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Palladium-catalyzed coupling of *N*-tosylhydrazones with ortho substituted aryl halides: synthesis of 4-arylchromenes and related heterocycles

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ABSTRACT

A convenient and efficient procedure for the synthesis of 4-arylchromenes, thiochromenes, and related heterocycles via a four step-sequence has been developed. The first three steps, which involve hydration of alkynes, hydrazones formation, and their Pd-coupling with ortho substituted aryl halides, furnished stereoselectively *Z*-trisubstituted olefins without any purification of the intermediates generated in each stage. These latter proved to be suitable precursors, in the last step, for the synthesis of the desired heterocycles of biological interest.

In an ongoing medicinal chemistry program directed toward the synthesis of anticancer[1] substances and particularly antimitotic agents,[2] we recently found that isocombretastatin A-4 (isoCA-4),[3] the third and '*forgotten*' structural isomer of the natural product, displayed biological activities comparable to that of CA-4 (Fig. 1). This substance having a 1,1-diarylethylene scaffold[4] is easy to synthesize without the need to control the olefin geometry. Bioisosteric replacement was successfully extended to compounds **1** and **2** having a tri- or tetra-substituted double bond.[3a,5] In this Letter we reconfigured the substitution pattern around the double bond by the preparation of 4-arylchromenes of type **3** that could be considered as constraint analogs of isoCA-4, in which the double bond is tri-substituted (Scheme 1).

A survey of the literature showed that few routes have been developed for the preparation of 4-arylchromenes **3**, including the coupling of 4-OTf-chromene derivatives with arylboronic acids,[6] a reaction of 4-methoxycarbonyl-chromane-3-one with aryllead triacetates,[7] ring-closing metathesis[8], and so on.[9]

The strategy envisioned herein to prepare the target chromenes **3** involves a four step-sequence based on regioselective hydration of alkynes[10] **7** or **8**, *N*-tosylhydrazones **5** and **6** formation, followed by their Pd-coupling reaction[3a,5a,11] with appropriate aryl halides (*paths a* or *b*, Scheme 1) and subsequent *O*-cyclization.

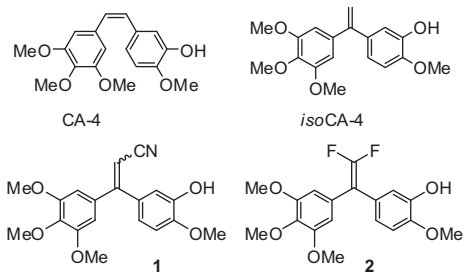

Figure 1. Structure of CA-4, isoCA-4 and synthetic tubulin assembly inhibitors **1** and **2**.

Previously we reported the hydration of internal alkynes, in EtOH under a catalytic amount of *p*-toluenesulfonic acid (PTSA). Under this environmentally friendly procedure, aliphatic arylalkynes were regioselectively converted into their corresponding carbonyl compounds according to Markovnikov's rules.[12] Because the reaction conditions for the hydration of arylalkynes and the tosylhydrazone formation from the corresponding carbonyl compounds are similar (cat. PTSA in EtOH), we decided to investigate whether it might be possible to carry out in a one-pot fashion

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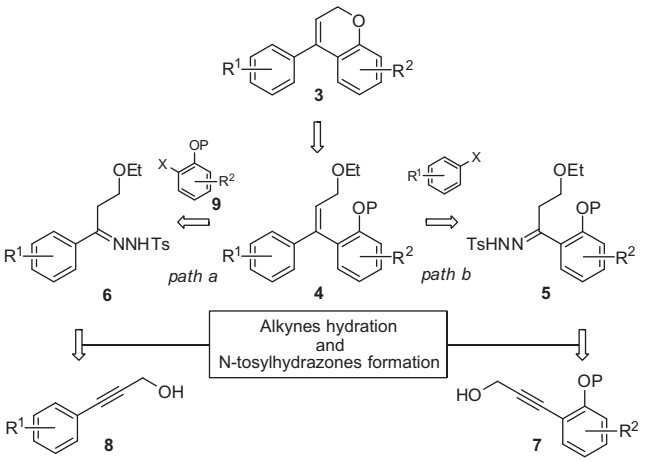
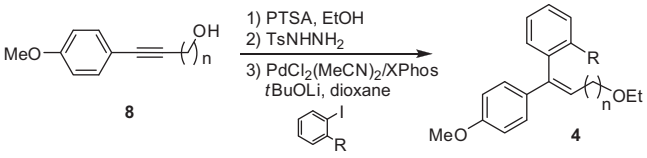


