ORGANIC LETTERS

2007
Vol. 9, No. 15
2815−2818

Regio- and Stereoselective Heck Arylations of *N*-Carbomethoxy-L-3-Dehydroproline Methyl Ester with Arenediazonium Salts. Total Synthesis of Neuroexcitatory Aryl Kainoids

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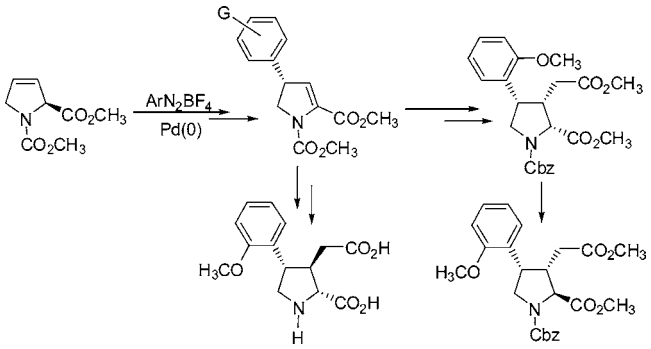
Received April 30, 2007

ABSTRACT



The Heck arylation of *N*-carbomethoxy-L-3-dehydroproline methyl ester with arenediazonium tetrafluoroborates produced chiral 4-aryldehydroproline derivatives in moderate to good yields in a highly regio- and stereocontrolled fashion. A rationale for the unexpected high regioselectivity is provided using Deeth's model. Heck adduct 15 (G = *o*-CH_3O) was converted into several aryl kainoids using concise and efficient routes.

The C−C coupling reactions promoted by palladium are pivotal constructive methodologies in modern organic synthesis.[1] The Heck arylation holds a prominent position in synthesis due to its exceptional versatility.[2] Of the many electrophiles available, the arenediazonium salts are probably the least explored ones in spite of some synthetic advantages.[3] Recently, we have shown that the Heck arylation of 3-pyrrolines using arenediazonium salts opens up opportunities in synthesis. For example, the synthesis of Rolipram, a selective phosphodiesterase IV inhibitor, was synthesized in 66% overall yield in three steps from 3-pyrroline in multigram scale.[4]

Encouraged by these results, we decided to extend this methodology to the versatile building block L-3-dehydroproline. However, to the best of our knowledge, there was no previous report for the Heck reaction on this nonactivated olefin. The closest precedents we have found were the Heck arylation of aminobutenols reported by Crisp and the recent intramolecular Heck reaction of 3-dehydroprolinol reported by Evans.[5]

(1) (a) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.: Wiley: Hoboken, NJ, 2002. (b) *Palladium Reagents and Catalysis*; Tsuji, J., Ed.; Wiley: Chichester, UK, 1995.

(2) (a) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2005**, *61*, 11771. (b) Tietze, L.; Ila, H.; Bell, H. P. *Chem. Rev.* **2004**, *104*, 3453.

(3) For a review of Pd-catalyzed cross-coupling reactions using diazonium salts, see: Roglans, A.; Pla-Quintana, A.; Moreno-Mañas, M. *Chem. Rev.* **2006**, *106*, 4622.

(4) Garcia, A. L. L.; Carpes, M. J. S.; Montes de Oca, A. C. B.; Santos, M. A. G.; Santana, C. C.; Correia, C. R. D. *J. Org. Chem.* **2005**, *70*, 1050.

10.1021/ol070980t CCC: $37.00
Published on Web 06/23/2007

Therefore, our objectives from the onset of this study were the evaluation of this Heck reaction as well as from the regio- and stereocontrol of the arylation process. On the synthetic standpoint, the Heck protocol would allow access to 4-arylprolines **1** (organic catalysts) and to complex aryl kainoids (Figure 1).[6]

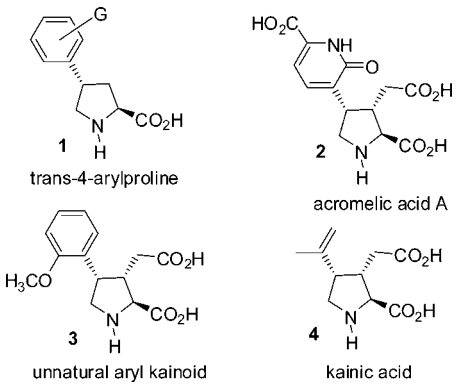
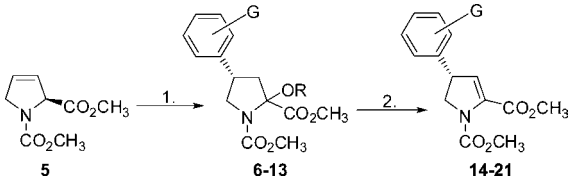


Figure 1. Examples of kainoid compounds.

