# *N*-Arylation of Isatins. A Direct Route to *N*-Arylisatoic Anhydrides



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The synthesis of *N*-arylisatoic anhydrides **3** has been accomplished by using a two-step process. The key reaction in the sequence is the direct *N*-arylation of isatin with an aryl bromide in the presence of cupric oxide. Subsequent oxidation of the resulting *N*-aryl isatin **2** with *m*-chloroperoxybenzoic acid furnishes the desired products.

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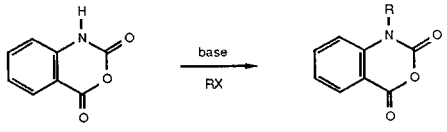
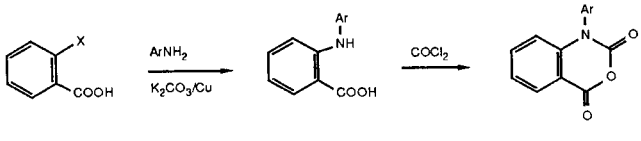
The isatoic anhydride nucleus has been well documented as a versatile synthon for the preparation of a wide variety of heterocyclic systems [1,2]. The nitrogen atom of the isatoic anhydride ring can accomodate a large assortment of functional groups. Alkyl groups are simply introduced by treating an *N*-unsubstituted isatoic anhydride with either sodium hydride or potassium carbonate in *N,N*-dimethylacetamide followed by the alkylating agent [3].

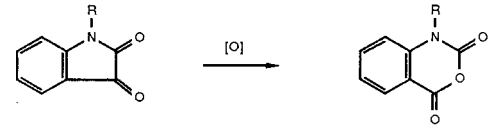



With *N*-arylisatoic anhydrides, however, direct substitution on nitrogen with an aryl moiety is not possible. Consequently, the aryl group must be introduced prior to the formation of the isatoic anhydride ring. Classically, this has been accomplished by use of an Ullmann reaction betwen an *o*-halobenzoic acid and an appropriate aniline (to produce an *N*-arylanthranilic acid) followed by ring closure with phosgene or ethyl chloroformate [3,4,5].




A major drawback of the Ullmann condensation is that it is frequently accompanied by reductive dehalogenation which consequently leads to low yields of product [6]. One isatoic anhydride in particular which was required for one of our projects was *N*-(4-fluorophenyl)isatoic anhydride (**3b**). Its preparation could be achieved by the two-step route shown above, however, the overall yield of the process consistently fell between 24-25%. It was therefore desirable to develop an alternate, higher-yielding route to **3b** which could be applied to other *N*-arylisatoic anhydrides as well.

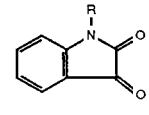
Another generally useful approach to the isatoic anhydride nucleus is the oxidation of isatins. The reaction can accomodate aryl substituents on the isatin nitrogen and oxidation can be effected with either chromium trioxide [7] or peracids [8,9].

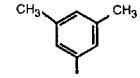



*N*-Arylisatins are usually prepared by reacting a diphenylamine with oxalyl chloride followed by cyclization of the resulting *N*-phenyloxamic acid chloride with aluminum chloride. A potential pitfall for the route is when unsymmetrical diphenylamines are used. Unless one phenyl ring can be biased either to favor or disfavor cyclization exclusively, a mixture of isomeric isatins will result.

It was therefore decided to investigate the possibility of direct *N*-arylation of the isatin nucleus. About 10 years ago

