Synthesis of Isatin 3-Oximes from 2-Nitroacetanilides

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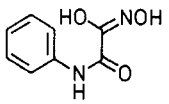
2-Nitroacetanilides, prepared by alkaline hydrolysis of 1-arylamino-1-methylthio-2-nitroethenes, are converted into isatin (1*H*-indole-2,3-dione) 3-oximes by treatment with concentrated sulfuric acid or trifluoromethanesulfonic acid at room temperature.

Isatins[1] (1*H*-indole-2,3-diones) are useful intermediates, for example in the synthesis of indolo[2,3-*b*]quinoxalines,[2] oxindoles,[3] *ortho*-aminobenzonitriles,[4] (via isatin oximes), the Pfitzinger modification of the Friedländer synthesis to produce 4-carboxyquinolines,[5] indole-2,3-dicarboxylic acids,[6] and various indole-related biologically active substances.[7] Indeed, isatin itself has been shown to be the biologically active chemical produced by an *Alteromonas* sp. strain inhabiting the surface of embryos of the caridean shrimp *Palaemon macrodectylus*, which protects them from the otherwise lethal effects of infection by the pathogenic fungus *Lagenidium callinectes*.[8]

The most frequently used route to isatins is that of Sandmeyer[1,9] in which an aniline is reacted with chloral hydrate and hydroxylamine to generate an anilide of glyoxylic acid oxime, which is then subsequently ring-closed using a strong acid. There have been reports that hydrogen cyanide can be a byproduct in such ring closures.[10]

A preliminary communication[11] reported the transformation of 2-nitroacetanilide into isatin 3-oxime using concentrated sulfuric acid at 30 °C or anhydrous hydrogen fluoride at 75 °C, the authors proposing the intermediacy of species **1** to rationalise their result.



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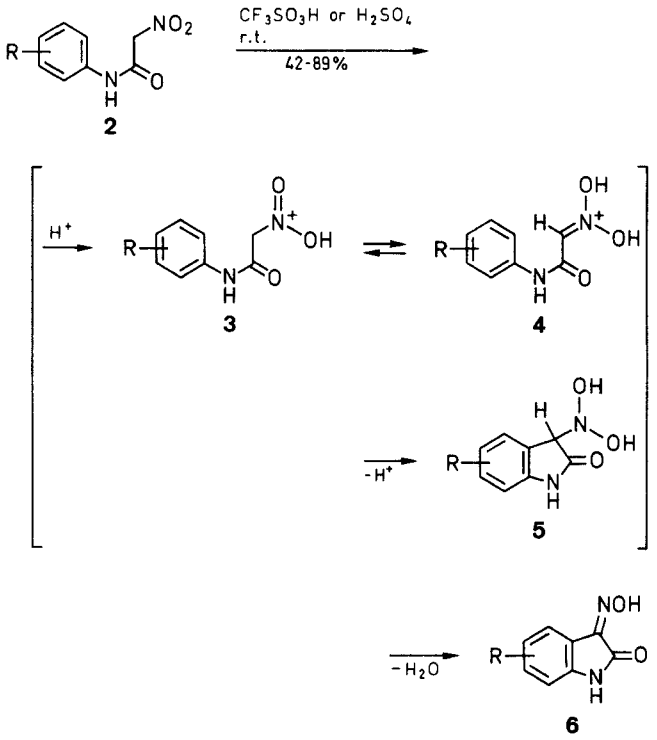
We have now examined the reaction of 2-nitroacetanilides **2** with strong acids and have established that the use of concentrated sulfuric acid at room temperature allows a variety of nitroacetanilides to be ring-closed to isatin 3-oximes **6** (Table 1) in good yields. In some cases we compared sulfuric acid with the more expensive trifluoromethanesulfonic (triflic) acid: somewhat better yields (Table 2) were realised with the latter. We suggest that the course of the process is better represented by the intermediates **3**–**5**.[12]

In cases where the aromatic ring carried an activating methoxy group, although starting material was consumed, no product isatin oxime could be obtained using sulfuric acid. Examination of aqueous extracts from such reactions showed them to have the typical UV/VIS absorption of isatin oximes indicating that benzene ring sulfonation had taken place, either before or after ring closure; no attempt was made to isolate sulfonic acids.



