Tetrahedron Letters 51 (2010) 2148–2150

Contents lists available at ScienceDirect

Tetrahedron Letters

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

An elegant approach for stereocontrolled synthesis of furopyran building blocks

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ARTICLE INFO

Article history:
Received 28 December 2009
Revised 7 February 2010
Accepted 12 February 2010
Available online 18 February 2010

Dedicated to Professor Girish Trivedi on the occasion of his 70th birthday

Keywords:
3-Oxidopyrylium
[5+2] Cycloaddition
Ketoxime
Beckmann fragmentation
Furopyran

ABSTRACT

An elegant approach for stereocontrolled synthesis of furopyran (hexahydro-2*H*-furo[3,2-*b*]pyran) building blocks was reported. The key steps in the sequence involved an efficient intramolecular 3-oxidopyrylium-alkene [5+2] cycloaddition for the synthesis of cycloadduct **6** and Beckmann fragmentation of ketoxime **13** to yield the furopyrans (**5a–c**).

One of the major goals of contemporary organic synthesis is to develop concise methods and strategies for the rapid generation of complex molecules from simple starting materials. Among the tools available to meet this challenge, cycloaddition reactions which allow two new bonds to be formed in one operation in a regio- and stereocontrolled fashion are particularly appealing.[1,2] Along these lines, dipolar cycloaddition reactions of 3-oxidopyrylium and related carbonyl ylides have proved to be a powerful method for the synthesis of diverse molecular architectures in relatively simple manner.[3,4]

Recently, the synthesis of furopyran ring systems has been receiving considerable interest due to increasing awareness of occurrence of these structures in a wide variety of bioactive natural products. For example, *cis*-fused hexahydrofuro[3,2-*b*]pyran ring system is an important structural component of dysiherbaine (**1**) and neodysiherbaine (**2**) natural products, which are subunit-selective kinate receptor (KAR) agonists with potent convulsant activities (Fig. 1). In this Letter, we describe a facile and efficient approach for the stereocontrolled synthesis of furopyran ring systems. The strategy employs an elegant intramolecular [5+2] cycloaddition reaction and subsequent transformation of the resultant cycloadducts to the targeted ring systems (Scheme 1). Our premise is that intrinsic stereochemical bias offered by the conformational rigidity coupled with diverse functionalization of the oxa-bridged

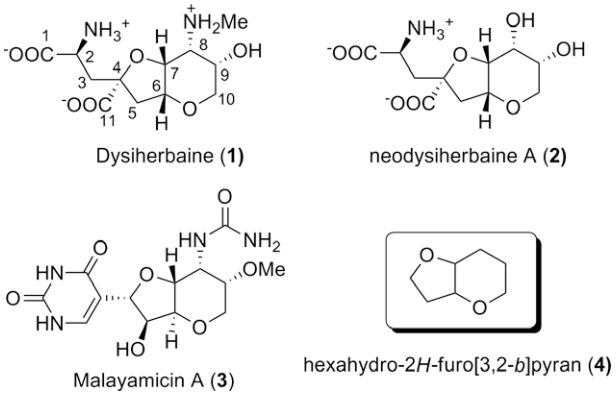

Figure 1. Furopyran ring containing compounds (**1–3**) and furopyran building block (**4**).

[5+2] cycloadducts would provide an excellent alternative route to the synthesis of targeted molecular systems.

