Synthesis of Aryl-Substituted 3-Alkenamides via Palladium-Catalyzed Cross-Coupling of Aryl Iodides and 4-Alkenyl-2-Azetidinones

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Abstract: Palladium catalyzes the cross-coupling of aryl iodides and 4-alkenyl-2-azetidinones to give good yields of aryl-substituted 3-alkenamides.

Although the cross-coupling of organometallics and vinylic epoxides¹ or oxetanes² provides a useful approach to allylic and homoallylic alcohols respectively (eq 1), only we have reported analogous chemistry of

$$RM + \bigwedge_{n=1,2}^{O} \bigcap_{n} \frac{H_2O}{R} R \longrightarrow_{n}^{OH} (1)$$

readily available³ 4-alkenyl-2-azetidinones using organomercurials and palladium salts (eq 2).⁴ Our recent

$$RHgCl + \bigvee_{N=0}^{H} \frac{Li_2PdCl_4}{H_2O} R \underbrace{CONH_2}$$
(2)

success in the palladium-catalyzed cross-coupling of organic *halides* with olefinic epoxides bearing one to ten carbons between the functional groups (eq 3),⁵ has encouraged us to look at analogous chemistry using 4-alkenyl-2-azetidinones (eq 4). We now report the success of that endeavor.

After an extensive survey of reaction conditions similar to those employed for olefinic epoxides,⁵ we have developed two basic procedures. Procedure A employs 1 equiv azetidinone, 2 equiv aryl iodide, 10% Pd(OAc)₂, 3 equiv *i*-Pr₂NEt, 1 or 5 equiv HCO₂Na, 2 equiv LiCl in DMF (2.0 ml/0.5 mmol azetidinone) at 80 °C. In Procedure B, the 2 equivs LiCl are replaced by 1 equiv *n*-Bu₄NCl. Our results using these two procedures are summarized in Table I.

A wide variety of aryl iodides can be employed in this process. Higher yields are obtained from aryl halides bearing electron-donating groups (entries 1, 2 and 6). With aryl halides bearing electron-withdrawing groups, lower yields are observed and it is best to use less of the formate reducing agent (entries 3, 4 and 7). In these cases it appears that the arylpalladium intermediate is reduced to the corresponding arene⁶ in competition with alkene insertion.

Using the above-described procedures, vinylic iodides afford yields of 31% or less. As noted earlier with vinylmercurials and 4-alkenyl-2-azetidinones,⁴ the best yields are obtained using more highly substituted vinylic iodides (eq 5). Cyclohexenyl triflate gave a 20% yield under similar conditions. With vinylic iodides, a mixture of side products is observed in which the azetidinone ring has failed to open.



A wide variety of readily available³ 4-alkenyl-2-azetidinones have successfully been employed in this process. As noted in the organomercurial process, 4-methyl-4-vinyl-2-azetidinone (1) gives higher yields than the less substituted 4-vinyl-2-azetidinone (2). With the latter substrate in fact, best yields were obtained by employing the azetidinone in excess (entries 5-7). With the more substituted carbon-carbon double bonds of 4-(E-1-propenyl)-2-azetidinone (3) and 4-isopropenyl-4-methyl-2-azetidinone (4), the yields drop significantly.

While organomercurials did not cross-couple with 4-alkenyl-2-azetidinones in which the double bond and the lactam moiety are separated by saturated carbons,⁴ to our surprise the present arylation process works nicely with such substrates (entries 10 and 11). Under these reaction conditions the palladium is able to migrate⁷ a considerable distance.

The stereoselectivity of this aryl iodide process is somewhat greater than that of the arylmercurial process. The E/Z ratio for the phenylation of azetidinone 2 increases from $3:1^4$ using phenylmercuric chloride to 4:1 when iodobenzene is employed. Whereas tri- and tetrasubstituted double bonds were formed in the arylmercurial process with little or no selectivity,⁴ an E/Z ratio of 60:40 to 66:34 is observed here.