2 **3** **4** **5** **6**

Table 1. Isatin 3-Oximes **6** Prepared Using conc. H_2SO_4

Product	R	Yield[a] (%)	mp (°C)[b]	Molecular Formula or Lit. mp (°C)
6a	H	45	221–222	202,[20] 224[21]
6b	4/6-Me	54	210–212	$C_9H_8N_2O_2$ (176.2)
6c	5-Me	57	222–224	248,[21] 224–225[22]
6d	7-Me	60	252–255	242–243[22]
6e	5-F	43	202–204	282,[21] 275[23]
6f	6-F	45	203–205	240[21]
6g	7-F	54	206–208	$C_8H_5FN_2O_2$ (180.1)
6h	5-Cl	42	208–210	$C_8H_5ClN_2O_2$ (196.6)
6i	6-Cl	46	218–221	225[21]
6j	7-Cl	52	202–204	300[24]
6k	5-Br	42	227–230	273[25]

[a] Yields are of column-purified materials.
[b] Melting points are of column-eluate-evaporated materials.

Table 2. Isatin 3-Oximes

Product	Yield (%)[a]	
	conc. H_2SO_4	CF_3SO_3H
6a	45	89
6e	43	65
6f	45	62
6g	54	67
6h	42	70

[a] Yields are of column-purified materials.

Table 3. 1-Arylamino-1-methylthio-2-nitroethenes **8** Prepared

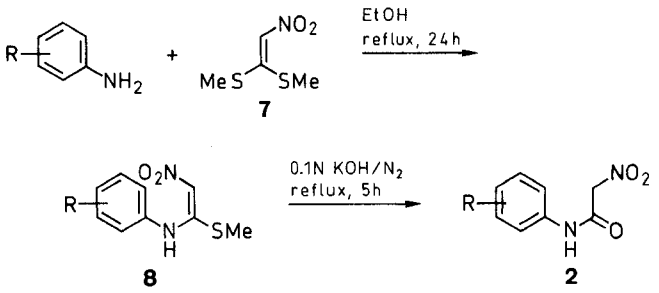
Product	R	Yield (%)	mp (°C)	Molecular Formula or Lit. mp (°C)
8a	H	90	145–147	147–148[26]
8b	3-Me	88	138–140	$C_{10}H_{11}N_2O_2S$ (224.2)
8c	4-Me	92	140–142	$C_{10}H_{12}N_2O_2S$ (224.2)
8d	2-Me	90	145–146	$C_{10}H_{12}N_2O_2S$ (224.2)
8e	3-F	86	156–158	154[27]
8f	4-F	83	154–156	154[27]
8g	2-F	84	100–102	105[27]
8h	3-Cl	72	129–130	$C_9H_9ClN_2O_2S$ (244.6)
8i	4-Cl	76	166–168	166–168[28]
8j	2-Cl	80	137–139	$C_9H_9ClN_2O_2S$ (244.6)
8k	4-Br	62	173–174	$C_9H_9BrN_2O_2S$ (289.1)
8l	4-MeO	91	156–158	158–159[28]
8m	3-MeO	56	128–130	$C_{10}H_{12}N_2O_3S$ (240.2)
8n	2-MeO	58	130–132	$C_{10}H_{12}N_2O_3S$ (240.2)
8o	4-PhO	65	116–117	$C_{15}H_{14}N_2O_3S$ (302.3)
8p	3-NO_2	53	163–165	$C_9H_9N_3O_4S$ (255.2)
8q	4-MeO_2C	57	139–141	$C_{11}H_{12}N_2O_4S$ (268.2)

