Pergamon

Tetrahedron Letters 39 (1998) 1885–1888

TETRAHEDRON
LETTERS

Synthesis of 2-Vinylic Dihydroindoles and Tetrahydroquinolines via Pd-Catalyzed Cross-Coupling of *o*-Alkenyl Anilides with Vinylic Halides and Triflates

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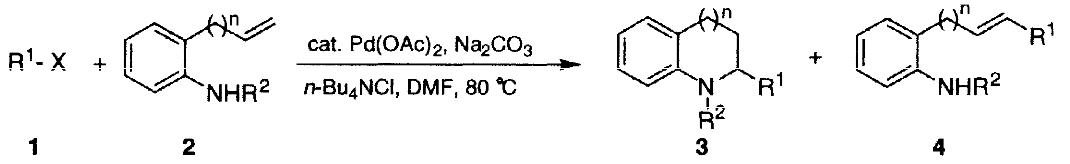
Received 14 November 1997; accepted 12 January 1998

Abstract: The palladium-catalyzed cross-coupling of *o*-vinylic and *o*-allylic anilides with vinylic halides and triflates produces 2-vinylic dihydroindoles and tetrahydroquinolines respectively in good to high yields.

Our ongoing interest in the synthesis of heterocycles by the palladium-catalyzed cross-coupling of functionalized olefins and vinylic halides or triflates[1] and our recent success in the development of an efficient procedure for the synthesis of unsaturated dihydrobenzofurans and dihydrobenzopyrans from vinylic halides or triflates and *o*-alkenyl phenols[2] encouraged us to investigate the possible application of this methodology to the synthesis of unsaturated dihydroindoles and tetrahydroquinolines (Scheme 1).

Scheme 1



R^1 = vinylic; X = I, Br, O_3SCF_3; n = 0, 1; R^2 = Ts, $COCF_3$, H

Readily available *o*-vinyl and *o*-allyl anilides (**2**) were selected as suitable building blocks and their reactions with a variety of vinylic halides and triflates (**1**) were examined as a useful route for the preparation of 2-vinylic dihydroindoles and tetrahydroquinolines (**3**), respectively. In general, we have used a procedure similar to that used by us for the cross-coupling of unsaturated phenols.[2] Sodium carbonate (3.5 equiv), n-Bu_4NCl (1.2 equiv) in the presence of 5 mol % $Pd(OAc)_2$ gave good results in the reactions of a variety of vinylic halides and triflates with both *o*-vinyl and *o*-allyl anilides (see Table 1).[3] Reactions employing unsaturated anilides proved more difficult than the analogous reactions with phenols and generally the process appears limited by the competitive formation of vinylic substitution products (**4**).

0040-4039/98/$19.00
PII: S0040-4039(98)00154-3

Table 1. Pd-Catalyzed Cross-Coupling of Vinylic Halides and Triflates (**1**) with Unsaturated Anilides (**2**).[a]

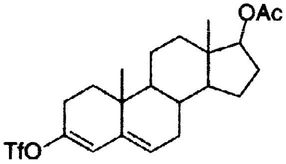
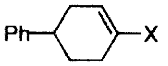
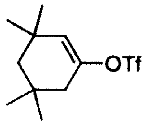
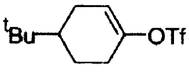
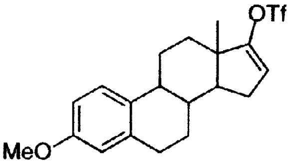
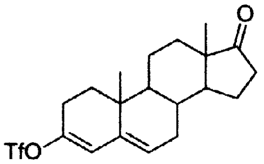
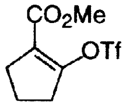
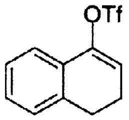
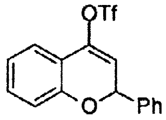
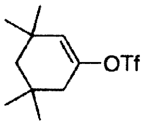
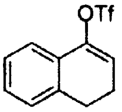
Entry	Vinylic halide or triflate (**1**)	*o*-Alkenyl anilide (**2**)	R^2	Time (h)	**3** (%)[b]	**4** (%)[b]
1		*o*-$R^2NHC_6H_4CH=CH_2$	Ts	4	70	24
2	 X = I			1	61	35
3	X = OTf			3	46	39
4				3	65	33
5				3	65	33
6				7	47	–
7				6	56	–
8				3	52	40
9				2	87	–
10	(*E*)-PhCH=CHBr			3	68	–
11			$COCF_3$	2	75	–
12			H	3	45	–
13	$PhCBr=CH_2$		Ts	3	59	–
14			$COCF_3$	4	64	–
15	(*E*)-*n*-BuCH=CHI		Ts	5	trace	63
16			$COCF_3$	2	39	42
17			H	3	-	28
18	(*E*)-MeCH=CBrMe		Ts	5	10	66
19			$COCF_3$	6	56	16
20	$Ph_2C=CHI$		Ts	2	12	70
21			$COCF_3$	2	71	13
22	(*Z*)-*t*-BuCH=CHI			5	52	36
23	(*E*)-*cyclo*-$C_6H_{11}CH=CHI$		$COCF_3$	4	64	33
24	$Ph_2C=CIPh$			12	–	–
25	(*E*)-PhCH=CHBr	*o*-$R^2NHC_6H_4CH_2CH=CH_2$	Ts	24	80	–
26	(*E*)-*n*-BuCH=CHI			24	75	13[c]

