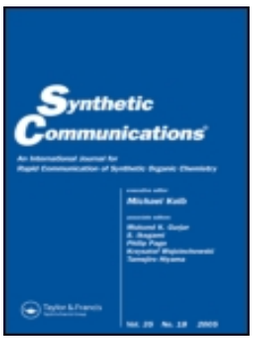

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A SYNTHESIS OF THE PYRANO[3,2-*b*]PYRIDINE RING SYSTEM UNDER MILD CONDITIONS

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ABSTRACT

A route to the relatively rare pyrano[3,2-*b*]pyridin-4-one template (**1**) is described starting from 3-hydroxypyridine. This synthesis allows for varying the substituents at the 2- and 3-positions of the bicycle. A diisopropylsilyloxy moiety was employed to direct lithiation of a pyridine intermediate to the less favored 2-position.

Benzopyranones are pharmacologically important compounds that exhibit a variety of biological activities (1–5). Owing to their poor solubility in water, appropriate solubilizing and suspending agents have to be employed in order for them to be useful pharmacologic agents. Simple aza congeners such as pyrano[3,2-*b*]pyridin-4-ones (and their salts) may serve to circumvent solubility liabilities, due to their higher hydrophilicity. In this paper, we describe a relatively straightforward synthesis to this relatively rare ring system, which is amenable for introduction of substituents at the 2- and 3-positions.

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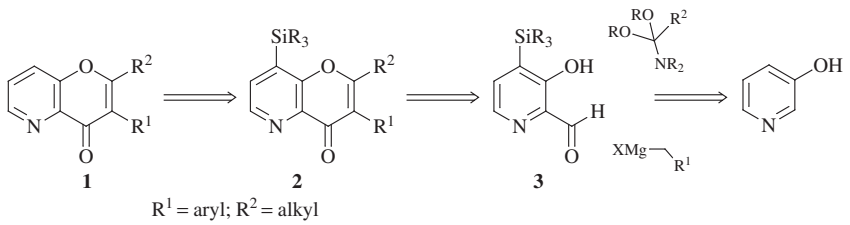
In spite of the spectrum of activities (antiallergy (6), bronchodialating (7), antiulcer (8), selective chronotropic negative (9) activities) exhibited by compounds with the pyrano[3,2-*b*]pyridin-4-one core structure, there are no reports on the synthesis of 2,3-disubstituted pyrano[3,2-*b*]pyridin-ones **1**. However, the synthesis of 2,3-*benzo*-fused and 3-aryl pyrano[3,2-*b*]pyridines is known. Furthermore, regardless of the substitution pattern, the synthesis of known pyrano[3,2-*b*]pyridin-4-one skeleta requires harsh acidic conditions in the ring forming step (typically refluxing acetic (10) or formic acid (6), or hot polyphosphoric acid (7)). Hence, methodology to synthesize this template under milder conditions would be of considerable utility. Therefore, our objective was to develop such conditions as part of an efficient route to this rare template.

Retrosynthetically, 2,3-disubstituted pyrano[3,2-*b*]pyridin-4-ones can be thought of as being derived from the aldehyde **3** (Scheme 1). The substituent at the 3-position can be introduced by Grignard reagents, while that at the 2-position can be derived from amide acetals or ortho esters. The aldehyde **3** can be obtained by ortho formylation of a suitably protected 3-hydroxypyridine. The reduction of this logic to practice is shown is Scheme 2. 3-Hydroxy pyridine **4** was protected as its MOM ether **5** (11). Preliminary CD_3OD quench studies indicated that reaction of compound **5** with *t*-BuLi in THF or ether gave exclusive lithiation at the 4-position. Hence, the 4-position was blocked as a silyl ether to direct subsequent lithiation to the 2-position. The benzyloxy diisopropyl silyl group was chosen over the more conventional trialkyl silyl moiety in the event we decided at a later stage to apply our methodology to the solid phase utilizing our previously described traceless silyl linker (12). Here the benzyloxy group would serve as a surrogate for polystyrene hydroxymethyl resin. Thus, compound **5** was lithiated selectively at the 4-position and quenched with dichlorodiisopropyl silane, followed by reaction with benzyl alcohol to give the silyl ether **6**. Ortho lithiation of compound **6**, followed by quenching the anion with DMF, afforded the aldehyde **7**. Addition of benzylmagnesium chloride to aldehyde **7**, followed by IBX oxidation, yielded ketone **8**. The MOM ether in compound **8** was removed selectively without affecting the silyl group by treatment with 20% TFA in dichloromethane at 0°C for 1 h. Longer reaction times at 25°C with lower concentrations of TFA led



Scheme 1.

