ORGANIC LETTERS

2010
Vol. 12, No. 18
4042−4045

Pd-Catalyzed Reaction of Sterically Hindered Hydrazones with Aryl Halides: Synthesis of Tetra-Substituted Olefins Related to *iso*-Combretastatin A4

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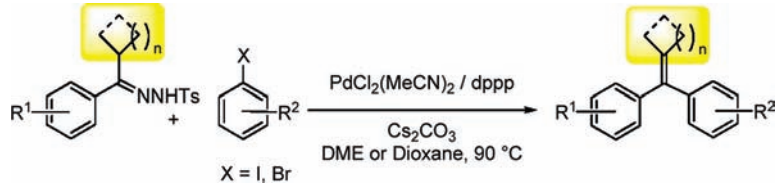
Received July 15, 2010

ABSTRACT



$PdCl_2(MeCN)_2$ in combination with dppp proved to be a powerful and efficient catalyst for the coupling of sterically hindered *N*-arylsulfonylhydrazones with aryl halides, thus providing a flexible and convergent access to tetrasubstituted olefins related to *iso*-combretastatin A4 in good yields. This new protocol has been applied successfully to the formal synthesis of biphenylisopropylidene 4-pyridine CYP17 inhibitor, 12b, of biological interest.

Several colchicine site inhibitors (CSI) are undergoing intensive investigation as vascular disrupting agents for cancer therapy.[1] Among them, the natural *Z*-stilbene combretastatin A-4[2] (CA-4, **1**) became one of the most interesting antitubulin agents because it displays strong cell growth inhibition even on multidrug-resistant cancer cell lines.[3] In addition, CA-4 induces rapid and reversible vascular shutdown in established tumors *in vivo*, consistent with an antivascular mechanism of action.[4] Currently, its water-soluble prodrug CA-4P is undergoing several advanced clinical trials for the treatment of anaplastic thyroid cancer.[5]

Despite its remarkable anticancer activity, the *cis* configuration of CA-4 is prone to isomerize to the thermodynamically more stable *trans* form during storage and administration, producing a dramatic reduction in both antitubulin and antiproliferative activities.[6] Thus, to retain the *cis*-olefin configuration of CA-4 required for bioactivity, extensive studies have been conducted to prepare *cis*-restricted analogues by incorporating the double bond in five-membered aromatic heterocyclic rings.[7]

Our interest in the 1,1-diarylethylene unit synthesis,[8] combined with our efforts to discover novel potent tubulin assembly inhibitors related to CA-4,[9] led us to identify a promising class of compounds (e.g., *iso*CA-4), with strong

(1) Prinz, H. *Exp. Rev. Anticancer Ther.* **2002**, *2*, 695.
(2) (a) Pettit, G. R.; Singh, S. B.; Hamel, E.; Lin, C. M.; Alberts, D. S.; Garcia-Kendall, D. *Experentia* **1989**, *45*, 209. (b) Pettit, G. R.; Singh, S. B.; Niven, M. L.; Hamel, E.; Schmidt, J. M. *J. Nat. Prod.* **1987**, *50*, 119. (c) Hill, S. A.; Tozer, G. M.; Pettit, G. R.; Chaplin, D. J. *Anticancer Res.* **2002**, *22*, 1453. (d) Eloff, J. N.; Katerere, D. R.; McGaw, L. J. *J. Ethnopharmacol.* **2008**, *119*, 686.
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(4) Dark, G. G.; Hill, S. A.; Prise, V. E.; Tozer, G. M.; Pettit, G. R.; Chaplin, D. J. *Cancer Res.* **1997**, *57*, 1829.
(5) Lippert, J. W. *Bioorg. Med. Chem.* **2007**, *15*, 605.
(6) Cushman, M.; Nagarathnam, D.; Gopal, D.; Chakraborti, A. K.; Lin, C. M.; Hamel, E. *J. Med. Chem.* **1991**, *34*, 2579.

