Pergamon

Tetrahedron Letters 43 (2002) 741–744

TETRAHEDRON LETTERS

Heck arylations of *N*-acyl-3-pyrroline and *N*-acyl-1,2,5,6-tetrahydropyridine with aryldiazonium salts. Short syntheses of aryl γ- and δ-lactams, baclofen, homobaclofen and analogues

Marcos José S. Carpes and Carlos Roque D. Correia*

Instituto de Química, Universidade Estadual de Campinas, UNICAMP, C.P. 6154, CEP 13083-970, Campinas, São Paulo, Brazil

Received 19 November 2001; accepted 28 November 2001

Abstract—Heck arylation of *N*-acyl-3-pyrrolines and an *N*-acyl-tetrahydropyridine with aryldiazonium tetrafluoroborates under phosphine-free conditions proceeded smoothly to give α-hydroxycarbamates (hemiaminals) or α-alkoxycarbamates which were oxidized to the desired γ- and δ-lactams. Acidic hydrolysis of the γ-lactams produced a series of arylated GABA derivatives, including baclofen, a useful therapeutic drug, in only three steps with an overall yield of 63–76%. Starting from *N*-acyl-tetrahydropyridine, aryl-δ-lactams and higher homologues of baclofen can be obtained.

The Heck arylation reaction has a prominent place among the key organic reactions leading to the construction of C–C bonds.[1] This has been the result of an enormous effort in the last two decades to develop this versatile reaction promoted by catalytic Pd. Most of the Heck procedures call for the use of phosphines in order to stabilize the active Pd(0), in which cases oxygen-free conditions should be applied. Moreover, the amount of phosphine added should be carefully monitored to maintain reasonable rates of the catalytic cycle. Despite their critical role in catalytic asymmetric synthesis,[2] there are occasions when the use of phosphines is undesirable. For this reason, Heck reactions under conditions avoiding the use of phosphines (phosphine-free conditions) has been an area of intensive investigation and much synthetic interest, not only for its practical aspects, but also for its economics.[1a]

We have been exploring the Heck arylation of endocyclic enecarbamates and pyrrolines with aryldiazonium salts as a feasible alternative to introduce aryl substituents into pyrrolidine and piperidine rings. Aryldiazonium tetrafluoroborates are stable intermediates that have been used as effective electrophiles in a straightforward and phosphine-free Heck arylation protocol.[3] Despite the fact that Heck arylations of 3-pyrrolines and tetrahydropyridines were already described in the literature, these traditional Heck protocols employing aryl triflates and aryl iodides require large excesses of the olefin to ensure good yields of the arylated products and frequently lead to mixtures of arylated and isomerized Heck adducts.[4] Recently, we applied the Heck

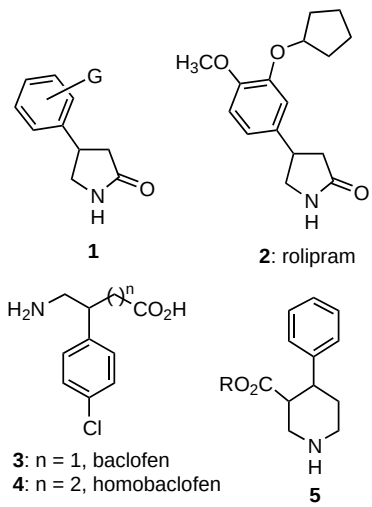


Figure 1.

* Corresponding author. Tel.: 55 019 7883086; fax: 55 019 7883023; e-mail: roque@iqm.unicamp.br

0040-4039/02/$ - see front matter
PII: S0040-4039(01)02267-5

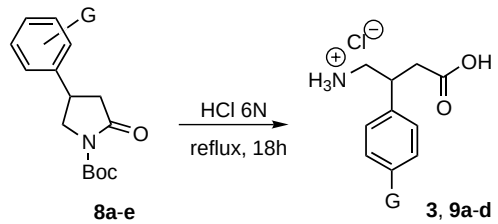
arylation of 3-pyrrolines and five-membered endocyclic enecarbamates with aryldiazonium salts for the construction of more elaborated 4-aryl enecarbamates[5] and the total stereoselective synthesis of the pyrrolidine alkaloid (−)-codonopsinine.[6] The Heck arylation using aryldiazonium salts were very fast, regioselective, and did not require an excess of the olefins to warrant good yields.

