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A novel one-pot two-component synthesis of tricyclic pyrano[2,3-*b*]quinoxalines

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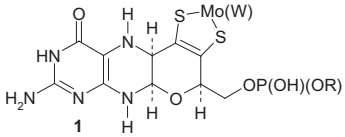
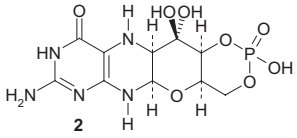
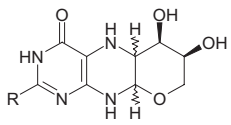
Abstract—A one-pot two-component synthesis of tricyclic pyrano[2,3-*b*]quinoxalines with a pendant hydroxymethyl fuction at the 2-position relevant to molybtopterin is described by the reaction of *o*-phenylenediamine and phenylhydrazone derivatives of sugars in good yields.

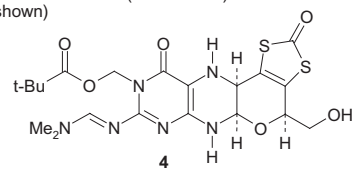
The metal-binding tetrahydropyranopterin enedithiolate or molybdopterin (MPT) is the organic ligand of the molybdenum co-factor (Moco), which has a reduced tricyclic pyranopterin nucleus that carries a terminal phosphate group and a Mo atom bound to an enedithiolate system **1**.[1] Detailed spectroscopic analysis and structural characterization[2a] recently demonstrated that the fully reduced pyranopterin system is present in the precursor **Z**, **2** of Moco, which is different from compound **Z**.[2b] In 1990, Pfleiderer and co-workers reported elegant work on the synthesis of pyranotetrahydropteridines, **3** from various 5,6-diaminopyrimidines and phenylhydrazones of pentoses.[3] Joule and co-workers have recently demonstrated the synthesis of the organic proligand **4** related to MPT in its protected and masked form.[4]



1
(R = H or nucleoside)
(other ligands on the metal not shown)

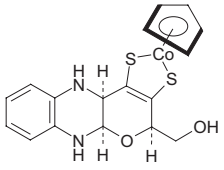

2
(Precursor Z)


3 (R = NH_2, SMe)

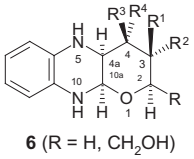


4

Pyrano[2,3-*b*]quinoxalines have proven to be the most promising model substrates related to the MPT of Moco.[4,5] Joule and co-workers have described a linear synthesis of pyranoquinoxalines and the cobalt complex **5** as a model complex related to MPT.[5] Thus, the development of pyrano[2,3-*b*]quinoxalines has been a field of intense investigation over recent years.[4–6] Herein we describe the synthesis of pyranoquinoxalines **6**, which involved in situ cyclization of a side-chain hydroxyl group of sugar hydrazones resulting in the pyran ring with the desired side-chain length as found in MPT.



5 (Quinoxaline analog)


6 (R = H, CH_2OH)

In our synthetic studies[7] on Moco, we recently reported a microwave-mediated Gabriel–Isay condensation for the fusion a pyrazine ring onto a preformed pyrimidine for the synthesis of 6-substituted pterins, and also onto a benzene ring for 2-substituted quinoxalines by reaction with D-glucose or D-galactose with appropriate diamines.[8] However, the use of phenylhydrazone derivatives of these aldohexoses for the synthesis of pyranoquinoxalines, and 6-substituted pteridines remains relatively unexplored, although the analogous phenylhydrazones

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of sugars (e.g., D-arabinose phenylhydrazone) have found applications in the synthesis of 6-polyhydroxyalkylpteridines or pyranopteridines.[9] Our synthesis represents for the first time, a one-step entry to the tricyclic pyranoquinoxaline system having the desired hydroxymethyl function as found in MPT.

We have synthesized pyrano[2,3-*b*]quinoxalines using phenylhydrazones **8a**–**c**, which in turn were prepared according to a literature procedure[10] (Scheme 1).

