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Reaction of Dimethyl Sulphoxide and Trifluoroacetic Anhydride with 3-Nitro-4-hydroxycoumarin

TABASSUM ARA† and KHALIQUZ ZAMAN KHAN*
Department of Chemistry, University of Kashmir, Srinagar-190 006, India
E-mail: saithfb7@rediffmail.com

The interaction of dimethyl sulphoxide-trifluoroacetic anhydride (DMSO-TFAA) with 3-nitro-4-hydroxycoumarin (**1**) gives four products, *viz*. 2-nitroso-3-oxo-2,3-dihydro-1-benzofuran-2-carboxylic acid (**2**), 3-(methylthiomethyl]-3-nitro-2*H*-chromene-2,4(3*H*)-dione (**4**), salicylic acid and 4*H*-[1,3]-dioxolo[4,5-c]chromene-2,4-dione (**6**).

Key Words: Trifluoroacetic anhydride, 3-Nitro-4-hydroxycoumarin, DMSO.

INTRODUCTION

Dimethyl sulphoxide (DMSO) has been used in synthetic organic chemistry as such and also in combination with electrophilic activators such as sulphur trioxide/pyridine, thionyl chloride, oxalyl chloride, acetyl chloride, dicyclohexylcarbodiimide, polyphosphoric acid, chlorine, bromine and acetic anhydride[1]. Trifluoroacetic anhydride (TFAA) has also been employed as an activator and the reagent has been used extensively for the preparation of sulfilimines from various arylamines, arylamides and arene sulphonamides and for the oxidation of alcohols to carbonyl compounds[2] and cysteine to cystine[3]. The reagent has also been used for the conversion of cyclopentadiene, trimethylsilyl cyclopentadiene and fulvenes to their mono, *bis* and tris sulphonio-substituted derivatives[4]. In the presence of $SnCl_4$, DMSO reacts with TFAA to form Pummerer intermediate which then reacts with aromatic hydrocarbons to give arylmethyl sulphides[5].

The reaction between TFAA and DMSO, in the absence of a moderating solvent, is explosive even at room temperature. However, the reaction has been made to take place at low temperature (≤ 30 °C) in an unreactive solvent like dichloromethane. At -60 °C the reagents react instantly and exothermically in dichloromethane to produce a white precipitate which is stable below -30 °C, but on warming the Pummerer rearrangement product is formed[6].

4-Hydroxycoumarin and its derivatives are of special importance because of their physiological properties[7]. DMSO either alone or activated by acetic anhydride has been found to bring about a lot of transformations in 4-hydroxycoumarin, dicoumarol and 3- substituted-4-hydroxycoumarin which are interesting both from mechanistic and pharmacological view points[8,9].

†Department of Chemistry, National Institute of Technology, Srinagar-190 006, India.

3-Nitro-4-hydroxycoumarin prepared by nitration of 4-hydroxycoumarin[10] has antiallergic and antihistaminic properties[11]. Apart from its base hydrolysis which affords 2-hydroxy-2-nitroacetophenone in good yields[10] not much work has been done involving its lactone ring. However, a variety of its derivatives have been prepared and found to be of great physiological importance[12-14]. This prompted us to investigate the reaction between 3-nitro-4-hydroxycoumarin and the DMSO-trifluoroacetic anhydride reagent.

