Temperature Dependence of the Reduction of Phthalic Thioanhydrides by $NaBH_4$: Competition between 3-Hydroxythiolactone and Phthalide Formation

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The reduction of phthalic thioanhydrides with $NaBH_4$ at between 0 and –20 °C leads to the selective formation of 3-hydroxy-2-thiophthalides, whereas higher temperatures favour the formation of the corresponding phthalide derivatives. A mechanism is proposed that can explain these observations. Kinetic control at low temperatures leads to an improved stability of the intermediate alkoxide, thus allowing isolation of the γ-hydroxythiolactone after subsequent acidification of the reaction mixture. In this way the formation of the thermodynamically favoured phthalide derivative is avoided. Further reduction of the γ-hydroxythiolactone with AcOH/57% aqueous HI yields 2-thiophthalides, useful precursors for conducting polymers.

Introduction

In 1969 Schlessinger and Ponticello[1] reported the reduction of phthalic thioanhydride (**1a**) with metal hydrides, giving different products depending on the hydride type and reaction conditions (Figure 1).

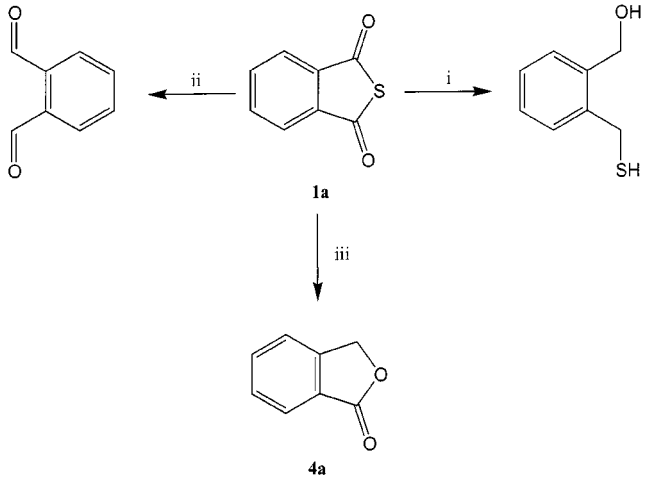

Figure 1. Phthalic thioanhydride reduction (ref.1): i) excess of LAH, ii) 1 equiv. of LAH, iii) $NaBH_4$/benzene/MeOH

Surprisingly, the literature of the last 30 years does not contain any other example of the reduction of phthalic thioanhydrides by metal hydrides, the only similar examples to be found concern the reduction of the more often utilised oxygen derivatives.[2–6] In 1967, Bloomfield and Lee[2] described an efficient method to synthesise lactones from cyclic anhydrides by reduction with lithium aluminium hydride (LAH) in Et_2O at −55 °C. They obtained the expected lactones with satisfactory yields of between 75% and 85%. Another example reported by Bailey and Johnson[3] concerns an efficient procedure using $NaBH_4$ as the reducing agent. This reaction was carried out in THF (or DMF) at temperatures around 0° C, and equimolar quantities of $NaBH_4$ and anhydride were used.

The introduction of a hydroxyl group at the 3-position of the lactone ring was first described by Trost et al. in 1980.[7] This method yields 3-hydroxyphthalide derivatives via bromine introduction at the lactone ring, followed by its substitution by a hydroxyl group in a reaction with potassium hydroxide. An alternative route, in which the corresponding phthalic anhydride is reduced with an organopalladium agent, proceeded in very low yields (16%).

Paulussen et al.[8] described the synthesis of 3-benzyl-3-hydroxy-2-thiophthalide in 1996 from the reaction of **1a** with benzylmagnesium chloride using a literature procedure.[9] The initially obtained disubstituted thiolactone was dehydrated to the benzylidene-2-thiophthalide, which was envisaged as a potential chain-stopper in the polymerisation reaction leading to poly(isothianaphthene) (PITN). Within a project focused towards PITN derivatives, we have reinvestigated the work of Schlessinger and Ponticello[1] and found a new and efficient synthesis of the 2-thiophthalide derivatives **3a**–**c**, passing through the stable 3-hydroxy-2-thiophthalide intermediates **2a**–**c**. These compounds were obtained in the low temperature reduction of phthalic thioanhydrides **1a**–**c** with $NaBH_4$ in THF. Furthermore, it became clear that formation of these hydroxy intermediates is the result of kinetic control of the process, and that thermodynamic control favours the formation of the phthalide derivatives **4a**–**c**.

