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# Unexpected Rearrangements in the Synthesis of Arylidene- or Alkylidene-2-thiophthalides

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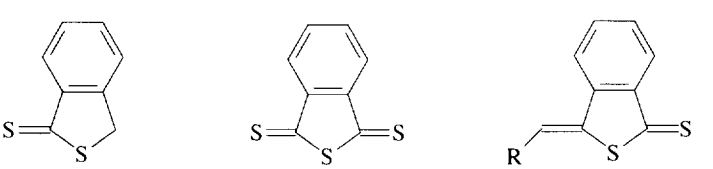
***Abstract:*** Mechanistic studies concerning the reaction by which poly(isothianaphthene) (PITN) is synthesized in one step from commercially available monomers by reacting them with phosphorus pentasulphide ($P_4S_{10}$), have led to the idea of synthesizing a chain-stopper molecule which should give rise to suitable quinoid model compounds for PITN. Within this context benzylidenedithiophthalide and pentylidene-dithiophthalide were chosen as target molecules. The unexpected rearrangements and the control of these rearrangements in the synthesis of benzylidenedithiophthalide and pentylidenedithiophthalide are reported.


## 1. Introduction

We have developed a new synthetic route to obtain poly(isothianaphthene) (PITN) in one step by reaction of phthalide or phthalic anhydride with phosphorus pentasulphide ($P_4S_{10}$).[1]

Mechanistic studies about this reaction, based on the intermediates observed during the polymerization process, show that for both monomers the reaction progresses by sequential thionation, isomerization and polymerization reactions.[2] Since these mechanistic studies indicate that dithiophthalide (1) and trithiophthalic anhydride (2) are the intermediates for the formation of PITN, we got the idea of synthesizing a chemically analogous chain-stopper (3), which cannot polymerize itself. (FIG. 1)



(1) (2) (3a: R=$C_6H_5$) (3b: R=$C_5H_{11}$)

FIG. 1: dithiophthalide (1), trithiophthalide (2) and a potential chain-stopper molecule (3) (R=$C_6H_5$ or $C_5H_{11}$)

Since PITN has a quinoid geometry, adding this chain-stopper (3) to the polymerization reaction mixture should result in new quinoid model compounds for PITN. This should allow further insight into the

quinoid geometry of PITN via UV-vis, NMR, FT-IR and FT-RAMAN spectroscopy.

The rearrangements and the control of these reactions in the synthesis of these chain-stoppers, benzylidenedithiophthalide and pentylidenedithiophthalide, are discussed.

## 2. Results and discussion

Benzylidenedithiophthalide (3) may easily be synthesized from benzylidene-2-thiophthalide (4) by the method of Scheerer et al. using phosphorus pentasulphide ($P_4S_{10}$) as thionating agent.[3] (FIG. 2, route (iv))

Consequently, benzylidene-2-thiophthalide (4) is a crucial intermediate in the synthesis of the dithiophthalide derivative (3). In this work we investigated several routes in an effort to obtain the product (4). (FIG. 2)

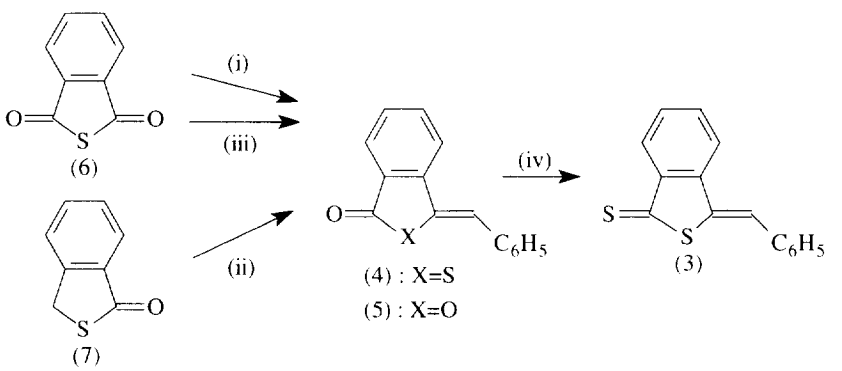



FIG. 2: (i) $C_6H_5CH_2CO_2H$, $CH_3CO_2Na$, $\Delta T$; (ii) $C_6H_5CHO$, tert.-BuOH, tert.-BuOK; (iii) $C_6H_5CH_2Cl$, Mg, $Et_2O$; (iv) $P_4S_{10}$, $CH_3CN$, $NaHCO_3$

Route (i) starting from thiophthalic anhydride (6), phenylacetic acid and sodium acetate, is known in literature.[4] This method is also used to synthesize the commercially available benzylidenephthalide (5), then starting from phthalic anhydride. Thiophthalic anhydride (6) was obtained by reaction of phthalic anhydride with $Na_2S.9H_2O$.[5] Structural analysis of the reaction mixture by GC/MS indicated that only 8% of the benzylidene-2-thiophthalide (4) is formed. Totally at odds with the literature[4] the main reaction product is the oxygen analogue, the benzylidenephthalide (5).

We therefore tried another synthetic pathway to benzylidene-2-thiophthalide (4) starting from 2-thiophthalide (7), benzaldehyde and potassium tert-butoxide as a base (route (ii), FIG. 2).

2-Thiophthalide (7) is not commercially available but can be synthesized by the procedure of Protiva et al.[6] Reaction of 2-thiophthalide (7) and potassium tert-butoxide results in the corresponding carbanion. Nucleophilic addition of this carbanion on the benzaldehyde, followed by acidification and dehydration should yield the desired benzylidene-2-thiophthalide (4).

Mass spectroscopy and NMR analysis showed that the benzylidene-2-thiophthalide (4) was not formed but a product which was characterized as 2-((E)-Alk-1'-phenyl)benzoic acid (8). These findings can be rationalized by a process in which the 2-thiophthalide (7) has undergone an isomerization and ring-opening

process yielding a trans-episulphide. Desulphurication at room temperature yields the 2-((E)-Alk-1'-phenyl)-benzoic acid (8).

