Pergamon

Tetrahedron Letters, Vol. 38, No. 6, pp. 1057-1060, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(96)02511-7

Palladium-Catalyzed Cyclization of 2-Heteroyl-1-Methylene-1,2,3,4-Tetrahydroisoquinolines. Studies on 6-endo- versus 5-exo-trig Cyclization.

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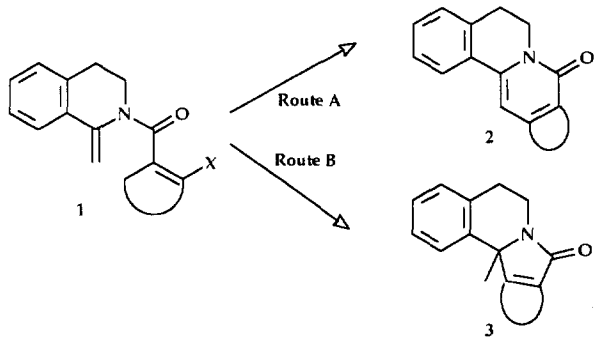
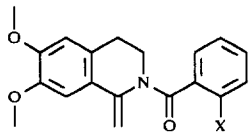
Abstract: In this paper we report our studies on 6-endo- versus 5-exo-trig cyclizations of 2-heteroyl-1-methylene-1,2,3,4-tetrahydroisoquinolines. This can be used for the construction of a variety of functionalized five- or six-membered heterocyclic rings.

During the syntheses of oxoberberine alkaloid derivatives, the Heck cyclization[2] of 2-heteroyl-1-methylene-1,2,3,4-tetrahydroisoquinolines **1** led to formation of products **2** and **3** (Scheme 1). In this communication we wish to report experimental conditions that favor regiocontrolled intramolecular cyclization of various aryl halides onto proximate double bonds of enamides of general formula **1**. We observed excellent regiocontrol in a thiophene serie while providing evidence for the mechanism of formation of the five-membered ring.

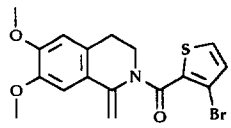


Scheme 1

Previous work of Grigg[3] on the cyclization selectivity of intermediate vinyl palladium species onto neighbouring alkenes showed that 2-aroyl-1-methylene-1,2,3,4-tetrahydroisoquinolines undergo a six-endo-trig cyclization (Route A) using a catalyst system containing palladium acetate (10 mol%), triphenylphosphine (20 mol%), tetraethylammonium chloride (1 equiv.) and potassium carbonate (2 equiv.). However addition of a hydride source leads preferentially to the formation of five-membered ring products (Route B). Using this background, we investigated the scope of the 6-endo- versus the 5-exo-trig cyclizations of heterocyclic derivatives such as **4a-b**, **5** and **6**.



4a, X = I
4b, X = Br



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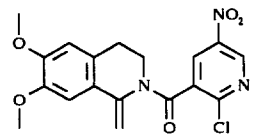
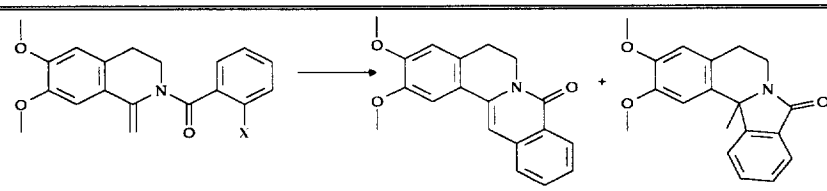


6

Enamides **4a-b**, **5** and **6** were obtained by treating a solution of commercially available 1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline in methylene chloride with the appropriate acid chloride in the presence of TEA at room temperature. Using the classical catalyst system (10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, 1 equiv. Et_4NCl, 2 equiv. K_2CO_3), enamides **4a-b** gave the 6-membered ring product (entry 1, table 1). Attempted palladium-catalyzed 5-exo-trig cyclization using known methods of addition of hydride (entry 2-3, table 1) gave poor regioselectivity. The bromide derivative **4b** (entry 3, table 1) gave a slightly better regioselectivity. Using formic acid and piperidine in a variable amount did not favor the formation of the 5-membered ring (entry 4, table1).

Table 1. Cyclization of 2-(2-halobenzoyl)-1-methylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines.[4]



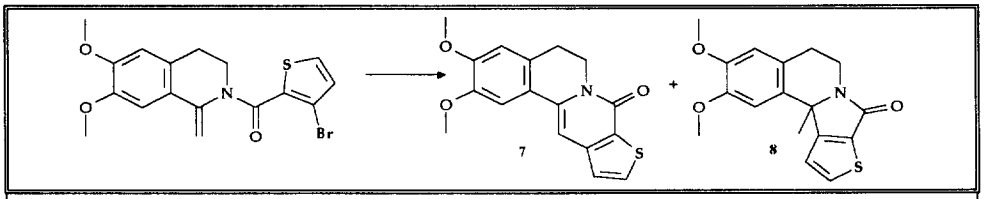
Entry	X	Catalyst system	Solvent	Yield (%)	6-endo *vs* 5-exo*
1	I, Br	10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, 2 equiv. Na_2CO_3, Et_4NCl	CH_3CN	68	99:1
2	I	10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, 5 equiv. HCO_2Na, 5 equiv. Et_4NCl	CH_3CN	84	40:60
3	Br	10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, 5 equiv. HCO_2Na, 5 equiv. Et_4NCl	CH_3CN	80	30:70
4	I	10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, HCO_2H, piperidine	CH_3CN	55	50:50

*The product ratio was calculated from integrals of ^1H NMR spectra of the crude products.