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Results and Discussion

Until now 2-thiophthalide (**3a**), utilised as one of the possible starting monomers in the polymerisation leading to PITN,[10] could be obtained by only a few methods, for example from phthalide (**4a**), upon reaction with $PhCH_2SNa$ and subsequent $(CF_3CO)_2O$ addition,[11] or from ethyl *o*-toluate upon reaction with NBS, thiourea and $NaHCO_3$ [12] (Figure 2). Recently, Ryu et al.[13] reported the synthesis of 2-thiophthalide (**3a**) by an intramolecular homolytic substitution of an acyl radical at the sulfur atom in *o*-iodobenzyl *tert*-butyl sulfide, with extrusion of the *tert*-butyl radical (Figure 2).

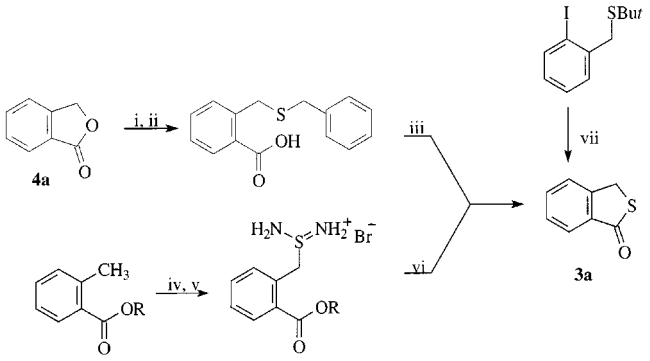

Figure 2. The possible pathways leading to 2-thiophthalide. (ref.[10]): i) $PhCH_2SH/NaH$; DMF, reflux, N_2, ii) H_3O^+, iii) $(CF_3CO)_2O$. (ref.[11]): iv) NBS, *hν*, CCl_4, v) thiourea, acetone, vi) $NaHCO_3$, heat. (ref.[12]): vii) CO, 80 atm., Bu_3SnH, AIBN, benzene, 100 °C, 5h

In the process of reinvestigating the findings of Schlessinger and Ponticello,[1] we discovered that the reduction of phthalic thioanhydride (**1a**) by $NaBH_4$ in THF at 0 °C led to the formation of 3-hydroxy-2-thiophthalide (**2a**) with an excellent yield of about 95%. Zn/AcOH reduction of phthalic thioanhydride (**1a**) also gave this hydroxylated thiolactone, although with a somewhat lower but still satisfactory yield (approx. 70%). However, small amounts of phthalide (**4a**) formed during the reduction process (GC-MS analysis). The synthesised intermediate underwent further reduction with AcOH/57% aq. HI solution.[14] The expected 2-thiophthalide (**3a**) was obtained with a good yield of about 75%. Following the same procedure we also obtained 5,6-disubstituted derivatives of 2-thiophthalide (**3b−c**), as well as their 3-hydroxylated intermediates **2b−c** (Figure 3).

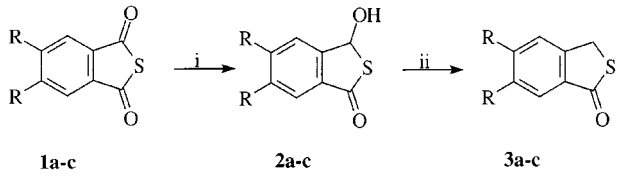

Figure 3. Synthesis of 2-thiophthalide from phthalic thioanhydride: i) $NaBH_4$/THF, 0 °C, ii) AcOH/HI 57% aq., heat

As substrates we used 4,5-dichloro- and 4,5-dimethoxyphthalic thioanhydrides (**1b−c**) to demonstrate the generality of this reductive sequence. We found that sodium borohydride reduction of thioanhydrides containing either electron donating or electron accepting substituents in the aromatic ring led to 3-hydroxy derivatives with moderate efficiency. The separation of the desired compound from the crude reaction mixture proved to be difficult as both phthalide and hydroxylated thiophthalide show a similar polarity — their R_f values are very close to each other in the TLC.

In order to improve the selectivity of this reduction, we investigated the effect of temperature, and thus we performed the reaction at −78 °C for 4,5-dichlorophthalic thioanhydride (**1b**). The reaction mixture was kept at this temperature for 1 h after thioanhydride addition, then it was acidified, also at −78 °C, followed by warming to ambient temperature. Although the rate of reduction was very slow in these conditions (there was still about 45% of thioanhydride present), it was clearly visible from the ^1H NMR spectrum that less than 5% of phthalide (**4b**) had been formed in the mixture and the reduction led selectively to 5,6-dichloro-3-hydroxy-2-thiophthalide (**2b**). When the reduction was performed at −78 °C, but the temperature of the reaction mixture was allowed to increase to +10 °C before acidification, almost 42% of **4b** was present, as estimated from the NMR spectra. The proposed mechanism for the reduction (Figure 4) may explain or give insight into the influence of the temperature on the course of the reaction.