Table 1
*N*-Arylated Isatines



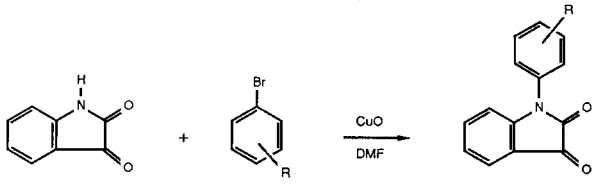

| No. | R | Yield % | Mp, °C | Solvent | Formula | Analysis (Calcd./Found) C | H | N | F |
|---|---|---|---|---|---|---|---|---|---|
| 2a |  | 55 | 137 - 139 [a] | [b] | $C_{14}H_9NO_2$ | | | | |
| 2b |  | 89 | 230 - 233 | [c] | $C_{14}H_8NO_2F$ | 69.7<br>69.3 | 3.3<br>3.4 | 5.8<br>5.9 | 7.9<br>8.3 |
| 2c |  | 38 | 169 - 171 | [d] | $C_{15}H_{11}NO_3$ | 71.1<br>70.8 | 4.4<br>4.3 | 5.5<br>5.8 | |
| 2d |  | 28 | 172 - 173 | [b] | $C_{16}H_{13}NO_2$ | 76.5<br>76.8 | 5.2<br>5.2 | 5.6<br>6.1 [e] | |

[a] Lit [11] mp 138°. [b] Methyl *t*-butyl ether. [c] Methylene chloride/ethyl acetate. [d] Methylene chloride/methyl *t*-butyl ether. [e] Reanalysis of nitrogen did not improve the value.

Khan and Rocha [10] described conditions where indoles can be *N*-arylated with either bromobenzene or a halonitrobenzene in the presence of potassium carbonate and copper(II) oxide in *N,N*-dimethylformamide. Extrapolation of these conditions to the *N*-arylation of isatin produces extremely messy reactions with only minor amounts of the desired product being formed. Nevertheless, the detection of product even in low yield was encouraging and provided a basis for potential optimization of the reaction.

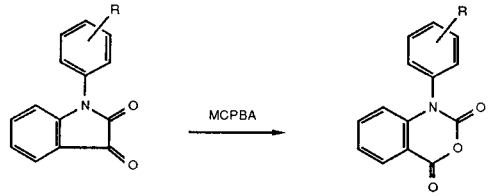
A systematic exploration of the ratio of reactants as well as varying reaction times provided conditions where the *N*-arylated isatins **2** were isolable in reasonable yields (Table 1). In fact, the *N*-(4-fluorophenyl) derivative **2b** was formed in nearly 90% yield.

The initial focus of the procedural modifications was to answer the question whether a stoichiometric amount of potassium carbonate was required for the reaction to occur. After some experimentation it was found that the potassium carbonate was not needed at all to effect efficient coupling of the reactants. Although, in order to achieve reasonable reaction rates, 2 equivalents of copper(II) oxide in conjunction with 1.4 equivalents of aryl bromide were required. Using this ratio of reactants, reactions (which were performed in refluxing dimethylformamide) were complete within 5-8 hours. Prolonged heating usually led to progressive degradation of the product.




1 2

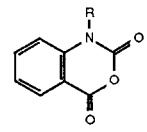
Now that the arylation step has been accomplished attention was turned to the oxidation of the isatin nucleus which should directly provide the desired *N*-arylisatoic anhydride. The first choice of oxidation conditions using chromium trioxide in a mixture of acetic acid and acetic anhydride (1:1), either at room temperature or at elevated temperatures, was not fruitful and only resulted in the reisolation of starting material. The use of peracids as the oxidizing agent gave better results with the desired product being formed in varying amounts. With peracetic acid, conversion to **3** was in the 20% range, however, when *m*-chloroperoxybenzoic acid (MCPBA) was used, yields increased dramatically to nearly quantitative (see Table 2).

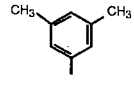



2 3

Table 2

*N*-Arylisatoic Anhydrides

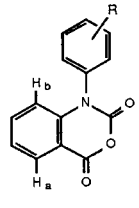



| No. | R | Yield % | Mp, °C | Formula | Analysis (Calcd./Found) C | H | N |
|---|---|---|---|---|---|---|---|
| 3a |  | 92 | 176 - 179 [a] | $C_{14}H_9NO_3$ | | | |
| 3b |  | 97 | 200 - 203 [b] | $C_{14}H_8NO_3F$ | | | |
| 3c |  | 71 | 209 - 212 [c] | $C_{15}H_{11}NO_4$ | | | |
| 3d |  | 81 | 226 - 229 | $C_{16}H_{13}NO_3$ | 71.90<br>71.63 | 4.90<br>4.66 | 5.24<br>5.22 |

[a] Lit [12] mp 177 - 179°. [b] Lit [13] mp 199 - 201°. [c] Lit [13] mp 214 - 216°.

