Preparation and Reaction of Isomeric Formyl-2,1-benzisoxazoles

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The novel 4-formyl-2,1-benzisoxazole and 7-formyl-2,1-benzisoxazole were prepared for conversion via the Hantzsch synthesis to 1,4-dihydropyridines. The 4-formyl derivative underwent efficient cyclization to the dihydropyridine while analogous reaction of the 7-formyl compound has proven problematic.

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Many 4-aryl dihydropyridines have been reported as calcium channel blockers, which are useful in the treatment of cardiovascular disease [2]. These include compounds 1 containing a benzoxadiazole group; specific examples of this class have been identified as effective calcium channel blockers [3]. It was therefore of interest to prepare dihydropyridines 2-4 containing isomeric 2,1-benzisoxazole groups as analogs of 1, and to determine their biological activity. Herein, we report the synthesis of the previously unknown 7-formyl- and 4-formyl-2,1-benzisoxazoles, 5 and 6, respectively, and the utilization of these in the Hantzsch dihydropyridine synthesis.



The only known formyl-2,1-benzisoxazole is the 3-isomer 7 [4], which is prepared most efficiently from 3-bromomethyl-2,1-benzisoxazole via the Kröhnke aldehyde synthesis [4b]. Application of this methodology to the present work required the preparation of the previously unknown 7-methyl and 4-methyl-2,1-benzisoxazoles, 17 and 11 respectively.

Thus, the acid chloride of 6-methyl-2-nitrobenzoic acid (8) [5] was reduced using sodium borohydride to benzyl alcohol 9 [6], and this was oxidized to 6-methyl-2-nitrobenzaldehyde (10) [6b] using pyridinium chlorochromate. Treatment of 10 with stannous chloride in concentrated hydrochloric acid [7] then afforded 4-methyl-2,1-benzisoxazole (11) (Scheme 1). In similar fashion, 3-methyl-2-nitrobenzoic acid (14) was converted into 7-methyl-2,1-benzisoxazole (17).



Employing the method of Smalley [4b], 11 was first brominated with N-bromosuccinimide. Treatment of bromomethyl compound 12 under Köhnke conditions then provided 4-formyl-2,1-benzisoxazole (6) (Scheme 2).



Attempts to similarly prepare the 7-formyl isomer 5 by the Smalley route were unsuccessful. Treatment of 7-bromomethyl-2,1-benzisoxazole (18) with pyridine gave the corresponding pyridinium bromide; however, oxidation to the aldehyde was problematic. Conversion of 18 to 5 under Sommelet [8] conditions was also unsuccessful. 7-Formyl-2,1-benzisoxazole (5) was successfully prepared employing the milder conditions developed by Kornblum *et al* [9]; that is 18 was converted with silver tosylate in acetonitrile to tosylate 19, which was subsequently treated with sodium bicarbonate in hot DMSO to give 5 (Scheme 3).



Aldehydes 6 and 7 were converted uneventfully to dihydropyridines 3 and 4 via Hantzsch methodology [2,10] using methyl acetoacetate and methyl 3-aminocrotonate. However, under the same conditions aldehyde 5 failed to give dihydropyridine 2. Pre-formation of the Knoevenagel adduct 20 from 5 and methyl acetoacetate, followed by



treatment with methyl-3-aminocrotonate, also failed to produce the dihydropyridine. In both cases complex mixtures resulted in which the crotonate remained unreacted and in which the isoxazole ring proton was absent in the nmr spectra, indicating that the Knoevengel adduct had undergone intramolecular reaction or degradation.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 297 spectrophotometer as chloroform solutions or on a Perkin-Elmer 621 spectrophotometer as potassium bromide pellets. The nmr spectra were recorded on a Varian T-60 or EM-390 spectrometer. High resolution mass spectra were determined using a VG 7035 spectrometer. Column chromatography was performed using E. Merck silica gel (230-400 mesh).