EXPERIMENTAL

Reaction of 3-nitro-4-hydroxycoumarin with DMSO-trifluoroacetic anhydride: To a solution of 3-nitro-4-hydroxycoumarin (4 g) and DMSO (5 mL) was added trifluoroacetic anhydride (2.5 mL) in dichloromethane (5 mL) at 0 °C. The reaction mixture was kept at room temperature for 0.5 h. Dilution with water afforded a brown coloured oil, which was extracted with ethyl acetate, the organic layer washed, dried and the solvent removed through distillation. Chromatography of the residue using benzene and benzene-ethyl acetate as eluents afforded 2-nitroso-3-oxo-2,3-dihydro-1-benzofuran-2-carboxylic acid (**2**): (yield: 0.551 g), m.p. 150 °C. IR (KBr, ν_{max}, cm^{-1}): 3239-2592, 1717-1630. ^1H NMR ($CDCl_3$, CFT-20): δ 6.7-7.9 (5H, m, ArH and OH). m/z: 207 (M^+), 149, 138, 120, 92 and 6 (nitrogen was present and $FeCl_3$ test was positive) and **3**-methylthiomethyl -3-nitro-2H- chromene-2,4-(3H)-dione (**4**): as yellow needles (yield: 30 mg), m.p. 230-232 °C (decomp.). IR (KBr, ν_{max}, cm^{-1}): 1434, 1569, 1732 and 1784. ^1H NMR ($CDCl_3$, CFT-20): δ 7.51-7.77 (4H, m, ArH), 5.10 (2H, s, $-CH_2-S$), 2.28 (3H, s, $-SCH_3$). m/z: 267 (M^+), 221, 206, 160, 147, 120 and 61. (Found C, 49.27; H, 3.52 %. $C_{11}H_9NO_5S$ requires C, 49.43, H, 3.37%).

When the reaction was repeated with 3-nitro-4-hydroxy coumarin (5 g), (**2**) was not found at all. Chromatography after usual workup afforded 3-nitro-3-methylthiomethyl -1-benzopyran-2,4-dione (**4**), (yield: 0.037 g) in minor amounts; salicylic acid: (yield: 0.700 g), m.p. 155-157 °C. IR (KBr, ν_{max}, cm^{-1}): 2840, 1650, 1600 and 1430. ^1H NMR ($CDCl_3$, EM-390, 90 MHz): δ 9.4-9.8 (-COOH), 7.2-7.8 (4H, m, Ar-H), 11.0 (OH). m/z: 138 (M^+), 120 (base peak), 92 and 64. (Found C, 60.13; H, 4.14 %. $C_7H_6O_3$ requires C, 60.68; H, 4.34 %) and 4H-[1,3]dioxolo[4,5-c]chromene-2,4-dione (**6**): (yield: 0.257 g), m.p. 305 °C. IR (KBr, ν_{max}, cm^{-1}): 1380, 1705 (broad), 1815 and 3190. ^1H NMR (DMSO-d_6, CFT-20): δ 7.2-8.1 (4H, m, ArH). m/z: 204 (M^+), 121, 120, 92 and 64. (Found C, 58.72; H, 2.12. $C_{10}H_4O_5$ requires C, 58.82; H, 1.96 %). It was a yellow amorphous compound and gave negative tests for nitrogen and sulphur.

RESULTS AND DISCUSSION

In 2:1 mixture of DMSO-acetic anhydride, 3-nitro-4-hydroxycoumarin suffers extensive decomposition even at room temperature. Its reaction with DMSO-trifluoroacetic anhydride, as expected proceeds explosively at room temperature.

However, it was brought under control by working at low temperatures and in dichloromethane. The reaction below 0 °C gave back the starting material. When conducted at room temperature for 0.5 h, the starting material was totally consumed and the viscous mass obtained after the usual workup was found to be a mixture of compounds. Chromatography of the crude product over silica gel afforded four pure compounds.

