Investigation of the Thionation Reaction of Cyclic Imides

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A series of monothioimides and dithioimides were synthesised using Lawesson's reagent. It has been found that two main effects affect thionation reaction. The high polarity of carbonyl groups leads to good yields of mono- and dithioimides. On the other hand, steric hindrance in the vicinity of the carbonyl group strongly inhibits the replacement of the oxygen atom by sulfur.

Introduction

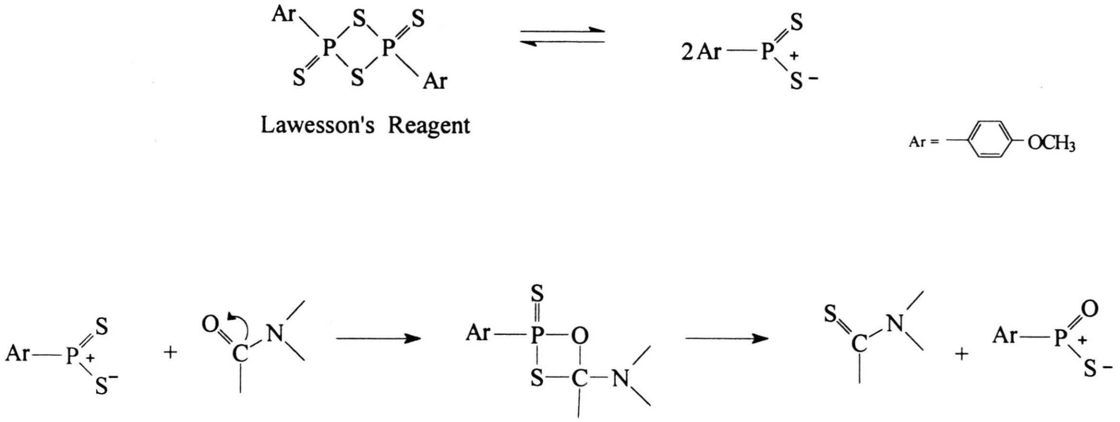
Thioimides, contrary to other types of thiocarbonyl compounds, are relatively stable materials. This prompted us to synthesise a series of monothio- and dithioimides which show interesting thermotropic properties and open the access to a new class of liquid crystals [1]. It has been recognized that monothioimides can be easily desulfurized with Raney nickel to give the corresponding lactams [2]. Photochemical reactions between thioimides and alkenes involve selective cycloaddition to the C=S bond and yield spiro-adducts [3, 4].

Thioimides and alkoxythiophthalimides were also used in the synthesis of phthalocyanines [5]. Thioimides undergo reaction, in a manner analogous to the Wittig reaction, with phosphorus ylides giving intermediates which may be valuable in tetrapyrrole pigment synthesis [6].

Results and Discussion

Thioimides can be simply obtained from the respective imides using Lawesson's reagent (LR) *i.e.* 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide [1,2,7,8]. There has been some speculation about the mechanism of the reaction of LR with carbonyl compounds [7]. The most probable mechanism is shown in Scheme 1.

It seems that a highly reactive dithiometaphosphate, rather than LR itself, may be the active thionating agent. However, according to the best of our knowledge, there have been no reports on



Scheme 1.