6-Methyl-2-nitrobenzylalcohol (9) [6].

This compound (mp 58-62°) was prepared in 52% yield from acid **8** [5] by the procedure described for the preparation of 15; nmr (deuteriochloroform): δ 2.5 (s, 3H), 2.8 (br s, 1H), 4.7 (s, 2H), 7.4 (m, 3H).

Anal. Caled. for C₆H₉NO₃: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.47; H, 5.51; N, 8.71.

6-Methyl-2-nitrobenzaldehyde (10) [6b].

This compound (mp 47.5-48.5°) was prepared in 82% yield from 9 by the procedure described for the preparation of 16; nmr (deuteriochloroform): δ 2.5 (s, 3H), 7.6 (m, 3H), 10.3 (s, 1H).

Anal. Calcd. for C₈H₇NO₃: C, 58.18; H, 4.27; N, 8.48. Found: C, 58.43; H, 4.20; N, 8.26.

4-Methyl-2,1-benzisoxazole (11).

To a solution of 49.64 g (220 mmoles) of stannous chloride dihydrate in 132 ml of concentrated hydrochloric acid cooled to 15° was added 9.08 g (55.0 mmoles) of aldehyde **10** with rapid stirring. After 2 hours the mixture was diluted with 250 ml of water and extracted with 3 x 150 ml of ether. The extract was washed successively with dilute sodium bicarbonate solution, water, and brine, dried and concentrated to give 6.78 g of oil. The oil was flash chromatographed, eluting with chloroform to give 6.10 g (83%) of 11 as an oil; nmr (deuteriochloroform): δ 2.5 (s, 3H), 6.7 (dd, 1H), 7.3 (m, 2H), 9.1 (s, 1H).

High resolution mass spectrum. Theoretical mass: 133.0528. Measured mass: 133.0526.

4-Bromomethyl-2,1-benzisoxazole (12).

To a solution of 5.99 g (45.0 mmoles) of 11 in 135 ml of carbon tetrachloride was added 8.81 g (49.5 mmoles) of N-bromosuccinimide and 100 mg of benzoyl peroxide. The mixture was refluxed while illuminated by a 250 watt sunlamp for 18 hours. The mixture was cooled and filtered, and the filtrate concentrated to give 9.9 g of a dark red oil. The oil was extracted with 500 ml of hot hexzane. The hexane solution was evaporated to 150 ml and cooled to give 6.60 g (69%) of crystalline 12, mp 51.0-52.5°; nmr (deuteriochloroform): δ 4.6 (s, 2H), 7.2 (m, 3H), 9.3 (s, 1H).

Anal. Caled. for C₈H₆BrNO: C, 45.31; H, 2.85; N, 6.61. Found: C, 44.97; H, 2.62; N, 6.58.

4-Formyl-2,1-benzisoxazole (6).

Step 1. To a solution of 3.99 g (18.8 mmoles) of 12 in 30 ml of ether under nitrogen was added 1.49 g (18.8 mmoles) of pyridine. A white precipitate formed and the mixture was stirred overnight. The precipitate was then filtered off, washed with ether and dried to give 3.64 g (66%) of 4-(2,1-benzisoxazolyl)methylpyridinium bromide (13), mp 172-174°; nmr (DMSO-d₆): δ 6.3 (s, 2H), 7.5 (m, 3H), 8.2 (m, 2H), 8.9 (m, 1H), 9.6 (dd, 2H), 10.3 (s, 1H).