The present palladium-catalyzed arylation process is believed to proceed by palladium(II) reduction to palladium(O) by formate anion, oxidative addition of the aryl iodide to palladium(O), arylpalladium addition to the carbon-carbon double bond, where necessary palladium migration via palladium hydride beta elimination and subsequent readdition with the opposite regiochemistry,⁷ palladium nitrogen beta elimination to form RCONHPdI, and formate reduction to the observed amide product and palladium(O). Generally less than 10% of the Heck-type vinyl hydrogen substitution products have been observed.

Recent efforts indicate that this chemistry can be extended to the cross-coupling of organic halides or triflates and vinylic epoxides or oxetanes. We shall report on this chemistry shortly.

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Entry	Azetidinone	Arī	Procedure	HCO ₂ Na Equiv.	Time (days)	3-Alkenamide	% Yield	E/Z Ratio
		XC6H41				CH3 XC6H4CH2CH=CCH2CONH2		
-004	> :	X = <i>o</i> -MeO X = <i>p</i> -Me X = <i>p</i> -COMe X = <i>p</i> -CO ₂ Et	£8 18 18 18 18 18 18 18 18 18 18 18 18 18	γγ 1 − − −			3288	60:40 66:34 63:37 60:40
		XC ₆ H4I				XC6H4CH2CH=CHCH2CONH2		
165	>	X = H $X = \rho - MeO$ $X = p - CO_{2}Et$	~~ ~	<u></u> У О –	36		73 74 11	80:20 a 83:17 b 85:15 b
00	H-N O 3	C ₆ H ₅ I	A	ŝ	Ľ	сн ₅ с ₆ н ₅ снсн=снсн ₂ соин ₂	43	91:9
6	H N N V V		¥	Ś	٢	CH3 C6H5CH2C=CCH2CONH2 CH3	z	60:40
10			۲	Ŷ	1	СН ₃ С ₆ Н ₃ (СН ₃)2СН=ССН ₂ СОNH ₂	82	57:43
Ħ			A	S	5	C ₆ H ₅ (CH ₂) ₉ CH=CHCH ₂ CONH ₂	42	82:18
a A 3:1	ratio of azetidinone to aryl l	halide was used.	b A 2:1 ratio	of azetidin	one to aryl l	alide was used.		

Table I. Palladium-Catalyzed Cross-Coupling of Aryl Iodides and 4-Alkenyl-2-azetidinones

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REFERENCES

- (a) Larock, R. C. Comprehensive Organic Transformations; VCH Publishers, Inc.: New York, 1989; pp 123-124.
 (b) Marshall, J. A. Chem. Rev. 1989, 89, 1503.
 (b) Larock, R. C.; Ilkka, S. J. Tetrahedron Lett. 1986, 27, 2211.
 (c) Miyaura, N.; Tanabe, Y.; Suginome, H. J. Organomet. Chem. 1982, 233, C13.
 (d) Echavarren, A. M.; Tueting, D. R.; Stille, J. K. J. Am. Chem. Soc. 1988, 110, 4039.
 (e) Tueting, D. R.; Echavarren, A. M.; Stille, J. K. Tetrahedron 1989, 45, 979.
- (2) (a) Larock, R. C.; Stolz-Dunn, S. K. Tetrahedron Lett. 1988, 29, 5069. (b) Larock, R. C.; Stolz-Dunn, S. K. Synlett 1990, 341.
- (3) (a) Moriconi, E. J.; Meyer, W. C. J. Org. Chem. 1971, 36, 2841. (b) Durst, T.; O'Sullivan, M. J. J. Org. Chem. 1970, 35, 2043. (c) Moriconi, E. J.; Meyer, W. C. Tetrahedron Lett. 1968, 3823.
- (4) Larock, R. C.; Ding, S. Tetrahedron Lett. 1989, 30, 1897.
- (5) Larock, R. C.; Leung, W.-Y. J. Org. Chem. 1990, 55, 6244.
- (6) (a) Helquist, P. Tetrahedron Lett. 1978, 1913. (b) Pri-Bar, I.; Buchman, O. J. Org. Chem. 1986, 51, 734. (c) Cortese, N. A.; Heck, R. F. J. Org. Chem. 1977, 42, 3491. (d) Pandey, P. N.; Purkayastha, M. L. Synthesis 1982, 876.
- (7) See reference 5 and references therein for other recent synthetic procedures employing palladium migration chemistry.

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