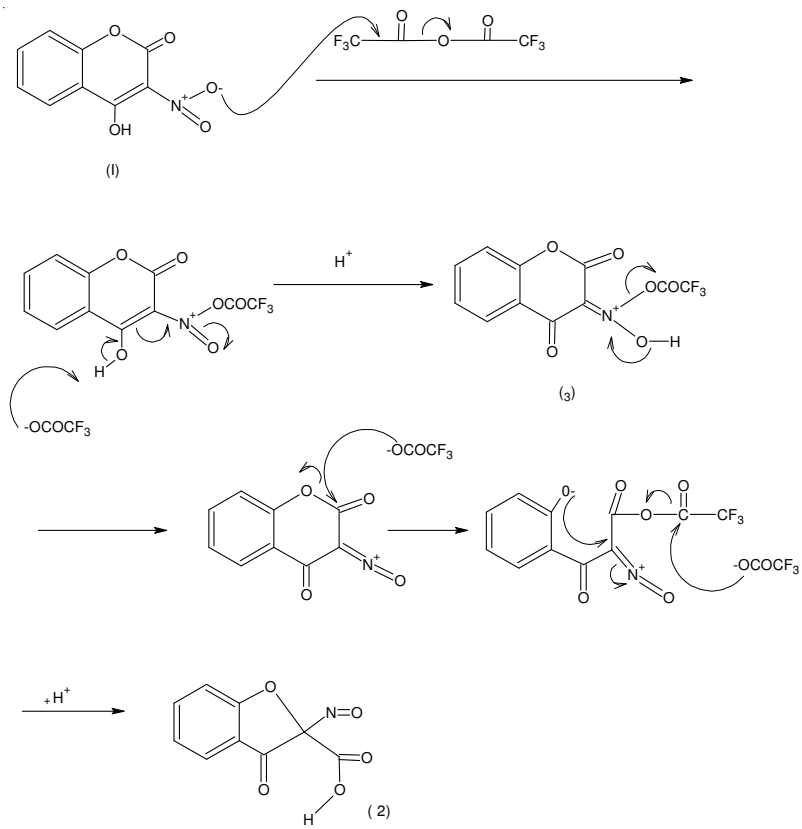
One of the products was found to be a nitrogen-bearing acid, which was isolated only once and then only in small amounts. We were unable to isolate it again even after the reaction was repeated several times. On the basis of spectral data, the compound was assigned structure (**2**). The IR spectrum of the compound shows a broad band between 3239-2592 cm^{-1} and a strong and broad band between 1717-1630 cm^{-1} which can be assigned to carboxylic and out of plane coumaranone carbonyls, the latter being partially hydrogen bonded to -OH of the carboxylic group. Other important peaks at 1630 and 1580 cm^{-1} are assigned to C-C aromatic and -N=O stretchings. The characteristic lactone, carbonyl and NO_2 bands are missing indicating opening up of the lactone ring and some modification of the NO_2 group. ^1H NMR spectrum shows a multiplet equivalent to five protons between δ 6.7-7.9 ppm accounting for four aromatic and one carboxylic group protons. The UV spectrum showing λ_{max} at 300 nm is in agreement with this structure. The M^+ at m/z 207 in its mass spectrum is same as that of 3-nitro-4-hydroxycoumarin and lacks a peak at M-46 due to the loss of NO_2 group.

Apart from two peaks of weak intensities at m/z 149 and 138 it has only three prominent peaks at m/z 120 (base peak), 92 and 61.

The formation of this compound can be explained on the basis that in the presence of trifluoroacetate ion, 3-nitro-4-hydroxycoumarin rearranged through loss of OH to (**3**) which being a β-diketone should suffer trifluoroacetate-catalyzed ring cleavage followed by cyclisation to give (**2**) (**Scheme-I**).

The second compound also obtained in small amounts gave positive tests for the presence of sulphur and nitrogen and was assigned structure (**4**). Its IR spectrum shows two strong carbonyl absorptions at 1784 and 1732 cm^{-1} which could be assigned to lactone and benzoyl carbonyl and characteristic bands at 1569 and 1434 cm^{-1} for the nitro group. An increase in the carbonyl frequencies can be due to the absence of the conjugated double bond and presence of the strongly electron-withdrawing NO_2 group at C-3. The effect of the NO_2 group on the lactone carbonyl is evident in the IR spectrum of 3-nitro-4-hydroxoycoumarin, which shows strong absorption between 1755 and 1735 cm^{-1} as against 1720-1710 cm^{-1}observed for 4-hydroxycoumarin.

