Cyclic Imides; 15. Reaction of 4,5-Dichlorophthalimides with Potassium Nitrite: Synthesis of 4-Hydroxy-5-nitrophthalimides

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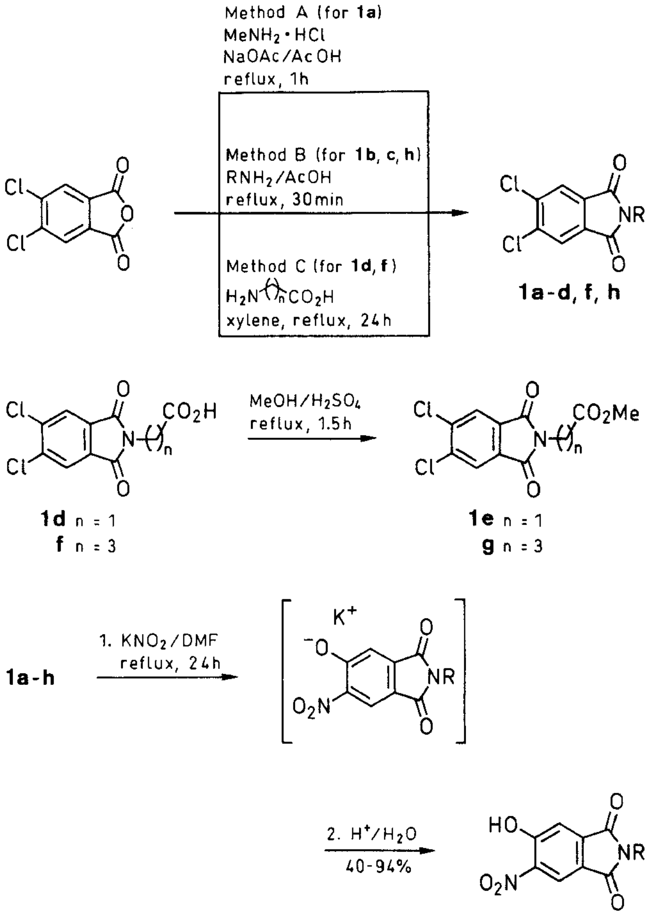
N-Substituted 4,5-dichlorophthalimides react with potassium nitrite in refluxing dimethylformamide to form *N*-substituted 4-hydroxy-5-nitrophthalimides.

In the course of investigations of aromatic nucleophilic substitution reactions activated by the cyclic imide group,[1-3] it was found that *N*-substituted 4,5-dichlorophthalimides **1** can be converted by the action of potassium nitrite to *N*-substituted 4-hydroxy-5-nitrophthalimides **2**. A search of the literature for examples of similar reactions revealed no examples involving phthalimide derivatives. Over a century ago, however, it was reported[4,5] that 2,3-dichlorobenzoquinones react with sodium nitrite to form 2-hydroxy-3-nitrobenzoquinones. In these cases, however, the activating carbonyl groups were ortho to the chlorines, rather than para as in the present reaction. The only prior case of para-activation of nitrohydroxylation was the reaction of 2,3,6,7-tetrachloroanthraquinone with sodium nitrite to give a mixture of isomeric dihydroxydinitroanthraquinones.[6] It has now been found that this nitrohydroxylation reaction is characteristic of *N*-substituted 4,5-dichlorophthalimides.

A variety of **1** were synthesized by reaction of 4,5-dichlorophthalic anhydride with amines. They were treated with potassium nitrite in dimethylformamide in a ratio of 4 moles of nitrite to one of **1**. A reddish-brown gas, evidently nitrogen dioxide, was evolved during the 24-hour refluxing period. The cooled reaction mixture was poured into aqueous acid to precipitate **2**. Compounds **1d** and **1f**, which contain a carboxy group, failed to react, but their esters **1e** and **1g** gave good results. The yields and properties of **1** and **2** are summarized in Tables 1 and 2, respectively.

The 4-hydroxy-5-nitrophthalimides are yellow powders. They dissolve in aqueous base to give yellow-orange solutions. The visible absorption spectra of these solutions closely resemble the spectrum of the *o*-nitrophenoxide anion, with the absorption maximum blueshifted 4–8 nm. Compounds **2** are sufficiently acidic to dissolve in aqueous sodium bicarbonate solution, and are conveniently purified by filtering the resulting solution and reprecipitating them by acidification. The absorption maxima of their ethanol solutions, at $\lambda = 350-360$ nm, do not obey the Beer–Lambert law. They do not give the ferric chloride test for phenols.

A plausible reaction sequence for the nitrohydroxylation reaction begins with a slow displacement of one chloride to form a chloronitrophthalimide, followed by a rapid displacement of the second chloride to form the observed product. This possibility is currently under investigation.



Scheme

Melting points were determined with an electrothermal melting point apparatus and are not corrected. Microanalyses were done by Atlantic Microlab, Inc. 4,5-Dichlorophthalic acid was purchased from Fluka Chemical Co. UV/VIS spectra were measured with a Cary 15 spectrophotometer; NMR spectra with a Varian EM-390 spectrometer; and IR spectra with a Pye-Unicam SP1100 spectrophotometer.