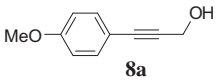
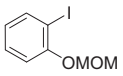
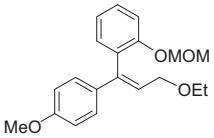
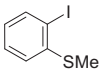
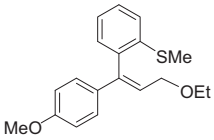
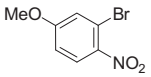
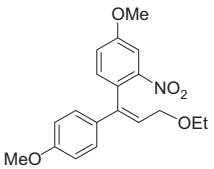
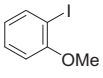
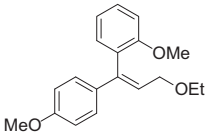
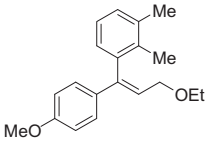
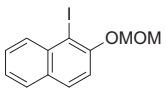
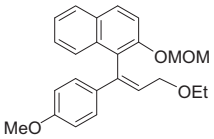
Scheme 1. Retrosynthetic analysis of targeted 4-arylchromene derivatives **3**.

the sequential hydration of **8**, in situ *N*-tosylhydrazone **6** formation, and palladium-catalyzed coupling reaction with ortho substituted aryl halides according to *path a* (Scheme 1). Herein we reported the results in this Letter and demonstrated that the resulting olefins **4**, which were formed in a stereoselective manner, are suitable precursors of 4-arylchromenes **3** and related heterocycles.

At the outset of this work, the one-pot synthesis of **4a** (Table 1, entry 1) was first examined from alkyne **8a**, easily available by Sonogashira–Linstrumelle coupling reaction.[13] We then decided to achieve this transformation in a sequential way by heating **8a** in EtOH in the presence of PTSA (20 mol %) in a first step then, by introducing *N*-tosylhydrazine in a second step, and finally by coupling the in situ obtained hydrazone with ortho substituted aryl iodide **9a** using $PdCl_2(MeCN)_2$/Xphos as the catalytic system.[14] Under these conditions, we were pleased to observe that this sequential process worked very well and provided the desired trisubstituted olefin **4a** in a 68% overall yield (Table 1, entry 1).[15] One can note that **4a** was isolated with a marked *Z*-selectivity of >9:1. To the

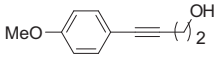
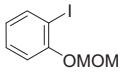
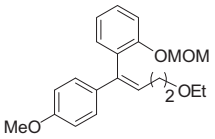
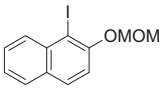
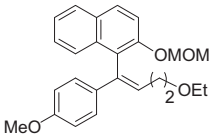
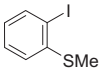
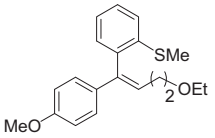
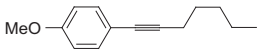
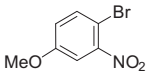
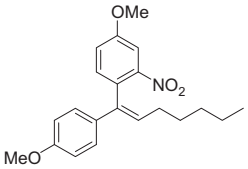
Table 1
Stereoselective synthesis of trisubstituted olefins **4** from arylalkynes **8** through a one-pot three step sequence based on hydration of **8**, *N*-tosylhydrazone formation and Pd-catalyzed coupling reaction with ortho substituted aryl halides



Entry	Alkyne **8**	Aryl halide **9**	Product *Z*-**4**		Yield[a] (%)	*Z*:*E* ratio[b]
1	 **8a**	**9a** 		**4a**	68	9:1
2	**8a**	**9b** 		**4b**	93	100:0
3	**8a**	**9c** 		**4c**	80	100:0
4	**8a**	**9d** 		**4d**	77	>9:1[c]
5	**8a**	**9e** 		**4e**	68	19:1
6	**8a**	**9f** 		**4f**	57	>19:1

(*continued on next page*)

Table 1 (*continued*)

