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Unexpected formation of a 5-trifluoromethyloxazole from a 1,2-dibenzamidoalkene

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Abstract

An unusual cyclisation of *Z*-1,2,4-tris(benzamido)butene with trifluoroacetic anhydride gives *Z*-4-[1,3-bis(benzamido)prop-1-enyl]-2-phenyl-5-trifluoromethyloxazole (**3**). The structure and stereochemistry were confirmed by ^{1}H, ^{13}C and ^{19}F NMR, together with ^{1}H-^{1}H COSY, ^{1}H-^{1}H NOESY and $^{1}H \rightarrow {}^{19}F$ and $^{19}F \rightarrow {}^{1}H$ heteronuclear NOE experiments. Trifluoroacetylation at the less sterically hindered *N*-acyl-enamine position, with subsequent cyclisation and 1,4-elimination is proposed.

Keywords: 5-Trifluoromethyloxazole; 1,2-Dibenzamidoalkene; Cyclisation; NMR spectroscopy; Stereochemistry

1. Introduction

As part of a programme of synthesis of trifluoromethyl-heterocycles for medicinal and pH sensor applications [1,2], we required 2-trifluoromethylhistamine. This compound has been prepared by Bamberger cleavage of histamine (**1**), followed by treatment with boiling trifluoroacetic anhydride and acid-catalysed hydrolysis of the side-chain benzamide. Kimoto et al. [3] also noted the formation of a significant unidentified side-product. We now report the preparation and characterisation of this material as a 5-trifluoromethyl-4-alkenyloxazole which is formed by an interesting alternative cyclisation.

2. Results and discussion

As expected [4], Bamberger fragmentation of histamine (**1**) gave *S*-1,2,4-tris(benzamido)butene (**2**). Treatment with boiling trifluoroacetic anhydride, followed by methanol, gave a poorly soluble solid in moderate yield. The high resolution CI mass spectrum showed a major $(M+H)^+$ peak at m/z 492.1535, corresponding to the molecular formula $C_{27}H_{20}F_3N_3O_3$. ^{19}F NMR spectroscopy showed only one singlet at δ −58.89 ppm; thus one CF_3 group or two equivalent CF_3 groups are present. The ^{1}H NMR spectrum revealed the presence of only one CH_2 (δ 4.19 ppm) and one alkene proton, along with 15 aromatic protons and two NH protons. Hence one of the CH_2 groups of the triamide **2** has become involved in the reaction. A ^{1}H-^{1}H COSY spectrum indicated coupling from the CH_2 to the vinylic-H and to the upfield NH (Fig. 1). No coupling was evident between the alkene-H and either NH. These data show compound **3** to have the alkenyloxazole structure shown. A ^{1}H-^{1}H NOESY experiment gave a cross-peak between the downfield NH (δ 10.50 ppm) and the CH_2, showing *Z* stereochemistry about the C=C double bond (Fig. 1). An NOE enhancement was observed in the ^{19}F signal of the CF_3 group on irradiation at the ^{1}H frequency of the alkene-H, but not on irradiation at the ^{1}H frequency of the CH_2, which corroborated this structural assignment (Fig. 1). The converse NOE experiment, involving irradiation at the δ_F of the CF_3 group, showed enhancement of the ^{1}H signals of the downfield NH, the vinylic-H and, more weakly, to the 2,6-H_2 of one benzamide (Fig. 1).

To rationalise this unexpected cyclisation, a mechanism such as that shown in Scheme 1 is proposed. Acylation of the triamide **2** at the more sterically accessible enamine position is followed by nucleophilic attack of the amide oxygen on the trifluoromethyl ketone. Trifluoroacetylation of the tetrahedral intermediate at oxygen provides an excellent leaving group for the 1,4-elimination to afford the alkenyloxazole **3**.

3. Experimental details

NMR spectra were obtained of a solution in $(CD_3)_2SO$ at 70 °C to ensure complete solution of **3**, using JEOL EX-400

