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Mendeleev Commun., 2017, **27**, 640–641

Mendeleev Communications

Ring opening in 1,2,3,4-tetrahydrochromeno[3,2-*c*]pyridines under the action of electron-deficient alkynes

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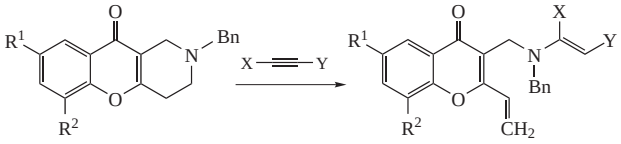
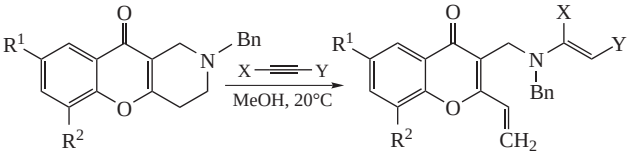
DOI: 10.1016/j.mencom.2017.11.035

2-Vinyl substituted chromones were obtained by the reaction between 1,2,3,4-tetrahydrochromeno[3,2-*c*]pyridines and electron-deficient alkynes.



Benzopyrans are important oxygenated heterocycles which exist as two isomers, benzo-α-pyran (2*H*-chromene) and benzo-γ-pyran (4*H*-chromene). Coumarin (chromen-2-one) and chromone (chromen-4-one) are the most interesting derivatives due to their high biological activity and extremely low toxicity.[1–12] Chromeno[3,4-*c*]pyridines combine two pharmacophore fragments in their molecules and show inhibitory activity against initiating RNA splicing and cancer provoking endonuclease IRE-1.[13] Structures related to chromeno[3,2-*c*]pyridines are also promising targets for the study of their chemical and biological activity.

Earlier we have shown[14] that the reactions of chromeno[3,4-*c*]pyridines with methyl propiolate and acetylacetylene yield substituted coumarins or chromeno[4,3-*d*]azocines depending on the solvent used. Herein we describe conversion of chromeno[3,2-*c*] pyridine derivatives **1a–c**† using the same conditions. We have found that the reactions of 2-benzyl-1,2,3,4-tetrahydro-10*H*-chromeno[3,2-*c*]pyridin-10-one with methyl propiolate, acetylacetylene or dimethyl acetylenedicarboxylate (DMAD) in methanol at room temperature lead to tetrahydropyridine ring opening followed by the formation of vinyl substituted chromones **2a–c** in high yields (Scheme 1). ‡ Electron donating substituents in the aromatic ring do not affect the reactions: in these cases we obtained chromones **2d–f**. We suppose that the intermediate ammonium salt formed during the addition of the nitrogen atom of the tetrahydropyridine fragment to the triple bond of the alkyne undergoes Hoffmann degradation under the action of methoxide anion.



1a $R^1 = R^2 = H$
1b $R^1 = Br$, $R^2 = H$
1c $R^1 = H$, $R^2 = OEt$

2a–f

	R^1	R^2	X	Y	Yield (%)
a	H	H	H	CO_2Me	71
b	H	H	CO_2Me	CO_2Me	72
c	H	H	H	C(O)Me	68
d	H	OEt	H	CO_2Me	74
e	H	OEt	CO_2Me	CO_2Me	69
f	Br	H	H	CO_2Me	73

Scheme 1

Reactions of compounds **1a**,**b** with DMAD in the presence of formic acid which deactivates methoxide anion were accompanied by N-debenzylation leading thus to N-vinylated derivatives **3a**,**b** (Scheme 2).§ The formation of possible product of tetrahydropyridine ring expansion does not occur.

† The synthesis of initial **1a** was described earlier.[15] Chromeno[3,2-*c*]-pyridines **1b**,**c** were obtained similarly (see Online Supplementary Materials).

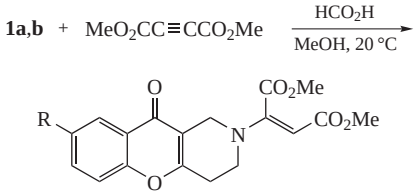
‡ *2-Vinyl substituted chromones* **2a–f** *(general procedure).* Alkyne (1.2 mmol) was added to the solution of compound **1a–c** (1.0 mmol) in methanol (5 ml). The mixture was stirred at room temperature for 1–3 h (TLC control, eluent EtOAc–hexane, 1 : 1). The solvent was evaporated *in vacuo*, the precipitate was recrystallized from EtOAc–hexane.

