Thiophthalides, a Novel Class of Arene-annulating Agents: Synthesis of Polynuclear Hydroaromatic Compounds

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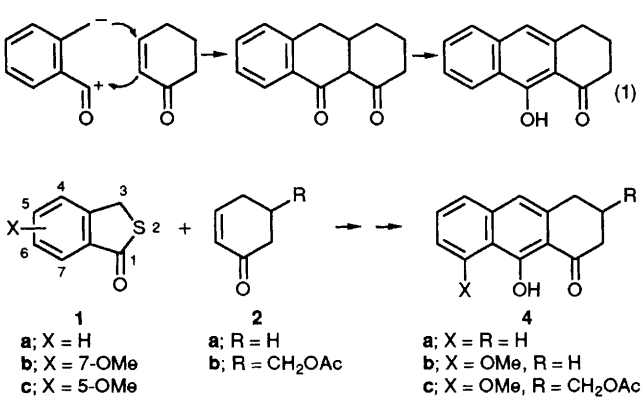
Anionic cyclocondensation reaction of thiophthalides **1** with cyclohex-2-enones **2** followed by aromatization gives oxygenated hydroanthracenones **4** in good yields.

The Michael-induced ring closure reaction of phthalides and *o*-toluates with various Michael acceptors is a popular method for regiospecific synthesis of peri-oxygenated anthracenes and naphthacene derivatives.[1] Ever since its discovery[2–5] this anionic [4 + 2] cycloaddition has enjoyed wide applications in convergent synthesis of polyketide-derived antibiotics.[6] However, the annulation [eqn. (1)] of cyclohex-2-enones with a 1,4-dipolar synthon, depicted in Scheme 1, that would provide a direct access to structural subunits of olivomycin,[7] and related antibiotics, has been elusive.[8] This problem has been ascribed to extensive polymerisation of cyclohexenones under basic conditions. We, however, reasoned that the reactivity of 1,4-dipole equivalents might play an important role in such annulations and examined the reactivity of thiophthalides **1**.

Initially, we examined the reactivity of the parent thiophthalide[9] **1a** towards methyl acrylate in the presence of lithium diisopropylamide (LDA) at −60 °C in order to assess how it compares with phthalide in its reactivity. Although the generation of the conjugate base of **1a** was indicated by the appearance of a yellow colour upon the addition of **1a** to a solution of LDA (2 equiv.), the quenching of the solution with methyl acrylate, after usual acid work-up, led to an intractable mixture of compounds. The same reaction, when performed in the presence of lithium *tert*-butoxide at −60 °C, gave **3a** (as an oil) in 26% yield. The identity of this product was authenticated by both its Raney-nickel degradation to 2-carboxy-α-tetralone and spectral data. Similarly, **1a** and acrylonitrile were annulated to yield **3b** in 13% yield along with a large amount of a polymeric solid material. The *trans* geometry of **3b** was ascertained on the basis of the coupling constants of the C-4 hydrogen.

The reaction between **1a** and cyclohex-2-eneone **2a** was performed in a similar way, and the crude product found to contain at least three compounds with enolic hydrogens indicating the success of the desired annulation. The ^{1}H NMR spectrum of the chromatographically purified product had three peaks δ at 16.64, 16.24 and 14.24. The former two peaks may be assigned to enolic protons of the isomers of **3c** and the third peak to that of the aromatized product **4a**. Without further purification, this mixture was exposed to Raney-nickel treatment. Usual work-up of this reaction afforded the anthracenone[10] **4a** in 17% overall yield. On the other hand, phthalide† **1b** was annulated to **2a** to give **3d** as a single isomer in 31% yield. Aromatization of **3d** with Raney-nickel gave **4b**.[11] Other examples of this condensation are presented in Table 1. The compound **4c** is of great importance because it bears a close resemblance to the core structure of olivomycinone. Interestingly, the thiophthalide **1c** underwent only Michael addition with **2a** furnishing the adduct **3e** as the sole isolable product. The inertness of this product to Dieckmann cyclisation, to give the corresponding annulated product, might possibly be explained in terms of decreased reactivity of thiolactone group which is in conjugation with a methoxy function. The reactivity of 7-methoxythiophthalide **1b** is



Scheme 1

Table 1 Anionic annulation of thiophthalides onto Michael acceptors[a]

Thiophthalide	Acceptor	Product (% yield)	
1a	CO_2Me	**3a**	(26)
1a	CN	**3b**	(13)
1a	**2a**	**3c**	(27)
1b	**2a**	**3d**	(31)
1b	**2b**	**4c**	(23)
1c	**2a**	**3e**	(35)
1c	**2a**		(14)[b]

[a] All the reactions were performed in the presence of lithium *tert*-butoxide. [b] This was done in the presence of LDA; the mixture was heated at reflux after 3 h at −60 to 0 °C.

† This was prepared from the corresponding *o*-toluate by benzylic bromination followed by thiourea treatment.

perhaps enhanced by the *ortho*-effect of the methoxy group present in it.

We have thus developed a simple synthesis of substituted anthracenones based on a straightforward application of anionic [4 + 2] cycloaddition, the success of which depends on the choice of 1,4-dipole equivalents. Absolute regiocontrol of bond formation, inherent in this methodology, might ultimately ease the enantioselective synthesis of structurally related natural products. Efforts to improve upon the yields of these reactions are underway.

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