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Stereoselective Intramolecular Aminocarbonylation of 3-Hydroxypent-4-enylamides Catalyzed by Palladium

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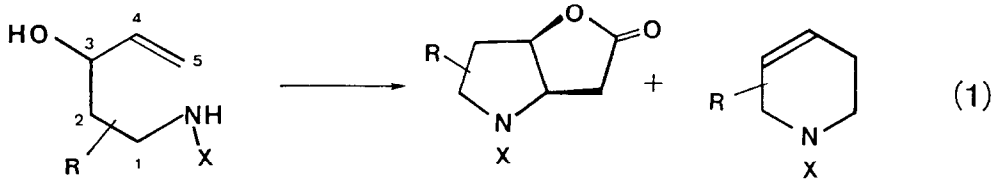
Summary: The urethanes and tosamides of 3-Hydroxypent-4-enylamine and its C_1 - C_4 substituted derivatives undergo the palladium catalyzed intramolecular aminocarbonylation (0.1 equiv of $PdCl_2$, 3.0 equiv of $CuCl_2$, 3.0 equiv of NaOAc in acetic acid under ca. 1 atm of CO) to give selectively cis 3-hydroxypyrrolidine 2-acetic acid lactone and its C_2 - C_5 substituted derivatives in good yields (66 - 90%), respectively.

In these years, a variety of methodologies has been developed for the syntheses of the stereochemically defined multi-functionalized pyrrolidines, owing to their utility as the key intermediates for the many physiologically interesting alkaloid syntheses. 1,3-Dipolar addition,[1] intramolecular Diels-Alder reaction,[2] acyliminium[3] or acylimino radical[4] mediated cyclization, aza-Cope rearrangement[5] and intramolecular haloamidation[6] are typical. Transition metal chemistry has also played an important role in this field.[7,8]

We now report a very efficient and stereoselective intramolecular aminocarbonylation of 3-hydroxypent-4-enylamides $\underset{\sim}{1}$[9] catalyzed by palladium, which provides cis 3-hydroxypyrrolidine 2-acetic acid lactones $\underset{\sim}{2}$ in good yields (eq 1). Judging from the limited success in the aminocarbonylation of 4-pentenylamides catalyzed or assisted (stoichiometric) by palladium,[8a,c,e] the present high yield and cis-selective[6] aminocarbonylation seem to owe its success to the allylic hydroxyl group. The products $\underset{\sim}{2}$, not only share the partial structure with many interesting alkaloids (e.g., anisomycin $\underset{\sim}{4}$,[10] retronecine $\underset{\sim}{5}$,[3c,11] slaframine $\underset{\sim}{6}$[12]), but also are assembled with functionalities desirable for the further manipulations. Indeed the parent $\underset{\sim}{2}$ (R = H) has been utilized for the syntheses of many pyrrolizidine alkaloids.[13]

The aminocarbonylation is highly solvent dependent. In dry THF, $\underset{\sim}{1}$ (R = H, X = CO_2Me) and $PdCl_2(CH_3CN)_2$ (2 equiv) under CO (a balloon) forms a copious purple precipitate. Addition of triethylamine (4 equiv) in four portions at 10 min intervals at 0°C, evaporation of the solvent and subsequent purification by column chromatography yielded $\underset{\sim}{2}$ in 50% yield. By the use of 1 equiv of $PdCl_2(CH_3CN)_2$ the reaction was incomplete and a 1:1 mixture of $\underset{\sim}{1}$ and $\underset{\sim}{2}$ resulted. In dry methanol, no amine bases were required to promote the reaction. Thus, stirring a mixture of $\underset{\sim}{1}$ (R = H, X = SO_2Tol) and $PdCl_2$ (1 equiv) in

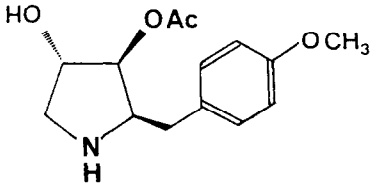


1 2 3 (1)

