Stereospecific Formation of 2-[(*E*)-Alk-1'-enyl]benzoic Acids in an Unusual Reaction of Thiophthalides with Aldehydes

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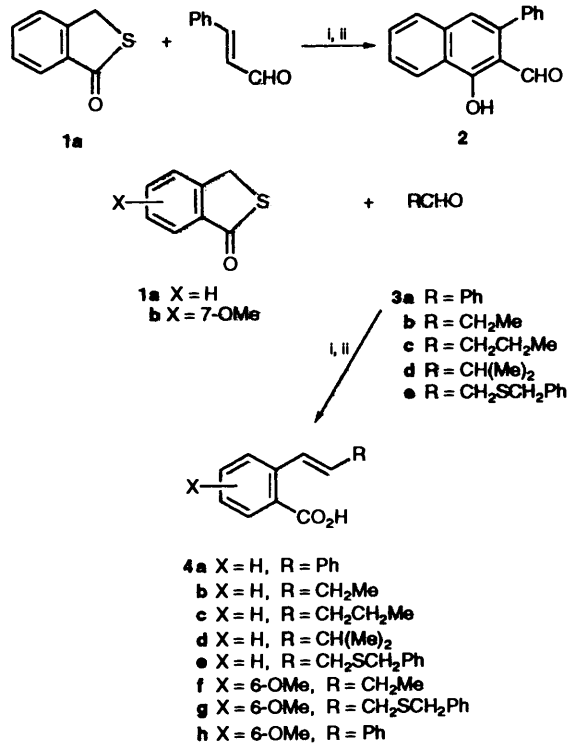
The reaction of thiophthalides **1** with aldehydes **3** in the presence of lithium *tert*-butoxide at −60 to 25 °C results in the stereospecific formation of only *trans* 2-(alk-1'-enyl)benzoic acids **4** in fairly good yields in one-pot operations. This reaction is proposed to proceed *via* episulfide formation followed by sulfur extrusion, and corroborated by an unprecedented reaction of phthalide with thiobenzophenone giving the acid **11a** under similar conditions.

We recently described the Michael-initiated ring closure (MIRC) reaction of thiophthalides **1** with various Michael acceptors, namely, α,β-unsaturated esters and enones.[1] In an extension of this study, we considered examining the reactivity of α,β-unsaturated aldehydes as Michael acceptors and applying this to the synthesis of 11-deoxydaunomycinone.[2] When cinnamaldehyde was reacted with thiophthalide **1a** in the presence of Bu^{t}OLi, the desired product **2** was obtained in only 6% yield. This product was accompanied by a large quantity of acidic products. To understand the nature of these acidic products, we decided to investigate the reaction of a simpler aldehyde. The reaction of benzaldehyde with thiophthalide **1a** under the above conditions unexpectedly furnished the *trans*-carboxylic acid **4a**.[3] The corresponding *cis* isomer of **4a** was not formed.

In view of the current interest in the preparation[4] and utilization[5] of 2-alkenylbenzoic acids in the synthesis of natural products, and the lack of stereospecific methods for obtaining these acids, we explored the generality of the reaction. Thus, thiophthalides[6] **1a** and **1b** were reacted with a series of aldehydes **3** in the presence of Bu^{t}OLi at −60 to 25 °C (Scheme 1). In all the cases, the products were 2-alkenylbenzoic acids **4** as presented in Table 1. Notably, all the products **4** contain *trans* double bonds; in none of the above reactions could the *cis* isomer be detected. Potassium *tert*-butoxide was found to be inferior to lithium *tert*-butoxide as the base. In the presence of sodium methoxide in methanol, under conditions[3] in which benzaldehyde is known to give the acid **4a**, the aliphatic aldehydes produced intractable mixtures of products. It is possible that both the aldehydes and the thiophthalides undergo destructive self-condensations.

