Tetrahedron Letters 54 (2013) 2645–2647

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Substituted 2,2′-bipyrroles and pyrrolylfurans via intermediate isoxazolylpyrroles

James H. Frederich, Jennifer K. Matsui, Randy O. Chang, Patrick G. Harran *

Department of Chemistry and Biochemistry, University of California at Los Angeles, 607 Charles E. Young Drive East, Los Angeles, CA 90095, United States

ARTICLE INFO

Article history:
Received 26 February 2013
Accepted 7 March 2013
Available online 16 March 2013

Keywords:
Prodiginine
Isoxazole
C–H bond functionalization
3-Alkoxyfurans
3-Chloro-(4′-alkoxy)-2,2′-pyrrolylfuran

ABSTRACT

We describe a new synthesis of the 3-chloro-(4′-methoxy)-2,2′-pyrrolylfuran segment (**3**) of (+)-roseophilin. The route exploits a isoxazoylpyrrole intermediate, wherein the isoxazole ring serves as a β-diketone equivalent and a directing group for palladium catalyzed chlorination of the attached pyrrole. Subsequent reduction of the N–O bond and acid promoted cyclization afford roseophilin segment **3b** in five steps and 19% overall yield. This strategy was extended to the synthesis of 3-chloro-(4′-alkoxy)-2,2′-pyrrolylfurans (**16a–c**) and 4-alkoxy-2,2′-bipyrroles (**20a–c**), which are building blocks to synthesize bioactive prodiginine natural products and their congeners.

As part of a program to synthesize (−)-marineosin A (**1**),[1] (+)-roseophilin (**2**),[2] and related complex prodiginines, we had occasion to revisit the problem of preparing selectively functionalized 2,2-bipyrroles and pyrrolylfurans (Fig. 1). Roseophilin segment **3** is a benchmark in this area.[3] Its 3,4′-substitution pattern presents an atypical challenge. Published syntheses of structures **3a**[4] and **3b**[5] require 8 and 12 steps, respectively. For our purposes, we sought more concise and generic access to targets **4**, wherein X, Y, and R groups could be varied along a common reaction sequence.

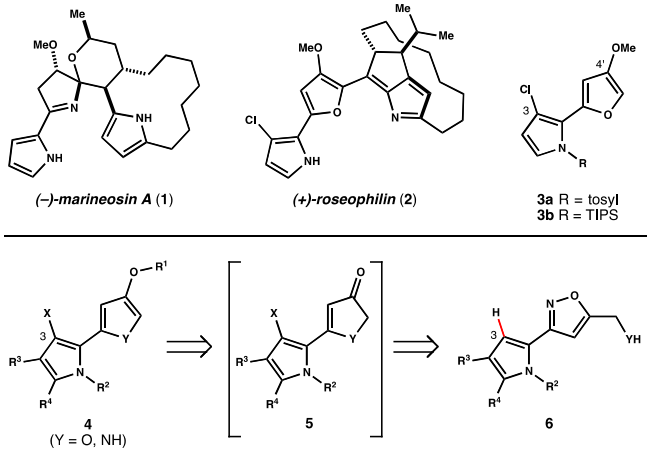


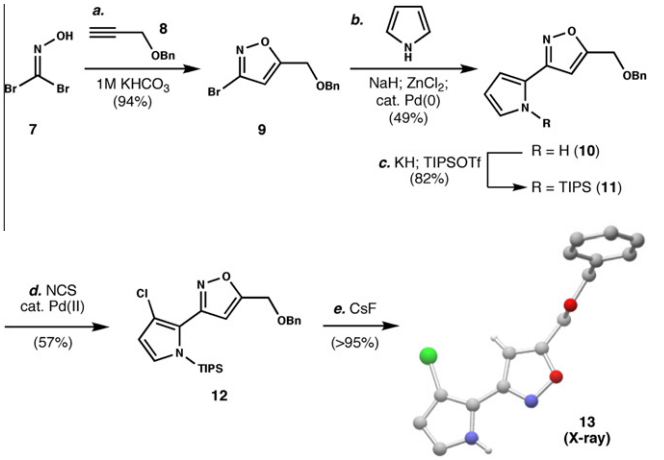
Figure 1. An approach to synthesize selectively functionalized 2,2′-pyrrolylfurans and bipyrroles employing an isoxazole ring as a directing group and β-diketone synthon.

