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Short communication

A green synthesis of isatoic anhydrides from isatins with urea–hydrogen peroxide complex and ultrasound

Todor Deligeorgiev [a,*], Aleksey Vasilev [a], Juan J. Vaquero [b], Julio Alvarez-Builla [b]

[a] *University of Sofia, Faculty of Chemistry, 1164 Sofia, Bulgaria*
[b] *University of Alcalá, Faculty of Pharmacy, 28871 Alcalá de Henares, Madrid, Spain*

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Abstract

The oxidation of isatins at room temperature, using the cheap and environmentally friendly urea–hydrogen peroxide complex and ultrasonic irradiation, has been investigated. The ultrasonic irradiation dramatically reduces the reaction time. With easy and reproducible reaction procedures, different isatoic anhydrides were obtained in excellent yield and with high purity.

1. Introduction

Isatoic anhydrides are generally used as intermediates in organic synthesis and lead to a wide variety of compounds, most often anthranilic acids [1], which are of use in the manufacture of dyes and pigments [2], in polymer and rubber chemistry [3], as modifiers in protein and carbohydrate substrates (wool, paper, textiles) [4–8], as petroleum additives (fuels and lubricants) [9,10], as blowing agents for polymer foams [8,9,11–14], as flame proofing agents [15], as corrosion inhibitors [16], soaps and detergents [17], perfumes and cosmetics [18] and medicines and pharmaceuticals [19]. Isatoic anhydrides are also used as intermediates in the synthesis of heterocyclic compounds, such as quinazolinones, quinazolones, benzimidazolones, phthalimides, pyrroloquinazolones, quinazolinediones and in the fluorescent labeling of mRNA and tRNA [1,20–22].

A study of the "green" oxidation of isatins with urea–hydrogen peroxide complex to isatoic anhydrides is described here.

2. Results and discussion

One of the first syntheses of isatoic anhydride was achieved by the oxidation of isatin with chromic acid [23,24] to give an overall yield of 65%. The process is very general and has become a commonly used preparation method (Scheme 1).

Isatoic anhydrides have been alternatively prepared by reacting the corresponding anthranilic acid with either ethyl chloroformate or phosgene [25,26]. Both reagents, however, are very toxic and the procedures are therefore not convenient. Alternatively, the oxidation of substituted phthalimides has been described [27], but the method normally gives mixtures of isomers.

In the oxidation of isatin to isatoic anhydride, the oxidizing agent selected should be able to introduce an oxygen atom between the two adjacent carbonyl groups without substantial decomposition of the ring system. In addition to chromium trioxide, several reagents have been successfully used in the process, mainly peracids, and have been reviewed in the oxidation of isatins [1,20,24,28]. As a general consideration, chromium trioxide oxidation methods are not convenient because the reagent in glacial acetic acid or acetic anhydride is prone to explode. Furthermore, chromium is very toxic, so contamination of the products presents additional safety problems.

* Corresponding author. Tel.: +3592 8161269; fax: +3592 9625439.
E-mail address: ohttgd@chem.uni-sofia.bg (T. Deligeorgiev).