10.1021/ol101639g
Published on Web 08/19/2010

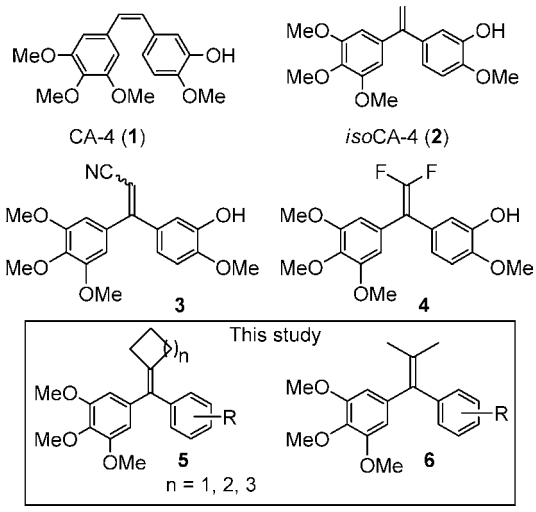

Figure 1. Structure of CA4, *iso*CA-4, synthetic tubulin assembly inhibitors **3**, **4**, and target structures **5**, **6**.

cytotoxic and antimitotic activities, simply by switching the trimethoxyphenyl moiety from the C(1) to the C(2) position of the ethylene bridge. In contrast to the parent natural product **1**, the double bond of *iso*CA-4 is not prone to isomerization (Figure 1). Bioisosteric replacement was successfully extended to compounds **3** and **4** having a tri- or tetra-substituted double bond.[9d] In this article, we reconfigured the substitution pattern around the double bond by the preparation of 1,1-diarylethylene analogues of type **5** and **6**, in which the double bond is tetra-substituted, including those with a cycloalkylidene unit. In these two series of designed analogues, we fixed one of the aryl groups as a 3,4,5-trimethoxyphenyl moiety, identical with the A-ring of *iso*CA-4, and examined several substitutions on the B-ring.

Although the double bond in compounds **5** and **6** could be generated by a Wittig reaction or by a two-step Grignard addition/dehydration sequence,[9b] these two approaches are not convergent and less suitable for the preparation of a library of compounds with variation of substituents on the B-ring. An alternative route consists of using the Pd-catalyzed coupling of aryl halides with *N*-tosylhydrazones[10] because these latter are readily available from the corresponding ketones and the reaction did not require the use of stoichiometric organometallic reagent. Although this procedure, initially developed by Barluenga et al.,[10] proved to be successful for the preparation of *iso*-combretastatins A-1 to A-5,[9d] to the best of our knowledge it was examined only for the synthesis of di- and trisubstituted olefins.[11] The purpose of this work was to explore the reaction of sterically hindered arylsulfonylhydrazones of ketones **7** with aryl halides to provide targeted tetra-substituted olefins of type **5** and **6** related to *iso*CA-4.

The reaction of sterically hindered tosylhydrazone **7a** with 4-iodoanisole was first examined under the conditions described by Barluenga (Pd_2dba_3/Xphos, LiO^tBu, dioxane, 90 °C).[10a] However, this transformation was inefficient and resulted in concomitant formation of the desired compound **9a** and byproduct trisubstituted olefin **10a** in a 30/70 ratio (Table 1, entry 1). After a tedious separation, **9a** was isolated in a low 15% yield. In this context, to circumvent the formation of byproduct **10a**, arising by thermal decomposition of **7a** under alkaline media,[12] we proceeded to optimize the reaction.

