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Synthesis of 2-Arylacrylates from Pyruvate by Tosylhydrazide-Promoted Pd-Catalyzed Coupling with Aryl Halides

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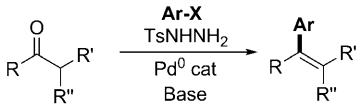
The Pd-catalyzed cross-coupling reaction between tosylhydrazones and aryl halides, recently developed by our group, constitutes a very efficient way to synthesize di- and trisubstituted olefins.[1a] Over the last few years we have shown that this reaction is an excellent way to employ carbonyl compounds as the nucleophilic component of a Pd-catalyzed cross-coupling reaction (Scheme 1).[1,2]



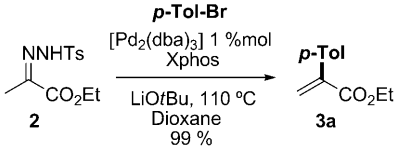
Scheme 1. Pd-catalyzed cross-coupling reactions employing carbonyls mediated by tosylhydrazide.

In the context of this study, we turned our attention to hydrazones derived from ethyl pyruvate (**1**), as a representative of α-oxoesters, in the hope that the coupling reaction would represent a new route to 2-arylacrylates.

The importance of this motif as a synthetic intermediate is noteworthy. For instance, 2-arylacrylates provide the main entry into the optically active version of prophens (α-arylpropionic acids),[3] the widely employed nonsteroidal anti-inflammatory agents. Moreover, these structures are activated olefins that are continuously employed as Michael acceptors,[4] dienophiles,[5] dipolarophiles,[6] alkenes for Heck and sequential Pd-catalyzed reactions,[7] intermediates in heterocyclic synthesis,[8] intermediates in the synthesis of cyclopropane carboxylic acids with biological activity,[9] and key fragments to generate diversity in drug discovery programs.[10]

While the classical method for the synthesis of 2-arylacrylates is the condensation of the corresponding arylacetate with paraformaldehyde,[11,12] more recently, these systems have been prepared through different Pd-catalyzed cross-coupling reactions: Suzuki cross-couplings with 2-chloracrylates,[13] and alkenyl boronates,[14] Negishi reaction with 2-metallated acrylates,[15] and Pd-catalyzed carbonylation of arylvinyl bromides.[16] In a very recent contribution, Wang et al. reported a new synthesis of 2-arylacrylates by Pd-catalyzed coupling between diazoesters and arylboronic acids.[17] Herein, we present a new Pd-catalyzed cross-coupling approach to these systems that employs the tosylhydrazone of ethyl pyruvate as nucleophilic component, and therefore obviates the need for a stoichiometric organometallic reagent.

Our initial experiments showed that the coupling between the tosylhydrazone **2**, derived from ethyl pyruvate, and *p*-bromotoluene proceeded in quantitative yield leading to acrylate **3a** by employing the reaction conditions presented in Scheme 2. Notably, the potentially sensitive ester functionality remained unaltered under the relatively harsh basic reaction conditions.



Scheme 2. Preliminary experiment of the coupling of the hydrazone **2** derived from ethyl pyruvate with an aryl bromide. Xphos: 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

To develop a more practical procedure, we studied the reaction starting directly from ethyl pyruvate (**1**), avoiding the isolation of the tosylhydrazone **2**. After some experimentation, a one-pot protocol was optimized. In this process, ethyl pyruvate and tosylhydrazide were stirred for 2 h at 70 °C, then the rest of the reagents were added to the reaction mixture. Following this procedure, similar yields were ob-

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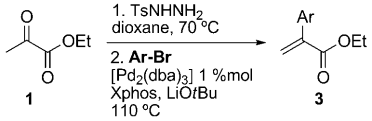
tained to those from the two-step protocol starting from the hydrazone **2**. The scope of this transformation was studied, and selected examples are presented in Table 1.