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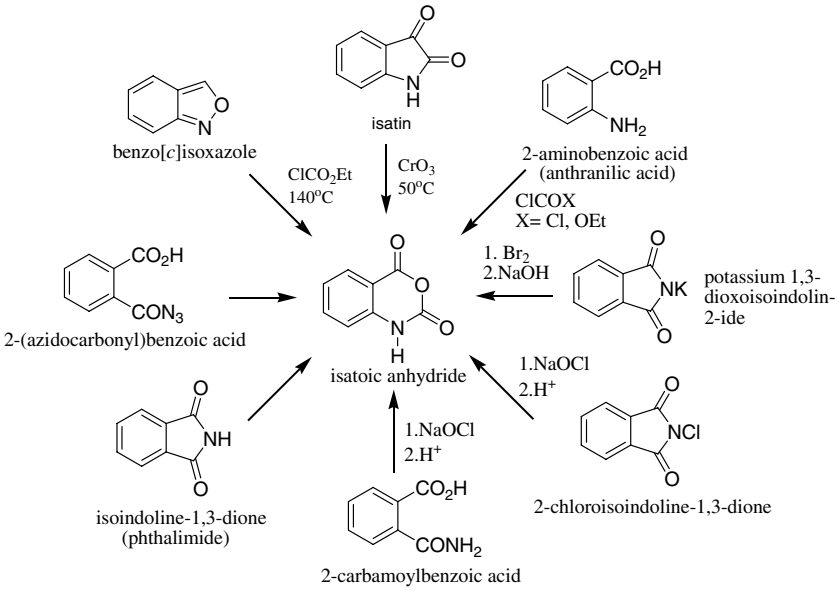
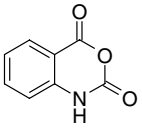
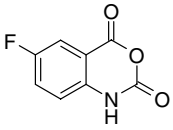
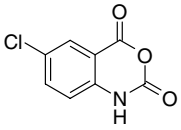
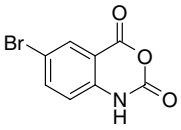
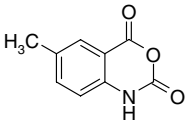
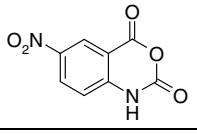


Scheme 1. Reactions commonly used to prepare isatoic anhydride [1].

An interesting oxidation alternative to obtain isatoic anhydrides from isatins has been reported by Reissenweber and Mangold [29,30]. In this case, the oxidizing agent is a mixture of aqueous hydrogen peroxide in acetic or formic acid in the presence of catalytic amounts of sulfuric acid. However, our efforts to repeat this procedure with good yields proved unsuccessful. This was probably due to the heating of the reaction mixture, which meant that the purity of the isatoic anhydride was never satisfactory. The possibility of accumulation of peracetic acid and loss of control over the reaction are also factors for concern. Attempts to convert 5-nitrosatin into 5-nitroisatoic anhydride were also unsuccessful.

We describe here a novel, cheap and environmentally friendly synthetic procedure for the oxidation of isatins through the use of the urea–hydrogen peroxide complex [31] (percarbamide, $H_2NCONH_2 \cdot H_2O_2$). The use of either a mixture of acetic acid/acetic anhydride or formic acid and sulfuric acid catalysis led to the oxidation producing yields in the range 44–97% after 24 h. Furthermore, the reactions were carried out at room temperature and gave isatoic anhydrides with high purity (Table 1). Irradiation of the mixture with ultrasound reduced the reaction time to 20–135 min. The purity and the chemical structures of the reaction products were unequivocally confirmed by HPLC-MS spectrometry, elemental analysis (Table 2) and NMR spectroscopy (Table 3). In the ^{1}H NMR spectra of the target compounds **2a**–**f** the signals of the characteristic groups show similar chemical shifts. Relatively large differences (about one ppm) are observed in the chemical shifts of the NH proton signals on comparing the target compounds and the starting isatins **1a**–**f** (Table 3). It should be pointed out that the conversion degrees (as percentages), as measured from the ^{1}H NMR spectra of the crude products, are in the range 93–100%.

Table 1
Synthesis of isatoic anhydrides **2a**–**f**

No.	Product	Method[a]	Reaction time	Yield (%)[b]
2a		A	24 h	76
		B	24 h	55
		C	120 min	65
		D	30 min	67
2b		A	24 h	72
		B	24 h	73
		C	25 min	77
		D	25 min	82
2c		A	24 h	90
		B	24 h	98
		C	30 min	95
		D	30 min	98
2d		A	24 h	51
		B	24 h	91
		C	135 min	60
		D	90 min	97
2e		A	120 min	44
		B	120 min	56
		C	20 min	46
		D	20 min	70
2f		A	24 h	91
		B	24 h	75
		C	35 min	75
		D	35 min	75

[a] A: $Ac_2O/AcOH/H_2SO_4$; B: HCO_2H/H_2SO_4; C: As method A, plus sonication; D: As method B, plus sonication.