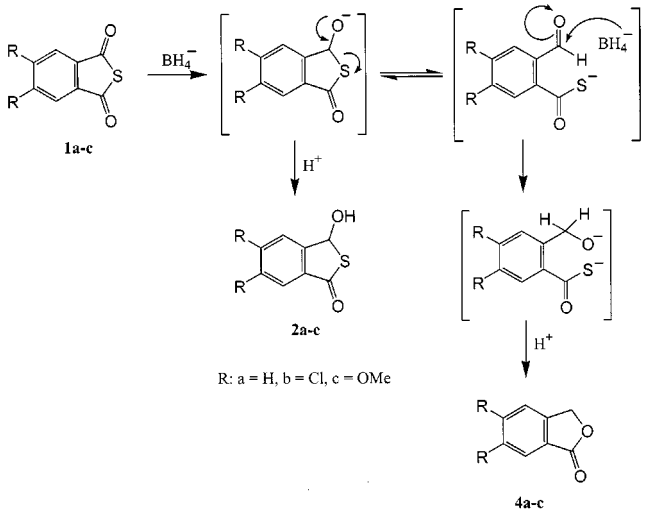

Figure 4. Mechanism of 3-hydroxy-2-thiophthalide and phthalide formation

The first step is the formation of an alkoxide. The relative stability of this intermediate at low temperature guarantees that the hydroxyl compound will be obtained after acidification of the reaction medium. In the case of electron donating groups (such as methoxy groups) we obtained a high selectivity of this reduction at −20 °C (only about 5% of the phthalide **4c** was formed). In the case of electron acceptors (such as chloro substituents) twice as much of

the by-product was formed at the same temperature. These results point to a kinetic control in the formation of the 3-hydroxy-2-thiophthalides **2a**−**c**. At temperatures higher than 0 °C thermodynamic control takes over and conversion into an intermediate aldehyde and further reduction could explain the formation of the phthalide derivatives. These results are also in agreement with earlier work[8] in which a similar behaviour to form phthalide derivatives rather than thiophthalide derivatives was observed at higher temperatures.

From the results above it is possible to conclude that under the conditions used by us for the phthalic thioanhydride reduction, the reaction is chemoselective in favour of the 3-hydroxylated thiolactone (**2**). In the case of the experiments described by Schlessinger and Ponticello[1] it is likely that the thioanhydride ring is opened and sulfur is liberated as H_2S after hydrolysis of the basic salt of the thioacid, followed by the phthalide ring closure. Comparing both sets of results we can conclude that the nature of the final product is strongly dependent on the temperature and the solvent used for the reduction.

Considering the simplicity of the process and the readily available reducing agents, the method of 2-thiophthalide (**3**) preparation described above could be useful for the synthesis of PITN and its derivatives. The 3-hydroxylated intermediates we obtained are new and stable chemical structures, and may be useful in the synthesis of conducting polymers.

Experimental Section

General Methods: All solvents used in the synthesis were distilled before use. THF was refluxed under nitrogen with sodium metal and benzophenone until a blue colour persisted, and was then distilled. Phthalic thioanhydride (**1a**), 4,5-dichlorophthalic thioanhydride (**1b**) and 4,5-dimethoxyphthalic thioanhydride (**1c**) were obtained according to existing literature procedures,[15,16] and were analysed by GC-MS spectrometry, which confirmed their molecular mass as 164 [M^+], 232 [M^+] and 224 [M^+], respectively. Sodium borohydride 98+% powder and Zn 30 mesh granules were purchased from Aldrich. Hydroiodic acid (57% H_2O solution), and the other substances used for the syntheses were analytically pure and were purchased from Acros Chimica. ^1H NMR spectra were obtained with a Varian Unity 300 spectrometer. For all synthesized substances spectra were recorded in deuterated chloroform; the chemical shift at δ = 7.24 (relative to TMS) for the residual protonated solvent was used as reference.

GC-MS analyses were performed on TSQ-70 and Voyager mass spectrometers (Thermoquest); capillary column: Chrompack CPsil5CB or CPsil8CB. Melting points (uncorrected) were measured on a digital melting point apparatus, Electrothermal IA 9000 series. TLC analyses were made on Merck aluminium sheets, 20 × 20 cm, covered with silica gel 60 F_{254}.