The screening conditions revealed that the source of palladium[13] used has an important influence on the reaction selectivity (entries 1−5). We were delighted to find that the use of $PdCl_2(MeCN)_2$ as the catalyst reversed the selectivity obtained with Pd_2dba_3 (compare entries 1 and 5), providing thus the desired compound **9a** as the major product. The screening reactions were continued with respect to the ligand, solvent, and base. Evaluation of ligands revealed that dppp (L7) or dppb (L8) in combination with $PdCl_2(MeCN)_2$ in dioxane at 90 °C is superior to all other choices (entries 5−13). Use of other diphenylphosphino-based ligands such as dppm (L5) or dppe (L6) leads to a decrease in the formation of **9a** (entries 10 and 11). With $PdCl_2(MeCN)_2$/dppp as the catalytic system, optimization with respect to the solvent showed that the reaction proceeds more efficiently in a polar solvent such as dioxane, dimethylacetamide or 1,2-dimethoxyethane (entries 13, 16, and 17) than in nonpolar solvent (entry 14). The influence of the inorganic base was finally investigated. KO^{t}Bu and NaO^{t}Bu afforded poor results in comparison to LiO^{t}Bu (entries 18, 19); however, we were pleased to find that Cs_2CO_3 seems to be the base of choice for this reaction and to exceed the threshold of 90% of the desired product **9a** (entry 20, **9a**/**10a** 91:9 ratio). Under these conditions, pure compound **9a** was obtained in an

(7) For a review, see: (a) Tron, G. C.; Pirali, T.; Sorba, G.; Pagliai, F.; Dusacca, S.; Genazzani, A. A. *J. Med. Chem.* **2006**, *49*, 3033. (b) Bellina, F.; Cauteruccio, S.; Monti, S.; Rossi, R. *Bioorg. Med. Chem. Lett.* **2000**, *16*, 5757. (c) Wu, M.; Li, W.; Yang, C.; Chen, D.; Ding, J.; Chen, Y.; Lin, L.; Xie, Y. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 869. For a recent clinical study see: (d) Rustin, G. J.; Shreeves, G.; Nathan, P. D.; Gaya, A.; Ganesan, T. S.; Wang, D.; Boxall, J.; Poupard, L.; Chaplin, D. J.; Stratford, M. R. L.; Balkissoon, J.; Zweifel, M. *Br. J. Cancer* **2010**, *102*, 1355.

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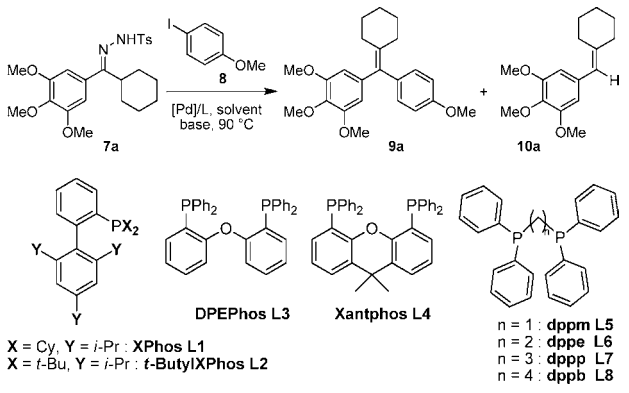
(11) For the coupling of *N*-tosylhydrazone with arylboronic acids under palladium catalysis, see: Zhao, X.; Jing, J.; Lu, K.; Zhang, Y.; Wang, J. *Chem. Commun.* **2010**, *46*, 1724. For the coupling of *N*-tosylhydrazones with benzyl Halides, see: Xiao, Q.; Ma, J.; Yang, Y.; Zhang, Y.; Wang, J. *Org. Lett.* **2009**, *11*, 4732.

(12) When heating **7a** in the presence of *t*BuOLi or Cs_2CO_3 (3 equiv) in dioxane at 90 °C for 2 h, only byproduct **10a** was formed; see: (a) Bamford, W. R.; Stevens, T. S. *J. Chem. Soc.* **1952**, 4735. (b) Fulton, J. R.; Aggarwal, V. K.; de Vicente, J. *Eur. J. Org. Chem.* **2005**, 1479.

(13) For more examples, please see Supporting Information.