Aryl kainoid **3** displays potent activity as a neuroexcitatory neurotransmitter related to kainic acid **4**, an important glutamate derivative often used as a pharmacological probe.[7] Acromelic acid **2** and aryl kainoid **3** display neurotoxic activity several times stronger than that of the kainic acid itself.[6a−c]

We began with the arylation of *N*-carbomethoxy-L-3-dehydroproline methyl ester **5** using several arenediazonium salts to test the feasibility of the intended protocol. Dehydroproline **5** was prepared in multigram scale from *trans*-4-hydroxyproline as described by Wong (61% yield over four steps).[8] Bearing in mind our previous results with 3-pyrroline, these reactions were devised as a two-step process (Table 1).[4] The first step consisted of the Heck arylation of dehydroproline **5** to the corresponding 4-aryl-2-hydroxy- or the 4-aryl-2-methoxyprolines (adducts **6a** to **13b**, Table 1). The second step encompassed the dehydration/methanol elimination to reconstruct the primary Heck adducts **14**−**21**.

Table 1. Synthesis of 4-Arylprolines from Dehydroproline 5[a]



entry	G	protocol	yield[b]	time (h)[d]	overall yield (%)[e]
1	4-OMe	A	nd (**6a**)[c]	4	60 (**14**)
2	2-OMe	A	nd (**7a**)[c]	4	65 (**15**)
3	4-OMe	B	86 (**6b**)	18	61 (**14**)
4	2-OMe	B	92 (**7b**)	12	82 (**15**)
5	4-Cl	B	95 (**8b**)	4	85 (**16**)
6	4-Br	B	70 (**9b**)	5	45 (**17**)
7	4-F	B	55 (**10b**)	18	0[f] (**18**)
8	4-NO_2	A	35 (**11a**)	4	10[g] (**19**)
9	4-NO_2	B	62 (**11b**)	4	15[g] (**19**)
10	3,4-Cl_2	B	61 (**12b**)	3.5	25 (**20**)
11	3-NO_2	B	57 (**13b**)	5.5	38 (**21**)

[a] Reaction conditions. Protocol A: step 1: ArN_2BF_4, $Pd(OAc)_2$ (10 mol %), CH_3CN/H_2O/AcOH (6/3/1), 60 °C, 3−4 h; step 2: 2,6-lutidine, TFAA, toluene, 0 °C to rt, then reflux. Protocol B: step 1: ArN_2BF_4, $Pd(OAc)_2$ (10 mol %), CH_3OH, reflux, 4−18 h; step 2: NH_4Cl, 120−150 °C. [b] Yields refer to a mixture of diastereomers after purification. The letter refers to the type of R group in the Heck adducts, **a**: R = H; **b**: R = CH_3. [c] Yields for the Heck step not determined. Adducts were purified and submitted to dehydration. [d] Heck step only. [e] Yields for the 2-dehydroprolines **14**−**21** after purification. [f] Low conversion of **10b**, together with decomposition products. [g] Low conversion of **11b**.

