SYNTHESIS OF 4-OXO-4*H*-CHROMENE DERIVATIVE WITH FUSED BENZODIAZEPINE RING

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Abstract: 6-Acetylbenzo[*b*]chromeno[2,3-*e*][1,4]diazepin-13(6*H*)-one **6** was synthesized by reaction of 4-oxo-4*H*-chromene-3-carboxaldehyde **1** with 1,2-diaminobenzene **2** followed by cyclisation of formed Schiff base **3** and spontaneous oxidation of dihydrodiazepine **4** by air oxygen. Finally, diazepine **5** was acetylated at N(6) by reaction with acetic anhydride.

Key words: 4-oxo-4*H*-chromene, 1,2-diaminobenzene, diazepine, fused heterocycles

1. Introduction

The title 4-oxo-4*H*-chromene-3-carboxaldehyde **1** (Fig.1) plays the crucial role in various reactions as oxidation and reduction, defunctionalisation, radical and nucleophilic addition, and many types of annulations and cycloaddition reactions (GHOSH and CHAKRABORTY, 2015).

Several strategies were developed to construct chromene derivatives fused with seven-membered carbocyclic (TURNER *et al*., 2011) or heterocyclic (KUMAR *et al*., 2000) rings. Among these compounds the key diazepine derivative **5** was synthesized by several pathways, e.g. from 2-(*N*-methyl-*N*-phenylamino)-4-oxochromene-3-karboxaldehyde (SINGH *et al*., 2002) or from 3-(1,3-dioxolan-2-yl)-4*H*-chromen-4-one (GHOSH *et al*., 1983).

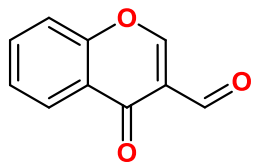

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Fig. 1. 4-oxo-4*H*-chromene-3-carboxaldehyde.

The importance of seven-membered rings consists on their biological activity, e.g. theaflavins from black tea possess antioxidant and antiviral activity (BHUYAN *et al*., 2013). Lenthionine which occurs in the shiitake mushrooms is known for its antithrombotic activity (SHIMADA *et al*., 2004). Seven-membered ring is also the structural unit of many alkaloids, e.g. strychnine, colchicine or samandaridine (GAŠPAROVÁ, 2010).

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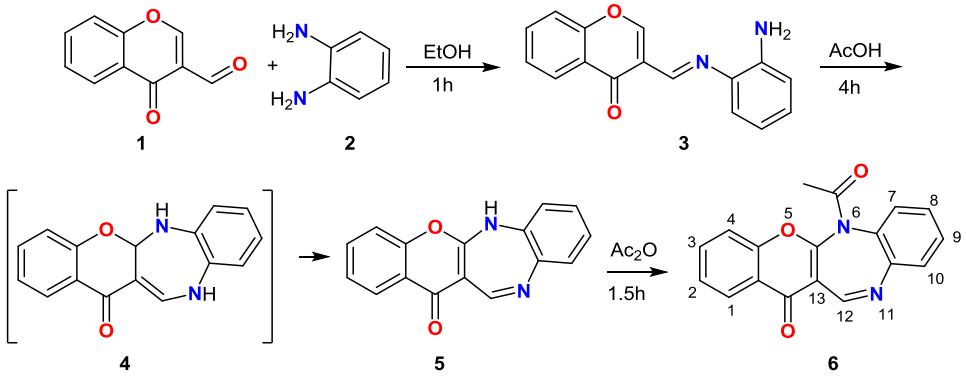
In the present work, benzo[*b*]chromeno[2,3-*e*][1,4]diazepin-13(6*H*)-one (**5**) was synthesized by reacting 3-{[(2-aminophenyl)imino]methyl}-4*H*-chromen-4-one (**3**) in presence of glacial acetic acid and further acetylation with acetanhydride gave 6-acetylbenzo[*b*]chromeno[2,3-*e*][1,4]diazepin-13(6*H*)-one (**6**) (Scheme 1).

2. Experimental

Melting points of products were determined on a Kofler hot plate apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained on a 300 MHz/75 MHz spectrometer VRX-300 in $CDCl_3$ or DMSO-d_6 with tetramethylsilane as the internal standard. The infrared spectra were taken on a FTIR IRAffinity-1 spectrophotometer using KBr technique. Elemental analyses were performed on FlashEA 2000 CHNS/O-OEA analyser. All solvents were distilled and dried appropriately prior to use. The course of reactions was monitored by TLC in ethyl acetate–hexane. 4-Oxo-4*H*-chromene-3-carbaldehyde **1** was synthesized by method, which was described by (NOHARA *et al*., 1974). 1,2-Diaminobenzene was a commercial product.



Scheme 1. Synthesis of 6-acetylbenzo[*b*]chromeno[2,3-*e*][1,4]diazepin-13(6*H*)-one.

