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Unexpected ring-expansion of 1,2-benzisoxazol-3-ones

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ABSTRACT

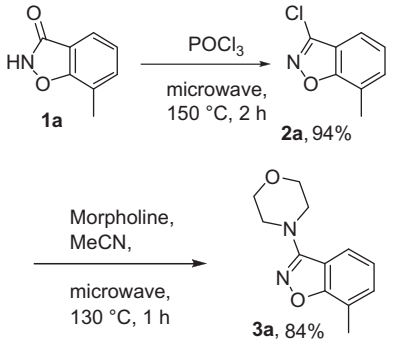
A novel and unexpected ring-expansion reaction of 1,2-benzisoxazol-3-ones is identified. The scope of this reaction is exemplified and the proposed mechanism is also implicated in another degradation process. This reaction also represents a new method for accessing the 4*H*-1,3-benzoxazin-4-one skeleton.

The construction and subsequent functionalisation of densely-substituted and/or unusual heterocyclic skeleta is a recurrent theme in industrial and academic research groups alike. Furthermore, there is a growing desire within the pharmaceutical industry to access hitherto unexplored chemical space.[1] Increasingly therefore, synthetic chemists might expect to encounter individual substrates, or even classes of substrates, which do not perform well in otherwise standard methodologies. The research described herein highlights this point, albeit on a relatively common heterocyclic skeleton.

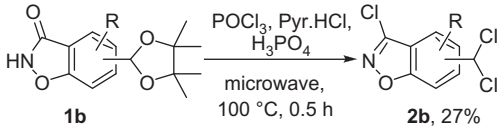
The 1,2-benzisoxazole motif is a common pharmacophore and, as such, is found in a wide range of pharmaceutically active compounds.[2] Due to this biological importance, construction and subsequent functionalisation of 1,2-benzisoxazoles has attracted much interest.[3,4] One of the more common methods used for functionalisation at the 3-position is chlorination of the corresponding 1,2-benzisoxazol-3-one followed by reaction with a nucleophile[4] (e.g., see Scheme 1).

As can be seen in this example, however, the conditions used are often quite harsh. Indeed, it appears that chlorination of the isoxazol-3-one unit in general is a difficult transformation. For example, as well as the microwave-mediated chemistry outlined above, Andersen and Begtrup found it necessary to develop highly acidic thermal conditions to accomplish chlorination of 4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridin-3-ones ($POCl_3$, H_3PO_4 and pyridinium hydrochloride at reflux).[5] As one might expect, neither methodology lends itself to application in the presence of sensitive functionality.

As part of an ongoing research programme, we had reason to investigate the functionalisation of polysubstituted 1,2-benzisoxazoles containing a protected aldehyde moiety. To this end, we attempted a microwave-mediated chlorination of a 1,2-benzisoxazol-3-one containing a reasonably robust pinacol acetal **1b**. 'Standard' conditions using $POCl_3$ with or without a solvent (e.g., acetonitrile)



Scheme 1. Functionalisation of a 1,2-benzisoxazol-3-one.[4a]



Scheme 2. Chlorination of an acetal-bearing 1,2-benzisoxazolone.

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resulted in no conversion. When the more forcing acidic conditions developed by Andersen and Begtrup were attempted, the only product isolated from this reaction was 3-chloro-1,2-benzisoxazole derivative **2b** in which the pinacol acetal had been transformed into a *gem*-dichloromethyl moiety (Scheme 2).

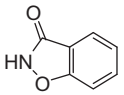
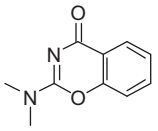
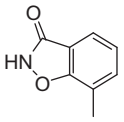
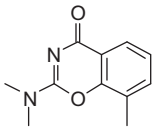
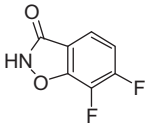
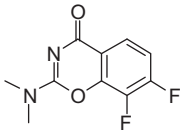
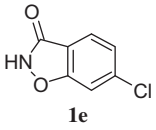
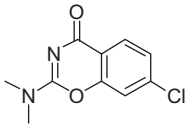
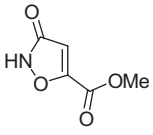
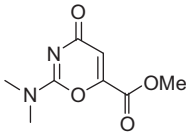
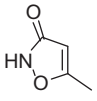
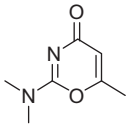
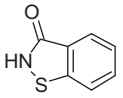
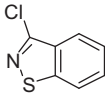
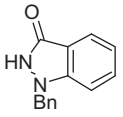
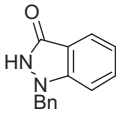
A subsequent survey of the literature identified only one example of the chlorination of a 2-oxoazacycle bearing a pendant acetal unit.[6] This employed a Vilsmeier $POCl_3$/DMF reagent system, a common alternative when confronted with stubborn substrates.