Synthesis of 3-Hydroxy-2-thiophthalide (2a). Method A: $NaBH_4$ (2.4 g, 63 mmol) was refluxed for 0.5 h in 100 mL of dry THF under N_2 atm. The suspension was then cooled to 0 °C and at this temp. phthalic thioanhydride (**1a**; 16.4 g, 100 mmol) in 100 mL of dry THF was added dropwise. After the addition was complete, the mixture was kept at 0 °C for 1 h, then the ice-bath was removed and the reaction mixture was kept at room temp. for 0.5 h. It was then cooled to 0 °C and 6 N HCl was added dropwise at this temperature to make the reaction mixture acidic. The THF was then evaporated under reduced pressure, and the product was extracted with Et_2O or EtOAc (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, the mixture filtered and the solvent evaporated. The remaining crude substance was purified by recrystallisation from hexane/EtOAc (9:1, v/v) to give the product as slightly beige crystals (15.9 g; 96%).

Method B: Zn granules (30 mesh diameter; 1.38 g, 20 mmol) and phthalic thioanhydride (**1a**; 1.64 g, 10 mmol) were refluxed in 20 mL of AcOH for 24 h. The mixture was then cooled to room temp., 40 mL of water was added, and extraction of the reaction mixture was carried out with 3 × 30 mL of EtOAc. The organic layers were washed with 5% aq. $NaHCO_3$ to pH ≈ 6, separated, dried over $MgSO_4$, and the solvent was evaporated. 1.1 g of product was obtained (69%) as a slightly yellow solid. M.p. from method B: 108−112 °C, from method A: 108.4−111.4 °C. R_f (hexane/EtOAc, 8:2, v/v) = 0.15 (ind. UV_{254}). GC-MS: *m*/*z* (%) = 166 (100) [M^+], 148 [$M^+ - H_2O$], 138 [$M^+ - CO$], 133 [$M^+ - SH$], 105 [$M^+ - CH(OH)S$], 77 [$M^+ - CH(OH)SCO$]. ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.96 (s, 1 H, O*H*), 6.69 (s, 1 H, C*H*OH), 7.50−7.75 (m, 4 H, arom.). HR-MS for $C_8H_6O_2S$: calcd. 166.00885; found 166.00914.

Synthesis of 2-Thiophthalide (3a): 3-Hydroxy-2-thiophthalide (**2a**; 15.9 g, 96.1 mmol) was added to a solution of 50 mL of acetic acid and 35 g of 57% hydroiodic acid (aqueous solution),. The mixture was kept at 125 °C for 1 h. It was then cooled to room temp., and poured into an aq. solution of 1 N NaOH (350 mL) containing 35 g of $NaHSO_3$. Next, the mixture was extracted with EtOAc (3 × 100 mL). The organic layers were dried over $MgSO_4$ and decolourized by treating with activated charcoal, then the solution was filtered and the solvent was evaporated. The obtained crude substance was recrystallised from hexane/EtOAc (9:1, v/v) to give the product as yellow crystals (10.7 g, 74%). M.p. 53.5−54.5 °C (58−60 °C: ref.[8,11]). R_f (hexane/EtOAc, 8:2, v/v) = 0.39 (ind. UV_{254}). GC-MS: *m*/*z* (%) = 150 (100%) [M^+], 121 (100) [$M^+ - CHO$], 105 [$M^+ - CH_2S$], 78 [$M^+ - CH_2SCO$]. ^1H NMR ($CDCl_3$, 300 MHz): δ = 4.45 (s, 2 H, CH_2), 7.40−7.70 (m, 4 H, arom.). HR-MS for C_8H_6OS: calcd. 150.01394; found 150.01665.

Synthesis of 5,6-Dichloro-3-hydroxy-2-thiophthalide (2b): 4,5-Dichlorophthalic thioanhydride (**1b**; 7.4 g, 31.9 mmol) [previously recrystallized from hexane/EtOAc (m.p. 95.5−96.4 °C)] dissolved in 100 mL of THF was added to a suspension of $NaBH_4$ (1.2 g, 31.9 mmol) in THF (50 mL) at −20 °C (NaCl-ice bath). After the substrate addition, the reaction mixture was kept at −20 °C for 2 h, and then left in the cooling bath until its temperature reached 0 °C (≈1 h).The solution was then acidified with dilute HCl, the solvent was evaporated and the residue was extracted with diethyl ether or ethyl acetate (3 × 150 mL). The organic layer was dried over $MgSO_4$, filtered, the ether was distilled off, and the obtained solid was washed with 50 mL of hexane. The hexane was then filtered off and the pale pink solid was dried in the air to 6.25 g of product (84%). M.p. 129.0−131.0 °C. R_f (hexane/EtOAc, 7:3, v/v) = 0.48 (ind. UV_{254}). GC-MS: *m*/*z* (%) = 234 (80) [M^+], 201 (90) [$M^+ - SH$], 188 (100) [$M^+ - CH_2S$], 173 (100) [$M^+ - CH_2OSH$]. ^1H NMR ($CDCl_3$, 300 MHz): δ = 6.65 (s, 1 H, C*H*OH), 7.82 (s, 1 H, arom.), 7.83 (s, 1 H, arom.). HR-MS for $C_8H_4O_2SCl_2$: calcd. 233.93091; found 233.93128.