Table 4. 2-Nitroacetanilides **2** Prepared

Product	R	Yield (%)	mp (°C)	Molecular Formula or Lit. mp (°C)
2a	H	60	138–140	136[25]
2b	3-Me	69	128–130	$C_9H_{10}N_2O_3$ (194.2)
2c	4-Me	73	130–132	$C_9H_{10}N_2O_3$ (194.2)
2d	2-Me	77	132–134	$C_9H_{10}N_2O_3$ (194.2)
2e	3-F	79	117–120	$C_8H_7FN_2O_3$ (198.1)
2f	4-F	80	115–117	$C_8H_7FN_2O_3$ (198.1)
2g	2-F	72	114–116	$C_8H_7FN_2O_3$ (198.1)
2h	3-Cl	82	123–125	$C_8H_7ClN_2O_3$ (214.6)
2i	4-Cl	76	143–145	$C_8H_7ClN_2O_3$ (214.6)
2j	2-Cl	80	115–117	$C_8H_7ClN_2O_3$ (214.6)
2k	4-Br	82	155–156	$C_8H_7BrN_2O_3$ (259.1)
2l	4-MeO	70	138–140	$C_9H_{10}N_2O_4$ (210.2)
2m	3-MeO	75	142–145	$C_9H_{10}N_2O_4$ (210.2)
2n	2-MeO	72	138–140	$C_9H_{10}N_2O_4$ (210.2)
2o	4-PhO	65	148–150	$C_{14}H_{12}N_2O_4$ (262.2)

An examination of the possibility of hydrolysing isatin oximes to produce the isatin itself was conducted using 5-chloroisatin 3-oxime; of the variety of methods available[13] for the hydrolysis of simpler oximes to the corresponding ketone/aldehyde it had been shown that hot aqueous sodium bisulfite,[14] hot aqueous acetic acid,[15] and hot aqueous sodium hydroxide/hydrogen peroxide[16] were of no use, when warm concentrated hydrochloric acid was found to be efficient in the present context.

The nitroacetanilides were produced via the reaction[17] of anilines with 1,1-bis(methylthio)-2-nitroethene (**7**) generating 1-arylamino-1-methylthio-2-nitroethenes **8** (Table 3) which were hydrolysed[18] with aqueous potassium hydroxide, in the absence of oxygen, to afford the nitroacetanilides (Table 4). This hydrolysis procedure worked efficiently in all cases examined except for the case where R = 3-NO_2.



The 1-arylamino-1-methylthio-2-nitroethenes are probably all *E* (shown) in which orientation intramolecular hydrogen-bonding is possible; this was verified for **8h** by the observation of an NOE between the thiomethyl protons and the alkene proton.

1-Arylamino-1-methylthio-2-nitroethenes 8; General Procedure:
1,1-Bis(methylthio)-2-nitroethene (**7**; 4 g, 24 mmol) and the aniline (26 mmol) were heated together in refluxing 95% EtOH (100 mL) for 24 h. On cooling, crystals were produced, filtered, and recrystallised from 95% EtOH.

Table 5. Data for Previously Unreported Isatin 3-Oximes **6**

Compound[a]	λ_{max} (log ε) (EtOH)	^{1}H NMR (CD_3OD) δ, *J* (Hz)	ν_{max} (Nujol) (cm^{-1})	EIMS *m/z* (%)
6b[b]	227 (4.30), 251 (4.63), 300 (4.08), 363 (3.76)	2.40 and 2.75 (3H, 2 × s), 6.80 (d, *J* = 9), 6.85 (s), 6.95 (d, *J* = 9), 7.05 (d, *J* = 9), 7.40 (t, *J* = 9), 7.95 (d, *J* = 9)	3238, 1718, 1621	176 (36), 159 (23), 131 (100)
6e[c]	250 (4.61), 289 (4.04), 359 (3.41)	7.11 (1H, dd, *J* = 4, 9), 7.30 (1H, dt, *J* = 3, 9), 7.95 (1H, dd, *J* = 3, 8)	3212, 1721, 1629	180 (39), 162 (83), 134 (44), 31 (100)
6f	255 (4.31), 291 (3.64), 359 (2.97)	6.75 (1H, dd, *J* = 2, 9), 6.85 (1H, m), 8.10 (1H, dd, *J* = 6, 8)	3235, 1734, 1629	180 (30), 163 (13), 135 (22), 108 (29), 40 (100)
6g	246 (3.17), 293 (3.51), 370 (2.71)	7.05 (1H, dt, *J* = 1, 5, 8), 7.25 (1H, dt, 1, 10), 7.90 (1H, dd, *J* = 1, 8)	3225, 1724, 1643	180 (7), 163 (3), 138 (4), 108 (23), 43 (100)
6h	256 (4.60), 285 sh (3.59), 360 (3.07)	6.92 (1H, d, *J* = 8), 7.40 (1H, dd, *J* = 2, 8), 7.91 (1H, d, *J* = 2)	3411, 3245, 1738, 1620	196 (100), 135 (36), 181 (34), 152 (51)
6i[c]	258 (4.35), 290 sh (3.95), 359 (3.26)	7.00 (1H, d, *J* = 3), 7.15 (1H, dd, *J* = 3, 9), 8.05 (1H, d, *J* = 9)	3441, 3277, 1751, 1675, 1638, 1620	196 (74), 179 (31), 154 (100), 126 (45)
6j[c]	255 (4.50), 292 sh (4.00), 365 (3.20)	7.10 (1H, t, *J* = 9), 7.45 (1H, dd, *J* = 3, 9), 8.10 (1H, dd, *J* = 3, 9)	3451, 3279, 1742, 1689, 1620	196 (91), 179 (100), 154 (54), 126 (70), 197 (86), 180 (50), 163 (61), 154 (33)
6k[c]	259 (4.71), 280 sh (4.50), 377 (4.13)	6.95 (1H, d, *J* = 9), 7.10 (1H, dd, *J* = 3, 9), 8.20 (1H, d, *J* = 3)	3441, 3274, 1737, 1678, 1650	242 (60), 197 (100)