Table 1. Initial Studies for Pd-Catalyzed Coupling of Sterically Hindered *N*-Tosylhydrazones **7a** with 4-Iodoanisole[a]



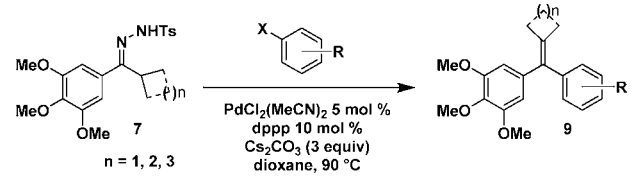
entry	Pd (mol %)	L (mol %)	solvent	base	ratio **9a/10a**[b]
1	Pd_2dba_3	L1	dioxane	LiO^{t}Bu	30/70[c]
2	$Pd(OH)_2$	L1	dioxane	LiO^{t}Bu	16/84
3	$Pd(OAc)_2$	L1	dioxane	LiO^{t}Bu	33/67[d]
4	$Pd(PPh_3)_4$		dioxane	LiO^{t}Bu	34/66
5	$PdCl_2(MeCN)_2$	L1	dioxane	LiO^{t}Bu	64/36[e]
6	$PdCl_2(MeCN)_2$	L2	dioxane	LiO^{t}Bu	0/100
8	$PdCl_2(MeCN)_2$	L3	dioxane	LiO^{t}Bu	44/56
9	$PdCl_2(MeCN)_2$	L4	dioxane	LiO^{t}Bu	52/48
10	$PdCl_2(MeCN)_2$	L5	dioxane	LiO^{t}Bu	14/86
11	$PdCl_2(MeCN)_2$	L6	dioxane	LiO^{t}Bu	55/45
12	$PdCl_2(MeCN)_2$	L7	dioxane	LiO^{t}Bu	80/20
13	$PdCl_2(MeCN)_2$	L8	dioxane	LiO^{t}Bu	80/20
14	$PdCl_2(MeCN)_2$	L7	toluene	LiO^{t}Bu	25/75
15	$PdCl_2(MeCN)_2$	L7	THF	LiO^{t}Bu	65/35
16	$PdCl_2(MeCN)_2$	L7	DMA	LiO^{t}Bu	80/20
17	$PdCl_2(MeCN)_2$	L7	DME	LiO^{t}Bu	88/12
18	$PdCl_2(MeCN)_2$	L7	DME	KO^{t}Bu	30/70
19	$PdCl_2(MeCN)_2$	L7	DME	NaO^{t}Bu	58/42
20	$PdCl_2(MeCN)_2$	L7	DME	Cs_2CO_3	91/9[f]
21	$PdCl_2(MeCN)_2$	L7	DME	Cs_2CO_3	91/9[g,h]
22	$PdCl_2(MeCN)_2$	L7	dioxane	Cs_2CO_3	91/9[g,i]

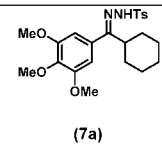
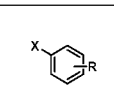
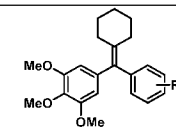
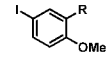
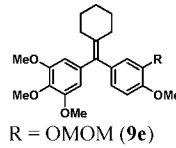
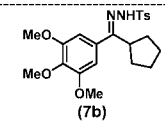
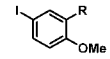
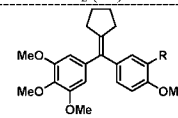
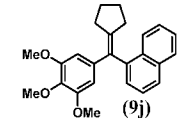
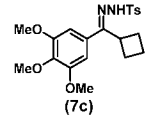
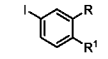
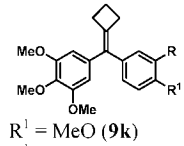
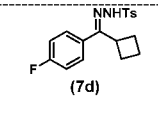
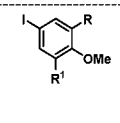
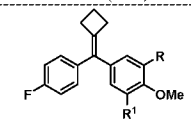
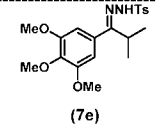
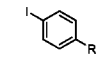
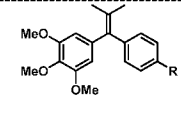
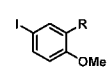
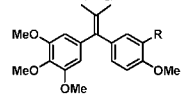
[a] The reactions were carried out with **7a** (1.2 mmol), **8** (1 mmol), [Pd] (10 mol %), ligand (20 mol %), and base (3 equiv) at 90 °C in 5.0 mL of solvent. [b] Ratio was determined by ^{1}H NMR in the crude reaction mixture. [c] Reaction with aryl bromide under this conditions gave the same ratio of **9a/10a**. [d] Reaction was heated in a sealed tube. [e] Performing the reaction without ligand gave a mixture of **9a** and **10a** in 10:90 ratio. [f] Isolated yield of **9a** was 85%. [g] Reaction conducted in the presence of $PdCl_2(MeCN)_2$ (5 mol %) and L7 (10 mol %). [h] Isolated yield of **9a** was 81%. [i] Isolated yield of **9a** was 82%.