Synthesis of 3-Hydroxy-5,6-dimethoxy-2-thiophthalide (2c): In an analagous procedure to that described above 4,5-dimethoxy-

phthalic thioanhydride (**1c**; 1.6 g, 7.1 mmol) [previously recrystallised from hexane/EtOAc (m.p. 197.3−198.5 °C; ref.[15] m.p. 181.3 °C)] dissolved in 30 mL of THF was reduced with $NaBH_4$ (0.27 g, 7.1 mmol) to give the product (1.18 g, 73%) as a pink solid. M.p. 123.5−126.0 °C. R_f (hexane/EtOAc, 6:4, v/v) = 0.16 (ind. UV_{254}). GC-MS: *m/z* (%) = 226 [M^+, 45%), 193 [M^+ − SH, 100%), 165 [M^+ − SC(OH)]. ^1H NMR: ($CDCl_3$, 300 MHz, ppm relative to TMS): 3.89 (s, 3 H, OCH_3), 3.97 (s, 3 H, OCH_3), 6.56 (d, 1 H, C*H*OH), 7.10 (s, 1 H, arom.), 7.12 (s, 1 H, arom.). HR-MS Calcd. for $C_{10}H_{10}O_4S$: 226.02998; found 226.03006.

Synthesis of 5,6-Dichloro-2-thiophthalide (3b): 5,6-Dichloro-3-hydroxy-2-thiophthalide (**2b**; 4.7 g, 20 mmol) was added to a solution of 10 mL of acetic acid and 7.0 g of 57% aq. soln. hydroiodic acid. The mixture was stirred at 110 °C for 3 h. It was then cooled to room temp. and poured into 70 mL of 1 N NaOH, containing 7.0 g (67.3 mmol) of $NaHSO_3$. The work up was the same as for **3a**. The crude substance was purified by column chromatography on silica gel (eluent: hexane/EtOAc, in gradient, start 95:5, end 65:35, v/v) to give 2.1 g (49%) of product as slightly yellow crystals. M.p. 161.0−163.2 °C. R_f (hexane/EtOAc, 7:3, v/v) = 0.72 (ind. UV_{254}). GC-MS: *m/z* (%) = 218 (80) [M^+], 189 (100) [M^+ − CHO], 146 [M^+ − CSCO]. ^1H NMR ($CDCl_3$, 300 MHz): δ = 4.41 (s, 2 H, CH_2, thiolactone cyclic ring), 7.64 (s, 1 H, arom.), 7.86 (s, 1 H, arom.). HR-MS for $C_8H_4OSCl_2$: calcd. 217.93599; found 217.93603.

Synthesis of 5,6-Dimethoxy-2-thiophthalide (3c): 5,6-Dimethoxy-3-hydroxy-2-thiophthalide (**2c**; 0.91 g, 4 mmol) was added to a solution of 2 mL of acetic acid and 1.4 g of 57% aq. hydroiodic acid. The mixture was stirred at 120 °C for 5 h. It was then cooled to room temp. and poured into 20 mL of 1 N NaOH containing 1.4 g (13.4 mmol) of $NaHSO_3$. The workup was the same as for **3a**. After separation of the product by column chromatography on silica gel (eluent: hexane/EtOAc, in gradient, start 95:5, end 65:35, v/v), 0.4 g of pure product was collected as slightly yellow crystals (48%). M.p. 150.0−152.5 °C. R_f (hexane/EtOAc,7:3, v/v) = 0.56 (ind. UV_{254}). GC-MS: *m/z* (%) = 210 (100) [M^+], 182 (65) [M^+ − CO], 167 [M^+ − CHS], 139 [M^+ − CSCO]. ^1H NMR ($CDCl_3$, 300 MHz): δ = 3.91 (s, 3 H, OCH_3], 3.95 (s, 3 H, OCH_3), 4.35 (s, 2 H, CH_2, thiolactone ring), 6.93 (s, 1 H, arom.), 7.20 (s, 1 H, arom.). HR-MS for $C_{10}H_{10}O_3S$: calcd. 210.03507; found 210.03557.

Acknowledgments

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