The mechanism and stereoselectivity of this one-pot transformation may be thought of as passing through the intermediates **5**–**10** as shown in Scheme 2. In order to minimize the lone pair–lone pair repulsion between the sulfur of the thiophthalide and the oxygen of the aldehyde and other non-bonded interactions, the thiophthalide C-3 anion approaches the aldehyde as shown in conformation **5**. The resulting adduct on 120° rotation adopts conformation **6** suitable for formation of isocoumarin **7**; this can then assume flipped conformation **8** in which S^- is oriented antiparallel to the ester function. The sulfide nucleophile then displaces the ester function leading to *trans* episulfide **9**. Stereospecific sulfur extrusion from **9** at room temperature results in the formation of *E*-alkene **10**.

Comparative analysis of the oxidation numbers[7] of the reactants and the products clearly indicates the liberation of zero valent sulfur in the reaction. This might be possible if an episulfide intermediate is considered, since episulfides are known to lose elemental sulfur even at room temperature.[8] In addition, our results on the reaction of thiophthalide **1a** with



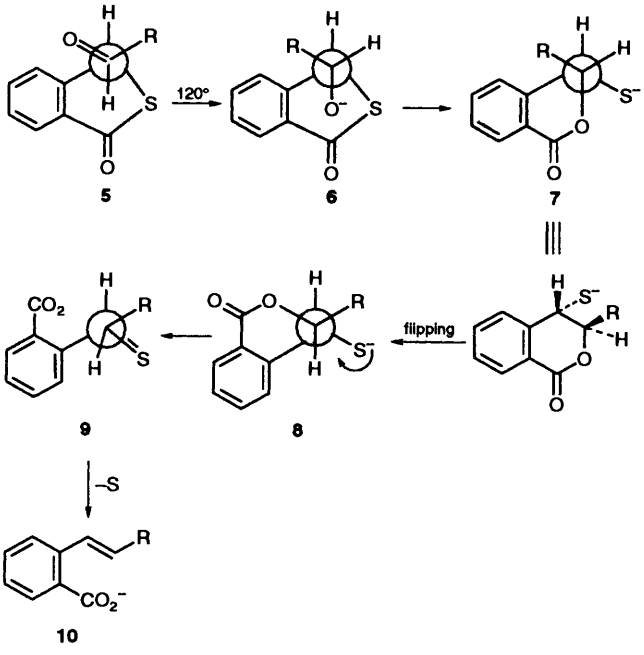
Scheme 1 *Reagents and conditions:* i, Bu^{t}OLi, THF, −60 °C; ii, H_3O^+

Table 1 Reaction of thiophthalides **1** with aldehydes **3**

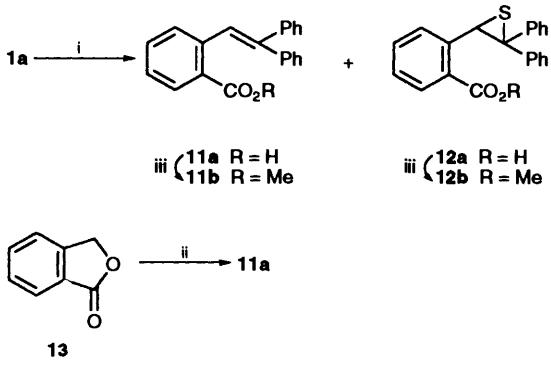
Thiophthalide	Aldehyde	Product[a]	Yield[b] (%)
1a	**3a**	**4a**	54
1a	**3b**	**4b**	43
1a	**3c**	**4c**	47
1a	**3d**	**4d**	51
1a	**3e**	**4e**	45
1b	**3b**	**4f**	42
1b	**3e**	**4g**	42
1b	**3a**	**4h**	40

[a] The products were homogeneous on TLC and characterized by ^{1}H NMR and mass spectroscopy and converted into their methyl esters. [b] The yields refer to isolated products.

benzophenone in the presence of Bu^{t}OLi provide convincing evidence of episulfide formation. The reaction furnished an inseparable mixture of two carboxylic acids **11a** and **12a** (Scheme 3). The mass spectrum of the mixture (homogeneous



Scheme 2 Mechanism of formation of *E*-alkene **10** from thiophthalide **1** and aldehyde **3**