Table 1. Synthesis of 2-arylacrylates **3** from ethyl pyruvate (**1**) and aryl bromides.[a]



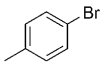
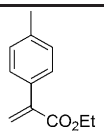
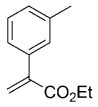
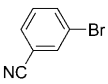
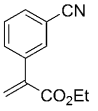
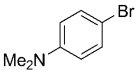
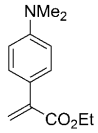
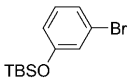
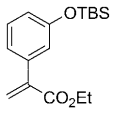
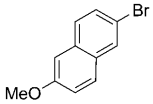
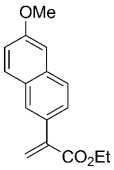
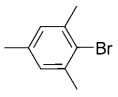
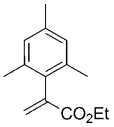
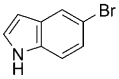
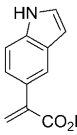
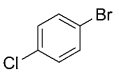
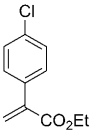
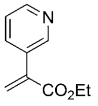
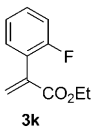
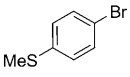
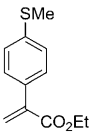
Entry	Ar-Br	Compound **3**	Yield [%][b]
1		 **3a**	99
2		 **3b**	89
3		 **3c**	90
4		 **3d**	98
5		 **3e**	92
6		 **3f**	60
7		 **3g**	97
8		 **3h**	89
9		 **3i**	98

Table 1. (Continued)

Entry	Ar-Br	Compound **3**	Yield [%][b]
10		 **3j**	86
11		 **3k**	99
12		 **3l**	98

[a] reaction conditions: ketone **1**, 1 mmol; $TsNHNH_2$, 1.1 mmol; dioxane, 2 h, 70 °C; then ArBr, 1 mmol; $[Pd_2(dba)_3]$ (dba = dibenzylideneacetone), 1.0 mol %; Xphos, 4 mol %; LiO*t*Bu, 2.4 equiv, 110 °C. [b] Yield of isolated products.

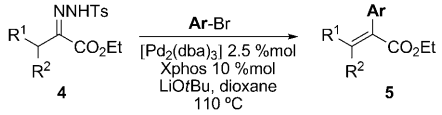
The reaction proceeds in very high yields for a variety of benzene rings with electron-donating (Table 1, entries 4, 5, 12) and electron-withdrawing (Table 1, entries 3, 11) substituents, including the sterically hindered bromomesitylene (Table 1, entry 7). As expected, the reaction with *p*-bromochlorobenzene leads exclusively to the chlorobenzene derivative (Table 1, entry 9). The process can be accomplished also with heterocycles (Table 1, entries 8, 10), and tolerates the presence of a free NH group. Finally, the reaction can be employed for the preparation of relevant molecules such as **3 f**, the direct precursor of Naproxen.

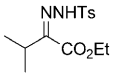
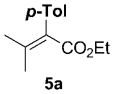
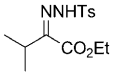
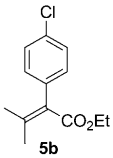
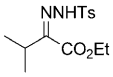
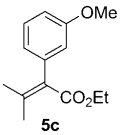
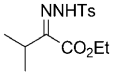
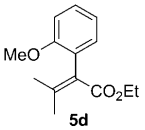
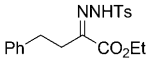
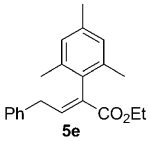
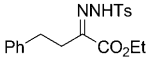
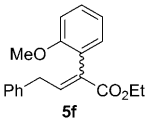
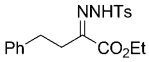
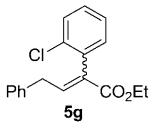
The coupling was also studied with hydrazones derived from other 2-oxoesters (Table 2). The reactions employing the hydrazone of ethyl 3-methyl-2-oxobutanoate provide the substituted 2-arylacrylates with moderate yields and require higher catalyst loading (Table 2, entries 1–4). Nevertheless, these are the first examples of the employment of the coupling reaction with tosylhydrazones in the synthesis of functionalized tetrasubstituted olefins.[18] Moreover, the 3,3-disubstituted-2-arylacrylates, in spite of their simplicity, are an unusual type of functionalized alkenes not easily available through other methodologies.[19]

