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A novel cyclization to isoxazolo[3,4-*e*][2,1]benzisoxazole

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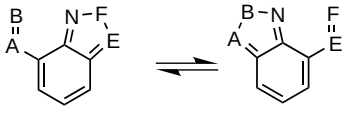
Abstract—Methylation of 2,1-benzisoxazole 4,5-dione 4-oxime **2** using dimethyl sulfate in DMF and in the presence of potassium carbonate gave a substantial yield of isoxazolo[3,4-*e*][2,1]benzisoxazole **4** by an unexpected cyclization reaction of the *O*-methylation product **3**.

The Boulton–Katritzky rearrangement (BKR) generalized in Scheme 1 has received considerable attention from both experimental and theoretical standpoints.[1a,1b] The rearrangement occurs with a wide variety of N-, O- and S-containing heterocycles the prototype of which is 4-nitrobenzofuroxan **1** which rearranges to an identical molecule probably via the transition state shown in Scheme 2 according to calculations at the MP4(SDQ)/6-31G* level.[2]

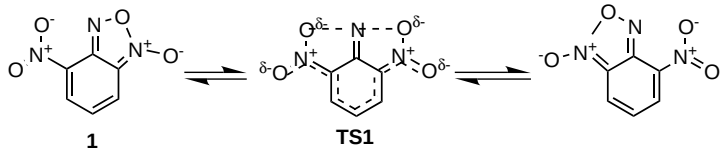
The common feature of all these rearrangements is a pivotal nitrogen atom that probably suffers minimal change in geometry during the molecular transition. Recently the possibility of using carbon as the pivotal atom in a BKR has been considered theoretically[3] and it was concluded that with suitable substituents (e.g. an alkoxy or dialkylamino group) attached to the 5-position of 4-nitroso-2,1-benzisoxazole, such a rearrangement might be energetically possible through deprotonation of the isoxazole ring. During an experimental program designed to test the theoretical predictions we synthesized **2** obtained as the keto-oximino tautomer via the route shown in Scheme 3.



Scheme 1.

It was hoped that methylation of **2** would give 5-methoxy-4-nitroso-2,1-benzisoxazole as a suitable precursor to attempt a base-catalyzed BKR but in fact the reaction gave a mixture of **3** (5%) and **4** (32%). The products were readily separated by chromatography on silica gel and characterized by MS, elemental analysis and $^{1}H/^{13}C$ NMR.

The cyclized product **4** was particularly intriguing since it appeared to be derived from **3** probably by the mechanism shown in Scheme 3. Convincing evidence to support this hypothesis was provided by heating a sample of pure **3** in DMF at 55°C for 1 h in the presence of anhydrous potassium carbonate. All the starting material was consumed and compound **4** was separated from the reaction mixture as the only isolable product. To the best of our knowledge there is no reported precedent for this cyclization. Apart from



Scheme 2.

Keywords: 2,1-benzisoxazole; cyclization; Boulton–Katritzky rearrangement.
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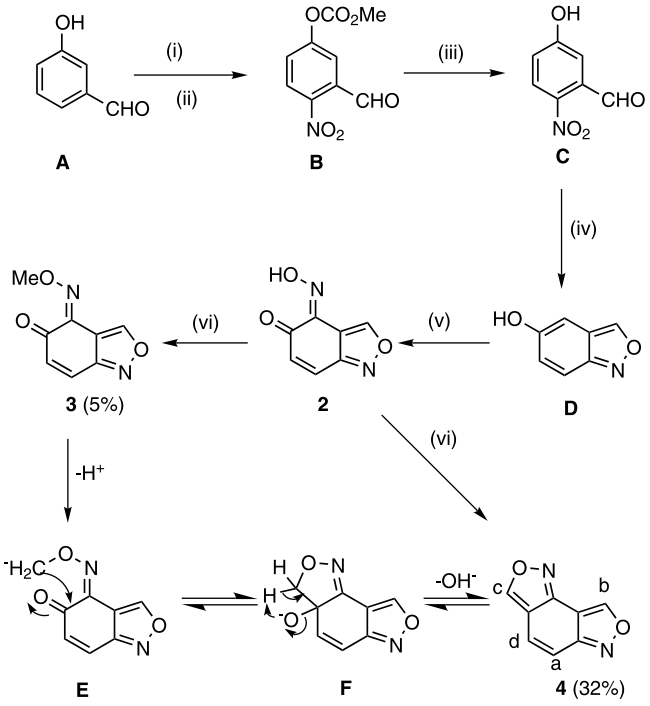

