ORGANIC LETTERS

2002
Vol. 4, No. 9
1591−1594

Palladium-Catalyzed Arylation of Ketone Enolates: An Expeditious Entry to Tamoxifen-Related 1,2,2-Triarylethanones

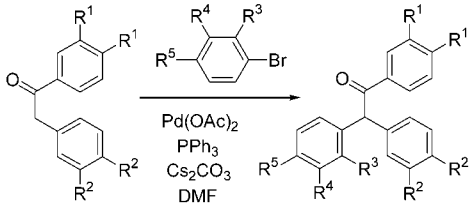
Fátima Churruca, Raul SanMartin, Imanol Tellitu, and Esther Domínguez*

Kimika Organikoa II Saila, Zientzi Fakultatea, Euskal Herriko Unibertsitatea, P.O. Box 644, 48080 Bilbao, Spain

qopdopee@lg.ehu.es

Received March 4, 2002

ABSTRACT



After a rigorous study on the effect of several catalytic systems, a simple, high yielding procedure for the preparation of 1,2,2-triarylethanones, skeletal analogues of tamoxifen, is presented. Apart from the economic and environmental advantages involved, this palladium-catalyzed arylation of deoxybenzoin enolates features a lack of ortho-arylation side reactions. In addition, an alternative approach from acetophenones to the target triarylethanone system is also announced.

In the course of our investigations on the synthesis of new phenanthrofused heterocycles,[1] 1,2,2-triarylethanones **1** were envisaged as suitable precursors of an appealing pentacyclic system, dibenzo[*a*,*c*]phenanthridines **2**, with an inherent interest due to their close relationship to biologically active benzo[*c*]phenanthridine alkaloids.[2] An additional feature of such ketone intermediates **1** is their structural resemblance to tamoxifen, the most widely used adjuvant drug therapy for the treatment of estrogen receptor breast cancer.[3] According to an obvious C_2-C_1''' bond disconnection, the α-arylation of deoxybenzoins **3**, readily available from arylacetic acids,[4] would be a direct approach to the key intermediates **1**.

In this context, during the past decade much effort has been made to achieve a reliable method for the α-arylation of ketones, as this reaction constitutes the key step in the

(1) (a) Olivera, R.; Pascual, S.; Herrero, M.; SanMartin, R.; Domínguez, E. *Tetrahedron Lett.* **1999**, *40*, 3479−3480. (b) Olivera, R.; SanMartin, R.; Domínguez, E. *J. Org. Chem.* **2000**, *65*, 7010−7019 and references therein.

(2) (a) After searching the literature, only one report of a related dibenzo-[*a*,*c*]phenanthridine was found. See: Kiselyov, A. S. *Tetrahedron Lett.* **1995**, *36*, 493−496. For recent reports on the biological properties of benzo[*c*]-phenanthridines, see: (b) Asano, Y.; Yamashita, M.; Nagai, K.; Kuriyama, M.; Yamada, K.; Tomioka, K. *Tetrahedron Lett.* **2001**, *42*, 8493−8495. (c) Salmore, A. K.; Hunter, M. D. *J. Chem. Ecol.* **2001**, *27*, 1713−1727. (d) Ito, C.; Itoigawa, M.; Tokuda, H.; Kuchide, M.; Nishino, H.; Furukawa, H. *Planta Med.* **2001**, *67*, 473−475. (e) Slaninova, I.; Taborska, E.; Bochorakova, H.; Slanina, *J. Cell Biol. Toxicol.* **2001**, *17*, 51−63. (f) Harayama, T.; Akiyama, T.; Akamatsu, H.; Kawano, K.; Abe, H.; Takeuchi, Y. *Synthesis* **2001**, 444−450. (g) Harayama, T.; Akiyama, T.; Nakano, Y.; Shibaike, K.; Akamatsu, H.; Hori, A.; Abe, H.; Takeuchi, Y. *Synthesis* **2002**, 237−241.