Undoubtedly, the most critical aspect in the synthesis of these natural products involves development of efficient routes for the construction of polyether fragments.[5] Our synthesis commenced with the generation of aldehyde **9** by Swern oxidation of 1,4-butanediol vinylether (**8**, 82% yield). Addition of 2-lithiofuran (prepared in situ by treating furan with *n*-BuLi at 0 °C) to aldehyde **9** at −78 °C afforded the furylcarbinol **10** in 68% yield. Oxidative rearrangement of **10** to produce the corresponding hydroxypyranone **11** under various reaction conditions was initially proved problematic. Eventually the synthesis of **11** was achieved employing singlet oxygen oxidation conditions ($^1O_2$, Me_2S),[6] and subsequent acetyla-

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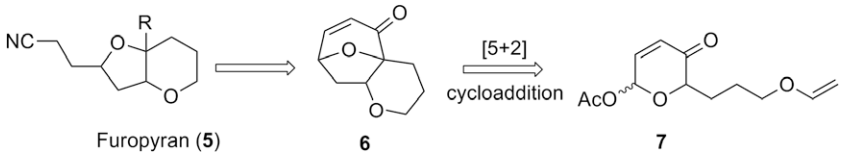
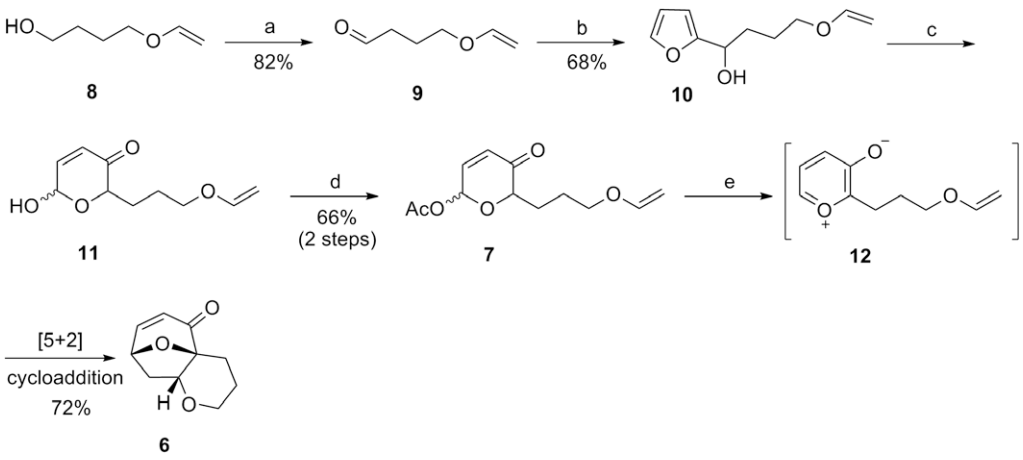
doi:10.1016/j.tetlet.2010.02.075



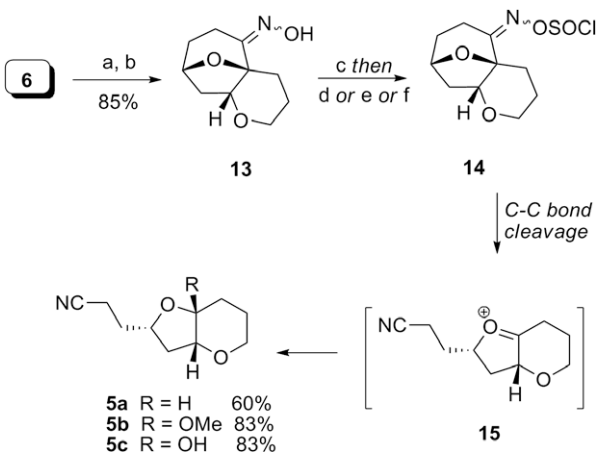
Scheme 1. Retrosynthetic approach for furopyran **5**.



