Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters

Tetrahedron Letters 45 (2004) 907–910

New synthesis of benzo[*b*]furan and indole derivatives from 1,1-dibromo-1-alkenes using a tandem Pd-assisted cyclization–coupling reaction

Sabine Thielges, Emilie Meddah, Philippe Bisseret* and Jacques Eustache

Laboratoire de Chimie Organique et Bioorganique associé au CNRS, Université de Haute-Alsace, Ecole Nationale Supérieure de Chimie de Mulhouse 3, rue Alfred Werner, F-68093 Mulhouse Cedex, France

Received 21 October 2003; revised 17 November 2003; accepted 25 November 2003

Abstract—We report a new flexible method for the synthesis of 2-functionalized benzo[*b*]furans and indoles from readily available *o*-(2,2-dibromovinyl)-phenol, -aniline or -acetanilide using a tandem Pd-assisted cyclization–coupling reaction.

1,1-Dibromo-1-alkenes are versatile synthons in organopalladium chemistry. For example, using the soft ligand tris(2-furyl)phosphine (TFP) in toluene or 1,4-dioxane, they can be coupled with boronic acids (Suzuki reaction) or organostannanes (Stille reaction) to afford (*Z*)-1-aryl-1-bromo-alkenes with high stereoselectivity.[1,2] In dipolar solvents like DMF, they behave as equivalents of 1-bromo-1-alkynes.[2–4] 1,1-Dibromo-1-alkenes have also been used in a new high yield synthesis of isocoumarins involving a tandem Stille coupling/ring formation that compared well with earlier preparations starting from 2-alkenyl or 2-alkynyl benzoic acids.[5] In this report, we describe a similar but (to the best of our knowledge) unprecedented synthesis of 2-substituted benzo[*b*]furans and indoles starting from suitable 1,1-dibromo-1-alkenes and involving a tandem Pd-assisted coupling–annulation process.[6]

For our studies, 2-(2,2-dibromovinyl)-substituted phenol **1** and aniline **5** as well as their respective MOM and N-protected derivatives **2**, **4** and **7** were prepared (Scheme 1). Compound **1** was obtained in one step from salicylaldehyde using the Corey–Fuchs procedure.[7] Running the reaction in the presence of zinc powder, a bromine scavenger, as originally reported,[7] enabled us to obtain a better yield than when using Topolski's conditions run without zinc.[8] A similar treatment was successfully applied to the readily available benzaldehydes **3** and **6** leading to the new protected derivatives **4** and **7**[9] as well as amine **5**, which had been previously prepared but in lower yield.[8]

In the course of a project dealing with the design of new inhibitors of mycobacterial enzymes, we became interested in phosphonate preparation.[10] The origin of the present work is an attempt to prepare the new aromatic alkynylphosphonates **8** and **9** by coupling the dibrominated precursors **1** and **2** with diethylphosphite according to the method recently described by Lera and Hayes:[11] $Pd(OAc)_2$ as a catalyst, 1,1′-bis(diphenylphosphino)ferrocene (dppf) or TFP as a ligand, propylene oxide (PO) as a HBr scavenger and DMF as a solvent. In this reaction, 1,1-dibromo-1-alkenes were efficiently converted into alkynylphosphonates thus acting as 1-bromoalkyne equivalents.[3,4,11] Using Lera and Hayes's conditions, we found that, in addition to the expected alkynes **8** and **9**, significant amounts of 2-(diethylphosphonyl)-benzo[*b*]furan **10** was also formed. From a preparative standpoint, this finding was quite interesting and we decided to investigate further this reaction, with the aim of maximizing benzofuran formation. We first examined the effect of solvent and base modification. Toluene was substituted for DMF and propylene oxide was replaced by triethylamine as a base (Table 1).

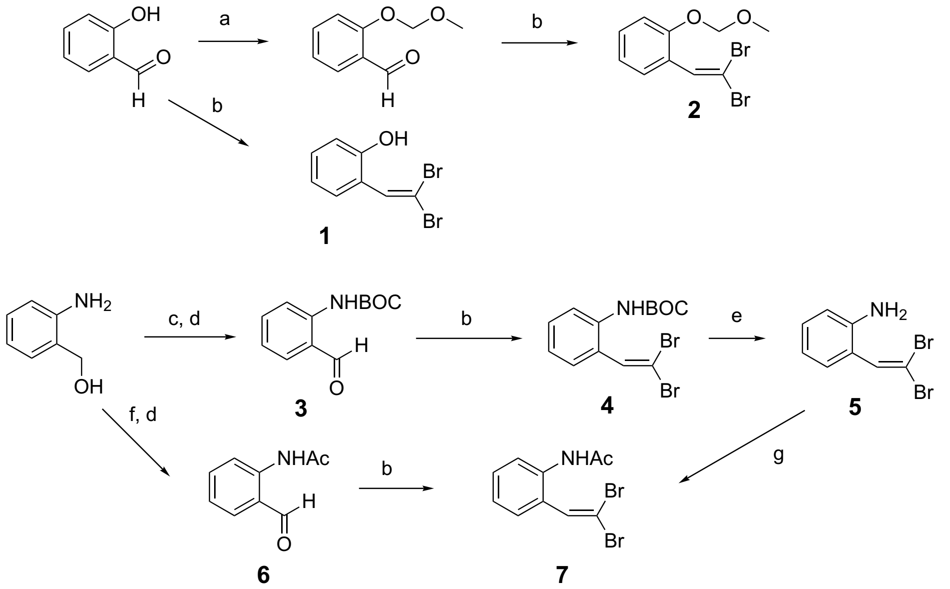
Although the formation of alkynes could not be avoided,[12] the phosphonylated benzofuran **10** was