When we applied these milder conditions to our densely-functionalised substrate **1b**, we were pleased to observe relatively clean conversion by HPLC to a new product which then crystallized directly from the reaction mixture. However, analysis by LCMS, ^1H and ^{13}C NMR spectroscopy was inconsistent with the desired 3-chloro-1,2-benzisoxazole. The product was identified as 2-(dimethylamino)-4*H*-1,3-benzoxazin-4-one derivative **4a** (Scheme 3).[7]

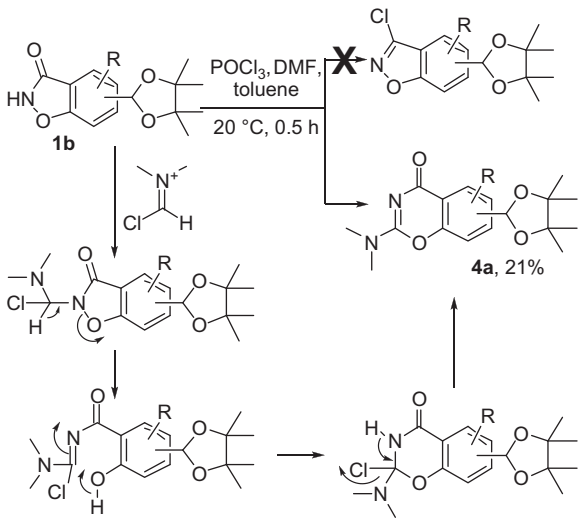
Given the intrinsic incompatibility of our substrate with common chlorination methodologies, we did not pursue this strategy any further in terms of target molecule delivery. Nevertheless, we were keen to understand if this unexpected ring-opening reaction pathway observed was specific to our densely-substituted 1,2-benzisoxazol-3-one **1b** or if it was a general effect. To this end, we subjected a range of 1,2-benzisoxazol-3-ones to the general reaction conditions[8] and, in all cases, we found the predominant reaction pathway to be that leading to the ring-expanded 4*H*-1,3-benzoxazin-4-one products **4**. The results are summarized in Table 1. As can be seen, the ring-opening pathway appears to be general to 1,2-benzisoxazol-3-ones (entries 1–4). It is noteworthy that 7-methyl-1,2-benzisoxazol-3-one (**1a**) gives the corresponding 4*H*-1,3-benzoxazin-4-one **4c** (entry 2) as this substrate furnishes the expected 3-chloro-1,2-benzisoxazole (**2a**) when reacted with neat $POCl_3$ (Scheme 1).[4a] The mechanism also operates when 1,2-isoxazol-3-ones **5a,b** are employed (entries 5 and 6), though we found the corresponding 4*H*-1,3-oxazin-4-one products **6a,b** were unstable to isolation and consequently were only detected using analytical methods. We then went on to investigate the fate of the related 1,2-benzisothiazol-3-one **7** and indazol-3-one **9** skeleta under these conditions. Neither appeared susceptible to such a ring-expansion mechanism: the 1,2-benzisothiazol-3-one furnished the expected 3-chloro-1,2-benzisothiazole **8** (entry 7) and the indazol-3-one **9** did not react under these conditions (entry 8).

Having examined the substrate-scope in terms of the heterocyclic component, we also investigated the performance of a range of

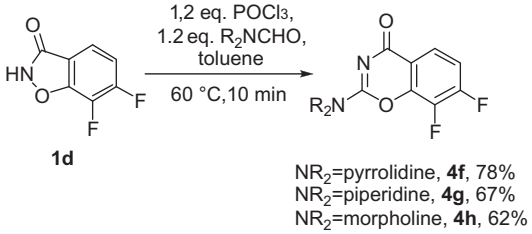
Table 1
Substrate scope of the ring-expansion[8]

Entry	Substrate	Product	Yield (%)
1	 **1c**	 **4b**	51
2	 **1a**	 **4c**	57
3	 **1d**	 **4d**	76
4	 **1e**	 **4e**	24
5	 **5a**	 **6a**	[a]
6	 **5b**	 **6b**	[b]
7	 **7**	 **8**	83
8	 **9**	 **9**	–

[a] Product confirmed by LC–MS and 2D NMR spectroscopy, not isolated or purified.
[b] Product visible as a minor component, confirmed by LC–MS and GC–MS only.



Scheme 3. Unexpected ring-expansion to a 4*H*-1,3-benzoxazin-4-one.

