Tetrahedron Letters, Vol. 34, No. 39, pp. 6211-6214, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

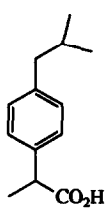
Palladium-Catalyzed Coupling of an α-Stannyl Acrylate to Aryl Iodides and Triflates. A One-Step Synthesis of Aryl Propenoic Esters.

Jeremy I. Levin

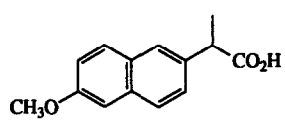
American Cyanamid Company
Medical Research Division, Lederle Laboratories
Pearl River, New York 10965

Abstract: Aryl iodides undergo a Pd(0)-CuI catalyzed coupling with methyl 3-(tributylstannyl)propenoate to provide the corresponding aryl propenoic esters. Triflates require Pd(0)-CuI-LiCl.

2-Arylpropenoic acids represent an important class of therapeutically valuable non-steroidal anti-inflammatory agents which relieve inflammation by inhibiting cyclooxygenase and therefore interdicting the arachidonic acid cascade.[1] Two commercially valuable examples of this group of compounds are ibuprofen and naproxen.



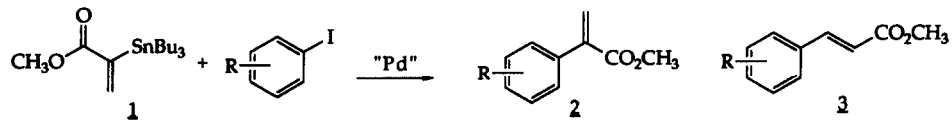
ibuprofen



naproxen

Since these drugs exert their primary pharmacologic effect through the S enantiomer only, an expedient route to enantiomerically pure material is extremely desirable. One such asymmetric synthesis involves the hydrogenation of the precursor aryl propenoic acids using a chiral catalyst.[2] Unfortunately, these acrylic acids and their esters are not readily available by present procedures.[3] Therefore, we now disclose a simple, general method for the synthesis of these important 2-aryl propenoic esters from the corresponding aryl iodides and triflates.

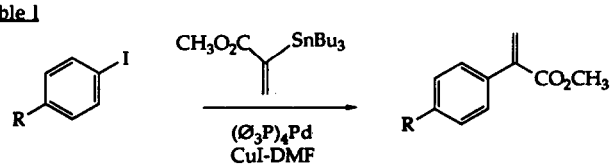
The palladium catalyzed coupling of simple vinyl stannanes to aryl halides has been known for some time.[4] However, although a convenient synthesis of methyl 3-(tributylstannyl)propenoate, 1 has been available for several years,[5] this compound has not been exploited for the preparation of propenoic esters 2 via palladium couplings (Scheme 1).



Scheme 1

To our knowledge only one example exists in the literature of the use of stannyl acrylate 1 in a palladium catalyzed coupling. In that example 1 is reacted with a uridine triflate in the presence of Pd(0) in refluxing dioxane to provide a 1:1 mixture of the acrylate ester and the undesired cinnamate ester in good overall yield.[6] Our own attempts at coupling 1 to substituted aryl iodides under standard Stille conditions[4] (Pd(0), toluene, 110°) resulted in the formation of the undesired cinnamate esters, 3, exclusively, presumably via a Heck reaction followed by protodestannylation. However, some time later several papers came to our attention describing the recent observation that copper(I)iodide significantly enhances the rate of certain palladium catalyzed coupling reactions.[7] Thus, we repeated the reaction of 1 with several iodides using the conditions described by Liebeskind[7b] (Pd(II), CuI, DMF). The coupling reaction now proceeded at room temperature to provide only the acrylate ester, in moderate yield.

Table 1



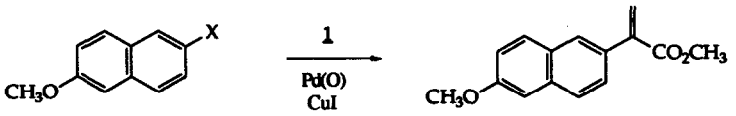
R	Time(h)[a]	Yield(%)[b,c]
NO_2	12	76
CF_3	24	72
	12	78
CO_2CH_3	12	66
H	48	87
CH_3	48	71
Br	24	92
OCH_3	48	42

a) 10 mol% Pd(0), 0.75 eq CuI, 2.5 eq stannane
b) isolated yields
c) all compounds had satisfactory IR, MS and ^1H NMR

The optimum conditions for this reaction were eventually determined to be 10 mol % tetrakis(triphenylphosphine)palladium(0), 2.5 equivalents of stannane 1 and 0.75 equivalents of copper(I)iodide in DMF at room temperature.[8] Lesser quantities of stannane or CuI result in incomplete consumption of starting aryl iodide due to competing homo coupling of 1.[5] Also, the use of 5 mol % $(Ph_3P)_2PdCl_2$ as the catalyst gave slightly diminished yields and, unfortunately, no reduction in the amount of homo coupling. Results are shown in Table 1. The reaction is general for both electron withdrawing and donating groups on the aryl ring, though it is clearly more sluggish with the latter.

