Novel Construction of Highly-Substituted Xanthones

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The xanthone core **1** is present in a large family of natural products with broad biological activities.[1−4] Many polyoxygenated, naturally-occurring xanthones possess intriguing biological properties, a factor that has led to interest in the development of new synthetic methodologies for construction of the ring system and to the total synthesis of various xanthone-based natural products.[5−25]

Deconstruction of the highly-substituted xanthone core reveals a concise synthetic strategy that generates the key dithiane-protected benzopyrone-fused cyclobutenedione **5** by fusing a dianion derived from the salicylaldehyde **2**, protected as the dithiane **3**, to a squaric acid derivative **4** (Scheme 1). Reaction of **5** with alkenyl, aromatic, and heteroaromatic lithiates should provide, after thermolysis and hydrolysis, the highly-oxygenated xanthones **1** following well-established cyclobutenedione-based technology.[26−31]

The synthesis of five dithiane-protected benzopyrone-fused cyclobutenediones is depicted in Table 1. A variety of 2-(*o*-hydroxyphenyl)-1,3-dithianes **3** was prepared, each in high yield from the corresponding salicylaldehyde under standard conditions.[32,33] Each of the dithianes **3** was dissolved in THF and

Scheme 1

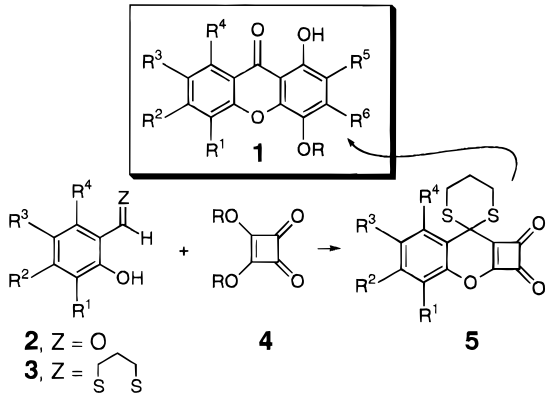
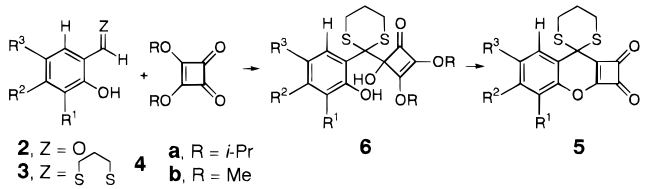


Table 1. Synthesis of Dithiane-Protected Benzopyrone-Fused Cyclobutenediones **5**



entry	R^1	R^2	R^3	cmpd, %	**4**	**6**, %	**5**, %
1	H	H	H	**3a**, 95	**4a**	**6a**, 87	**5a**, 82
2	H	H	Cl	**3b**, 90	**4a**	**6b**, 94	**5b**, 76
3	MeO	H	H	**3c**, 95	**4b**	**6c**, 89	**5c**, 80
4	H	H	MeO	**3d**, 98	**4b**	**6d**, 77	**5d**, 79
5	MeO	MeO	H	**3e**, 91	**4b**	**6e**, 86	**5e**, 46

treated with 2.2 equiv of *t*-BuLi in pentane at −78 °C, and the resulting solution was warmed to 0 °C to generate a slurry of the corresponding O-, C-dianion. Reaction of the dianions with the dialkyl squarates (**4**) took place at 0 °C to afford the 1,2-adducts **6** in excellent yield in all cases.

The choice of squarate ester **4** was dictated by the ability to promote the transformation of **6** into **5** using *p*-toluenesulfonic acid monohydrate (*p*TSA) in CH_2Cl_2 at room temperature (**6a**, 10 mol % of *p*TSA for 72 h; **6b**, 20 mol % of *p*TSA for 12 h and then an additional 10 mol % of *p*TSA for 12 h). Notably, the purification of **5a**,**b** was achieved by simple trituration in ether and hexanes, thus avoiding a tedious chromatography. Under a variety of conditions, the adducts derived from diisopropyl squarate and the methoxylated phenyldithianes (**3c**−**e**) did not efficiently transform into the corresponding ring-fused cyclobutenediones **5**. To overcome this limitation adducts **6c**−**e** derived from dimethyl squarate, although not stable enough for complete characterization (their structures were confirmed by ^{1}H NMR spectra, alone), were obtained in good yields and did undergo the desired acid-promoted reaction to provide **5c**−**e** in moderate to very good yields (Table 1, entries 3−5). It is noteworthy that these reactions can be conducted on a large scale. Thus, without chromatography, 7.5 g of diisopropyl squarate **4a** and 7.3 g of dithiane **3a** gave 13.5 g of adduct **6a** (87%), of which 7.0 g in turn was transformed into 4.1 g (82%) of cyclobutenedione **5a**, again without chromatography.