Finally, the reaction with unbranched 2-oxoesters leads to trisubstituted alkenes as a mixture of *Z/E* isomers in variable ratio depending on the substrate. Interestingly, in the particular case of the very bulky mesitylene derivative (Table 2, entry 5), the *Z/E* mixture of isomers that is obtained after a reaction time of 2.5 h, undergoes isomerization by leaving the reaction for up to 12 h under the reaction conditions, giving rise exclusively to the *E* isomer.

In summary, we have described a very straightforward synthesis of 2-arylacrylates, very useful synthetic intermediates, by a Pd-catalyzed cross-coupling reaction that employs ethyl pyruvate—a commodity chemical—as cross-coupling partner. The reaction is experimentally simple, very efficient, general, and functional-group tolerant, and therefore

Table 2. Synthesis of substituted 2-arylacrylates **5** from hydrazones **4** and aryl bromides.[a]



Entry	Hydrazone **4**	Compound **5**	Yield [%][b]
1		 **5a**	53
2		 **5b**	56
3		 **5c**	51
4		 **5d**	52
5		 **5e**	60(56)[c]
6		 **5f**	70
7		 **5g**	65

[a] Reaction conditions: hydrazone **4**, 1 mmol; ArBr, 1 mmol; $[Pd_2(dba)_3]$, 2.5 mol %; Xphos 10 mol %; LiO*t*Bu, 2.4 equiv; dioxane, 110 °C. [b] Yield of isolated product. [c] Yield of the *E* isomer isolated after a reaction time of 12 h.

this new procedure undoubtedly represents a very attractive alternative for the preparation of these systems. Moreover, the reaction can be also applied to other 2-ketoesters, to produce the corresponding 2-aryl-α,β-unsaturated esters. In particular, the reaction has been employed for the preparation of functionalized tetrasubstituted alkenes.

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Keywords: arylacrylates · cross-coupling · hydrazones · palladium · pyruvate

[1] a) J. Barluenga, P. Moriel, C. Valdés, F. Aznar, *Angew. Chem.* **2007**, *119*, 5683; *Angew. Chem. Int. Ed.* **2007**, *46*, 5587; b) J. Barluenga, M. Tomás-Gamasa, P. Moriel, F. Aznar, C. Valdés, *Chem. Eur. J.* **2008**, *14*, 4792; c) J. Barluenga, M. Escribano, P. Moriel, F. Aznar, C. Valdés, *Chem. Eur. J.* **2009**, *15*, 13291; d) J. Barluenga, M. Escribano, F. Aznar, C. Valdés, *Angew. Chem.* **2010**, *122*, 7008; *Angew. Chem. Int. Ed.* **2010**, *49*, 6856.

[2] a) X. Xiao, J. Ma, Y. Yang, Y. Zhang, J. Wang, *Org. Lett.* **2009**, *11*, 4732; b) X. Zhao, J. Jing, K. Lu, Y. Zhang, J. Wang, *Chem. Commun.* **2010**, *46*, 1724; c) Z. Zhang, Y. Liu, M. Gong, X. Zhao, Y. Zhang, J. Wang, *Angew. Chem.* **2010**, *122*, 1157; *Angew. Chem. Int. Ed.* **2010**, *49*, 1139; d) B. Tréguier, A. Hamze, O. Provot, J.-D. Brion, M. Alami, *Tetrahedron Lett.* **2009**, *50*, 6549.

[3] a) T. Ohta, M. Takaya, M. Kitamura, K. Nagai, R. Noyori, *J. Org. Chem.* **1987**, *52*, 3174; b) A. S. C. Chan, S. A. Laneman, US Patent 5198561, **1993**; c) S. J. Mahmood, C. Brennan, M. M. Hossain, *Synthesis* **2002**, 1807.