Table 1. (continued)

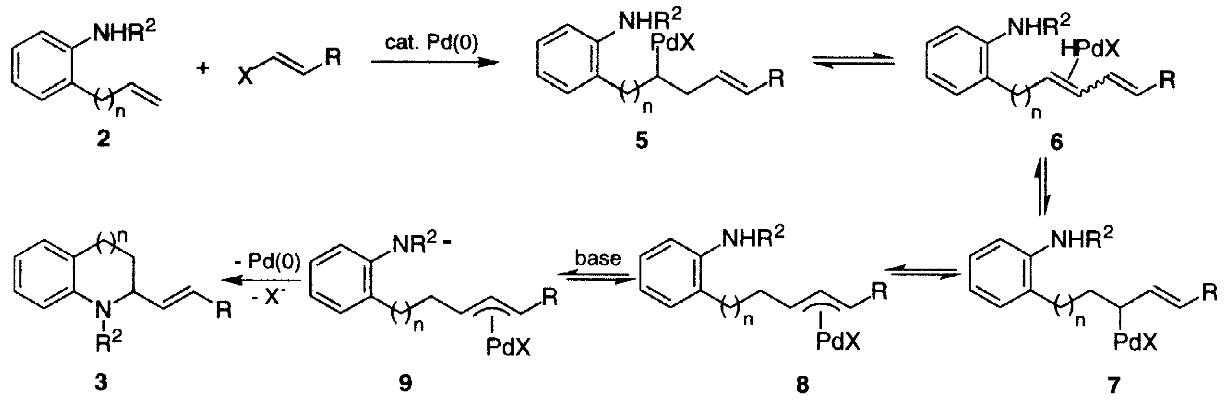
Entry	Vinylic halide or triflate (**1**)	*o*-Alkenyl anilide (**2**)	R^2	Time (h)	**3** (%)[b]	**4** (%)[b]
27	(*E*)-*n*-BuCH=CHBr	*o*-$R^2NHC_6H_4CH_2CH=CH_2$	Ts	24	70	4[c]
28	(*E*)-*t*-BuCH=CHBr			24	68	4[c]
29	(*Z*)-EtCH=CIEt			24	28	3[c]
30				2	76	–
31				3	58	15
32				5	16	60

[a]Reactions were carried out on a 0.6-0.8 mmol scale in DMF as the solvent (3 mL) at 100 °C using the following molar ratios: **1**: **2**: Na_2CO_3: *n*-Bu_4NCl: $Pd(OAc)_2$ = 1: 1.2: 3.5: 1.2: 0.05. [b]Yields are calculated based on pure, isolated compound, fully characterized by ^1H NMR, ^{13}C NMR, IR and mass spectral analysis. [c] Compound **4** was obtained as a mixture with **3** and the yield was determined by ^1H NMR analysis.

Although we have not done a thorough comparative study, the nature of the substituent on the nitrogen has a major impact on the success of the reaction. Although *o*-vinylaniline itself on occasion gave the anticipated nitrogen heterocycle (entries 12 and 17), the yields were always low. Introduction of a tosyl group onto the nitrogen of *o*-vinylaniline generally afforded a substantial increase in the yield of the desired product, although the heterocycle was often accompanied by significant amounts of vinylic substitution product **4**. In fact, when a vinylic halide was used instead of a triflate, the vinylic substitution product was often the major product. This difficulty can be overcome by employing the corresponding trifluoroacetanilide (R^2 = $COCF_3$) instead. When employing *o*-allylaniline derivatives, satisfactory yields could generally be obtained using the simple tosyl derivative (entries 25-32). Comparable results were generally obtained using either triflates or halides, although certain highly substituted systems gave very poor results (entries 24 and 29). In general, this methodology provides a simple direct synthesis of a variety of 2-vinylic dihydroindoles and tetrahydroquinolines from readily available starting materials.

