A General Oxindole Synthesis

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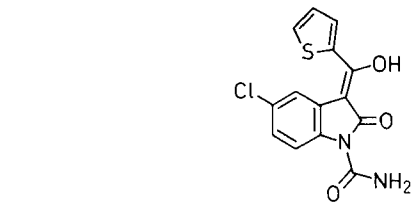
A general synthesis of indol-2(3*H*)-ones (oxindoles), was developed based on the addition of dimethyl malonate to commercially available halonitrobenzenes. The advantage of this route over many other oxindole syntheses was the regiochemical control of the substitution pattern on the aromatic ring.

The search for new and better anti-inflammatory agents has been pursued at many institutions with the aim of discovering agents with improved efficacy in the treatment of rheumatoid and osteoarthritis.[1] During the program which led to the discovery of Tenidap (1-carbamoyl-5-chloro-3-[hydroxy(2-thienyl)methylene]indol-2-(3*H*)-one, **1**) it was clear that a key synthon would be a substituted oxindole although the precise substitution pattern was not known at the outset of our research.[2] Thus, a general synthetic method for preparation of oxindoles which controlled the regiochemistry about the aromatic ring was targeted as the goal. Many oxindole syntheses in the literature have not controlled the aromatic substitution pattern because they were based on intramolecular bond connections of aniline derivatives which did not effectively discriminate between the two available ortho positions.[3] These include the Friedel–Crafts alkylations of α-chloro acetanilides,[4] Gassman cyclization of azasulfonium salts,[5] and thermally induced cyclization of *N*-acyl phenylhydrazides.[6] Ring closure to the oxindole by the aforementioned methods often afforded a mixture of products unless the starting material was symmetrical (para substituted). In addition, other limitations are imposed on the ring substituents due to the harsh conditions of the preceeding methods.[7] Vicarious nucleophilic substitution[8] and addition of ketene silyl acetals[9] to nitrobenzenes has also been employed to prepare oxindoles, but these methods do not always provide regiocontrol. One method which had given control over the oxindole regiochemistry was the functionalization of nitrotoluenes,[10] but the lack of commercial availability of these compounds was a limitation. Substitution of a triflate[11] or bromide[12] in a nitrobenzene by malonate and subsequent conversion into an oxindole was precedented although the generality of these routes was not known. Therefore, a general synthesis of oxindoles was sought in which the design would control the substitution pattern on the aromatic ring.

Regiochemical control about the aromatic ring of the oxindole was envisioned to occur by a directed displacement of a leaving group. Conceptually this displacement could occur in at least two ways; intramolecular SRN1[13] of an acetanilide or intermolecular displacement with an acetate carbanion, SNAr type. This note elaborates the utility of the latter of these two methods.

Displacement of ortho-halo substituents in nitrobenzenes by a variety of heteroatomic or carbon nucleophiles was precedented.[14] A general three-step synthesis of oxindoles was formulated based on employing a malonate addition to a substituted α-halonitrobenzene to control regiochemistry as depicted in the Scheme.

The substitution products, **3**, were formed in good yield from α-halonitrobenzenes and the anion of dimethyl malonate in all the cases except where an electron-donating substituent was present (Table). The lower yield in this case, **3c**, was attributed to the rate determining malonate addition step, generation of an ipso species, which would be stabilized by electron-withdrawing groups and destabilized by electron-donating substituents. Excess carbanion (2.2 equivalents) was required in all cases since the displacement products were more acidic than the malonate anion. Formation of the benzylic carbanion, by anion exchange, functioned to protect the product from double displacement when both ortho and para leaving groups were present in the nitrobenzene. Competitive displacement of the para halogen in 2,4-dichloro and 2,4-difluoronitrobenzene was observed in contrast to what has been previously reported.[15] The ortho/para substitution ratios obtained in the displacement products were 87 : 13 for the 2,4-dichloro and 84 : 16 for the 2,4-difluoronitrobenzene. The malonate methine proton was consistently found at lower field in the ortho



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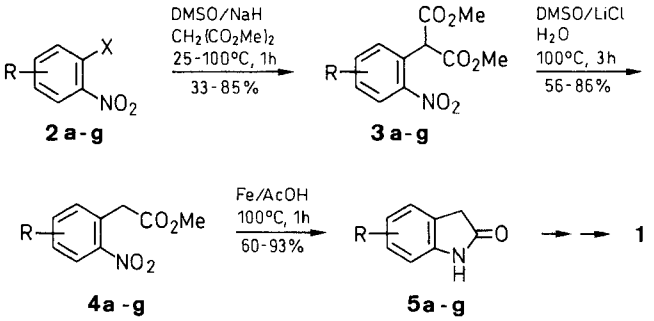

