Novel reaction of 3,4-dibromofuran with azo diesters to give tetrahydropyrpyridazinones†

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Cycloaddition of 3,4-dibromofuran with azo diesters proceeds by a Diels–Alder reaction followed by a novel rearrangement to give 3,5-dibromotetrahydropyridazin-4-ones. Variable-temperature NMR spectroscopy shows four separate conformations at low temperature attributed to restricted rotation about the carbamate functions. The ethyl compound decomposes upon storage with loss of the carbamate groups and aromatisation to give a simple bromohydropyryridazinidium salt.

We recently described the generation and spectroscopic characterisation of 1,4-oxazine, the first parent fully unsaturated six-membered ring heterocycle containing one group 15 and one group 16 atom. Although the successful method ultimately involved pyrolytic deprotection of the N-Boc derivative, we also investigated several other approaches including a cycloaddition – double bond functionalisation – cycloreversion route that led to the discovery of a novel and unexpected heterocyclic rearrangement described here.

The approach involves Diels–Alder cycloaddition with an azo diester, functionalisation of the newly formed double bond to give a cyclopropane, epoxide or aziridine, hydrolysis of the esters and decarboxylation followed by mild oxidation to give the aziridine, and finally spontaneous extrusion of N₂ to give the target heterocycle 2 (Scheme 1). This strategy has previously been successful in forming 1,4-cyclohexadiene (X = Y = CH₂), 1,4-dihydropyridines (X = CH₂, Y = NR), and 4H-pyran (X = CH₂, Y = O), but to our knowledge has not been attempted with X = O, although a related strategy involving extrusion of maleic anhydride rather than N₂ was used to produce 1,4-dioxin 2 (X = Y = O). The Diels–Alder cycloaddition between furan and diethyl azodicarboxylate is well known, having been first reported over 50 years ago, and it has also been extended to other azo diesters such as dibenzyl azodicarboxylate, although caution has to be exercised in altering the dienophile since azodibenzoyl (PhCO=N=N-COPh) instead gives the apparent [2 + 2]-cycloadduct with furan. Since we experienced problems in forming an aziridine directly from the double bond of the furan – diethyl azodicarboxylate adduct, we decided to prepare the adduct of a 3,4-difunctionalised furan which, following hydrogenation, could be converted into an aziridine in a stepwise manner.

3,4-Dibromofuran 3 was readily prepared in moderate yield by oxidative cyclodehydration of (E)-2,3-dibromobut-2-en-1,4-diol,† The only previous reports of cycloadditions involving 3 are [4 + 2]-cycloaddition with benzene and [4 + 3]-cycloaddition with allyl cation equivalents. When 3 was allowed to react with either diethyl or disopropyl azodicarboxylate at room temperature for 7 days a new single product was formed in each case which was isolated in pure form by column chromatography. The structures of these products were initially obscured by the occurrence of a dynamic process leading to extremely broad NMR spectra at room temperature. However at 55 °C, sharper spectra were observed, and these were incompatible with either the [4 + 2]- or [2 + 2]-cycloadducts or (Scheme 2). In particular, although the compounds had the expected molecular formulae, they were...
unsymmetrical and there was clear evidence for the presence of a ketone carbonyl group in addition to the carbamate esters. The matter was finally resolved by a single crystal X-ray diffraction study on the isopropyl compound (Fig. 1) which clearly showed the 3,5-dibromotetrahydropyridazin-4-one structure. Although the formation of pyridazin-4-ones has been reported in the cycloaddition of azo diesters with a range of functionalised dienes, none of these involve furans and the current process is clearly quite different, requiring a fundamental rearrangement. We propose that the expected [4 + 2]-adduct is formed initially but this undergoes a spontaneous rearrangement by one of the two mechanisms shown in Scheme 3.

The occurrence of dynamic processes in hydrogenated pyridazine carbamate systems is a well-studied area that has elicited some controversy in the past. There are three main phenomena that can occur: restricted rotation about the carbamate N–C(O) bond, inversion at the pyramidal carbamate N, and ring inversion in half chair forms, and the occurrence of each of these in various 1,2-dialkoxycarbonyl-1,2,3,6-tetrahydropyridazines has been described in detail. While these earlier studies were based on $^1$H NMR, additional insight was provided by a detailed variable temperature $^{13}$C NMR study, which was also backed up by X-ray structure determinations of the compounds involved, including 8–10 (Scheme 4). As compared to these model compounds, 6 is devoid of symmetry and so shows separate $^1$H and $^{13}$C NMR signals for each atom at high temperature. The spectra at –30 °C show a full set of signals for four separate forms in a 1 : 1 : 1 : 1 ratio. Upon warming these coalesce first into two forms, which then further coalesce into one, with all the free energies of activation in the range 57–61 kJ mol$^{-1}$ (13.7–14.5 kcal mol$^{-1}$). A significant difference between 6 and the model systems 8–10 in the solid state is its high degree of planarity. The values of the angle sum at N shown in Scheme 4 show that one nitrogen (N2) is completely planar and the other (N1) nearly so, in stark contrast to compounds 8 and 9 which adopt half chair conformations with distinctly pyramidal N atoms, but rather similar to the dibromo compound 10 which exists in a chair conformation.
The diethyl compound 7 was observed to be significantly less stable than 6 and, after storage for a period of weeks, it was found to have decomposed with formation of a completely new compound with unexpected spectroscopic properties. This was found by X-ray diffraction to be the monohydrate of 5-bromo-4-hydroxyypyridazinium bromide 11.\(^\text{**}\)

The structure (Fig. 2) features a hydrogen bonded network containing water molecules, with each water molecule being bonded by oxygen to the OH of 11 and by hydrogen to two bromide ions, while each bromide is bonded to two waters and to the NH of 11.

