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Air Oxidation of Oxindoles to Isatins

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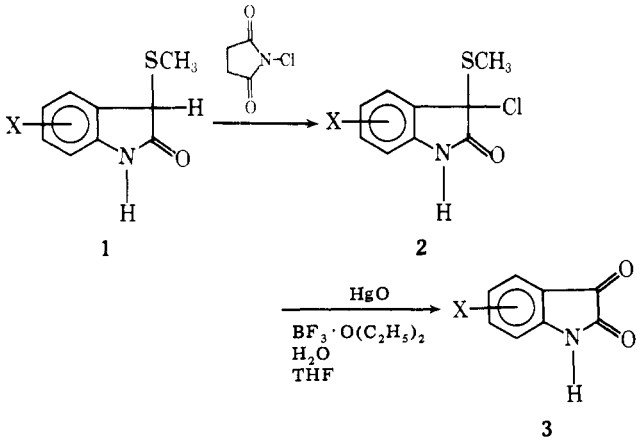
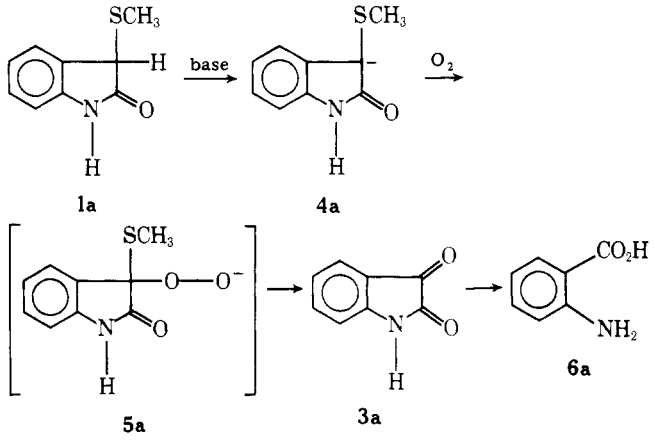
Received August 29, 1978

Recently, we described a general method for the synthesis of isatins.[2] This method involved the chlorination of readily available oxindoles[3] of general formula **1** to give 3-chloro-3-methylthiooxindoles, **2**. Hydrolysis of **2** using red mercuric oxide and boron trifluoride etherate in aqueous tetrahydrofuran then gave the desired isatin, **3**. In view of the problems associated with the use of mercuric oxide and boron trifluoride etherate on a large scale, and considering the long history of isatins as valuable synthetic intermediates in the preparation of both pharmaceuticals and dyes, we decided to seek a more direct route for the conversion of **1** into **3**. We now wish to report on the direct air oxidation of the anion of **1** into **3**.



1 **2** **3**

In our initial studies, we attempted to utilize aqueous base in the direct oxidation of **1a** to **3a**. It was hoped that the base would convert **1a** into **4a**,[4] which would react with oxygen to give **5a**. Breakdown of **5a** under the reaction conditions should have yielded **3a**. Utilizing sodium carbonate, sodium bicarbonate, or potassium hydroxide with air in aqueous methanol



1a **4a** **5a** **3a** **6a**

appeared to give the desired oxidation of **1a** to **3a**. Unfortunately **3a** was unstable under these reaction conditions and was further converted into anthranilic acid (**6**). This was demonstrated by an increase in the amount of anthranilic acid and a decrease in the amount of isatin with increased reaction time.[5] Under the best conditions, we obtained approximately a 2:1 ratio of **6a** to **3a**.

The difficulties encountered in the use of aqueous base prompted us to turn our attention to nonaqueous conditions. We found that the nonnucleophilic base potassium *tert*-butoxide in either ether or anhydrous tetrahydrofuran worked very well for the desired conversion. Table I lists the yields and melting points obtained by this method. In general, contamination by anthranilic acid was not a problem under the anhydrous conditions. In fact, in all of the examples listed, purification of the product was achieved by recrystallization without any prior chromatography of the product.