[a] Satisfactory microanalyses obtained: C ±0.3, H ±0.4, N ±0.4 (except **6k** −0.7), F ±0.5 (**6f, g**), Cl ±0.4 (**6h–j**), Br −0.7 (**6k**).
[b] Data for inseparable mixture of 4- and 6-methylisatin oximes.
[c] Data also included for products for which literature mps differ by more than 20 °C from those measured in this work.

Table 6. Data for Previously Unreported 1-Arylamino-1-methylthio-2-nitroethenes **8**

Compound[a]	λ_{max} (log ε) (EtOH)	^{1}H NMR ($CDCl_3$) δ, J (Hz)	EIMS m/z[c] (%)
8b	235 (3.95), 280 (3.67), 358 (4.32)	2.35 (6H, s), 6.65 (1H, s), 7.20 (4H, m)	224 (100), 177 (38), 131 (62)
8c	232 (3.83), 285 (3.60), 358 (4.16)	2.10 (3H, s), 3.05 (3H, s), 6.45 (1H, s), 6.95 (4H, brs)	224 (33), 177 (24), 131 (100)
8d	231 (3.92), 271 (3.74), 355 (4.41)	2.30 (3H, s), 2.35 (3H, s), 6.30 (1H, s), 7.25 (4H, m)	224 (48), 177 (29), 131 (100), 91 (26)
8e[b]	223 (3.90), 270 sh (3.65), 352 (4.34)	2.40 (3H, s), 6.71 (1H, s), 7.20 (2H, m), 7.40 (2H, m), 11.70 (1H, s)	228 (24), 181 (22), 135 (100)
8h	229 (4.26), 285 sh (3.99), 355 (4.55)	2.40 (3H, s), 6.70 (1H, s), 7.35 (4H, m), 11.70 (1H, s)	244 (47), 197 (34), 151 (100), 111 (26)
8j	230 sh (3.86), 351 (4.06)	2.40 (3H, s), 6.70 (1H, s), 7.30 (1H, d, J = 8), 7.40 (1H, d, J = 8), 7.53 (2H, m), 11.70 (1H, s)	244 (36), 197 (27), 151 (100), 111 (22)
8k	244 (4.83), 286 (4.04), 358 (4.40)	2.40 (3H, s), 6.70 (1H, s), 7.15 (2H, d, J = 9), 7.55 (2H, d, J = 9)	290 (21), 243 (26), 197 (100), 163 (39)
8m	264 (3.63), 280 (3.63), 358 (4.30)	2.33 (3H, s), 2.85 (3H, s), 6.65 (1H, s), 6.85 (1H, s), 6.95 (1H, d, J = 8), 7.30 (2H, m)	240 (25), 193 (16), 147 (100), 132 (11)
8n	239 (3.53), 266 (3.42), 360 (4.29)	2.35 (3H, s), 3.85 (3H, s), 6.65 (1H, s), 6.95 (4H, m)	240 (38), 193 (22), 147 (100), 132 (27)
8o	236 sh (4.42), 357 (4.62)	2.30 (3H, s), 6.65 (1H, s), 7.40 (9H, m)	302 (25), 268 (7), 236 (31), 211 (100)
8p	292 (3.80), 352 (4.32)	2.40 (3H, s), 6.65 (1H, s), 7.60 (2H, m), 8.20 (2H, m)	255 (23), 208 (44), 162 (100), 149 (6)
8q	290 (3.98), 355 (4.20)	2.40 (3H, s), 3.90 (3H, s), 6.65 (1H, s), 7.40 (2H, d, J = 9), 8.10 (2H, d, J = 9)	268 (16), 221 (24), 177 (20), 175 (100)