Scheme 3. (i) $ClCO_2Me$, pyridine; (ii) fuming HNO_3, conc. H_2SO_4; (iii) 10% aqueous NaOH; (iv) $SnCl_2 \cdot H_2O$, conc. HCl, 10–15°C; (v) $NaNO_2$, HCl, 0–5°C; (vi) Me_2SO_4, DMF, K_2CO_3, 55–60°C.

elemental analysis and HRMS, **4** was characterized by some unusual NMR features. In $CDCl_3$ just three proton signals with no fine structure were observed at 9.43, 8.19, and 7.65 ppm in a ratio of 1:1:2, respectively. In toluene-d_8 however, four signals were observed at 8.53 (d, $J=1.05$ Hz, 1H), 7.19 (s, 1H), 7.12 (dd, $^3J=9.6$ Hz, $^4J=1.05$ Hz, 1H) and 6.80 ppm (d, $J=9.6$ Hz, 1H), which were assigned to protons c, b, d, and a, respectively. Selective homonuclear decoupling at 6.80 ppm collapsed proton b to a doublet ($J\sim1$ Hz) and selective decoupling at 7.12 ppm collapsed protons a and c to singlets consistent with the proposed structure. Presumably an intermolecular complex with the solvent toluene promoted separation of the ^1H NMR signals. The ^{13}C NMR in $CDCl_3$ showed eight signals again consistent with **4** and ^1H–^{13}C COSY correlation spectra enabled the final carbon assignments to be made.

In conclusion, although the original objectives of the project are still to be realized, a novel cyclization has been established involving formation of a carbon–carbon bond which may well afford a new route to derivatives of 2,1-benzisoxazoles through *o*-nitroso phenols or their keto-oxime tautomers.

Acknowledgements

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7. Methyl 3-formylphenyl carbonate, methyl 3-formyl-4-nitrophenyl carbonate, **B**, and 2-nitro-5-hydroxybenzaldehyde, **C**, were prepared from 3-hydroxybenzaldehyde, **A**, using procedures described in Ref. 4. *Methyl 3-formylphenyl carbonate* was obtained in 66% yield as colorless crystals, mp 47–49°C; ^1H NMR (300 MHz, $CDCl_3$): $\delta=3.94$ (s, 3H), 7.46 (dd, $J=8.1$, 1.0 Hz, 1H, H-6), 7.57 (t, $J=7.8$ Hz, 1H, H-5), 7.72 (d, $J=0.7$ Hz, 1H, H-2), 7.79 (dd, $J=7.7$, 1.0 Hz, 1H, H-4), 10.01 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=55.6$, 121.7, 127.1, 127.4, 130.2, 137.8, 151.6, 153.9, 190.9. Anal. Calcd for $C_9H_8O_4$: C, 60.00; H, 4.48. Found: C, 59.75; H, 4.49.
Methyl 3-formyl-4-nitrophenyl carbonate **B**, was obtained in 95% yield as purple prisms, mp 76–78°C; ^1H NMR (300 MHz, $CDCl_3$): $\delta=3.97$ (s, 3H), 7.60 (dd, $J=8.8$, 2.6 Hz, 1H, H-6), 7.76 (d, $J=2.6$ Hz, 1H, H-2), 8.21 (d, $J=8.8$ Hz, 1H, H-5), 10.43 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ, 56.1, 121.9, 125.7, 126.6, 133.2, 146.4, 152.8, 154.8, 186.9. Anal. Calcd for $C_9H_7NO_6$: C, 48.01; H, 3.13; N, 6.22. Found: C, 48.07; H, 3.07; N, 6.09.
2-Nitro-5-hydroxybenzaldehyde **C**, was obtained in 92% yield as yellow needles, mp 167–169°C, [lit. mp 167–168°C[4]]; ^1H NMR (300 MHz, DMSO-d_6): $\delta=5.24$ (brs, 1H), 6.92 (s, 1H, H-6), 6.97 (d, $J=8.9$ Hz, 1H, H-4), 8.07 (d, $J=8.9$ Hz, 1H, H-3), 10.28 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) $\delta=115.3$, 119.6, 127.9, 135.7, 138.2, 166.5, 190.7.
5-Hydroxy-2,1-benzisoxazole **D**, was obtained in 90% yield as colorless prisms, mp 150–152°C by the procedure detailed in Ref. 5. ^1H NMR (300 MHz, DMSO-d_6): $\delta=$ 6.74 (s, 1H, H-4), 7.07 (d, $J=9.5$ Hz, 1H, H-6), 7.57 (d, $J=9.5$, Hz, 1H, H-7), 9.42 (s, 1H, H-3), 9.85 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) $\delta=96.0$, 115.9, 118.5, 128.2, 153.0, 153.3, 153.4. Anal. Calcd for $C_7H_5NO_2$: C, 62.22; H, 3.73; N, 10.37. Found: C, 62.32; H, 3.73; N, 10.16.
2,1-Benzisoxazole-4,5-dione 4-oxime **2** was obtained in 100% yield as a grey-brown powder, mp 228–229°C (d) by the method outlined in Ref. 6. ^1H NMR (300 MHz, DMSO-d_6): $\delta=6.64$ (d, $J=10.0$ Hz, 1H, H-7), 7.89 (d, $J=10.0$ Hz, 1H, H-6), 9.70 (s, 1H, H-3), 14.12 (s, 1H, NOH); ^{13}C NMR (75 MHz, DMSO-d_6) $\delta=108.2$, 130.3, 134.8, 140.9, 154.1, 161.3, 181.7. Anal. Calcd for $C_7H_4N_2O_3$: C, 51.23; H, 2.46. Found: C, 51.58; H, 2.61.
*2,1-Benzisoxazole-4,5-dione-4-(*O*-methyloxime)* **3** *and isoxazolo[3,4-*e*][2,1]benzisoxazole* **4** were obtained as a mixture by methylation of **2** using the procedure outlined in Ref. 4. A mixture of **2** (1.0 g, 6.09 mmol), anhydrous potassium carbonate (1.57 g, 11.36 mmol), dimethyl sulfate (1.28 g, 10.18 mmol) and dry DMF (42 mL) was heated with stirring at 54–60°C for 3 h under argon. The