4,5-Dichlorophthalic Anhydride:

A mixture of 4,5-dichlorophthalic acid (39.4 g, 0.168 mol) and Ac_2O (34.2 g, 0.335 mol) was refluxed 2 h in a 250-mL 3-neck round bottom flask fitted with a dropping funnel. After the flask had cooled to r.t., the reflux condenser was reset for distillation and distillation was carried out with simultaneous addition of xylene (85 mL) from the dropping funnel at such a rate as to maintain constant volume in the pot. The residue was chilled in an ice bath and filtered. The precipitate was washed with cold benzene and dried; yield: 35.5 g (97%); mp 188–190 °C (CCl_4) [Lit.[7] mp 187.5–188 °C].

IR (Nujol): $\nu_{CO} = 1791$ cm^{-1}.

^1H NMR (DMSO-d_6/TMS): $\delta = 8.44$ (s).

4,5-Dichlorophthalimides 1a–d,f,h; General Procedures:

Method A (for 4,5-dichloro-*N*-methylphthalimide **1a**): To a 250-mL round bottom flask were added in the following order: 4,5-dichlorophthalic anhydride (21.7 g, 0.100 mol), anhydr. NaOAc (10.3 g, 0.125 mol), $MeNH_2 \cdot HCl$ (8.44 g, 0.125 mol) and glacial AcOH (60 mL). The mixture was refluxed with stirring 1 h, cooled to

Table 1. 4,5-Dichlorophthalimides **1**

Product	R	Yield (%)	mp (°C)[a] (solvent)	Molecular Formula[b] or Lit. mp (°C)	IR (Nujol)[c] ν_{CO} (cm^{-1})	UV/Vis[d] λ_{max} (nm) log ε (solvent)	^{1}H NMR[e] (DMSO-d_6/TMS) δ
1a	Me	88–91	184–185 (AcOH)	$C_9H_5Cl_2NO_2$ (230.1)	1716	297 (3.12), 236 (4.68) (EtOH)	3.07 (s, 3H), 8.13 (s, 2H)
1b	Bu	77	84.5–86.5 (hexane)	$C_{12}H_{11}Cl_2NO_2$ (272.1)	1728	298 (3.10), 239 (4.64) (EtOH)	0.91 (t, 3H), 1.10–1.80 (m, 4H), 3.59 (t, 2H), 8.16 (s, 2H)
1c	$(CH_2)_2OMe$	52–70	130.5–131.5 (MeOH)	$C_{11}H_9Cl_2NO_3$ (274.1)	1723	296 (3.12), 236 (4.65) (EtOH)	3.15 (s, 3H), 3.55 (t, 2H), 3.78 (t, 2H), 8.02 (s, 2H)
1d	CH_2CO_2H	87–92	244–245 (EtOH)	$C_{10}H_5Cl_2NO_4$ (274.1)	1794, 1638	298 (3.19), 236 (4.68) (EtOH)	4.33 (s), 8.21 (s)
1e	CH_2CO_2Me	89–96	151–152 (EtOH)	$C_{11}H_7Cl_2NO_4$ (288.1)	1727, 1610	298 (3.20), 236 (4.69) (EtOH)	3.71 (s, 3H), 4.46 (s, 2H), 8.28 (s, 2H)
1f	$(CH_2)_3CO_2H$	96	189–190 (MeOH)	$C_{12}H_9Cl_2NO_4$ (302.1)	1775, 1693	298 (3.13), 238 (4.64) (EtOH)	1.92 (m), 2.31 (t), 3.67 (t), 8.11 (s)
1g	$(CH_2)_3CO_2Me$	97	99–100 (MeOH)	$C_{13}H_{11}Cl_2NO_4$ (316.1)	1767, 1715	298 (3.14) (EtOH)	1.87 (m, 2H), 2.37 (t, 2H), 3.52 (s, 3H), 3.59 (t, 2H), 8.12 (s, 2H)
1h	Ph	75–89	214–215 (EtOH)	212.5–213[8]	1751	299 (3.17), 290 (3.18), 235 (4.66) (MeCN)	7.49 (s, 5H), 8.12 (s, 2H)

[a] Uncorrected, measured with an electrothermal apparatus.

[b] Satisfactory analyses obtained: C ±0.20, H ±0.10, N ±0.12.

[c] Recorded on a Pye-Unicam SP 1100 IR spectrophotometer.

[d] Measured using a Cary 15 recording spectrophotometer.

[e] Obtained on a Varian EM-390 spectrometer.