To this end we started with D-arabinose **7a** and D-glucose **7b**, which upon reaction with phenylhydrazine (freshly prepared from sodium acetate and phenylhydrazine hydrochloride) in water at 22 °C gave phenylhydrazones **8a** and **8b** in 40% and 42% yields. D-Galactose **7c** afforded D-galactose phenylhydrazone **8c** in 80% yield.[11]

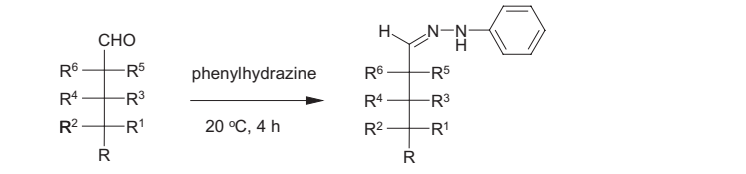
The synthesis of pyranoquinoxalines **6a**–**c** was achieved starting from these phenylhydrazones **8a**–**c** (Scheme 2).

Thus the condensation reaction between *o*-phenylenediamine and phenylhydrazones **8a**–**c** in methanol–water (1:1), concd HCl and 2-mercaptoethanol at 50–60 °C led to the formation of pure pyrano[2,3-*b*]quinoxalines **6a**–**c** in moderate yields.[12] Formation of pyranoquinoxalines **6b**–**c** suggests that the C5 hydroxyl group of the phenylhydrazones is always involved in the cyclization process resulting in a pyran ring and also the formation of one diastereoisomer almost exclusively. Polyhydroxypyranoquinoxalines **6b**–**c** are soluble in alcohol and DMSO, which make isolation of the products difficult, so the more soluble penta-acetyl derivatives **9a**–**b** were prepared (acetic anhydride, DMAP, 60–80 °C, 6–8 h) in 68–80% yield for ease of purification.[13]

The structures of tricyclic pyrano[2,3-*b*]quinoxalines **6** and **9** were established by spectroscopic studies.[11,12] In their ^{1}H NMR spectra, the three methine protons appeared in the range of 6.22–6.06 ppm (H-10a), 5.86–5.78 ppm (H-2), and 5.54–5.34 ppm (H-4a), which are consistent with this class of compounds.[5]

The stereochemistry at the two chiral centers (C3 and C4) of **6** and **9** were already known from the configuration of the starting phenylhydrazones of D-arabinose, D-glucose, and D-galactose used. The *cis* stereochemistry of the pyrazine/pyran ring junction was established using ^{1}H NMR data based on both the coupling constant values and also by observations from the selective NOESY experiments (Fig. 1).

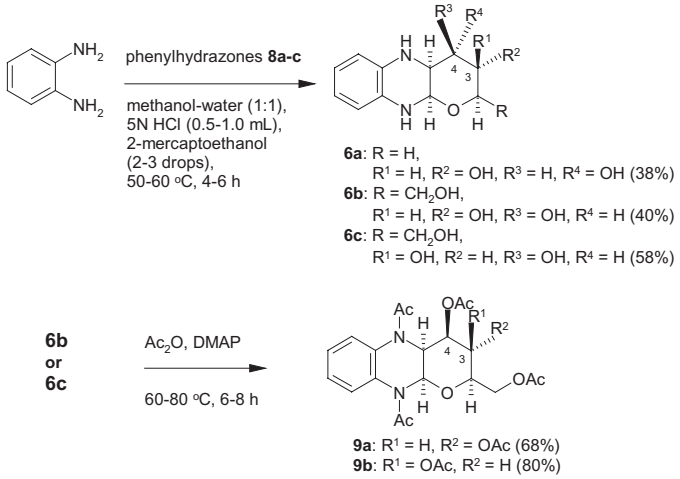
In compound **9b**, the proton at H-4a (δ 5.54 ppm, dd, J = 2.0, 2.0 Hz), showed a strong NOE to the two



7a: R = CH_2OH, R^1 = OH, R^2 = H, R^3 = OH, R^4 = H, R^5 = H, R^6 = OH
7b: R = $CH(OH)CH_2OH$, R^1 = OH, R^2 = H, R^3 = H, R^4 = OH, R^5 = OH, R^6 = H
7c: R = $CH(OH)CH_2OH$, R^1 = H, R^2 = OH, R^3 = H, R^4 = OH, R^5 = OH, R^6 = H

8a: R = CH_2OH, R^1 = OH, R^2 = H, R^3 = OH, R^4 = H, R^5 = H, R^6 = OH (40%)
8b: R = $CH(OH)CH_2OH$, R^1 = OH, R^2 = H, R^3 = H, R^4 = OH, R^5 = OH, R^6 = H (42%)
8c: R = $CH(OH)CH_2OH$, R^1 = H, R^2 = OH, R^3 = H, R^4 = OH, R^5 = OH, R^6 = H (80%)

Scheme 1.