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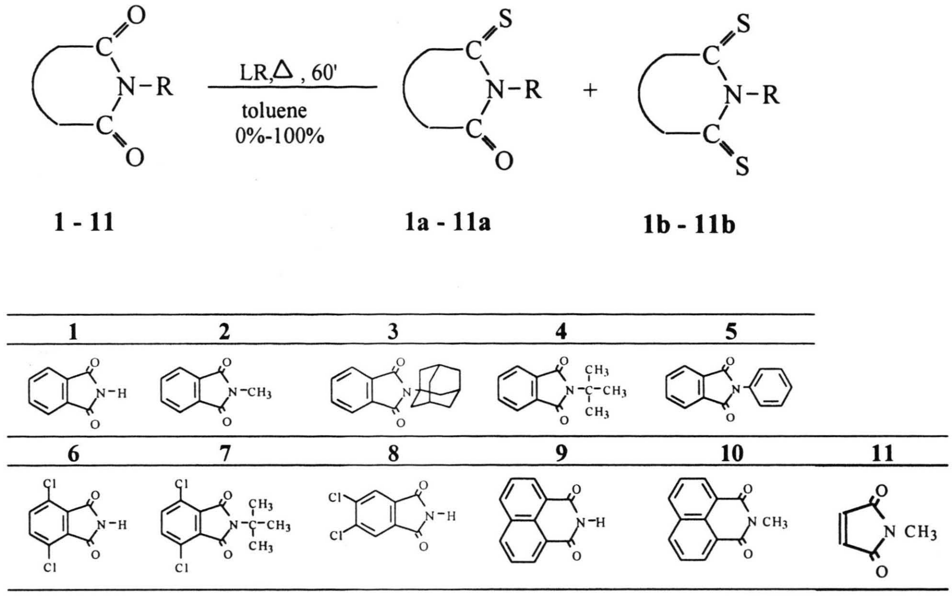

Scheme 2.

the influence of the imide structure on the thionation reaction. In this paper, we show some limitations that have appeared in the synthesis of thioimides.

Table 1. Formal charges of carbonyl groups and yields of thioimides.

Substrate	Formal charge $^{+\delta}C{=}O^{-\delta}$ C	O	Yield [%] of monothioimide[a]	Yield [%] of dithioimide[a]
1	0.360 (0.353)[b]	−0.295 (−0.287)	26	66
2	0.361 (0.355)	−0.296 (−0.290)	20	78
3	0.361 (0.360)	−0.301 (−0.289)	24	0
4	0.367 (0.360)	−0.301 (−0.289)	11	0
5	0.361 (0.354)	−0.319 (−0.272)	16	16
6	0.362 (0.354)	−0.277 (−0.272)	11	0
7	0.368	−0.282	0	0
8	0.362 (0.356)	−0.286 (−0.284)	20	15
9	0.358 (0.348)	−0.336 (−0.325)	0	98
10	0.359 (0.348)	−0.339 (−0.323)	10	88
11	0.325 (0.320)	−0.280 (−0.273)	53	0

[a] Expressed as a consumption of Lawesson's Reagent; [b] in parantheses are given formal charges calculated for monothioimides (**a**).

The imides **1–11**, listed in Scheme 2, were converted into the respective thioimides by the reaction with LR in boiling toluene. We have found that treatment of imides **1**, **2**, **5**, **8** and **10** with LR leads to mixtures of two main products, which form two distinct spots on TLC and could be easily separated by column chromatography. The respective reaction yields are given in Table 1.

The products were identified by FTIR, NMR and elemental analysis similarly as described previously [1,2,9]. The spectral data are given in Table 2.

The absorption bands characteristic of imide groups in the range from 1780 to 1720 cm^{-1} were absent in the spectra of the gold-brown compounds corresponding to the TLC spots with highest R_f values. Instead, absorption bands characteristic of C=S groups in the range 1360–1265 cm^{-1} are present. Therefore we described the products as dithioimides **1b** through **11b**. The red-orange products corresponding to the low mobility spots which showed both imide and thioimide absorption bands were assigned to compounds **1a** through **11a**.

Table 1 shows that the imides **3**, **4**, **6**, **9** and **11** give only one main product. They are the dithioimide **9b** and the monothioimides **3a**, **4a**, **6a**, **11a**, respectively. *N*-(*t*-Butyl)-3,6-dichlorophthalimide (**7**), (2-*t*-butyl-4,7-dichloro-isoindole-1,3-dione)

Table 2. Melting points and spectroscopic data of monothio- (**a**) and dithioimides (**b**).