Furthermore, if desired, stannyl acrylate 1 may be prepared by the $(Ph_3P)_4Pd$ catalyzed reaction of tributylin hydride with methyl propiolate in DMF and then coupled to the aryl iodide in the same pot, without isolation and purification of 1. This procedure converted p-iodonitrobenzene to the corresponding acrylate ester in 44% yield.

In order to extend the scope of the palladium catalyzed coupling of stannyl acrylate 1 we next investigated the reactivity of aryl bromides and triflates. The starting materials chosen were 2-bromo-6-methoxynaphthalene (Aldrich) and 6-methoxy-2-naphthol (Fluka). If the coupling reactions were successful on either of these compounds it would provide an exceptionally simple and expedient route to naproxen.



4 X = Br
5 X = OSO_2CF_3

6

Scheme 2

In the event the bromonaphthalene 4 was unreactive, yielding only recovered starting material after 24 h at room temperature. The triflate 5 provided only a trace of the desired olefin 6 under the same conditions for 48 h. However, if by analogy with Stille's work on the palladium-catalyzed coupling of vinyl triflates with organostannanes,[9] lithium chloride is added to the usual reaction conditions ($Pd(Ph_3P)_4$, CuI, DMF, room temp.) the coupling on triflate 5 proceeds to completion in 48 h providing a 71% yield of the olefin 6. Ester 6 has previously been converted into naproxen.[3d]

In conclusion we have developed an efficient synthesis of 2-aryl propenoic esters from the corresponding aryl iodides or triflates. The reaction is operationally simple, gives high yields of products and is general.[10]

References:

1. Rieu, J.-P.; Boucherle, A.; Cousse, H.; Mouzin, G.; Tetrahedron 1985, 41, 4095.

2. Ohta, T.; Takaya H.; Kitamura, M.; Nagai, K.; Noyori, R.; J. Org. Chem. 1987, 52, 3174.

3. For some recent approaches see:
a) Kudo, S.; Naraoka, T.; Nishino, H.; Chem. Abstr. **1980**, 93, 95001h.
b) Itoh, K.; Miura, M.; Nomura, M.; Tet. Lett. **1992**, 33, 5369.
c) Torii, S.; Okumoto, H; Sadakane, M.; .Xu, L. H.; Chem. Lett. **1991**, 1673.
d) Himaya, T.; Wakasa, N.; Veda, T.; Kusumoto, T.; Bull. Chem. Soc. Jpn. **1990**, 63, 640.

4. McKean, D. R.; Parrinello, G.; Renaldo, A. F.; Stille, J. K.; J. Org. Chem. **1987**, 52, 422.

5. a) Zhang, H. X.; Guibe, F.; Balavoine, G.; J. Org. Chem. **1987**, 55, 1857.
b) Miyake, H.; Yamamura, K.; Chem. Lett. **1989**, 981.
c) Cochran, J. C.; Bronk, B. S.; Terrence, K. M.; Phillips, H. K.; Tet. Lett. **1990**, 31, 6621.

6. Flynn, B.; Macolino, V.; Crisp, G. T.; Nucleosides & Nucleotides **1991**, 10, 763.

7. a) Liebeskind, L. S.; Wang, J.; Tet. Lett. **1990**, 30, 4293.
b) Liebeskind, L. S.; Fengl, R. W.; J. Org. Chem. **1990**, 55, 5359.
c) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W.; Tet.Lett. **1992**, 33, 919.
d) Marino, J. P.; Long, J. K.; J. Am. Chem. Soc. **1988**, 110, 7916.

8. For the use of Pd(O) and CuI as catalyst see:
Hobbs, F. W., Jr.; J. Org. Chem. **1989**, 54, 3420.

9. Scott, W. J.; Stille, J. K.; J. Am. Chem. Soc. **1986**, 108, 3033.

10. A general procedure is as follows:

To a solution of 1.00 mmol of the aryl iodide in 10 mL of DMF was added 0.93 g (2.50 mmol) of stannane 1 and 0.116 g (0.10 mmol) of tetrakis(triphenylphosphine)palladium(0). To this stirred reaction mixture was then added 0.143 g (0.75 mmol) of copper(I) iodide in one portion. After 15 min at room temperature the reaction has turned dark brown and is homogeneous. The reaction is then stirred at room temperature until all of the starting iodide has been consumed (TLC), usually 12-48 h. The reaction mixture is then diluted with 100 mL of ether and filtered through Celite®. The filtrate is then washed with water and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue is purified by flash chromatography on silica gel, eluting with ethyl acetate/hexanes to provide the product.

(Received in USA 2 June 1993; accepted 30 July 1993)