6a: R = H, R^1 = H, R^2 = OH, R^3 = H, R^4 = OH (38%)
6b: R = CH_2OH, R^1 = H, R^2 = OH, R^3 = OH, R^4 = H (40%)
6c: R = CH_2OH, R^1 = OH, R^2 = H, R^3 = OH, R^4 = H (58%)

9a: R^1 = H, R^2 = OAc (68%)
9b: R^1 = OAc, R^2 = H (80%)

Scheme 2.

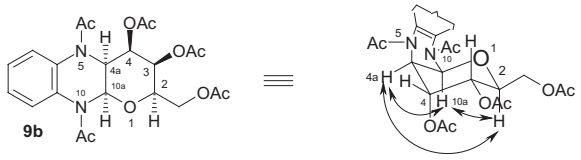


Figure 1. Key NOESY interactions observed in **9b**.

methine proton signals at δ 6.22 ppm (d, J = 3.0 Hz, H-10a) and at δ 5.78 ppm (dd, J = 3.0, 3.0 Hz, H-2), for H-10a and H-2, respectively, and thus established their *cis* relationships. The small coupling constant values (J = 2.0–3.0 Hz) of H-4a with H-10a, and H-2 also suggested that these protons are *cis* with an axial–equatorial arrangement in a chair conformation (see Fig. 1).[9d]

The instabilities of pyranoquinoxalines or pyranopteridines are mainly due to the reversible proton-catalyzed cleavage of the N–C–O system followed by irreversible aerial oxidation, which ultimately produces 2- and 6-substituted derivatives.[14] Therefore, protection is required in order to avoid such oxidation of the tricyclic form. The pyranoquinoxalines **6** are relatively stable compounds and did not undergo such oxidative cleavage to 2-substituted dihydro- or fully oxidized systems during acetylation as suggested from the ^{1}H NMR studies of **9**.

In conclusion, we have developed a novel one-step procedure for the synthesis of tricyclic pyrano[2,3-*b*]quinoxalines, which have the desired side-chain length as found in MPT of the molybdenum co-factor. Further work on pteridine derivatives is underway.

Acknowledgements

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11. All compounds gave satisfactory spectroscopic data. Selected physical data for compound **8c**: Pale-yellow solid. Mp 150–153 °C [lit.[10b] 154–155 °C]. UV/vis ($CHCl_3$): λ_{max} (log ε): 274 nm (5.0). FT-IR (KBr): 3480, 2925, 1751, 1435, 1374, 1221, 1046, 746 cm^{-1}. ^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) = 10.13 (s, 1H), 7.63 (d, 1H, J = 6.3 Hz), 7.51 (t, 2H, J = 7.9 Hz), 7.28 (d, 2H, J = 7.6 Hz), 7.03 (t, 1H, J = 7.2 Hz), 5.10 (d, 1H, J = 6.2 Hz), 4.79 (t, 2H, J = 5.2 Hz), 4.72 (t, 1H, J = 6.3 Hz), 4.53 (t, 2H, J = 8.9 Hz), 4.10 (q, 1H, J = 6.5 Hz), 3.89 (p, 2H, J = 8.7 Hz), 3.82–3.74 (m, 2H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ_C (ppm) = 146.72 (d), 143.28, 129.80, 118.82, 112.45, 73.29 (d), 71.08 (d), 70.70 (d), 70.04 (d), 63.92 (d). MS (ESI): m/z (%) = 270 (M^+, 8), 149 (32), 108 (9), 93 (100), 65 (10), 28 (27).
12. Typical experimental procedure for the condensation of *o*-phenylenediamine with D-galactose phenylhydrazone. Synthesis of pyrano[2,3-*b*]quinoxaline **6c**. To a stirred solution of *o*-phenylenediamine (0.12 g, 1.11 mmol) in a 50% mixture of methanol–water (20 mL) were added freshly prepared D-galactose phenylhydrazone (0.33 g, 1.21 mmol), two drops of 2-mercaptoethanol and HCl (5 N, 0.5 mL). The reaction mixture was heated for 4 h at 50 °C and then allowed to cool to room temperature and then cooled at 0 °C. The resulting brown precipitate was collected by filtration, washed with cold water, acetone,

