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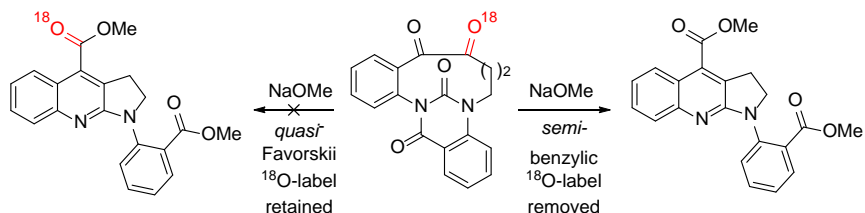
Mechanistic Investigation of a Novel Medium-sized Ring Rearrangement

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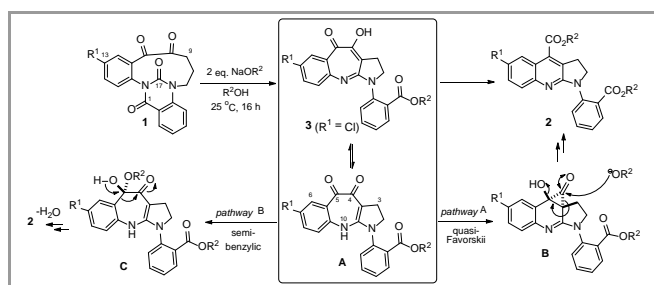
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Abstract The dominant mechanism operating in a recently disclosed ring-contraction is revealed for the first time. Providing new insight and supporting evidence into a classic ring contraction strategy within a rigidified larger ring system.

Key words Favorskii, mechanism, medium-sized ring, ¹⁸O labelling, Rearrangement, Ring contraction, Semi-benzylic.

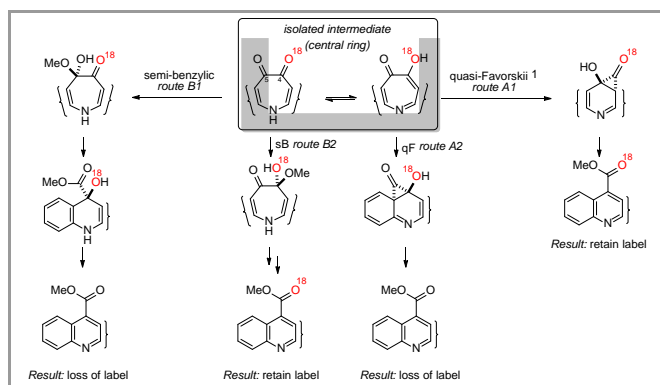


Scheme 1 Observed ring contraction of **1** to **2** and isolated intermediate **3**.

One of the elegant solutions in the organic chemists' toolbox, when constructing a densely functionalised smaller ring system, for purposes as varied as natural product synthesis¹ to medicinal chemistry,² is to contract an easier to access larger ring system.³ Ring contractions can proceed *via* one of three dominant mechanisms: cationic, carbenoid or anionic in nature.⁴ The importance of this class can easily be seen with named reactions such as the Pinacol, semi-Pinacol, Benzilic acid, semi-Benzylic and Favorskii rearrangements.⁵ Recently, we identified within a class of 10-membered heterocyclic ring systems (7,8,9-trihydrobenzo[*d*]quinazolo[1,2,3-*a,b*,1,3]diazecane-1,10,11,17-tetrones (**1**))⁶ a one-pot, multi-step rearrangement under mild conditions to pyrrolo[2,3-*b*]quinolines (such as **2**, Scheme 1) exemplified with alkoxides and amines in up to 77% yield.⁷ Fortuitously, a competent isolated intermediate (**3**) was found in certain examples, that when re-submitted to the reaction conditions for a further length of time afforded the same product as **2**. We previously hypothesised that it was likely either a benzylic or Favorskii-type rearrangement occurred from reaction intermediate (**3**) that led to the ring contraction product (**2**).

In Scheme 1 it can be seen that isolated intermediate **3** can exist in equilibria with its diketone tautomeric structure (**A**). *Pathway A*, depicts a quasi-Favorskii rearrangement proceeding *via* cyclisation of the *N*(10) enamine of **A** onto the *C*(5) carbonyl group will form a strained cyclopropanone (intermediate **B**). The cyclopropanone (**B**) will be labile to attack by a nucleophile and in doing so the ring strain will be relieved. Elimination of hydroxide from **B** will in turn generate an aromatic quinoline ring. An equally likely route to **2** from **1** is *Pathway B*, a semi-benzylic rearrangement of **A** due to the non-enolizable diketone functionality present and in particular, the highly electrophilic *C*5 carbonyl group (δ 178.3 ppm, ¹³C NMR). Therefore, attack of a nucleophile at the *C*5 position of **A** could induce a ring contraction *via* intermediate **C** to **2**.⁷ Herein we show for the first time, using isotopic labelling studies, the major mechanism in operation.

