Organic Process Research & Development **1997**, *1*, 163–164

Technical Notes

One-Step Synthesis of Biphenylacetic Acids via Pd/C-Catalyzed Arylation

D. Gala,* A. Stamford, J. Jenkins, and M. Kugelman

Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, New Jersey 07033

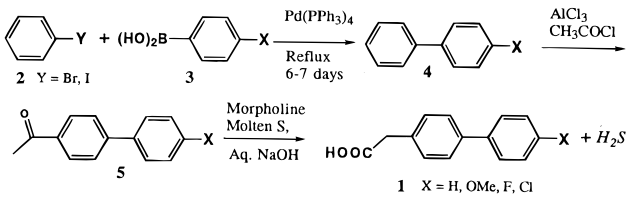
Abstract:

An efficient, convenient, one-step synthesis of biphenylacetic acids using Pd/C as a catalyst is described. This has been successfully used for the preparation of mole amounts of acids.

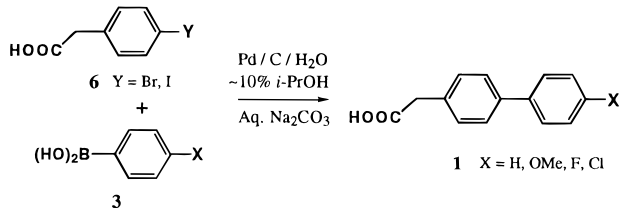
Catalytic methods are often the processes of choice due to their efficiency. One such method, the arylation catalyzed with a solubilized form of Pd, i.e., [$Pd(PPh_3)_4$], commonly referred to as the Suzuki coupling reaction, is of tremendous potential.[1,2] Factors such as the cost of catalyst; the need for scrupulously degassed solvents to minimize the catalyst poisoning; the contamination of the product with the byproducts, resulting from ligand exchange, which often necessitates chromatographic purification of the product; high dilutions and hence long reaction times; substrate compatibility; and occasional irreproducibility have kept this reaction as one of mainly research interest. Recently, the efforts to render this reaction less demanding, e.g., by using a cheaper catalyst, using solubilizing reagents, utilizing ambient temperature, and/or extending its application to a broader substrate base, have been published.[3−7] The publication of the use of Pd/C for arylation[4] prompts us to report our finding which involves the use of Pd/C for an efficient, one-step synthesis of biphenylacetic acids. To the best of our knowledge, this is the first report where the carboxylic acid group has been shown to be compatible with the Suzuki reaction.

The biarylacetic acids have been of current biological as well as physical chemistry interest.[8,9] To date they have been synthesized mainly by Willgerodt−Kindler[10] rearrangement of the biaryl ketones **5** as depicted in Scheme 1. The exhaustive extractive workup of the reactions needed to purify the intermediates and product **1** and the generation of toxic sulfide are undesirable for the large-scale preparation of these compounds. Furthermore, recent regulatory changes restrict the storage and shipping of the halobiphenyls **4**.[11] Hence a new, efficient, and environmentally friendly synthesis of **1** was sought.

Scheme 1



Scheme 2



During our investigations to prepare the halobiphenyls **4** and use them soon after their preparation to avoid the storage and shipping problems, we investigated various Pd catalysts. Specifically, when a recently published $Pd(OAc)_2$ procedure[5] was used for this coupling, it was noticed that within minutes the entire reaction flask was coated with a shiny mirror. Nevertheless, the reaction did go to completion after a prolonged heating period as reported in the literature. We hypothesized that the mirror on the flask was the result of Pd metal depositing on the flask. Consequently, when $Pd(OAc)_2$ was replaced with cheaper 5% Pd/C, the reaction did progress to generate the biphenyls. Since similar observation has been independently reported recently,[4] our findings made on the preparation of these biphenyls are not repeated here. On the other hand, since no ligand was needed for metallic palladium to drive this coupling, we reasoned that the coupling of (4-halophenyl)acetic acids **6** with the substituted phenylboric acids **3** should also progress to generate the desired biarylacetic acids **1** as shown in Scheme