The ^1H NMR spectrum showing a singlet for the S-methyl protons at δ 2.28 ppm is at the correct value but a singlet for methylene proton attached to sulphur showing a downfield shift at δ 5.10 can be justified on the basis that C-3 being flanked on either side by carbonyl groups and directly attached to NO_2 is extremely electron deficient and can shift these protons further downfield. The multiplet equivalent to four protons in the aromatic region (δ 7.51-7.77) appears at the correct value.

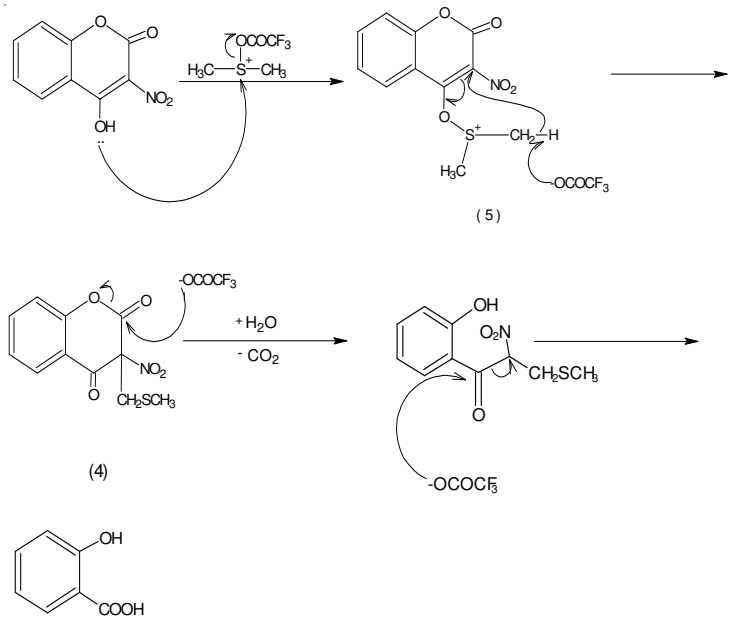


Scheme-I: Mechanism of formation of (**2**)

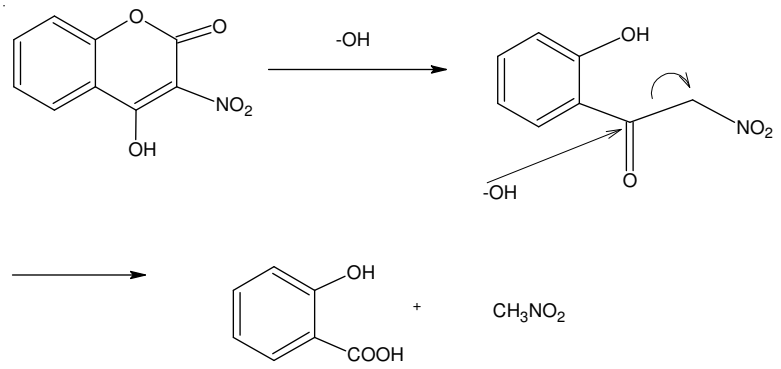
The mass spectrum of this compound shows a weak M^+ at m/z 267 and the peak observed at m/z 147, though of weak intensity, can only arise through retro Diels Alder fragmentation of (**4**).

Formation of (**4**) in this reaction parallels that of the reaction between phenols, 3-phenyl- and 3-allyl-4-hydroxycoumarin with DMSO-acetic anhydride[9]. The oxo-sulphonium salt (**5**) resulting from the interaction of DMSO-TFAA and 3-nitro-4-hydroxycoumarin isomerizes under the reaction conditions to (**4**). Being a β-diketone, under the reaction conditions, it should readily suffer acetolysis to give salicylic acid and, therefore, its isolation in minimal amounts is understandable. (**Scheme-II**).