Experimental Section[10]

General Procedure. In a general procedure, 0.3 to 2.0 g of sublimed potassium *tert*-butoxide was suspended in 200–250 mL of dry ether or tetrahydrofuran (THF) at 0 °C and an equimolar amount of the corresponding 3-methylthiooxindole was added. The solution immediately became colored. The reaction mixture was then stirred

Table I. Yields of Isatins Obtained from the Air Oxidation of 3-Methylthiooxindoles

oxindole	registry no.	% yield of isatin (3)	registry no.	mp, °C	lit. mp, °C
3-methylthiooxindole (**1a**)	40800-64-4	32	91-56-5	199–200	200–202,[2] 200–201[6]
5-carboethoxy-3-methylthiooxindole (**1b**)	61394-56-7	60	25128-35-5	205–206	206–207[2]
5-methyl-3-methylthiooxindole (**1c**)	40800-66-6	41	608-05-9	184–185	185–187[2]
7-methyl-3-methylthiooxindole (**1d**)	40800-67-7	40	1127-59-9	268–270	270–272,[2] 267[7]
5-chloro-3-methylthiooxindole (**1e**)	61394-53-4	49	17630-76-1	246–247	249–252[2], 247[8]
5-methoxy-3-methylthiooxindole (**1f**)	50461-38-6	27	39755-95-8	201–203	202–204,[2] 201–202[9]
5-cyano-3-methylthiooxindole (**1g**)	61394-58-9	35	61394-92-1	273–274 dec	270–272 dec[2]

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and aerated at 0 °C for 4–9 h and then at 25 °C for 15–20 h. A solution of 0.2–1.4 mL of concentrated hydrochloric acid in 20–50 mL of water was added to the reaction mixture and stirring was continued for 20–30 min. The product was then isolated, by either extraction or filtration, and recrystallized.

Isatin (3a). According to the general procedure, 0.48 g of 3-methylthiooxindole in 200 mL of dry diethyl ether was aerated for 4 h at 0 °C and 20 h at 25 °C. Acidification with 0.22 mL of concentrated hydrochloric acid in 25 mL of water followed by extraction with ether, drying of the extracts over anhydrous magnesium sulfate, filtration, and evaporation of the filtrate gave an orange solid. Recrystallization from chloroform gave 0.13 g (32% yield) of pure isatin, mp 199–200 °C.

5-Carboethoxyisatin (3b). According to the general procedure, 4.06 g of **1b** in 250 mL of dry THF was stirred and aerated for 6 h at 0 °C and 18 h at 25 °C. Acidification with 1.35 mL of concentrated hydrochloric acid in 25 mL of water, followed by extraction with ether and normal workup (vide supra), gave a yellow solid which was recrystallized from ethyl acetate to yield 2.20 g (60%) of **3b,** mp 205–206 °C.

5-Methylisatin (3c). According to the general procedure, 1.58 g of **1c** in 250 mL of dry THF was stirred and aerated for 5 h at 0 °C and 19 h at 25 °C. Acidification with 0.68 mL of concentrated hydrochloric acid in 50 mL of water, followed by extraction with ethyl acetate and normal workup (vide supra), gave 1.21 g of an orange solid. Recrystallization from 95% ethanol gave 0.54 g (41% yield) of **3c,** mp 184–185 °C.

7-Methylisatin (3d). Utilizing the general procedure, 3.30 g of **1d** in 250 mL of THF was stirred and aerated for 6 h at 0 °C and 18 h at 25 °C. Acidification with 1.42 mL of concentrated hydrochloric acid in 20 mL of water, followed by addition of a saturated brine solution, gave an organic layer which was separated and worked up as described above to give 1.98 g of crude product. Recrystallization from methanol gave 1.09 g (40% yield) of **3d,** mp 268–270 °C.

5-Chloroisatin (3e). According to the general procedure, 2.10 g of **1e** in 250 mL of THF was stirred and aerated for 4 h at 0 °C and 20 h at 25 °C. Acidification with 0.8 mL of concentrated hydrochloric acid in 25 mL of water resulted in the precipitation of an orange solid (1.10 g), which was collected by filtration. Addition of a saturated sodium chloride solution to the filtrate gave an organic phase which was separated and worked up as described above to give an additional 0.57 g of orange solid. Recrystallization of the crude product from 95% ethanol gave 0.90 g (49% yield) of **3e,** mp 246–247 °C.

