Tetrahedron Letters 52 (2011) 4189–4191

Contents lists available at ScienceDirect

Tetrahedron Letters

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

The reaction of tetrahydrochromeno[3,4-*c*]pyridines with activated alkynes. The first synthesis of tetrahydrochromeno[4,3-*d*]azocines

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ARTICLE INFO

Article history:
Received 4 April 2011
Revised 20 May 2011
Accepted 3 June 2011
Available online 13 June 2011

Keywords:
Coumarins
Ring-expansion
Domino-reaction
Azocine

ABSTRACT

The first synthesis of tetrahydrochromeno[4,3-*d*]azocines via an alkyne-induced expansion reaction is described.

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Coumarins have been found to exhibit a wide range of biological and controlled therapeutic activities. They occur extensively in nature and exhibit low toxicity.[1,2] In many cases, the type of biological action is predetermined by the substituents present on the main benzopyran skeleton.

Fused 3,4-heterocyclic coumarin derivatives[2,3] also show a wide range of biological activity. Specifically, those bearing a benzopyranone–pyridine or piperidine skeleton were found to: interact with DNA,[4] transfer energy in photophysical processes,[5] act as potential platelet activating factor antagonists,[6] depressant or hypotensive activators[7] and potent antipsychotic agents,[8] whereas others exhibited antibacterial,[9] antitumor,[10] anticholinergic,[11] antiinflammatory[12] and antimicrobial[13] activities. Much less is known about coumarins fused with medium-sized azacycles, that is, azocines. To the best of our knowledge, the only example reported is [1]benzopyrano[3,4-*c*]azocine **1** (Fig. 1), formed via a multi-component reaction between 2-oxo-2*H*-1-benzopyran-3-carboxamide and ethyl 3-aminocrotonate.[14]

The lack of synthetic approaches obviously hampers the biological evaluation of this promising heterocyclic system. As part of a research program related to the development of medium-sized azacycle synthesis via the alkyne-induced ring-expansion domino-reaction,[15] we herein report the first synthesis of the previously unknown chromeno[4,3-*d*]azocine system from readily available chromenopyridine derivatives. 3-Benzyl-8-hydroxy-3,4-dihydro-1*H*-chromeno[3,4-*c*]pyridin-5(2*H*)-one (**2**), prerequisite for this study, was prepared via Pechmann condensation of 3-carboethoxy-4-piperidone with resorcinol according to the published procedure.[16] To avoid possible side-reactions with alkynes, the phenolic OH was transformed into OAc by reaction with acetic anhydride to yield 8-acetoxychromenopyridine **3** (Scheme 1).

The reaction of **3** with methyl propiolate (MP) or acetyl acetylene in dry dichloromethane at room temperature[17] yielded the unexpected products, dienes **4** and **5** in 80% and 70% yields, respectively. A plausible mechanism for this transformation is shown in Scheme 2. Michael addition of the N atom to the triple bond of the alkyne to form the zwitterionic intermediate **A** is followed by tetrahydropyridine ring cleavage and a 1,5-proton shift. The driving force for this unusual transformation is most likely the creation of extended conjugation in the resulting products.

The structure of **4** was elucidated unambiguously by the X-ray diffraction analysis of a single crystal[18] (Fig. 2). The molecule of **4** contains two planar fragments, a 2*H*-chromen-2-one and a vinylamino-2-propenoate (–CH=CH–N–CH=CH–COOMe). The dihedral

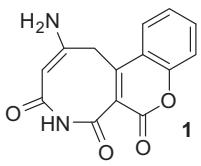

Figure 1.

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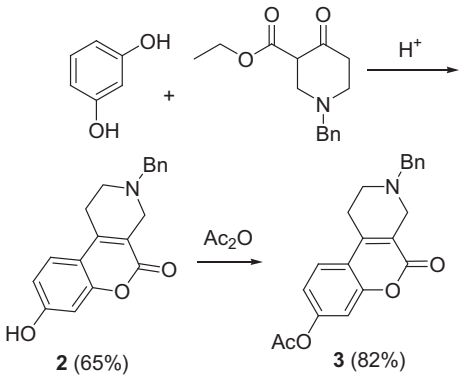
doi:10.1016/j.tetlet.2011.06.012