[a] Satisfactory microanalyses obtained: C ±0.3, H ±0.3, N ±0.4, S ±0.3 (**8b–d, h, j, m, n, q**, except: **8k, o** S −1.0, **8p** +0.5), F +0.2 (**8e**), Cl ±0.0 (**8h**), Br +0.6 (**8k**).
[b] Data also included for product for which literature mp differs by more than 20°C from those measured in this work.
[c] For bromo- and chloro-compounds only the lower isotope-containing peaks are listed.

Table 7. Data for Previously Unreported 2-Nitroacetanilides **2**

Compound[a]	λ_{max} (log ε) (EtOH)	^{1}H NMR (CD_3OD)[c] δ, J (Hz)	ν_{max} (Nujol) (cm^{-1})	EIMS m/z[b] (%)
2b	231 (2.85), 277 (2.69), 316 (2.87)	2.35 (3H, s), 7.05 (1H, d, J = 9), 7.35 (1H, t, J = 9), 7.45 (1H, d, J = 9), 7.50 (1H, s)	3283, 3204, 1669	194 (48), 148 (18), 133 (14), 120 (100)
2c	231 (2.95), 280 (2.90), 316 (3.12)	2.40 (3H, s), 7.20 (2H, d, J = 9), 7.40 (2H, d, J = 9)	3317, 3214, 1670	194 (37), 148 (18), 133 (13), 120 (100)
2d	226 (3.14), 272 (2.87), 314 (3.05)	2.35 (3H, s), 7.10 (1H, dd, J = 3, 9), 7.25 (1H, dt, J = 3, 9), 7.35 (dt, J = 3, 9), 7.50 (1H, dd, J = 3, 9)	3268, 3212, 1666	194 (21), 148 (58), 133 (20), 120 (100)
2e	225 (4.06), 275 sh (4.01), 313 (4.17)	($CDCl_3$) 5.30 (2H, s), 6.90 (1H, m), 7.20 (1H, d, J = 9), 7.45 (1H, m), 7.60 (1H, d, J = 9)	3296, 1687	198 (63), 152 (11), 137 (56), 124 (100)
2f	240 (4.37), 275 (4.06), 311 (4.02)	($CDCl_3$) 5.3 (2H, s), 7.0 (2H, m), 7.5 (2H, m), 8.5 (1H, s)	3284, 1670	198 (55), 152 (13), 137 (32), 124 (100)
2g	241 (4.5), 275 sh (4.19), 313 (4.16)	($CDCl_3$) 5.30 (2H, s), 7.15 (3H, m), 8.20 (1H, m)	3289, 1670	198 (68), 152 (10), 137 (53), 124 (89), 111 (64), 43 (100)
2h	230 sh (4.33), 275 sh (4.23), 318 (4.51)	7.20 (1H, ddd, J = 1, 3, 9), 7.40 (1H, t, J = 9), 7.55 (1H, ddd, J = 1, 3, 9), 7.80 (1H, d, J = 3)	3279, 1675	214 (96), 153 (32), 140 (100), 99 (25)
2i	230 sh (4.46), 275 sh (4.40), 317 (4.63)	($CDCl_3$) 5.50 (2H, s), 7.40 (2H, d, J = 8), 7.6 (2H, d, J = 8)	3255, 1669	214 (91), 168 (25), 153 (42), 142 (31), 140 (100)
2j	220 sh (4.27), 278 sh (4.16), 319 (4.42)	7.30 (1H, dt, J = 3, 9), 7.40 (1H, dt, J = 3, 9), 7.55 (1H, dd, J = 3, 9), 7.95 (1H, dd, J = 1, 3)	3275, 1675	214 (100), 153 (38), 140 (92), 99 (31)
2k	230 sh (4.21), 270 (4.16), 319 (4.43)	7.55 (2H, dd, J = 3, 9), 7.65 (2H, dd, J = 3, 9)	3254, 1670	259 (32), 257 (33), 133 (100), 105 (38)
2l	235 sh (4.24), 255 (4.3), 316 (4.07)	[$(CD_3)_2CO$] 3.75 (3H, s), 5.45 (2H, s), 6.95 (2H, d, J = 8), 7.55 (2H, d, J = 8)	3294, 1673	210 (76), 164 (23), 149 (24), 136 (100)
2m	245 (4.37), 288 (4.00), 316 (4.10)	3.90 (3H, s), 6.80 (1H, ddd, J = 1, 3, 9), 7.15 (1H, ddd, J = 1, 3, 9), 7.32 (1H, t, J = 9), 7.37 (1H, t, J = 3)	3295, 1672	210 (100), 164 (25), 149 (20), 136 (58)
2n	244 (4.41), 284 (4.22), 322 (3.99)	4.00 (3H, s), 7.00 (1H, dt, J = 3, 9), 7.10 (1H, dt, J = 3, 9), 7.25 (1H, dt, J = 3, 9), 8.15 (1H, dd, J = 3, 9)	3260, 1676	210 (61), 164 (22), 149 (21), 136 (100)
2o	275 sh (4.42), 319 (4.62)	7.05 (4H, d, J = 9), 7.20 (1H, t, J = 9), 7.45 (2H, t, J = 9), 7.65 (2H, d, J = 9)	3280, 1673	272 (44), 211 (100), 198 (32), 133 (82), 105 (23)