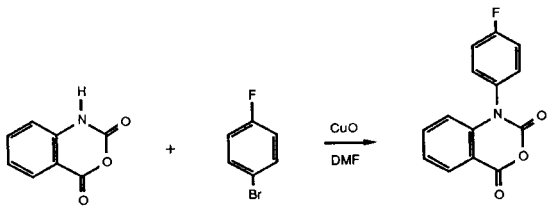
Hence, this methodology represents an alternate and relatively simple two-step sequence for the preparation of *N*-arylisatoic anhydrides from readily available starting materials.

In the nmr spectra of these isatoic anhydrides both protons *ortho* to the heterocyclic portion of the molecule exhibit characteristic shifts. Proton $H_{a'}$, which is *peri* to the carbonyl group, is shifted downfield from the aromatic region and is seen as a doublet of doublets centered between 8.17 and 8.11 ppm. The signal for $H_b$ is shifted upfield from the remainder of the aromatic protons and is seen as a broadened doublet centered between 6.59 and 6.53 ppm.




An important question which comes to mind is whether the arylation reaction can be performed directly on an *N*-unsubstituted isatoic anhydride. This reaction was attempted with isatoic anhydride and 4-bromofluorobenzene using the same conditions described previously in this paper. At the reflux temperature of dimethylformamide only decomposition of the isatoic anhydride was observed. This is not surprising due to the thermal instability of isatoic anhydride at high temperature [14,15]. When the temper-

ature of the reaction was lowered to 130° no reaction was observed even after 24 hours.




**3b**

In summary, a two-step process has been developed where *N*-arylisatoic anhydrides can be prepared by direct *N*-arylation of isatin followed by peracid oxidation of the isatin nucleus to an isatoic anhydride nucleus. This offers an attractive complement to existing procedures for the synthesis of these compounds.

## EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. The infrared spectra were recorded on either Perkin-Elmer Model 257 and 457, or Analect FX-6200 spectrophotometers. Absorption frequencies are quoted in reciprocal centimeters. The proton nmr spectra were recorded on EM-360 and Jeol FX-90-Q spectrometers using tetramethylsilane as an internal reference. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet).

General Procedure for the Preparation of 1-Aryl-1*H*-indole-2,4-diones (**2**).

A mixture of 0.04 mole of isatin, 0.057 mole of the corresponding aryl bromide, and 6.4 g (0.08 mole) of cupric oxide in 100 ml of dimethylformamide was refluxed for 5-8 hours. While hot, any insoluble material was filtered from the mixture. The filtrate was poured into cold water and the resulting precipitate was filtered and dried. The product was the recrystallized from the solvent listed in Table 1.

Spectral Data.

1-Phenyl-1*H*-indole-2,3-dione (**2a**).

This compound had ir (chloroform): 1747, 1615 $cm^{-1}$; nmr (deuteriochloroform): δ 7.75-7.30 (m, 7H), 7.28-7.14 (m, 1H), 6.87 (dd, 1H).

1-(4-Fluorophenyl)-1*H*-indole-2,3-dione (**2b**).

This compound had ir (potassium bromide): 1739, 1612, 1499 $cm^{-1}$; nmr (DMSO-$d_6$): δ 7.71-7.36 (m, 6H), 7.30-7.03 (m, 1H), 6.76 (d, 1H).

1-(4-Methoxyphenyl)-1*H*-indole-2,3-dione (**2c**).

This compound had ir (chloroform): 1744, 1612, 1519, 1469 $cm^{-1}$; nmr (deuteriochloroform): δ 7.74-6.75 (m, 8H), 3.83 (s, 3H).

