Thiol-induced Conversion of (*Z*)-4-*o*-Acetoxybenzylidene-2-phenyl-4,5-dihydro-oxazol-5-ones into 3-Benzoylaminocoumarins

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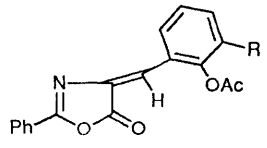
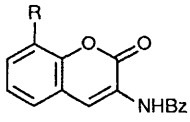
Toluene-α-thiol induces cleavage of the 1,5-bond of (*Z*)-4-*o*-acetoxybenzylidene-2-phenyl-4,5-dihydrooxazol-5-ones in triethylamine-containing ethanol to give 3-benzoylaminocoumarins

Requiring 3-aminocoumarin in one of our projects, we were interested in 3-benzoylaminocoumarin **2a** as the possible starting material. Attempted acetic anhydride-mediated condensation of hippuric acid **5** with salicylaldehyde **6a**[1] produced **2a** and (*Z*)-4-*o*-acetoxybenzylidene-2-phenyl-4,5-dihydrooxazol-5-one **1a** (Scheme 1), the separation of which was not only tedious but gave low yields of contaminated



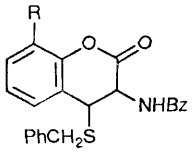
1

a; R = H
b; R = OAc



2

a; R = H
b; R = OAc
c; R = OH



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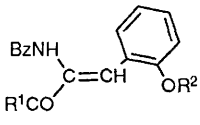
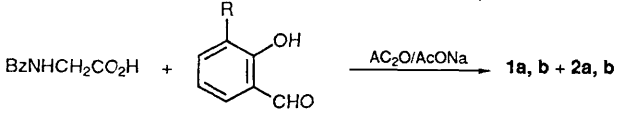


4

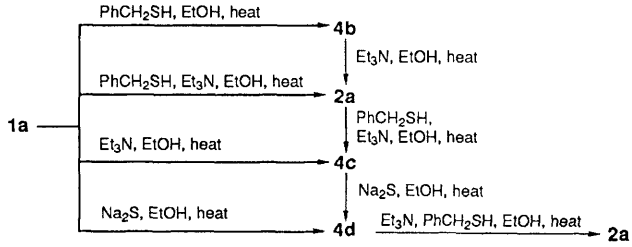
a; R^1 = OH, R^2 = H
b; R^1 = $PhCH_2S$, R^2 = Ac
c; R^1 = EtO, R^2 = Ac
d; R^1 = EtO, R^2 = H



6

a; R = H
b; R = OH

Scheme 1



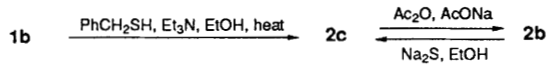
Scheme 2

compounds. Potassium hydroxide hydrolysis of the crude product followed by acidification gave 2-benzoylamino-*o*-hydroxycinnamic acid **4a** and coumarin **2a** which was separable. However, since the coumarin **2a** underwent partial isomerisation to **4a** upon saponification,[2,3] this procedure was unsuitable for its preparation.

The Michael addition of thiols to α,β-unsaturated acid derivatives,[4–6] suggested the feasibility of thiol-aided conversion of **1a** into **2a**. Pure **1a** was prepared by the condensation of *O*-acetylsalicylaldehyde with 2-phenyl-4,5-dihydrooxazol-5-one or, alternatively, by the acetic anhydride-mediated cyclodehydration of **4a**. When heated with toluene-α-thiol in ethanol compound **1a** gave a sulphur-containing product, characterised as *S*-benzyl (*Z*)-2-benzoylamino-*o*-(acetoxy)thiocinnamate **4b**. This cyclised to **1a**, even on passage through a silica gel column; spectroscopic evidence [IR, ^{1}H NMR; *m*/*z* 308 (M^+ – $PhCH_2S$)] were consistent with the proposed structure.

When heated with toluene-α-thiol in triethylamine-containing ethanol, **1a** gave the coumarin **2a** in good yield. However, it underwent ethanolysis when heated alone in triethylamine-containing ethanol, to afford ethyl (*Z*)-2-benzoylamino-*o*-acetoxycinnamate **4c**. The thiol ester **4b** furnished the coumarin **2a** when heated in triethylamine-containing ethanol. On the other hand, the conversion of **4c** into **2a** required the presence of toluene-α-thiol and triethylamine.

The reaction of **1a** with sodium sulphide gave ethyl (*Z*)-2-



Scheme 3

benzoylamino-*o*-hydroxycinnamate **4d**. Similarly, the acetyl derivative **4c** when heated with sodium sulphide in ethanol gave **4d** and this in the presence of triethylamine underwent thiol-aided cyclisation to the coumarin **2a**.

These results indicate that the conversion of **1a** into **2a** involves first, thiolysis of the 1,5-bond to give the thioester **4b** which upon transesterification with ethanol under the basic conditions, liberates the thiol moiety; this, in turn, leads to deacetylation of **4c**. *S*-Benzyl thioacetate generated in the medium, subsequently undergoes ethanolysis, to liberate the free thiol which, once again, reacts with the ethyl ester **4d**, acting as a Michael acceptor, to give 3-benzoylamino-4-benzylthio-3,4-dihydrocoumarin **3**; this then undergoes β-elimination to afford **2a**.

In the light of the success of the thiol–triethylamine combination to effect the desired isomerisation, the mixture of **1a** and **2a**, obtained by the Erlenmeyer procedure, was subjected to the reaction conditions described to give considerably improved yields of **2a**. Similarly, a mixture of **1b** and **2b** (see earlier) furnished 3-benzoylamino-8-hydroxycoumarin **2c** when heated with toluene-α-thiol under the conditions described. Although **2c** underwent acetylation to give **2b**, deacetylation of **2b** with sodium sulphide afforded **2c**, in excellent yield.[7]

In summary, the present reaction avoids separation of compounds **1** and **2** and increases the yield of the desired coumarin. It also has a potential in the conversion of *Z*-2,3-didehydro acid derivatives into their corresponding *E*-isomers.

The products reported were characterised on the basis of spectral data, elemental analyses and/or by comparison with authentic samples.

Experimental

Reaction of **1a** *with Toluene-α-thiol in the Presence of Triethylamine to give Compound* **2a**: *Typical Procedure.*—A mixture of compound **1a**, toluene-α-thiol, and triethylamine (molar ratio 1:1:2) was heated under reflux in ethanol (30 ml g^{-1} of **1a**) for 2 h. The mixture was concentrated to dryness under reduced pressure, triturated with ethanol, filtered under suction, and recrystallised from ethanol–benzene to give compound **2a** (69%).

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