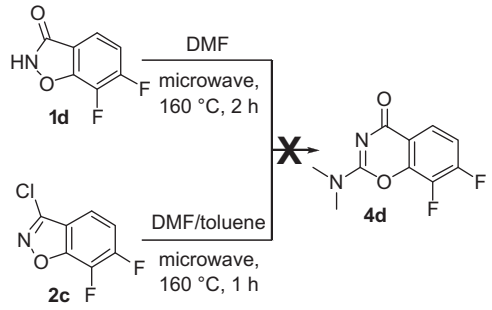


Scheme 4. Alternative *N*-formyl amines in the ring-expansion.[8]

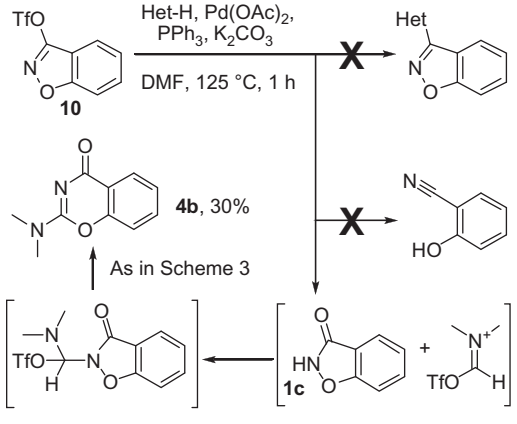
formamides in this methodology. The results are summarized in Scheme 4. As shown, in addition to *N*,*N*-dimethylformamide (Table 1), *N*-formyl-pyrrolidine, -piperidine and -morpholine all performed well under standard conditions to furnish the corresponding 4*H*-1,3-benzoxazin-4-one products **4f–h**, in good yields.

The mechanism we propose for this ring-expansion is outlined in Scheme 3. Though we have no experimental evidence (e.g., isolated intermediates, kinetics, etc.), this proposal is based on a similar mechanism outlined for 1,2-oxazolin-5-ones.[10] Further, we have shown the implicit intermediacy of the Vilsmeier species (rather than, for instance, a sequential chlorination/ring-opening sequence or some nucleophilic attack of DMF) by exposing 1,2-benzisoxazol-3-one **1d** and 3-chloro-1,2-benzisoxazole **2c** to "dummy" reactions containing no $POCl_3$ (Scheme 5). Neither of these reactions returned even traces of the 4*H*-1,3-benzoxazin-4-one product **4d**, both resulting in no detectable reaction of the substrate.

We have one final cautionary tale relating to this unexpected ring-expansion mechanism: in an unrelated piece of work, we were attempting a palladium-catalysed cross-coupling of 1,2-benzisoxazol-3-yl trifluoromethanesulfonate (**10**). We were cognizant of the risk associated with ring-opening of the aryl palladium intermediate to yield *o*-hydroxybenzonitrile. However, after complete consumption of **10**, neither this byproduct nor the desired 3-aryl-1,2-benzisoxazole were observed. We eventually discerned that, with DMF as the reaction solvent, trifluoromethanesulfonate **10** was participating in the same ring-expansion mechanism to give **4b** in 30% isolated yield (Scheme 6). As shown, we propose transfer of the triflate group from **10** to DMF to give a Vilsmeier-type iminium species which then mediates a ring-expansion via a mechanism analogous to that outlined in Scheme 3.



Scheme 5. Functionalised benzisoxazoles under "dummy" conditions.



Scheme 6. Ring-expansion as another side reaction.

In summary, we have identified a new ring-expansion[11] of 1,2-benzisoxazol-3-ones mediated by Vilsmeier reagents which results in the incorporation of the *N*-formylamine moiety into the N–O bond furnishing 4*H*-1,3-benzoxazin-4-ones **4**. We have shown this mechanism to be general to a range of 1,2-benzisoxazol-3-ones **1**, 1,2-isoxazol-3-ones **5** and *N*-formylamines. Further, we have observed this mechanistic pathway operating in other activated 1,2-benzisoxazole systems, such as **10**.

The primary focus for this communication was to highlight the difficulties encountered when applying apparently standard methodology to unusual heterocyclic systems and to describe the new, unexpected ring-expansion pathway of 1,2-benzisoxazol-3-ones. We acknowledge that this work does not represent a powerful new methodology for the construction of 4*H*-1,3-benzoxazin-4-ones **4** as the prerequisite 1,2,-benzisoxazol-3-one substrates **1** are often difficult to access themselves. Nevertheless, this work does represent a new approach to the 4*H*-1,3-benzoxazin-4-one ring system, which itself appears to be underexploited in the chemical space and, as such, suffers from a paucity of synthetic approaches.[12]

Acknowledgements

The authors would like to thank Dr. Anthony W. T. Bristow for QTOF LCMS analysis and Dr. Steven R. Coombes and Dr. Andrew Phillips for NMR spectroscopic analysis and interpretation (all of Pharmaceutical Development, AstraZeneca).

