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Isoxazole to oxazole: a mild and unexpected transformation†

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3-Aryltetrahydrobenzisoxazoles prepared en route to the coleophomone natural products and analogues, were found to undergo a remarkable base-mediated rearrangement to 2-aryltetrahydrobenzoxazoles. The scope of this unprecedented, facile transformation was probed: a range of analogues was produced, a mechanism proposed, and an application demonstrated by synthesis of a known herbicidal compound.

As an extension of our interest in natural products containing the cyclic trione unit,1,2 we were attracted to the coleophomone natural products, exemplified by coleophomones A (2) and B (3), reported as being in equilibrium via an aldol process.3,4 This group of metabolites have enzyme inhibitory properties towards bacterial cell wall transglycosylase and human heart chymase.4,5

Applying our previously reported isoxazole masking strategy for the cyclic trione unit1,2 led us to propose the disconnection of Scheme 1, requiring 3-aryltetrahydrobenzisoxazole building blocks to access the natural products and (masked) analogues. Whilst manipulating one such arybenzisoxazole, we observed a remarkable rearrangement to a 2-arylbenezoxazole. We report here our exploration of this unprecedented, facile transformation.

Scheme 1 Strategic disconnection of coleophomones.

A suitable set of 3-aryltetrahydrobenzisoxazoles 4 was prepared by 1,3-dipolar cycloaddition of aryl nitrile oxides [available from benzaldehyde oximes via C-chlorination (NCS, CHCl3 reflux) and 1,3-elimination] with cyclohexane-1,3-diones under basic conditions (Scheme 2).6

During attempts to complete O-allylation of 3-(2-hydroxyphenyl)benzisoxazole 4a (R = R1 = H) under standard basic conditions (Cs2CO3, THF reflux), we did not observe the expected product but instead isolated 2-(2-allyloxy)tetrahydrobenzoxazole 5.

Scheme 2 Synthesis and rearrangement of 3-aryltetrahydrobenzisoxazoles 4. Reagents: (i), NaO-i-Pr, i-PrOH; (ii), Cs2CO3, THF reflux; (iii), H2C=CHCH2Br, Cs2CO3, THF reflux.
This rearrangement also took place in the absence of alkylating agent (Scheme 2); the phenolic product 6a (R = R1–4 = H) was stable to the basic conditions, and was successfully O-allylated to give ether 5 on addition of allyl bromide. We have verified the structures of both isoxazole 4a and dimethyl product oxazole 6b (R = Me, R1–4 = H; vide infra) through X-ray crystal structure determinations, Fig. 1a and b.

We further investigated the scope of the remarkable rearrangement of benzisoxazoles 4 to benzoxazoles 6. Using isoxazole 4a, rearrangement was found to occur in aprotic solvents with reaction time of 4 h under a range of basic conditions (Table 1) including carbonates, alkoxide and amidine, but failed with tertiary amines. In the presence of water or ethanethiol (entries 12, 13) the amide products 7a,b, respectively, of ring opening of the oxazole 6a were isolated; the constitutions of the amides were confirmed by X-ray crystal structures.

A range of 3-(2-hydroxyphenyl)tetrahydrobenzisoxazoles 4a–i, differently substituted in the aryl and the cyclohexane ring were shown to undergo rearrangement (Table 2) using the convenient Cs2CO3 conditions (THF reflux) to afford oxazoles 6a–i.§

We propose the mechanism illustrated in Scheme 3 for the rearrangement. Until the oxazole structure was determined, we had supposed that a Boulton–Katritzky ring transposition (similar to that reported by Suzuki et al.) was taking place.
so we retain this as the initial step in this remarkable isoxazole-to-oxazole conversion.\textsuperscript{16} This can be followed by a Neber rearrangement\textsuperscript{11} to give an azirine, thus overall replacing the N–O bond of the isoxazole by a N–C bond. The azirine may be envisaged to be in equilibrium with a nitrile ylide\textsuperscript{12} stabilised at the formal positive end by the electron-rich 2-hydroxyphenyl substituent. The 1,3-dipole finally collapses to the oxazole in a 6π electrocyclic ring closure.

Previous reports indicate that it is possible to form oxazoles from azirines, and also that an azirine can be generated from an isoxazole either thermally or photolytically.\textsuperscript{13,14} However, the energies required well exceed those of our reaction conditions and thus an alternative rationale was required. The Neber rearrangement is an alternative way of generating azirines given the appropriate leaving group.\textsuperscript{15} This mechanism implies that the base is catalytic, and this was supported by isolation of 6a (66%) from 4a using 0.1 mol equiv. of Cs\textsubscript{2}CO\textsubscript{3} (THF reflux, 1.5 h). An intermediate with \textit{m/z} identical to both the isoxazole and oxazole was observed by LC-MS during the rearrangements of 4a and 4c to 6a,\textit{c}, respectively, and isolated by HPLC. We were not able to unambiguously identify the structure, but NMR studies indicate the cyclohexane portion to be symmetrical, supporting either the azirine or nitrile ylide formulation.\textsuperscript{16} An attempt to crystallise the dimethyl intermediate formed from 4c led merely to recovery of the oxazole 6c. The oxazole ring opening to form amides 7a,\textit{b} is consistent with nucleophilic attack at C-5 of the oxazole.