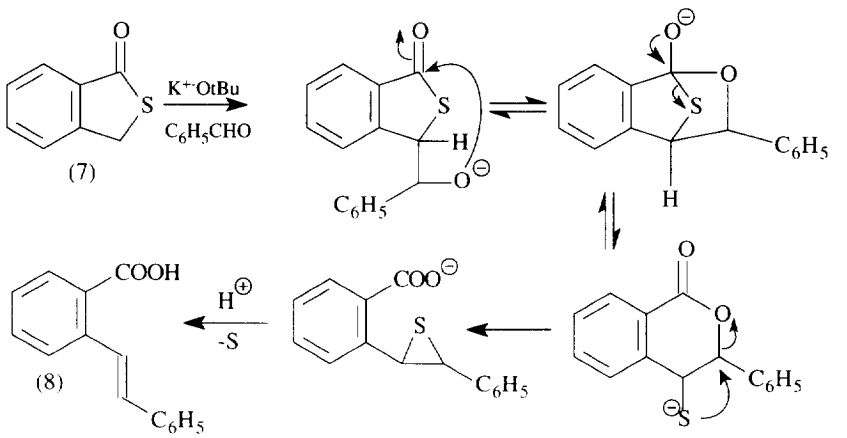



FIG. 3: Reaction of 2-thiophthalide (7) and benzaldehyde yielding 2-((E)-Alk-1'-phenyl)-benzoic acid (8)

Formation of the 2-((E)-Alk-1'-phenyl)benzoic acid (8) was confirmed by treatment of (8) with sodium hydride followed by addition of methyl iodide to the carboxylate. NMR analysis proved the formation of the methyl-2-((E)-Alk-1'-phenyl)-benzoate. Quite recently an analogous process was described and an identical mechanism was proposed by Mal et al.[7]

Since route (ii) was not successful we tried to synthesize benzylidene-2-thiophthalide (4) starting from 3-hydroxy-3-benzyl-2-thiophthalide (9) (FIG. 2, route (iii)). 3-Hydroxy-3-benzyl-2-thiophthalide (9) can be synthesized by a Grignard reaction of benzylmagnesiumchloride with thiophthalic anhydride.[3] Simple dehydration of (9) should result in benzylidene-2-thiophthalide (4). (FIG. 4)

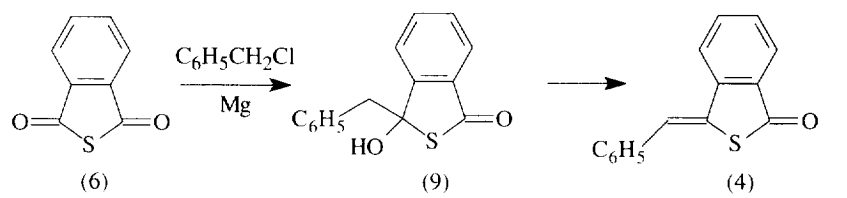



FIG. 4: Synthesis of benzylidene-2-thiophthalide (4) via 3-hydroxy-3-benzyl-2-thiophthalide (9).

However, complications were observed. Heating the reaction mixture resulted in the formation of benzylidenephthalide (5) instead of the thiophthalide derivative (4). Since Hanack[8] describes a procedure to convert an alcohol into a iodine group with subsequent elimination by treatment with aqueous hydrogen iodide (57%) and sodium dithionite, we tried this procedure on (9), but again benzylidenephthalide (5) was formed. The use of a phase transfer catalyst (aliquat) in this reaction did not make any difference. Reaction of (9) with potassium tert-butoxide in tert-butanol also yields the benzylidenephthalide (5). These results seem to indicate that the thiohemi-acetal (9) preferentially converts into the unexpected benzylidenephthalide (5), in basic conditions as well as in acidic conditions and even under thermal treatment. A possible explanation for this conversion is shown in figure 5. Attack of a free electron pair of the hydroxylic group of

(9) on the electrophilic carbonyl carbon atom results in the formation of an intermediate for which two routes, **a** and **b**, can be followed. Route **a** leads back to the initial product (9) and benzylidene-2-thiophthalide (4) can be formed, whereas route **b** results in the formation of (10) which can be converted into benzylidenephthalide (5) with loss of hydrogen sulphide.

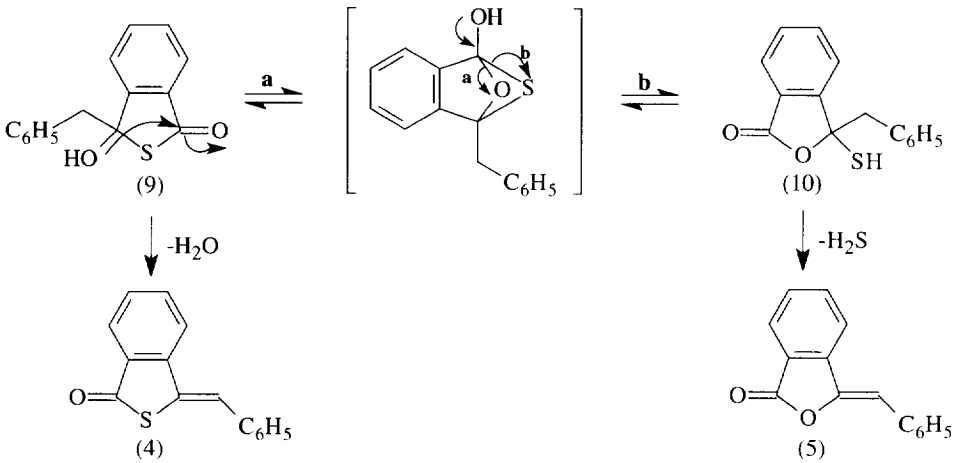



FIG. 5: Two routes (**a** and **b**) for reactions with 3-hydroxy-3-benzyl-2-thiophthalide (9), yielding benzylidene-2-thiophthalide (4) or benzylidenephthalide (5)

In acidic media the carbonyl function will be protonated and this will increase the electrophilic character of the carbonyl carbon atom, whereas in basic media the nucleophilic character is emphasized by the removal of the proton of the hydroxylic function. Since $H_2S$, due to the polarizability of sulphur, is a better leaving group than $H_2O$ it is to be expected that under the conditions described above route **b** is preferred, resulting in the formation of benzylidenephthalide (5).