Compound	^{1}H NMR (CDCl$_3$): δ, J(Hz)	FTIR	(KBr) ν [cm^{-1}]	m.p. [°C]
		CO	CS	
1a	7.66 (m, 2H, C_6H_4), 7.93 (m, 1H, C_6H_4), 8.19 (m, 1H, C_6H_4), 10.30 (s, 1H, N–H)	1742	1297,	176 (lit. 174) [11]
1b	7.45 (m, 2H, C_6H_4), 8.24 (m, 2H, C_6H_4), 13.31 (s, 1H, N–H)		1322	198 (lit. 184) [10, 11]
2a	3.46 (s, 3H, CH_3), 7.77 (m, 3H, C_6H_4), 7.96 (m, 1H, C_6H_4)	1737	1322	102 (lit. 94) [2]
2b	3.76 (s, 3H, CH_3), 7.60 (m, 1H, C_6H_4), 7.72 (m, 2H, C_6H_4)		1323	107 (lit. 104) [5]
3a	2.85–1.71 (m, 15H, adam.), 7.62 (m, 3H, C_6H_4), 7.87 (m, 1H, C_6H_4)	1747	1256	134
4a	5. 11 (s, 9H, CH_3), 7.73 (m, 2H, C_6H_4), 7.87 (m, 1H, C_6H_4), 7.91 (m, 1H, C_6H_4)	1742	1311	115
5a	7.34–7.18 (m, 5H, C_6H_5), 7.86 (m, 3H, C_6H_4), 8.12 (m, 1H, C_6H_4)	1747	1302	140
5b	6.89 (m, 1H, C_6H_5), 7.20 (m, 4H, C_6H_5), 7.68 (m, 2H, C_6H_4), 8.16 (m, 2H, C_6H_4)		1298	156
6a	7.60 (d,^2J= 8.6, 1H, C_6H_2), 7.67 (d, ^2J= 8.6, 1H, C_6H_2), 8.83 (s, 1H, N–H)	1745	1262	250–252
8a	7.88 (s, 1H, C_6H_2), 8.04 (s, 1H, C_6H_2), 8.85 (s, 1H, N–H)	1754	1268	201–204
8b	7.95 (s, 2H, C_6H_2), 9.75 (s, 1H, N–H)		1270	212–215
9b	7.45 (m, 2H, $C_{10}H_6$), 7.99 (m, 2H, $C_{10}H_6$), 8.78 (m, 2H, $C_{10}H_6$), 9.40 (s, 1H, N–H)		1265	296–299
10a	3,66 (s, 3H, CH_3), 7.80 (m, 5H, $C_{10}H_6$), 8.73 (m, 1H, $C_{10}H_6$)	1685	1286	218–219
10b	4.16 (s, 3H, CH_3), 7.56 (m, 2H, $C_{10}H_6$), 7.99 (m, 2H, $C_{10}H_6$), 8.60 (m, 2H, $C_{10}H_6$)		1291	302–306
11a	3.35 (s, 3H, CH_3), 8.22 (d, ^2J= 5.8, 1H, C_2H_2), 9.66 (d, ^2J= 5.8, 1H, C_2H_2)	1732	1342	82

does not react with LR at all. The yields of thionation reactions differ substantially. These phenomena could be explained in two ways: The mechanism shown in Scheme 1 suggests that the polarity of the carbonyl group should play an important role in this reaction. In Table 1 the formal charges calculated for carbonyl groups of the starting imides and, in parentheses of the respective monothioimides are given. The naphthalimides **9** and **10**, possessing the most polar carbonyl bands, react with LR almost quantitatively and give mainly dithioimides. *N*-methylmaleimide **11**, the substrate with the least polar C=O bonds, forms only the monothioimide with 53% yield. The replacement of one of the carbonyl oxygen atoms by sulfur does not influence the polarity of the second carbonyl group.

