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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 827–830

Short synthesis of 4-aryl-3-pyrrolin-2-ones

Sarah J. P. Yoon-Miller, Suzanne M. Opalka and Erin T. Pelkey*

Department of Chemistry, Hobart and William Smith Colleges, Geneva, NY 14456, USA

Received 7 August 2006; revised 22 November 2006; accepted 27 November 2006
Available online 14 December 2006

Abstract—A three step, convergent synthesis of 4-aryl-3-pyrrolin-2-ones from a tetramic acid has been developed. The key transformation utilized a Suzuki–Miyaura cross-coupling reaction between a 4-tosyloxy-3-pyrrolin-2-one and an arylboronic acid. This work also provides access to 4-arylpyrrolidin-2-ones, cyclic analogs of γ-aminobutyric acid (GABA). Hydrogenation of 4-(4′-chlorophenyl)-3-pyrrolin-2-one proceeded smoothly to give baclofen lactam.
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3-Pyrrolin-2-ones [1*H*-pyrrol-2(5*H*)-ones] are an important class of five-membered ring nitrogen heterocycles closely related to pyrroles. They are structural components of oligopyrrole plant pigments[1] (i.e., bilirubins) and the indolocarbazole alkaloids[2] (i.e., staurosporine). 4-Aryl-3-pyrrolin-2-ones **1** serve as convenient precursors to 3-arylpyrroles[3] **2** by partial reduction of the lactam carbonyl and to 4-arylpyrrolidin-2-ones **3**[4–7] by hydrogenation of the alkene (Fig. 1). The latter are cyclic analogs[4,8] of the neurotransmitter, γ-aminobutyric acid (GABA), and these compounds in turn have been utilized to prepare acyclic GABA analogs[5a] such as baclofen.[9] In addition, simple 3-pyrrolin-2-one derivatives serve as precursors to 2-silyloxypyrroles[10] and 2-triflyloxypyrroles.[11] The former have been elaborated into nitrogen heterocycles utilizing vinylogous enolate chemistry,[12] while the latter were converted into prodigiosins via cross-coupling chemistry.[13] Collectively, this chemistry demonstrates the value of developing a general synthesis of 4-substituted-3-pyrrolin-2-ones.

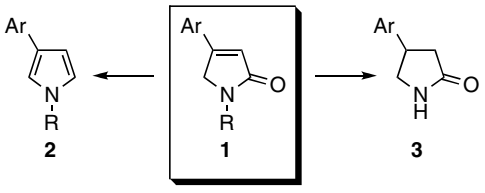


Figure 1. Selected transformations of 3-pyrrolin-2-ones **1**.

A few synthetic routes to 4-aryl-3-pyrrolin-2-ones lacking substitution at the 3- and 5-positions have been reported.[6,7,14] The most ubiquitous approach to this class of molecules involves the cyclocondensation of ammonia (or amines) with β-aryl-γ-halo-α,β-butenoates.[5,15] Predominantly, these approaches employ de novo ring syntheses where the aryl moiety is incorporated early in the sequence limiting their utility. One notable exception involved a multicomponent reaction.[7]

In continuation of our interest in the chemistry of 3-pyrrolin-2-ones,[16] we set out to develop a convergent synthesis of 4-aryl-3-pyrrolin-2-ones **6** with the introduction of aryl substituents at a late stage. We reasoned that these molecules could be put together utilizing a Suzuki–Miyaura reaction[17] of a 4-triflyloxy- or 4-tosyloxy-3-pyrrolin-2-one **5** as the key step (Fig. 2). The latter could be prepared from the known tetramic acid **4**.[18] This approach has been successfully employed by others to couple aryl groups to structurally related heterocycles including furan-2-ones,[19,20] coumarones,[21] quinol-4-ones,[22] and maleimides.[23] To the best of our knowledge,

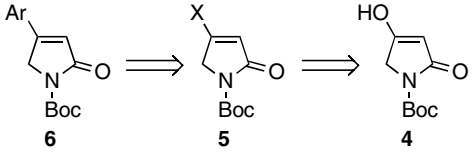


Figure 2. Retrosynthetic analysis to 4-aryl-3-pyrrolin-2-ones **6**.