In our first attempt, in which we used phenyl acetic acid as nucleophilic agent (route (i)), benzylidene-phthalide (5) is obtained as the major product. Elaboration of the mechanism for this conversion shows that the same intermediate of type (9) can be formed and so the formation of product (5) is consistent with the mechanism proposed in figure 5. A potential solution to avoid the attack of the free electron pair of the hydroxylic group in (9) on the carbonyl function is to substitute it by a better leaving group with decreased nucleophilic character. However, reacting (9) with p-toluenesulphonyl chloride did not result in a tosylate group. This might be due to steric hindrance.

An alternative way was to treat (9) with thionyl chloride ($SOCl_2$). Reflux of the reaction mixture until gas-evolution (HCl & $SO_2$) stops, gave a mixture of predominantly benzylidenephthalide (5) and some benzylidene-2-thiophthalide (4), as indicated by I.R. spectroscopy (1762 $cm^{-1}$, X=O; 1667 $cm^{-1}$, X=S). At room temperature again a mixture of products was obtained, but now the IR-peak at 1667 $cm^{-1}$ was the major one. The important role of temperature motivated us to do two more experiments: one at -10°C for which the IR-spectrum showed a further decrease of the phthalide peak (1762 $cm^{-1}$) and the final experiment at -35°C where only the desired benzylidene-2-thiophthalide (4, X=S) is formed. It seems that in this case kinetic control allows for the selective formation of the benzylidene-2-thiophthalide (4).

Pentylidenedithiophthalide (3, R=$C_5H_{11}$, FIG. 1) is synthesized in an analogous way. Grignard reaction of hexyl magnesiumbromide on thiophthalic anhydride (6) allows the formation of 3-hydroxy-3-hexyl-2-

thiophthalide. Treatment of 3-hydroxy-3-hexyl-2-thiophthalide with thionyl chloride at -35°C does not give any gas evolution, while performing the experiment at -5°C results in the formation of pentylidene-2-thiophthalide which in its turn can be converted to the pentylidenedithiophthalide by use of phosphorus pentasulphide.

### 3. Full $^{1}H$ and $^{13}C$ Chemical Shift Assignment

For the structural analysis of the compounds described above, we need to perform a full proton and carbon chemical shift assignment. We therefore applied *1D-* (APT) and *2D-NMR techniques* (HETCOR, COSY,...) which permit discrimination between proton and carbon atoms even if their NMR resonances are only partially resolved in the spectra. For the assignment one always starts with a carbon or proton atom for which the chemical shift is unambiguously determined (based on chemical shift, integration, *J*-coupling pattern...). The chemical shift of this atom is the starting point to elaborate a pathway for further assignment of the chemical shifts of the other atoms. In most cases a full proton and carbon shift assignment can be achieved based on a direct $^{1}H$-$^{13}C$ heteronuclear correlation spectrum (optimized for $J_{CH}$ = 140 Hz) and on a long range $^{1}H$-$^{13}C$ heteronuclear correlation spectrum (optimized for $J_{CH}$ = 8 Hz), showing mainly vicinal couplings. In situations where the molecular structure does not allow a full chemical shift assignment based on two-dimensional $^{1}H$-$^{13}C$ heteronuclear correlations (HETCOR) alone, additional 2D-NMR experiments (e.g. COSY) can be performed in order to obtain an unambiguous assignment. COSY is especially useful if the compound carries longer aliphatic chains.

The full $^{1}H$ and $^{13}C$ chemical shift assignment of benzylidene-2-thiophthalide (4), based on a long range $^{1}H$-$^{13}C$ heteronuclear correlation spectrum (FIG. 9, $J_{CH}$ = 8 Hz), on a direct $^{1}H$-$^{13}C$ heteronuclear correlation spectrum (FIG. 10, $J_{CH}$ = 140 Hz) and on a 1D-APT or Attached-Proton-Test spectrum (quaternary and methylene carbons atoms are negative while methyl and methine carbon atoms show positive signals) (FIG. 8) is discussed in detail. The chemical shifts of all the other compounds are analogously determined and represented in the experimental part. 2D-COSY NMR was used for the structural assignment of the aliphatic chain of the pentylidenethiophthalide derivatives.

The atomic numbering of these compounds is shown in the numbering scheme beneath. (FIG. 7)

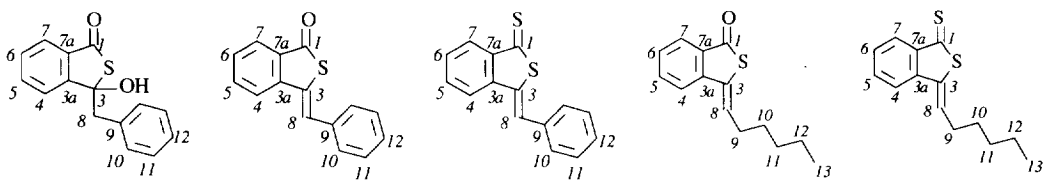



FIG. 7: Numbering of the discussed compounds.

### 3.1. Benzylidene-2-thiophthalide (4)

The $^1$H-proton spectrum shows two doublets at 7.98 and 7.85 ppm which can only correspond with $H_4/H_7$. Further we see three triplet signals at 7.67, 7.48 and 7.33 ppm belonging to $H_5/H_6/H_{12}$. The singlet at 7.60 ppm belongs to $H_8$. Based on the intensity, we can assign the signals at 7.59 and 7.43 ppm to $H_{10}/H_{11}$.

To make a full structural assignment of a molecule, one needs at least one resonance (carbon or proton) which can be unambiguously linked to one carbon or hydrogen atom.