mixture was cooled to 20°C and water (70 mL) was added slowly with stirring. The mixture was extracted with Et_2O (3×50 ml) and the combined ether extracts dried over anhydrous $MgSO_4$. The solvent was evaporated and the residue was purified by column chromatography (hexanes/ethyl acetate, 6/1–3/1) to afford pure **3** as the first fraction (0.05 g, 5%) and **4** as the second fraction (0.31 g, 32%).

*2,1-Benzisoxazole-4,5-dione-4-(*O*-methyloxime)* **3**, colorless powder, mp 164–165°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=4.30$ (s, 3H), 6.64 (d, $J=10.4$ Hz, 1H, H-7), 7.43 (d, $J=10.4$ Hz, 1H, H-6), 9.31 (s, 1H, H-3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=64.5$, 109.3, 131.6, 139.5, 141.6, 153.1, 161.0, 178.2. LSIMS, Calcd for $C_8H_7N_2O_3$ (M+1): 179.0457. Found: 179.0451.

*Isoxazolo[3,4-*e*][2,1]benzisoxazole* **4**, colorless powder, mp 155–157°C; ^{1}H NMR, (300 MHz, toluene-d_8): $\delta=6.80$ (d, $J=9.6$ Hz, 1H), 7.12 (dd, $^3J=9.6$ Hz, $^4J=1.0$ Hz, 1H) 7.19 (s, 1H), 8.53 (d, $J=1.0$ Hz, 1H), which were assigned to protons a, d, b and c, respectively (see Scheme 3). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=111.9$, 113.9, 118.0, 129.7, 146.8, 152.1, 152.3, 156.2. LSIMS, Calcd for $C_8H_5N_2O_2$ (M+1)=161.0351. Found: 161.0360. Anal. Calcd for $C_8H_4N_2O_2$: C, 60.01; H, 2.52; N, 17.49. Found: C, 59.61; H, 2.35; N, 17.10.

Conversion of ***3*** *to* ***4***

A mixture of 2,1-benzisoxazole-4,5-dione 4-(*O*-methyloxime) **3** (0.1 g, 0.56 mmol), anhydrous potassium carbonate (0.134 g, 0.94 mmol) and dry DMF (3 mL) was stirred at 54–57°C for 1 h under nitrogen. DMF was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using hexanes/ethyl acetate (6:1, v/v) as eluent to afford isoxazolo[3,4-*e*][2,1]benzisoxazole **4** (0.045 g, 0.28 mmol) as the only isolable product in 50% yield.