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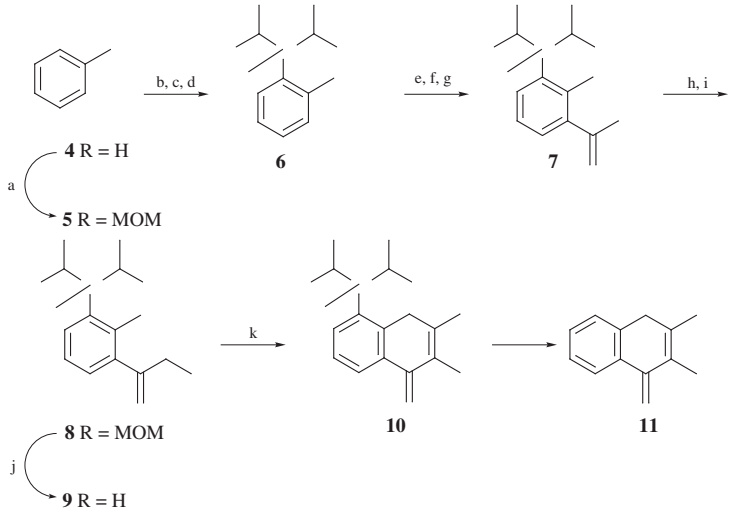

a. MOMCl, Hunigs base, CH_2Cl_2. b. t-BuLi, THF, −78°C. c. iPr_2SiCl_2, −78°C to 25°C. d. BnOH, Imidazole, DMF. e. n-BuLi, TMEDA, THF, −78°C. f. DMF, −78°C − 0°C. g. sat. aq. NH_4Cl. h. BnMgCl, THF, 0°C. i. IBX, DMSO, 25°C. j. 20% TFA/DCM, 0°C. k. $MeC(OMe)_2NMe_2$, THF, 35°C. I. TBAF/THF.

Scheme 2.

to competitive cleavage of the silyloxy group to yield the corresponding silanol. Treatment of compound **9** with *N,N*-dimethylacetamide dimethyl acetal in THF gave the pyranone **10**. The silyl group was cleaved cleanly with TBAF to obtain the target pyrano[3,2-*b*]pyridin-4-one **11**.

In summary, we have designed an efficient route to the synthesis of 2,3-disubstituted pyrano[3,2-*b*]pyridin-4-ones under mild conditions. Extensions of this methodology promise facile access to other heterobicycles containing the 2,3-fused pyridine nucleus.

EXPERIMENTAL

Materials and Methods

Standard reagents were obtained from commercial suppliers and used without further purification. Column chromatography was carried out using E. Merck 60 (230–400 mesh) silica gel. Thin layer chromatography was performed using Merck 60 F254 0.25 μm silica gel plates. ^1H and ^{13}C NMR spectra were obtained on a Varian Unity 400 MHz spectrometer at 400 MHz and 101 MHz,

respectively. Spectra were obtained in $CDCl_3$ with TMS as the internal standard and are reported in ppm. Atmospheric pressure chemical ionization mass spectra (APCIMS) were recorded using a VG Trio 2000 mass spectrometer in a matrix of MeOH/CH_3CN/DMSO. Following normal work-up procedures, organic extracts were dried over anhydrous Na_2SO_4 prior to concentration.

4-(Benzyloxy-diisopropyl-silanyl)-3-methoxymethoxy-pyridine **6**

To a solution of 3-methoxymethoxy-pyridine **5** (11) (5.0 g, 35.9 mmol) in anhydrous diethyl ether (125 mL) at −78°C was added dropwise *t*-BuLi (1.7 M in pentane, 23.2 mL, 39.4 mmol). A white precipitate was formed during the addition. The mixture was stirred for 15 min at −78°C and dichlorodiisopropyl silane (7.1 mL, 39.4 mmol) was added quickly. The mixture was gradually warmed to 25°C and stirred for 9 h. DMF (15 mL) was added to the mixture, which was then concentrated to remove volatiles. To the solution of crude chlorosilane in DMF was added imidazole (4.2 g, 61.7 mmol), followed by benzyl alcohol (4.1 mL, 39.4 mmol), and the mixture was stirred at 25°C for 4 h. The mixture was diluted with ether (250 mL) and washed with water (3 × 250 mL), followed by brine (100 mL). The ether phase was dried, concentrated, and chromatographed on 300 g of SiO_2, eluting with 20:1 then 10:1 Hex:EtOAc, to give the silyl ether **6** (6.8 g, 52%) as a colorless oil, $R_f \sim 0.2$ (10:1, Hex:EtOAc). The material was pure by NMR and mass spectrometry, and was suitable for direct use in the next reaction. ^{1}H NMR δ 8.44 (s, 1H), 8.24 (d, $J = 4.4$ Hz, 1H), 7.42 (d, $J = 4.4$ Hz, 1H), 7.38–7.31 (m, 4H), 7.24 (t, $J = 7.1$ Hz, 1H), 5.14 (s, 2H), 4.92 (s, 2H), 3.42 (s, 3H), 1.38 (sep, $J = 7.4$ Hz, 2H), 1.05 (d, $J = 7.3$ Hz, 6H), 1.00 (d, $J = 7.6$ Hz); ^{13}C NMR δ 157.6, 142.9, 140.9, 135.1, 132.7, 130.4, 128.3, 127.0, 125.8, 94.4, 65.6, 56.2, 17.6, 17.4, 12.7; APCIMS *m/z*: 360.1 (MH^+, 100%).

