ORGANIC LETTERS

2012
Vol. 14, No. 9
2323–2325

Synthesis of Polysubstituted Isoquinolines through Cross-Coupling Reactions with α-Alkoxytosylhydrazones

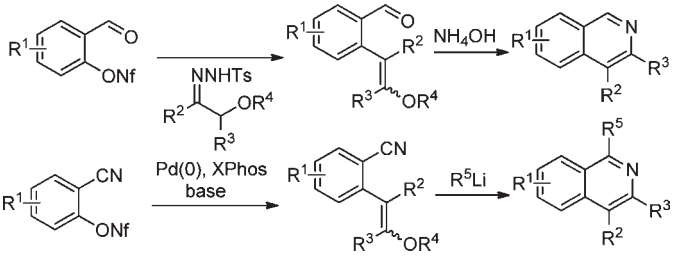
Lucía Florentino, Fernando Aznar, and Carlos Valdés*

Instituto Universitario de Química Organometálica "Enrique Moles", Universidad de Oviedo, c/Julián Clavería 8, 33006, Oviedo, Spain

acvg@uniovi.es

Received March 30, 2012

ABSTRACT



A Pd-catalyzed cross-coupling reaction of α-alkoxytosylhydrazones with sulfonates derived from salicyl aldehydes gives rise to protected 1,5-dicarbonyl compounds. Treatment with ammonium hydroxide readily transforms these alkenes into isoquinolines with diverse substitution patterns at positions 3 and 4. In a similar way, the employment of *o*-cyanononaflates in the coupling reaction, followed by treatment with an organometallic, provides isoquinolines that incorporate substitution also at position 1. The combination of both approaches represents a versatile method for the preparation of isoquinolines substituted at any position of the heterocyclic ring.

The Pd-catalyzed cross-coupling reaction between tosylhydrazones and aryl halides[1] has been established in recent years as a very versatile method for the synthesis of substituted alkenes.[2,3] A quite interesting application of this reaction is the preparation of enol ethers and enamines by employing hydrazones derived from α-functionalized carbonyl compounds (Scheme 1a).[4] In these reactions, a new masked carbonyl compound is formed during the cross-coupling process that could be eventually deprotected or employed in a further transformation, for instance a heterocyclization reaction.

More recently, proper reaction conditions have been developed for the coupling reactions of aryl sulfonates and tosylhydrazones, expanding the applicability of the coupling reaction to phenol derivatives.[5,6] To further exploit the synthetic potential of these reactions, we turned our attention to *o*-substituted phenols, in particular, to salicylic aldehyde derivatives, which are commercially very abundant, or otherwise very easily prepared. We envisioned that the cross-coupling reaction of a nonaflate **I**[7] derived from a salicylic aldehyde with an α-alkoxy substituted tosylhydrazone **II** would provide the coupling product **III** that features two differently protected carbonyl groups in a 1,5-relationship and that could be a very versatile platform for the synthesis of heterocycles (Scheme 1b).[8]

Thus, as a model reaction, we selected the coupling between nonaflate **1a** that features the unprotected formyl group and the tosylhydrazone **2a**. The reaction under the standard

(1) Barluenga, J.; Moriel, P.; Valdés, C.; Aznar, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 5587.

(2) (a) Barluenga, J.; Tomas-Gamasa, M.; Moriel, P.; Aznar, F.; Valdés, C. *Chem.—Eur. J.* **2008**, *14*, 4792. (b) Barluenga, J.; Tomas-Gamasa, M.; Aznar, F.; Valdés, C. *Chem.—Eur. J.* **2010**, *16*, 12801. (c) Xiao, Q.; Ma, J.; Yang, Y.; Zhang, Y.; Wang, J. *Org. Lett.* **2009**, *11*, 4732. (d) Brachet, E.; Hamze, A.; Peyrat, J.-F.; Brion, J.-D.; Alami, M. *Org. Lett.* **2010**, *12*, 4042.

(3) For a recent review, see: Barluenga, J.; Valdés, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 7486.

(4) Barluenga, J.; Escribano, M.; Moriel, P.; Aznar, F.; Valdés, C. *Chem.—Eur. J.* **2009**, *15*, 13291.

(5) For coupling reactions with aryl triflates: Treguier, B.; Hamze, A.; Provot, O.; Brion, J.-D.; Alami, M. *Tetrahedron Lett.* **2009**, *50*, 6549.