Scheme 2. Reagents and conditions: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 2 h; (b) *n*-BuLi, furan, THF, −78 °C, 3 h; (c) O_2, rose bengal, CH_2Cl_2–MeOH (3:1), −78 °C, *hν*, 2 h then Me_2S, 0 °C, 0.5 h; (d) Ac_2O, pyridine, DMAP, CH_2Cl_2, 0 °C, 3 h; (e) Et_3N, CH_3CN, reflux, 24 h.

tion (Ac_2O, pyridine, DMAP) of the anomeric hydroxyl group in **11** provided the corresponding acetoxypyranone **7** in 66% yield in two steps. Intramolecular 3-oxidopyrylium-alkene [5+2] cycloaddition reaction proceeded without any problem upon treatment of the acetoxypyranone (**7**) with Et_3N in CH_3CN under reflux, to afford the cycloadduct **6** as the only observed product in 72% yield (Scheme 2).[7]

After having sufficient quantities of **6** in hand, next steps involved elaborating the cycloadduct to the targeted systems. Beckmann fragmentation (abnormal Beckmann rearrangement) of oximes is a powerful tool for the synthesis of nitrile derivatives. The reaction proceeds through a C–C bond cleavage and occurs particularly when there is assistance from the neighboring center in stabilizing the intermediary carbocation, leading to the formation of nitrile derivatives.[8] In these lines α-heteroatom-assisted Beckmann fragmentation is well documented.[9,10] The cycloadduct **6** was converted to the corresponding ketoxime **13** in two steps by hydrogenation of the double bond followed by refluxing the resultant ketone with an excess of hydroxylamine hydrochloride (85%, two steps). The oxime **13** on treatment with $SOCl_2$ in carbon tetrachloride, underwent an efficient heteroatom-assisted Beckmann fragmentation and furnished the oxonium ion intermediate **15** which was further elaborated to functionalized furopyran derivatives (**5a–c**) in good yields (Scheme 3).[7] The stereostructure of the products was confirmed on the basis of prominent NOEs between H-6/H-7, H-4/H-7 and H-4/H-6 (Fig. 2). It is worth emphasizing that complete control over the C–C bond cleavage as well as the approach of the incoming nucleophile by the



Scheme 3. Reagents and conditions: (a) H_2, Pd/C (10%), EtOH, rt, 3 h; (b) $NH_2OH{\cdot}HCl$, NaOAc, EtOH–H_2O (1:1), reflux, 4 h; (c) $SOCl_2$, CCl_4, 0 °C, 15 min; (d) MeOH, 0 °C, 0.5 h; (e) H_2O, 10 °C, 10 min; (f) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_3CN, rt, 1 h.

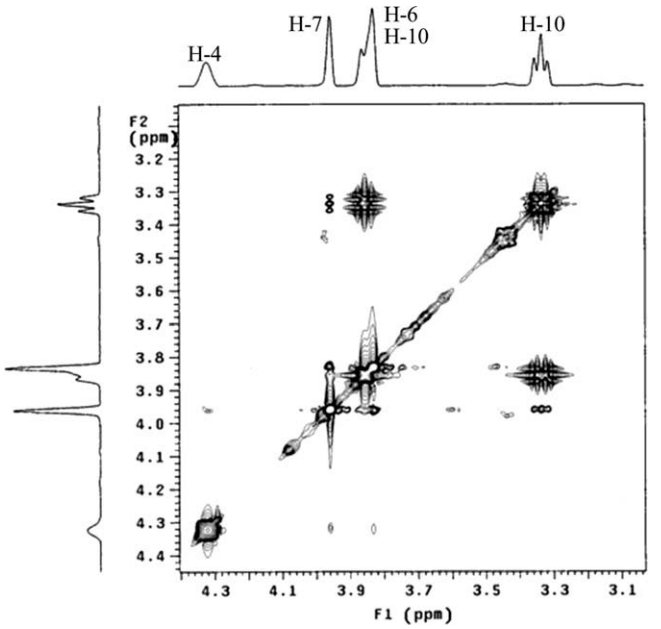


Figure 2. Part of the NOESY spectrum of furopyran **5a** in $CDCl_3$, recorded at 600 MHz with a mixing time of 0.4 s.

oxa-bridge leading to the exclusive formation of the furopyrans is remarkable.[10]

In summary, a simple and elegant method for the synthesis of furopyran building blocks was developed. The most attractive features of this methodology are (a) efficient intramolecular [5+2] cycloaddition and (b) heteroatom-assisted Beckmann fragmentation. In addition, high degree of stereocontrol and operational simplicity of the strategy together with the presence of maneuverable functional groups around the ring would facilitate application of the method in the synthesis of natural products and designed analogs. Studies toward the development of asymmetric versions of the reaction[11] and further exploration toward the synthesis of natural products[12,13] are currently underway and will be reported in due course.