To conclusively prove whether either of these rearrangements (*pathway A* or *B*, *quasi-Favorskii* or semi-benzylic reactions, respectively) occurred we decided upon a microscale ¹⁸Oxygen-labelling experiment of the carbonyl group's installed *via* oxidative fragmentation in the preceding step (Scheme 2).



Scheme 2 Potential ring-contraction mechanisms in operation. Key: sB = semi-Benzylic; qF = quasi-Favorskii.

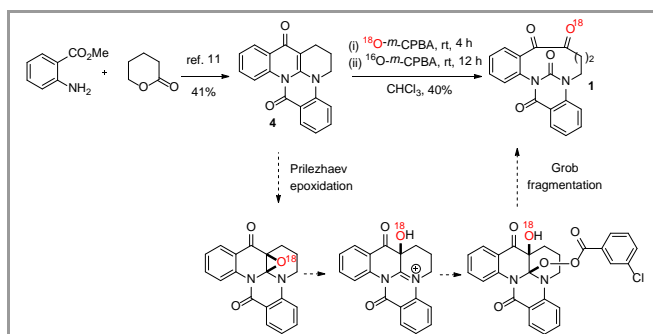
This step would determine if the ^{18}O -enriched C(4) carbonyl oxygen was retained or lost during the ring contraction step. In Scheme 2 it can be seen that labelling the C(4) carbonyl of intermediate **3** (and its tautomer **A**) would yield binary results. The alternative incorporation of a ^{13}C label from a reaction precursor would be retained in both rearrangement route products (not depicted).⁸

Operative mechanisms (Scheme 2) include two routes to a semi-benzylic mediated ring contraction and two routes to a quasi-Favorskii mediated ring contraction, respectively. Addressing the four potential routes in turn; the *quasi-Favorskii* route A1 which would proceed with retention of aromaticity and retention of label and route A2 via an anti-aromatic intermediate and loss of label. In turn, *semi-Benzylic* route B1 mechanism proceeds through nucleophilic attack at the more electrophilic C5 carbonyl of **3** (178.3 ppm, ^{13}C NMR). Whilst *semi-Benzylic* route B2 mechanism proceeds through nucleophilic attack at the less electrophilic C4 carbonyl of **3** (153.1 ppm, ^{13}C NMR). Comparison of route B1 with route B2 would lead to different outcomes, loss of label (route 1) and retention of label (route 2), respectively. Therefore, if the ^{18}O label was retained a *quasi-Favorskii* mechanism (route A1) would be the most likely mechanism in operation (due to ground state carbonyl electrophilicity measurements) and loss of label would be most likely due to a *semi-Benzylic* rearrangement (Route B1, mitigating the need to undergo a strained anti-aromatic intermediate). The further possibility on an internal 6π electrocycloisatation (*c.f.* Karimi)⁹ of intermediate species **3** was ruled out due to the internal strain within the multi-ring fused system.

Due to the scarcity of ^{18}O -labelling reagents, a microscale experiment was chosen to prepare ^{18}O -*m*-CPBA from commercially available (90% labelled) ^{18}O -hydrogen peroxide (Scheme 3).¹⁰ Briefly, fusion of methyl anthranilate with δ -valerolactam in a sealed reactor vessel afforded **4** in 41% yield.¹¹ Compound **4** was exposed to a single equivalent of freshly prepared ^{18}O -*m*-CPBA under high-dilution conditions, until consumption of **4** was indicated by TLC. The intermediate species was treated with a further equivalent of unlabelled *m*-CPBA to ensure all of the ^{18}O -labelled epoxide was intercepted to undergo Grob-type fragmentation to **1** in a 40% isolated yield. The location of the ^{18}O carbonyl group can be inferred from the well-known nitrogen assisted ring opening of epoxides from previously reported trapping experiments.¹² Furthermore, ground state measurement of the infrared carbonyl absorption