---

Keywords: Benzofuran; Indole; Palladium chemistry; Tandem reaction; Dibromo-alkenes.

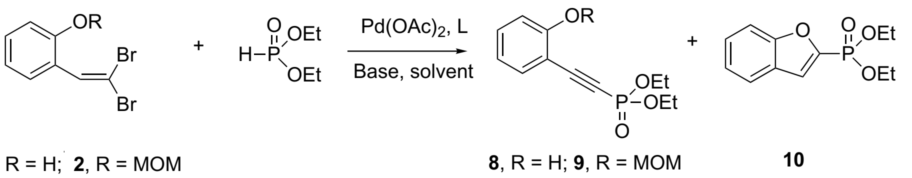
* Corresponding author. Tel.: +33-389336859; fax: +33-389336860; e-mail: p.bisseret@uha.fr

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.11.118



Scheme 1. Reagents and conditions: (a) NaH, DMF then MOMCl, 12 h, rt, 40%; (b) CBr_4, PPh_3, Zn, CH_2Cl_2, 12 h, rt, 52% for **1**, 70% for **2**, 66% for **4**, 35% for **7**; (c) BOC_2O, $ClCH_2CH_2Cl$, 2 h, reflux; (d) DMSO, Ac_2O, 0 °C, 12 h, rt, 95% (two steps); (e) TFA, H_2O, 1 h, rt, 84%; (f) AcCl, Et_3N, CH_2Cl_2, 12 h, rt, 94%.

Table 1. Palladium-assisted formation of alkynyl- and benzofuranyl(diethyl)phosphonates



Entry	Starting material	Base	Solvent, T	Ligand (L)	**8** or **9**/**10**[a]	Yield (%)[b]
1	**1**	Et_3N	Toluene, 100 °C	dppf	1/1	91
2	**1**	Et_3N	DMF, 80 °C	dppf	1/1	60
3	**2**	None	DMF, 80 °C	dppf	Degradation	
4	**2**	PO	DMF, 80 °C	dppf	2/1	65
5	**2**	PO	Toluene, 100 °C	dppf	1/1	75
6	**2**	PO	Toluene, 100 °C	TFP	No reaction	

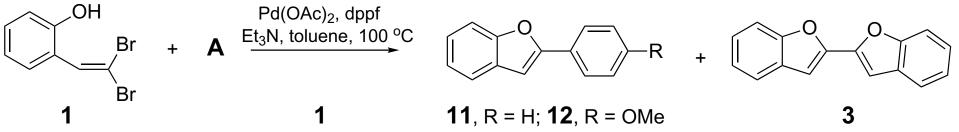
[a] Ratio determined after TLC purification of individual compounds.
[b] Isolated yield.

obtained in satisfactory yield starting from phenol **1**, when the reaction was run in toluene in the presence of triethylamine as base and dppf as the ligand. The TFP ligand, which had been recommended for the Pd-assisted coupling reaction of 1,1-dibromo-1-alkenes,[1–3] was ineffective in our case. Remarkably, the formation of **10** was also observed when using the protected MOM-derivative **2** as coupling partner. The presence in the medium of an excess of propylene oxide renders MOM removal by HBr unlikely (formed in the Pd catalytic cycle).[13] The cleavage may result from the known Lewis acidity of the Pd(II) species also formed in the catalytic cycle.[14]

Having selected the best conditions for the formation of the benzo[*b*]furan **10**, we decided to explore the scope of the reaction further and studied the coupling of phenol derivative **1** with trimethyl(phenyl)tin (Stille coupling) or *p*-methoxyphenylboronic acid as well as phenylboronic anhydride (the Suzuki reaction) (Table 2). For this purpose, the coupling experiments were conducted with an increasing excess of the tin or boron reagents relative to phenol **1**. The results are reported in Table 2.

