Convenient Synthesis of *N*-Aryl-2-hydroxysuccinimides and Characterization of Their Hydrolysis Products

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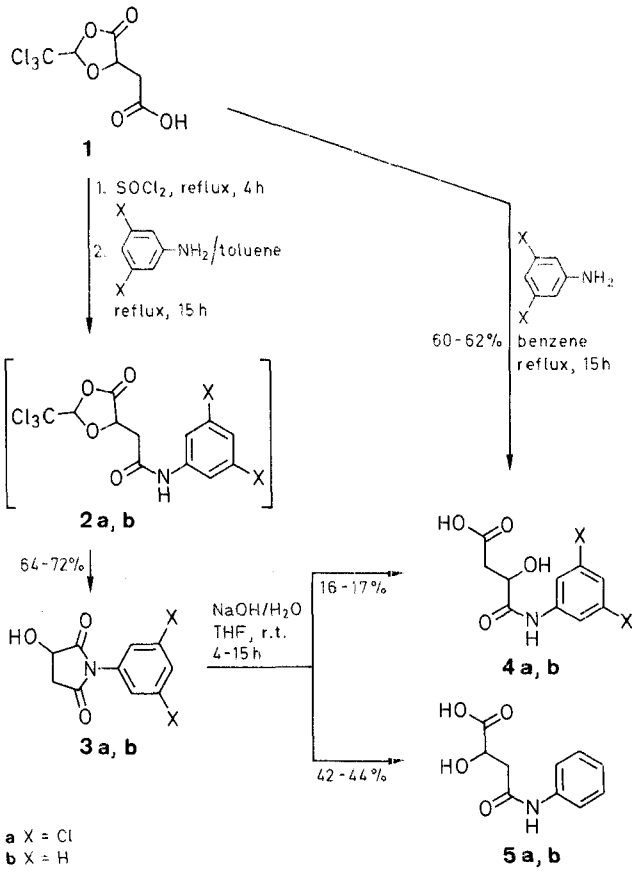
The chloralide of malic acid can be used to synthesize *N*-aryl-2-hydroxysuccinimides and characterize their hydrolysis products.

N-Arylsuccinimides have been examined as potential agricultural fungicides,[1] especially *N*-(3,5-dichlorophenyl)succinimide (NDPS).[2] The biotransformation of NDPS has been reported by Ohkawa et al.[3] We became interested in the synthesis of potential hydroxy metabolities of *N*-arylsuccinimides to address their related selectively nephrotoxic mechanism.[4,5] Although the dioxolane group of chloralide **1** (5-carboxymethyl-2-trichloromethyl-4-oxo-1,3-dioxolane),[6] which provides a temporary masking of the carboxy and α-hydroxy group of malic acid, can be cleaved under acidic conditions, the further application of **1** has not been published. Herein, we report a convenient method where **1** can be converted directly to *N*-aryl-2-hydroxysuccinimides, which we have failed to synthesize using conventional methods,[7,8] or to one of their hydrolysis products, *N*-aryl-3-hydroxysuccinamic acids, under weakly basic conditions.

D,L-Malic acid is converted to its chloralide (**1**; 96%) by reaction with chloral and sulfuric acid.[6] Reflux of **1** with thionyl chloride followed by the addition of 3,5-dichloroaniline affords *N*-(3,5-dichlorophenyl)-2-hydroxysuccinimide (**3a**; 72%) as the major product instead of the intermediate **2a**. This result suggests that the dioxolanone moiety of **2a** is labile under weakly basic conditions with subsequent intramolecular nucleophilic cyclization via the amide N-atom to afford **3a**. Furthermore, reflux of **1** with 3,5-dichloroaniline gives **4a** (60%) as the only product resulting from direct nucleophilic attack of the 3,5-dichloroaniline amino group at the carbonyl group of **1**. Compound **4a** is a minor product (16%) of hydrolysis of **3a** with 0.2 N aqueous sodium hydroxide in tetrahydrofuran; this result is helpful in the identification of its isomer **5a**, a major component (44%) of the hydrolysis of **3a**. Similar results are obtained when reflux of **1** with thionyl chloride is followed by the addition of aniline to give **3b** (64%) instead of intermediate **2b**, while direct reaction of **1** with aniline gives **4b** (62%) as the major product. Alkaline hydrolysis of **3b** yields **5b** (42%) as the major component and **4b** (17%) as a minor product. Previously, these two isomeric structures, **4b** and **5b**, have been assigned on the basis of their pK_a values such that **5b** with an α-hydroxy group is the stronger acid.[7]