Surprisingly, the conditions developed for the arylation of 3-pyrroline (2 mol % of $Pd(OAc)_2$ at 30 °C)[4] proved noneffective, leading to the recovery of dehydroproline **5** almost quantitatively. However, Heck arylations were effective at 60 °C, requiring an increase in the catalyst loading (10 mol %). After much experimentation, we found out that the Heck arylation of dehydroproline **5** can be carried out effectively with a variety of arenediazonium salts to provide the 4-aryl-2-hydroxy- or 4-aryl-2-methoxyproline derivatives (protocols A and B, Table 1). Interestingly, the use of base inhibits Heck arylation. The Heck reaction employing protocol A (CH_3CN/H_2O) works best in the presence of catalytic amounts of acetic acid to furnish the corresponding lactamols. Protocol B, employing methanol as solvent, was the most effective, furnishing the diastereomeric Heck addition products in higher yields and fewer side products. In spite of its advantages, methanol elimination proved to be a nontrivial step, due to some erratic results employing Shono's protocol[9] (NH_4Cl, 140−160 °C). Heck arylation using a mixture of $DMSO/H_2O$ also seemed to be a viable alternative, providing the expected lactamols in yields comparable to those obtained with CH_3CN/H_2O/AcOH. Attempts to perform the Heck arylation in anhydrous CH_3CN failed or resulted in very low yields of the desired Heck adducts. The Heck addition products 2-hydroxyprolines **6a**, **7a**, and **11a** were converted to the 4-aryl-2-dehydroprolines **14**, **15**,

(5) (a) Crisp, G. T.; Gebauer, M. G. *Tetrahedron* **1996**, *52*, 12465. (b) Evans, P. *J. Org. Chem.* **2007**, *72*, 1830. Evans attempts to carry out Heck arylation of a L-3-dehydroproline derivative yielded mainly 2-carboethoxy pyrrole.

(6) (a) Maeda, K.; Kadama, T.; Tanaka, T.; Yoshiziemi, H.; Takemoto, T.; Nomoto, K.; Fujita, T. *Chem. Pharm. Bull.* **1986**, *34*, 4892. (b) Shinozaki, H.; Ishida, M.; Okamoto, T. *Brain Res.* **1986**, *399*, 395. (c) Ishida, M.; Shinozaki, H. *Brain Res.* **1988**, *474*, 386. (d) For a review, consult: Parsons, A. F. *Tetrahedron* **1996**, *52*, 4149.

(7) (a) Itadami, S.; Takai, S.; Tanigawa, C.; Hashimoto, K.; Shirahama, H. *Tetrahedron Lett.* **2002**, *43*, 7777. (b) Ahmed, A.; Bragg, R. A.; Clayden, J.; Tchabanenko, K. *Tetrahedron Lett.* **2001**, *42*, 3407. (c) Bragg, R. A.; Clayden, J.; Bladon, M.; Ichihara, O. *Tetrahedron Lett.* **2001**, *42*, 3411. (d) Maeda, H.; Selvakumar, N.; Kraus, G. A. *Tetrahedron* **1999**, *55*, 943. (e) Maeda, H.; Kraus, G. A. *J. Org. Chem.* **1997**, *62*, 2314. (f) Baldwin, J. E.; Fryer, A. M.; Spyvee, M. R.; Whitehead, R. C.; Wood, M. E. *Tetrahedron Lett.* **1996**, *37*, 6923. (g) Hashimoto, K.; Shirahama, H. *Tetrahedron Lett.* **1991**, *32*, 2625. (h) Hashimoto, K.; Horikawa, M.; Shirahama, H. *Tetrahedron Lett.* **1990**, *31*, 7047.

(8) Lin, C.-C.; Shimazaki, M.; Heck, M.-P.; Aoki, S.; Wang, R.; Kimura, T.; Ritzen, H.; Takayama, S.; Wu, S.-H.; Weitz-Schmidt, G.; Wong, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 6826.

(9) Shono, T.; Matsumura, Y.; Inoue, K. *J. Chem. Soc., Chem. Commun.* **1983**, 1169.

and **19** according to a protocol developed in our laboratory.[10] These protocols provided the key 4-aryl-2-dehydroprolines **14**−**21** in overall yields ranging from 10 to 85% (Table 1).

Although some results still need optimization, several key features of these Heck arylations are noteworthy: (a) The protocols developed are base-free, and the arylations were actually carried out under acidic conditions. (b) The capture of the primary Heck adduct by water or methanol is apparently beneficial as it prevents conversion of the Heck products to the corresponding pyrroles. (c) Heck arylation occurred in a highly regio- and stereoselective manner, as single stereoisomeric 4-aryl-2-dehydroprolines **14**−**21** were obtained in optically active form in all cases. The absolute configuration at C-4 was assigned as *S* on mechanistic grounds, which was confirmed upon completion of the total synthesis of a known aryl kainoid **3**. (d) The high regioselectivity of the Heck arylation was unexpected since no clear bias for the exclusive arylation at C-4 was obvious when we initiated this study. (e) Heck arylations performed in methanol provided the Heck adduct in all cases, in moderate to excellent yields. (f) Heck arylations can be performed with arenediazonium salts bearing electron-withdrawing (EWG) or electron-donating substituents.