For this molecule we can e.g. use the carbon carbonyl resonance of $C_1$ at 193.67 ppm and the proton resonance of $H_8$ at 7.60 ppm. From the direct HETCOR experiment one can assign $C_8$ to the resonance at 124.91 ppm since this integrates for one (FIG. 10). From the long range HETCOR experiment (FIG. 9) one can assign $H_7$ at 7.85 ppm since this is the only proton that can couple with $C_1$. So, the remaining proton doublet integrating for one should be $H_4$ at 7.98 ppm. Based on the direct HETCOR experiment (FIG. 10), $C_7$ and $C_4$ can be assigned to 123.73 ppm and 120.85 ppm respectively. Figure 9 shows a long range coupling for $H_7$ between a protonated carbon (FIG. 8, positive APT-signal) at 133.56 ppm and a quaternary carbon atom (FIG. 8, negative APT-signal) at 144.48 ppm. Since a long range HETCOR (FIG. 9), optimized for $J_{CH}$ = 8 Hz, mainly show vicinal couplings in aromatic systems, $C_5$ and $C_{3a}$ resonate at 133.56 ppm and 144.48 ppm respectively. Direct HETCOR (FIG. 10) shields $H_5$ at 7.67 ppm. The assignment of $C_{3a}$ at 144.48 ppm is further confirmed by the long range coupling with $H_8$ and $H_6$. (FIG. 9)

Besides the two quaternary carbons (APT, FIG. 8) $C_{7a}$ and $C_3$, $H_4$ also gives a long range coupling (FIG. 9) to $C_6$ at 129.07 ppm. From the direct HETCOR experiment (FIG. 10) $H_6$ can be assigned at 7.48 ppm, leading to $C_{7a}$ at 133.04 ppm (long range HETCOR, FIG. 9). This leaves $C_3$ at 131.14 ppm as the remaining quaternary carbon atom, coupled long range to $H_4$.

Now only the second aromatic ring still has to be determined. $H_{12}$ can be assigned as the only remaining triplet at 7.33 ppm. Direct HETCOR (FIG. 10) yields $C_{12}$ at 128.80 ppm. $H_{12}$ only shows long range coupling (FIG. 9) to $C_{10}$ at 129.75 ppm (so $H_{10}$ at 7.59 ppm; FIG. 10), which is confirmed by the long range coupling between $H_{11}$ at 7.43 ppm and the remaining quaternary carbon resonance $C_9$ at 135.38 ppm. Based on the direct HETCOR (FIG. 10) we can finally assign $C_{11}$ to the resonance at 129.00 ppm.

This leaves several unused long range correlation signals which further confirm this complete structural assignment.

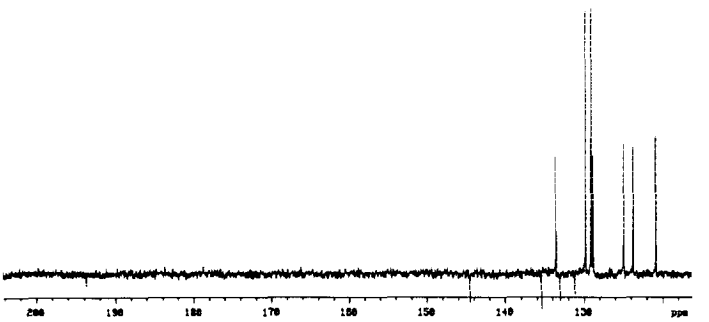



FIG. 8: APT or Attached-Proton-Test spectrum of benzylidene-2-thiophthalide (4).

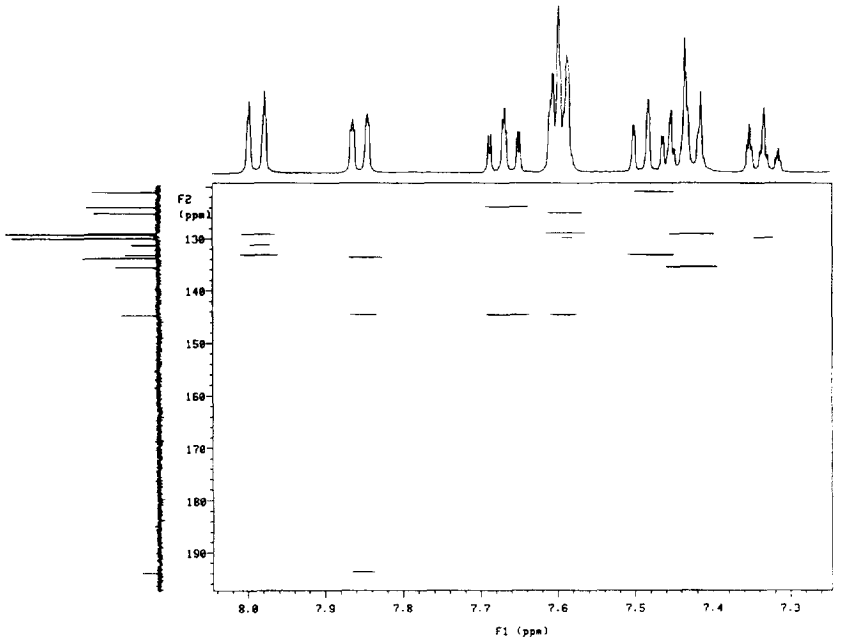



FIG. 9: Long range $^{1}H$-$^{13}C$ heteronuclear correlation spectrum of benzylidene-2-thiophthalide (4).

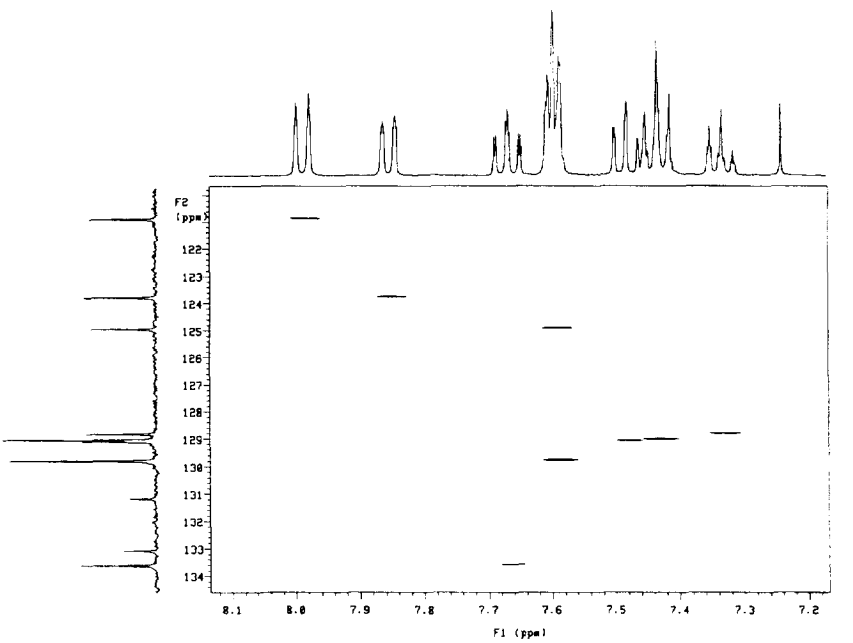



FIG. 10: Direct $^{1}H$-$^{13}C$ heteronuclear correlation spectrum of benzylidene-2-thiophthalide (4).

