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The Regiospecific Synthesis of Angularly-Fused Xanthones via the Benzannulation of 1,2-Adducts Derived from 3-(*o*-Anisoyl)-4-substituted Cyclobutenediones and Their Dithianyl Derivatives.

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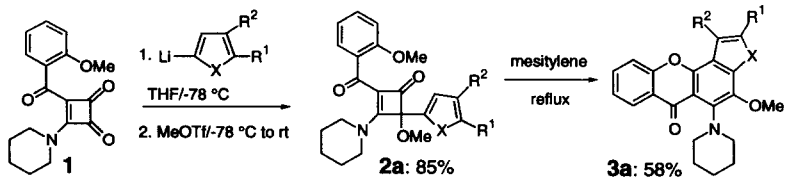
Abstract: *Described in this paper is a new synthetic approach to angularly-fused and simpler substituted xanthones that is based upon the benzannulation of 2-(o-anisoyl)-4-heteroaryl-2-cyclobutenones and 2-(2-(o-anisyl)-1,3-dithian-2-yl)-4-alkenyl-2-cyclobutenones followed by facile intramolecular loss of methanol and cyclization to the xanthone.*

The occurrence of the xanthone substructure in many natural products possessing a broad spectrum of biological and pharmacological activities[1-7] has led to various investigations of the synthesis of substituted, polyoxygenated xanthones.[8-19] A novel approach to *linearly*-fused, highly-substituted xanthones was recently disclosed[20] using a process based on the benzannulation of alkenyl, aromatic, and heteroaromatic lithiates with dithiane-protected benzopyrone-fused cyclobutenediones. Herein is disclosed a complementary, convergent synthesis of *angularly*-fused and simpler substituted xanthones using well-established cyclobutenedione-based technology[21-26] to generate a series of 2-hydroxy-2'-methoxybenzophenones that undergo intramolecular elimination of methanol providing the target structures.[27]

Following an established protocol,[28] 3-(*o*-anisoyl)-4-(1-piperidinyl)-3-cyclobutene-1,2-dione (**1**)[29] was treated at -78 °C with heteroaryl lithiates generated from 2-bromofuran, 2-bromothiophene, and N-methylindole. After quenching the reaction mixture at -78 °C with methyl triflate and warming to room temperature, adducts **2** were isolated in good yields (Equation 1). It was previously established that regiocontrolled 1,2-addition occurs at the non-vinylogous amide carbonyl group in 3-acyl-4-(substituted amino)-3-cyclobutene-1,2-dione.[28] After prolonged thermolysis in refluxing mesitylene (56 h for **2a**, 17 h for **2b**, and 64 h for **2c**), **2a-c** were transformed into the angularly-fused xanthones **3a-c** in 53 – 97% yields.

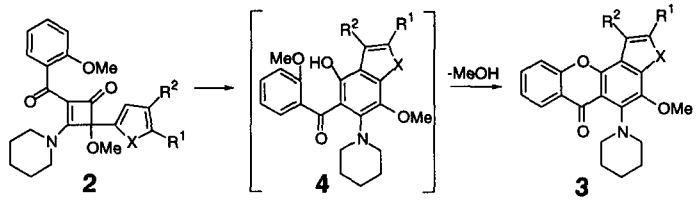
Equation 1



a: X = S, R^1= R^2 = H; **b**: X = O, R^1 = Me, R^2 = H; **c**: X = NMe, R^1,R^2 =benzo

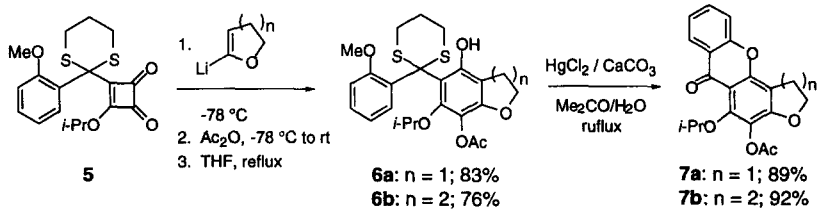
The formation of **3** most likely proceeds through the benzannulation product **4** which is produced by a cascade of electrocyclization reactions initiated by ring-opening of the cyclobutenedione.[21-26] The initially formed *o,o'*-oxygenated benzophenone **4**, produced during the early stages of the reaction (deduced from TLC evidence after 1h), underwent precedented[11] *in situ* cyclization and elimination of methanol to produce the angularly-fused xanthone **3** (Equation 2).