More interestingly, the regiochemistry of the intramolecular Heck reaction of thiophene derivatives was easier to control. When compound **5** was submitted to the classical catalyst system in acetonitrile, formation of the 6-membered ring was observed (entry 1, table 2). Using DMF as solvant and omitting the phosphine ligand gave the same regioselectivity with a slightly better yield (entry 2, table 2). Using a simple mixture of Pd(II) and PPh_3 as the catalyst system and switching to THF as solvent gave a better yield (entry 3, table 2) but with an unexpected favorable formation of the 5-membered ring. Addition of an hydride source gave the 5-membered ring with an excellent regioselectivity (entry 4-5, table 2). Again, in our hands the use of piperidine gave a poor yield (entry 5, table 2).

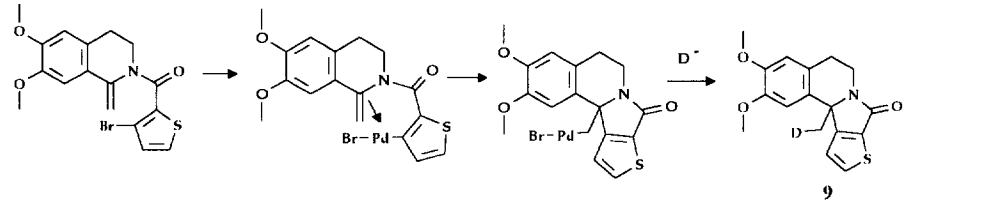
Since the regiochemistry of the cyclization of compound **5** could be well controlled, it was interesting to explore the formation of the 5-membered ring. It is well established that in the Heck reaction a Pd-R moiety is usually formed *in situ* by oxidative addition of an aryl halide to a Pd(0) complex. It adds to the olefin via a *cis* olefin-Pd-R and can undergo either a 6-endo-trig cyclization (Route A) to yield, after β-hydride elimination, compound **7**, or a 5-endo-trig cyclization. In the latter case, in the presence of a hydride source, the lack of a β-hydrogen yields compound **8**. We have used deuterated sodium formate as the hydride source (Scheme 2) and observed the exclusive formation of compound **9**. The analysis of compound **9** by ^{1}H NMR in $CDCl_3$ showed a methyl signal at δ1.7 ppm which integrates for only 2H.

Table 2. Cyclization of 2-(3-bromo-2-thienoyl)-1-methylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline.[4]



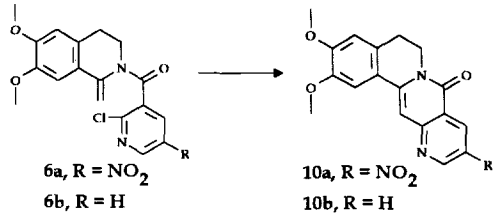
Entry	Catalyst system	Solvent	Yield (%)	6-exo *vs* 5-endo *
1	10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, 3.5 equiv. Na_2CO_3, Et_4NCl	CH_3CN	47[#]	99:1
2	10 mol% $Pd(OAc)_2$, 3.5 equiv. Na_2CO_3, Et_4NCl	DMF	55[#]	99:1
3	10 mol% $Pd(OAc)_2$, 20 mol% PPh_3,	THF	80	30:70
4	10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, 1.1 equiv. HCO_2Na, 1.1 equiv. Et_4NCl	CH_3CN	62[#]	>4:96
5	10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, HCO_2H, piperidine	CH_3CN	31[#]	>4:96

*The product ratio was calculated from integrals of ^{1}H NMR spectra of the crude products.
[#]The yield was calculated after purification via radial chromatography.



Scheme 2

Cyclization of pyridine halides such as compound **6** turned out to be more difficult. Using the classical catalyst system[4], only 40% of the 6-membered ring **10a** could be obtained (Scheme 3). When the pyridine ring does not bear an electron-withdrawing substituent such as a nitro group, the intramolecular Heck reaction was not successful but photocyclization can circumvent this problem.[5]



Scheme 3

In conclusion, intramolecular Heck cyclization of heterocyclic enamides can be regiocontrolled especially in a thiophene series. This work complements the extensive results of Grigg and the results of Ninomiya[6] and Lenz[7] on photocyclization.

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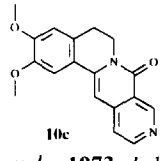
4. Procedure of cyclization (entry 1, table 1): a mixture of enamide and catalyst system in dry solvent was boiled under reflux for 2-12 hours. After completion of the reaction the solvent was evaporated *in vacuo*. The residue was extracted with dichloromethane. After washing with a saturated aqueous solution of ammonium chloride, the combined organic extracts were dried over sodium sulfate and concentrated.
5. Irradiation of a solution of 6,7-dimethoxy-1-methylene-2-(3-pyridinoyl)-1,2,3,4-tetrahydroisoquinoline in degassed methanol with a mercury lamp gave **10b** (^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.8 (dd, J = 5.0, 2.0 Hz, 1H), 8.6 (dd, J = 8.0, 2.0 Hz, 1H), 7.28 (m, 1H), 7.26 (s, 1H), 7.1 (s, 1H), 6.7 (s, 1H), 4.2 (tr, 2H), 3.9 (s, 3H), 3.85 (s, 3H), 2.9 (tr, 2H)) with **10c** (^{1}H NMR ($CDCl_3$, 250 MHz) δ 9.5 (s, 1H), 8.55 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.2 (s, 1H), 6.7 (d, 2H), 4.2 (tr, 2H), 3.9 (s, 3H), 3.85 (s, 3H), 2.9 (tr, 2H)).



10c

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(*Received in France* 13 *November* 1996; *accepted* 20 *December* 1996)