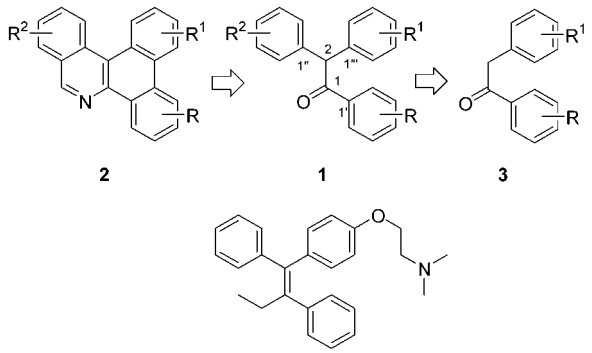
(3) The synthesis and biological effect of tamoxifen and its analogues have attracted much attention. See: (a) Delcey, C. D.; Huel, C.; Bisagni, E. *Heterocycles* **1995**, *41*, 1721−1730. (b) Lashley, M. R.; Nantz, M. H. *Tetrahedron Lett.* **2000**, *41*, 3295−3298 and references therein. (c) Valliant, J. F.; Paul Schaffer, P.; Stephenson, K. A.; Britten, J. F. *J. Org. Chem.* **2002**, *67*, 383−387.

(4) (a) Al-Maharik, N. I.; Kaltia, Seppo, A. A.; Mutikainen, I.; Waehaelae, K. *J. Org. Chem.* **2000**, *65*, 2305−2308. (b) SanMartin, R.; Martínez de Marigorta, E.; Domínguez, E. *Tetrahedron* **1994**, *50*, 2255−2264. Other complementary procedures that allow a wider range of substitution paterns are described in: (c) Olivera, R.; SanMartin, R.; Domínguez, E. Solans, X.; Urtiaga, M. K.; Arriortua, M. I. *J. Org. Chem.* **2000**, *65*, 6398−6411 and references therein.

10.1021/ol025811h CCC: $22.00
Published on Web 04/09/2002

synthesis of a wide number of complex systems.[5] Despite the variety of procedures developed to effect such transformations, described as fundamental as the classical alkylation of enolates, serious limitations concerning a lack of regioselectivity and versatility of the process or the need of specific, usually toxic main group aryl reagents have been reported in many cases.[6] However, the use of palladium catalysts has emerged as a very promising alternative,[5d,7] overcoming most of the problems related to this reaction, historically difficult to conduct.

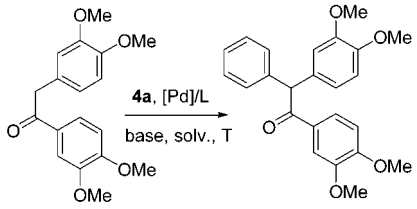
As a supporting step in this field, we wish to report an easy, high yielding procedure for the coupling of aryl halides **4** with deoxybenzoins **3** catalyzed by palladium(II) acetate.



As shown in Table 1, 1,2-bis(3,4-dimethoxyphenyl)-ethanone **3a** was treated with bromobenzene **4a** under the action of different palladium catalyst/ligand/base systems in order to promote phenylation of position 2 to give 1,2-bis-(3,4-dimethoxyphenyl)-2-phenylethanone **1a**.

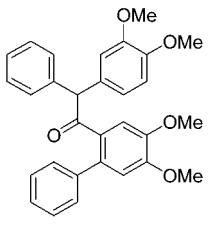
Despite previous reports,[5d,7a−c,8] no target triaryl derivative **1a** was obtained in the absence of ligand or by using bulky bidentate phosphine ligands such as BINAP or DPPF. In addition, the use of the $PdCl_2$ catalyst provided low yields of phenylated **1a**, even when iodobenzene **5** was employed as the haloarene reagent (Table 1, entries 6 and 8). Miura and co-workers[9] have reported the $PdCl_2$-catalyzed arylation of 1,2-diphenylethanone, but according to the latter results this procedure seems to be seriously limited by the electronic nature of the ketone precursor. Although better yields were obtained from the system $Pd(OAc)_2/PPh_3/Cs_2CO_3$ in both DMF and *o*-xylene solvents, there still remained the drawback of the ortho-arylation side reaction[7d,e] to give diphenylated derivative **6**. This problem was ultimately overcome by a careful choice of the temperature, reaction times, and relative amount of bromobenzene **4a** (Table 1, entries 11 and 12), thus affording **1a** in good yields.