The overall yields for some 4-aryl-2-dehydroprolines were hampered due to experimental difficulties in performing methanol elimination using Shono's conditions (entries 7−9, Table 1).[11]

Although rationalization for the high stereoselectivity is straightforward, the reasons for the high regioselectivity are not. According to Deeth, the regiochemistry of the Heck reaction of monosubstituted alkenes is controlled mainly by the electronic nature of the double bond.[12] We hypothesize that, in analogy to Deeth's proposition, the regioselectivity is controlled by the electronic nature of the carbamate and carboalkoxy groups located at C-2. Both groups would act in synergy having an electronic influence similar to that displayed by a single EWG directly attached to the double bond.[13] A model for such putative TS is presented in Figure 2. The EWGs located at C-2 probably impart a negative

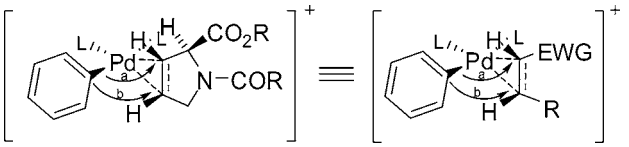


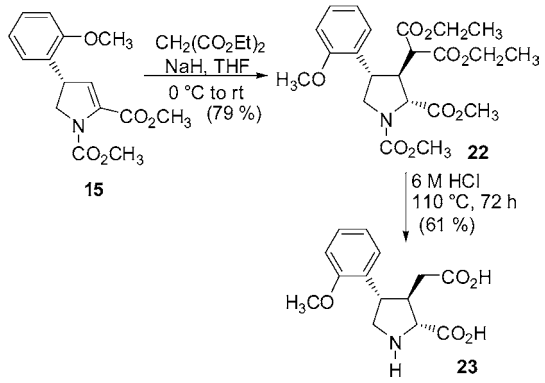
Figure 2. Rationale for the regioselectivity.

selectivity index (Ω)[12] to the system, favoring formation of the linear adduct (pathway b, arylation at C-4).

The 4-aryl-2-dehydroprolines **14**−**21** were envisioned as precursors for new prolines and aryl kainoids. In particular, the synthesis of the Heck aryl dehydroproline **15** (entries 2 and 4, Table 1) posed as a key starting material for the total synthesis of the neurotoxic aryl kainoid **3**. Additionally, the synthesis of this aryl kainoid would be instrumental to provide definitive evidence for the stereochemical assignments made for the Heck arylations described above, including its absolute stereochemistry.

We initiated the synthesis by preparing simpler aryl kainoids. The Heck adduct 4-(*o*-methoxyphenyl)dehydroproline **15** was obtained in a multigram scale from dehydroproline **5** in 82% yield (entry 4, Table 1). Following the protocol reported by Rubio and co-workers,[14] the 2-dehydroproline **15** underwent a smooth Michael addition reaction with sodium ethylmalonate to provide the all *trans* triester **22** in 79% yield (Scheme 1). Acidic hydrolysis (6 M HCl,

Scheme 1. Synthesis of the All *trans* Aryl Kainoid **23**



110 °C, 72 h) of the triester **22** followed by in situ decarboxylation and N-deprotection afforded the all *trans* (allo) aryl kainoid **23** in 61% overall yield. The *trans* relationship between H-2 and H-3 was secured on the basis of the chemical shift for H-2 at 4.08 ppm, as described by Shirahama.[15]

To obtain the C-3,C-4 *cis* configuration, we once again adopted a strategy similar to that reported by Rubio.[14] Deprotonation of intermediate **22** with LHMDS at 0 °C followed by addition of phenylselenyl bromide provided the phenylselenylated triester **24** in 72% yield (Scheme 2). Standard oxidative deselenylation of **24** with hydrogen peroxide in THF at 0 °C provided the desired tetrasubstituted unsaturated triester intermediate **25**, which proved unstable during purification. Therefore, to avoid losses, the intermedi-

(10) Oliveira, D. F.; Miranda, P. C. L.; Correia, C. R. D. *J. Org. Chem.* **1999**, *64*, 6446.