The third and major product of this reaction was identified as salicylic acid through direct comparison (m.m.p., IR, PMR, mass spectrum). Base catalyzed hydrolysis of 4-methoxycoumarin has been found to give acetophenone[15], whereas that of 3-nitro-4-hydroxycoumarin provides 2'-hydroxy-nitro acetophenone in good yields[10]. The latter on prolonged treatment or under stronger basic milieu should degrade further to give salicylic acid and nitro-methane as loss of resonance-stabilized carbanion, $-CH_2NO_2$ will be facile (**Scheme-III**).



Scheme-II: Machanism of formation of (**4**) and its degradation to salicylic acid

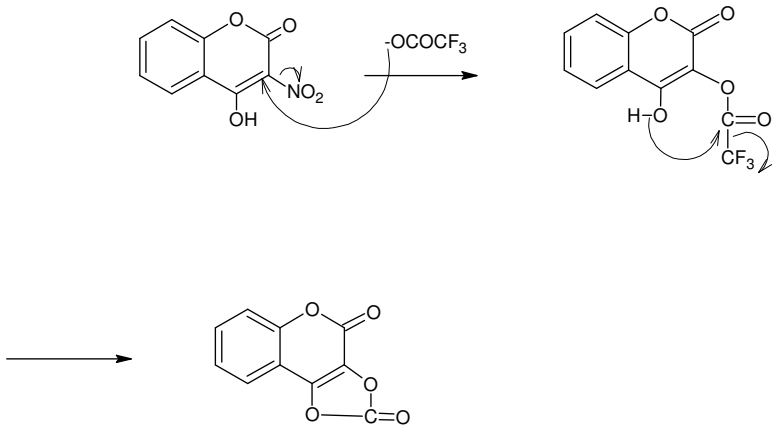


Scheme-III: Mechanism of formation of salicylic acid

Similarly, trifluoroacetate catalyzed degradation of 3-nitro-4-hydroxycoumarin can occur when it is exposed to DMSO-TFAA to give salicylic acid. Formation of salicylic acid can also be accounted from **4** which being a β-diketone should suffer trifluoroacetate catalyzed degradation (**Scheme-II**).

The fourth product from this reaction was insoluble in the majority of organic solvents and responded negatively when treated for the presence of sulphur and nitrogen. It was found to have molecular formula $C_{10}H_4O_5$ on the basis of its elemental analysis and mass spectrum. The absence of nitrogen indicates loss of NO_2 as HNO_2 from the starting material (m.f. $C_9H_5NO_5$) and addition of 44 mass units in the form of CO_2 to give the desired molecular weight and formula for this compound.

This leads to an assumption that probably 3-nitro group in the parent molecule gets substituted by trifluoroacetate ion, a phenomenon observed elsewhere as well[16]. The resulting 3-trifluoroacetoxy group can undergo cyclization with the neighbouring hydroxy group at C-4 with loss of trifluoromethane to give a cyclic carbonate structure **6** which has the desired mass and molecular formula (**Scheme-IV**).



(6)

Scheme-IV: Mechanism of formation of (**6**)

The ^{1}H NMR spectrum of this compound shows multiples of only aromatic protons between δ 7.2-8.1 and agrees with the structure **6**. The IR spectrum is in full agreement with the structure, showing strong carbonyl absorptions at 1815 and 1705 (broad) cm^{-1}. The former can easily be assigned to carbonate carbonyl and is in agreement with the data reported in literature[17]. The latter, a broad peak, between 1720-1680 cm^{-1} centered at 1705 cm^{-1} can be assigned to lactone carbonyl and enol ether. Its mass spectrum, apart from showing M^+ at m/z 204 has strong signals only at m/z 121, 120, 92 and 64 which can be easily accounted for with retro Diels Alder fragmentation of the lactone ring.

Though there is no doubt about the structure of this compound, no system or its analogue has ever been reported from either 4-hydroxycoumarin or its derivatives.

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