5-Methoxyisatin (3f). Oxidation, according to the general procedure, of 1.80 g of **1f** in 250 mL of dry THF was carried out for 6 h at 0 °C and 18 h at 25 °C. Acidification with 0.72 mL of concentrated hydrochloric acid in 25 mL of water, followed by extraction with ether and a standard workup procedure (vide supra), gave a dark red solid which was recrystallized from methanol to give 0.42 g (27% yield) of **3f,** mp 201–203 °C.

5-Cyanoisatin (3g). According to the general procedure, 0.62 g of **1g** in 200 mL of dry THF was stirred and aerated for 9 h at 0 °C and 15 h at 25 °C. Acidification with 0.25 mL of concentrated hydrochloric acid in 25 mL of water, followed by extraction with ether and standard workup (vide supra), gave an orange solid. Recrystallization from 95% ethanol gave 0.18 g (35% yield) of **3g,** mp 273–274 °C dec.

Acknowledgment. We are indebted to the National Science Foundation Undergraduate Research Participation program and to the General Electric Foundation for summer support for K.M.H.

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Simple Method for the Synthesis of Some Pyridazines

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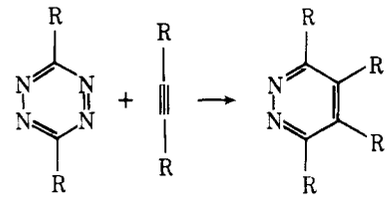
Received August 14, 1978

The reaction of olefinic and acetylenic compounds with 3,6-disubstituted-1,2,4,5-tetrazines (**1**) to give substituted pyridazines (**2**) was first reported by Carboni and Lindsey.[1]

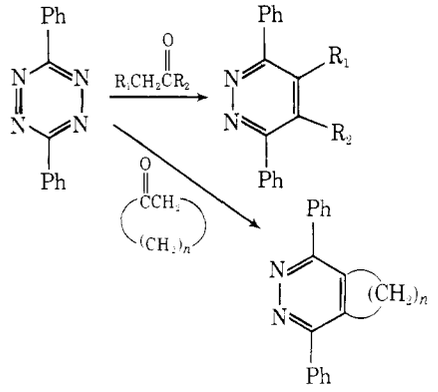


1 **2**

Analogous reactions of **1** with enol ethers, ketene acetals, enol esters, and enamines were shown by Sauer and co-workers[2a] to yield pyridazine derivatives. We report a simple one-step method for the synthesis of substituted pyridazines.

Treatment of 3,6-diphenyl-1,2,4,5-tetrazine (**1**, R = Ph) with a variety of aldehydes and ketones (Table I) in base, at room temperature, proceeded smoothly to give the corresponding pyridazines. The reaction is often immediate and accompanied by the evolution of nitrogen and the disappearance of the violet-red color of **1**. It was observed that aldehydes were more reactive than their isomeric ketones. The

Table I



R_1	R_2	n	product[g]	% yield	reaction time, min	mp, °C
H	H		**3**	88	8	220–222[a]
CH_3	H		**4**	81	3	132–134[b]
C_2H_5	H		**5**	41	2	77–79
H	$CH(OCH_3)_2$		**6**	56	4	79–81
Ph	H		**7**	74	1.5	168–170[c]
H	Ph		**7**	58	13	168–170
H	CH_3		**4**	72	5	132–134[d]
$PhCH_2$	H		**8**	51	1.5	111–113
CH_3	CH_3		**9**	52	25	208–210[e]
CH_3	C_2H_5		**10**	30	120	119–121
		3	**11**	67	1	158–159[f]
		4	**12**	58	3	171–173
		5	**13**	61	8	150–152
		6	**14**	11	12 h	138–139

[a] Lit.[1,3] mp 220–222 and 228–229 °C. [b] Lit.[3] mp 135–136 °C. [c] Lit.[1,3,4] mp 176–177 and 170 °C. [d] Neat. [e] Pyridazine **5** (10%) was isolated by TLC. [f] Lit.[3] mp 156.5–157.5 °C. [g] Satisfactory analytical data (±0.3% for C, H, and N) were provided for compounds **5, 6, 8–10,** and **12–14** (Ed.).

0022-3263/79/1944-0629$01.00/0