2.1 Synthesis of 3-{[(2-aminophenyl)imino]methyl}-4H-chromen-4-one (3)

The mixture of 4-oxo-4*H*-chromene-3-carboxaldehyde **1** (1 g, 5.7 mmol) and 1,2-diaminobenzene **2** (0.62 g, 5.7 mmol) was refluxed in 15 mL of ethanol for 1 h. After cooling the formed solid precipitate was filtered off, washed with ethanol and purified by crystallisation from ethanol to give product **3** as red solid. Yield 76 %; m.p. 214-216 °C. Anal. Calcd. for $C_{16}H_{12}N_2O_2$ (264.3) C, 72.72; H, 4.58; N, 10.60. Found: C, 72.61; H, 4.54; N, 10.40%. IR (KBr): 3483, 3411 (NH_2); 1635 (C=O) cm^{-1}. ^{1}H NMR spectrum was unmeasurable because of the low solubility of **3**

2.2 Synthesis of benzo[b]chromeno[2,3-e][1,4]diazepin-13(6H)-one (5)

3-{[(2-Aminophenyl)imino]methyl}-*4H*-chromen-4-one **4** (1.04 g, 4 mmol) was refluxed in glacial acetic acid (10 mL) for 4 h. After cooling reaction mixture was

poured on ice and precipitate was filtered off, washed with water and crystallized from chloroform to give yellow product **5**. Yield 58 %; m.p. 265-268 °C. Anal. Calcd. for $C_{16}H_{10}N_2O_2$ (262.3): C, 73.27; H, 3.84; N, 10.68. Found: C, 73.08; H, 3.82; N, 10.47%. IR (KBr): ν 3310 (NH); 1658 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): 11.79 (bs, 1H, NH); 9.40 (s, 1H, CH=N); 8.47 (dd, 1H, J = 8.9 Hz, 1.7 Hz, H-1); 8.02-7.81 (m, 3H, Ar-H); 7.65-7.28 (m, 4H, Ar-H).

*2.3 Synthesis of 6-acetylbenzo[b]chromeno[2,3-e][1,4]diazepin-13(6H)-one (**6**)*

Compound **5** (1 g, 3.84 mmol) was refluxed in acetic anhydride (3.6 mL) for 1.5 h. After cooling the solid product was filtered off, washed with acetic acid (20 mL) and crystallized from ethanol to give product **6** as yellow solid. Yield 69 %; m.p. 264-265 °C. Anal. Calcd. for $C_{18}H_{12}N_2O_3$ (304.3) C, 71.05; H, 3.97; N, 9.21. Found C, 70.37; H, 3.62; N, 8.94%. IR (KBr): ν 1662 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6): 8.83 (s, 1H, CH=N); 8.17 (dd, 1H, *J* = 7.8, 1.5 Hz, H-1); 7.95-7.89 (m, 2H, H-3, H-7); 7.81-7.74 (m, 1H, H-4); 7.70 (dd, 1H, *J* = 7.8, 1.5 Hz, H-2); 7.62-7.56 (m, 1H, H-8); 7.47-7.41 (m, 1H, H-9); 7.28-7.24 (m, 1H, H-10); 3.31 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): 178.9, 170.2, 162,7, 151,8, 144.3, 140.7, 134.1, 129.1, 128.7, 127.6, 126.7, 125.1, 123.0, 122.7, 119.1, 118.7, 102.3, 25.7.

3. Results and discussion

4-Oxo-4*H*-chromene-3-carbaldehyde **1** was easily prepared from 2-hydroxyacetophenone under Vilsmeier-Haack conditions in 75% yield (NOHARA *et al*., 1974).

6-Acetylbenzo[*b*]chromeno[2,3-*e*][1,4]diazepin-13(6*H*)-one **6** was synthesized by three-step synthesis (Scheme 1). In the first step 4-oxo-4*H*-chromene-3-carboxaldehyde **1** was treated with 1,2-diaminobenzene **2** for 1h under reflux in ethanol and Schiff´s base **3** was formed in 76 % yield. 1,2-diaminobenzenes as 1,4-binucleophiles have been already introduced into the reactions with 4-oxo-4*H*-chromene-3-carbaldehydes **1** (Plaskon *et al*., 2012). Although variety of products was obtained, it is obvious that imine **3** was formed initially and it was isolated if the reaction was performed under relatively mild conditions (GHOSH and KHAN, 1980). Subsequently derivative **3** undergo intramolecular cyclization at the C-2 atom of the chromone ring by reflux in glacial acetic acid for 4h to form unisolable 6,11-dihydrobenzo[*b*]chromeno[2,3-*e*][1,4]diazepin-13(5a*H*)-one **4**, which oxidized spontaneously by influence of air oxygen (EL-DESOKY and AL-SHIHRY, 2008) to product **5** (58 %). Compound **5** displays in its ^1H NMR spectrum, in addition to other signals, broad singlet of NH proton at 11.79 ppm, singlet of H-12 proton at 9.40 ppm. The important feature of the above methodology is the fact that the chromone moiety remains intact, because the synthetic utility of chromones is limited due to facile opening of the chromone ring (SHUTOV *et al*., 2011) and strategies are being developed to circumvent this (BORRELL *et al.*, 2001).

In order to exploit the N(6)-derivatization of diazepine ring of **5**, we have realized *N*-acetylation of **5** by method of (BETAKIS *et al.,* 1984) in acetic anhydride for 4h,

when *N*-acetylfuro[3,2-*b*]pyrrole-5-carboxylate **6** was obtained in 69% yield. Compound **6** display in its ^{1}H NMR spectrum the singlet at 8.83 ppm spectra due to H-12 proton. The methyl protons of acetyl group resonate as singlet at 3.31 ppm. Finally, aromatic protons appear as multiplets at 8.17-7.26 ppm region. ^{13}C NMR spectrum shows signals of two carbonyl groups at 178.9 and 162.7 ppm, respectively. Signals of 5a and 4a carbons appear at 170.2 and 151.8 ppm, respectively.

4. Conclusion

In summary, we have developed the synthesis of 6-acetylbenzo[*b*]chromeno[2,3-*e*][1,4]diazepin-13(6*H*)-one **6** 69% yield by three-step reaction of 4-oxo-4*H*-chromene-3-carboxaldehyde **1** with 1,2-diaminobenzene **2** followed by cyclisation of formed Schiff base **3** and spontaneous oxidation of dihydrodiazepine **4** by air oxygen and subsequent acetylation of diazepine **5** was at N(6) by reaction with acetic anhydride.

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