The 2,2,2-trichloroethylidene group (from chloral) is not the only protecting group which could have been selected for protecting the α-hydroxy and the carboxy groups of malic acid. For example, malic acid acetonide has been prepared in

75–85% yield by reacting (*S*)-(−)-malic acid with 2,2-dimethoxypropane and *p*-toluenesulfonic acid.[9] However, we were able to obtain the chloralide of malic acid (**1**) in a higher yield (96%). In addition, the use of the 2,2,2-trichloroethylidene group as a protecting group introduces a second chiral center into the protected α-hydroxycarboxylic acids, a feature not found in acetonides. This formation of diastereoisomeric pairs could assist in the separation of enantiomeric α-hydroxycarboxylic acids as an adjunctive procedure to other commonly used techniques.

In summary, the method described here is a general and convenient synthetic route to *N*-aryl-2-hydroxysuccinmides and useful for characterization of their hydrolysis products.

5-Carboxymethyl-2-trichloromethyl-4-oxo-1,3-dioxolane (1, Chloralide of Malic Acid):
A mixture of chloral hydrate (18.8 g, 113.6 mmol), D,L-malic acid (13.2 g, 98 mmol), and conc. H_2SO_4 (25 mL) is stirred until solidified, then kept standing overnight. The mixture is added into ice water (250 mL) with stirring, the collected precipitate is washed with H_2O, and dissolved in EtOAc (250 mL). The organic layer is dried (Na_2SO_4) and evaporated to give **1**; yield: 25 g (96%); mp 172–174 °C (Lit.[6] mp 175 °C).

IR (KBr): ν = 1800, 1680 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 3.02 (dd, 1 H, J = 3.6 Hz, CH); 3.14 (dd, 1 H, J = 4.2 Hz, CH); 5.05 (m, 1 H, CH); 6.06 (s, 1 H, $CHCCl_3$).

D,L-(3,5-Dichlorophenyl)-2-hydroxysuccinimide (3a):
A mixture of chloralide **1** (10 g, 38 mmol) and $SOCl_2$ (30 mL) is refluxed for 4 h. The excess $SOCl_2$ is distilled out, the residue is dissolved in dry toluene (75 mL), 3,5-dichloroaniline (6 g, 37 mmol) is added, and the mixture is refluxed under N_2 overnight. The mixture is then concentrated and the residue is chromatographed on silica gel, eluting with EtOAc/$CHCl_3$ (0–30%) to give product **3a**; yield: 6.94 g (72%); mp 144–145 °C.

$C_{10}H_7Cl_2NO_3$	calc.	C 46.18	H 2.17	Cl 27.27	N 5.39
(260.1)	found	46.20	2.73	27.35	5.38

IR (KBr): ν = 3480, 3080, 1690, 1560 cm^{-1}.

^{1}H-NMR (acetone-d_6/TMS): δ = 2.75 (dd, 1 H, J = 5.2 Hz, CH); 3.25 (dd, 1 H, J = 8.6 Hz, CH); 4.85 (m, 1 H, CH); 7.45 (s, 2 H, 2,6-H_{arom}); 7.57 (s, 1 H, 4-H_{arom}).

D,L-*N*-(3,5-Dichlorophenyl)-3-hydroxysuccinamic Acid (4a):
A mixture of chloralide **1** (2 g, 7.6 mmol) and 3,5-dichloroaniline (2.4 g, 14.7 mmol) in dry benzene (75 mL) is refluxed overnight. The mixture is concentrated and to the residue is added 0.2 N aqueous NaOH (20 mL) with stirring at room temperature for 4 h. The mixture is then acidified to yield a viscous paste, which is collected and dried to give **4a**; yield: 1.27 g (60%); mp 150–151 °C.

$C_{10}H_9Cl_2NO_4$	calc.	C 43.19	H 3.26	Cl 25.50	N 5.04
(278.1)	found	43.31	3.30	25.41	5.03

IR (KBr): ν = 3320, 3200–2500, 1700, 1650, 1570, 1510 cm^{-1}.

^{1}H-NMR (acetone-d_6/TMS): δ = 2.70 (dd, 1 H, J = 8.0 Hz, CH); 2.93 (dd, 1 H, J = 4.0 Hz, CH); 4.60 (q, 1 H, J = 3.8 Hz, CH); 7.19 (s, 1 H, 4-H_{arom}); 7.92 (s, 2 H, 2,6-H_{arom}); 9.56 (s, 1 H, NH).