Step 2. A solution of 12.5 ml (12.5 mmoles) of 1 N sodium hydroxide was added to a suspension of 3.64 g (12.5 mmoles) of **13** and 1.88 g (12.5 mmoles) of N,N-dimethyl-4-nitrosoaniline [11] in 19 ml of 95% ethanol, and the mixture was stirred overnight. A solution of 21 ml of 6 N hydrochloric acid was added and, after stirring for 30 minutes, the resulting red solution was extracted with 3 x 150 ml of ether. The ether extract was washed successively with dilute sodium bicarbonate solution, water and brine, dried, and concentrated to give 1.50 g of orange solid. The solid was flash chromatographed eluting with chloroform to give 1.32 g of solid. Recrystallization from *n*-butyl chloride gave 0.94 g (51%) of **6**, mp 137-141°; ir (chloroform): 2800, 1680 (> C = 0), 1630, 1400, 1080, 820 cm⁻¹; nmr (deuteriochloroform): δ 7.6 (m, 3H), 9.7 (s, 1H), 9.9 (s, 1H).

High resolution mass spectrum. Theoretical mass: 147.0320. Measured mass: 147.0321.

3-Methyl-2-nitrobenzylalcohol (15).

A suspension of 1.99 g (50.0 mmoles) of sodium borohydride in 25 ml of dimethylformamide and 50 ml of THF was cooled to 0° under nitrogen. A solution of 9.98 g (50.0 mmoles) of 3-methyl-2-nitrobenzoil chloride (prepared by the treatment of 3-methyl-2-nitrobenzoic acid (14) [11] with thionyl chloride and dimethylformamide) in 50 ml THF was added dropwise. After 3 hours at room temperature, the reaction was quenched by dropwise addition of 50 ml of 3 N hydrochloric acid, diluted with 50 ml of water and extracted with 3 x 125 ml of ether. The extract was washed with water and brine, dried and concentrated to give 10.6 g of oil. The oil was flash chromatographed eluting with 2% methanol/chloroform. Recrystallization from *n*-butyl chloride/hexane gave 5.13 g (61%) of 15, mp 45-47°; nmr (deuteriochloroform): δ 2.3 (s, 3H), 2.6 (br s, 1H), 4.6 (s, 2H), 7.3 (m, 3H).

Anal. Calcd. for C₈H₉NO₃: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.58; H, 5.64; N, 8.46.

3-Methyl-2-nitrobenzaldehyde (16).

A solution of 4.51 g (27.0 mmoles) of 15 in 20 ml of methylene chloride was added to a rapidly stirred suspension of 8.62 g (40.0 mmoles) of pyridinium chlorochromate [12] in 35 ml of methylene chloride. The resulting dark gummy mixture was stirred for 2 hours and diluted with 150 ml of ether. The supernatant was filtered through a pad of silica gel. The pot residue was washed with 2 x 100 ml of ether and the washings were also filtered. The combined filtrate was concentrated and the residue was recrystallized from *n*-butyl chloride/hexane to give 3.98 g (89%) of **16**, mp 59-61°; nmr (deuteriochloroform): δ 2.4 (s, 3H), 7.6 (m, 3H), 9.9 (s, 1H).

Anal. Calcd. for C₈H₇NO₃: C, 58.18; H, 4.27; N, 8.48. Found: C, 58.01; H, 4.33; N, 8.59.

7-Methyl-2, 1-benzisoxazole (17).

This compound was prepared in 88% yield as an oil from 16 by the procedure described for the preparation of 11; nmr (deuteriochloroform): δ 2.4 (s, 3H), 6.9 (m, 2H), 7.3 (m, 1H), 9.0 (s, 1H).

High resolution mass spectrum. Theoretical mass: 133.0528. Measured mass: 133.0526.

7-Bromomethyl-2,1-benzisoxazole (18).

This compound (mp 81-84°) was prepared in 66% yield from 17 by the procedure described for the preparation of 12; nmr (deuteriochloroform): δ 4.8 (s, 2H), 7.2 (m, 3H), 9.1 (s, 1H).

Anal. Calcd. for C₀H₆BrNO: C, 45.31; H, 2.85; N, 6.61. Found: C, 44.97; H, 2.83; N, 6.55.

7-Formyl-2,1-benzisoxazole (5).