(1) For a recent review on this reaction, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2475. (b) Suzuki, *Pure Appl. Chem*. **1994**, *66*, 213.
(2) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun*. **1981**, *11*, 513.
(3) Zhang, H.; Chan, K. S.; Shatin, N. T. *Tetrahedron Lett*. **1996**, *37*, 1043.
(4) Marck, G.; Villiger, A.; Buchecker, R. *Tetrahedron Lett*. **1994**, *35*, 3277.
(5) Campi, E. M.; Roy, J. W.; Marcuccio, S. M.; Naeslund, C. G. M. *J. Chem. Soc., Chem. Commun*. **1994**, 2395.
(6) Frenette, R.; Friesen, R. W. *Tetrahedron Lett*. **1994**, *35*, 9177.
(7) Anderson, J. C.; Namli, H. *Synlett* **1995**, 765.
(8) Duplantier, A. J.; Biggers, M. S.; Chambers, R. J.; Cheng, J. B.; Cooper, K.; Damon, D. B.; Eggler, J. F.; Kraus, K. G.; Marfat, A.; Masamune, H.; Pillar, J. S.; Shirley, J. T.; Umland, J. P.; Watson, J. W. *J. Med. Chem*. **1996**, *39*, 120.
(9) Michaeli, S.; Hugerat, M.; Leavanon, H.; Bernitz, M.; Natt, A.; Neumann, R. *J. Am. Chem. Soc*. **1992**, *114*, 3612.
(10) (a) Willgerodt, C. *Ber. Dtsch. Chem. Ges*. **1887**, *20*, 2467; **1888**, *21*, 534. (b) Kindler, K. *Justus Liebigs Ann. Chem*. **1923**, *431*, 193.

(11) Although the halobiphenyls were available in the past, the recent classification of these compounds as potential ozone-depleting chemicals has limited the quantities that could be stored or shipped.

S1083-6160(96)00035-7 CCC: $14.00

Table 1. **Preparation of biarylacetic acids 1**

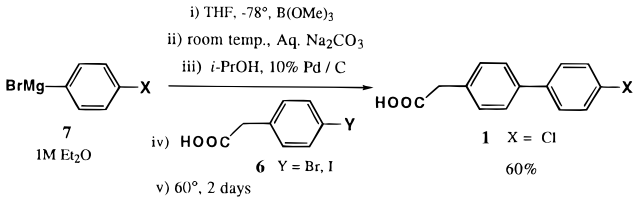
no.	substituent X (**3**)[a]	substituent Y (**6**)[a]	method[b]	yield,[c] %
1	F	I	A	85
2	F	Br	A	90
3	Cl	I	A	90
4	Cl	Br	A	92
5	H	Br	A	85
6	OMe	Br	A	84
7	F	Br	B	97

[a] All starting materials were commercially available and were used without additional purification. [b] Only a minimal optimization has been carried out on either of the two methods listed below. Method A: To a stirred mixture of 37.1 g (0.18 mol) of (4-bromophenyl)acetic acid, 28.75 g (0.2 mol) of (4-fluorophenyl)boric acid, and 18.4 g of 50% water wet 5% Pd/C in 370 mL of *i*-PrOH at room temperature was added 24.25 g (0.23 mol) of Na_2CO_3 dissolved in 71 mL of water over 20 min. The reaction mixture was then heated to reflux for 4 days to consume most of the phenylacetic acid (HPLC).[12] The mixture was cooled to room temperature, diluted with 50 mL of 1:1 H_2O/*i*-PrOH containing 2.5 mL of N NaOH, and then filtered. The carbon cake was washed with the above solvent mixture (3 × 20 mL). The combined filtrate and washes were neutralized to pH 2 with 2 N H_2SO_4 (∼15 mL) and then subjected to vacuum distillation to remove *i*-PrOH. The resultant suspension was diluted with 200 mL of H_2O, filtered, washed with 5 × 10 mL of H_2O (the final wash was at pH 5), followed by heptane, and dried to a constant weight in a vacuum oven (55 °C) to obtain 33.5 g (84% yield) of the product (**1**, X = F): mp 160−162 °C; NMR (d_6-DMSO); δ (ppm) CH_2 at 3.7. The following were similarly obtained. **1** (X = Cl): mp 157−159 °C; NMR (d_6-DMSO); δ (ppm) CH_2 at 3.7. **1** (X = H), mp 159−162 °C; NMR (d_6-DMSO); δ (ppm) CH_2 at 3.7. **1** (X = OMe), mp 184−187 °C; NMR (d_6-DMSO); δ (ppm) CH_2 at 3.7, OCH_3 at 3.8. In all cases, the correct number of aromatic protons were observed between δ (ppm) 7 and 7.8. Method B: To a stirred mixture of 120 g (0.57 mol) of (4-bromophenyl)acetic acid, 86.9 g (0.62 mol) of (4-fluorophenyl)boric acid, and 54 g of 50% water wet 5% Pd/C in 600 mL of water containing 100 mL of 2-propanol at room temperature was added 80 g (0.75 mol) of Na_2CO_3 dissolved in 200 mL of water over 35 min. The reaction mixture was then heated to 65 °C and maintained at this temperature for 3 h to consume most of the phenylacetic acid (HPLC).[12] The reaction mixture was cooled to 40 °C, diluted with 150 mL of 70:15:1 *i*-PrOH/H_2O/2 N NaOH, and filtered. The catalyst was washed with 3 × 50 mL of the above solvent mixture. Next, the filtrate was diluted with 350 mL of water, stirred, and slowly treated with 100 mL of 2 N H_2SO_4 (to a pH of ∼2). This mixture was subjected to vacuum distillation to remove *i*-PrOH, diluted with 1 L of H_2O, cooled to ∼10 °C, and filtered. The white solid was washed with 5 × 200 mL of water (the final wash was of pH 5.5) and then dried in vacuo at 55−60 °C to a constant weight to obtain 125 g (97% yield) of 4′-fluorobiphenylacetic acid. [c] This represents isolated yields of >97% pure (HPLC area) product. Satisfactory analytical data were obtained on all the products.