Table 1. Selected α-Arylation Assays Performed on Deoxybenzoin **3a**



entry	reaction conditions	product (%)[a]
1	$Pd(OAc)_2$, KO^{t}Bu, toluene, 90 °C, 3 h[b]	**3a**
2	$Pd(OAc)_2$, K_2CO_3, toluene, 90 °C, 23 h[b]	**3a**
3	$Pd_2(dba)_3$/BINAP, KO^{t}Bu, THF, 70 °C, 6 h[b,c]	**3a**
4	$Pd_2(dba)_3$/DPPF, KO^{t}Bu, THF, 70 °C, 6 h[b,c]	**3a**
5	$PdCl_2$, K_2CO_3, DMF, 100 °C, 6 h[d]	*e*
6	$PdCl_2$, Cs_2CO_3, DMF, 100 °C, 6 h[d,f]	**1a** (20)
7	$PdCl_2/PPh_3$ K_2CO_3, DMF, 130 °C, 6 h[d,g]	**1a** (24)
8	$PdCl_2/PPh_3$ K_2CO_3, DMF, 100 °C, 6 h[d,f,g]	*e*
9	$Pd(OAc)_2/PPh_3$, K_2CO_3, *o*-xylene, 170 °C, 22 h[b,c]	**1a** (55) **6** (29)
10	$Pd(OAc)_2/PPh_3$, Cs_2CO_3, DMF, 170 °C, 0.7 h[b,c]	**1a** (52) **6** (35)
11	$Pd(OAc)_2/PPh_3$, K_2CO_3, *o*-xylene, 150 °C, 9 h[h]	**1a** (83)
12	$Pd(OAc)_2/PPh_3$, Cs_2CO_3, DMF, 150 °C, 0.5 h[h]	**1a** (85)

[a] Isolated yields measured on the basis of the starting amount of diaryl ketone **3a**. [b] 1.3 equiv of **4a**, 2.5 equiv of base, and 0.02 equiv of palladium catalyst were used. [c] 0.05 equiv of ligand was used. [d] 1.2 equiv of of **4a**, 1.2 equiv of base, and 0.05 equiv of $PdCl_2$ were used. [e] Complex mixtures of products were obtained. [f] 1.2 equiv of iodobenzene **5** was used instead of **4a**. [g] 0.2 equiv of PPh_3 was used. [h] **3a**/**4a**/$Pd(OAc)_2/PPh_3/Cs_2CO_3$ ratio was 1:1:0.02:0.08:2.5.



Once DMF was elected as the most convenient solvent, mainly because of its shorter required reaction time, the

(5) (a) Piers, E.; Oballa, R. M. *Tetrahedron Lett.* **1995**, *36*, 5837−5860. (b) Ryan, J. H.; Stang, P. J. *Tetrahedron Lett.* **1997**, *38*, 5061−5064. (c) Muratake, H.; Hayakawa, A.; Natsume, M. *Chem. Pharm Bull.* **2000**, *48*, 1558−1566. (d) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360−1370 and references included therein. (e) Deng, H. B.; Konopelski, J. P. *Org. Lett.* **2001**, *3*, 3001−3004.

