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An unexpected triethylsilane-triggered rearrangement of thioaurones to thioflavonols under SPPS conditions

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ABSTRACT

Thioaurones are converted to a mixture of thiaindenes and thioflavonols when exposed to reaction conditions employed in SPPS, that is, treatment with trifluoroacetic acid in the presence of triethylsilane.

1. Introduction

Flavonoids constitute an important group of natural products with a variety of physiological properties.[1] Among these, the aurones constitute a particular subgroup, where the usual C ring is replaced by a five-membered heterocyclic ring. Their thio-analogues, the thioaurones (hemithioindigos), have a long history as dyes,[2] and only recently has their potential use as cytotoxic agents[3] and components for the cosmetics industry[4] been addressed. Thioaurones have also attracted some interest as photoisomerizable chromophores.[5–7] However, their chemical behavior is less well studied.[2,6d] For any use in practical applications, knowledge about chemical stability under various reaction conditions is of great importance. In this Letter, we report on new findings related to the chemical instability of thioaurone derivatives under conditions encountered during solid-phase peptide synthesis (SPPS).

In an extension to our previous work on photoswitchable peptidomimetics incorporating a stilbene moiety,[8] we found it interesting to investigate whether the conformationally more rigid thioaurone chromophore might be a useful complement. However, initial attempts to utilize the previously reported thioaurone amino acid mimetics[6] resulted frequently in degradation into a multitude of decomposition products during peptide synthesis, unlike the chemically stable stilbene analogues. Although there has been some speculation about the chemical reason for this instability,[6d] there is no evidence so far for the reactions involved. One obvious possibility is nucleophilic or electrophilic attack on the double bond or the sulfur atom, respectively.

Interconversions between various types of flavonoids are biochemical processes,[1] and these have also been used in the synthesis of both flavonoids and their thio-analogues. Ring expansions of aurones to flavones,[9] or ring contractions of thioflavones to thioaurones[10] have been reported, transformations which often involve redox reactions.

2. Results and discussion

During our own attempts to incorporate thioaurones into the backbone of linear peptidomimetics, decomposition occurred during cleavage from the SPPS matrix. This was apparent following workup as indicated by a fading of the typical yellow color of the thioaurone, suggesting a reaction involving the chromophore.

In order to clarify these reactions, we synthesized model compound **1a**,[6a] which was exposed to SPPS conditions, that is, treatment with TFA/DCM (85:15) and 0.4% triethylsilane (TES). The main components of the resulting product mixture were a reduction product, that is, the thiaindene derivative **2a**, and a rearranged compound, the thioflavonol **3a**. The corresponding products were

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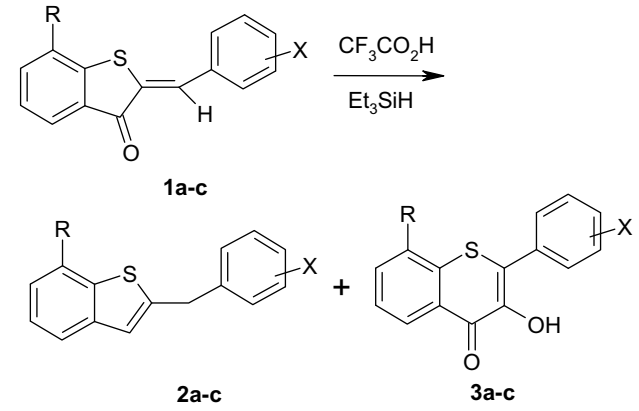

a, R = COOH, X = H; **b**, R = COOH, X = *p*-CH_2NHBoc;
c, R = CO-Ala, X = *p*-CH_2NH-Val-OAc

Scheme 1.

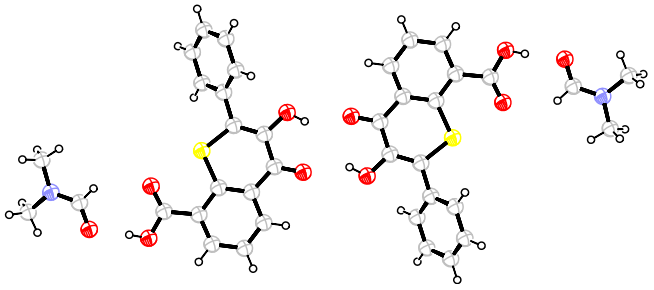

Figure 1. Arrangement of hydrogen-bonded thioflavonol and associated DMF molecules in the crystal lattice of **3a**·**DMF**. ORTEP plot[13] showing displacement ellipsoids at the 50% probability level.

obtained from the Boc-protected thioaurone amino acid **1b**[6a] and from the linear tripeptide **1c**[6a] (Scheme 1). Notably, products from retro-aldol condensation, or nucleophilic or electrophilic addition, which were suggested previously as possible decomposition pathways, were observed only in trace amounts.

In the reaction mixtures, the thioflavonols **3a–c** accounted for between 11% and 38% of the material, and the thiaindenes **2a–c** for between 8% and 88%. The remaining material represented a mixture of polymers and by-products, which were not characterized further. An interesting observation was that thioaurone **1a** was stable in a solution of 50% TFA in DCM for three days, but decomposed immediately upon addition of a few drops of TES.