Step 1. A solution of 1.91 g (9.0 mmoles) of **18** in 7 ml of acetonitrile was added to a suspension of 3.14 g (11.2 mmoles) of silver tosylate in 20 ml of acetonitrile cooled in an ice-bath in the dark. The mixture was stirred overnight while warming to room temperature, then poured into 22 ml of ice-water and extracted with 3 x 50 ml of ether. The extract was washed with brine, dried and concentrated to give 2.56 g (94%) of 7-(4-tolylsulfonylmethyl)-2,1-benzisoxazole (**19**), mp 105-106.5°; nmr (deuteriochloroform): δ 2.4 (s, 3H), 5.4 (s, 2H), 7.4 (m, 7H), 9.1 (s, 1H).

Step 2. To a suspension of 5.80 g (69 mmoles) of sodium bicarbonate in 43 ml of DMSO at 100° through which a stream of nitrogen was bubbling was added 2.56 g (8.5 mmoles) of **19**. The mixture was heated 5 minutes, cooled rapidly to room temperature, taken up in 100 ml of water and extracted with 4 x 100 of ether. The extract was washed with 3 x 20 ml of water and brine, dried and concentrated to give 1.04 g of yellow oil. The oil was flash chromatographed eluting with 2% methanol/chloroform to give 0.57 g of solid. The solid was recrystallized from *n*-butyl chloride/hexane to give 0.35 g (26%) of **5**, mp 93-95°; ir (chloroform): 2800, 1690 (C=O), 1630, 1530, 1440, 1380, 1260, 1100, 830 cm⁻¹; nmr (deuteriochloroform): δ 7.2 (dd, 1H), 7.9 (d, 1H), 8.0 (s, 1H), 9.4 (s, 1H), 10.3 (s, 1H).

Anal. Calcd. for $C_0H_5NO_2$: C, 65.30; H, 3.43; N, 9.52. Found: C, 65.27; H, 3.29; N, 9.63.

Dimethyl 4-[3-(2,1-benzisoxazolyl)]-2,6-dimethyl-1,4-dihydropyridine-3,5dicarboxylate (4).

A solution of 0.29 g (2.0 mmoles) of 7 [4], 0.23 g (2.0 mmoles) methyl acetoacetate [10] and 0.23 g (2.0 mmoles) of methyl 3-aminocrotonate [11] in 2 ml of 2-propanol was refluxed for 4 hours. The mixture was cooled

and the resulting precipitate was filtered off to give 0.47 g (69%) of crude product which was recrystallized from ethanol to give 0.35 g (51%) of 4, mp 237-238°; ir (potassium bromide pellet): 3450, 3330, 1680, 1640, 1490, 1430, 1220, 1120, 1020, 800, 750 cm⁻¹; nmr (deuteriochloroform): δ 2.3 (s, 6H), 3.6 (s, 6H), 5.7 (s, 1H), 7.4 (m, 4H), 9.4 (br s, 1H).

Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 63.15; H, 5.30; N, 8.18. Found: C, 63.12; H, 5.42; N, 8.22.

Dimethyl

4-[4-(2,1-Benzisoxazolyl)]-2,6-dimetyl-1,4-dihydropyridine-3,5-dicarboxylate (3).

This compound (mp 211-213°) was prepared in 21% yield from **6** by the procedure described for the preparation of **4**; ir (potassium bromide pellet): 3350, 3150, 2950, 1660, 1480, 1430, 1330, 1300, 1210, 1110, 1040, 860 cm⁻¹; nmr (deuteriochloroform): δ 2.3 (s, 6H), 3.6 (s, 6H), 5.3 (s, 1H), 6.3 (br s, 1H), 6.9 (d, 1H, J = 6 Hz), 7.3 (m, 2H), 9.3 (s, 1H).

Anal. Calcd. for C₁₈H₁₈NO₅: C, 63.15; H, 5.30; N, 8.18. Found: C, 62.96; H, 5.50; N, 8.05.

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