With the objective of extending this methodology to the synthesis of other pharmacological active compounds and to probe the scope of the Heck arylation with diazonium salts, we pursued the concise syntheses of (i) 4-aryl-γ-lactams, such as **1**, from which rolipram (**2**), a phosphodiesterase inhibitor used as an anti-asthma drugs is a representative example;[7] (ii) a short synthesis of the γ-amino acid baclofen **3**[8] and some aromatic analogues; (iii) the synthesis of the homobaclofen **4**, and (iv) the synthesis of aryl-δ-lactams that might be used as precursors to arylpiperidines (Fig. 1). Of particular interest was the short synthesis of baclofen, a $GABA_B$ receptor agonist used to treat spasms caused by spinal cord injuries and which shows some potential as treatment for cocaine addiction.[9] Arylpiperidines, such as **5**, has been attracting much attention due to its pronounced pharmacological activity as inhibitors of dopamine and serotonine reuptake systems, and constitutes a common pharmacophore to many active compounds, such as morphine, pentazocine, etc.[10]

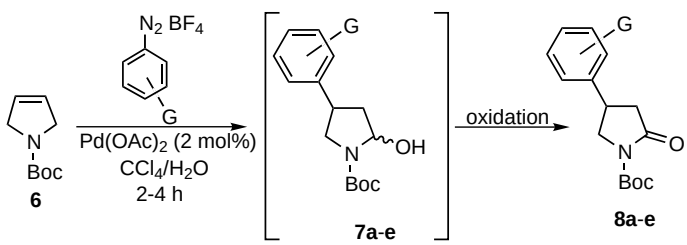
We started by preparing the known *N*-Boc-3-pyrroline **6** from the *N*-Boc-bisallyl amine according to the procedure of Grubbs in 80% yield.[11] The Heck arylation of 3-pyrroline **6** was carried out with several aryldiazonium tetrafluoroborates (Scheme 1) under three different conditions: (A) 2 mol% of $Pd(OAc)_2$ in aqueous acetonitrile; (B) 2 mol% of $Pd(OAc)_2$ in methanol or (C) 2 mol% of $Pd(OAc)_2$ in a biphasic system CCl_4/H_2O (1:1, v/v). The protocol using aqueous acetonitrile (1:1, v/v) was the most practical one providing slightly higher yields of the lactamols **7a–e**. To avoid losses during the purification process, the lactamols were directly oxidized using either (i) $RuCl_3/NaIO_4$ (G = NO_2, Cl); (ii) PCC (G = OMe, diOMe, naphthyl) or (iii) CrO_3/acetone (Jones reagent) to yield the corresponding arylated lactams **8a–e** in good overall yields (Table 1).

Oxidation employing $RuCl_3/NaIO_4$ or Jones' reagent (CrO_3/acetone) of lactamols **7a**, **7c** and **7e** led to lower yields of the corresponding lactams, probably due to partial oxidation of the electron-rich aromatic rings. Oxidation with pyridinium chlorochromate (PCC) in CH_2Cl_2 worked well for all lactamols **7a–e**, providing the corresponding lactams in good overall yields (75–90%), thus performing as our oxidant of choice in this study.

Preparation of the γ-amino acids from the arylated lactams was straightforward (Eq. (1)). Acidic hydrolysis (6N HCl/reflux) of the arylated lactams **8a–e** occurred smoothly to provide the corresponding γ-amino acids **3**, and **9a–d** in good yields (84–95%). This procedure permitted the synthesis of (±)-baclofen **3** and a number of new analogues bearing electron-withdrawing and electron-donating substituents in the aromatic ring (Table 2).