The polarity of the C=O groups is not the only factor determining the thionation reaction. While compounds **1** and **2** have partial charges similar to *N*-(adamant-1-yl) and *N*-(*t*-butyl) substituted imides, they yield quite different amounts of products. The unsubstituted phthalimide **1** and *N*-methylphthalimide **2** are easily converted quantitatively into both monothio- and dithioimides. Substrates with large *N*-substituents, **3** and **4,** give only small amounts of monothio- derivatives, and in the case of *N*-phenylphthalimide **5** monothio- and dithioimide. Also, isomers **6** and **8** react differently. Chlorine atoms in position 3 and 6, but not in positions 4 and 5, exert a steric hindrance which inhibits thionation reactions. As mentioned above, the most significant effect appears for *N*-(*t*-butyl)-3,6-dichlorophthalimide **7**. In this case the *t*-butyl group and the two chlorine atoms in the vicinity of the carbonyl groups suppress thionation completely.

The different reactivity of phthalimides, naphthalimides and maleimide could be explained as a result of different formal charges in their carbonyl groups, but the different reactivity of the reported group of imides might be ascribed to the steric effects. Despite being intuitively predictable, this behaviour needs to be studied more closely. We decided, therefore, to investigate the crystal structures of some imide substrates and their thionation products. Because the structure of the *N*-phenylphthalimide **5**, as well as *N*-(*p*-tolyl)phthalimide were known [12,13], we decided to study the case of *N*-(*t*-butyl)- and *N*-(adamant-1-yl)phthalimide. Crystals of **3**, **3a** and **4a** were obtained and X-ray diffraction data were collected (Table 3).

In Fig. 1 the independent part of the unit cell for **3** is shown. It consists of 1.5 molecules and more exactly 3 halves of similar molecules. Each molecule lies in a special position on the mirror plane passing through the phthalimide fragments, four carbon and two hydrogen atoms of the adamantyl group.

Molecules **3a** and **4a** are shown in Fig. 2 and 3, respectively. Closer inspection of the drawings shows that the carbonyl oxygen atoms in compound **3** are not equivalent and that the thionation occurs in the less crowded position. The first statement could be verified comparing O1···C11 and O2···C15 non-bonded distances in all three molecules shown in Fig. 1. The mean O1···C11 distance is 2.769 Å whereas the mean O2···C15 distance is 3.050 Å. The second statement is derived from Figures 2 and 3. The respective O···C distances in the **3a** and **4a** structures are even shorter (2.720 and 2.691 Å, respectively).

In contrast to compounds **3** and **4**, the carbonyl positions in **5** are fully equivalent. In the crystal structure of **5** [13], the phenyl ring is rotated by 58.2° with respect to the phthalimide moiety. This inclination corresponds to O1(O2)···C distances of 3.118 and 3.177 Å, respectively. This in our opinion explains, why in the case of **5** both mono- and dithioderivatives are obtained. A similar effect was observed for α-substituted aliphatic imides [2]. Due to steric constrains the thionation of

Table 3. Crystal data for **3**, **3a** and **4a**.