References and notes

1. Pitt, W. R.; Parry, D. M.; Perry, B. G.; Groom, C. R. *J. Med. Chem.* **2009**, *52*, 2952.
2. The patent and academic literature yields many examples of pharmacologically active 1,2-benzisoxazoles. To exemplify, we cite some of the literature we read whilst conducting this work: Anticoagulants: (a) Lee, Y.-K.; Parks, D. J.; Lu, T.; Thieu, T. V.; Markotan, T.; Pan, W.; McComsey, D. F.; Milkiewicz, K. L.; Crysler, C. S.; Ninan, N.; Abad, M. C.; Giardino, E. C.; Maryanoff, B. E.; Damiano, B. P.; Player, M. R. *J. Med. Chem.* **2008**, *51*, 282–297; Anti-inflammatory: (b) Pettus, L. H.; Xu, S.; Cao, G.-Q.; Chakrabarti, P. P.; Rzasa, R. M.; Sham, K.; Wurz, R. P.; Zhang, D.; Middleton, S.; Henkle, B.; Plant, M. H.; Saris, C. J. M.; Sherman, L.; Wong, L. M.; Powers, D. A.; Tudor, Y.; Yu, V.; Lee, M. R.; Syed, R.; Hsieh, F.; Tasker, A. S. *J. Med. Chem.* **2008**, *51*, 6280–6292; Antipsychotic: (c) Yevich, J. P.; New, J. S.; Smith, D. W.; Lobeck, W. G.; Catt, J. D.; Minielli, J. L.; Eison, M. S.; Taylor, D. P.; Riblet, L. A.; Temple, D. L., Jr. *J. Med. Chem.* **1986**, *29*, 359–369.
3. For examples of recent advances, see: (a) Dubrovskiy, A. V.; Larock, R. C. *Org. Lett.* **2010**, *12*, 1180–1183; (b) Spiteri, C.; Sharma, P.; Zhang, F.; MacDdonald, S. J. F.; Keeling, S.; Moses, J. E. *Chem. Commun.* **2010**, *46*, 1272–1274. and references cited therein; (c) Spiteri, C.; Mason, C.; Zhang, F.; Ritson, D. J.; Sharma, P.; Keeling, S.; Moses, J. E. *Org. Biomol. Chem.* **2010**, *8*, 2537–2542. and references cited therein.
4. For example, see: (a) Smith, J. A.; Le, G.; Jones, E. D.; Deadman, J. *Future Med. Chem.* **2010**, *2*, 215–224; (b) Yamada, A.; Spears, G.; Hayashida, H.; Tomishima, M.; Ito, K.; Imanishi, M. Int. Patent WO 01/87845; *Chem. Abstr.* **2001**, *135*, 371759.
5. Andersen, K.; Begtrup, M. *Acta Chem. Scand.* **1992**, *46*, 1130–1132.
6. Annis, G. D.; Int. Patent WO 06/124657; *Chem. Abstr.* **2006**, *146*, 7979.
7. Kokel, B.; Menichi, G.; Hubert-Habart, M. *Tetrahedron Lett.* **1984**, *25*, 3837–3840.
8. *General procedure*: The substrate was dissolved or suspended in toluene (or acetonitrile where specified below) and DMF (2.5 equiv) or formamide (1.2 equiv) was added. Under an atmosphere of nitrogen, $POCl_3$ (1.2 equiv) was added dropwise to control any exotherm. The mixture was either stirred at 20 °C or warmed in an Emrys Optimizer microwave reactor (see below) until complete reaction was observed by HPLC. The mixture was cooled when necessary and poured into saturated K_2CO_3 solution. The solid product was then isolated by vacuum filtration and drying in vacuo at 40 °C.
4a—20 °C, 30 min; **4b—**60 °C, 40 min; ^{1}H NMR (400 MHz, DMSO-d_6): 3.12 (3H, s), 3.19 (3H, s), 7.38 (1H, ddd, *J* = 7.7, 7.3, 1.1 Hz), 7.42 (1H, ddd, *J* = 8.4, 1.0, 0.3 Hz), 7.70 (1H, ddd, *J* = 8.4, 7.3, 1.7 Hz), 7.88 (1H, ddd, *J* = 7.7, 1.7, 0.3 Hz). MS (ESI) *m*/*z* 191 [M+H$^+$]; **4c—**60 °C, 20 min; ^{1}H NMR (400 MHz, $CDCl_3$): 2.38 (3H, s), 3.24 (3H, s), 3.26 (3H, s), 7.21 (1H, dd (app. t), *J* = 7.6 Hz) , 7.40 (1H, ddq (app. dsext.), *J* = 7.6, 0.8 Hz) , 7.59 (1H, ddq, *J* = 7.6, 0.8, 0.5 Hz). MS (ESI) *m*/*z* 205 [M+H$^+$]; **4d—**20 °C, 30 min; ^{1}H NMR (400 MHz, DMSO-d_6): 3.14 (3H, s), 3.18 (3H, s), 7.44 (1H, ddd, *J* = 10.4, 8.9, 7.0 Hz), 7.71 (1H, ddd, *J* = 8.9, 5.7, 2.3 Hz). MS (ESI) *m*/*z* 227 [M+H$^+$]; **4e—**60 °C, 20 min; ^{1}H NMR (400 MHz, $CDCl_3$): 3.23 (3H, s), 3.26 (3H, s), 7.26 (1H, d, *J* = 1.9 Hz), 7.32 (1H, dd, *J* = 8.4, 1.9 Hz), 8.05 (1H, d, *J* = 8.4 Hz). MS (ESI) *m*/*z* 225/227 [M+H$^+$]; **4f—**20 °C, 30 min; ^{1}H NMR (400 MHz, DMSO-d_6): 1.88–2.02 (4H, m), 3.52 (2H, app. t, *J* = 6.6 Hz), 3.63 (2H, app. t,