*Methyl (2*E*)-3-{*N*-benzyl-*N*-[(2-ethenyl-4-oxo-4*H*-chromen-3-yl)methyl]-amino}prop-2-enoate* **2a**. Yield 71%, pink crystals, mp 112–113 °C. IR (ν/cm^{-1}): 1645 (CO), 1687 (CO_2Me). ^{1}H NMR, δ: 3.64 (s, 3 H, CO_2Me), 4.31 (s, 2 H, NCH_2), 4.41 (s, 2 H, CH_2Ph), 4.76 (d, 1H, CH=C*H*–CO_2Me, *J* 12.8 Hz), 5.78 (d, 1H, *J* 11.2 Hz, CH=CH_2), 6.39 (d, 1H, *J* 16.5 Hz, CH=CH_2), 6.69 (dd, 1H, C*H*=CH_2, *J* 11.2, 16.5 Hz), 7.10–7.25 (m, 5 H, CH_2*Ph*), 7.37 (t, 1H, H-7, *J* 7.3 Hz), 7.44 (d, 1H, H-8, *J* 8.2 Hz), 7.65 (t, 1H, H-6, *J* 7.3 Hz), 7.78 (d, 1H, C*H*=CH–CO_2Me, *J* 12.8 Hz), 8.16 (d, 1H, H-5, *J* 8.2 Hz). ^{13}C NMR, δ: 44.2, 50.7, 53.4, 85.8, 117.8 (2 C), 122.9, 125.2, 125.3, 126.1 (2 C), 126.4, 127.2, 127.5, 128.7 (2 C), 134.2, 152.4, 155.4, 159.5, 170.1, 178.0. MS, *m/z*: 376 [M+H]$^+$. Found (%): C, 73.50; H, 5.56; N, 3.88; O, 17.13. Calc. for $C_{23}H_{21}NO_4$ (%): C, 73.58; H, 5.64; N, 3.73; O, 17.05.

For characteristics of compounds **2b–f**, see Online Supplementary Materials.

§ *Synthesis of debenzylation products* **3a**,**b** *(general procedure).* DMAD (1.2 mmol) and formic acid (1.0 mmol) were added to a solution of chromenopyridine **1a**,**b** (1.0 mmol) in methanol (5 ml). The mixture was stirred at room temperature for 3 h (TLC control, eluent EtOAc–hexane, 1 : 1). The product precipitated from the reaction mixture as white crystals.

*Dimethyl (2*E*)-2-{10-oxo-4,10-dihydro-10*H*-chromeno[3,2-c]pyridin-2(3*H*)-yl}but-2-enedioate* **3a**. Yield 86%, colourless crystals, mp 199–200 °C. IR (ν/cm^{-1}): 1630 (CO), 1694 (CO_2Me), 1731 (CO_2Me). ^{1}H NMR, δ: 2.87 (t, 2 H, C^4H_2, *J* 5.3 Hz), 3.50 (t, 2 H, C^3H_2, *J* 5.3 Hz), 3.65 (s, 3 H, CO_2Me), 3.96 (s, 3 H, CO_2Me), 4.16 (s, 2 H, NCH_2), 5.00 (s, 1H, C=C*H*–CO_2Me), 7.39–7.41 (m, 2 H, H-8,9), 7.67 (t, 1H, H-7, *J* 7.8 Hz), 8.18–8.20 (m, 1H, H-6). ^{13}C NMR, δ: 28.0, 42.9, 44.1, 51.2, 53.3, 88.1,



3a R = H (86%)
3b R = Br (84%)

Scheme 2

Analogous reactions in dichloromethane affords products of both debenzylation and tetrahydropyridine fragment degradation in ~1:1 ratio.¶ From dimethyl acetylenedicarboxylate and substrate **1a**, products **2b** and **3a** were obtained (yields 43 and 40%, respectively), while substrate **1b** gave products **2f** and **3b** (yields 41 and 39%, respectively).