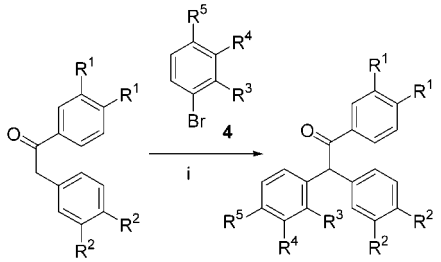
(6) (a) Beugelmans, R.; Boudet, B.; Quintero, L. *Tetrahedron Lett.* **1980**, *21*, 1943−1944. (b) Kessar, S. V. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: New York, 1991; Vol. 4, Chapter 2.3. (c) Pinhey, J. T. *Pure Appl. Chem.* **1996**, *68*, 819−824. (d) Mino, T.; Matsuda, T.; Maruhashi, K.; Yamashita, M. *Organometallics* **1997**, *16*, 3241−3242.

(7) (a) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108−11109. (b) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382−12383. (c) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473−1478 (d) Satoh, T.; Kametani, Y.; Terao, Y.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1999**, *40*, 5345−5348. (e) Terao, Y.; Kametani, Y.; Wakui, H.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron*, **2001**, *57*, 5967−5974. (f) Mutter, R.; Campbell, I. B.; Martin de la Neva, E, V.; Merritt, A. T.; Wills, M. *J. Org. Chem.* **2001**, *66*, 3284−3290. (g) Solé, D.; Vallverdú, L.; Peidró, E.; Bonjoch, J. *Chem. Commun.* **2001**, 1888−1889. (h) Hamada, T.; Chieffi, A.; Åhman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261−1268.

(8) (a) Mutter, R.; Martin de la Neva, E, V.; Wills, M. *Chem. Commun.* **2000**, 1675−1676. See also: (b) Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546−6553.

(9) Satoh, T.; Inoh, J.-I.; Kawamura, Y.; Kawamura, Y.; Kametani, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2239−2246.

Table 2. Synthesis of 1,2,2-Triarylethanones 1 by Palladium-Catalyzed α-Arylation of Deoxybenzoins **3**



3 **1**

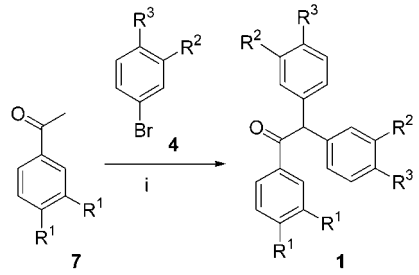
entry	R^1	R^2	R^3	R^4	R^5	**1** (%)[a]
1	OMe	OMe	H	H	H	**1a** (85)
2	OMe	OMe	H	OMe	H	**1b** (51)
3	OMe	OMe	H	H	OMe	**1c** (46)
4	OMe	OMe	H	OMe	OMe	**1d** (47)
5	OMe	OMe	H	OCH_2O		**1e** (55)
6	OMe	OMe	OMe	OMe	OMe	**1f** (12)
7	OMe	OMe	H	H	NO_2	**1g** (44)
8	OMe	H	H	H	H	**1h** (74)
9	H	H	H	H	H	**1i** (80)
10	H	H	H	OMe	H	**1j** (73)
11	H	H	H	H	OMeH	**1k** (71)
12	H	H	H	OMe	OMeH	**1l** (57)
13	H	H	H	OCH_2O		**1m** (70)
14	H	H	H	H	NO_2	**1n** (54)

[a] Isolated yield.

already optimized coupling conditions[10] were applied to a number of deoxybenzoins **3** and bromoarenes **4**. The results are summarized in Table 2. It should be remarked that no excess of any of the coupling reagents was employed, whereas previous works on the intermolecular arylation of ketones or esters with haloarenes usually report (i) a required 1.1−2.3 excess of the carbonyl compound or the haloarene and (ii) yields measured on the basis of the starting amount of the haloarene.[5d,7a,d−f,9,11]