Table I Stereoselective Intramolecular Aminocarbonylation of 1

entry	starting material 1	reaction conditions[a]	% yield[b] 2	3
1	1a: R = H, X = CO_2Me	A, 1 day	35	24
2	1a: R = H, X = SO_2Tol	A, 1 day	37[c]	43
3	1a: R = H, X = SO_2Tol	B, 1 day	90	0
4	1b: R = 1-Ph, X = SO_2Tol[d]	B, 2 days	80[e]	0
5	1c: R = 2-Me, X = SO_2Tol[f]	B, 1 day	70	g
6	1d: R = 2-Me_2, X = CO_2Me	A, 1 day	70	g
7	1e: R = 3-Me, X = SO_2Tol	B, 1 day	66	30
8	1f: R = 4-Me, X = SO_2Tol	B, 2 days	no reaction	
9	1f: R = 4-Me, X = CO_2Me	B, 3 days	80[h]	0

a) Conditions A: 1 (1 mmol), $PdCl_2$ (0.1 mmol), $CuCl_2$ (3 mmol) in 5 mL of dry methanol at room temp. under CO (a balloon). Conditions B: 1 (1 mmol), $PdCl_2$ (0.1 mmol), $CuCl_2$ (3 mmol), AcONa (3 mmol) in 5 mL of acetic acid at room temp. under CO (a balloon).
b) Yields are for the isolated pure material. All the products were fully characterized spectroscopically (IR, ^1H, ^{13}C NMR and high resolution mass specta)
c) Small amount (ca. 7%) of ester, whose structure was tentatively assigned as trans 1-toluenesulfonyl-2-methoxycarbonylmethyl-3-hydroxypyrrolidine, was isolated.
d) 1-(R)*,3-(S)* isomer was used: Jäger, V.; Baß, V.; Schwab, W. Tetrahedron Lett. 1978, 3133.
e) Based on 93% conversion.
f) Diastereomeric mixture (1:1) was used.
g) Less than 5% of 3 may be formed.
h) Based on 35% conversion.



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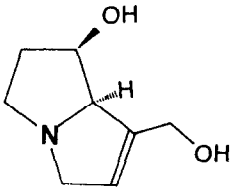

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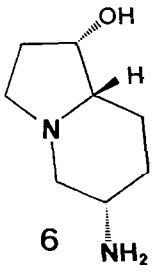

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methanol at room temp. under CO for 1 day furnished 2 in a quantitative yield. The reaction can be catalytic with respect to Pd. A mixture of 1, $PdCl_2$ (0.1 equiv) and $CuCl_2$ (3 equiv) was stirred in dry methanol at room temp. under CO for 1 day (conditions A). In this case, however, a substantial amount of tetrahydropyridine 3 was produced together with 2 (entries 1 and 2 in Table I). In acetic acid, the formation of 3 could be significantly suppressed. Thus, a heterogeneous mixture of 1 (R = H, X = SO_2Tol), $PdCl_2$ (0.1 equiv), $CuCl_2$ (3 equiv), and AcONa (3 equiv) in acetic acid was stirred under CO at room temp. for 1 day (conditions B). Evaporation of the solvent in vacuo and purification by column chromatography over silica gel provided 2 in 90% yield (entry 3).

In Table I are summarized the results of aminocarbonylation of 1 with a variety of C_1 - C_4 substituents. It seems pertinent to give some comments about the substituent effects on the reaction. Even under the conditions A, the 2,2-dimethyl derivative 1d selectively underwent the cyclization to give 2 (entry 6). This high selectivity (2 vs. 3) may be ascribed to the buttressing[14] of these methyl groups. The exceptionally high proportion of 3 in the reaction of 1e may be due to the high leaving ability of the quarternary hydroxyl group (via a π-allylpalladium or allyl cation intermediate, entry 7). Usually urethanes and tosamides gave parallel results (cf. entries 1 and 2). However, the very contrasting results were obtained in the case of 1f (entries 8 and 9). The tosylamide was unreactive and recovered completely, while the urethane underwent cyclization to give 2 selectively, though rather sluggishly (35% conversion, 3 days).

The present method is widely applicable to other systems. For instance, under the similarly mild conditions, 4-penten-1,3-diols[15] and 3-hydroxy-4-pentenoic acids were converted to cis 3-hydroxytetrahydrofuran 2-acetic acid lactones and bis-lactones, respectively. Details and applications to natural product synthesis will be reported shortly.[16]

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