Entry	Alkyne **8**	Aryl halide **9**	Product *Z*-**4**		Yield[a] (%)	*Z*:*E* ratio[b]
7	 **8b**	 **9a**		**4g**	71	19:1
8	**8b**	 **9f**		**4h**	58	100:0
9	**8b**	 **9b**		**4i**	55	100:0
10	 **8c**	 **9c**		**4j**	51	100:0

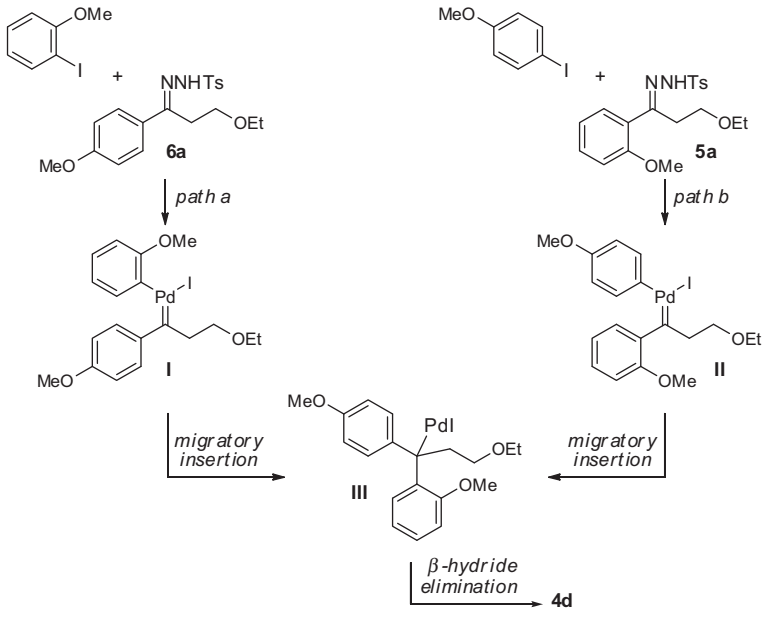
[a] Overall isolated yield based from alkyne **8**, for the 3 three step-sequence (alkyne hydration, *N*-tosylhydrazone formation and palladium-coupling reaction). All reactions were performed according to general procedure; see: Ref. 15.

[b] Ratio of stereoisomer *E* and *Z* determined in the crude reaction mixture by ^{1}H NMR. The *Z*-configuration of all compounds described herein was assigned by NOESY experiments.

[c] A low diastereoisomeric Z-preference (dr = 1.5:1, yield = 78%) was obtained when using 3-iodoanisole instead of 2-iodoanisole.

best of our knowledge, only one example with such *Z*-preference was reported very recently by Barluenga et al.[16] in the synthesis of a 2-arylacrylate, readily obtained from the coupling of a functionalized hydrazone with an ortho substituted aryl bromide. On the basis of these observations, we reasoned that this co-operative ortho effect could be exploited to give *Z*-trisubstituted olefins **4** with high diastereoisomeric ratio (dr).

In seeking a further enhancement of *Z*-selectivity, we next applied the one-pot three-step sequence to ortho substituted aryl halides **9b–f** (entries 2–6). In the most cases studied, an improvement in dr (*Z*/*E* from >9:1 to 100:0) was observed in comparison to the aforementioned result obtained in entry 1. As expected, the process can be accomplished also with other aliphatic arylalkynes (entries 7–10). Alkyne **8b** with a butynol chain (entries 7–9) provided stereoselectively olefins **4g–i** in good overall yields (55–71%). Finally alkyne **8c** having an *n*-pentyl chain was also efficiently transformed into olefin **4j** as a single *Z*-isomer in a 51% overall yield (entry 10). Altogether, these results (entries 7–10)



Scheme 2. Palladium-catalyzed formation of olefin **4d** according to *paths a* and *b*.

