Mechanistic Investigation of a Novel Medium-sized Ring Rearrangement

Aneesa J. Al-Ani and Alan M. Jones

A Division of Chemistry and Environmental Science, Manchester Metropolitan University, M1 5GD, UK
B School of Pharmacy, University of Birmingham, Edgbaston, B15 2TT, UK
* Corresponding author: Dr Alan M. Jones, email a.m.jones.2@bham.ac.uk; phone +44(0)1214-147288, web: www.jonesgroupresearch.wordpress.com

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.

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 synthesis to medicinal chemistry, is to contract an easier to access larger ring system. Ring contractions can proceed via one of three dominant mechanisms: cationic, carbenoid or anionic in nature. The importance of this class can easily be seen with named reactions such as the Pinacol, semi-Pinacol, Benzilic acid, semi-Benzylic and Favorksii rearrangements. Recently, we identified within a class of 10-membered heterocyclic ring systems (7,8,9-trihydrobenzo[1,2,3-\(d\)]quinazolo[1,2,3-\(a,b,1,3\)]diazecane-1,10,11,17-tetrones (1)) 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. 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 Favorksii-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-Favorksii 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 C5 carbonyl group (δ 178.3 ppm, \(^{13}\)C NMR). Therefore, attack of a nucleophile at the C5 position of A could induce a ring contraction via intermediate C to 2. 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-Favorksii 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 18O-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 13C label from a reaction precursor would be retained in both rearrangement route products (not depicted). 3

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, 13C NMR) whilst semi-Benzylic route B2 mechanism proceeds through nucleophilic attack at the less electrophilic C4 carbonyl of 3 (153.1 ppm, 13C 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 18O label was retained a quasi-Favorskii mechanism (route A1) would be the most likely mechanism in operation (due to ground state measurement of the infrared carbonyl absorption from previously reported trapping experiments). 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 18O 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 13C NMR spectroscopic analyses were in accordance with the previously reported structure of unlabelled 1, 4 furthermore electrospray mass spectroscopic analyses indicated a mono-incorporation of an 18O-label with slight loss of labelling.

18O-labelled 1 was treated 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).

Analysis of the mass spectrum of 2 revealed no trace of the 18O-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.

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 18O-isotopic labelling studies. Providing new insight into ring contraction mechanisms within complex substructures.
Acknowledgment

Dr Maira Guzman (Manchester Metropolitan University) is thanked for mass spectroscopic analyses.

Supporting Information

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

Primary Data

NO (this text will be deleted prior to publication)

References and Notes


(14) Typical procedure: To a solution of 1 (10 mg, 0.03 mmol) in anhydrous methanol (1.0 mL) was added potassium methoxide (3 mg, 0.06 mmol). The reaction mixture was stirred at room temperature for 16 h, then evaporated in vacuo, and the residue was redissolved in dichloromethane (4.0 mL) and washed with NaHCO 3(aq.) (2 × 2.0 mL). The organic layer was dried (MgSO 4), filtered and concentrated in vacuo to give a solid which was purified by flash column chromatography (SiO 2; ethyl acetate:hexane (3:7)) to afford the title compound as a yellow powder (8 mg, 75%).

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, and the residue was redissolved in dichloromethane (4.0 mL) and washed with NaHCO 3(aq.) (2 × 2.0 mL). The organic layer was dried (MgSO 4), filtered and concentrated in vacuo to give a solid which was purified by flash column chromatography (SiO 2; ethyl acetate:hexane (3:7)) to afford the title compound as a yellow powder (8 mg, 75%).


Checklist (have these on hand for manuscript submission in ScholarOne):

- cover letter, including a statement of the work’s significance
- full mailing address, telephone and fax numbers, and e-mail address of the corresponding author
- email address for each author
- original Word file
- original graphics files zipped into one zip file
- eye-catching graphical abstract as an individual file
- 5–8 key words
- separate Supporting Information file
- separate zipped Primary Data files including cover sheet (optional)

Useful links:

- SYNLLETT homepage
- SYNLLETT information and tools for authors
- Graphical abstract samples (PDF file download)
- What is “Primary Data”?
- ScholarOne (manuscript submission)