In line with Terishima's original approach to **3a**, the alkoxy substituted heterocycle in **4** was viewed as an enolic derivative of its keto tautomer **5**, which itself is a cyclocondensation product of a functionalized β-diketone.[5] However, rather than append an acyclic β-diketone to a substituted pyrrole, we planned a ring-to-ring conversion to generate the requisite heterocycle. The isoxazole in **6** could serve as a β-diketone equivalent, wherein mild reduction of the N–O bond unveils an intermediate able to convert into **4** by way of **5**.[6,7] This strategy had the benefit of positioning a non-conjugated nitrogen lone pair proximal to C_3 of the pendant pyrrole in **6**, an arrangement that lends itself to directed C–H bond functionalization.[8] We could therefore plan routes to **4** that required no initial tailoring of the pyrrole ring.

To prepare pyrrolylfuran **3b** along these lines, commercial dibromoformaldoxime (**7**)[9] was reacted with benzyl propargyl ether (**8**) to afford 3-bromoisoxazole **9** in high yield (Scheme 1).[10] Subsequent Sadighi cross-coupling[11] with in situ generated pyrrolylzinc chloride gave pyrrolylisoxazole **10**.[12] The pyrrole in **10** was then converted into a triisopropylsilyl derivative (**11**) and treated with NCS in the presence of catalytic amounts of $Pd(OAc)_2$. This provided chlorinated pyrrole **12** in 57% isolated yield.[13] Regioisomeric mono-chlorides and/or products resulting from over-chlorination were not detected in the crude reaction mixture.[14] In contrast, when **11** was subjected to the same reaction conditions in the absence of $Pd(OAc)_2$, a mixture of chlorinated products was isolated along with recovered starting material (ca. 50%). These results

* Corresponding author. Tel.: +1 310 825 6578; fax: +1 310 206 0204.
E-mail address: harran@chem.ucla.edu (P.G. Harran).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.03.034



Scheme 1. Regioselective synthesis of 3-chloro-pyrrolylisoxazole **13**. Reagents and conditions: (a) **8** (1.2 equiv), 1 M $KHCO_3$, DME, rt, 6 h 94%; (b) pyrrole (4 equiv), NaH (4 equiv), DMF, rt, 4 h; $ZnCl_2$ (4 equiv), rt, 1 h; 10 mol % Pd_2dba_3, 10 mol % X-Phos, DMF, 100 °C, 16 h 49%; (c) KH (1.1 equiv), 18-crown-6 (1.1 equiv), THF, rt, 1 h; TIPSOTf, rt 18 h, 82%; (d) NCS (1.05 equiv), 12 mol % $Pd(OAc)_2$, MeCN, reflux, 8 h, 57%; (e) CsF, THF:H_2O (10:1), rt, 2 h, >95%.

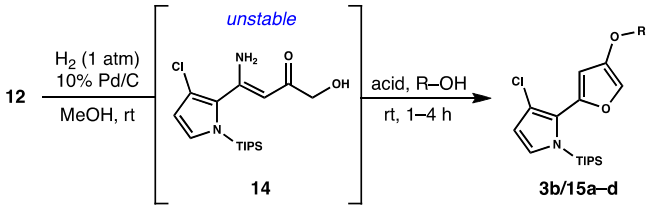
are consistent with directed, Pd-catalyzed functionalization of the C_3–H bond during formation of **12**.[15] The structure of **12** was confirmed by X-ray crystallographic analysis of desilylated material **13**.[16] The sequence from **7** to **12** was easily executed on multigram scale.

With **12** in hand, we explored conditions to convert the benzyloxymethylated isoxazole into a methoxyfuran. Hydrogenolysis of **12** over 10% Pd/C in MeOH (0.5 M) reduced the isoxazole N–O bond and cleaved the benzyl ether to afford enaminone **14**. Crude solutions of this unstable substance were filtered to remove solids and immediately treated with Brønsted acids in attempts to generate the target furan. The results of these experiments are summarized in Table 1. The use of methanolic HCl caused decomposition (entry 1). However, treatment with an equivalent of $TsOH{\cdot}H_2O$ gave desired pyrrolylfuran **3b** in 31% yield within 15 min. The mass balance was largely desilylated **3b**. Camphor sulfonic acid (CSA) and pyridinium *p*-toluene sulfonate (PPTS) provided more controlled reactions, affording **3b** in 89% and 86% yields, respectively (entries 3 and 4). CSA had the added advantage of shorter reaction times (1–2 h) at rt.