(11) At present, reaction conditions were optimized only for arenediazonium containing the *p*-OMe, *o*-OMe, and *p*-Cl.

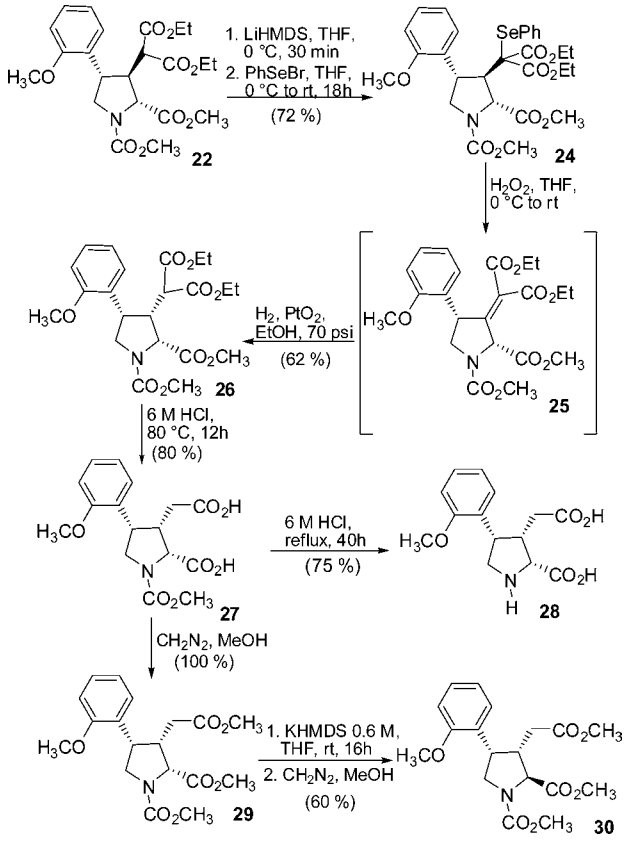
(12) Deeth, R. J.; Smith, A.; Brown, J. M. *J. Am. Chem. Soc*. **2004**, *126*, 7144.

(13) This assumption is precedented in the work of Deeth and co-workers (ref 12). It is also conceivable that such a model would explain the results obtained by Crisp and Evans (ref 5).

(14) (a) Ezquerra, J.; Escribano, A.; Rubio, A.; Remuiñán, M. J.; Vaquero, J. J. *Tetrahedron: Asymmetry* **1996**, *7*, 2613. (b) Ezquerra, J.; Escribano, A.; Rubio, A.; Remuiñán, M. J.; Vaquero, J. J. *Tetrahedron Lett.* **1995**, *36*, 6149.

(15) H-2 chemical shift for kainate **23** appears at δ 4.08 (d, ^3J = 7.8 Hz), suggesting a C-2, C-3 *trans* relationship, as described by Shirahama (ref 6b). The stereochemistry of the substituents at C-3 and C-4 can be established by the empirical rules proposed by Baldwin and Shirahama: (a) Baldwin, J. E.; Fryer, A. M.; Pritchard, G. J. *J. Org. Chem.* **2001**, *66*, 2597. (b) Hashimoto, K.; Konno, K.; Shirahama, H. *J. Org. Chem.* **1996**, *61*, 4685.

Scheme 2. Synthesis of Aryl Kainoids **27**−**30**

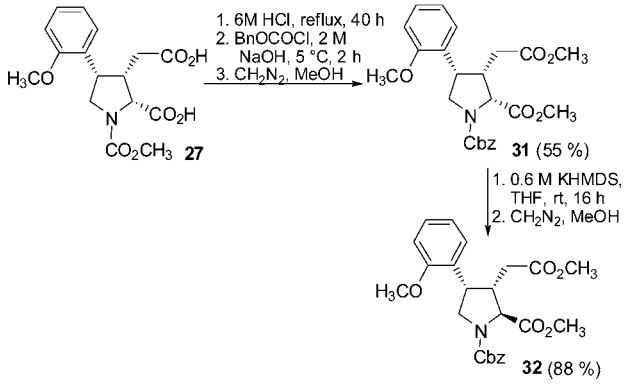


ate **25** was hydrogenated just after its preparation to provide the expected all *cis* triester aryl kainoid **26** in 62% yield over two steps. Gratifyingly, catalytic hydrogenation occurred with high stereoselectivity.

