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SYNTHESIS OF β,γ-UNSATURATED AMIDES VIA PALLADIUM-PROMOTED COUPLING OF ORGANOMERCURIALS AND VINYLIC β-LACTAMS

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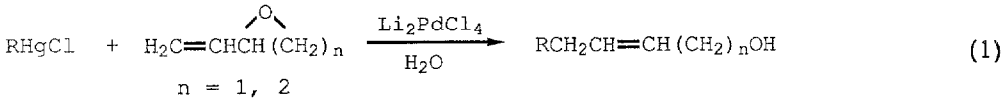
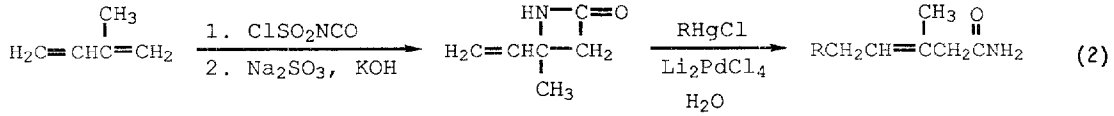
Summary. The reaction of aryl or vinylic mercurials, Li_2PdCl_4 and vinylic β-lactams affords good yields of the corresponding ring-opened β,γ-unsaturated amides.

The organometallic S_N2' ring opening of three- and four-membered ring vinylic oxygen heterocycles provides a useful route to a variety of functionally-substituted alkenes. Organomercurials have recently proven valuable in such processes. For example, we have reported that the palladium-catalyzed ring opening of vinylic epoxides[1] and oxetanes[2] provides a convenient route to allylic and homoallylic alcohols respectively (eq. 1). The success of



(1)

these endeavors and the ready availability of vinylic β-lactams via chlorosulfonyl isocyanate addition to 1,3-dienes[3,4] encouraged us to examine the palladium-promoted coupling of these substrates and organomercurials (eq. 2). To our knowledge, the organometallic ring opening of



(2)

such nitrogen heterocycles has never been reported. Our foremost concern upon initiation of this project was that the β-lactam moiety might prove sufficiently unreactive that vinyl hydrogen substitution products, rather than ring-opened amides, would predominate.

We wish to communicate at this time the success of our efforts which are summarized in Table I. In general, we have been able to use reaction conditions virtually identical with those reported earlier for vinylic epoxides[1] or oxetanes.[2] Procedures either stoichiometric or catalytic in palladium chloride have been employed. The latter procedure tends to give somewhat lower yields than the former.

Arylmercurials generally give good to excellent yields in these reactions. Both electron-donating (Entries 9 and 10) and electron-withdrawing (Entries 11 and 12) groups are readily accommodated in these reactions and give comparable yields. Some slight variations in the general procedure are desireable in some of these reactions however. Thus, better yields have been obtained by omitting either the NH_4Cl (Entries 9 and 11) or the saturated aqueous NH_4Cl solution (Entry 12).

Vinylmercurials tend to give significantly lower yields of amides than arylmercurials. As with the analogous reactions of epoxides[1] and oxetanes,[2] the more sterically hindered the

TABLE I. SYNTHESIS OF β,γ-UNSATURATED AMIDES

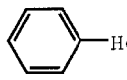
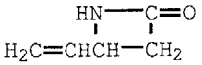
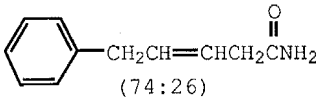
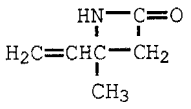
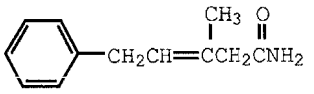
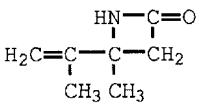
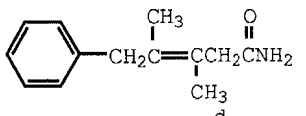
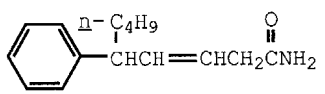
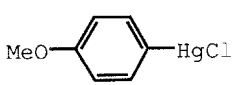
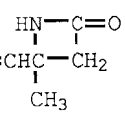
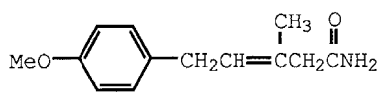
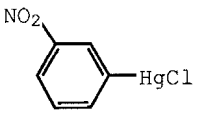
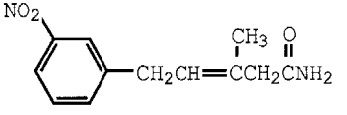
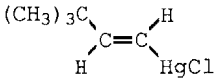
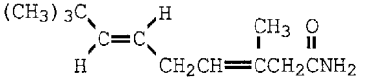
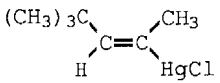
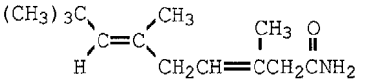
Entry	Organomercurial	β-Lactam	Li_2PdCl_4 Equivalents	Reaction Conditions[a]	Product[b] (*E*/*Z* ratio)	% Isolated Yield
1			1.0	0°C, 11 h; then RT, 3 h	 (74:26)	60[c]
2			0.1	0°C, 3 h; then RT, 24 h	(72:28)	57
3			1.0	0°C, 12 h; then RT, 2.5 h	 (52:48)	90
4			0.1	0°C, 2 h; then RT, 10 h	(49:51)	91
5			1.0	0°C, 12 h; then RT, 2 h	 (52:48)[d]	85
6			0.1	0°C, 3 h; then RT, 15 h	(83:17)[d]	41
7			1.0	0°C, 12 h; then RT, 24 h	 (95:5)	55
8			0.1	0°C, 1 h; then RT, 8 h[e]	*E* only	42
9			1.0	0°C, 6 h[f]	 (44:56)	77