Save for the low yield obtained for **1f**, probably as a result of a sterically hindered transition state for the oxidative addition step,[12] the moderate to good yields obtained in most of the range of models assayed feature a slight dependence on the electronic nature of the coupling partners, feeble

Table 3. Palladium-Catalyzed α,α-Diarylation of Acetophenones **7**



7 **1**

R^1	R^2	R^3	**1** (%)[a]
H	H	H	**1i** (96)
OMe	H	H	**1h** (85)
Me	OMe	H	**1o** (74)
H	OMe	OMe	**1p** (49)

[a] GC−MS yields.

enough to propose that the latter method constitutes a suitable, general tool for the preparation of 1,2,2-triarylethanones **1**, thus establishing a rival alternative to the recently reported Heck-type triarylation approach.[13] Moreover, in contrast with the relatively complex phosphine ligands usually employed in previous reports on the arylation of enolates,[7a−c,f,8,14] a simple, cheap ligand such as triphenylphosphine proved to be most efficient.

Encouraged by the simplicity and mild conditions of our procedure, we foresaw that slight modification, such as an increase in the amount of the arylating agent **4**, could be the key to obtain target ketones **1** in one step starting from commercially available acetophenones **7**. At present, the results obtained so far are very promising (Table 3) and suggest that the use of such a relatively small ligand (PPh_3) would be the decisive factor that enables this relevant tandem double arylation process.[15]

To summarize, an easy, general procedure for the preparation of 1,2,2-triarylethanones from deoxybenzoins is presented. This palladium-catalyzed α-arylation reaction is conducted with a simple ligand such as triphenylphosphine and avoids unwanted side reactions such as ortho-arylation or dehalogenation of the arylbromide reagent. Moreover, according to the latest assays performed, a slight modification of the same experimental conditions applied to acetophenones can constitute an additional alternative approach to the tamoxifen-related framework of 1,2,2-triarylethanones.

We are presently exploring the feasibility of such methods along with the synthetic potential associated with the use of 1,2-dihaloarenes in the hope of promoting further coupling reactions.

(10) **General Procedure.** Dry degassed DMF (20 mL) was added to an oven-dried reaction flask charged with $Pd(OAc)_2$ (0.065 mmol), Cs_2CO_3 (7.75 mmol), PPh_3 (0.25 mmol), ketone **1** (3.1 mmol), and arylbromide **4** (3.1 mmol) under argon at room temperature. The resultant stirred suspension was heated to 150 °C for 0.5−1 h. After cooling, HCl (50 mL of a 1.4 M solution in water) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl (5 × 100 mL), dried over anhydrous sodium sulfate, and evaporated in vacuo to give a residue that was purified by flash chromatography on silicagel using 10−50% EtOAc/hexane as eluent.

(11) (a) Moradi, W. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7996−8002. (b) Lee, S.; Beare, N. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 8410−8411.

(12) Useful insights into the mechanism of the Pd-catalyzed arylation of enolates and other related cross-coupling reactions can be found in: (a) Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 5816−5817. (b) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314−321. See also refs 7a and 7d.

(13) Nilsson, P.; Larhed, M.; Hallberg, A. *J. Am. Chem. Soc.* **2001**, *123*, 8217−8225.

(14) (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722−9723. (b) Åhman, J.; Wolfe, J. P.; Trotman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918−1919.

(15) For previous reports on one-pot α,α-diarylation reactions of ketones see refs 5d, 7a, 7c,d, and 14a. Similar diarylations of other carbonylic compounds have been reported in refs 8b and 11a.

Acknowledgment. This research was supported by the University of the Basque Country (Project UPV 170.310G37/98), the Spanish Ministry of Education and Culture (PB97-0600), and the Basque Government (GV170.310-G0053/96). F.C. thanks the Ministry of Education and Culture (MEC) for a predoctoral scholarship.

Supporting Information Available: Characterization data for all unknown triarylethanones **1b**−**h** and **1j**−**m**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL025811H