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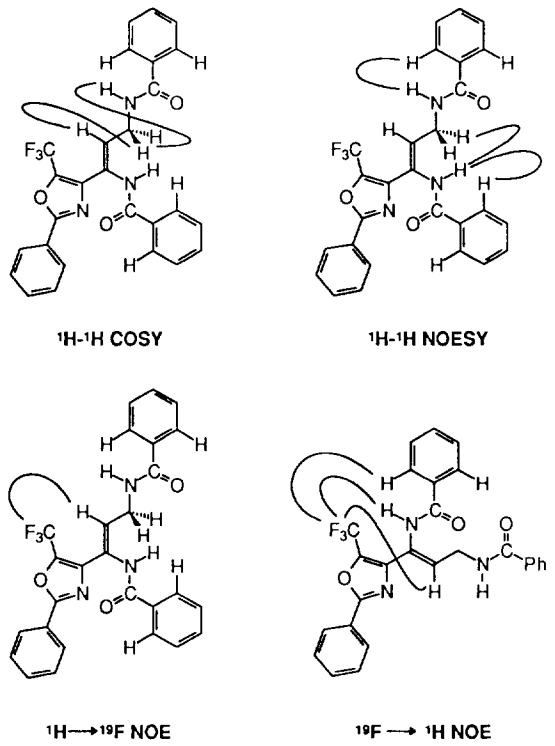
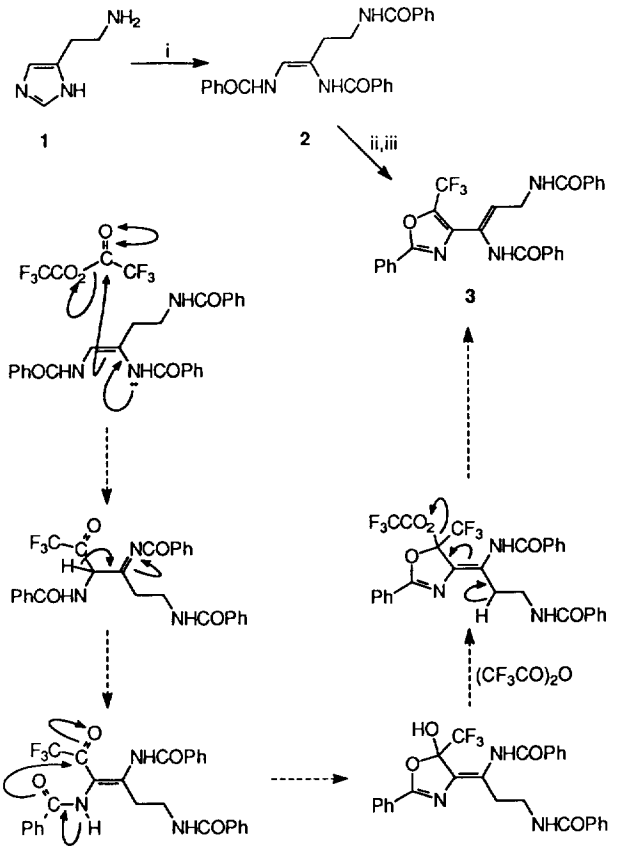


Fig. 1. Principal COSY and NOE interactions for the characterisation of **3**. Other interactions were observed between the protons attached to the individual benzene rings.

and Bruker AC-250 instruments. The ^{19}F NMR chemical shift is referenced to $CFCl_3$.

3.1. Z-4-(1,3-Bis(benzamido)prop-1-enyl)-2-phenyl-5-trifluoromethyloxazole (3)

Z-1,2,4-Tris(benzamido)butene (**2**) [4] (388 mg, 0.91 mmol) was boiled under reflux with trifluoroacetic anhydride (4 ml) for 16 h. The excess reagent was evaporated and the residue was boiled under reflux in methanol (5 ml) for 1 h. The solid was collected by filtration from the cooled mixture to give the oxazole **3** (78 mg, 18%) as a white solid, m.p. 216–217 °C. ^1H NMR δ: 4.19 (br t, 2H, $J=5$ Hz, CH_2); 6.29 (br t, 1H, $J=5$ Hz, C=CH); 7.58–7.68 (m, 9H, 3 × Ar 3,4,5-H_3); 7.99 (d, 2H, $J=6.7$ Hz, 2,6-H_2 of oxazole-2-Ph); 8.08–8.13 (m, 4H, 2 × benzamide 2,6-H_2); 9.08 (br t, 1H, N*H*CH_2); 10.50 (s, 1H, NH) ppm. ^{13}C NMR δ: 36.59, 119.07 (q, $J_{C-F}=268$ Hz, CF_3); 124.87; 126.00; 126.48; 126.53; 129.90; 127.17; 127.94; 128.11; 128.98; 130.96; 131.38; 131.73; 132.53 (q, $J_{C-F}=44$ Hz, C–CF_3); 133.43; 133.83; 140.54; 160.38; 164.96; 166.62 ppm. ^{19}F NMR δ: −58.89 (s) ppm. MS (CI) m/z: 492.1535 (M+H) ($C_{27}H_{21}F_3N_3O_3$ requires 492.1535).



Scheme 1. Synthesis of the trifluoromethyloxazole **3** and proposed mechanism. Reagents: i, PhCOCl; ii, $(CF_3CO)_2O$; iii, MeOH.

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