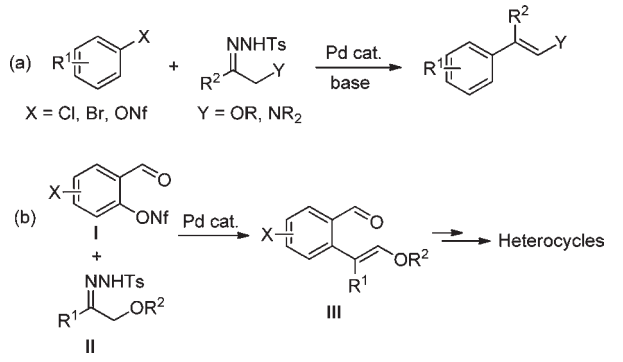
(6) Barluenga, J.; Florentino, L.; Aznar, F.; Valdés, C. *Org. Lett.* **2011**, *13*, 510.

(7) For a review of Pd-catalyzed cross-couplings with aryl nonaflates, see: Högermeier, J.; Reissig, H.-U. *Adv. Synth. Catal.* **2009**, *351*, 2747.

(8) For a different approach to the synthesis of heterocycles based on the cross-coupling reaction of tosylhydrazones: Rasolofonjatovo, E.; Treguier, B.; Provot, O.; Hamze, A.; Morvan, E.; Brion, J.-D.; Alami, M. *Tetrahedron Lett.* **2011**, *52*, 1036.

10.1021/ol300810p
Published on Web 04/18/2012

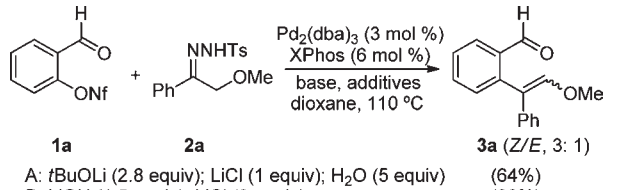
Scheme 1. Pd-Catalyzed Cross-Coupling Reactions with Tosylhydrazones: (a) Synthesis of Enol Ethers and Enamines; (b) This Work



conditions previously described for the couplings of aryl nonaflates produced the desired product **3a** in only moderate yield (Scheme 2, conditions A) probably due to the severe steric requirements of this particular nonaflate. For this reason, a reoptimization study was conducted. After some experimentation we discovered that the coupling could be best accomplished employing LiOH as a base (1.5 equiv) and in the presence of 3 equiv of LiCl, leading to **3a** in excellent yield as a 3:1 mixture of *Z*/*E* isomers (Scheme 2, conditions B). Remarkably, the reaction proceeds nicely in the presence of the unprotected aldehyde functionality.

Compound **3a**, an unprecedented structure, is indeed a masked 1,5-dicarbonyl derivative that can be envisioned as a platform for the synthesis of a large variety of condensed heterocycles and carbocycles. As a proof of concept, we initially focused on one of the simplest transformations, the reaction with ammonium hydroxide, which should lead to polysubstituted isoquinolines.[9,10] Although the cyclization can be accomplished simply by adding a solution of ammonium hydroxide to the reaction mixture, better yields are obtained if the mixture is concentrated by evaporation of the dioxane prior to the addition of the ammonium hydroxide solution. In this manner, a set of isoquinolines **4** was prepared by combining nonaflates derived from substituted salicylaldehydes **1** with tosylhydrazones derived from α-alkoxycarbonyls **2**[11] (Table 1).

Scheme 2. Pd-Catalyzed Cross-Coupling between the Tosylhydrazone **2a** and Nonaflate **1a**



The reaction can be employed very efficiently for the preparation of 4-substituted isoquinolines with different substitutions on the benzene ring, including both electron-donating and -withdrawing groups. Notably, chlorine-substituted isoquinolines can be prepared taking advantage of the higher reactivity of nonaflates than chlorides in Pd-catalyzed cross-couplings (Table 1, entry 4).

Variations at position 4 of the isoquinoline can be achieved starting from a different alkoxyketone and includes aromatic and heteroaromatic substituents (Table 1, entries 10−12). Interestingly, the employ of the hydrazone derived from α-diethoxy acetophenone led to the 3-ethoxy substituted isoquinoline (Table 1, entry 7), while the reaction with the hydrazone obtained from α-methoxy-α-phenylacetophenone enabled the synthesis of a 3,4-diphenyl isoquinoline (Table 1, entry 8). Both examples show the ability of this methodology in the synthesis of 3,4-disubstituted isoquinolines. Finally, the reaction with the hydrazone of benzyloxyacetaldehyde led to the preparation of isoquinolines unsubstituted in the heterocyclic ring (Table 1, entry 9).