When unpurified solutions containing **14** were evaporated and dissolved in other alcohols prior to acid treatment, various alkoxy groups could be incorporated into the target heterocycle (entries 5–7). A variety of primary alcohols were tolerated, providing high yields of products **15a**–**c**. However, to date, secondary alcohols are unreactive using these conditions (entry 8).[17] Further studies aimed at more general introduction of alkoxy and thiol groups in this reaction are ongoing.

Having completed a versatile synthesis of roseophilin segment **3b** (five steps, 19% overall yield), we sought to adapt the route to syntheses of 4-alkoxy-2,2′-bipyrroles (Scheme 2). 4-methoxy-(2,2′-bipyrrole) carboxaldehyde (MBP, **16**) is a key intermediate for the synthesis of prodiginines.[18] Tripathy and coworkers have developed a three-step synthesis of **16** (36% overall yield) from 4-methoxy-3-pyrolin-2-one and *N*-Boc-pyrrole.[19] Decarbonylated variants of **16** are less conveniently available.[20] Toward this end, commercial pyrrole-2-carboxaldehyde was converted into *N*-tosyl oxime **17** in two-steps. Both reactions scaled effectively (>100 mmol) and provided crystalline **17** (toluene/hexanes; mp = 136–138 °C) as a 2:1 mixture of geometric isomers in 92% yield. Generating a nitrile oxide from this material in situ with aqueous NaOCl in the presence of (*tert*-butoxycarbonyl)propargyl

Table 1
Preparation of 3-chloro-(4′-alkoxy)-2,2′-pyrrolylfurans **3b** and **15a–d**

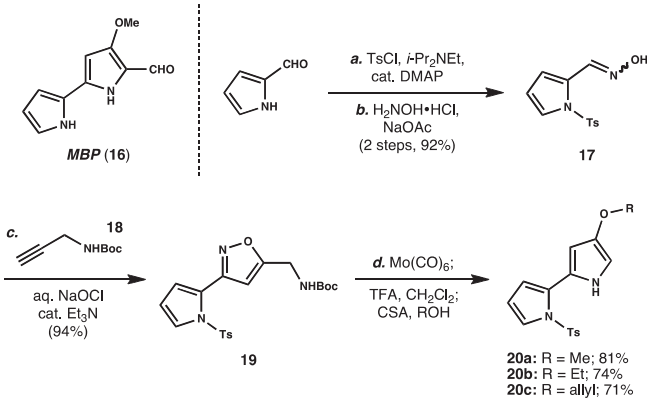


Entry[a]	R–OH	Acid	R	Yield[b] (%)
1[c]	MeOH	HCl	Me (**3b**)	0
2[d]	MeOH	$TsOH{\cdot}H_2O$	Me (**3b**)	31
3	MeOH	CSA	Me (**3b**)	89
4[e]	MeOH	PPTS	Me (**3b**)	85
5	$PhCH_2OH$	CSA	Bn (**15a**)	83
6	CF_3CH_2OH	CSA	CH_2CF_3 (**15b**)	85
7	H_2CCHCH_2OH	CSA	allyl (**15c**)	72
8[f]	*i*-PrOH	CSA	*i*-Pr (**15d**)	<10

[a] General conditions: 12 (1.5 mmol), 10 mol % Pd/C, H_2 (1 atm) 0.5 M MeOH, rt, 3 h; acid (1.1 equiv), 0.2 M 1:1 R–OH/$(CH_2Cl)_2$, rt.
[b] Isolated yield (±3%).
[c] 0.2 M HCl in MeOH.
[d] Mass balance was primarily desilylated **3b**.
[e] Requires 10 h reaction time.
[f] Cyclodehydration performed at 50 °C, 18 h.

