VNU Journal of Science: Natural Sciences and Technology, Vol. 33, No. 3 (2017) 98-104

Synthesis of 4-hydroxy-1-methyl-4-(2-furyl)-3-(2-furylhydroxymethyl)piperidine and Transformation into perhydro[1,3,2]dioxaborinino[5,4-c]pyridine

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Received 08 May 2017
Revised 08 June 2017; Accepted 12 September 2017

Abstract: Having been synthesized successfully heterocyclic system, namely 2-aryl-N-methyl-4,8a-di(2-furyl)perhydro[1,3,2]dioxaborinino-[5,4-c]pyridine contains two piperidine and dioxaborinine rings. This new heterocyclic system was prepared from the reaction of 4-hydroxy-1-methyl-4-(2-furyl)-3-(2-furylhydroxymethyl)piperidine and some derivatives of arylboronic acid. The structure of new substances was confirmed by physical-chemical method including ^{1}H NMR, IR, MS. Futhermore, *PASS online* program investigated that di(2-furyl) perhydro[1,3,2]dioxaborinino[5,4-c]pyridine derivatives have high potential of bioactivities such as dermatology, spasmology, anticoagulant and antipsoriatic agent … which promote us to develop the new method affording this kind of compounds.

Keywords: piperidine, dioxaborinine, Mannich reaction, multicomponent condensation reaction, azacrown ether.

1. Introduction

Heterocycles containing nitrogene atom are the key moiety of substances showing good bioactivities and widely applied in different disciplines including medicine, pharmaceutics, agronomy as pharmaceutical drug, plant growth regulators, plant protection products ... [1,2]. Especially, piperidine derivatives having substituent at 4-position show diversely bioactivities and have great attraction of scienctists around the world [3,4].

By basing on here mentioned facts and as a part of our ongoing research effort focusing on transfer diol-1.3 (3) to azacrown ethers [5] and also synthesis of novel dioxaborinine [6,7,8], we have successfully prepared perhydrodioxaborinine (5 a-e) from (3) and a variety of arylboronic acid. In constrast, the azacrown ether (6) was not obtained by the Perdesen reaction. The structure of these novel

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https://doi.org/10.25073/2588-1140/vnunst.4456

compounds verified by ^{1}H NMR, IR, MS has showed a good accordance with our prediction.

2. Experiment

2.1. Chemicals

Reagents were purchased from commercial sources (Sigma-Aldrich) and were used without any additional purification.

2.2. Instruments

Metting point was recorded on STUART SMP3. ^{1}H and ^{13}C NMR spectra were recorded on Bruker- 500 MHz in $CDCl_3$ solutions at 25ºC, using TMS as internal standard; peak positions are given in parts per million (δ) referenced to the appropriate solvent residual peak. Mass spectra were recorded on Finnigan MAT 95 XL (EI, 70eV) at Russian Academy of Sciences and LTQ Orbitrap XL using electrospray ionization source at Faculty of Chemistry, HUS. IR spectra were recorded in FTIR Affinity – 1S SHIMADZU.

2.3. Experiment

Synthesis of bis-[2-(2-furoyl)ethyl]methylamine hydrochloride (1)

A mixture of 15,0 gr (0,136 mol) 2-acetylfuran, 11ml (0,136 mol) HCHO 37%, 4,59 gr (68 mol) methylamine hydrochloride and 5 ml 10% HCl solution was stirred 65 – 70^{0}C for 2h. When the reaction was completed (checked by TLC), the mixture was cooled to room temperature. The solid was filtered and washed with water (20ml), cold acetone (5ml) and diethyl ether (10ml), dried and obtained compound (1) in yield of 39% (7,75 gr) – Mannich salt, mp 172-174^{0}C. ^{1}H NMR (500 MHz, $CDCl_3$), ppm, (*J*, Hz): 2,53 (3H, s), 2,78 (4H, m), 3,19 (4H, m), 6,76 (2H, d, J=3.0), 7,53 (2H, d, J=3.0), 8,04 (2H, s), 10.24 (1H, brs, HCl).