When the coupling partner was omitted (entry 1), the starting material was efficiently converted to dibenzofuran **13**. This compound subsequently proved to be the only significant by-product in all Stille and Suzuki coupling experiments and, remarkably, alkynyl derivatives were never detected. Regarding benzofuran formation, increasing the amount of coupling partner generally leads to higher yields. The best conditions

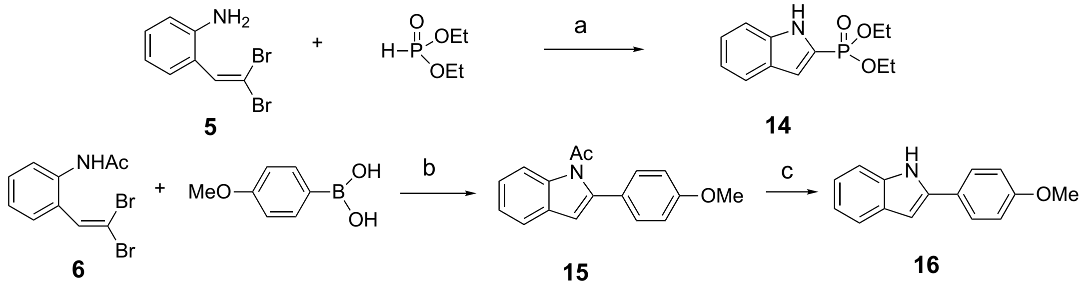
Table 2. Tandem palladium-assisted coupling–annulation of phenol **1**



Entry	A	**11** or **12**/**13**[a]	Yield (%)[b]
1	No reactant	0/1	82
2	$PhSnMe_3$/1.2 equiv	1/1	70
3	$PhSnMe_3$/3 equiv	4/1	75
4	$(PhBO)_3$/1.2 equiv	3/2	91
5	$(PhBO)_3$/3 equiv	1/0	80
6	*p*-$MeOC_6H_4B(OH)_2$/1.2 equiv	1/1	78
7	*p*-$MeOC_6H_4B(OH)_2$/3 equiv	1/0	82

[a] Ratio determined after TLC purification of individual compounds.

[b] Isolated yield.



Scheme 2. Reagents and conditions: (a) $Pd(OAc)_2$, dppf (3 equiv), Et_3N, toluene, 100 °C, 12 h, 63%; (b) $Pd_2(dba)_3$, dppf (3 equiv), Et_3N, toluene, 100 °C, 12 h, 52%; (c) 1 M NaOH, $EtOH/H_2O$ (4/1, v/v), 70 °C, 10 min, 100%.

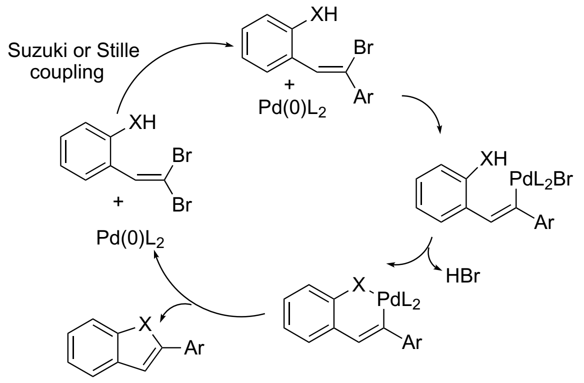
involved the use of excess boronic acid or boronic anhydride, resulting ultimately in the total suppression of the formation of **13** and giving very good yields of the known 2-(*p*-methoxyphenyl)-benzo[*b*]furan **12**[15] as well as 2-phenylbenzo[*b*]furan **11**[16] (entries 5 and 7). A positive but less impressive influence of reagent excess was also observed in the Stille coupling experiments (compare entries 2 and 3).

We next turned our attention to the formation of indoles starting from the dibrominated precursors **4** and **5**. Using the conditions selected for the formation of phosphonylbenzofuran **10** from **2** (see Table 1, entry 5), the BOC-derivative **4** yielded only complex mixtures. In contrast, starting from the free aniline **5**, the known stable phosphonylated-2-indolyl derivative **14**[17] was easily obtained using the conditions determined previously for coupling of the free dibromovinylphenol **1** (Table 1, entry 1). Remarkably, in this case no alkynyl derivative was formed.

Suzuki or Stille coupling experiments run under the conditions previously selected for the preparation of 2-arylbenzofurans were very disappointing. When *p*-methoxyphenylboronic acid was used as a Suzuki coupling partner, the expected compound **16** was obtained in very low yield (<15%) along with a complex mixture of aromatic derivatives. In all other experiments, **16** could not be isolated. This failure can be attributed in part to the instability of this compound to air, which rendered work-up and TLC purifications very difficult.[18] The answer to this problem was provided by using acetanilide **6** instead of the free aniline **5** or the BOC derivative **4**. Using the typical reaction conditions and preferably in the presence of tris(dibenzylideneacetone)dipalladium [$Pd_2(dba)_3$] instead of palladium acetate[19] we obtained a satisfactory yield of the new product **15**, a yellow solid that could be quantitatively converted into **16** under basic conditions (Scheme 2).