amine (**18**) provided isoxazole **19** in high yield.[21] When **19** was exposed to 1 equiv $Mo(CO)_6$ in wet MeCN[22] and the resultant crude reduction product treated with CSA (0.5 M in MeOH), target methoxypyrrole **20a** was isolated in 81% yield. Analogous to results shown in Table 1, changing the alcohol vehicle for CSA treatment allowed congeners **20b** and **20c** to be prepared in good yield.[23]

In summary, we have developed new, concise routes to linked heterocycles **4**, wherein X, Y, and R groups can be controllably varied. By utilizing an isoxazole as a β-diketone equivalent, 3-chloro-(4′-alkoxy)-2,2′-pyrrolylfurans can be accessed using directed C–H bond functionalization. This considerably simplifies the preparation of roseophilin segment **3b**. We anticipate variations of the directed functionalization will allow for incorporation of aryl and alkyl groups at C_3 of the target heterocycles.[24,25] Lastly, we have demonstrated a straightforward synthesis of 4-methoxy-2,2′-bipyrrole **20a** (four steps, 70% overall yield) and related alkoxy congeners. The use of this chemistry to support total syntheses of (−)-**1** and (+)-**2**[26] is the subject of on-going experiments.



Scheme 2. Synthesis of 4-alkoxy-2,2′-bipyrroles **20a**–**c**. Reagents and conditions: (a) TsCl (1.1 equiv), *i*-Pr_2NEt (1.5 equiv), 5 mol % DMAP, CH_2Cl_2, rt, 18 h; (b) $H_2NOH{\cdot}HCl$ (1.1 equiv), NaOAc (1.5 equiv), MeOH/H_2O (10:1), rt, 2 h, 92% (two steps); (c) **18** (1.3 equiv), 6.15% aq NaOCl, 10 mol % Et_3N, CH_2Cl_2, 0 °C, 5 h, 94%. (d) $Mo(CO)_6$, MeCN/H_2O (20:1), 85 °C, 3 h; 1:1 CH_2Cl_2/TFA, rt, 2 h; CSA (1.1 equiv), 0.2 M 1:1 R–OH/$(CH_2Cl)_2$, rt, 81%.

Acknowledgments

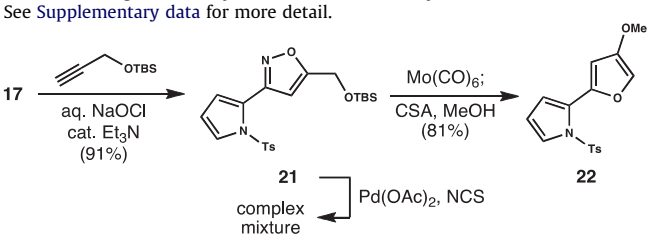
This research was supported by a program project grant from the National Cancer Institute (PO1CA95471) and the Donald J. and Jane M. Cram Endowment. R. Chang thanks the UCLA Undergraduate Research Scholars Program for support. We thank Dr. Saeed I. Kahn for X-ray crystallographic analysis of **13**.

Supplementary data

Supplementary data (experimental procedures and copies of ^{1}H and ^{13}C NMR data for all new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.03.034.