Compound	**3**	**3a**	**4a**
Empirical formula	$C_{18}H_{19}NO_2$	$C_{18}H_{19}NOS$	$C_{12}H_{13}NOS$
Formula weight	281.34	297.40	219.29
Temperature	100(2) K	100(2) K	293(2) K
Wavelength	0.71073 Å	0.71073 Å	0.71073 Å
Crystal system	m	m	o
Space group	$P2_1/m$	$P2_1/c$	$Pna2_1$
Unit cell dimensions	a = 17.333(4) Å b = 6.6392(13) Å, c = 19.711(4) Å β = 115.01(3)°	a = 15.4944(7) Å b = 6.3939(3) Å, c = 14.9899(7) Å β = 105.4660(10)°	a = 13.203(2) Å b = 11.960(2) Å c = 7.0220(12) Å $\alpha = \beta = \gamma = 90°$
Volume	2055.5(7) $Å^3$	1431.27(11) $Å^3$	1108.8(3) $Å^3$
Z	6	4	4
Density (calculated)	1.364 g/cm^3	1.380 g/cm^3	1.314 g/cm^3
Absorption coefficient	0.089 mm^{-1}	0.224 mm^{-1}	0.263 mm^{-1}
F(000)	900	632	464
Crystal size	$1.0 \times 0.01 \times 0.01$ mm^3	$0.2 \times 0.2 \times 0.4$ mm^3	$0.5 \times 0.2 \times 0.19$ mm^3
θ Range for data collection	1.14 to 22.20°	1.36 to 29.98°	2.30 to 29.99°
Index ranges	$-18 \le h \le 18$, $-7 \le k \le 6$, $-14 \le l \le 20$	$-21 \le h\, 21$, $-8 \le k \le 8$, $-21 \le l \le 20$	$-18 \le h \le 18$, $-15 \le k \le 0$, $0 \le l \le 9$
Reflections collected	9385	16446	3363
Independent reflections	2854 [R(int) = 0.0818]	4159 [R(int) = 0.0301]	1716 [R(int) = 0.0440]
Completeness	100.0%	100.0%	99.0%
Absorption correction	Not applied	Empirical by ψ-scans	Not applied
Max. and min. transmission		0.928 and 0.691	
Refinement method		Full-matrix least-squares on F^2	
Data/restraints/parameters	2854/0/353	4159/0/266	1716/1/140
Goodness-of-fit on F^2	0.972	1.057	0.979
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0589$, $wR2 = 0.1223$	$R1 = 0.0444$, $wR2 = 0.1199$	$R1 = 0.0479$, $wR2 = 0.1234$
R indices (all data)	$R1 = 0.1135$, $wR2 = 0.1401$	$R1 = 0.0504$, $wR2 = 0.1237$	$R1 = 0.1137$, $wR2 = 0.1558$
Absolute structure parameter			−0.1(4)
Extinction coefficient	0.0007(6)		
Largest diff. peak and hole	0.345 and −0.264 e · $Å^{-3}$	0.612 and −0.226 e · $Å^{-3}$	0.504 and −0.250 e · $Å^{-3}$

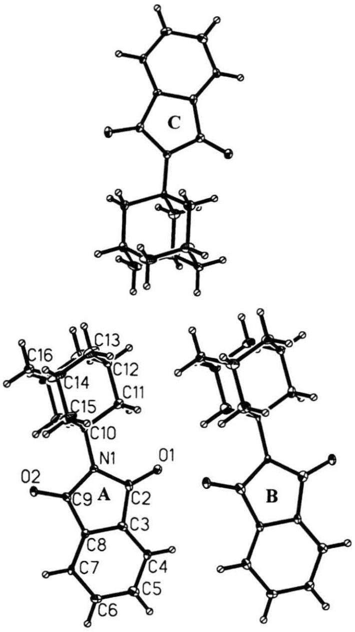

Fig. 1. Independent part of the unit cell for **3**. All molecules have mirror plane symmetry. The scheme of numbering is shown for molecule A only. The unlabeled carbon atoms of molecule A are symmetry related to the labeled ones.

such compounds occurs at the less-hindered carbonyl group giving exclusively monothioimides.

Experimental Section

General: All imides, except for **3**, **4** and **7** as well as other chemicals used were analytical grade commercial products (Aldrich) and were used without further purification. TLC plates silica gel 60 and silica gel 60 (200–400 mesh) were purchased from Merck. Melting points were measured in open capillaries on a Gallenkamp-5 apparatus and were uncorrected. The FTIR spectra (in KBr) were recorded on a Perkin-Elmer 2000 spectrometer. The NMR spectra were recorded in $CDCl_3$ using a Varian Gemini 200 MHz spectrometer. Formal charges were calculated by means of a semi-empirical methods (MM^+ and AM1) using the HyperChem software.