Scheme 1. Synthesis of the starting compound **3.**

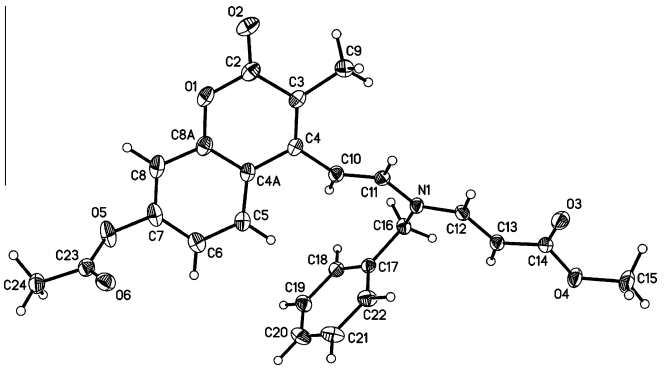
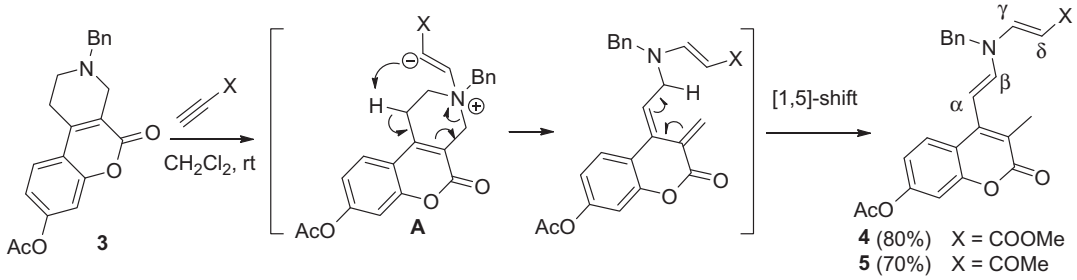
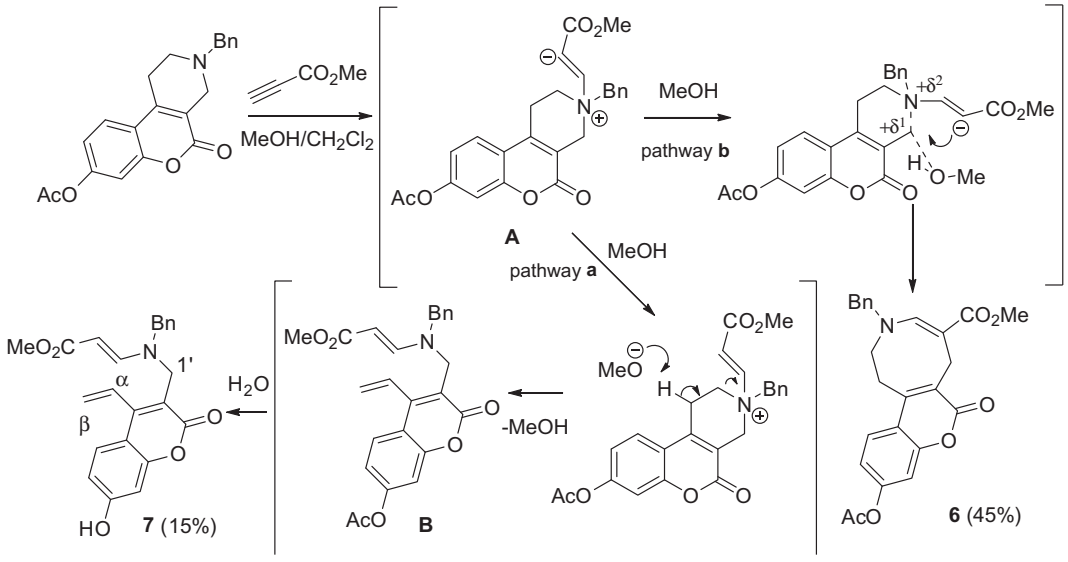


Figure 2. The ORTEP plot of **4.**



Scheme 2. Reactions of compound **3** with activated terminal alkynes.



Scheme 3. Reactions of compound **3** with methyl propiolate in MeOH.

angle between the corresponding planes is 43.1°. The acetyl group is almost perpendicular to the plane of the 2*H*-chromen-2-one (the interplanar angle is 76.8°), and the benzyl group is almost perpendicular to the plane of the vinylamino-2-propenoate (the interplanar angle is 87.7°). The N1 nitrogen atom has a trigonal-planar configuration. In the crystal state, molecules of **4** are arranged at van-der-Waals distances.