and ether, dried, which consisted of mainly the title compound **6c** (0.14 g, 58%). Mp 240 °C (dec); UV/vis (CH_3OH): λ_{max} (log ε): 280 (3.2), 273 (3.2), 243 nm (3.2). FT-IR (KBr): 3558, 3399, 2926, 1624, 1433, 1269, 1105, 1036 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ (ppm) = 7.58–7.56 (m, 2H), 7.16–7.08 (m, 2H), 6.90 (d, 1H, J = 7.8 Hz), 6.50 (dd, 1H, J = 3.4, 2.1 Hz), 6.38 (dd, 1H, J = 3.5, 2.2 Hz), 5.52 (d, 1H, J = 6.5 Hz), 5.14 (d, 2H, J = 6.0 Hz), 3.91 (t, 2H, J = 7.7 Hz), 3.75 (br s, 2H), 3.62 (d, 2H, J = 9.3 Hz). ^{13}C NMR (DMSO-d_6, 125 MHz): δ_C (ppm) = 158.53, 148.51, 123.69, 122.02, 73.59, 70.78, 70.03, 68.35, 63.98. MS (ESI): m/z (%) = 269.2 (M^++NH_3, 100), 251.2 (20), 215.4 (10), 174.9 (15), 161.2 (25), 147.2 (30).

13. The pyrano[2,3-*b*]quinoxaline **6c** (0.08 g, 0.23 mmol), acetic anhydride (1.0 mL), and DMAP (10 mg) were heated at 60–80 °C for 4–6 h and then evaporated under reduced pressure. The residue was dissolved in methylene chloride, washed with 5% $NaHCO_3$, water, and dried (Na_2SO_4). The organic layer after evaporation and purification by preparative thin layer chromatography using 1% methanol in methylene chloride afforded the penta-acetyl derivative **9b** as a light-yellow solid. Mp 144–145 °C; UV/vis ($CHCl_3$): λ_{max} (log ε): 271 (8.3), 245 nm (8.3). FT-IR (KBr): 3479, 2925, 1752, 1435, 1374, 1220, 1047 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 7.27–7.23 (m, 4H), 6.22 (d, 1H, J = 3.0 Hz), 5.78 (dd, 1H, J = 3.0, 3.0 Hz), 5.54 (dd, 1H, J = 2.0, 2.0 Hz), 5.32 (dt, 1H, J = 2.0, 4.0, 2.2 Hz), 4.30 (dd, 1.5H, J = 5.1, 5.1 Hz), 3.90 (dd, 1.5H, J = 7.3, 7.3 Hz), 2.19, 2.09, 2.05, 2.02, and 1.97 (5 × s, 15H, 2 × $NHCOCH_3$ and 3 × $OCOCH_3$). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 170.86, 170.71, 170.48, 170.34, 169.46, 148.51, 131.32, 129.25, 69.37, 68.47, 68.02, 67.92, 62.39, 21.11, 21.07, 21.03, 20.91, 20.88. MS (FAB): m/z (%) = 479 (M^++NH_3, 100), 419 (M–Ac, 10), 377 (M − 2 × Ac, 10), 317 (15), 257 (5), 203 (10), 161 (40), 147 (35). Anal. Calcd for $C_{22}H_{26}N_2O_9$: C, 57.13; H, 5.66; N, 6.05. Found: C, 57.01; H, 5.78; N, 5.99.
14. For a discussion on the stability of reduced pyranoquinoxalines or pyranopteridines, see: (a) Ref. 4a; (b) Greatbanks, S. P.; Hillier, I. H.; Garner, C. D.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1529–1534.