References and notes

1. Boonlarppradab, C.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Org. Lett.* **2008**, *10*, 5505–5508.
2. Hayakawa, Y.; Kawakami, K.; Seto, H.; Furihata, K. *Tetrahedron Lett.* **1992**, *33*, 2701–2704.
3. Fürstner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3582–3603.
4. Kim, S. H. Ph.D. Thesis, Purdue University, 1998.
5. Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, *120*, 2817–2825.
6. Baraldi, P. G.; Barco, A.; Pollini, G. P.; Simoni, D. *Synthesis* **1987**, 857–869.
7. Curran, D. P.; Singleton, D. H. *Tetrahedron Lett.* **1983**, *24*, 2079–2082.
8. Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *36*, 8960–9009.
9. Dibromoformaldoxime is also conveniently prepared: (a) Berrier, J. V.; Umarvadia, A. S.; Rohm and Haas Company; Improved synthesis of haloformimine compounds. Eur. Pat. Appl. 979814, Feb 16, 2000.; (b) Rohloff, J. C.; Rubinsun, J.; Gardner, J. O. *Tetrahedron Lett.* **1992**, *33*, 3113–3116.
10. Chiarino, D.; Napoletano, M.; Sala, A. *J. Heterocycl. Chem.* **1987**, *24*. 43.
11. Rieth, R. D.; Mankad, N. P.; Calimano, E.; Sadighi, J. P. *Org. Lett.* **2004**, *6*, 3981–3983.
12. When the reaction was carried out in the absence of Pd_2dba_3 (DMF, 100 °C, 18 h), product **10** was isolated in 14% yield. S_NAr addition of the pyrrolylzinc reagent to the bromoisoxazole can be a competing pathway. For uncatalyzed reactions of nitrogen nucleophiles with 3-halo-isoxazoles, see: (a) Moore, J. E.; Spinks, D.; Harrity, J. P. A. *Tetrahedron Lett.* **2004**, 3189–3191; (b) Girardin, M.; Alsabeh, P. G.; Lauzon, S.; Dolman, S. J.; Ouellet, S. G.; Hughes, G. *Org. Lett.* **2009**, *11*, 1159–1162.
13. Chlorination of **10** using NCS and 10 mol % $Pd(OAc)_2$ afforded the undesired α-chloropyrrole.
14. The mass balance consisted primarily of a complex mixture of desilylated chloropyrroles suggesting the TIPS group facilitates controlled catalysis.
15. (a) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 2523–2526; (b) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Stanford, M. S. *Tetrahedron* **2006**, *62*, 11483–11498.
16. X-ray diffraction data for **13** have been deposited at The Cambridge Crystallographic Data Center as entry CCDC 924179 and can be obtained free of charge at www.ccdc.cam.ac.uk.
17. Exposure of crude **14** to CSA at ambient temperature in *i*-PrOH (0.5 M) afforded no product after 10 h. Heating of the reaction mixture to 50 °C resulted in decomposition.
18. (a) Rapoport, H.; Holden, K. G. *J. Am. Chem. Soc.* **1962**, *84*, 635–642; (b) Rapoport, H.; Castagnoli, N. *J. Am. Chem. Soc.* **1962**, *84*, 2178–2181; (c) Boger, D. L.; Patel, M. *J. Org. Chem.* **1988**, *53*, 1405–1415; (d) Wasserman, H. H.; Lombardo, L. J. *Tetrahedron Lett.* **1989**, *30*, 1725–1728; (e) Wasserman, H. H.; Xia, M.; Wang, J.; Petersen, A. K.; Jorgensen, M.; Power, P.; Parr, J. *Tetrahedron* **2004**, *60*, 7419–7425.
19. Dairi, K.; Tripathy, S.; Attardo, G.; Lavallée, J.-F. *Tetrahedron Lett.* **2006**, *47*, 2605–2606.
20. (a) Dohi, T.; Morimoto, K.; Maruyama, A.; Kita, Y. *Org. Lett.* **2006**, *8*, 2007–2010; (a) Jolicoeur, B.; Lubell, W. D. *Org. Lett.* **2006**, *8*, 6107–6110; (b) Jolicoeur, B.; Lubell, W. D. *Can. J. Chem.* **2008**, *86*, 213–218.
21. Attempts to chlorinate *N*-tosyl pyrrole **19** using NCS and catalytic $Pd(OAc)_2$ resulted in formation of the undesired 2-chloropyrrole as the major product. For similar outcomes see Ref. 15b.
22. Nitta, M.; Kobayashi, T. *J. Chem. Soc., Chem. Commun.* **1982**, 877–878.
23. As outlined below, this route also provided access to 4′-methoxy-2,2′-pyrrolylfuran **22**. Consistent with our earlier observations, *N*-tosyl pyrrole **21** could not be regioselectively chlorinated via Pd-catalyzed C–H bond activation. See Supplementary data for more detail.



24. (a) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094–5115; (b) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788–802.
25. C–H activation/C–C bond formation: (a) Giri, R.; Maugel, N. L.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510–3511; (b) Engle, K. M.; Thuy-Boun, P. S.; Dang, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 18183–18193.
26. Frederich, J. H.; Harran, P. G. J. *Am. Chem. Soc.* **2013**, *135*, 3788–3791.