A FACILE GENERAL SYNTHESIS OF ARYLMALEIC ANHYDRIDES.  
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By a sequence involving Knoevenagel condensation, Michael addition of cyanide, hydrolysis, and selenium dioxide oxidation, a series of seven aryl maleic anhydrides were prepared in excellent overall yields. The regiospecificity of reaction of these anhydrides with various nucleophilic species, e.g. Me\textsubscript{3}SiN\textsubscript{3}, NH\textsubscript{3}, and PhNH\textsubscript{2} was investigated. Except for a few cases, the nucleophile attacks the more hindered carbonyl, in a reaction controlled by electronic rather than steric factors. These anhydrides are of particular utility in the synthesis of 4- and 5-Aryl Substituted 1,3(3H) Oxazine-2,6-Diones (Oxauracils)\textsuperscript{1,2}.

Piperidine 1) KCN
\[
\text{ArCH}=\text{O} + \text{CH\textsubscript{2}(CO\textsubscript{2}Et)\textsubscript{2}} \quad \rightarrow \quad \text{ArCH}=(\text{CO\textsubscript{2}Et})\textsubscript{2} \quad \rightarrow \quad \text{ArCH(CO\textsubscript{2}H)CH\textsubscript{2}CO\textsubscript{2}H} \\
\begin{array}{c}
1 \\
2)
\end{array}
\text{HCl}
\text{2}
\]

\[\text{2a, Ar= Ph, 2b, Ar= p-F,} \]
\[\text{2c, Ar=pOMe, 2d, Ar= p-Br,} \]
\[\text{2e, Ar=3-Cl-4-Me, 2f, Ar= o-Cl,} \]
\[\text{2g, Ar= 3,4-diCl} \]

\[\text{2a-g, SeO\textsubscript{2}/acetic anhydride} \]

\[\text{3a, Ar= Ph, 3b, Ar= p-F, 3c Ar}= p\text{-OMe, 3d, Ar= p-Br,} \]
\[\text{3e, Ar= 3-Cl-4-Methyl, 3f, Ar= o-Cl, 3g, Ar= 3,4-diCl} \]

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**Experimental**

**Phenyl Maleic Anhydride (3a)**

A 250 ml round bottom flask with heating mantel, magnetic stirrer and water condenser was charged with 14.7 g (0.076mol) phenyl succinic acid (2a), 8.3g (0.075 mol) selenium dioxide, and 60 ml acetic anhydride. The solution was heated at reflux for 6 hours and filtered hot through a sintered glass Buchner funnel. Concentration of the filtrate on a rotovap gave an orange solid. The solid was boiled with 150 ml diethyl ether for one hour, then again suction filtered, yielding 9.8 g (73.7%) phenylmaleic anhydride, 3a, mp 118-22°, (Lit 3 mp 119-199.5°C).

**p-Fluorophenyl Maleic Anhydride (3b)**

A 100ml round bottom flask with heating mantel, magnetic stirrer and water condenser was charged with 3.3 g (0.0156mol) p-fluoro phenyl succinic acid (2b), 1.9 g (0.0171 mol) selenium dioxide and 40 ml acetic anhydride. Mixture was refluxed for 24 hrs and worked up as in 3a above, yielding 1.8g (60%) of 3b, tan crystals, mp 111-114°C.

IR (CDCl₃) 3140(w), 1860(m), 1840(m), 1810(m), 1770(vs). 1620(m), 1600(s), 1505(s), 1415(w), 1310(m), 1300(m), 1290(w), 1225(vs), 1160(s), 1090(m), 1050(m), 1005(w), 830(s), 800(m) cm⁻¹.

Nmr (60 Mhz, DMSO-D₆ Delta ), 8.1 (d of d, 2H, meta to F, Jom= 10Hz, JoF= 5Hz), 7.55 (s, 1H, olefinic), 7.26(t, 2H, ortho to F, Jom=JoF = 10Hz).