J = 6.6 Hz), 7.44 (1H, ddd, J = 10.4, 9.0, 7.0 Hz), 7.72 (1H, ddd, J = 9.0, 5.7, 2.3 Hz). MS (ESI) m/z 253 [M+H$^+$]; **4g—**60 °C, 10 min; ^{1}H NMR (400 MHz, DMSO-d_6): 1.64 (6H, br s), 3.71 (4H, br s), 7.44 (1H, ddd, J = 10.5, 8.9, 7.0 Hz), 7.70 (1H, ddd, J = 8.9, 5.7, 2.3 Hz). MS (ESI) m/z 267 [M+H$^+$]; **4h—**60 °C, 10 min; ^{1}H NMR (400 MHz, DMSO-d_6): 3.73 (8H, br s), 7.45 (1H, ddd, J = 10.5, 8.9, 7.1 Hz), 7.73 (1H, ddd, J = 8.9, 5.7, 2.3 Hz). MS (ESI) m/z 269 [M+H$^+$]; **6a—**MeCN, 60 °C, 30 min; **6b—**60 °C, 20 min. The structure of proprietary compound **4a** was characterised unambiguously by ^{1}H and ^{13}C NMR spectroscopy and various 2D correlation experiments and also by QTOF and HRMS analysis (+1.4 ppm). Unfortunately, this data cannot be disclosed at this point. Observed data and those previously described for compounds **4b**[7] and **8**[9] were in agreement.

9. (a) Selva, A.; Gaetani, E. *Org. Mass. Spectrom.* **1973**, *7*, 327–328; (b) Tanikawa, H.; Ishii, K.; Kubota, S.; Sasanuma, T.; Yagai, S.; Kitamura, A.; Karatsu, T. *Heterocycles* **2010**, *81*, 659–674.
10. Beccalli, E. M.; Marchesini, A. *J. Org. Chem.* **1987**, *52*, 3426–3434.
11. During the preparation of this manuscript, we encountered a single reference to the transformation of **5b** into **6b** under similar conditions: Jones, G.; Stanforth, S. P. In Paquette, L. A., Beak, P., Ciganek, E., Curran, D., Czarnik, A. W., Denmark, S. E., Hegedus, L., Kelly, R. C., Overman, L. E., Roush, W., Smith, A. B., III, White, J. D., Eds.; Organic Reactions; John Wiley & Sons: New York, 1997; Vol. 49,. Chapter 1 This appears simply as a table entry and cites Tomita, K.; Murakami, T. Jpn. Kokai Tokkyo Koho JP 54020504, 1979; *Chem Abstr.* **1979**, *91*, 157755b. Unfortunately, we have thus far been unable to obtain a copy of the original document.
12. In July 2011, a SciFinder® database search using compound **4b** as a substructure unit returned only 26 individual references. The same search performed in Reaxys® returned only 19 individual references.