Synthesis of 1-methyl-4-(2-furyl)-3-(2-furoyl) piperidin-4-ol (2)

To a solution of 7,0 gr (22 mmol) Mannich salt (1) in 70 ml water was added slowly 10% NaOH solution (until pH reached 10-11), with stirring vigorously at room temperature. When the reaction finished, the solid formed was filtered and washed with cold acetone (5ml) and diethyl ether (5ml) affording the target compound (2) in yield of 76% (4,76 gr), mp. 114-116^{0}C.

^{1}H NMR (500 MHz, $CDCl_3$), ppm, (*J*, Hz): 2.36 (3H, s, N-CH_3), 2.71 & 2.82 (1H,d,J=11.6 & 1H,dd, J=11.6,4.0, CH_2), 4.1(dd,J=11.6,3.9, CH_2), 1.86 & 2.07 ([1H, dd,J=13.9, 2.5 & 1H,tt ,J=13.9,13.6,3.6], CH_2), 2.61 (2H, m, CH_2), 4.82 (1H, s, OH), 6.17(2H$_{furan}$, d, J=1.2), 7.17 (1H$_{furan}$, d ,J=1.2), 7.23 (1H$_{furan}$, d, J=3.3), 6.51(1H$_{furan}$, dd, J= 3.3;1.3), 7.59 (1H$_{furan}$, d, J=1.3). EI-MS (70eV, m/z, I_{td}): 275[M]$^+$(7), 165(23),148(30), 95(100), 81(24), 70(22), 55(42), 44(44), 43(63), 42(98), 39(70).

Synthesis of 4-hydroxy-1-methyl-4-(2-furyl)-3-(2-furylhydroxymethyl)piperidine (3)

To a solution of 0,55gr (2 mmol) 2-furylpiperidine-4-ol (2) in 20 ml ethanol was added slowly 0,15gr (4 mmol) $NaBH_4$ during 20 minutes. The mixture was stirred for 1h at room temperature and at 50^{0}C for 30 minutes. The excessive solvent was removed *in vacuo*, 20ml water was added to this residue and extracted with ethylacetate (3x20 ml). The organic extracts were combined, and dried over anhydrous MgSO4. Removing solvent to dryness under vacuum gives a solid product which was purified by recrystallization from Ethanol in 48% yield (0,26 gr), mp.114-116^{0}C.

^{1}H NMR (500 MHz, $CDCl_3$), ppm, (*J*, Hz): 2.04 (3H, s, N-CH_3), 2.33(2H,m, CH_2), 3.38(2H, br.s, CH_2), 1.66 & 1.98 [(1H, brs, J=13.0 & 1H,m), CH_2], 2.13(2H,m, CH_2), 4.70(1H,brs,CHOH), 5.01 and 5.27(1H each, brs, OH), 6.23(1H$_{furan}$, d, J=3.0), 6.31(1H$_{furan}$, t, J=3.0,1.7), 7.53(1H$_{furan}$, s), 6.08(1H$_{furan}$, d, J=2.8), 6.31(1H$_{furan}$, t, J=3.0,1.7), 7.50 (1H$_{furan}$,

d, J=3.0). EI-MS (70eV, m/z, Itd): 277[M]+(43), 179(14), 162(58), 154(22), 99(23), 95(39), 70(29), 57(39), 44(100)

General method for the synthesis of di(2-furyl)perhydro[1,3,2]dioxaborinino[5,4-c]pyridine derivatives (5 a-e)

A mixture of 0.8 gr (3 mmol) γ-piperidol (3) and 3 mmol arylboronic acid (4 a-e) in 25 ml toluene was refluxed for 3 – 4h (Dean-Stark). When the reaction finished (TLC controlled), the reaction mixture was cooled to room temperature and the excess solvent was evaporated under vacuum. The obtained residue was purified by column chromatography (eluent: hexane:ethylacetate = 1 : 1) to give compound (5 a-e) as white crystals.

(5a): 58 %, m.p: 118-120^{0}C, ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si, δH, ppm): 1.8-2.1 (2H, m, CH_2), 2.18 (3H, s, N-CH_3), 2.40 (2H, m, CH_2), 2.48 - 2.71 (2H, m, CH_2), 3.07 (2H, m, CH_2), 5.51 (1H, brs, CHO), 6.31 (2H$_{furan}$, brs), 7.38 (1H$_{furan}$, d, J=1.2), 6.31 (2H$_{furan}$, brs), 7.31 (1H$_{furan}$, brs), 7.86 (3H$_{Ar}$, m), 7.86 (2H$_{Ar}$, d, J=7.2). EI-MS (70eV, m/z, Itd): 363[M]+(26), 259(17), 164(78), 149(28), 95(23), 70(32), 57(64), 44(100).