2	X	R	3–4	R	5	R
a	Cl	4-Cl	**a**	5-Cl	**a**	5-Cl
b	Cl	5-Cl	**b**	4-Cl	**b**	6-Cl
c	Cl	5-OMe	**c**	4-OMe	**c**	6-OMe
d	Br	5-Br	**d**	4-Br	**d**	6-Br
e	F	4-F	**e**	5-F	**e**	5-F
f	F	5-F	**f**	4-F	**f**	6-F
g	Cl	3-Cl	**g**	6-Cl	**g**	4-Cl

Scheme

Table. Compounds **3**–**5** Prepared

Product[a]	Yield (%)[b]	mp (°C) (Lit. mp)	IR ($CHCl_3$) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)
3a	61	67–70	1705	8.30–7.50 (m, 3H), 5.43 (s, 1H), 3.87 (s, 6H)
3b	80	83–84	1742	8.28–7.65 (m, 3H), 5.40 (s, 1H), 3.87 (s, 6H)
3c[c]	33	62–63	1755	7.80–7.20 (m, 3H), 5.31 (s, 1H), 4.33 (q, J = 8, 4H), 3.93 (s, 3H), 1.28 (t, J = 8 Hz, 6H)
3d	76		1756	8.35–7.30 (m, 3H), 5.35 (s, 1H), 3.85 (s, 6H)
3e	73	78–79	1754	8.14 (dd, J = 5.6, 3.4, 1H), 7.25–7.17 (m, 2H), 5.38 (s, 1H), 3.81 (s, 6H)
3f	85	80–81	1742	7.79 (dd, J = 3, 8, 1H), 7.53 (dd, J = 3, 4.3, 1H), 7.40–7.35 (m, 1H), 5.30 (s, 1H), 3.80 (s, 6H)
3g	72	137–138	1750	7.99 (dd, J = 8, 1, 1H), 7.72 (dd, J = 8, 1, 1H), 7.47 (t, J = 8, 1H), 5.55 (s, 1H), 3.78 (s, 6H)
4a	86		1750	8.25–7.50 (m, 2H), 7.50 (s, 1H), 4.07 (s, 2H), 3.78 (s, 3H)
4b	69	74–75	1735	8.21 (d, J = 2, 1H), 7.85–7.30 (m, 2H), 4.06 (s, 2H), 3.77 (s, 3H)
4c	71		1735	7.74 (d, J = 2, 1H), 7.5–7.10 (m, 3H), 4.23 (q, J = 7, 2H), 3.98 (s, 2H), 3.90 (s, 3H), 1.23 (t, J = 7, 3H)
4d	83		1735	8.36 (d, J = 2, 1H), 7.89 (dd, J = 2, 8, 1H), 7.37 (d, J = 8, 1H), 4.05 (s, 2H), 3.78 (s, 3H)
4e	56	44–45	1741	8.20 (dd, J = 9, 5, 1H), 7.19–7.13 (m, 1H), 7.07 (dd, J = 3, 9, 1H), 4.02 (s, 2H), 3.73 (s, 3H)
4f	74	33–34	1738	7.85 (d, J = 7, 1, 1H), 7.34–7.31 (m, 2H), 3.99 (s, 2H), 3.70 (s, 3H)
4g	93		1732	7.94 (dd, J = 8, 1, 1H), 7.71 (dd, J = 8, 1, 1H), 7.42 (t, J = 8, 1H), 4.18 (s, 2H), 3.74 (s, 3H)
5a	60	195–197 (197–199)[20]	1704[d]	10.45 (br s, 1H), 7.22–7.15 (m, 2H), 6.76 (d, J = 8, 1H), 3.46 (s, 2H)
5b	87	196–198 (189–192)[20]	1725[d]	8.26 (br s, 1H), 7.14 (d, J = 8, 1H), 7.00 (dd, J = 8, 2, 1H), 6.98 (d, J = 2, 1H), 3.51 (s, 2H)
5c	70	159–160 (158)[21]	1707	8.37 (br s, 1H), 7.10 (d, J = 8, 1H), 6.54 (dd, J = 8, 2, 1H), 6.48 (d, J = 2, 1H), 3.79 (s, 3H), 3.48 (s, 1H)
5d	93	213–214 (216)[22]	1695[d]	10.40 (br s, 1H), 7.27 (s, 2H), 7.10 (s, 1H), 3.47 (s, 2H)[e]
5e	87	142–143 (134–135)[20]	1703	8.30 (br s, 1H), 6.99–6.89 (m, 2H), 6.80 (dd, J = 8, 4, 1H), 3.55 (s, 2H)
5f	91	139–140 (139–141)[20]	1710	8.64 (br s, 1H), 7.15 (dd, J = 5.5, 1, 1H), (ddd, J = 2, 8, 1, 1H), 6.63 (dd, J = 2, 8, 1H), 3.50 (s, 2H)
5g	80	215–216 (217–218)[10] (211–213)[20]	1700[d]	8.2 (br s, 1H), 7.18 (t, J = 8, 1H), 7.01 (d, J = 8, 1H), 6.78 (d, J = 8, 1H), 3.55 (s, 2H)