The triester intermediate **26** was then hydrolyzed under controlled acidic conditions to furnish the dicarboxylic acid **27** in 80% yield. Removal of the *N*-carbomethoxy group of **27** was accomplished employing more harsh acidic hydrolysis (6 N HCl, reflux, 40 h) to provide the amino acid **28** (75% yield). Alternatively, diacid **27** can be esterified with diazomethane to provide the all *cis* aryl kainoid diester **29** in 80% yield over two steps from **26**.[16] Epimerization at C-2 of diester **29** to the highly neuroexcitatory 2,3-*trans*-3,4-*cis* aryl kainoid **30** proceeded smoothly under the protocol developed by Mann.[17] Deprotonation of aryl kainoid **29** with KHMDS, followed by esterification with diazomethane of the incipient diacid, produced the desired C-2, C-3 *trans* epimer **30** in a moderate 60% yield.

The *N*-carbomethoxy aryl kainoids **29** and **30** constitute new compounds. Therefore, to confirm the stereochemical assignments made along the synthesis, *N*-carbomethoxy aryl kainoid **27** was converted to the known *N*-carbobenzyloxy derivatives **31** and **32**, previously reported by Shirahama and Kraus (Scheme 3). Kraus obtained both compounds in

Scheme 3. Synthesis of Aryl Kainoids **31** and **32**



racemic form,[7d,e] and Shirahama[7h] described the synthesis of **32** as an advanced chiral intermediate in the total enantioselective synthesis of the aryl kainoid **3**. The spectroscopic data obtained by us for compounds **31** and **32** were in full agreement with those reported in the literature. However, the critical specific rotation values for the aryl kainoids **31** and **32** were not available. Fortunately, the specific rotation value for compound **32** ($[\alpha]_D^{24}$ −36.6 (*c* 1.0, $CHCl_3$)) was kindly provided by Professor Kimiko Hashimoto (Kyoto Pharmaceutical University) which compared well with the value obtained by us ($[\alpha]_D^{24}$ −38.6 (*c* 0.7, $CHCl_3$)). These data combined confirm the absolute stereochemistry for aryl kainoid **30** as 2*S*, 3*S*, 4*S*, and also set the stereocenter for the Heck adduct **15** as 4*S*. By analogy, the stereogenic center present in **14**−**21** can also be attributed as 4*S*.

In summary, the Heck arylation of dehydroproline **5** was successfully accomplished employing several arenediazonium tetrafluoroborates to produce the (4*S*)-aryl-2,3-dehydroprolines **14**−**21** in yields ranging from 10 to 85%. These arylations were carried out with remarkable regio- and stereocontrol. The regioselectivity observed for these arylations is a striking example of regiocontrol for a nonactivated disubstituted alkene. The Heck adduct *o*-methoxyphenyl-2-dehydroproline **15** was employed as key starting material in the stereocontrolled total syntheses of the neurotoxic aryl kainoids **27**−**32**, in a few steps in good overall yields.

Acknowledgment. We thank FAPESP for financial support, and CNPq and CAPES for fellowships. We are also thankful to Dr. Katsuhiro Konno from Butantã Institute, Brazil, and Professor Kimiko Hashimoto, from Kyoto Pharmaceutical University, Japan, for their helpful assistance concerning the specific rotation value for the aryl kainoid **32**.

Supporting Information Available: General experimental procedures for the Heck arylations and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL070980T

(16) Attempts to perform hydrolysis under basic conditions led to a mixture of the all *cis* diester with its C-2 epimer in a 1:1 ratio.

(17) Klotz, P.; Mann, A. *Tetrahedron Lett.* **2003**, *44*, 1927.