Keywords: Suzuki–Miyaura reaction; Tosylate; 3-Pyrrolin-2-one; Pyrrol-2(5*H*)-one; Pyrrolidin-2-one; Tetramic acid.
* Corresponding author. Tel.: +1 315 781 3708; fax: +1 315 781 3860; e-mail: pelkey@hws.edu

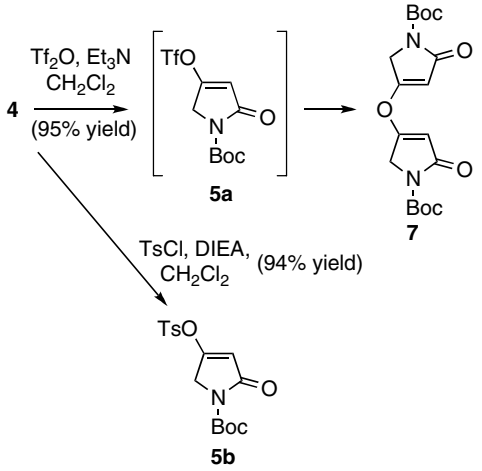
0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.11.156

cross-coupling reactions of 4-halo- or 4-sulfonyloxy-3-pyrrolin-2-ones **5** have not been reported.[24,25] Overall, this strategy would provide a novel, flexible synthesis to 4-aryl-3-pyrrolin-2-ones, which in turn would afford access to 4-arylpyrrolidin-2-ones, 3-arylpyrroles, and related nitrogen heterocycles.

Our synthesis commenced with the preparation of tetramic acid **4** from Meldrum's acid following a precedented procedure.[18b] Next, treatment of **4** with triflic anhydride in the presence of triethylamine seemingly gave a product with NMR spectral data consistent with triflate **5a** with the exception that ^{13}C NMR lacked a signal associated with a CF_3 group. Not deterred, we attempted Suzuki–Miyaura cross-coupling reactions [$Pd(PPh_3)_4$, [Na_2CO_3, $ArB(OH)_2$] with this material to no avail. Later, with the assistance of combustion data that showed a 0.0% abundance of sulfur in the 'triflate product,' we reasoned that we had instead obtained dimer **7** presumably arising from the Michael addition of **4** onto intermediate triflate **5a** (Scheme 1). The combustion data also supported the structure of **7**. Our inability to isolate **5a** was somewhat unexpected given that the corresponding furan-2-one triflate is known.[19] Interestingly, a 5,5-disubstituted-4-triflyloxy-3-pyrrolin-2-one has been reported, although no details of its preparation were provided.[26]

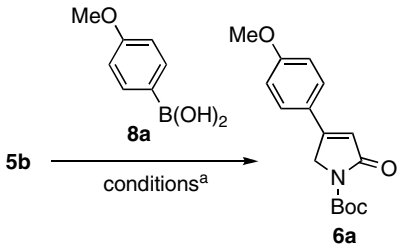
We next turned our attention to preparing and investigating reactions of known tosylate **5b**. The synthesis of **5b** proceeded without incident following a literature procedure as noted (Scheme 1).[18b] Treatment of **5b** with 4-methoxyphenylboronic acid (**8a**) in the presence of $Pd(PPh_3)_4$ and sodium carbonate gave **6a** albeit in a low yield (~10%). We were encouraged by this positive result and subsequently investigated this reaction using different catalyst systems as suggested by the literature for related systems (Table 1): $PdCl_2(PPh_3)_2/Na_2$-CO_3,[21b,27] $PdCl_2(PPh_3)_2$/KF,[20] and $PdCl_2(dppf)/Cs_2$- CO_3.[28] After some experimentation, we were gratified to find that the latter provided **6a** in excellent yields.

We briefly explored Suzuki–Miyaura reactions of **5b** using the optimal conditions (Table 2). Treatment of



Scheme 1. Preparation of cross-coupling substrates **5**.

Table 1. Suzuki–Miyaura reaction conditions

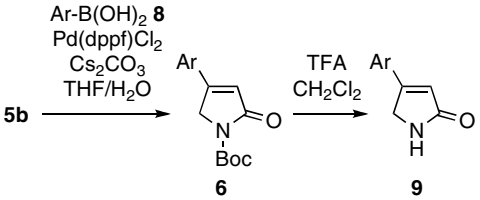


Entry	Pd catalyst	mol %	Base	Yield[b] (%)
1	$Pd(PPh_3)_4$	5	Na_2CO_3	35
2	$Pd(PPh_3)_4$	5	Cs_2CO_3	40
3	$PdCl_2(PPh_3)_2$	5	Na_2CO_3	21
4	$PdCl_2(PPh_3)_2$	5	KF	13
5	$Pd(PhCN)_2Cl_2$	10	Ag_2O	Trace
6	$PdCl_2$(dppf)	10	Na_2CO_3	80
7	$PdCl_2$(dppf)	10	Cs_2CO_3	82
8	$PdCl_2$(dppf)	20	Cs_2CO_3	81
9	$PdCl_2$(dppf)	5	Cs_2CO_3	84