8a-e **3, 9a-d** (1)



Scheme 1.

Table 1. β-Aryl-γ-lactams from Heck arylation of *N*-Boc-3-pyrroline

Entry	Diazonium salt	Lactam (yield, %)[a]
1	G = 3,4-diOMe	**8a** (76)
2	G = 4-Cl	**8b** (75)
3	G = 4-OMe	**8c** (75)
4	G = 4-NO_2	**8d** (90)
5	2-Naphthyl	**8e** (70)[b]

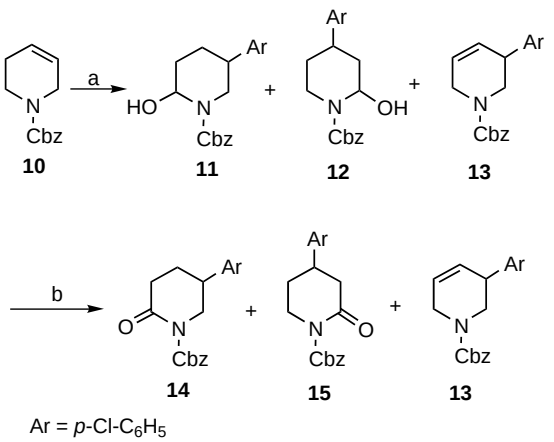
[a] Yield of purified compound over two steps.
[b] Reaction performed in CH_3CN/H_2O (1:1 ratio, v/v).

Table 2. γ-Amino acids (AA) from acidic hydrolysis of lactams **8a–e**

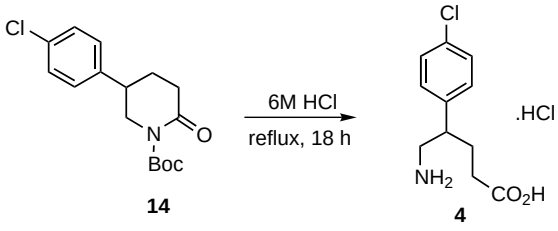
Entry	Diazonium salt	AA (yield, %)[a]
1	G = 3,4-diOMe	**9a** (86)
2	G = Cl	**3** (90)
3	G = OMe	**9b** (84)
4	G = NO_2	**9c** (85)
5	2-Naphthyl	**9d** (95)

[a] Yield of purified product.

With the underlining objective of comparing the Heck arylation of non-symmetrical double bonds with aryldiazonium salts, we also carried out an investigation into the Heck arylation of a tetrahydropyridine derivative as an alternative synthetic entry to arylpiperidines. Heck arylation of tetrahydropyridine substrates with aryl iodides were carried out previously by Hallberg and co-workers with quite interesting results and the basic idea here was to test how diazonium salts compare with aryl iodides as electrophiles.[12] We started our studies by converting the commercially available 1,2,5,6-tetrahydropyridine into the *N*-Cbz tetrahydropyridine **10** using standard procedures (Cbz-Cl, Et_3N, CH_2Cl_2, 90% yield). Heck arylation of tetrahydropyridine **10** with *p*-Cl-benzenediazonium tetrafluoroborate was then performed under conditions similar to those used for the Heck arylation of pyrroline **6** (Scheme 2). Thus, Heck arylation with $Pd(OAc)_2/CH_3CN–H_2O$ led to three products as analyzed by Cap. GC. Although these compounds could be separated by chromatography on silica gel, lactamol **11** and **12** proved rather unstable.[13] Therefore, the reaction mixture was directly oxidized after workup with tetrapropylammonium perruthenate (TPAP) to provide a mixture of lactams **14** and **15** together with a minor amount of the olfefinic compound **13** in an overall yield of 66% over the two steps. Compounds **14**, **15** and **13** were obtained in a ratio of 50:36:13 after flash chromatography. Lactams **14** and **15** are known compounds and both have been used as precursors to the synthesis of isomeric homobaclofens.[14]



Scheme 2. (a) $p\text{-}ClC_6H_4N_2BF_4$, 2 mol% $Pd(OAc)_2$, CH_3CN/H_2O (2:1 ratio, v/v); (b) TPAP, NMO, CH_2Cl_2, 4 Å MS (66% over two steps).