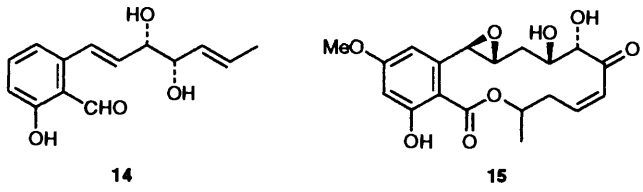
Scheme 3 *Reagents and conditions:* i, PhCOPh, Bu^{t}OLi, THF; ii, PhCSPh Bu^{t}OLi, THF; iii, CH_2N_2

on TLC) contained a peak at *m/z* 332 which could be due to the molecular ion of the episulfide **12a**. The presence of sulfur in **12a** was further confirmed by a positive sodium nitroprusside test on a sodium-fused sample of the mixture. The ^{1}H NMR spectrum of a TLC-homogeneous sample of the esters **11b** and **12b**, which were also inseparable, showed a singlet at δ 5.52 besides two methyl ester resonances at δ 3.9 and 3.82. The peak at δ 5.52, assigned to 1′-H in **12b**, vanished on subsequent heating in toluene, the mixture of esters converting into the ester **11b**. Further corroboration of the proposed mechanism was obtained from a hitherto unreported reaction of phthalide **13** with thiobenzophenone giving the same acid **11a** in 45% yield, which is presumably formed *via* episulfide **12a**.

Exploratory studies on the application of this unusual reaction of thiophthalides to the synthesis of pyriculol[9] **14** and hypothemycin[10] **15** are underway.

Experimental

General Procedure.—To a magnetically stirred solution of lithium *tert*-butoxide (6.7 mmol) in tetrahydrofuran (THF) (20 cm^3) under an Ar atmosphere at −60 °C was added a solution



of thiophthalide **1** (3.3 mmol) in THF (5 cm^3). The resulting yellowish solution was stirred at −60 °C for 20 min. Then aldehyde **3** (1.5 equiv. in 5 cm^3 THF) was introduced into the reaction flask. After about 30 min at −60 °C, the cooling bath was removed and the mixture was stirred for 18 h. It was then acidified with 10% HCl (4 cm^3). The resulting solution was concentrated at reduced pressure and extracted with diethyl ether (3 × 50 cm^3). The combined extracts were washed with water (20 cm^3), brine, dried (Na_2SO_4) and then evaporated to give a residue which on silica gel chromatographic purification furnished the corresponding product.

Physical data of selected compounds. (*J* Values are given in Hz.) **4a**: M.p. 159–160 °C (lit.,[3] m.p. 161–162 °C); ν/cm^{-1} 1680; δ_H($CDCl_3$) 8.2–8.0 (m, 2 H), 7.8–7.7 (m, 1 H), 7.65–7.45 (m, 3 H), 7.45–7.25 (m, 4 H) and 7.02 (d, 1 H, *J* 16.1); δ_C 140.23, 137.36, 133.13, 131.85, 131.67, 128.69, 127.93, 127.55, 127.33, 127.24 and 126.95; one aromatic carbon and the carboxylic carbon are missing. **4b**: Oil, ν/cm^{-1} 1690; δ_H 7.72 (d, 1 H, *J* 7), 7.45–6.85 (m, 4 H), 5.95 (dt, 1 H, *J* 6.0, 16.0), 2.22 (m, 2 H) and 1.08 (t, 3 H, *J* 6.0). **4d**: M.p. 62–63 °C; ν/cm^{-1} 1689; δ_H 8.0 (d, 1 H, *J* 7.5), 7.8–7.0 (m, 4 H), 6.1 (dd, 1 H, *J* 7.0, 16.0), 2.52 (m, 1 H) and 1.10 (d, 6 H, *J* 7.0). **4e**: M.p. 103–105 °C; ν/cm^{-1} 1680; δ_H 8.08 (d, 1 H, *J* 7.0), 7.6–7.4 (m, 2 H), 7.4–7.15 (m, 7 H), 6.14 (dt, 1 H, *J* 7.4, 15.6), 3.76 (s, 2 H) and 3.2 (d, 2 H, *J* 7.4).

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