Acknowledgments

The author thanks Professor Timothy Snowden (The University of Alabama, Tuscaloosa AL), Professor Elliot Chaikof (Emory University, Atlanta GA), and Dr. Shaoxiong Wu (Director of NMR facility, Emory University) for helpful discussions.

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7. All compounds are characterized by proper spectroscopic data.
   Cycloadduct **6**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (dd, J = 4.8, 10 Hz, 1H), 5.93 (d, J = 10 Hz, 1H), 4.88 (m, 1H), 3.92 (dd, J = 2, 6.4 Hz, 1H), 3.88 (m, 1H); 3.42 (dt, J = 3.2, 10.8 Hz, 1H), 2.62 (m, 1H), 2.31–2.20 (m, 2H), 1.92–1.82 (m, 1H), 1.8–1.63 (m, 1H), 1.59–1.55 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.5, 155.6, 125.9, 88.3, 75.9, 71.7, 65.7, 40.8, 23.6, 19.9; HRMS (ESI) calcd for $C_{10}H_{13}O_3$: 181.0865 (MH^+), found 181.0860.
   *3-(Hexahydro-2H-furo[3,2-b]pyran-2-yl)propanenitrile (***5a***):* ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.32 (m, 1H), 3.95 (d, J = 1.2 Hz, 1H), 3.86–3.82 (m, 2H), 3.35–3.31 (m, 1H), 2.53–2.41 (m, 2H); 2.11 (dd, J = 6, 13.2 Hz, 1H), 2.0 (m, 1H), 1.89–1.76 (m, 3H), 1.70–1.62 (m, 2H), 1.34–1.31 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 119.9, 77.6, 76.8, 75.5, 66.6, 40.4, 32.4, 25.8, 20.4, 14.6; HRMS (APCI) calcd for $C_{10}H_{16}NO_2$: 182.1181 (MH^+), found 182.1173.
   *3-(***7a***-Methoxyhexahydro-2H-furo[3,2-b]pyran-2-yl)propanenitrile (***5b***):* ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.36 (m, 1H), 3.84–3.81 (m, 1H), 3.73 (d, J = 3.6 Hz, 1H), 3.30 (dt, J = 1.2, 11.4 Hz, 1H), 3.19 (s, 3H); 2.52–2.46 (m, 2H), 2.29 (m, 1H), 2.20–1.95 (m, 2H), 1.88–1.78 (m, 2H), 1.71–1.68 (m, 1H), 1.55 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 119.8, 104.6, 81.2, 78.2, 66.3, 47.6, 37.5, 33.4, 27.9, 22.9, 14.7; HRMS (APCI) calcd for $C_{11}H_{18}NO_3$: 212.1287 (MH^+), found 212.1281.
   *3-(***7a***-Hydroxyhexahydro-2H-furo[3,2-b]pyran-2-yl)propanenitrile (***5C***):* ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.39 (m, 1H), 3.86–3.84 (m, 1H), 3.83–3.80 (m, 1H), 3.37–3.30 (m, 1H), 2.81 (br s, 1H); 2.53–2.41 (m, 2H), 2.15–2.12 (m, 1H), 2.11–1.87 (m, 4H), 1.79–1.72 (m, 2H), 1.57–1.52 (m, 1H); ^{13}C NMR (100 MHz): δ 120.1, 102.1, 80.9, 78.1, 66.3, 37.2, 33.4, 32.9, 23.4, 14.5.
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