## 4. Conclusion

The results show that creating a double bond by the dehydration in intermediates such as 3-hydroxy-3-alkyl-2-thiophthalide (9), obtained by nucleophilic attack of a Grignard reagent on thiophthalic anhydride derivatives (6), is attendant by an unexpected rearrangement.

In acid or basic media or by heating the reaction mixture one has to take account of the isomerization of the thiolacton functional group of (9) into a lacton functional group.

The only remedy at hand for this rearrangement is the substitution of the nucleophilic hydroxylic group in the intermediates by a superior leaving group at low temperature. In this way the nucleophilic attack of the hydroxylic group cannot occur and elimination of the new leaving group yields the desired double bond. In this way benzylidene-2-thiophthalide (4) and pentylidene-2-thiophthalide can be synthesized. The latter compounds can in their turn be converted into their dithiophthalide derivatives by reaction with $P_4S_{10}$.

This same kind of chemistry also seems to occur if 2-thiophthalide (7) is used as nucleophile against carbonyl functional groups, e.g. benzaldehyde. Isomerization followed by a ring-opening process gives rise to a trans-episulphide. Desulphurization at room temperature yields 2-((E)-Alk-1'-phenyl)benzoic acid (8).

In this case no simple remedy seems at hand.

## 5. Experimental

All syntheses were performed in a nitrogen atmosphere. Commercially available products were used without further purification. Melting points were recorded with an Electrothermal IA9000 Digital Melting Point apparatus. IR spectra were obtained with a Philips Pye Unicam SP-300 spectrophotometer. Mass Spectroscopy was performed with a Finigan 1020 or a TSQ70 apparatus. $^{1}H$- and $^{13}C$-NMR analysis were carried out with a Varian Unity 400 spectrometer in $CDCl_3$, using TMS as internal standard. Chemical shifts are expressed in $\delta$ (ppm).

### 5.1. Synthesis of benzylidene-2-thiophthalide (4)

*5.1.1. From thiophthalic anhydride (6), phenyl acetic acid and sodium acetate (route (i))*

5g (30.5 mmol) Thiophthalic anhydride, 4.95g (36.4 mmol) phenyl acetic acid and 0.12g (1.46 mmol) are slowly boiled with continuous removal of $H_2O$. Afterwards the reaction mixture is cooled to 100°C and poured into ethanol. A yellow precipitate was filtered off and was characterized as sulphur. The ethanol is evaporated under reduced pressure and the residue is dissolved in chloroform. The organic phase was washed with a 10% NaOH-solution to remove the unreacted phenyl acetic acid. Mass spectroscopy indicated that benzylidenephthalide (5) ($M^+ = 222$) was the main product (83%).

Using an excess of phenyl acetic acid (91.2 mmol) did not result in the benzylidene-2-thiophthalide (4) either.

Thiophthalic anhydride (6): Phthalic anhydride (recrystallized from chloroform - 30.0 g; 0.2 mol) is intimately mixed with $Na_2S.9H_2O$ (60.0 g; 0.25 mol) for 5h. Afterwards an equal amount of water is added and stirring continued for 0.5h. This solution is added dropwise to 1.5 L of diluted hydrochloric acid (5%). After 1h the solid formed is collected and dissolved in chloroform. Then the organic layer is washed with a

saturated $NaHCO_3$-solution, with water, dried over $MgSO_4$ and evaporated under reduced pressure. This yields 75% thiophthalic anhydride.

mp: 114°C; IR (KBr, $cm^{-1}$): 1685 ($\nu_{COS}$) , 1655 ($\nu_{COS}$); MS (m/e): 164 ($M^+$, 85%), 136 ($M^+$-CO, 10%), 104 ($M^+$-COS, 84%), 76 ($M^+$-$(CO)_2S$, 100%); $^1$H-NMR ($CDCl_3$, 400 MHz, in ppm relative to TMS): 7.79 (dxd, $^3$J=5.6 & $^4$J=3.0, 2H), 7.95 (dxd, $^3$J=5.6 & $^4$J=3.0, 2H); $^{13}$C-NMR ($CDCl_3$, 400 MHz, in ppm relative to TMS): 123.8, 135.0, 138.7 (quat. C), 189.8 (C=O).

*5.1.2. From 2-thiophthalide (7), benzaldehyde and potassium tert-butoxide (route (ii))*

1.25g (11 mmol) potassium tert-butoxide in 45 ml dry THF is cooled to 0°C. To this suspension a solution of 2-thiophthalide (1.5g; 10 mmol) and benzaldehyde (1.6 ml; 15 mmol) in 8 ml THF is slowly added. After one night the reaction mixture is evaporated under reduced pressure. Then water is added and acidified with HCl. The water layer is finally extracted with chloroform and dried over $MgSO_4$. Evaporation under reduced pressure does not yield benzylidene-2-thiophthalide (4), but a crystalline product which was characterized as 2-((E)-Alk-1'-phenyl)benzoic acid (8) (52%).

mp: 159-160 °C; IR (KBr, $cm^{-1}$): 1670 ($\nu_{C=O}$), 1595 ($\nu_{C=C,\ arom}$), 755 ($\nu_{C=C,\ arom}$); MS (m/e): 224 ($M^+$, 100%), 179 ($M^+$-COOH, 10%); $^1$H-NMR ($CDCl_3$, 400 MHz, in ppm relative to TMS): 8.09 (d, $^3$J=10 Hz, 1H) , 8.06 (d, $^3$J=19.16 Hz, 1H, HC=CH), 7.75 (d, $^3$J=10 Hz, 1H), 7.56 (t, $^3$J=8.11 Hz, 1H), 7.55 (d, $^3$J=10.55 Hz, 2H: ortho) 7.35 (t, $^3$J=8.11 Hz, 3H: 2H meta + 1H ), 7.27 (t, $^3$J=7.54 Hz, 1H: para), 7.02 (d, $^3$J=19.16 Hz, 1H, HC=CH); $^{13}$C-NMR ($CDCl_3$, 400 MHz, in ppm relative to TMS): 172.28 (C=O), 140.32, 137.43, 133.22, 131.96, 131.72, 128.79, 128.04, 127.42, 127.35, 127.03, 112.90.