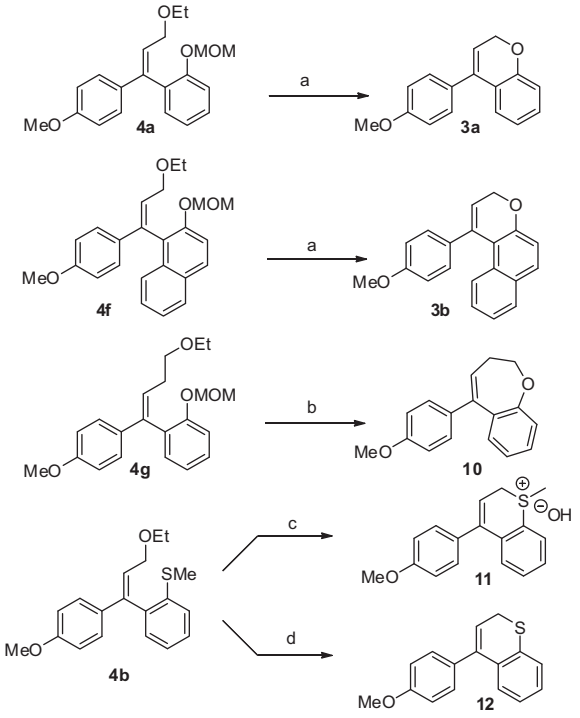
clearly demonstrated that the substituent attached to the triple bond had no deleterious effect on the *Z*/*E* distribution, and olefins 4g–**j** were isolated with a total *Z*-preference.

In the coupling step of *N*-tosylhydrazones with aryl halides, a migratory insertion of Pd carbene species has been suggested as the key step.[11a] According to this reaction mechanism, coupling of *N*-tosylhydrazone **6a** with ortho iodoanisole (*path a*, Scheme 2) would form Pd carbene species **I**, whereas the reaction of ortho methoxy *N*-tosylhydrazone **5a** with 4-iodoanisole would furnish **II** (*path b*, Scheme 2). These intermediate species **I** and **II** should evolve according to the migratory insertion of the anisyl ring to give the same alkylpalladium complex **III**. Further β-hydride elimination on **III** would give olefin **4d**, logically with the same diastereoisomeric ratio. To check this hypothesis, we carry out the coupling of ortho methoxy *N*-tosylhydrazone **5a** with 4-iodoanisole according to *path b* (Scheme 2). Although **4d** was formed in a low 18% yield, a similar dr (*Z*/*E* = ca. 19:1) was observed and may be compared to the one obtained according to *path a* (Table 1, entry 4).

Altogether, the results depicted in Table 1 show that the use of ortho substituted aryl halides as electrophilic partners in the coupling with *N*-tosylhydrazones provides mainly to exclusively olefins **4** with a *Z*-configuration, even if the exact origin of this diastereoselectivity remains unclear.

To achieve our goal, we next treated olefins having an ortho OMOM substituent **4a**, **4f**, and **4g** in acidic media. Thus, when heating **4a** and **4f** with PTSA in EtOH we were delighted to observe rapidly the formation of the desired 4-arylchromene derivatives **3a,b** in excellent yields (Scheme 3).[17] With substrate **4g**, TfOH was found to be superior than PTSA, and achieved the cyclization reaction efficiently providing the expected 5-aryl-2,3-dihydrobenzo[*b*]oxepine **10**.

To extend the scope of this transformation, we finally examined the cyclization of olefin **4b** having an ortho methylthio substituent. We were pleased to find that upon heating in the presence of TfOH, **4b** cyclized to afford after hydrolysis the arylthiochromenylium hydroxide **11** in good yield (85%). When the cyclization reaction of **4b** was conducted in the presence of TfOH followed by addition of Et_3N, the expected 1-arylthiochromene **12** was isolated in a 78% overall yield (Scheme 3).



Scheme 3. Reagents and conditions: (a) PTSA (3 equiv) EtOH, reflux, 1 h, **3a**: 98%, **3b**: 78%. (b) TfOH cat. dioxane, reflux, 15 h, 62%. (c) TfOH cat. CH_2Cl_2, rt, 30 min., 85% (d) (i) TfOH cat. CH_2Cl_2, 20 °C, 30 min; (ii) Et_3N (2 equiv) EtOH, 20 °C, 78%.