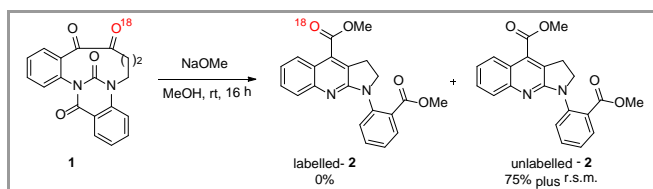
frequency would be expected to undergo a subtle change. Due to the overlapping of the diketone absorption, the discrimination of the two carbonyl groups was not possible. However, a subtle difference in the absorption frequency of the diketone unit (1707 cm^{-1} in the labelled versus 1709 cm^{-1} in the unlabelled infrared spectra) and no change in the urea/amide carbonyl stretching frequency gave further credence to the location of the ^{18}O carbonyl location being on the newly installed carbonyl of the diketone in **1** versus the urea carbonyl, in accordance with the proposed reaction mechanism.

^1H and ^{13}C NMR spectroscopic analyses were in accordance with the previously reported structure of unlabelled **1**,⁶ furthermore electrospray mass spectroscopic analyses indicated a mono-incorporation of an ^{18}O -label with slight loss of labelling.¹³



Scheme 3 Preparation of ^{18}O -labelled reaction precursor **1** and mechanistic rationale.

^{18}O -labelled **1** was treated¹⁴ under the reported conditions of methanolic sodium methoxide to afford the ring contraction product **2** in a 75% isolated yield, as confirmed by NMR spectral analyses (Scheme 4).



Scheme 4 Treatment of **1** with NaOMe could afford labelled-**2** or unlabelled-**2**

Analysis of the mass spectrum of **2** revealed no trace of the ^{18}O -label presence (other than at background levels) indicating **2** was unlabelled. Therefore, based on the possible reaction pathways outlined in Schemes 1 and 2, the predominant pathway in operation was *semi-benzylic*, in agreement with avoiding a strained anti-aromatic reaction intermediate (Scheme 2) and being driven by nucleophilic attack at the more electrophilic carbonyl. Further supporting evidence for this identified reaction pathway can be observed by the migratory aptitude trend of a phenyl group over a carbonyl group migration in related systems.¹⁵

In this letter we have identified the predominant mechanism of ring contraction within a 10-membered ring system (via a 7,5-ring system) to a 6,5-ring system is *semi-benzylic* in nature through ^{18}O -isotopic labelling studies. Providing new insight into ring contraction mechanisms within complex substructures.

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

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- (14) Typical procedure: To a solution of **1** (10 mg, 0.03 mmol) in anhydrous methanol (1.0 mL) was added sodium methoxide (3 mg, 0.06 mmol). The reaction mixture was stirred at room temperature for 16 h then evaporated *in vacuo*, re-dissolved in dichloromethane (4.0 mL) and washed with NaHCO_{3(aq)} (2 × 2.0 mL). The organic layer was dried (MgSO₄), filtered and concentrated *in vacuo* to give a solid which was purified by flash column chromatography (SiO₂; ethyl acetate:hexane (3:7)) furnished to afford the title compound as a yellow powder (8 mg, 75%). Mp 148-149 °C (lit.^{S3} 149-150 °C); ¹H NMR (400 MHz, CDCl₃): δ 8.18 (dd, ³J = 8.5 Hz, ⁴J = 1.0 Hz, 1H), 7.88 (dd, ³J = 8.0 Hz, ⁴J = 1.5 Hz, 1H), 7.63-7.52 (m, 2H), 7.49-7.42 (m, 1H), 7.36-7.31 (m, 1H), 7.30-7.23 (m, 2H), 4.20 (t, ³J = 8.0 Hz, 2H), 4.04 (s, 3H), 3.55-3.47 (m, 5H); ¹³C NMR (100 MHz, CDCl₃): δ 168.0, 166.8, 158.3, 147.6, 139.2, 132.3, 131.2, 130.7, 128.9, 128.6, 127.0, 126.9, 124.9, 124.8, 123.4, 122.9, 120.9, 52.3, 51.9, 50.3, 26.9; IR (KBr): ν_{max} = 2945 (m), 1725 (s) (C=O), 1717 (s) (C=O), 1617 (m), 1597 (m), 1483 (m), 1228 (w), 754 (w) cm⁻¹; LRMS (ESI⁺): m/z (%) 363 [M+H]⁺; HRMS (ESI⁺): m/z calcd for C₂₁H₁₉N₂O₄ [M+H]⁺: 363.1345; found 363.1341.
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