Scheme 3.

Acidic hydrolysis of the isolated major lactam **14**, carried out as applied for compounds **8a–e**, furnished homobaclofen **4** in 97% yield (Scheme 3).

The Heck arylation of 1,2,5,6-tetrahydropyridine **10** with diazonium salts was demonstrated to be milder than the one employing aryl iodides, did not require excess of the olefin to attain reasonable yields, but provided the Heck adduct in slightly lower yields than those reported by Hallberg and co-workers (72% yield).[12] An interesting aspect of the Heck arylation with diazonium salts was the overall regioselectivity of the process (1.7:1), very similar to the one reported by Hallberg. We made no attempts to obtain the six-membered enecarbamate directly from the Heck arylation with diazonium salts in view of their instability under acidic conditions. However, these enecarbamates can be easily obtained from the intermediate lactamols with the use of trifluoroacetic anhydride, as previously described by us.[5] Heck arylation of **10** using 2 mol% $Pd(OAc)_2$ in MeOH provided results similar to the ones described in Scheme 2, but contrary to the six-membered lactamols **11** and **12** the α-methoxy carbamates were quite stable.

In summary, Heck arylation of *N*-acyl pyrrolines with several aryldiazonium salts proceeded in a fast and exothermic process to competently produce the corresponding Heck adducts. In view of their instability these Heck α-hydroxy carbamates products were directly oxidized to the corresponding lactams in good overall yields. The key *p*-Cl-aryl-γ-lactam **8b** was effectively converted into the therapeutically valuable drug baclofen in a three-step process with an overall yield of 67% from pyrroline **6**. Heck arylation of tetrahydropyridine **10** followed by oxidation of the lactamol intermediates provided the corresponding *p*-Cl-phenyl-δ-lactams **14** and **15** in a 60% overall yield in a ratio of ~1.5:1. The major regioisomeric *p*-Cl-phenyl-δ-lactam **14** was converted to the 5-amino-4-(4-chlorophenyl)-pentanoic acid **4**, a higher homologue of baclofen. Compounds **3** (baclofen) and **4** (homobaclofen) were prepared in a concise manner using a new synthetic strategy. The synthesis of other γ-lactams (pyrrolidones) and δ-lactams are in progress in our laboratory.

Acknowledgements

This work was supported by a grant from the Research Supporting Foundation of the State of São Paulo (FAPESP 99/06566-7). We also thank CNPq and FAPESP for fellowships.

References

1. (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066; (b) Reetz, M. T. In *Transition Metal Catalyzed Reactions*; Davies, S. G.; Murahashi, S.-I., Eds.; Blackwell Science: Oxford, 1999; (c) Crisp, G. T.

Chem. Soc. Rev. **1998**, *27*, 427–436; (d) Link, J. T.; Overman, L. E. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: New York, 1998; (e) Brase, S.; de Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: New York, 1998; (f) Cabri, W.; Candiani, E. *Acc. Chem. Res.* **1995**, 28; (g) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *36*, 2379–2411.