[b] Yields in isolated pure product. All products were crystallized once from acetic acid. Purity was checked by melting point, elemental analysis and HPLC-MS (Table 2). It should be pointed out that the literature data for the melting points of the obtained isatoic anhydrides **2a**–**2f** are quite inconsistent (Table 2).

Table 2
Melting points, elemental analysis data and HPLC-MS spectra of isatoic anhydrides **2a–f**

Comp./method	M.p. (°C)/(lit)	Molecular formula (MW)	Elemental analysis[b] Calc./found		HPLC-MS (*m/z*)	
			C	H	Calc.	Found
2a/A	215–217[a]	$C_8H_5NO_3$ (163.13)	58.89/58.74	3.09/3.20	163.13	163.1
2a/B	214–216					
2a/C	217–219					
2a/D	215–216					
2b/A	240–241[a]	$C_8H_4FNO_3$ (181.02)	53.05/53.44	2.23/2.00	181.12	181.1
2b/B	239–241					
2b/C	240–241					
2b/D	238–240					
2c/A	234–236[a]	$C_8H_4ClNO_3$ (197.58)	48.63/48.84	2.04/2.05	196.99	197.1
2c/B	237–239					
2c/C	234–235					
2c/D	233–235					
2d/A	245–246[a]	$C_8H_4BrNO_3$ (240.94)	39.70/39.48	1.67/1.86	240.94	240.9
2d/B	244–246					
2d/C	245–247					
2d/D	244–245					
2e/A	233–235[a]	$C_9H_7NO_3$ (177.16)	61.02/60.97	3.98/3.65	177.16	177.1
2e/B	234–235					
2e/C	233–235					
2e/D	235–236					
2f/A	240–242[a]	$C_8H_4N_2O_5$ (208.13)	46.17/46.34	1.94/1.89	208.01	208.0
2f/B	241–243					
2f/C	241–243					
2f/D	242–244					

[a] Literature melting points: **2a**: 252–253 °C [29], 250–252 °C [36], 240 °C (dec) [37]; **2b**: 265–268 °C [29], 270 °C (dec) [38]; **2c**: 278–281 °C [39], 265–268 °C [40]; **2d**: 270–275 °C [29], 270–275 °C [40]; **2e**: 233 °C (dec) [41], 245 °C (dec) [42]; **2f**: 224–232 °C [29], 244–245 °C [43].
[b] Elemental analysis correspond to the compound obtained following the method affording the best yield (**2a** and **2f**: method A; **2b–e**: method D).

In addition, the urea–hydrogen peroxide complex is a cheap commercially available product that can be easily obtained by crystallization of urea from commercial 30% aqueous hydrogen peroxide [32,33]. The material is stable at room temperature [31], has a high hydrogen peroxide content and the potential to release it in a controlled manner [34], and is soluble in organic solvents. These characteristics make it a good and safe alternative for the generation of anhydrous hydrogen peroxide in most oxidation reactions. In the method of Reissenweber and Mangold [29,30] the addition of liquid hydrogen peroxide leads to an increase in the reaction temperature, while the oxidation with urea–hydrogen peroxide complex can be carried out at room temperature.

Four synthetic procedures were tested in the oxidation of isatins, all of them using urea–hydrogen peroxide as the oxidant and catalytic amounts of sulfuric acid (Scheme 2). In Procedure A, a mixture of acetic anhydride:acetic acid (8:1 mL) was used as the solvent at room temperature.