In order to achieve the synthesis of 1-substituted isoquinolines, we examined a similar reaction starting from the corresponding ketone; however, although the cross-coupling reaction proceeded with moderate yields, we were not able to promote the cyclization efficiently. For this reason, we turned our attention to *o*-cyano nonaflates **5** with the idea that the same type of cross-coupling reaction would lead to *o*-cyanoalkenes **6**, which could be transformed into 1-substituted isoquinolines by addition of an organometallic reagent, as previously described by Kobayashi et al.[12] As expected, the cross-coupling reaction proceeded smoothly under the reaction conditions developed for the formyl substituted derivatives **1**, leading to the cross-coupling products in high yields. Then, treatment with organolithium derivatives afforded the 1-substituted isoquinolines (Scheme 3). It is noteworthy that, as in the preceding reaction, it is not necessary to isolate the intermediate enol ether **6**, and the process can be conducted in one pot. The best experimental conditions found included evaporation of the dioxane once the cross-coupling has finished, followed by dilution in THF and addition of the organolithium derivative at −78 °C, to afford the 1-substituted isoquinolines with good yields.

In summary, we have reported that the cross-coupling of *o*-functionalized nonaflates, readily available from salicyl aldehydes or *o*-cyanophenols, with functionalized

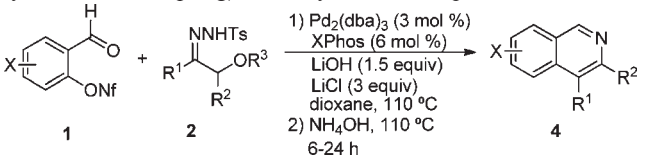
(9) Alajarín, R.; Burgos, C. *Modern Heterocyclic Chemistry*; Wiley-VCH: Weinheim, 2011; p 1527.

(10) For some recent leading references on the synthesis of isoquinolines: (a) Gilmore, C. D.; Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 1558. (b) Wang, B.; Lu, B.; Jiang, Y.; Zhang, Y.; Ma, D. *Org. Lett.* **2008**, *10*, 2761. (c) Hui, B. W.-Q.; Chiba, S. *Org. Lett.* **2009**, *11*, 729. (d) Niu, Y.-N.; Yan, Z.-Y.; Gao, G.-L.; Wang, H.-L.; Shu, X.-Z.; Ji, K.-G.; Liang, Y.-M. *J. Org. Chem.* **2009**, *74*, 2893. (e) Guimond, N.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 12050. (f) Roy, S.; Roy, S.; Neuenswander, B.; Hill, D.; Larock, R. C. *J. Comb. Chem.* **2009**, *11*, 1061. (g) Dell'Acqua, M.; Abbiati, G.; Rossi, E. *Synlett* **2010**, 2672. (h) Liu, C.-C.; Parthasarathy, K.; Cheng, C.-C. *Org. Lett.* **2010**, *12*, 3518. (i) Zhang, X.; Chen, D.; Zhao, M.; Zhao, J.; Jia, A.; Li, X. *Adv. Synth. Catal.* **2011**, *353*, 719. (j) Si, C.; Myers, A. G. *Angew. Chem., Int. Ed.* **2011**, *50*, 10409.

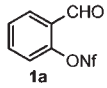
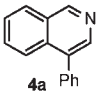
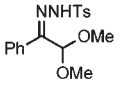
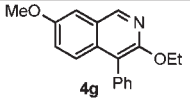
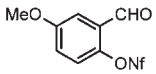
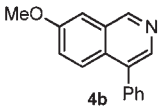
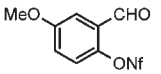
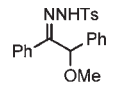
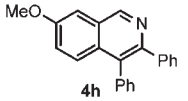
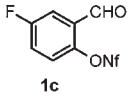
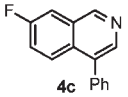
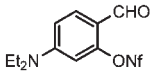
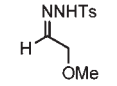
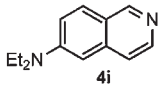
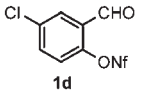
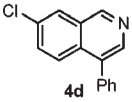
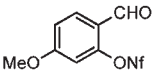
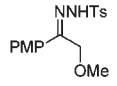
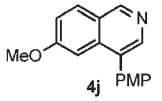
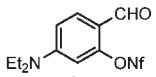
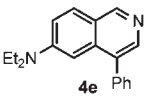
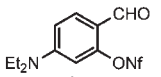
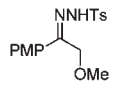
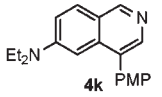
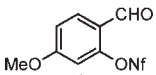
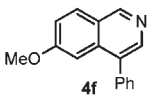
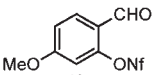
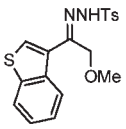
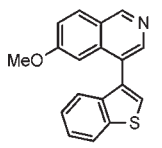
(11) For the synthesis of α-alkoxy carbonyl compounds: (a) Muthusamy, S.; Babu, S. A.; Gunanathan, C. *Tetrahedron Lett.* **2002**, *43*, 3133. (b) Tudjarian, A. A.; Minehan, T. G. *J. Org. Chem.* **2011**, *76*, 3576.