(5b): 48%, m.p:122-124^{0}C; ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si, δH, ppm): 1.9-2.2 (2H, m, CH_2), 2.37 (2H, m, CH_2), 2.45 - 2.70 (2H, m, CH_2), 3.17 (2H, m, CH_2), 2.51 (3H, s, N-CH_3), 2.81 (3H,s,C-Me); 6.21 (2H$_{furan}$, brs), 5.50 (1H, brs, CHO), 7.3 (1H$_{furan}$, d, J=1.3), 6.21 (2H$_{furan}$, brs), 7.89 (1H$_{furan}$, brs), 7.20-7.43 (2H$_{Ar}$,m), 7.81 (1H$_{Ar}$, s); 8.02 (1H$_{Ar}$,d, J=7.2). EI-MS (70eV, m/z, Itd): 377[M]$^+$(5), 354(54), 353(41), 262(26), 164(32), 144(38), 119(73), 118(63), 117(100), 91(74), 65(40), 57(33), 44(53).

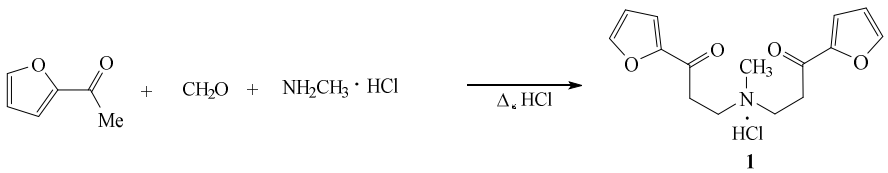
(5c): 50%, 130-132^{0}C; ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si, δH, ppm): 2.0-2.24 (2H, brs, CH_2), 2.21 (3H, s, N-CH_3), 2.0-2.41 (2H, brs, CH_2), 2.52 & 2.71 (2H, m, CH_2), 2.82 (3H,s, C-Me), 3.09 (2H, m, CH_2), 5.52 (1H br. s.,CHO), 6.31(4H$_{furan}$, m), 7.26 (1H$_{furan}$, brs), 7.40 (1H$_{furan}$, d, J=1.2), 7.18 (2H$_{Ar}$, d, J=7.1), 7.79 (2H$_{Ar}$, d, J=7.1). EI-MS (70eV, m/z, Itd): 377[M]+(26), 259(21), 182(30), 164(79), 149(29), 95(23), 91(25), 81(17), 70(33), 57(68), 44(100).

(5d): 68%, 114-116^{0}C; ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si, δH, ppm): 1.20-2.23 (2H, brs, CH_2), 2.16 (3H, s, N-CH_3), 2.20 & 2.51 (2H, m, CH_2), 2.38 & 2.77 (1H, dd, J=12.7 &1.1 & 1H, m, CH_2), 3.06 (2H, brs, CH_2), 5.59 (1H, br.s, CHO), 6.34(4H$_{furan}$, m), 7.31 (1H$_{furan}$, brs), 7.31(1H$_{Ar}$, d, J=7.8); 7.40 (1H$_{furan}$, d, J=1.3), 7.50 (1H$_{Ar}$ d, J=7.8). ESI-MS (M+H, m/z, Itd): 416 [M+H]$^+$ (100).

(5e): 75%, 124-126^{0}C, ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si, δH, ppm): 2.15 (3H, s, N-CH_3), 2.35 & 2.72 (1H, dd, J=11.5, 4.1 and 1H,m, CH_2), 2.0 – 2.25(2H, m, CH_2), 2.24 & 2.49 (2H,m, CH_2), 3.03(2H, brs, CH_2), 3.90 (3H,s,OMe), 5.51(1H, br s, CHO), 6.31(4H$_{furan}$, m), 7.31 (1H$_{furan}$, brs), 7.38 (1H$_{furan}$, d, J=1.3), 7.86 (2H$_{Ar}$,d,J=7.8), 7.94 (2H$_{Ar}$,d,J=7.8). EI-MS (70eV, m/z, Itd): 421[M]$^+$(32), 259(50), 164(100), 162(21), 149(31), 95(14), 81(16), 70(31), 57(57), 44(75).

