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Substituted 2,2'-bipyrroles and pyrrolylfurans *via* intermediate isoxazolylpyrroles

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Abstract

We describe a new synthesis of the 3-chloro-(4'-methoxy)-2,2'-pyrrolylfuran segment (**3**) of (+)-roseophilin. The route exploits a isoxazolylpyrrole 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 affords 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.

Keywords

prodiginine; isoxazole; C–H bond functionalization; 3-alkoxyfurans; 3-chloro-(4'-alkoxy)-2,2'-pyrrolylfuran

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 (Figure 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.

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 to **4** by way of **5**.^{6,7} This strategy had the benefit of positioning a non-conjugated nitrogen lone pair proximal to C₃ of the pendant pyrrole in **6**, an arrangement that lends itself to directed C–H bond

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Supplementary Material Supplementary data (experimental procedures and copies of ¹H and ¹³C NMR data for all new compounds) associated with this article can be found online.

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-coupling¹¹ with *in situ* generated pyrrolylzinc chloride gave pyrrolylisoxazole **10**.¹² The pyrrole in **10** was then converted to 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 are consistent with directed, Pd-catalyzed functionalization of the C₃-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 multi-gram scale.

With **12** in hand, we explored conditions to convert the benzyloxymethylated isoxazole to 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·H₂O 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% yield, 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** (5 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 3-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 Towards this end, commercial pyrrole-2-carboxaldehyde was converted to *N*-tosyl oxime **17** in 2-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 amine (**18**) provided isoxazole **19** in high yield.²¹ When **19** was exposed to 1 equiv Mo(CO)₆ in wet MeCN²² 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 C₃ of the target heterocycles.^{24,25} Lastly, we have demonstrated a straightforward synthesis of 4-methoxy-2,2'-bipyrrole **20a** (4 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 ongoing experiments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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

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 % $\text{Pd}(\text{OAc})_2$, MeCN, reflux, 8 h, 57%. (e) CsF, THF: H_2O (10:1), rt, 2 h, >95%.

Scheme 2.

Synthesis of 4-alkoxy-2,2'-bipyrroles **20a–c**. Reagents and conditions: (a) TsCl (1.1 equiv), Et₂N*i*-Pr (1.5 equiv), 5 mol % DMAP, CH₂Cl₂, rt, 18 h. (b) H₂NOH·HCl (1.1 equiv), NaOAc (1.5 equiv), MeOH/H₂O (10:1), rt, 2 h, 92% (2 steps). (c) **18** (1.3 equiv), 6.15% aq. NaOCl, 10 mol % Et₃N, CH₂Cl₂, 0 °C, 5 h, 94%. (d) Mo(CO)₆, MeCN/H₂O (20:1), 85 °C, 3 h; 1:1 CH₂Cl₂/TFA, rt, 2h; CSA (1.1 equiv), 0.2 M 1:1 R–OH/(CH₂Cl)₂, rt, 81%.

Table 1Preparation 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•H ₂ O	Me (3b)	31
3	MeOH	CSA	Me (3b)	89
4 ^e	MeOH	PPTS	Me (3b)	85
5	PhCH ₂ OH	CSA	Bn (15a)	83
6	CF ₃ CH ₂ OH	CSA	CH ₂ CF ₃ (15b)	85
7	H ₂ CCHCH ₂ OH	CSA	allyl (15c)	72
8 ^f	<i>i</i> -PrOH	CSA	<i>i</i> -Pr (15d)	< 10

^aGeneral conditions: **12** (1.5 mmol), 10 mol % Pd/C, H₂ (1 atm) 0.5 M MeOH, rt, 3 h; acid (1.1 equiv), 0.2 M 1:1 R-OH/(CH₂Cl)₂, rt.^bIsolated yield (±3%).^c0.2 M HCl in MeOH.^dMass balance was primarily desilylated **3b**.^eRequires 10 h reaction time.^fCyclodehydration performed at 50 °C, 18 h.