2. In fact, with 5% Pd/C, all four target compounds were prepared, and the results are summarized in Table 1.

Having accomplished this synthesis in one step, we undertook a minimal optimization of the reaction. In this work it was established that (i) 2-propanol, a preferable solvent for large-scale work, was an acceptable substitute for ethanol (method A); (ii) although degassed solvents were used in the early stages of this work, the degassing of the solvents was unnecessary; (iii) readily available, inexpensive

Scheme 3



(4-bromophenyl)- in place of (4-iodophenyl)acetic acid could be used for this coupling albeit with an increase in the reaction time of 4 days vs 2 days; (iv) the use 2−3 mol % of either dry or water wet 5% Pd/C led to similar yields in these reactions; (v) the recovery of Pd/C was quantitative at the end of the reaction, which avoided product contamination with Pd; and (vi) washing the product with water so that the wash is of pH >5 removed traces of unreacted **6** from the product, resulting in high purity of **1**. Finally, the use of water as a primary solvent with 2-propanol as a cosolvent (to improve the solubility of **3**) significantly shortened the reaction time while improving the yields (method B). The latter condition has been scaled up to prepare multikilo batches of 4′-fluorobiphenylacetic acid in our laboratory.

Finally, the use of 10% Pd/C could decrease the reaction time in method A. In view of the success of method B, the use of more palladium would be unnecessary. However, this use becomes more interesting for the direct conversion of Grignard reagents to the biaryl acids.[13] The robustness of the above Pd/C coupling condition is illustrated by the fact that the commercially available ethereal solution of Grignard reagent **7** can be converted to the biphenylacetic acid in one pot via in situ generated, unpurified **3** as shown in Scheme 3 using 10% Pd/C.[14] In brief, to the ethereal solution of **7** at −78 °C in THF was added 2 equiv of $B(OMe)_3$. The reaction mixture was then allowed to attain room temperature. Next, aqueous Na_2CO_3 solution followed by the reagents listed in Scheme 3 were added, and the solution was heated to obtain the product in an unoptimized yield of 60%.

Thus a high-yielding, one-step, environmentally friendly synthesis of biphenylacetic acids using inexpensive, readily available Pd/C has been established, and it has been scaled up to prepare several kilos of 4′-fluorobiphenylacetic acid. The experimental conditions for this efficient synthesis are reported.

Acknowledgment

We thank Ms. Mayra Cordero for developing the HPLC procedure and the Physical Analytical Group at SPRI for obtaining the analytical data on the products.

Received for review June 7, 1996.[⊗]

OP960035C

[⊗] Abstract published in *Advance ACS Abstracts,* December 1, 1996.

(12) HPLC: Zorbax RX-C8 25 cm × 4.6 mm column; 1:1:0.2 $CH_3CN/H_2O/CH_3COOH$ mobile phase at 1 mL/min; UV detection at 220 nm. This wavelength is preferred as compounds **6** have stronger absorption at this wavelength compared to the products, thus assuring complete consumption/removal of **6**.

(13) The phenylboric acids are typically prepared from the corresponding Grignard reagents: (a) Chan, K. S., Zhou, X.; Au, M. K.; Tam, C. Y. *Tetrahedron* **1995**, *51*, 3129. (b) Thompson, W. J.; Gaudino, J. *J. Org. Chem.* **1984**, *49*, 5237.

(14) It is anticipated that the reaction would progress with 5% Pd/C, albeit at a slower rate.