, 10024;(c) Z. Shao and H. Zhang, Chem. Soc. Rev., 2012, 41, 560;(d) Q. Xiao, Y. Zhang and J. Wang, Acc. Chem. Res., 2012, 46, 236.
 - (a) J. Barluenga, N. Quiñones, M.-P. Cabal, F. Aznar and C. Valdés, *Angew. Chem. Int. Ed.*, 2011, **50**, 2350;(b) Z. Huang, Y. Yang, Q. Xiao, Y. Zhang and J. Wang, *Eur. J. Org. Chem.*, 2012, 6586;(c) L. Zhou, Y. Shi, Q. Xiao, Y. Liu, F. Ye, Y. Zhang and J.

ARTICLE

Wang, Org. Lett., 2011, **13**, 968;(d) Y. Xia, Y. Zhang and J. Wang, ACS Catal., 2013, **3**, 2586.

- (a) B. Tréguier, A. Hamze, O. Provot, J.-D. Brion and M. Alami, *Tetrahedron Lett.*, 2009, **50**, 6549;(b) E. Brachet, A. Hamze, J.-F. o. Peyrat, J.-D. Brion and M. Alami, *Org. Lett.*, 2010, **12**, 4042;(c) M. Roche, A. Hamze, O. Provot, J.-D. Brion and M. Alami, *J. Org. Chem.*, 2013, **78**, 445;(d) M. Lawson, A. Hamze, J.-F. Peyrat, J. Bignon, J. Dubois, J.-D. Brion and M. Alami, *Org. Biomol. Chem.*, 2013, **11**, 3664.
- (a) J. Aziz, G. Frison, M. Gómez, J.-D. Brion, A. Hamze and M. Alami, *ACS Catal.*, 2014, 4, 4498;(b) A. Hamze, B. Treguier, J.-D. Brion and M. Alami, *Org. Biomol. Chem.*, 2011, 9, 6200;(c) J. Aziz, J.-D. Brion, A. Hamze and M. Alami, *Adv. Synth. Catal.*, 2013, 355, 2417;(d) M. Roche, G. Frison, J.-D. Brion, O. Provot, A. Hamze and M. Alami, *J. Org. Chem.*, 2013, 78, 8485.
- 5. J. Aziz, G. Frison, P. Le Menez, J.-D. Brion, A. Hamze and M. Alami, *Adv. Synth. Catal.*, 2013, **355**, 3425.
- For the palladium-catalyzed oxidative cross-coupling of *N*-tosylhydrazones with terminal alkynes providing conjugated enynes, see: L. Zhou, F. Ye, J. Ma, Y. Zhang and J. Wang, *Angew. Chem. Int. Ed.*, 2011, **50**, 3510.
- K. Inamoto, M. Katsuno, T. Yoshino, Y. Arai, K. Hiroya and T. Sakamoto, *Tetrahedron*, 2007, 63, 2695.
- X. Creary, W. W. Tam, K. F. Albizati and R. V. Stevens, Org. Synth., 1986, 64, 207.
- Only the (Z)-isomer of the hydrazone undergo the intramolecular amination reaction while the (E)-isomer decomposes under the reaction conditions, see: (a)K. Inamoto, M. Katsuno, T. Yoshino, I. Suzuki, K. Hiroya and T. Sakamoto, Chem. Lett., 2004, 33, 1026;(b) T. Kylmälä, A. Hämäläinen, N. Kuuloja, J. Tois and R. Franzén, Tetrahedron, 2010, 66, 8854.
- 10. Preliminary essays, for one-pot and auto-tandem reaction (coupling + cyclisation) catalyzed by the same palladium species, afforded complex crude mixtures.
- 11. W. R. Bamford and T. S. Stevens, J. Chem. Soc., 1952, 4735.
- 12. NOESY experiments for compounds **7a** and **7b** are represented in the supporting information section.
- E. Brachet, A. Hamze, J. F. Peyrat, J. D. Brion and M. Alami, Org. Lett., 2010, 12, 4042.
- D. D. Perrin, W. L. F. Armarego and D. R. Perrin, *Purification of Laboratory Chemicals*, 2nd edn., Pergamon Press, Oxford, 1980.
- X. Creary, W. W. Tam, K. F. Albizati and R. V. Stevens, Org. Synth., 1986, 64, 207.