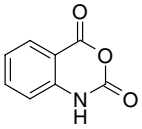
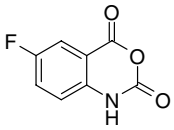
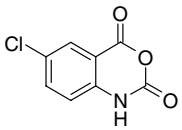
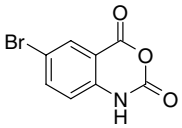
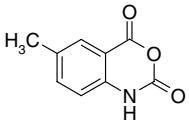
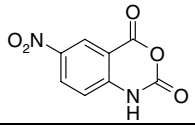
Initial attempts to perform the reaction either in acetic acid or in acetic anhydride did not produce satisfactory results, but on using acetic anhydride/acetic acid (8:1 mL) mixtures, the yields and purities of the products improved (Table 1). Alternatively, in Procedure B, formic acid was used as a solvent, also at room temperature. Procedures C and D correspond to Procedures A and B but with the application of ultrasonic irradiation. Moreover, it should be pointed out that the best results were obtained by combining formic acid and ultrasound. Although cavitation in a bath may not be homogeneous, a possible explanation is related to the characteristics of the solvents; the temperature at which the maximum cavitation intensity (relative to water) is reached may be lower in formic acid or, alternatively, the maximum intensity is reached in formic acid in the range of temperatures studied [35]. All results obtained are shown in Table 1.

Although the differences are variable depending of the product, it seems that formic acid (Procedure B) produces better yields in the oxidation of 5-chloroisatin (**1c**), 5-bromoisatin (**1d**), and 5-methylisatin (**1e**). As expected, the use of ultrasound dramatically reduces the reaction time from 2–24 h to 20–135 min in all cases and, in some cases, even increases the reaction yields. With the exception of **2a** and **2f**, method D, involving a combination of formic acid and ultrasound, seems to produce the best results.

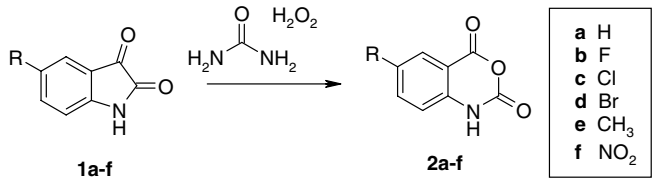
3. Experimental part

Melting points were determined on a Kofler apparatus and are uncorrected. HPLC-MS analyses were performed on an Agilent 1100 apparatus. A Luna C18

Table 3
Comparison between the NMR spectra of the isatoic anhydrides and starting isatins

No	Product	NMR spectra (DMSO-d_6, δ (ppm)) of the isatoic anhydrides[a]	^{1}H NMR spectra (DMSO-d_6, δ (ppm)) of the isatins[a]
2a		^{1}H NMR: 7.10–7.90 (4H, Ar); 11.70 s (1H, NH)	^{1}H NMR: 7.12–7.61 (4H, Ar); 11.03 s (1H, NH)
2b		^{1}H NMR: 7.11–7.65 (3H, Ar); 11.75 s (1H, NH)	^{1}H NMR: 6.63–7.28 (3H, Ar); 10.85 s (1H, NH)
2c		^{1}H NMR: 6.90–7.87 (3H, Ar); 11.87 s (1H, NH)	^{1}H NMR: 6.89–7.63 (3H, Ar); 11.12 s (1H, NH)
2d		^{1}H NMR: 7.83–7.96 (3H, Ar); 11.82 s (1H, NH)	^{1}H NMR: 7.74–7.54 (3H, Ar); 11.05 s (1H, NH)
2e		^{1}H NMR: 2.20 s (3H, CH_3); 6.60–7.61 (3H, Ar); 11.60 s (1H, NH)	^{1}H NMR: 2.17 s (3H, CH_3); 6.71–7.34 (3H, Ar); 10.86 s (1H, NH)
2f		^{1}H NMR: 6.46–8.57 (3H, Ar); 11.85 s (1H, NH)	^{1}H NMR: 6.95–8.36 (3H, Ar); 11.03 s (1H, NH)

[a] The NMR spectra of the starting and the target compounds were compared and the data coincide with the published structures in the NMR library on the internet site: http://www.aist.go.jp/RIODB/SDBS/cgi-bin/direct_frame_top.cgi?lang=eng.