(12) (a) Kobayashi, K.; Shiokawa, T.; Morikawa, O.; Konishi, H. *Chem. Lett.* **2004**, *33*, 236. (b) Kobayashi, K.; Hayashi, K.; Miyamoto, K.; Morikawa, O.; Konishi, H. *Synthesis* **2006**, 2934. (c) Kobayashi, K.; Shiokawa, T.; Omote, H.; Hashimoto, K.; Morikawa, O.; Konishi, H. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1126.

Table 1. Isoquinolines **4** Prepared by the Cross-Coupling/Heterocyclization Sequence[a]

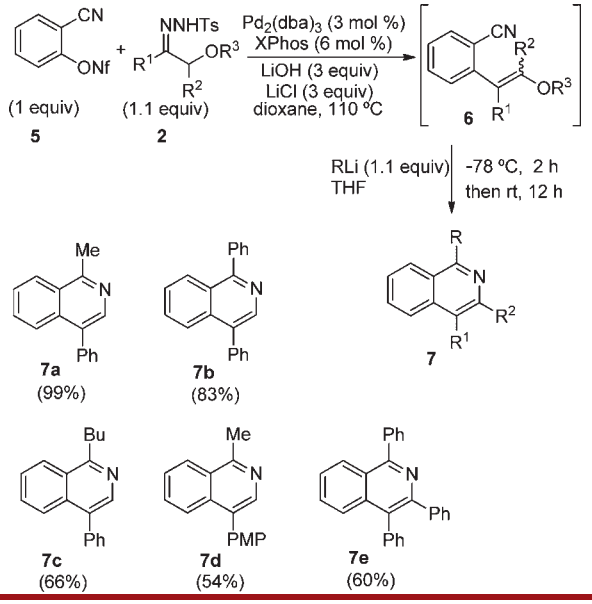


1 2 4

entry	1	2	isoquinoline 4	yield (%)[d]	entry	1	2	isoquinoline 4	yield (%)[d]
1[b]	 **1a**		 **4a**	81	7[c]	 **1b**		 **4g**	76
2[b]	 **1b**		 **4b**	75	8[b]	 **1b**		 **4h**	53
3	 **1c**		 **4c**	80	9[b]	 **1e**		 **4i**	83
4[b]	 **1d**		 **4d**	90	10[e]	 **1f**		 **4j**	74
5[c]	 **1e**		 **4e**	82	11[e]	 **1e**		 **4k**	66
6	 **1f**		 **4f**	82	12	 **1f**		 **4l**	70

[a] Reaction conditions: (1) Nonaflate **1**, (0.3 mmol), hydrazone **2** (0.33 mmol, 1.1 equiv), LiCl (0.9 mmol), LiOH (1.5 equiv), Pd_2dba_3 (3 mol %), XPhos (6 mol %), dioxane 2 mL; (2) NH_4OH sat. aqueous sol. 3 mL, 110 °C, 6−24 h. [b] Reaction conducted with LiOH (3 equiv). [c] Reaction conducted employing *t*BuOLi (2.8 equiv) as base, LiCl (1 equiv), H_2O (5 equiv). [d] Isolated yields for the one pot/two step process after column chromatography. [e] PMP: *p*-methoxyphenyl.

Scheme 3. Synthesis of 1-Substituted Isoquinolines



tosylhydrazones gives rise to protected 1,5-dicarbonyl and 1-cyano-5-carbonyl derivatives, which are useful intermediates in the preparation of isoquinolines substituted at any position of the heterocyclic ring. Further applications of this methodology, oriented to the preparation of other types of heterocycles, are underway and will be reported in due course.

Acknowledgment. Financial support of this work by DGI of Spain (CTQ2010-16790) and Consejería de Educación y Ciencia of Principado de Asturias (IB08-088). A predoctoral fellowship to L.F. from FICYT of the Principado de Asturias is gratefully acknowledged. We are deeply indebted to Prof. José Barluenga for his permanent stimulus and support.

Supporting Information Available. Experimental details. Characterization data for aryl nonaflates **1**, **5** and isoquinolines **4**, **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.