When the reaction of **3** with MP was carried out in a protic solvent ($MeOH/CH_2Cl_2$, 1:1 mixture),[19] surprisingly no trace of **4** was detected in the reaction mixture, and the only products isolated in this case were the target chromeno[4,3-*d*]azocine derivative **6**[20] (45%) and 4-vinylchromene **7**[21] (15%) (Scheme 3).

The difference in reactivity can most likely be explained by the crucial role methanol plays in this reaction. This reaction again starts with formation of the zwitterion **A**.

The anionic part of the latter accepts a proton from methanol (pathway **a**), thus producing a potent base (methoxide anion), that causes Hofmann-like cleavage of the tetrahydropyridine ring, yielding derivative **B**, which undergoes hydrolysis during column chromatography, providing **7**. The alternative pathway **b** consti-

tutes a 6-membered ring-expansion reaction, facilitated by the nucleophilic assistance of MeOH as depicted in Scheme 3.

In conclusion, we have demonstrated, that the reaction of chromeno[3,4-*c*]pyridine with activated alkynes is solvent-dependent and yields either [(2-oxo-2*H*-chromen-4-yl)vinyl]amines **4** and **5** (aprotic solvent) or chromeno[4,3-*d*]azocine **6** and 4-vinylchromene **7** (protic solvent). Further work aimed at exploring the scope and limitations of this reaction is underway and the results will be reported in due course.

Acknowledgments

This work was supported by a Grant of the RF President (MK-1048.2010.3) and The Russian Foundation for Basic Research (Grant 11-03-00164)