Scheme 2. Oxidation of isatins **1a**–**f** with urea–hydrogen peroxide complex.

(150 × 4.6 mm) 5 μm Phenomenex chromatographic column was used, with a mobile phase formed by a triple gradient of 4% aq formic acid (A), water (B) and acetonitrile (C). The gradient started as A (2.5%), B (93%) and C (4.5%) and, in 30 min reached A (2.5%), B (4.5%) and C (93%). In the mass detector, the fragmenter operated at 70 eV. ^{1}H NMR spectra were obtained on a Varian UNITY 300 MHz instrument in DMSO-d_6. Elemental analyses were performed on a LECO CHNS-932 instrument. Ultrasound was applied using a Branson 200 (40 kHz, 0.5 l) ultrasonic bath in 50 mL flat-bottomed flasks at 20–35 °C. Isatin (**1a**), 5-methylisatin (**1b**), 5-bromoisatin (**1c**), 5-chloroisatin (**1e**) and 5-fluoroisatin (**1f**) are commercial products. 5-Nitroisatin (**1d**) [44] and urea–hydrogen peroxide complex ($H_2NCONH_2 \cdot H_2O_2$) [33] were prepared according to literature procedures.

3.1. Preparation of isatoic anhydrides *2a*–*2f*

3.1.1. Method A

In a three-necked round-bottomed flask equipped with thermometer, a mechanical stirrer, and a reflux condenser, 1 g of finely ground isatin (**1a**–**1f**), 8 mL acetic anhydride, 1 mL acetic acid, 3 drops of concentrated H_2SO_4, and a 30% molar excess of the urea–hydrogen peroxide complex were added. The reaction mixture was stirred at room temperature for the time described in Table 1. The resulting precipitate was filtered off, washed with ethyl acetate, and dried. The product was crystallized from acetic acid.

3.1.2. Method B

In a three-necked round-bottomed flask, equipped with thermometer, a mechanical stirrer, and a reflux condenser, 1 g of the finely ground isatin (**1a**–**1f**) and 8 mL of formic acid, 3 drops of concentrated H_2SO_4, and a 30% molar excess of the urea–hydrogen peroxide complex were added. The reaction mixture was stirred at room temperature for the time described in Table 1. The resulting precipitate

was filtered off, washed with ethyl acetate and dried. The product was crystallized from acetic acid.

3.1.3. Method C

To 1 g of the finely grounded isatin (**1a**–**1f**) was added 8 mL of acetic anhydride, 1 mL acetic acid, 3 drops of concentrated H_2SO_4 and a 30% molar excess of urea–hydrogen peroxide complex. The mixture was ultrasonically irradiated for 20–135 min (Table 1) at room temperature. The resulting precipitate was filtered off, washed with ethyl acetate and dried. The product was crystallized from acetic acid.

3.1.4. Method D

To 1 g of the finely ground isatin (**1a**–**1f**) was added 8 mL of formic acid, 3 drops of concentrated H_2SO_4 and a 30% mol excess of urea–hydrogen peroxide complex. The mixture was ultrasonically irradiated for 20–90 min at room temperature (Table 1). The resulting precipitate was filtered off, washed with ethyl acetate and dried. The product was crystallized from acetic acid.

4. Conclusions

In summary, the oxidation of isatins to isatoic anhydrides has been achieved using a safe, cheap, stable and green oxidation reagent – urea–hydrogen peroxide complex. The reaction time was substantially reduced by using ultrasonic irradiation. Moreover, the isatoic anhydrides were isolated with high purity, the reaction media (solvents) can be recycled by distillation, and the results are reliable and highly reproducible.

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