85% isolated yield. It should be noted that decreasing the amount of Pd/L from 10:20 to 5:10 mol % had no effect on the yield and the selectivity when the reaction was conducted in DME or dioxane (entries 21 and 22).

With these optimized conditions in hand, the scope of this reaction was then studied by coupling a series of sterically hindered polyoxygenated arylsulfonylhydrazones **7** with different aryl halides. As shown in Table 2, this new protocol furnished the expected 1,1-diarylethylenes **9** in good to excellent yields, whatever the nature of the arylsulfonylhydrazone **7** (n = 1, 2, or 3).[14] The reaction displays little dependence upon electronic and steric nature of the aryl halide. Electron-rich and electron-poor substrates as well as *meta*-, *ortho*-, and *para*-

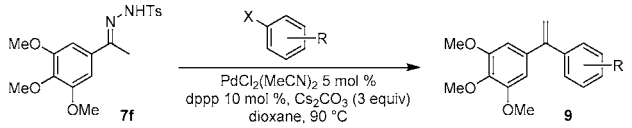
Table 2. Synthesis of 1,1-Diarylcycloalkylidenes by Pd-Catalyzed Coupling of Sterically Hindered *N*-Tosylhydrazones with Aryl Halides

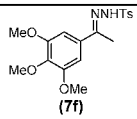
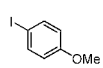
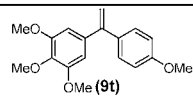
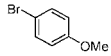
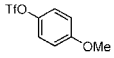
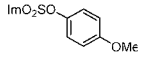
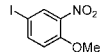
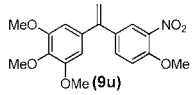
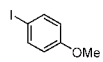
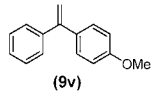


entry	hydrazone **7**	ArX	1,1 diarylethylenes **9**	yield (%)[a]
	 (**7a**)			
1		X = I	R = 4-MeO (**9a**)	82
2		X = Br	R = 4-MeO (**9a**)	70
3		X = I	R = 3-MeO (**9b**)	79
4		X = I	R = 2-MeO (**9c**)	68
5		X = I	R = 4-CN (**9d**)	63
	(**7a**)			
6			R = OMOM (**9e**)	75
7			R = NO_2 (**9f**)	78
	 (**7b**)			
8			R = H (**9g**)	68
9			R = OMOM (**9h**)	70
10			R = NO_2(**9i**)	64
11	(**7b**)		 (**9j**)	73
	 (**7c**)			
12		R = H	R^1 = MeO (**9k**)	80
13		R = H	R^1 = NMe_2 (**9l**)	65
14		R = OMOM	R^1 = MeO (**9m**)	62
	 (**7d**)			
15		R = H	R^1 = H (**9n**)	70
16		R = MeO	R^1 = MeO (**9o**)	66
	 (**7e**)			
17			R = MeO (**9p**)	64
18			R = CN (**9q**)	73
	(**7e**)			
19			R = OMOM (**9r**)	63
20			R = NO_2 (**9s**)	70

[a] Isolated yield.