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17. *Methyl(E)-3-benzyl[(E)-2-(3-methyl-7-methylcarbonyloxy-2-oxo-2H-4- chromen yl)-1-ethenyl]amino-2-propenoate* (**4**): To a solution of 8-acetoxychromen opyridine **3** (160 mg, 0.46 mmol) in dry CH_2Cl_2 (5 mL) was added methyl propiolate (0.05 mL, 0.55 mmol). The reaction mixture was stirred at room temperature for 3 d (TLC monitoring). After completion, the solvent was evaporated in vacuo. The residue was purified by recrystallization (EtOAc). Yield 143 mg, (80%), yellow solid, mp 166–168 °C (EtOAc); Anal. Calcd for $C_{25}H_{23}NO_6$: C, 69.27; H, 5.35; N 3.23. Found C, 69.4; H, 5.3; N 3.3. R_f (silufol, EtOAc/hexane, 1:1) 0.64; ν_{max} (KBr) 1752, 1709, 1614 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.66 (1H, s, γ-CH) 7.22–7.37 (4H, m, CH-Ar), 7.12–7.17 (2H, m, CH-Ar), 6.98 (1H, s, 8-H), 6.84 (1H, d, *J* 8.7 Hz, 6-H), 6.76 (1H, d, *J* 14.3 Hz, β-CH), 5.56 (1H, d, *J* 14.3 Hz, α-CH), 5.12 (1H, d, *J* 13.7 Hz, δ-CH), 4.76 (2H, s, CH_2-Ar), 3.64 (3H, s, CO_2CH_3), 2.24 (3H, s, $COCH_3$), 2.04 (3H, s, 3-CH_3); δ_C (100 MHz, $CDCl_3$) 168.8, 168.5, 161.9, 152.8, 152.1, 148.3, 148.0, 144.3, 140.1, 135.2, 134.2, 129.3, 128.8, 128.1, 126.7, 126.5, 126.3, 126.1, 117.8, 110.2, 100.9, 93.9, 51.3, 21.1, 14.7; *m*/*z* (LC–MS) 434 [M+H].
18. The crystal of **4** ($C_{25}H_{23}NO_6$, M = 433.44) is triclinic, space group *P*-1, at T = 100 K: a = 9.8565(4) Å, b = 10.6047(4) Å, c = 12.3764(8) Å, α = 108.001(1)°, β = 92.462(1)°, γ = 117.401(1)°, V = 1065.70(9) Å^3, Z = 2, d_{calc} = 1.351 g/cm^3, F(0 0 0) = 456, μ = 0.097 mm^{-1}; 13745 total reflections (6225 unique reflections, R_{int} = 0.024) were measured on a three-circle Bruker SMART APEX II CCD diffractometer (λ(MoK$_\alpha$)-radiation, graphite monochromator, ϕ and ω scan mode, $2\theta_{max}$ = 60°). The structure was solved by direct methods and refined by full-matrix least squares technique with anisotropic displacement parameters for non-hydrogen atoms. The hydrogen atoms were placed in calculated positions and refined within the riding model with fixed isotropic displacement parameters [U_{iso}(H) = 1.5 U_{eq}(C) for the CH_3-groups and U_{iso}(H) = 1.2 U_{eq}(C) for the other groups]. The final divergence factors were R_1 = 0.045 for 4806 independent reflections with $I > 2\sigma(I)$ and wR_2 = 0.119 for all independent reflections, S = 1.002. All calculations were carried out using the SHELXTL program.[22] Crystallographic data for compound **4** have been deposited with the Cambridge Crystallographic Data Centre, CCDC 819323. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or www.ccdc.cam.
19. *Experimental procedure for the synthesis of chromenoazocine* **6** *and chromene* **7**: To a solution of 8-acetoxychromenopyridine **3** (130 mg, 0.37 mmol) in a mixture of MeOH/CH_2Cl_2 (10 mL, 1:1) was added methyl propiolate (0.42 mL, 0.45 mmol). The mixture was stirred at room temperature for 1 d (TLC monitoring). After completion the solvent was evaporated in vacuo. The residue was purified by column chromatography to give chromenoazocine **6** as a white solid and chromene **7** as a yellow oil.
20. *Methyl3-benzyl-10-methylcarbonyloxy-7-oxo-1,3,6,7-tetrahydro-2H-chromeno[4, 3-d]azocine-5-carboxylate* (**6**): Purified by column chromatography (SiO_2, MeOH/$CHCl_3$, 1:50), yield 72 mg, (45%), as a white solid, mp 273–274 °C (EtOAc); Anal. Calcd for $C_{25}H_{23}NO_6$: C, 69.27; H, 5.35; N 3.23. Found: C, 69.2; H, 5.1; N 3.3. R_f (silufol, EtOAc/hexane, 1:1) 0.67; ν_{max} (KBr) 1763, 1709, 1613 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.60 (1H, s, 4-H) 6.95–7.00 (7H, m, CH-Ar), 6.80 (1H, dd, *J* 2.4, 8.8 Hz, 12-H), 4.22 (2H, s, 2-CH_2), 3.97 (2H, s, *CH*$_2$-*Ar*), 3.82 (2H, t, *J* 6.5 Hz, 2-CH_2) 3.70 (3H, s, CO_2CH_3), 2.98 (2H, t, *J* 6.5 Hz, 1-CH_2), 2.26 (3H, s, $COCH_3$); δ_C (100 MHz, $CDCl_3$) 169.9, 168.8, 161.2, 152.4, 152.2, 152.0, 145.6, 137.1, 128.8 (2C), 128.2, 127.5 (2C), 124.9, 124.5, 188.4, 117.6, 110.0, 95.1, 62.0, 51.5, 48.8, 31.1, 23.7, 21.2; *m*/*z* (LC–MS) 434 [M+H]$^+$.
21. *Methyl (E)-3-benzyl(7-hydroxy-2-oxo-4-vinyl-2H-3-chromenylmethyl)amino-2-propenoate* (**7**): Purified by column chromatography (SiO_2, MeOH/$CHCl_3$, 1:20), yield 24 mg, (15%), as a yellow oil; Anal. Calcd for $C_{23}H_{21}NO_5$: C, 70.58; H, 5.41; N 3.58. found C, 70.4; H, 5.5; N, 3.7. R_f (silufol, EtOAc/hexane, 1:1) 0.25; ν_{max} (KBr) 1720, 1612 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 9.80 (1H, br s, OH), 7.61 (1H, d, *J* 13.1 Hz, N-*CH*=CH), 6.64–7.26 (6H, m, CH-Ar), 6.63 (1H, t, *J* 2.4 Hz, 6-H), 6.61 (1H, d, *J* 2.1 Hz, 8-H), 6.58 (1H, dd, *J* 11.8, 17.8 Hz, α-CH), 5.77 (1H, dd, *J* 1.2, 11.8 Hz, β-CH), 5.41 (1H, d, *J* 17.8 Hz, β-CH), 4.62 (1H, d, *J* 13.1 Hz, N–CH=*CH*), 4.46 (2H, s, *CH*$_2$-Ar), 4.24 (2H, s, 1′-CH_2), 3.57 (3H, s, $COCH_3$); *m*/*z* (LC–MS) 392 [M+H]$^+$
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