Methyl-2-((E)-Alk-1'-phenyl)benzoate: To a suspension of 0.88g NaH (60% dispersion in Nujol, 22 mmol) in 8.5 ml dry THF a solution of 0.5g 2-((E)-Alk-1'-phenyl)benzoic acid (22 mmol) in 17 ml THF is added. After 30 minutes an excess of methyl iodide (2.5 ml; 0.04 mol) is added and the reaction mixture is stirred for 16h at 35°C yielding methyl-2-((E)-Alk-1'-phenyl)benzoate (85%).

IR (KBr, $cm^{-1}$): 2940 ($\nu_{CH3}$) , 2850 ($\nu_{CH3}$), 1720 ($\nu_{C=O}$), 1445 ($\nu_{CH3}$), 1370 ($\nu_{CH3}$); MS (m/e): 238 ($M^+$, 100%) , 207 ($M^+$-$OCH_3$, 65%) ; $^1$H-NMR ($CDCl_3$, 400 MHz, in ppm relative to TMS): 7.99 (d, $^3$J=18.96 Hz, 1H, HC=CH), 7.91 (d, $^3$J=9.48 Hz, 1H), 7.71 (d, $^3$J=9.48 Hz, 1H), 7.52 (d, $^3$J=9.48 Hz, 2H: ortho), 7.50 (t, $^3$J=9.48 Hz, 1H) 7.36 (t, $^3$J=7.48 Hz 1H), 7.35 (t, $^3$J=9.48 Hz, 2H: meta), 7.27 (t, $^3$J=9.48 Hz, 1H: para), 7.00 (d, $^3$J=18.96 Hz, 1H, HC=CH), 3.91 (s, 3H, $OCH_3$).

2-Thiophthalide (7): NaH (4g; 0.1 mol (60% dispersion in nujol)) is washed with dry hexane under nitrogen atmosphere. Then benzyl mercaptane (12.5 ml; 0.1 mol) in 33 ml DMF is added dropwise to the residue on an ice-bath. To this mixture a solution of phthalide (5.37 g; 0.04 mol) in 33 ml DMF is added. Then the reaction mixture is refluxed for 24h under nitrogen atmosphere. After cooling to room temperature the reaction mixture is poured out in 300 ml ice and 18 ml HCl (conc.). The water layer is then extracted with diethyl ether and the combined ether phases are washed with $K_2CO_3$ (10%-solution) and at 0°C the water layer is acidified with 20% HCl yielding 95-99% 2-(benzylmercaptomethyl)benzoic acid.

To 2-(benzylmercaptomethyl)benzoic acid (9.5g; 37 mmol) 12 ml trifluoroacetic anhydride is added dropwise. After 0.5h stirring and 0.5h refluxing the mixture is cooled to room temperature and poured into ice. The water layer is extracted with ether and washed with a 5% $K_2CO_3$-solution till the water is basic. The combined ether layers are dried over $MgSO_4$ and evaporated under reduced pressure. This yields 50-55% orange-red crystalline 2-thiophthalide (7).

*2-(benzylmercaptomethyl)benzoic acid*: mp: 108.1-109.7 °C; IR (KBr, $cm^{-1}$): 3450 ($\nu_{OH}$) , 1670 ($\nu_{C=O}$), 1580 ($\nu_{C=C\ arom}$); MS (m/e): 258 ($M^+$, 10%) , 176 ($M^+$-$C_7H_7$, 25%), 122 ($M^+$-$C_7H_7$-$CO_2H$, 70%), 91 (tropyliumion, 100%), 77 ($C_6H_5$, 30%); $^1$H-NMR ($CDCl_3$, 400 MHz, in ppm relative to TMS): 8.05 (d, $^3$J=7.6 Hz, 1H), 7.46 (t, $^3$J=7.6 Hz, 1H), 7.33 (t, $^3$J=7.6 Hz, 1H), 7.20-7.30 (m, 6H), 4.08 (s,2H, $CH_2$), 3.65 (s, 2H, $CH_2$); $^{13}$C-NMR ($CDCl_3$, 400 MHz, in ppm relative to TMS): 171.2 (C=O), 141.3, 138.1, 132.7, 132.0, 131.2, 129.0, 128.5, 128.3, 127.1, 127.0, 36.4 ($CH_2$), 34.2 ($CH_2$).

*2-thiophthalide (7)*: mp: 58-60 °C; IR (KBr, $cm^{-1}$): 1685 ($\nu_{C=O}$), 1600 ($\nu_{C=C\ arom}$), 1580 ($\nu_{C=C\ arom}$), 1455 ($\delta$s, $CH_2$-C=C); MS (m/e): 150 ($M^+$, 100%), 121 ($M^+$-CHO, 90%), 105 ($M^+$-CHS, 10%), 91 (tropyliumion), 77 ($C_6H_5$, 20%); $^1$H-NMR ($CDCl_3$, 400 MHz, in ppm relative to TMS): 7.76 (d, $^3$J=7.5 Hz, 1H), 7.58 (t, $^3$J=7.5 Hz, 1H), 7.49 (d, $^3$J=7.5 Hz, 1H), 7.42 (t, $^3$J=7.5 Hz, 1H), 4.42 (s, 2H, $CH_2$); $^{13}$C-NMR ($CDCl_3$, 400 MHz, in ppm relative to TMS): 197.8 (C=O), 146.9, 135.6, 133.0, 127.9, 126.3, 123.6, 34.5 ($CH_2$).

*5.1.3. From 3-hydroxy-3-benzyl-2-thiophthalide (9), $Na_2S_2O_4$ and hydrogen iodide*

0.5g (2 mmol) 3-hydroxy-3-benzyl-2-thiophthalide (9) was dissolved in 30 ml toluene. 1.74g (10 mmol) $Na_2S_2O_4$ in 10 ml $H_2O$ and 0.75 ml (5eq.) of a 57% HI-solution were added to this solution. The reaction mixture was stirred over night. Mass spectroscopy indicated that no benzylidene-2-thiophthalide (4) but only benzylidenephthalide (5) was formed.

The use of 0.18g (0.44 mmol) aliquat as phase transfer catalyst did not yield the benzylidene-2-thiophthalide (4) either.