[4] X. Berzosa, X. Bellatriu, J. Teixidó, J. I. Borrell, *J. Org. Chem.* **2010**, *75*, 487.

[5] a) T. Watanabe, M. Arisawa, K. Narusuye, M. S. Alam, K. Yamamoto, M. Mitomi, Y. Ozoe, A. Nishida, *Bioorg. Med. Chem.* **2009**, *17*, 94; b) A. Padwa, H. Zhang, *J. Org. Chem.* **2007**, *72*, 2570.

[6] G. Pandey, N. R. Gupta, T. Pimpalpalle, *Org. Lett.* **2009**, *11*, 2547.

[7] F.-X. Felpin, J. Coste, C. Zakri, E. Fouquet, *Chem. Eur. J.* **2009**, *15*, 7238.

[8] B. C. G. Söderberg, S. R. Banini, M. R. Turner, A. R. Minter, A. K. Arrington, *Synthesis* **2008**, 903.

[9] a) C. Molinaro, D. Gauvreau, G. Hughes, S. Lau, S: Lauzon, R. Angelaud, P. D. O'Shea, J. Janey, M. Palucki, S. R. Hoerrner, C. E. Raab, R. R. Sidler, M. Belley, Y. Han, *J. Org. Chem.* **2009**, *74*, 6863; b) Z. Zhu, R. Mazzola, L. Sinning, B. McKittrick, X. Niu, D. Lundell, J. Sun, P. Orth, Z. Guo, V. Madison, R. Ingram, B. M. Beyer, *J. Med. Chem.* **2008**, *51*, 725.

[10] a) A. Tizot, G. C. Tucker, A. Pierre, J. Hickman, S. Goldstein, *J. Med. Chem.* **2009**, *52*, 208; b) I. S. Mitchell, J. F. Blake, R. Xu, N. C. Kallan, D. Xiao, K. L. Spencer, J. R. Bencsik, J. Liang, B. Safina, B. Zhang, C. Chabot, S. Do, WO 2008006040, **2008**; c) I. Islam, J. Bryant, K. May, R. Mohan, S. Yuan, L. Kent, J. Morser, L. Zhao, R. Vergona, K. White, M. Adler, M. Whitlow, B. O. Buckman, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1349.

[11] G. Holan, R. A. Walser, EP0003670(A1), **1979**.

[12] For the synthesis of 2-arylacrylates by nucleophilic addition to pyruvate followed by dehydration, see: a) L. A. Arnold, R. K. Guy, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5360; b) Y.-G. Si, J. Chen, F. Li, J.-H. Li, Y.-J. Qin, B. Jiang, *Adv. Synth. Catal.* **2006**, *348*, 898.

[13] a) F. Berthiol, H. Doucet, M. Santelli, *Synth. Commun.* **2006**, *36*, 3019; b) F. Berthiol, H. Doucet, M. Santelli, *Eur. J. Org. Chem.* **2003**, 1091.

[14] B. H. Lipshutz, Z. V. Boskovic, D. H. Aue, *Angew. Chem.* **2008**, *120*, 10337; *Angew. Chem. Int. Ed.* **2008**, *47*, 10183.

[15] A. A. Jalil, N. Kurono, M. Tokuda, *Tetrahedron* **2002**, *58*, 7477.

[16] P. B. Silveira, A. L. Monteiro, *J. Mol. Catal. A* **2006**, *247*, 1.

[17] C. Peng, Y. Wang, J. Wang, *J. Am. Chem. Soc.* **2008**, *130*, 1566.

[18] The synthesis of nonfunctionalized tetrasubstituted alkenes by Pd-catalyzed cross-coupling with tosylhydrazones has been recently reported: E. Brachet, A. Hamze, J.-F. Peyrat, J.-D. Brion, M. Alami, *Org. Lett.* **2010**, *12*, 4042.

[19] T. Tsuda, T. Yoshida, T. Saegusa, *J. Org. Chem.* **1988**, *53*, 607.

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