In summary, we have described a convenient sequence to 4-arylchromenes and related heterocycles. This protocol is based on the one-pot regioselective hydration of alkynes, *N*-tosylhydrazones formation, followed by their palladium-catalyzed coupling with aryl halides to form trisubstituted olefins with *Z*-selectivity. Further Brönsted acid-mediated cyclization provided the desired oxygen- and sulfur-containing heterocycles. This process is very convenient and efficient because it significantly reduced reaction times and tedious procedures such as work-up and purification at each step. Reaction is general with respect to alkyne and ortho substituted aryl halides. Good yields and convenient isolation of the targeted heterocycles are the distinct characteristics of the developed protocol. Studies are currently under way for the synthesis of heterocycles related to isoCA-4 and will be reported in due course.

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14. With $Pd_2(dba)_3$ as the catalyst, a lower yield of **4a** was obtained (29%).
15. *General procedure for the synthesis of* **4**: To an Emrys Optimizer 0.5–2 mL pyrex reaction vessel were added alkyne (1.2 mmol) and PTSA·H_2O (0.25 mmol) in EtOH (1 mL). The reaction vessel was then placed in the Emrys Optimizer and exposed to microwave irradiation according to the following specifications: temperature, 120 °C; time, 30 min; fixed hold time, on; sample absorption, high; pre-stirring, 60 s. After cooling to room temperature, 4-methylbenzenesulfonhydrazide (1.35 mmol) was added and the reaction vessel was exposed once again to microwave irradiation according to the following specifications: temperature, 50 °C; time, 15 min; fixed hold time, on; sample absorption, high; pre-stirring, 60 s. After cooling to room temperature, $PdCl_2(MeCN)_2$ (0.15 mmol), Xphos (0.3 mmol), lithium *tert*-butoxide (6.15 mmol) and dioxane (1 mL) were added, and the mixture was stirred at room temperature. After 3 min, the aryl halide (1.5 mmol) was finally added, the vessel was closed and the mixture was stirred at 90 °C for 1 h. After cooling to room temperature, H_2O was added and the mixture was extracted with CH_2Cl_2 (3 × 2 mL). Organic layers were dried, concentrated, and the crude was purified by column chromatography on silica gel.
All the compounds gave satisfactory spectroscopic data. Data for the selected compound **4b** are given below (Yield = 93%). R_f 0.50 (cyclohexane/EtOAc, 9:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34 (t, J = 8.4 Hz, 1H), 7.28–7.14 (m, 4H), 7.10 (dd, J = 7.4 and 1.7 Hz, 1H), 6.81 (d, J = 8.9 Hz, 2H), 6.29 (t, J = 6.5 Hz, 1H), 3.98–3.79 (m, 2H), 3.78 (s, 3H), 3.43 (q, J = 7.0 Hz, 2H), 2.35 (s, 3H), 1.17 (t, J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.1, 140.7, 138.2, 137.5, 132.4, 129.9, 128.1, 127.6 (2C), 125.5, 124.5, 124.4, 113.7 (2C), 68.5, 65.6, 55.2, 15.3 (2C). IR (ν cm^{-1}): 1510, 1247, 1181, 1098, 904, 727, 650. MS (APCI+) m/z 315.1 $(M+H)^+$.
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17. *Typical procedure for the synthesis of 4-arylchromene* **3b**: PTSA (3 equiv) and **4f** (1 equiv) were refluxed in EtOH for 1 h. After cooling to room temperature, H_2O was added and the mixture was extracted with CH_2Cl_2 (3 × 2 mL). Organic layers were dried, concentrated, and the crude was purified by column chromatography on silica gel. Compound **3b** (Yield = 78%). R_f 0.75 (cyclohexane/EtOAc, 9:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.77 (d, J = 8.5 Hz, 2H), 7.34–7.06 (m, 6H), 6.88 (d, J = 8.8 Hz, 2H), 5.96 (t, J = 4.9 Hz, 1H), 4.68 (d, J = 4.9 Hz, 2H), 3.84 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.0, 155.1, 137.6, 133.6, 130.35, 130.3, 130.1, 128.8 (2C), 128.4, 126.6, 125.2, 123.3, 119.1, 117.75, 117.7, 113.8 (2C), 64.5, 55.3. IR (ν cm^{-1}): 1658, 1596, 1509, 1462, 1246, 1226, 1143, 1099, 1029, 994, 907, 837, 803, 781, 749, 728, 648, 615. MS (APCI+) m/z 289.0 $(M+H)^+$.