4-(Benzyloxy-diisopropyl-silanyl)-3-methoxymethoxy-pyridine-2-carbaldehyde **7**

To a solution of silyl ether **6** (6.0 g, 16.6 mmol) in anhydrous diethyl ether (100 mL) at −78°C was added TMEDA (6.3 mL, 41.5 mmol), followed by *n*-BuLi (1.6 M in hexanes, 20.8 mL, 33.2 mmol). The mixture was stirred at −78°C for 30 min. Anhydrous DMF (11.4 mL, 83.0 mmol) was added and the mixture was allowed to warm to 0°C, and then stirred for 1 h. The mixture was diluted with sat. aq. NH_4Cl (10 mL), stirred at 0°C for 30 min and then at 25°C for 30 min, and extracted with ether (200 mL). The ether extract was washed with water (3 × 200 mL), then brine (1 × 100 mL), and concentrated to an oil that was chromatographed (Hex:EtOAc) to leave aldehyde **7** (3.5 g, 55%) as a yellow

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oil. ^{1}H NMR δ 10.2 (s, 1H), 8.53 (d, $J = 4.3$ Hz, 1H), 7.70 (d, $J = 4.3$ Hz, 1H), 7.40–7.27 (m, 5H), 5.10 (s, 2H), 4.96 (s, 2H), 3.52 (s, 3H), 1.46 (sep, $J = 7.5$ Hz, 2H), 1.13 (d, $J = 7.3$ Hz, 6H), 1.05 (d, $J = 7.5$ Hz, 6H); ^{13}C NMR δ 191.9, 159.0, 144.7, 143.6, 141.1, 140.6, 135.6, 128.4, 127.3, 126.0, 101.1, 65.9, 58.0, 17.8, 17.5, 12.9; APCIMS m/z: 388.1 (MH^+, 100%).

1-[4-(Benzyloxy-diisopropyl-silanyl)-3-methoxymethoxy-pyridin-2-yl]-2-phenyl-ethanone **8**

To a solution of benzylmagnesium chloride (2.0 M in THF, 7.7 mL, 15.4 mmol) in THF (30 mL) at 0°C was added dropwise a solution of aldehyde **7** (3.0 g, 7.7 mmol) in THF (30 mL). The mixture was gradually warmed to 25°C, stirred for 30 min, and again cooled to 0°C. The reaction mixture was carefully quenched with water (5 mL) and extracted with ether (250 mL). The ether extract was washed with water (2 × 200 mL) and then sat. aq. NH_4Cl (1 × 100 mL), dried, and concentrated to a residue that was chromatographed to afford purified intermediate alcohol. To the alcohol (2.6 g, 5.4 mmol) was added a solution of IBX (6.1 g, 21.7 mmol) in DMSO (75 mL) and the mixture was stirred at 25°C for 2 h. Water (150 mL) was added to the mixture and the precipitated solid was filtered off and washed with water. The filtrate was extracted with ether (150 mL) and then the extract was washed successively with 100-mL portions of water, sat. aq. $NaHCO_3$, water, and brine. The ether phase was dried and concentrated to leave ketone **8** (2.2 g, 60% from aldehyde **7**) as a pale yellow oil. ^{1}H NMR δ 8.37 (d, $J =$ 4.3 Hz, 1H), 7.64 (d, $J = 4.3$ Hz, 1H), 7.42–7.22 (m, 10H), 4.96 (s, 2H), 4.89(s, 2H), 4.49 (s, 2H), 3.30 (s, 3H), 1.43 (sep, $J = 7.5$ Hz, 2H), 1.12 (d, $J = 7.5$ Hz, 6H), 1.04 (d, $J = 7.5$ Hz, 6H); ^{13}C NMR δ 200.1, 155.7, 145.7, 142.3, 140.8, 139.9, 134.7, 133.9, 130.2, 128.4, 127.2, 126.7, 125.9, 99.1, 65.8, 57.4, 46.9, 17.8, 17.6, 12.9; APCIMS m/z: 478.2 (MH^+, 100%).