As we have previously proposed, these reactions presumably proceed by the addition of a σ-vinylic palladium intermediate, generated *in situ*, to the carbon-carbon double bond, followed by elimination and readdition of Pd-H to form a π-allylpalladium intermediate, which subsequently undergoes intramolecular nucleophilic displacement by the deprotonated amide nitrogen (see Scheme 2). The initial carbopalladation step regioselectively affords only the σ-alkylpalladium intermediate **5**. We have no evidence for products arising from vinylic addition to the internal carbon of the carbon-carbon double bond as sometimes observed in related reactions.[4] The major limitation of the present methodology appears to be the irreversible elimination of palladium hydride from the η^2-complex **6**, which is presumably responsible for formation of the vinylic substitution side products **4**.

Scheme 2



In conclusion, the reaction reported here further illustrates the synthetic potential of π-allylpalladium complexes derived from the cross-coupling of vinylic halides and triflates with functionally-substituted olefins for the synthesis of heterocyclic compounds.

Acknowledgments. The Larock group gratefully acknowledges partial support of this research by the National Institutes of Health and the donors of the Petroleum Research Fund administered by the American Chemical Society, and Johnson Matthey, Inc. and Kawaken Fine Chemical Co., Ltd. for the palladium acetate. Dr. Pace acknowledges the NATO-CNR Advanced Fellowships Program, sponsored by the Consiglio Nazionale delle Ricerche. The Cacchi group gratefully acknowledges the Ministero dell' Università e della Ricerca Scientifica (MURST) and the Consiglio Nazionale delle Ricerche (CNR) for financial support.

References and Notes

1. See for example: (a) Larock, R. C.; Leuck, D. *Tetrahedron Lett.* **1988**, *29*, 6399; (b) Larock, R. C.; Yum, E. K. *Synlett* **1990**, 529; (c) Larock, R. C.; Yang, H.; Weinreb, S. M.; Herr, R. J. *J. Org. Chem.* **1994**, *59*, 4172.
2. Larock, R. C.; Yang, H.; Pace, P.; Cacchi, S.; Fabrizi, G. *Tetrahedron Lett.* **1997**, *38*, 0000.
3. A typical procedure follows: to a solution of 0.130 g (0.60 mmol) of 2-vinyl trifluoroacetanilide and β-bromostyrene (0.092 g, 0.50 mmol) in DMF (3 mL) were added Na_2CO_3 (0.187 g, 1.76 mmol), *n*-Bu_4NCl (0.168 g, 0.60 mmol) and $Pd(OAc)_2$ (0.006 g, 0.025 mmol). The reaction mixture was stirred under argon at 100 ° C for 2 h and then diluted with ethyl acetate and washed with brine. The organic layer was dried (Na_2SO_4), filtered, concentrated under vacuum, and chromatographed on silica gel, eluting with a 90/10 (v/v) mixture of *n*-hexane/EtOAc, to afford 0.119 g (75% yield) of *N*-trifluoroacetyl-2,3-dihydro-2-[(*E*)-β-styryl]indole, as a colorless oil: IR (liquid film) 1683, 843, 764 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.22 (d, *J* = 7.8 Hz, 1 H), 7.35-7.18 (m, 9 H), 6.50 (d, *J* = 16.0 Hz, 1 H), 6.20 (dd, *J* = 6.9, 16.0 Hz, 1 H), 5.37 (t, *J* = 7.6 Hz, 1 H), 3.63 (dd, *J* = 8.4, 15.7 Hz, 1 H), 3.00 (d, *J* = 15.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 155.53 (q, *J* = 37 Hz, $\underline{C}OCF_3$), 141.13, 135.86, 131.12, 130.69, 128.71, 128.25, 128.04, 127.62, 126.65, 126.28, 125.34, 118.84, 116.22 (q, *J* = 286 Hz, CF_3), 62.04, 36.80; MS *m/z* (relative intensity) 317 (M^+, 100), 220 (18).
4. See ref. 2 and (a) Larock, R. C.; Leung, W. Y.; Stolz-Dunn, S. *Tetrahedron Lett.* **1989**, *30*, 6629; (b) Larock, R. C.; Leung, W. Y. *J. Org. Chem.* **1990**, *55*, 6244.