[a] Satisfactory microanalyses obtained: C ±0.4 (except: **2b** −1.7, **2o** −0.5), H ±0.3, N ±0.4 (except: **2b** −0.6), F ±0.4 (**2e–g**), Cl ±0.2 (**2h–j**), Br −2.4 (**2k**). Satisfactory HRMS obtained: ±0.0006 (**2e, l**).
[b] For bromo- and chloro-compounds only the lower isotope-containing peaks are listed.
[c] Unless otherwise specified.

2-Nitroacetanilides 2; General Procedure:
The 1-arylamino-1-methylthio-2-nitroethene **8** (2 g, ca. 10 mmol) and aq. KOH (0.1 N, 100 mL) were heated together at reflux under N_2 for 5 h. while the starting material gradually went into solution. The solution was cooled to r.t., acidified with HCl and product extracted into $CHCl_3$ to give, after drying ($MgSO_4$) and evaporation, the crude product, containing some **8** and some of the aniline. Pure material was obtained by recrystallisation from toluene.

Isatin 3-Oximes 6; General Procedure:
The 2-nitroacetanilide **2** (0.5 g, ca. 3 mmol) was dissolved in the acid (CF_3SO_3H or conc. H_2SO_4 (5 mL)) at r.t. When TLC showed all starting material to have been consumed, the solution was added to ice-cold H_2O (50 mL), and product extracted into $CHCl_3$ after basification with solid $NaHCO_3$. Purification was effected by column chromatography over silica gel eluting with $CHCl_3$/EtOH (95:5).

5-Chloro-1*H*-indole-2,3-dione:
5-Chloroisatin 3-oxime **6h** (100 mg) was dissolved in conc. HCl (5 mL). After 8 h at 80 °C the solution was poured into H_2O (50 mL) and the product isolated via extraction with Et_2O. The crude material thus obtained was purified by chromatography over silica gel, eluting with $CHCl_3$/EtOH (95:5) producing 5-chloroisatin (60 mg, 64%), mp 246–248 °C (Lit.[19] 247 °C).

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