*5.1.4. From 3-hydroxy-3-benzyl-2-thiophthalide (9) and potassium tert-butoxide*

0.5g (2 mmol) 3-hydroxy-3-benzyl-2-thiophthalide (9) and 0.22g (2 mmol) potassium tert-butoxide were dissolved in 30 ml tert-butanol and stirred over night at room temperature. Only benzylidenephthalide (5) was formed in this way as indicated by mass spectroscopy and TLC.

*5.1.5. From 3-hydroxy-3-benzyl-2-thiophthalide (9) and p-toluenesulfonyl chloride*

0.5g (2 mmol) 3-hydroxy-3-benzyl-2-thiophthalide (9) and 0.38g (2 mmol) p-toluenesulfonyl chloride were dissolved in toluene and stirred over night. TLC indicated that no reaction had occurred. Refluxing the reaction mixture did not result in the 3-tosylate-3-benzyl-2-thiophthalide either.

*5.1.6. From 3-hydroxy-3-benzyl-2-thiophthalide (9) and thionyl chloride (route (iii))*

0.5g (2 mmol) 3-hydroxy-3-benzyl-2-thiophthalide (9), 15 ml thionyl chloride and one drop of dimethylformamide are stirred at -35°C until evolution of HCl and $SO_2$ stops. Then the solution is evaporated under reduced pressure while some toluene is added. Purification by column chromatography (silica, $CCl_4$/$CHCl_3$ (90/10)) yields 79% benzylidene-2-thiophthalide (4).

mp: 99.7-101.9 °C; IR (KBr, $cm^{-1}$): 1667 ($\nu_{COS}$), 1575 ($\nu_{C=C\ arom}$); MS (m/e): 239 ($MH^+$, 100%); $^1$H-NMR ($CDCl_3$, 400 MHz, in ppm relative to TMS): 7.98 (d, $^3$J=8.41 Hz, $H_4$), 7.85 (d, $^3$J=8.41 Hz, $H_7$), 7.67 (t, $^3$J=7.46 Hz, $H_5$), 7.60 (s, $H_8$), 7.59 (d, $^3$J=7.54 Hz, 2H, $H_{10}$), 7.48 (t, $^3$J=7.54 Hz, $H_6$), 7.43 (t, $^3$J=7.54 Hz, 2H, $H_{11}$), 7.33 (t, $^3$J=7.54 Hz, $H_{12}$); $^{13}$C-NMR ($CDCl_3$, 400 MHz, in ppm relative to TMS): 193.67 ($C_1$), 144.48 ($C_{3a}$), 135.38 ($C_9$), 133.56 ($C_3$), 133.04 ($C_{7a}$), 131.14 ($C_3$), 129.75 ($C_{10}$), 129.07 ($C_6$), 129.00 ($C_{11}$), 128.80 ($C_{12}$), 124.91 ($C_8$), 123.73 ($C_7$), 120.85 ($C_4$).

3-Hydroxy-3-benzyl-2-thiophthalide (9): The Grignard reagent is formed by dropping 2.56ml (22mmol) benzyl chloride in 10ml ether at 0.53g (22mmol) magnesium turnings in 10ml ether at 0°C. After two hours the Grignard reagent is added dropwise to a solution of 3g (18.3mmol) thiophthalic anhydride in 68ml ether. After refluxing for two hours and one night at room temperature 13ml of water and 36ml of sulphuric acid (10% solution) is added. The water-layer is extracted with ether and the combined ether-phases are dried over $Na_2SO_4$ and concentrated under reduced pressure. Purification by column chromatography (silica/chloroform) yields 60% 3-hydroxy-3-benzyl-2-thiophthalide (9).

mp: 127-128 °C; IR (KBr, $cm^{-1}$): 3378 ($\nu_{OH}$), 2910 ($\nu_{as\text{-}CH2}$), 1655 ($\nu_{COS}$), 1585 ($\nu_{C=C\ arom}$); MS (m/e): 257 ($MH^+$, 5%), 239 ($MH^+$-$H_2O$, 48%), 223 ($MH^+$-$H_2S$, 46%), 179 ($MH^+$-$H_2O$-COS, 25%),; $^1$H-NMR ($CDCl_3$, 400 MHz, in ppm relative to TMS): 7.66 (t, $^3$J=7.71 Hz, H5), 7.63 (d, $^3$J=7.71 Hz, $H_7$, $H_4$), 7.48 (t, $^3$J=6.89 Hz, $H_6$), 7.26 (5H, $H_{10,11,12}$), 3.48 ($H_a$/$H_b$, $^2$J=16.15 Hz, 2H, $H_8$); $^{13}$C-NMR ($CDCl_3$, 400 MHz, in ppm relative to TMS): 194.78 ($C_1$), 152.30 ($C_{3a}$), 135.41 ($C_9$), 135.00 ($C_{7a}$), 134.09 ($C_5$), 130.85 ($C_{10}$), 130.10 ($C_6$), 128.30 ($C_{11}$), 127.61 ($C_{12}$), 124.37 ($C_4$), 123.45 ($C_7$), 94.85 ($C_3$), 48.94 ($C_8$).

### 5.2. Synthesis of benzylidenedithiophthalide (3) (route (iv))

0.29g (1.2 mmol) benzylidene-2-thiophthalide, 0.22g (0.5 mmol) phosphorus pentasulphide and 0.048g $NaHCO_3$ are dissolved in 10 ml $CH_3CN$. The reaction mixture is refluxed under nitrogen atmosphere for 30h. Then the mixture is evaporated under reduced pressure, dissolved in chloroform and filtered over a short silica-column. The orange-red filtrate is evaporated and purified by column chromatography (hexane/chloroform : 80/20). After evaporation 60-65% of the yellow-orange benzylidenedithiophthalide (3) is obtained.