D,L-*N*-(3,5-Dichlorophenyl)-2-hydroxysuccinamic acid (5a):
To a solution of compound **3a** (1.5 g, 51.7 mmol) in THF (18 mL) is added 0.2 N aqueous NaOH (2 mL) and the mixture stirred at room temperature overnight. It is then acidified with AcOH and concentrated to give a viscous residue, which is chromatographed on silica gel, eluting subsequently with EtOAc/$CHCl_3$ (0–30%) and with EtOH to give **4a** [yield: 0.26 g (16%)] and **5a** [yield: 0.70 g (44%); mp 140–142 °C].

$C_{10}H_9Cl_2NO_4$	calc.	C 43.19	H 3.26	Cl 25.50	N 5.04
(278.1)	found	43.25	3.28	25.42	5.04

IR (KBr): ν = 3650–2500, 1680 (br); 1570 cm^{-1}.

^{1}H-NMR (acetone-d_6/TMS): δ = 2.30 (dd, 1 H, J = 8.0 Hz, CH); 2.88 (dd, 1 H, J = 4.0 Hz, CH); 4.57 (q, 1 H, J = 4.0 Hz, CH); 7.15 (s, 1 H, 4-H_{arom}); 7.71 (s, 2 H, 2,6-H_{arom}); 10.28 (s, 1 H, NH).

D,L-2-Hydroxy-*N*-phenylsuccinimide (3b):
A mixture of chloralide **1** (5 g, 19 mmol) and $SOCl_2$ (25 mL) is refluxed for 4 h. The excess thionyl chloride is distilled out, the residue is dissolved in dry toluene (70 mL), aniline (1.7 mL, 18.2 mmol) is added, and this mixture is refluxed under N_2 overnight. The mixture is then concentrated and the residue is chromatographed on silica gel, eluting with EtOAc/$CHCl_3$ (0.30%) to give **3b**; yield: 2.22 g (64%); mp 179–180.5 °C (Lit.[7] mp 179–180 °C).

IR (KBr): ν = 3420, 1690, 1595 cm^{-1}.

^{1}H-NMR (acetone-d_6/TMS): δ = 2.7 (dd, 1 H, J = 4.2 Hz, CH); 3.2 (dd, 1 H, J = 8.4 Hz, CH); 4.85 (m, 1 H, CH); 7.37 (m, 1 H, 4 H_{arom}); 7.45 (m, 4 H, 2,3,5,6-H_{arom}).

D,L-3-Hydroxy-*N*-phenylsuccinamic Acid (4b):
A mixture of chloralide **1** (1.0 g, 3.8 mmol) and aniline (1.0 mL, 10.7 mmol) in dry benzene (75 mL) is refluxed overnight. The mixture is then concentrated and the residue is added to 0.2 N aqueous NaOH (20 mL). The resultant mixture is stirred at room temperature for 4 h, then acidified to yield a viscous paste, which is collected and dried to give **4b**; yield: 0.49 g (62%); mp 146–147 °C (Lit.[7] mp 149–150 °C).

IR (KBr): ν = 3400, 3340, 1700, 1665, 1600 cm^{-1}.

^{1}H-NMR (acetone-d_6/TMS): δ = 2.64 (dd, 1 H, J = 8.4 Hz, CH); 2.92 (dd, 1 H, J = 2.8 Hz, CH); 4.55 (dd, J = 3.4 Hz, 1 H, CHOH); 7.07 (t, 1 H, J = 7.2 Hz, 4-H_{arom}); 7.30 (t, 2 H, J = 7.8 Hz, 3,5-H_{arom}); 7.77 (d, 2 H, J = 8.4 Hz, 2,6-H_{arom}); 9.2 (s, 1 H, NH).

D,L-2-Hydroxy-*N*-phenylsuccinamic Acid (5b):
To a solution of imide **3b** (1 g, 5.2 mmol) in THF (20 mL) is added 1 N aqueous NaOH (5 mL), and the mixture is stirred at room temperature for 4 h. The mixture is then acidified with AcOH and concentrated to yield a viscous residue, which is chromatographed on silica gel, eluting subsequently with EtOAc/$CHCl_3$ (0.50%) and with EtOH to give **4b** [yield: 0.19 g, (17%)] and **5b** [yield: 0.46 g, (42%); mp 141 °C (dec) Lit.[7] mp 139.5–140.5 °C].

IR (KBr): ν = 3200–2500, 1680 (br); 1600 cm^{-1}.

^{1}H-NMR (acetone-d_6/TMS): δ = 2.85 (br, 2 H, CH_2); 6.8 (m, 1 H, CH); 7.15 (m, 1 H, 4-H_{arom}); 7.38 (m, 2 H, 3,5-H_{arom}); 7.75 (d, 2 H, J = 8.4 Hz, 2,6-H_{arom}); 9.65 (s, 1 H, NH).

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