A possible simplified mechanism, which accounts for the formation of the heteroaryl derivatives is shown in Scheme 3. It is based on the known higher reactivity of the *trans* C–Br bond relative to the *cis* C–Br bond towards oxidative Pd(0) insertion[1,2] and on the mechanism advocated by Shen and co-workers for the related formation of isocoumarin derivatives.[5] Concurrent simultaneous mechanisms implying the intervention of alkynyl palladium species[2] must be operative accounting for the formation of alkynyl derivatives.

In conclusion, we have developed a new, flexible, one-pot procedure involving a tandem cyclization–coupling process for the preparation of 2-functionalized indoles



Scheme 3.

and benzo[*b*]furans starting from readily accessible 1,1-dibromo-1-alkenylphenol or aniline derivatives. This method competes well with the most efficient palladium-based,[15,20] or copper-based[21] one-pot procedures currently available for the preparation of similar heteroaryls, which involves alkynes instead of dibromoalkenes. Application of this method to the preparation of structurally more complex indoles or benzofurans of biological interest is in progress.

Acknowledgements

We thank the French Ministère de la Jeunesse, de l'Education Nationale et de la Recherche and the CNRS for financial support and for a fellowship to S.T. The project is also supported through the ACI 'Molécules et Cibles Thérapeutiques'.

References and notes

1. Shen, W. *Synlett* **2000**, 737–739.
2. Shen, W.; Wang, L. *J. Org. Chem.* **1999**, *64*, 8873–8879.
3. Shen, W.; Thomas, S. A. *Org. Lett.* **2000**, *2*, 2857–2860.
4. Zapata, J. A.; Ruíz, J. *Organomet. Chem.* **1994**, C6–C8.
5. Wang, L.; Shen, W. *Tetrahedron Lett.* **1998**, *39*, 7625–7628.
6. An alkynylbenzofuran derivative was observed as a by-product on one occasion during a novel synthesis of symmetrical diynes starting from dibromoalkenes (see Ref. 3). No comment on its formation was made.
7. Corey, E.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769–3772.
8. Topolski, M. *J. Org. Chem.* **1995**, *60*, 5588–5594.
9. All new compounds presented satisfactory analytical data.
10. (a) Bisseret, P.; Boiteau, J.-G.; Eustache, J. *Tetrahedron Lett.* **2003**, *44*, 2351–2354; (b) Bosco, M.; Bisseret, P.; Eustache, J. *Tetrahedron Lett.* **2003**, *44*, 2347–2349.
11. Lera, M.; Hayes, C. J. *Org. Lett.* **2000**, *2*, 3873–3875.
12. Attempts to enhance the production of benzofuran by prolonging the reaction after further addition of Pd catalyst was unsuccessful.
13. On the use of propylene oxide as an HBr scavenger see Ref. 11 and: Abbas, S.; Hayes, C. J. *Tetrahedron Lett.* **2000**, *41*, 4513–4517.
14. For an example of a related Lewis acid catalysis see: Bossharth, E.; Dessbordes, P.; Monteiro, N.; Balme, G. *Org. Lett.* **2003**, *5*, 2441–2444.
15. Kabalka, G. W.; Wang, L.; Pagni, R. M. *Tetrahedron* **2001**, *57*, 8017–8028.
16. Katritzky, A. R.; Zhang, Z.; Lan, X.; Lang, H. *J. Org. Chem.* **1994**, *59*, 1901–1903.
17. Haelters, J. P.; Corbel, B.; Sturtz, G. *Phosphorus Sulfur* **1988**, *37*, 41–63.
18. Analytical data for the indole derivative **16** are in agreement with the literature: Hughes, I. *Tetrahedron Lett.* **1996**, *37*, 7595–7598, Although colourless once isolated, we noticed that **16** degraded rapidly in air, becoming pink.
19. With Pd(OAc)$_2$ a more complex mixture was obtained resulting in a difficult purification of **15** in a slightly lower yield.
20. (a) Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270–3271; (b) Arcadi, A.; Cacchi, S.; Rosario, M. D.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280–9288; (c) Kamijo, S.; Yamamoto, Y. *J. Org. Chem.* **2003**, *68*, 4764–4771, and references cited therein.
21. Cacchi, S.; Fabrizi, G.; Parisi, L. M. *Org. Lett.* **2003**, *5*, 3843–3846, and references cited therein.