The formation of thiaindenes **2** is likely to follow a previously reported mechanism via formation of an alcohol, which is then dehydrated under the acidic conditions.[11] The thioflavonols **3a–c** are formally obtained by disproportionation of the starting material under reductive conditions, followed by rearrangement.

Thioflavonol **3a** co-crystallizes with hydrogen-bonded solvent molecules from a solution in *N*,*N*-dimethylformamide (DMF). In the crystal, molecules are arranged as hydrogen-bonded dimers, similar to previously reported 3-hydroxyflavone derivatives, for example, 2′-methyl-3-hydroxyflavone.[12] Molecules of **3a** are arranged in pairs, hydrogen-bonded via the C=O and C=C–OH groups of thioflavonol ring C (Fig. 1).

3. Experimental

Thioaurones **1a–c** were dissolved in TFA/DCM (85–99.5% TFA) and TES (0.4–2.5%) was added. After stirring at rt for 15–180 min, the product composition was determined by ^{1}H NMR spectroscopy. The main components were isolated chromatographically and characterized by NMR and IR spectroscopy (see Supplementary data for details).

2-Benzylbenzo[b]thiophene-7-carboxylic acid (**2a**): Faintly yellow needles (46 mg, 0.17 mmol, 48%). mp = 168–170 °C. ^{1}H NMR (500 MHz, $CDCl_3$ solution, 25 °C), δ = 8.12 (dd, J = 7.6, 1.2 Hz, 1H, H-6), 7.90 (dd, J = 7.6, 1.2 Hz, 1H, H-4), 7.42 (dd, J = 7.6, 7.6 Hz, 1H, H-5), 7.33 (m, 3H, *o* + *p*-Ph), 7.26 (m, 2H, *m*-Ph), 7.08 (t, J = 1.1 Hz, 1H, H-3), 4.27 (d, J = 1.1 Hz, 2H, CH_2). ^{13}C NMR (125.7 MHz, $CDCl_3$ solution, 25 °C), δ = 170.3 (COO), 147.8 (C-2), 141.4 (C-7/C-3a), 140.6 (C-7a), 139.1 (*ipso*-Ph), 128.8 (2C, *o*-Ph), 128.6 (2C, *m*-Ph), 128.1 (C-4), 127.0 (C-6), 126.4 (*p*-Ph), 123.9 (C-5), 122.6 (C-7/C-3a), 120.8 (C-3), 36.6 (CH_2). IR (neat): 3023, 2825, 2538, 1682, 1547, 1426, 1278, 1157, 891, 835, 745, 692 cm^{-1}. MS (EI, 70 eV): m/z (%) = 268 (100, M^+), 223 (31%, $[M-COOH]^+$), 191 (22%, $[M-Ph]^+$).

3-Hydroxy-4-oxo-2-phenyl-4H-1-benzothiopyran-8-carboxylic acid (**3a**): A crystalline material was obtained by recrystallization from *N*,*N*-dimethylformamide solution, colorless crystals, mp = 248–250 °C. ^{1}H NMR (500 MHz, DMSO-d_6 solution, 25 °C), δ = 13.83 (br s, 1H, COOH), 9.49 (s, 1H, OH), 8.77 (dd, J = 8.1, 1.7 Hz, 1H, H-5), 8.47 (dd, J = 7.5, 1.6 Hz, 1H, H-7), 7.74 (dd, J = 8.1, 7.5 Hz, 1H, H-6), 7.69 (m, 2H, *o*-Ph), 7.54 (m, 2H, *m*-Ph), 7.49 (m, 1H, *p*-Ph). ^{13}C NMR (125.7 MHz, DMSO-d_6 solution, 25 °C), δ = 175.0 (C-4), 167.6 (C-9), 144.3 (C-3), 139.3 (C-8a), 135.7 (C-7), 134.8 (*ipso*-Ph), 134.2 (C-5), 131.6 (C-8), 130.04 (2C, *o*-Ph), 130.0 (*p*-Ph), 129.3 (2C, *m*-Ph), 127.8 (C-2), 127.2 (C-4a), 127.0 (C-6). MS (ESI, 30 eV): m/z (%) = 298.9 (100, $[M+H]^+$).

Compound **3a**·**DMF** ($C_{19}H_{17}NO_5S$), M_r = 371.40, crystal dimensions 0.62 × 0.52 × 0.28 mm^3, monoclinic, space group $P2_1/c$, a = 10.9536 (5) Å, b = 11.1121 (5) Å, c = 14.6582 (7) Å, β = 100.656 (1)°, V = 1753.39 (14) Å^3, Z = 4, ρ_{calcd} = 1.407 g/cm^3, absorption coefficient 0.215 mm^{-1}, θ = 2.31–32.96°. $F(000)$ = 776, T = 153 (2) K, R_1 = 0.0319, wR_2 = 0.0913. Independent reflections = 6278 [R(int) = 0.0218], restraints = 0, parameters = 256. Crystallographic data of **3a**·**DMF** have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication No. CCDC 686651.

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Supplementary data

Synthetic details, experimental data for compounds **1**–**3** and details of the X-ray crystallographic structure analysis for **3a**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.054.

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