Table 2. 4-Hydroxy-5-nitrophthalimides **2**

Product	R	Yield (%)	mp (°C)[a] (solvent)	Molecular Formula[b]	IR (Nujol)[c]			UV/Vis[d] λ_{max} (nm) log ε (0.1 M NaOH)	^{1}H NMR[e] (DMSO-d_6/TMS) δ
					ν_{OH}	ν_{CO} (cm^{-1})	ν_{NO}		
2a	Me	82–91	231–232 (acetone)	$C_9H_6N_2O_2$ (174.1)	3240	1720	1554	412 (3.70)	3.01 (s, 3H), 7.44 (s, 1H), 8.26 (s, 1H)
2b	Bu	40–42	150–151 (2 : 1 benzene/cyclohexane)	$C_{12}H_{12}N_2O_5$ (264.2)	3240	1712	1552	410 (3.65)	0.90 (t, 3H), 1.1–1.8 (m, 4H), 3.56 (t, 2H), 7.46 (s, 1H), 8.27 (s, 1H)
2c	$(CH_2)_2OMe$	70	121.5–122[f]	$C_{11}H_{10}N_2O_6$ (266.2)	3250	1715	1550	408 (3.67)	3.23 (s, 3H), 3.53 (t, 2H), 3.69 (t, 2H), 7.49 (s, 1H), 8.27 (s, 1H)
2e	CH_2CO_2Me	87	159–160.5[f]	$C_{11}H_8N_2O_7$ (280.2)	3185	1713, 1640	1560	409 (3.72)	3.67 (s, 3H), 4.40 (s, 2H), 7.49 (s, 1H), 8.33 (s, 1H)
2g	$(CH_2)_3CO_2Me$	94	122–123[f]	$C_{13}H_{12}N_2O_7$ (308.2)	3170	1767, 1715	1550	410 (3.66)	1.89 (m, 2H), 2.37 (t, 2H), 3.54 (s, 3H), 3.60 (t, 2H), 7.47 (s, 1H), 8.25 (s, 1H)
2h	Ph	71–75	228–229 (acetone)	$C_{14}H_8N_2O_5$ (284.2)	3120	1736	1574	409 (3.73)	7.46 (s, 5H), 7.55 (s, 1H), 8.27 (s, 1H)

[a] Uncorrected, measured with an electrothermal apparatus.

[b] Satisfactory analyses obtained: C ±0.20, H ±0.10, N ±0.12.

[c] Recorded on a Pye-Unicam SP 1100 infrared spectrophotometer.

[d] Measured using a Cary 15 recording spectrophotometer.

[e] Obtained on a Varian EM-390 spectrometer.

[f] Purified by dissolving in 5% $NaHCO_3$, filtering and acidifying the filtrate.

r.t. and filtered. The precipitate was vigorously mixed with H_2O (120 mL), refiltered, washed on the filter with H_2O and dried; yield: 20.9 g (91%); mp 183–184 °C (glacial AcOH).

Method B (for **1b,c,h**); Typical Procedure (for 4,5-dichloro-*N*-butylphthalimide **1b**): To a stirred, refluxing solution of 4,5-dichlorophthalic anhydride (17.4 g, 0.080 mol) in glacial AcOH (100 mL) in a 250-mL 3-neck round bottom flask was added dropwise 1-aminobutane (12.4 g, 0.170 mol). The mixture was refluxed 30 min, cooled to r.t. and poured into ice-water (100 mL). The precipitate was filtered, washed on the filter with H_2O and dried; yield, 16.7 g (77%); mp 85.5–86.5 °C (hexane).

Method C (for **1d, f**); Typical Procedure [for 4-(4,5-dichlorophthalimido)butanoic acid (**1f**)]: A stirred mixture of 4,5-dichlorophthalic anhydride (21.7 g, 0.100 mol), 4-aminobutanoic acid (11.3 g, 0.110 mol) and xylene (100 mL) was refluxed 24 h, cooled and filtered. The precipitate was washed with cold H_2O and dried; yield, 29.0 g (96%); mp 189–190 °C (MeOH).

Methyl (4,5-Dichlorophthalimido)acetate (1e); Typical Procedure:
A mixture of 4,5-dichlorophthalimidoacetic acid **1d** (6.85 g, 0.025 mol), MeOH (100 mL) and conc. H_2SO_4 (2 mL) was refluxed 1.5 h, cooled to r.t. and poured into ice-water (500 mL). The aqueous mixture was neutralized with freshly prepared sat. $NaHCO_3$ and filtered. The precipitate was washed with H_2O and dried; yield 6.41 g (89%); mp 150.5–151.5 °C (MeOH).

Yields and properties of **1a–h** were summarized in Table 1.

4-Hydroxy-5-nitrophthalimides 2a–h; General Procedure:
A mixture of the 4,5-dichlorophthalimide **1** (9.40 mmol), KNO_2 (37.6 mmol) and anhydr. DMF (40 mL) was placed in a 100-mL

round bottom flask equipped by a reflux condenser topped by a drying tube. The stirred mixture was refluxed 24 h in a hood (NO_2 was evolved during the reaction), cooled to r.t. and poured slowly with stirring into 0.2 M HCl (100 mL). The yellow precipitate was removed by filtration, washed on the filter with H_2O (10–20 mL) and dissolved in freshly prepared 5% aq $NaHCO_3$ (50 mL). This mixture was immediately filtered, chilled in an ice bath, neutralized with 0.2 M HCl, and filtered to obtain pale-yellow **2**.

The yields and properties of **2** are summarized in Table 2.

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