[a] Conditions: 1.0 equiv **5b**, 1.2 equiv **8a**, 5–20 mol % Pd catalyst, base (3.0 equiv of Cs_2CO_3; 2.0 equiv for all other bases), 12–24 h, refluxing 10:1 THF/H_2O.

[b] Yields are for isolated, chromatographed materials (>95% purity by ^1H NMR).

Table 2. Preparation of 3-pyrrolin-2-ones **9**



Ar-B(OH)$_2$	Ar	Yield **6**[a] (%)	Yield **9**[a,d] (%)
8a[b]	4-OMePh	84	98
8b[c]	Ph	73	95
8c[c]	4-ClPh	73	90
8d[c]	Thiophen-2-yl	62	95

[a] Yields are for isolated, chromatographed materials (>95% purity by ^1H NMR).

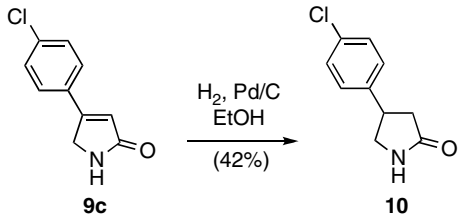
[b] 1.2 equiv boronic acid **8a**.

[c] 1.5 equiv boronic acid **8b–d**.

[d] Conditions: 1:1 TFA/CH_2Cl_2, 15–60 min, rt.

5b with different commercially available arylboronic acids **8** proceeded to give the corresponding unknown *N*-*t*-butoxycarbonyl-3-pyrrolin-2-ones **6** in good yields. These materials were then converted into the parent 3-pyrrolin-2-ones **9** by treatment with TFA. Utilizing this method, we prepared unknown **9a** along with the known 4-aryl-3-pyrrolin-2-ones **9b**,[29] **9c**,[4] and **9d**.[15c] All new compounds (**6a–d**, **9a**) gave spectral and analytical (CHN) data consistent with the given structures, while the known materials (**9b–d**) gave spectral and analytical (MP) data consistent with the literature (see Supplementary data in the online version).

Finally, hydrogenation of compound **9c** with 10% Pd/C under 1 atm of H_2 gave the cyclic GABA analog, baclo-



Scheme 2. Preparation of baclofen lactam **10**.

fen lactam **10**, in an unoptimized 42% yield (Scheme 2). Improvement of the yield and/or determination of the structure of by-products is still under investigation, but in each trial, no starting material was recovered. Several syntheses of **10** (both racemic and single enantiomer) have been reported with the common theme that de novo ring syntheses of *p*-chlorophenyl-containing substrates were utilized.[9,30] Our approach to 4-aryl-pyrrolidinone **10** is unique in that the aryl group was introduced late in the synthesis via a Suzuki–Miyaura reaction.[31] The implementation of this strategy has the potential to provide a ready access to analogs given the wide range of commercially available arylboronic acid derivatives.

In conclusion, we have demonstrated a novel, three step approach to 4-aryl-3-pyrrolin-2-ones **9** starting from tetramic acid **4**. The key step involved the convergent Suzuki–Miyaura cross-coupling of tosylate **5b** with arylboronic acids **8**. In addition to the preparation of 4-arylpyrrolidin-2-ones, we are continuing to investigate the chemistry of 4-aryl-3-pyrrolin-2-ones and this will be reported elsewhere.

Acknowledgments

Support of this research through a Camille and Henry Dreyfus start-up grant, Research Corporation, Patchett Foundation, and Hobart and William Smith Colleges is greatly appreciated.

Supplementary data

Experimental procedures, spectral data, and photocopies of ^{1}H NMR and ^{13}C NMR spectra for new compounds are included in the Supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.11.156.

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31. Notably, a sequence to related 4-arylpyrrolidin-2-ones (i.e., rolipram) utilized a Heck reaction of a 3-pyrroline substrate: see Ref. 8b.