Efficient nucleophilic addition of different alkenyl (styrene, dihydropyran), aryl (benzene, substituted benzenes, naphthalenes), and heteroaryl (furan, thiophene, pyrrole, indole) lithiates

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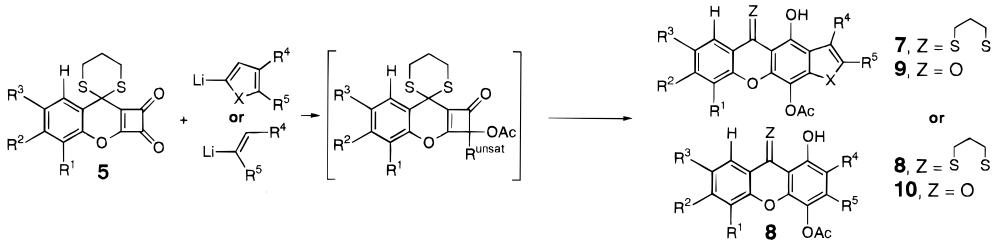
Table 2. Highly-Substituted Xanthones From Dithiane Protected Benzopyrone-fused Cyclobutenediones



entry	5[a]	organolithium reagent	X	R^4	R^5	cmpd, %	cmpd, %
1	**5a**	phenyllithium	-CH=CH-	H	H	**7a**, 81	**9a**, 77
2	**5a**	2-naphthyllithium	-CH=CH-	benzo		**7b**, 89	**9b**, 71
3	**5a**	1-naphthyllithium	*o*-phenylene	H	H	**7c**, 75	**9c,** 80
4	**5a**	*p*-methoxyphenyllithium	-CH=CH-	H	OMe	**7d**, *b*	**9d**, 33[c]
5	**5a**	2-((1-dimethylamino)pyrrolyl)lithium	$NNMe_2$	H	H	**7e**, 57	**9e**, 81
6	**5a**	2-(1-methylindolyl)lithium	NMe	benzo		**7f**, 76	**9f**, 56
7	**5a**	2-thienyllithium	S	H	H	**7g**, 50	**9g**, 67
8	**5a**	(*E*)-*β*-styrenyllithium		Ph	H	**8a**, *b*	**10a**, 21[c]
9	**5b**	2-thienyllithium	S	H	H	**7h**, 41	**9h**, 68
10	**5b**	2-((5-trimethylsilyl)furanyl)lithium	O	$SiMe_3$	H	**7i**, 55	**9i**, 54
11	**5b**	2-dihydropyranyllithium		$-(CH_2)_3O-$		**8b**, 66	**10b**, 62
12	**5c**	*p*-(dimethylamino)phenyllithium	H	NMe_2	H	**7j**, *b*	**9j**, 41[c]
13	**5d**	2-(1-(dimethylamino)pyrrolyl)lithium	$NNMe_2$	H	H	**7k**, 71	**9k**, 88
14	**5e**	3-furanyllithium		-OCH=CH-		**8c**, 73	**10c**, 53

[a] Refer to Table 1 for a listing of substituents R^1 to R^3 of **5**. [b] Not purified; the crude product was directly exposed to the dithiane hydrolysis conditions. [c] Overall yield from **5**.

to the dithiane-protected *γ*-benzopyrone-fused cyclobutenediones **5** took place exclusively at the carbonyl group opposite the bulky dithiane moiety (Table 2).[34] The 1,2-adducts (bracketed structure in Table 2) were exceptionally prone to benzannulation; even at room temperature the aromatized products slowly formed, and the alkenyl adducts were so reactive toward benzannulation that they were seen only by TLC. Although the *O-acetylated* 1,2-adducts derived from phenyl and substituted phenyl lithiates had longer lifetimes and could be isolated in pure form in some cases, facile room temperature benzannulation in solution and in the solid state prevented their comprehensive characterization. It proved most efficient to isolate the benzannulated products **7** or **8** directly, after heating THF solutions of the crude 1,2-adducts for about 2 h. Following this protocol, the dithiane-protected xanthones **7** or **8** could be easily obtained in moderate to excellent yields in pure form by chromatographic purification, in most cases. However, attempts to obtain analytically pure **7d**, **7j**, and **8a** were not successful. Nevertheless, the corresponding analytically pure xanthones **9d**, **9j**, and **10a** could be obtained after hydrolysis of the crude dithiane-protected products. In these three cases, overall yields are reported on the basis of the cyclobutenediones **5** used in those reactions. In all other cases, the targeted xanthone structures **9** and **10** were obtained in moderate to excellent yields after chromatographic purification when a standard $HgCl_2$-promoted deprotection protocol[32,33]was applied to compounds **7** and **8** (Table 2).

In conclusion, a concise and synthetically flexible approach to highly-substituted xanthones has been demonstrated which relies on the versatility of cyclobutenediones as scaffolds for the construction of a diverse range of molecular structures. Dithiane-protected *γ*-benzopyrone-fused cyclobutenediones **5**, easily prepared on a large scale from dialkyl squarates and the dianions of 2-(*o*-hydroxyphenyl)-1,3-dithianes, are the key to accessing in a regiocontrolled fashion a variety of highly-substituted xanthones and xanthones fused to aromatic and heteroaromatic rings.

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Supporting Information Available: A complete description of the synthesis and characterization of all compounds in the manuscript (23 pages). See any current masthead page for ordering and Internet access instructions.

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(34) 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 nonvinylogous 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.