Equation 2



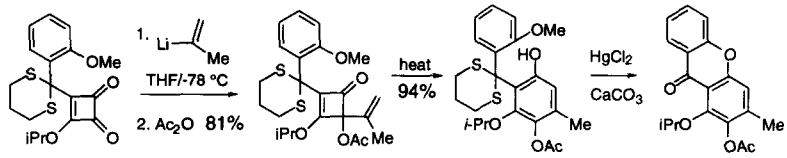
In order to expand the scope of the synthesis of angularly-substituted xanthones, 3-aroyl-3-cyclobutene-1,2-diones *not* possessing a 4-(1-piperidinyl) substituent were investigated (Equation 3). Because 3-acylcyclobutenediones without a 4-amino substituent are *not* stable,[30] the synthetically equivalent 3-isopropoxy-4-(2-(*o*-anisyl)-1,3-dithian-2-yl)-3-cyclobutene-1,2-dione (**5**) was prepared.[31] Treatment of **5** with 2-lithiodihydrofuran and 2-lithiodihydro-2H-pyran, generated from the corresponding alkenylstannanes and *n*-BuLi at -78 °C, followed by *in situ* quenching with acetic anhydride and thermal benzannulation provided substituted phenols (**6**), regiospecifically and in good yields.[32] The angularly-fused xanthones **7** were directly formed as reaction products under the Hg(II)-catalyzed reaction conditions used for hydrolyzing the dithiane group.[33] The core structure of dihydrofuran-and dihydropyran-fused angular xanthones **7a** and **7b** has been found in many natural products with a variety of biological activities.[1-4,6,7]

Equation 3



The above strategy was also extended to the synthesis of simpler substituted xanthones. Thus, via the same reaction sequence, substituted xanthone **8** was prepared in 56% overall yield, regiospecifically (Equation 4). It is noteworthy that the reaction sequence described here provides angularly-fused xanthones **7a,b** and xanthone **8** bearing differently protected hydroxyl groups. Selective deprotection would provide opportunities for the regioselective modification of these compounds.

Equation 4



In conclusion, angularly-fused and simpler substituted xanthones can be synthesized in a convergent and regiocontrolled fashion via the vinylketene-based benzannulation of 3-(*o*-anisoyl)-4-(1-piperidinyl)-3-cyclobutene-1,2-diones and 3-alkoxy-4-(2-(*o*-anisyl)-1,3-dithian-2-yl)-3-cyclobutene-1,2-diones. Regiocontrolled nucleophilic addition of heteroaryl-, cycloalkenyl, and alkenyl lithiates followed by a cascade of electrocyclizations (with subsequent deprotection in cases of dithiane derivatives) and cyclization of the *o*-anisoylphenols afforded a variety of xanthones with unique structures. The excellent control of regiochemistry combined by the short reaction sequences and high efficiency of the method should allow its application to the total synthesis of naturally-occurring xanthones.

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(31) A full study of the use of 3-(1,3-dithian-2-yl)-4-substituted-3-cyclobutene-1,2-diones as synthetic equivalents of 3-acyl-4-substituted-3-cyclobutene-1,2-diones in benzannulation reactions has been completed and will be disclosed in due course (L. Sun and L. S. Liebeskind, *J. Org. Chem.* to be submitted).

(32) The regiochemistry of the nucleophilic addition was assigned on the basis of two factors: (1) Nucleophilic addition to cyclobutenediones is known to occur with high regioselectivity at the non-vinylogous ester (or vinylogous amide) carbonyl group, and (2) an extensive but yet unpublished study has demonstrated highly selective nucleophilic attack at the cyclobutenedione carbonyl group most distant from sterically encumbering substituents at the 3- or 4-position of the cyclobutenedione ring.

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