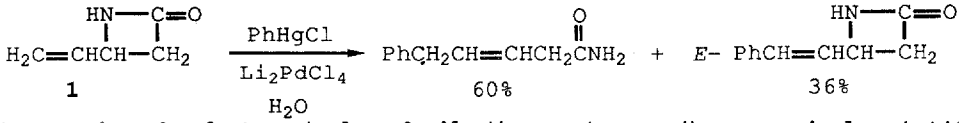
TABLE I. CONTINUED

Entry	Organomercurial	β-Lactam	Li_2PdCl_4 Equivalents	Reaction Conditions[a]	Product[b] (*E*/*Z* ratio)	% Isolated Yield
10			0.1	0°C, 12 h; then RT, 3 h	(50:50)	74
11			1.0	0°C, 6 h[f]	 (53:47)	79
12			0.1	RT, 8 h[g]	(48:52)	52
13			1.0	0°C, 11 h; then RT, 3 h	 (81:19)	34
14			1.0	0°C, 11 h; then RT, 5 h	 (68:32)	54
15			0.1	0°C, 2 h; then RT, 8 h[e]	(51:49)	35

[a]All reactions were run using $PdCl_2$ (0.50 or 0.05 mmol), LiCl (1.00 or 0.10 mmol), β-lactam (1.00 mmol), organomercurial (0.50 mmol), 12 ml of THF and 0.6 ml of saturated aqueous NH_4Cl solution unless otherwise specified. When 0.1 equivalents of Li_2PdCl_4 was employed, 0.50 mmol of anhydrous $CuCl_2$ was also added and the reaction was run under one atmosphere of oxygen. RT = room temperature. [b]All new compounds gave correct ^{13}C and ^1H NMR, IR and exact mass or combustion analysis data. [c]A 36% yield of 4-*E*-styrylazetidinone was also obtained. [d]Stereochemistry established by 2D NOESY ^1H NMR spectroscopy. [e]1.00 mmol of $CuCl_2$ used instead of 0.50 mmol. [f]0.6 Ml of H_2O used instead of 0.6 ml of saturated aqueous NH_4Cl. [g]No H_2O or saturated aqueous NH_4Cl solution used.

vinylmercurial, the higher the yield of amide product (Entries 13 and 14). No product was even observed when *E*-1-hexenylmercuric chloride was employed in the procedure using stoichiometric amounts of palladium. In general lower yields were obtained when the catalytic procedure was employed with vinylmercurials (Entry 15). These difficulties are presumably due to the facile dimerization of the less hindered vinylmercurials to 1,3-dienes.[5,6]

A wide variety of substituted β-lactams are available from 1,3-dienes and chlorosulfonyl isocyanate[3,4] and all lactams that we have examined have afforded good yields of ring-opened amide products. As expected, best results are obtained from β-lactams bearing terminal double bonds, but even reactions with β-lactams containing internal disubstituted double bonds (Entries 7 and 8) afford respectable yields. It is noteworthy that the simplest unsubstituted β-lactam employed (Entry 1) gave significant amounts of vinyl hydrogen substitution product (eq. 3). The failure to observe analogous side products with vinylic oxetanes suggests that

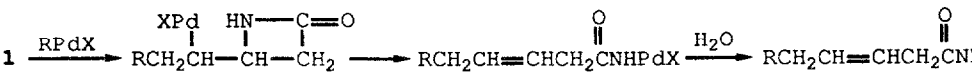


(3)

the ring-opening of β-lactams is less facile than oxetanes. However, simple substitution of a methyl group on the lactam ring (Entry 3) gives an excellent yield of ring-opened amide and no substitution products. The regioselectivity of the organopalladium addition to internal double bonds is apparently quite high, since no products arising from addition of the aryl group next to the nitrogen moiety have ever been observed.

The stereoselectivity of these reactions is virtually identical to that observed in the corresponding vinylic oxetane[2] reactions. Amide products bearing disubstituted double bonds are formed from β-lactams with terminal double bonds with an *E*/*Z* preference of about three to one (Entries 1 and 2), but disubstituted olefinic lactams give almost exclusively the *E*-disubstituted product (Entries 7 and 8). There is no selectivity in the formation of trisubstituted alkenes from arylmercurials (Entries 3, 4 and 9-12), but vinylmercurials afford reasonable selectivity when the procedure stoichiometric in palladium is employed (Entries 13 and 14). Even tetrasubstituted alkene products can be formed from these reactions and reasonable stereoselectivity has been observed using the procedure catalytic in palladium (Entries 5 and 6).

Mechanistically, we believe these reactions proceed as described earlier for the analogous epoxide[1] and oxetane[2] reactions (eq. 4).



(4)

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