We postulate that this is formed by HBr catalysed dealkylation and decarboxylation followed by aromatisation as shown in Scheme 6.

Although 3,4-dibromofuran has not been widely investigated as a 1,3-diene before, the reactions reported here show that it has the potential to provide access to highly functionalised pyridazines by reaction with readily available azo diesters. Its reactions with other types of dienophile may lead to useful functionalised products and this is currently under investigation.

Notes and references

\(\text{**}\) Compound 6: colourless plates, mp 104–106 °C (found: C, 33.8; H, 3.7; N, 6.3; m/ 2 428.9484. \(\text{C}_{12}\text{H}_{16}\text{Br}_{2}\text{N}_{2}\text{O}_{5}\) requires C, 33.7; H, 3.8; N, 6.5%; 79Br, 81Br – M + H, 428.9484); \(\nu_{\text{max}}\) cm\(^{-1}\) 1746, 1695 and 1590; \(\delta_{\text{H}}\) (CDCl\(_3\), 55 °C) 8.38 (1H, br s, CH); 6.80 (1H, br s, CHBr); 5.13 (1H, septet, J 6.3); 5.04 (1H, septet, J 6.3); 1.37 (6H, d, J 6.3); 1.33 (3H, d, J 6.3) and 1.32 (3H, d, J 6.3); \(\delta_{\text{C}}\) (55 °C) 175.4, 150.0 (br, N-Co), 141.6 (br, C), 98.9 (br, CBr), 74.4 and 73.9 (CHMe\(_3\)), 57.2 (CHBr), 21.79, 21.70, 21.68 and 21.60 (CHMe\(_3\)).

\(\text{‡}\) Crystal data for 6, \(\text{C}_{12}\text{H}_{16}\text{Br}_{2}\text{N}_{2}\text{O}_{5}\), \(M_{r} = 428.08\), colourless prism, monoclinic, space group \(P2_1/c\), \(a = 11.676(5)\) \(\AA\), \(\beta = 92.350(11)°\), \(V = 1636.3(13) \text{ Å}^3\), \(Z = 4\), \(D_t 1.738\) \text{Mg m}^{-3}, \(\tau = 93(2)\) \text{K}, \(R_1 = 0.1080\) and \(wR_2 = 0.2634\) for 2091 reflections \( \{ \theta > 2\sigma(n) \} \) and 194 parameters.

\(\text{§}\) Crystal data for 6, \(\text{C}_{12}\text{H}_{16}\text{Br}_{2}\text{N}_{2}\text{O}_{5}\), \(M_{r} = 428.08\), colourless prism, monoclinic, space group \(P2_1/c\), \(a = 11.676(5)\) \(\AA\), \(\beta = 92.350(11)°\), \(V = 1636.3(13) \text{ Å}^3\), \(Z = 4\), \(D_t 1.738\) \text{Mg m}^{-3}, \(\tau = 93(2)\) \text{K}, \(R_1 = 0.1080\) and \(wR_2 = 0.2634\) for 2091 reflections \( \{ \theta > 2\sigma(n) \} \) and 194 parameters.

\(\dagger\) Compound 11: colourless needles, mp 176–178 °C; \(\delta_{\text{H}}\) (CDCl\(_3\), –30 °C) 8.60, 8.51, 8.41, 8.33 (1H, 4 x s, = CH), 7.00, 6.95, 6.85, 6.79 (1H, 4 x s, CHBr), 5.25–5.00 (2H, m) and 1.49–1.27 (12H, m); \(\delta_{\text{C}}\) (–30 °C) 176.0, 175.8, 175.7, 175.6, 150.4, 149.8, 149.4, 149.1, 148.9, 148.6, 147.5, 147.2, 142.3, 142.1, 141.8, 141.1, 99.6, 98.4, 98.1, 97.7, 74.8, 74.7, 74.2, 74.1, 74.0, 73.8, 73.6, 56.9, 56.8, 56.4, 56.2, 21.8, 21.7, 21.6, 21.5, 21.3, 21.2, 21.0 and 21.4.

\(\text{§}\) Crystal data for 11, \(\text{H}_{2}\text{O}, \text{C}_{12}\text{H}_{16}\text{Br}_{2}\text{N}_{2}\text{O}_{5}, M_{r} = 273.91\), colourless prism, orthorhombic, space group \(Pbc\), \(a = 13.4208(15)\) \(\AA\), \(b = 6.0747(7)\) \(\text{Å}\), \(c = 19.193(2)\) \(\text{Å}\), \(V = 1564.8(3) \text{ Å}^3\), \(Z = 8\), \(D_t 2.325\) \text{Mg m}^{-3}, \(\tau = 93(2)\) \text{K}, \(R_1 = 0.0326\) and \(wR_2 = 0.0756\) for 1253 reflections \( \{ \theta > 2\sigma(n) \} \) and 107 parameters. Data were recorded using a Rigaku Mercury 70, MoKα radiation (confocal optic, \(\lambda 0.71073\) Å) and Saturn detector. The structures were solved by direct methods and refined using full-matrix least-squares methods.

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