[a] Satisfactory microanalyses were obtained: C ± 0.29, H ± 0.25, N ± 0.28.
[b] Yield of pure isolated product.
[c] Diethyl malonate was employed.
[d] KBr.
[e] DMSO-d_6.

substitution product relative to the undesired para product.[16] Removal of the undesired para isomer could be achieved by chromatography, or by crystallization after oxindole formation. Dimethyl malonate was preferred over diethyl malonate because the diester products derived from the former were all crystalline which aided in purification.[17] Krapcho decarboxylation with lithium chloride in dimethyl sulfoxide uneventfully afforded the monoesters.[18] Reduction of the nitro group with iron and acetic acid yielded the oxindoles (Table).[19]

In summary a general synthesis of oxindoles has been demonstrated which allowed control of regiochemistry about the aromatic ring. This regiocontrol was achieved by displacement of the halide in an α-halonitrobenzene by an anion of a malonate ester. The malonate displacement products exemplified in this route have the potential to be exploited for the synthesis of other heterocyclic ring systems.

Melting points were determined with Thomas–Hoover capillary melting point apparatus and are uncorrected. Microanalyses were performed by the Pfizer Analytical Department. The halonitrobenzenes were purchased from Aldrich Chemical Co. and used without purification. AcOH and DMSO were used without further purification.

6-Chloroindol-2(3*H*)-one (5b); Typical Procedures:

Dimethyl (4-Chloro-2-nitrophenyl)malonate **(3b):**

To hexane washed NaH (50% in oil, 13.75 g, 286 mmol) was added DMSO (286 mL) followed by dropwise addition of dimethyl malonate neat (37.8 g, 286 mmol). The reaction was heated to 100 °C for 40 min. The reaction was cooled to r.t., 2,5-dichloronitrobenzene (25 g, 130 mmol) was added, the reaction stirred for 30 min at r.t., and heated to 100 °C for 1 h. The reaction was inversely quenched into aq sat. NH_4Cl (1 L), EtOAc (200 mL), and hexane (200 mL). The organic layer was separated and washed with aq sat. NH_4Cl (500 mL), H_2O (3 × 500 mL), brine (500 mL), and treated with $MgSO_4$. Removal of the solvent afforded a light orange solid. Recrystallization from 20% EtOAc/hexane gave the diester **3b** (30.05 g, 80%) as a white solid.

Methyl (4-Chloro-2-nitrophenyl)acetate **(4b):**

The diester **3b** (12.1 g, 42 mmol) was dissolved in DMSO (286 mL), LiCl (3.6 g, 84 mmol) and H_2O (750 mg, 42 mmol) were added and the reaction heated to 100 °C for 3 h. The reaction was cooled and poured into EtOAc (500 mL) and brine (500 mL). The phases were separated and the organic phase washed with brine (500 mL) and treated with Na_2SO_4. Chromatography on silica eluting with 10% EtOAc/hexane yielded the monoester **4b** as an off white solid (6.60 g, 69%).

6-Chloroindol-2(3H)-one **(5b):**

The monoester **4b** (8.0 g, 35 mmol) was dissolved in AcOH (75 mL), Fe powder was added (7.8 g, 140 mmol) and the reaction heated with an oil bath to 100 °C for 1 h. The AcOH was stripped off under

vacuum and the product taken up in EtOAc (100 mL). The brown solids were filtered off and the resulting organic phase washed with aq HCl (1N, 3 × 100 mL), brine and treated with Na_2SO_4. Removal of the solvent under vacuum afforded the **5b** as a white crystalline solid (5.1 g, 89%).

(1) Ottertness, I.; Lewis, A.; Capetola, R. *Advances in Inflammation Research*, Raven Press: New York, 1986; Vol. 11.
Rainsford, K.D.; Path, M.R.C. *Anti-Inflammatory and Anti-Rheumatic Drugs*; CRC: Boca Raton, Florida, 1985.