To discount the possibility of the oxazoles being formed by retro-cycloaddition from the isoxazoles and recombination via a different connectivity, we have shown that treatment of a mixture of the two tetrahydrobenzoxazoles 4c and 4i under the Cs\textsubscript{2}CO\textsubscript{3}–THF reflux conditions led only to the tetrahydrobenzoxazoles 6c and 6i predicted by the mechanism of Scheme 3, with no crossover products observed.

The tetrahydrobenzoxazoles prepared herein are closely related to a series of herbicides described in a patent by Ueda \textit{et al.}\textsuperscript{17} Using benzoxazole 6a we have prepared an example 8 of this group by reaction with 2-chloropyrimidine (47%) (Scheme 4).

In conclusion, we have discovered an unexpected, remarkably facile novel base-mediated rearrangement of tetrahydrobenzoxazoles to tetrahydrobenzoxazoles, demonstrated the scope and probed the reaction mechanism of this surprising transformation. The synthetic utility of this rearrangement has been demonstrated by synthesis of a known bioactive compound.

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**Notes and references**

\textsuperscript{‡} Crystal data for 4a: C\textsubscript{13}H\textsubscript{11}NO\textsubscript{3}, M = 229.23, orthorhombic, Pca\textsubscript{2}1, a = 15.024(3) Å, b = 21.464(4) Å, c = 13.309(3) Å, V = 4291.8(15) Å\textsuperscript{3}, Z = 16, µ(Mo-K\textsubscript{α}) = 0.102 mm\textsuperscript{-1}, 36812 reflections measured, 8811 unique, R\textsubscript{int} = 0.064, R\textsubscript{1} for 5081 data with F\textsuperscript{2} > 2σ(F\textsuperscript{2}) = 0.056, wR\textsubscript{2} (all data) = 0.168, absolute structure x = 0.4(19). Four molecules in asymmetric unit. For 6b: C\textsubscript{13}H\textsubscript{13}NO\textsubscript{3}, M = 237.28, orthorhombic, Pna\textsubscript{2}1\textsubscript{1}1, a = 12.930(2) Å, b = 9.3159(15) Å, c = 21.663(4) Å, V = 2609.4(8) Å\textsuperscript{3}, Z = 8, µ(Mo-K\textsubscript{α}) = 0.09 mm\textsuperscript{-1}, 25390 reflections measured, 6484 unique, R\textsubscript{int} = 0.034, R\textsubscript{1} for 5459 data with F\textsuperscript{2} > 2σ(F\textsuperscript{2}) = 0.033, wR\textsubscript{2} (all data) = 0.088, absolute structure x = 0.2(4). Two molecules in asymmetric unit. CCDC 962972 and 962973.

\textsuperscript{§} Typical procedure for oxazole formation: 3-(2-hydroxyphenyl)-6,7-dihydrobenzoxazole4|5H|one 4a (0.500 g, 2.18 mol) and Cs\textsubscript{2}CO\textsubscript{3} (1.42 g, 4.37 mMol) in dry THF (30.0 mL) was heated under reflux for 4 h. Hydrochloric acid (2 M; 5 mL) and CH\textsubscript{2}Cl\textsubscript{2} (25 mL) were added after the reaction mixture had cooled to 20 °C. The mixture was separated and the combined organic layer washed with water (2 × 25 mL) and brine (25 mL). The organic layer was dried (MgSO\textsubscript{4}), filtered and evaporated to dryness under reduced pressure to yield 2-(2-hydroxyphenyl)-6,7-dihydrobenzoxazole[4|5H|]one 4a (0.435 g, 87%) as a beige solid, mp 202–204 °C (decomp.).

\textsuperscript{1} 3-Acyltetramic acids. For leading references, see: R. C. F. Jones, C. C. M. Law and M. R. J. Elsegood, \textit{ARKIVOC}, 2013, ii, 81–97.


\textsuperscript{7} Crystallographic data for amides 7a and 7b are deposited at the Cambridge Crystallographic Data Centre, CCDC 962974, 962975 respectively.
10 Studies with the 3-phenyltetrahydrobenzisoxazole confirm the requirement for the phenolic substituent: unpublished observations.
16 Selected spectral data for the intermediate in rearrangement of 4a to 6a: $\delta_H$ (500 MHz, CDCl$_3$) 2.05–2.15 (m, 2H, CH$_2$CH$_2$CH$_2$), 2.67 (4H, t, J = 6.4, 2 × CH$_2$CO), 7.30–7.33 (1H, m, Ar–H), 7.52–7.60 (2H, m, 2 × Ar–H), 8.21 (1H, d, J = 8.2, Ar–H), 11.18 (s, 1H, OH).