1-[4-(Benzyloxy-diisopropyl-silanyl)-3-hydroxy-pyridin-2-yl]-2-phenyl-ethanone **9**

To a vigorously stirred solution of ketone **8** (0.2 g, 0.42 mmol) in dichloromethane, cooled to 0°C, was added TFA (2.0 mL), and the mixture was stirred for 1.5 h. The mixture was diluted with cold dichloromethane (10 mL), and the solution was washed carefully with cold 5% aq. $NaHCO_3$ (4 × 20 mL). The organic phase was dried and concentrated to a residue that was chromatographed (25:1, Hex:EtOAc) to give the hydroxypyridine **9** (0.162 g, 89%) as an oil. ^{1}H NMR δ 12.09 (s, 1H), 8.28 (d, $J = 4.2$ Hz, 1H), 7.70 (d, $J = 4.4$ Hz, 1H), 7.44–7.24

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(m, 10H), 4.99 (s, 2H), 4.63 (s, 2H), 1.50 (sep, $J = 7.6$ Hz, 2H), 1.11 (d, $J = 7.6$ Hz, 6H), 1.07 (d, $J = 7.3$ Hz, 6H); ^{13}C NMR δ 206.8, 163.0, 140.9, 140.4, 137.4, 135.1, 134.6, 134.4, 130.1, 128.5, 128.4, 127.2, 126.9, 126.0, 65.8, 43.9, 17.6, 17.4, 12.7; APCIMS m/z: 434.2 (MH^+, 100%); Anal. calcd. for $C_{26}H_{31}NO_3Si$: C, 72.02; H, 7.21; N, 3.23. Found: C, 72.12; H, 7.04; N, 3.15.

8-(Benzyloxy-diisopropyl-silanyl)-2-methyl-3-phenyl-pyrano[3,2-b]-pyridin-4-one **10**

To a solution of the hydroxypyridine **9** (100 mg, 0.23 mmol) in anhydrous THF (1 mL) was added *N*,*N*-dimethylacetamide dimethyl acetal (0.14 mL, 0.92 mmol). The mixture was stirred for 12 h at 35°C. The solvent was removed by concentration and the crude product was chromatographed (1:1, Hex:EtOAc) to give the pyranone **10** (96 mg, 91%) as an oil. ^{1}H NMR δ 8.77 (d, $J = 4.2$ Hz, 1H), 7.80 (d, $J = 4.2$ Hz, 1H), 7.44–7.23 (m, 10H), 4.98 (s, 2H), 2.24 (s, 3H), 1.53 (sep, $J = 7.4$ Hz, 2H), 1.12 (d, $J = 7.3$ Hz, 6H), 1.07 (d, $J = 7.5$ Hz, 6H); ^{13}C NMR δ 176.1, 162.5, 156.4, 147.5, 140.3, 138.4, 135.9, 134.6, 132.5, 130.4, 128.5, 128.4, 128.1, 127.4, 126.1, 125.9, 66.1, 19.3, 17.6, 17.3, 12.9; HRMS m/z calc. 458.2151 (MH^+), found: 458.2153.

2-Methyl-3-phenyl-pyrano[3,2-b]pyridin-4-one **11**

To pyranone **10** (22.5 mg, 0.05 mmol) was added a solution of TBAF (1.0 M in THF, 0.15 mL, 0.15 mmol) and the mixture was stirred for 2 min at 25°C. Water (5 mL) was added and the solution was extracted with $CHCl_3$ (2×10 mL). The combined extracts were washed with water (3×5 mL) and then brine (1×5 mL). The organic phase was dried and concentrated to a residue that was chromatographed (EtOAc) to give the pyranopyridinone **10** (9.0 mg, 76%) as a colorless crystalline solid. Mp 150°–153°C; ^{1}H NMR δ 8.83 (m, 1H), 7.85 (d, $J = 8.4$ Hz, 1H), 7.62 (m, 1H), 7.47–7.25 (m, 5H), 2.34 (s, 3H); ^{13}C NMR δ 175.5, 163.1, 152.9, 147.9, 139.2, 132.5, 130.3, 128.5, 128.1, 127.5, 126.7, 126.1, 19.5; HRMS *m/z* calc. 238.0868 (MH^+), found: 238.0865; Anal. calcd for $C_{15}H_{11}NO_2 \cdot 0.3H_2O$: C, 74.25; H, 4.82; N, 5.77. Found: C, 73.99; H, 4.93; N, 5.60.

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