Table 3. Synthesis of 1,1-Diarylethylenes by Pd-Catalyzed Coupling of Unhindered Tosylhydrazone **7f** with Aryl Halides and Pseudohalides



entry	hydrazone	ArX	1,1 diarylethylenes **9**	yield (%)[a]
1	 (7f)		 **9t**	95
2	(7f)		**9t**	82
3	(7f)		**9t**	77
4	(7f)		**9t**	75
5	(7f)		 **9u**	71
6	 (7g)		 **9v**	92

[a] Isolated yield.

substituted aryl iodides (entries 1, 3, and 4) all reacted completely and effectively within 3 h. Aryl bromides also can be employed with similar results (entry 2 and 11). In addition, this new protocol allows one to utilize aryl halides with strong electron-withdrawing groups such as a cyano or a nitro function (entries 5, 10, 18, and 20).

To extend the scope of this transformation, we then examined under our optimized conditions the coupling of unhindered arylsulfonylhydrazones. As summarized in Table 3, polyoxygenated hydrazone **7f** undergoes the coupling reaction efficiently with various aryl halides or pseudohalides under the catalytic system $PdCl_2(MeCN)_2$/dppp. The representative examples in Table 3 clearly demonstrated the generality of this reaction. A comparative study with aryl triflate (entry 3) or imidazolylsulfonate (entry 4) gave a slight reduction in yield in comparaison to aryl iodide (entry 1). Finally, the coupling with 4-iodo-2-methoxynitrobenzene gave **9u**, precursor of *iso*NH_2CA-4 of biological interest.[9b]

Recently, introduction of isopropylidene substituents onto the linker of 1,1-diarylethylenes resulted in several strong CYP17 inhibitors as a promising therapy for prostate cancer.[15] To

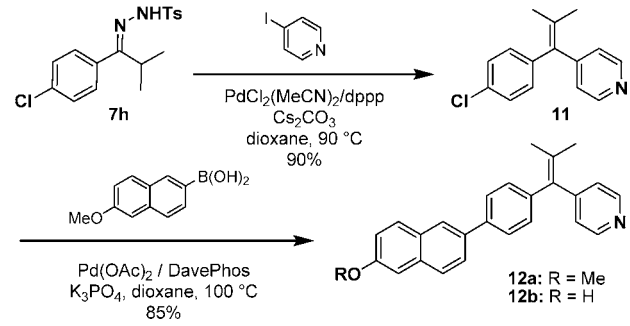


Figure 2. Synthesis of isopropylidene CYP17 inhibitor.

illustrate the synthetic potential of our protocol, we decided to perform the formal synthesis of compound **12b** of biological interest (Figure 2). Reaction of tosylhydrazone **7h** with 4-iodopyridine under our optimized conditions gave the expected coupling product **11** in 90% yield, clearly demonstrating its effeciency with heteroaryl halides. Further Suzuki coupling of the carbon−chlorine bond of **11** with 6-methoxynaphthyl-2-boronic acid under Buchwald conditions[16] resulted in the formation of **12a** in 85% yield, which can be converted to the active product **12b** by a known procedure.[15]

In conclusion, the combination of $PdCl_2(MeCN)_2$ and dppp affords an efficient catalytic system for the coupling of sterically hindered as well as unhindered tosylhydrazones with aryl halides or pseudohalides. This new protocol is chemoselective and general and provides an efficient synthetic route to a wide range of tetrasubstituted olefins, including those having a cycloalkylidene unit. The utility of this method was demonstrated by the formal synthesis of compound **13b** of biological interest. The synthesis and evaluation of a library of tetra-substituted olefins related to *iso*CA-4 will be reported in due course.

Acknowledgment. The CNRS is gratefully acknowledged for financial support of this research.

Supporting Information Available: Experimental procedures and characterization data, including copies of ^1H and ^{13}C NMR spectra, are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

OL101639G

(14) Coupling of 4-iodoanisole with arylsulfonylhydrazone **7** having a cyclopropyl moiety ($n = 0$) under our optimized conditions failed and provided a complex mixture.

(15) Hu, Q.; Yin, L.; Jagusch, C.; Hille, U. E.; Hartmann, R. W. *J. Med. Chem.* **2010**, *53*, 5049.

(16) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722.