2. (a) Shibasaki, M.; Vogl, E. M. *J. Organomet. Chem.* **1999**, *576*, 1–15; (b) Loiseleur, O.; Hayashi, M.; Keenan, M.; Schmees, N.; Pfaltz, A. *J. Organomet. Chem.* **1999**, *576*, 16–22; (c) Shibasaki, M.; Boden, D. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371–7397.
3. (a) Oliveira, D. F.; Severino, E. A.; Correia, C. R. D. *Tetrahedron Lett.* **1999**, *40*, 2083; (b) Brunner, H.; Courcy, N. C.; Genêt, J.-P. *Tetrahedron Lett.* **1999**, *40*, 4815; (c) Metha, G.; Sengupta, S. *Tetrahedron Lett.* **1996**, *37*, 8625; (d) Kikukawa, K.; Nagira, K.; Matsuda, T. *Tetrahedron* **1981**, *37*, 31.
4. (a) Sonesson, C.; Larhed, M.; Nyqvist, C.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 4756; (b) Sonesson, C.; Wikstrom, H.; Smith, M. W.; Svensson, K.; Carlsson, A.; Waters, N. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 241.
5. Carpes, M. J. S.; Correia, C. R. D. *Synlett* **2000**, 1037–1039.
6. Severino, E. A.; Correia, C. R. D. *Org. Lett.* **2000**, *2*, 3039–3042.
7. (a) Kleinman, E. F.; Campbell, E.; Giordano, L. A.; Cohan, V. L.; Jenkinson, T. H.; Cheng, J. B.; Shirley, J. T.; Pettipher, E. R.; Salter, E. D.; Hibbs, T. A.; DiCapua, F. M.; Bordner, J. *J. Med. Chem.* **1998**, *41*, 266–270; (b) Bacher, E.; Boer, C.; Bray-French, K.; Denmitz, F. W. J.; Keller, T. H.; Mazzoni, L.; Muller, T.; Walker, C. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3229–3234.
8. Bowery, N. E. *Trends Pharm. Sci.* **1982**, *31*, 400. For recent syntheses of baclofen, see: (a) Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **2000**, *2*, 4257–4259; (b) Baldoli, C.; Maiorana, S.; Licandro, E. *Tetrahedron: Asymmetry* **2000**, *11*, 2007–2014; (c) Resende, P.; Almeida, W. P.; Coelho, F. A. S. *Tetrahedron: Asymmetry* **1999**, *10*, 2113–2118; (d) Coelho, F. A. S.; de Azevedo, M. B. M.; Boschiero, R.; Resende, P. *Synth. Commun.* **1997**, *27*, 2455–2465.
9. (a) Ahmadi-Abhari, S. A.; Akhondzadeh, S.; Shabestari, O. L.; Farzanehgan, Z. M.; Kamlipour, A. *J. Clin. Pharm. Ther.* **2001**, *26*, 67–71; (b) Negus, S. S.; Mello, N. K.; Fivel, P. A. *Psychopharmacology* **2000**, *152*, 398–407.
10. (a) Tamiz, A. P.; Zhang, J.; Flippen-Anderson, J. L.; Zhang, M.; Johnson, K. M.; Deschaux, O.; Tella, S.; Kozikowski, A. P. *J. Med. Chem.* **2000**, *43*, 1215–1222; (b) Gringauz, A. *Introduction to Medicinal Chemistry. How Drugs Act and Why*; Wiley-VCH: New York, 1997; pp. 167–189.
11. This compound is commercially available, but it is expensive. However, its synthesis from *N*-carboalkoxy bis-allyl amines is rather straightforward. For details, see: Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426–5427.
12. Nilsson, K.; Hallberg, A. *J. Org. Chem.* **1992**, *57*, 4015–4017.
13. As we previously noticed in related studies, six-membered lactamols readily dehydrated in the presence of catalytic amounts of acid (HBF_4 is generated during arylation) to form the corresponding enecarbamates.
14. (a) Karla, R.; Ebert, B.; Thorkildsen, C.; Herdeis, C.; Johansen, T. N.; Nielsen, B.; Krogsgaard-Larsen, P. *J. Med. Chem.* **1999**, *42*, 2053–2059; (b) Jensen, A. A.; Madsen, B. E.; Krogsgaard-Larsen, P.; Brauner-Osborne, H. *Eur. J. Pharmacol.* **2001**, *417*, 177–180; (c) Ebrik, A. A.; Rigo, B. *J. Heterocyclic Chem.* **1998**, *35*, 579.