The structures of the obtained compounds were confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis. IR spectra of products **2** and **3** exhibit bands at 1627–1649 and 1667–1743 cm^{-1} confirming that the molecules contain carbonyl groups of chromone and ester fragments. ESI mass spectra reveal intense peaks of molecular ions.

The structure of 4-oxo-4*H*-chromene **2b** was confirmed by a single crystal X-ray analysis (Figure 1).††

In conclusion, the main route of reaction between chromeno-[3,2-*c*]pyridines and electron-deficient alkynes is the Hoffmann degradation of tetrahydropyridine fragment yielding substituted chromones. The synthesized compounds seem promising since they are structurally related to 2-styryl substituted chromones having high biological activity against cancer cells PC-3 (prostate carcinoma cell), A-549 (non-small lung adenocarcinoma cell), HCT-15 (colon cancer cell), SK-MEL-2 (malignant melanoma), and KB (epidermoid carcinoma).[20,21]

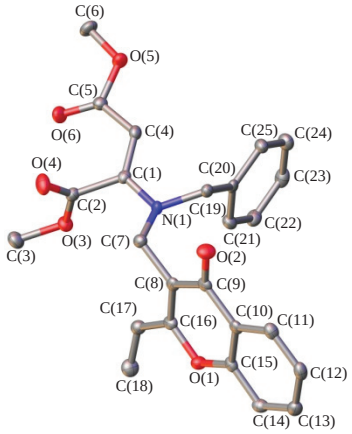


Figure 1 Molecular structure of **2b** presented in ADP ellipsoids at 50% probability.

The publication was prepared with the support of the 'RUDN University Program 5-100'.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2017.11.035.

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Received: 23rd January 2017; Com. 17/5155

114.6, 117.9, 123.1, 125.3, 125.7, 133.9, 153.8, 156.0, 160.9, 166.0, 167.9, 175.7. MS, *m*/*z*: 344 $[M+H]^+$. Found (%): C, 62.85; H, 4.90; N, 4.18; O, 27.85. Calc. for $C_{18}H_{17}NO_6$ (%): C, 62.97; H, 4.99; N, 4.08; O, 27.96.

For characteristics of compound **3b,** see Online Supplementary Materials.

¶ *Reaction of chromenopyridines* **1a**,**b** *with DMAD in dichloromethane*. DMAD (1.2 mmol) was added to a solution of chromenopyridine **1a**,**b** (1.0 mmol) in CH_2Cl_2 (5 ml). The mixture was stirred at room temperature (TLC control, eluent EtOAc–hexane, 1 : 1). The reaction time was 1 day. After completion of the reaction, the solvent was evaporated *in vacuo*, the residue was separated by column chromatography, eluent EtOAc–hexane (1 : 3) (compounds **2b**,**f**) and EtOAc–hexane (1 : 1) (compounds **3a**,**b**).

Yields of compounds: **2b** (43%) and **3a** (40%); **2f** (41%) and **3b** (39%). All physicochemical characteristics of these substances were the same as described previously.

†† *Crystal data for* **2b**. At 120 K, single crystals of **2b** ($C_{25}H_{23}NO_6$, M = 433.44) were colourless blocks, monoclinic, space group $P2_1/n$ (no. 14), a = 8.6471(16), b = 10.1741(19) and c = 23.497(5) Å, β = = 92.669(4)°, V = 2065.0(7) Å^3, Z = 4, T = 120 K, μ(MoKα) = = 0.100 mm^{-1}, d_{calc} = 1.394 g cm^{-3}. A suitable crystal was selected and dataset was measured on a Bruker APEX-II CCD diffractometer. Total of 18876 reflections were measured (4.364 ⩽ 2θ ≤ 52.042°), 4044 unique (R_{int} = 0.0, R_σ = 0.0548) which were used in all calculations. The final R_1 = 0.0757 [$I > 2\sigma(I)$] and wR_2 = 0.1697 (all data). Using Olex2,[16] the structure was solved with the ShelXT[17] structure solution program using Intrinsic Phasing and refined with the ShelXL[18] refinement package using least squares minimization. Analysis of the values of F_{calc} against F_{obs} has shown the presence of twinning, that was refined using TWIN procedure implemented in PLATON[19] software.

CCDC 1525635 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.