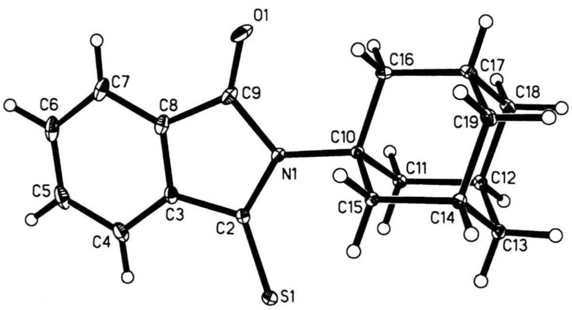

Fig. 2. Molecular structure of **3a** and the numbering scheme.

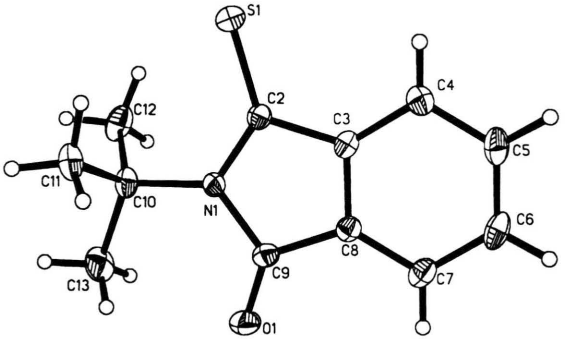

Fig. 3. Molecular structure of 4a and the numbering scheme.

Phthalimides **3**, **4** *and* **7**: The proper anhydride (10 mmol) was dissolved in dry DMF (20 ml). Then 10 mmol of amine (1-adamantanamine or *t*-butylamine) was added. The mixture was refluxed for 3 h and after cooling poured into diluted (5%) HCl. After filtration, the crude products were crystallized from 70% EtOH.

N-(Adamant-1-yl)phthalimide (**3**), 2-(adamant-1-yl)-isoindole-1,3-dione: m.p. 142–143 °C (lit. [11]; 139 °C); yield 55%.

N-(t-Butyl)phthalimide (**4**), 2-*tert*-butyl-isoindole-1,3-dione: m.p. 64 °C (lit. [12]; 58–59 °C); yield 59%.

N-(t-Butyl)-3,6-dichlorophthalimide (**7**), 2-*tert*-butyl-4,7-dichloroisoindole-1,3-dione: m.p. 145–147 °C; yield 32%; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.69$ (s, 2H, C_6H_2), 1.57 (s, 9H, CH_3); FTIR (KBr): $\nu = 1777, 1714\ cm^{-1}$ (C=O).

Thionation procedure: A mixture of imide (**1–11**) (5 mmol) and Lawesson's reagent (1.51 g, 5 mmol) in dry toluene (10 ml) was refluxed for 1 h. Then toluene was evaporated. The crude products were separated and purified by column flash chromatography using a EtOAc/hexane mixture (2:1) for unsubstituted imides and benzene/hexane (1:1) for others as eluent. Evaporation of the solvents afforded the mono- and dithioimides as orange, red, brown or yellow crystals. Analyses indicated by symbols were within ±0.4% of theoretical values. Monocrystals of **3**, **3a** and **4a** for X-ray studies were obtained by crystallization from MeOH/diethyl ether mixture. Because of very small linear dimentions of monocrystals of **3** (0.01×0.01×1.5 mm) the data for this structure were collected using a CCD equipment SMART-APEX at the Bruker-AXS laboratory in Karlsruhe. The data for the thionation product **3a** were collected using this technique. The data for structure **4a**, were collected using a serial diffractometer Kuma KM-4. The full crystallographic data have been deposited with the Cambridge Crystallographic Data Center (CCDC-160628-16030).

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