3. Results and discussion

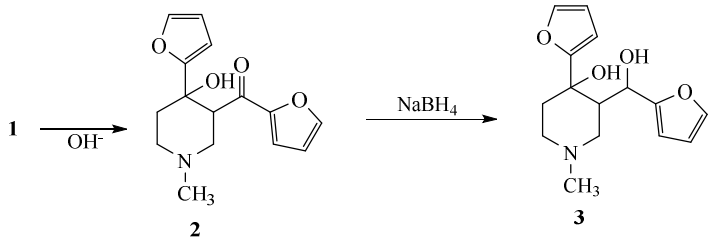
Bis[2-(2-furoyl)ethyl]methylamine hydrochloride (1) was synthesized from 2-acetylfuran, formalin solution and methylamine hydrochloride by multicomponent condensation reaction – Mannich reaction (*Scheme 1)*:



1

Scheme 1. Synthesis of Mannich salt (1)

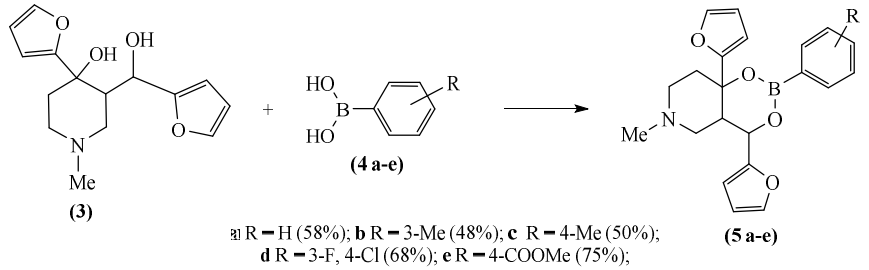
Mannich salt (1) then participated in the intramolecular cylization in the presence of 10% NaOH solution in the same manner of the aldol condensation affording γ-piperidol (2).



Scheme 2. Pathway to synthesize diol-1,3 (3)

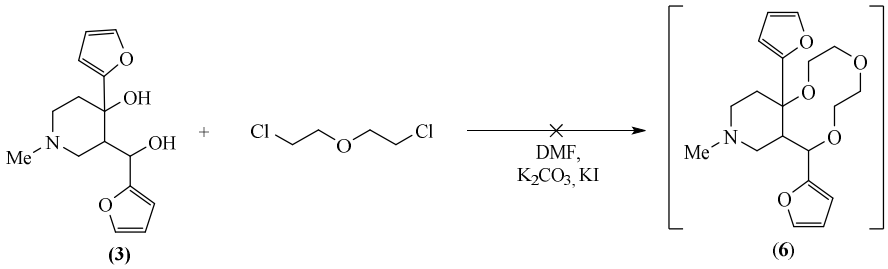
The aldol condensation was carried out under mild condition, at 65°C for 2h. Compound (2) obtained as intermediate substance with high yield (76%) which was reduced to 1,3-diol (3) in the presence of $NaBH_4$ in ethanol (*Scheme 2*).

Dioxaborinine (5a-e) were formed from the reaction of (3) and arylboronic acid (4) derivatives. From our experiments showing that the presence of with-drawing susbtituents at bezene zing of arylboronic acid enhanced the yield of this reaction. The cyclic esters have gained acceptance as an important procedure for the synthesis of difficulty accessible ortho-substituted biaryls and phenols – the Suzuki reaction [9,10].



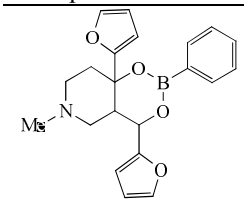
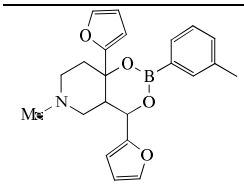
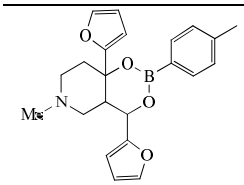
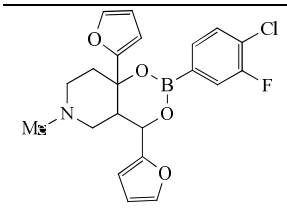
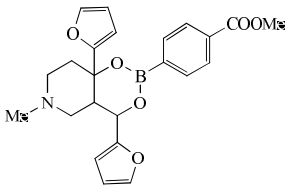
Scheme 3. Synthesis of di(2-furyl)perhydro [1,3,2] dioxaborinino [5,4-c] pyridine derivative.