mp: 122-122.8 °C; IR (KBr, $cm^{-1}$): 1572 ($\nu_{C=C\ arom}$), 1445 ($\nu_{C\text{-}S}$), 1244 ($\nu_{C=S}$); MS (m/e): 255 ($MH^+$, 13%), 221 ($MH^+$-$H_2S$, 100%), 179 ($MH^+$-$CS_2$, 10%); $^1$H-NMR ($CDCl_3$, 400 MHz, in ppm relative to TMS): 8.10 (d, $^3$J=7.70 Hz, $H_7$), 7.94 (d, $^3$J=7.70 Hz, $H_4$) , 7.70 (t, $^3$J=7.46 Hz, $H_5$), 7.61 (d, $^3$J=7.46 Hz, 2H, $H_{10}$), 7.52 (s, $H_8$), 7.50 (t, $^3$J=7.46 Hz, $H_6$), 7.45 (t, $^3$J=7.46 Hz, 2H, $H_{11}$), 7.36 (t, $^3$J=7.46 Hz, $H_{12}$); $^{13}$C-NMR ($CDCl_3$, 400 MHz, in ppm relative to TMS): 219.32 ($C_1$), 143.31 ($C_{3a}$), 141.64 ($C_{7a}$), 136.81 ($C_3$), 135.31 ($C_9$), 132.62 ($C_5$), 129.88 ($C_{10}$), 129.15 ($C_6$), 129.08 ($C_{11}$), 128.92 ($C_{12}$), 123.90 ($C_7$), 122.95 ($C_8$), 120.42 ($C_4$).

### 5.3. Synthesis of pentylidene-2-thiophthalide

The Grignard reagent is formed by dropping 27.2 ml (0.19 mol) 1-bromohexane in 67 ml ether at 4.86g (0.20 mol) magnesium turnings in 77 ml ether at 0°C. After two hours the Grignard reagent is added dropwise to a solution of 20g (0.12 mol) thiophthalic anhydride in 450 ml ether. After refluxing for two hours and one night at room temperature 90 ml of water and 240 ml of sulphuric acid (10% solution) is added. The water-layer is extracted with ether and the combined ether-phases are dried over $Na_2SO_4$ and concentrated under reduced pressure yielding the 3-hydroxy-3-hexyl-2-thiophthalide. To this 3-hydroxy-3-hexyl-2-thiophthalide 300 ml thionyl chloride is directly added and a drop of DMF as catalyst and the reaction mixture is stirred for 2h at -5°C. Afterwards the mixture is brought to room temperature and evaporated under reduced pressure. Purification by column chromatography (silica, $CCl_4$/$CHCl_3$ (90/10)) yields 68% pentylidene-2-thiophthalide (brown-red oil).

IR (KBr, $cm^{-1}$): 2965 ($\nu_{as\ CH3/CH2}$), 2860 ($\nu_{s\ CH3/CH2}$), 1660 ($\nu_{COS}$),, 1600 ($\nu_{C=C,\ arom}$), 1465 ($\delta_{as\ CH2/CH3}$); MS (m/e): 232 ($M^+$, 20%), 162 ($M^+$-$C_5H_{11}$, 100%); $^1$H-NMR ($CDCl_3$, 400 MHz, in ppm relative to TMS): 7.95 (d, $^3$J=8.50 Hz, $H_{4/7}$), 7.59 (t, $^3$J=7.50 Hz, $H_5$), 7.42 (t, $^3$J=7.50 Hz, $H_6$), 6.68 (t, $^3$J=7.50 Hz, $H_8$), 2.37 (q, $^3$J=7.77 Hz, 2H, $H_9$), 1.55 (m, 2H, $H_{10}$), 1.33 (m, 4H, $H_{11/12}$), 0.87 (t, $^3$J=6.66 Hz, 3H, $H_{13}$); $^{13}$C-NMR ($CDCl_3$, 400 MHz, in ppm relative to TMS): 192.79 ($C_1$), 144.48 ($C_{3a}$), 134.63 ($C_{7a}$), 133.14 ($C_5$), 132.44 ($C_3$), 128.45 ($C_6$), 127.80 ($C_8$), 123.37 ($C_7$), 120.74 ($C_4$), 32.06 ($C_9$), 31.35 ($C_{11}$), 28.52 ($C_{10}$), 22.40 ($C_{12}$), 13.94 ($C_{13}$).

### 5.4. Synthesis of pentylidenedithiophthalide

4.0g (16 mmol) pentylidene-2-thiophthalide, 6.22g (14 mmol) phosphorus pentasulphide and 1.34g $NaHCO_3$ are dissolved in 140 ml $CH_3CN$. The reaction mixture is refluxed under nitrogen atmosphere for 30h. Then the mixture is evaporated under reduced pressure, dissolved in chloroform and filtrated over a short silica-column. The orange-red filtrate is evaporated and purified by column chromatography (hexane/chloroform : 80/20). Evaporation yields 60-65% of the yellow-orange pentylidenedithiophthalide (oil).

IR (KBr, $cm^{-1}$):2935 ($\nu_{as\ CH3/CH2}$), 2860 ($\nu_{s\ CH3/CH2}$), 1610 ($\nu_{C=C,\ arom}$), 1590 ($\nu_{C=C,\ arom}$), 1455 ($\nu_{C-S}$), 1260 ($\nu_{C=S}$); MS (m/e): 249 ($MH^+$, 5%), 173 ($MH^+$-$CS_2$, 100%); $^1$H-NMR ($CDCl_3$, 400 MHz, in ppm relative to TMS): 8.05 (d, $^3$J=8.20 Hz, $H_7$), 7.75 (d, $^3$J=8.20 Hz, $H_4$), 7.62 (t, $^3$J=7.46 Hz, $H_5$), 7.43 (t, $^3$J=7.46 Hz, $H_6$), 6.63 (t, $^3$J=7.80 Hz, $H_8$), 2.37 (q, $^3$J=8.40 Hz, 2H, $H_9$), 1.58 (m, 2H, $H_{10}$), 1.35 (m, 4H, $H_{11/12}$), 0.89 (t, $^3$J=7.00 Hz, 3H, $H_{13}$); $^{13}$C-NMR ($CDCl_3$, 400 MHz, in ppm relative to TMS): 219.04 ($C_1$), 143.11 ($C_{7a}$), 141.52 ($C_{3a}$), 138.49 ($C_3$), 132.46 ($C_5$), 128.77 ($C_6$), 126.58 ($C_8$), 123.90 ($C_7$), 120.46 ($C_4$), 32.41 ($C_9$), 31.37 ($C_{11}$), 28.51 ($C_{10}$), 22.40 ($C_{12}$), 13.93 ($C_{13}$).

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