**p-Methoxyphenyl (Anisyl) Maleic Anhydride (3c)**

A 250 ml round bottom flask with heating mantel, magnetic stirrer and water condenser was charged with 33.5 g (0.150 mol) p-Methoxyphenyl succinic acid, 2c), 19.4 g, (0.150 mol) selenium dioxide, and 125 ml acetic anhydride. The solution was heated for 21 hours and filtered hot through a sintered glass funnel. The filtrate was concentrated on the rotovap yielding brown semisolids, which were titrated with hexane then ether, then hot CCl₄, yielding 9.3 g (43.2%) 3c, mp 140-143°C, (Lit 3 mp 142.5-143.5°C).

Nmr (60 Mhz, DMSO-D₆), delta 3.9 (s, 3H, OCH₃), 7.1 (d, J= 9Hz, 2H, Aromatics), 8.1 (d, J= 9Hz, 2H, Aromatics), 7.5 (s, 1H, olefinic).
p-Bromo Phenyl Maleic Anhydride (3d)

A 250 ml round bottom flask with heating mantel, magnetic stirrer and water condenser was charged with 8.0 g (0.0293 mol) 3-bromophenyl succinic acid (2d), 3.5 g (0.0310 mol) selenium dioxide and 70 ml acetic anhydride. The mixture was refluxed for 22 hrs and worked up by concentrating to 40 ml on a rotovap, cooling, and washing with 50/50 ether/hexane. Vacuum drying gave 4.75 g (64.2%) 3d, mp 152-154°C, tan crystals.

IR (CDCl₃), 1860(m), 1820(m), 1800(m), 1775(vs), 1620(m), 1405(m), 1320(w), 1300(w), 1250(w), 1230(w), 1185(w), 1160(w), 1090(m), 1070(m), 1050(m), 1005(m), 820(s) cm⁻¹.

3-Chloro-4-Methyl Phenyl Maleic Anhydride (3e)

A 250ml round bottom flask with heating mantel, magnetic stirrer and water condenser was charged with 7.5g (0.031 mol) 3-chloro-4-methyl succinic acid, 2e, and 100 ml acetic anhydride. Mixture was refluxed for 22 hrs and worked up as in 3a above, yielding 4.3 g (62.3%) 3e, mp 98-102°C.

IR (CDCl₃) 3070(w), 2990(w), 1840(m), 1770(s), 1610(m), 1550(w), 1490(m), 1310(m), 1290(m), 1270(m), 1220(s), 1150(w), 1080(m), 1060(m), 1040(m), 980(m), 810(m) cm⁻¹.

Nmr (60 Mhz, DMSO-D₆ Delta ), 7.95(d, 1H, aromatic, J=0.4 Hz, ), 7.75 (d of d, 1H, H ortho, Jom = 8Hz, J=0.4 Hz), 7.40 (d, 1H, Hm, Jom= 8Hz), 7.05(s, 1H, olefinic), 2.50 (s, 3H, methyl).

Chlorophenyl Maleic Anhydride (3f)

A 300 ml round bottom flask with heating mantel, magnetic stirrer and water condenser was charged with 15.6 g (0.069 mol) o-chlorophenyl succinic acid (2f), 8.3 g (0.075 mol) selenium dioxide and 60 ml acetic anhydride. The mixture was refluxed for 8 hours. The acetic anhydride was removed on a rotovap, yielding a dark brown oil, which was taken up in 15 ml benzene and cooled to room temperature. 5 ml cyclohexane was added and the solution cooled in an ice icechest, yielding 9.9 g (70.2 %) 3f, mp 64-5°C, (Lit mp 68-9°C).

3,4-Dichlorophenyl Maleic Anhydride (3g)

A 250 ml round bottom flask with heating mantel, magnetic stirrer and water condenser was charged with 32.2 g (0.122 mol) 3,4-dichloro phenyl succinic acid (2g), 14.7 g (0.1325 mol) selenium dioxide and 130 ml acetic anhydride. The mixture was refluxed for 20 hrs and worked up as in 3a above, yielding 22.8 g (77%) 3g, mp 110 –115°C, mp 115-116°C.

IR (CDCl₃), 3120(w), 1840(m), 1770(vs). 1620(m), 1590(w), 1300(w)1250(w), 1220(s), 1130(m), 1080(m), 1050 (m), 1020 (m). 980(m), 810(m) cm⁻¹

NMR (60 Mhz, CDCl₃), delta 7.71 (m, 3H, aromatics), 7.0(s, 1H, olefinic).
References:


4) Farbirke, Chem. Abstr., 50, 16864c