(2) Lewis, A.J.; Doherty, N.S.; Ackerman, N.R. *Therapeutic Approaches to Inflammatory Diseases*; Elsevier: New York, 1989; pp 229–239.
Kadin, S.B. U.S. Patent 4556672, 1985; *Chem. Abstr.* **1986**, *105*; 24187.

(3) For an overview of the synthesis and chemistry of oxindoles see: Sundberg, R.J. *The Chemistry of Indoles*; Academic: New York, p 341, 1970.
Sumpter, W.C. *Chem. Rev.* **1945**, *37*, 443.

(4) Abramovitch, R.A.; Hey, D.H. *J. Chem. Soc.* **1954**, 1697.

(5) Gassmann, P.G.; Gruetzmacher, G.; van Bergen, T.J. *J. Am. Chem. Soc.* **1974**, 5508.

(6) Carlson, D.F.; Mann, F.G. *J. Chem. Soc.* **1965**, 5419.
Endler, A.S.; Becker, E.I. *Org. Synth. Vol. IV* **1963**, 657.

(7) Oxindoles could also be synthesized by oxidation of a 3-substituted indole:
Szabo-Pusztay, K.; Szabo, L. *Synthesis* **1979**, 276.
For conversion of 8-substituted 3-hydroxyquinolines into oxindoles see:
Nakashima, T.; Suzuki, I. *Chem. Pharm. Bull.* **1969**, 2293.

(8) Mudryk, B.; Makosza, M. *Synthesis* **1988**, 1007.

(9) RajanBabu, T.V.; Chenard, B.L.; Petti, M.A. *J. Org. Chem.* **1986**, *51*, 1704.

(10) Beckett, A.H.; Daisley, R.W.; Walker, J. *Tetrahedron* **1968**, 6093.

(11) Atkinson, J.G.; Wasson, B.K.; Fuentes, J.J.; Girard, Y.; Rooney, C.S. *Tetrahedron Lett.* **1979**, 2857.

(12) Walsh, D.A.; Moran, H.W.; Shamblee, D.A.; Uwaydah, I.M.; Welstead, W.J.; Sancilio, L.F.; Dannenburg, W.N. *J. Med. Chem.* **1984**, *27*, 1379.

(13) Wolfe, J.F.; Sleevi, M.C.; Goehring, R.R. *J. Am. Chem. Soc.* **1980**, *102*, 3646.
Goehring, R.R.; Sachdeva, Y.P.; Pisipati, J.S.; Sleevi, M.C.; Wolfe, J.F. *J. Am. Chem. Soc.* **1985**, *107*, 435.

(14) Bunnett, J.F.; Zahler, R.E. *Chem. Rev.* **1951**, *49*, 273.
For nucleophilic displacement of nitro groups: Beck, J.R. *Tetrahedron* **1978**, *34*, 2057.
For copper assisted nucleophilic substitution of aryl halogen: Lindey, J. *Tetrahedron* **1984**, *40*, 1433.

(15) There is one report in the literature that displacement of 2,4-dichloronitrobenzene with diethyl malonate generates only the ortho substitution product.
Makasoza, M.; Jagusztyn-Grochowska, J.M.; Jawdosiuk, M. *Rocz. Chem. Ann. Soc. Chim. Polonorum* **1976**, *50*, 1841.

(16) In displacement of 2,4-dichloronitrobenzene the malonate methine of ortho diester **3a** was at $\delta = 5.43$ and the para substitution product at $\delta = 4.84$. For 2,4-difluoronitrobenzene the malonate methine of ortho diester **3e** was at $\delta = 5.50$ and the para substitution product at $\delta = 4.84$.

(17) Use of dimethyl malonate was not evaluated for nitrobenzene **2c**.

(18) Krapcho, A.P.; Weimaster, J.F. *J. Org. Chem.* **1980**, *45*, 4105.

(19) For other reduction conditions see Giovannini, E.; Portmann, P. *Helv.* **1948**, *31*, 1392.
Walker, G.N. *J. Am. Chem. Soc.* **1955**, *77*, 3844.

(20) Molloy, B.B. US Patent 3882236, 1975; *Chem. Abstr.* **1975**, *83*; 79075.

(21) Weiland, T.; Unger, O. *Chem. Ber.* **1963**, *96*, 253.

(22) Kosuge, T.; Ishida, H.; Inaba, A.; Nuyaya, A. *Chem. Pharm. Bull.* **1985**, 1414.