In constrast, the condensation of compound 1,3-diol (3) with bis(2-chloroethyl) ether upon heating in DMF under the condition of Perdesen reaction leads not to the crown ether (6).



PASS is a software used to evaluate the general biological potential of an organic drug-like molecule [11]. PASS provides simultaneous predictions of many types of biological activity based on the structure of organic compounds. Thus, PASS can be used to estimate the biological activity profiles for virtual molecules, prior to their chemical synthesis and biological testing. Therefore, we applied this computer-aided drug discovery program to predict the biological activity of our compounds. A portion of the predicted biological activity spectra for compounds (5a-e) is given in Table 1. (*Pa is the estimates of probability for the compounds to be active while Pi is the probability for the compounds to be inactive. Only activities with Pa >Pi may be revealed by the compounds*).

Table 1. Prediction of bioactivity of compounds (5a-e) by PASS.
(The date of prediction is 08th May 2017)

Compounds	Bioactivity (Pa – active probability/Pi inactive probability)
 5a	Restenosis treatment (0.749/0.004) Antipsoriatic (0.695/0.005) Spasmolytic, Papaverin-like (0.666/0.010) Dermatologic (0.559/0.021)
 5b	Restenosis treatment (0.914/0.002) Urokinase inhibitor (0.756/0.002) Factor IXa inhibitor (0.653/0.000) Antipsoriatic (0.643/0.007) Anticoagulant (0.625/0.005) Spasmolytic, Papaverin-like (0.604/0.014)
 5c	Restenosis treatment (0.692/0.004) Antipsoriatic (0.665/0.005) Spasmolytic, Papaverin-like (0.667/0.010) Dermatologic (0.548/0.023)
 5d	Restenosis treatment (0.645/0.004) Antipsoriatic (0.622/0.009)
 5e	Spasmolytic, Papaverin-like (0.781/0.004) CYP2H substrate (0.761/0.024) Restenosis treatment (0.677/0.004) Antipsoriatic (0.660/0.006)

4. Conclusion

From 2-acetylfuran and through 4 steps, we have synthesized successfully five derivatives of di(2-furyl)perhydro[1,3,2]-dioxaborinino[5,4-c]pyridine with the yield from moderate to high. Azacrown ether (6) was not performed under Perdesen condition. Especially, *PASS* online program showed the high bioactivities of these compounds in treatment of dermatology, spasmology and anticoagulant… which encourages our attention on this topic to develop synthetic methods and find the new compounds applied in pharmaceutical and medicine chemistry.

Acknowledgement

This research was funded by the Vietnam National Foundation for Science and Technology Development (NAFOSTED) under grant number 104.01-2015.27

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Nghiên cứu tổng hợp 4-hydroxy-1-methyl-4-(2-furyl)-3-(2-furylhydoxymethyl)piperidine và chuyển hóa thành dẫn xuất perhydro[1,3,2]dioxaborinino[5,4-c]pyridine

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Tóm tắt: Đã tổng hợp thành công các dẫn xuất 2-aryl-N-methyl-4,8a-di(2-furyl)perhydro[1,3,2] dioxaborinino-[5,4-c]pyridine từ phản ứng ngưng tụ của 4-hydroxy-1-methyl-4-(2-furyl)-3-(2-furylhydroxymethyl)piperidine và axit arylboronic. Cấu trúc của các hợp chất mới được xác định bằng các phương pháp hóa-lý hiện đại IR, ^{1}H NMR và MS. Khảo sát hoạt tính sinh học bằng chương trình *PASS online* cho thấy các hợp chất này có tiềm năng ứng dụng làm thuốc chống co thắt ngực, hẹp van tim, chống đông tụ hoặc điều trị bệnh ngoài da.

Từ khóa: Piperidine, dioxaborinine, phản ứng Mannich, phản ứng ngưng tụ đa tác nhân, azacrown ether.