1-(3,5-Dimethylphenyl)-1*H*-indole-2,3-dione (**2d**).

This compound had ir (chloroform): 1785, 1741, 1613 $cm^{-1}$; nmr (deuteriochloroform): δ 7.71-7.39 (m, 2H), 7.23-6.76 (m, 5H), 2.38 (s, 6H).

General Procedure for the Oxidation of *N*-Arylisatins **2** to *N*-Arylisatoic Anhydrides **3**.

To a solution of 0.021 mole of *m*-chloroperoxybenzoic acid in 250 ml of methylene chloride was added 0.02 mole of **2**. The mixture was allowed to stir at room temperature for 48 hours. The reaction mixture was washed with an aqueous sodium bicarbonate solution (2.5 g of sodium bicarbonate in 250 ml of water) followed by a sodium bisulfite solution. The organic phase was dried over sodium sulfate and the solvent removed under reduced pressure to give essentially pure **3**. The product was recrystallized from methylene chloride/methyl *t*-butyl ether to give analytically pure **3** (Table 2).

Spectral Data.

*N*-Phenylisatoic Anhydride (**3a**).

This compound had ir (chloroform): 1787, 1736, 1606, 1482, 1348, 1179, 1027 $cm^{-1}$; nmr (deuteriochloroform): δ 8.17 (dd, 1H), 7.73-7.20 (m, 7H), 6.55 (d, broad, 1H).

*N*-(4-Fluorophenyl)isatoic Anhydride (**3b**).

This compound had ir (chloroform): 1789, 1741, 1606, 1511, 1474, 1347, 1319, 1242, 1032 $cm^{-1}$; nmr (deuteriochloroform): δ 8.14 (dd, 1H), 7.68-7.12 (m, 6H), 6.53 (d, broad, 1H).

*N*-(4-Methoxyphenyl)isatoic Anhydride (**3c**).

This compound had ir (chloroform): 1784, 1736, 1600, 1250, 1027 $cm^{-1}$; nmr (deuteriochloroform + DMSO-$d_6$): δ 8.11 (dd, 1H), 7.72-7.48 (m, 1H), 7.42-7.03 (m, 5H), 6.59 (d, broad, 1H), 3.93 (s, 3H).

*N*-(3,5-Dimethylphenyl)isatoic Anhydride (**3d**).

This compound had ir (chloroform): 1785, 1741, 1704, 1596, 1495, 1350, 1024 $cm^{-1}$; nmr (deuteriochloroform): δ 8.15 (dd, 1H), 7.66-7.08 (m, 3H), 6.94 (m, 1H), 6.55 (d, broad, 1H), 2.42 (s, 6H).

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## REFERENCES AND NOTES

[1] G. M. Coppola, *Synthesis*, 505 (1980).

[2] T. Kappe and W. Stadlbauer, "Advances in Heterocyclic Chemistry", Vol **28**, Academic Press, New York, NY, 1981, p 127.

[3] G. E. Hardtmann, G. Koletar, and O. R. Pfister, *J. Heterocyclic Chem.*, **12**, 565 (1975).

[4] M. R. Bell, U. S. Patent 3,819,637 (1974); *Chem. Abstr.*, **85**, 46425a (1976).

[5] Ferlux, French Patent 2,104,930 (1972); *Chem. Abstr.*, **78**, 29493j (1973).

[6] J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 392 (1951).

[7] R. A. Scherrer, German Patent 1,190,951 (1965); *Chem. Abstr.*, **63**, 4209d (1965).

[8] R. A. Scherrer, U. S. Patent 3,238,201 (1966); *Chem. Abstr.*, **64**, 17614c (1966).

[9] J. W. Cusic and W. E. Coyne, U. S. Patent 3,509,149 (1970); *Chem. Abstr.*, **73**, 3931x (1970).

[10] M. A. Khan and E. K. Rocha, *Chem. Pharm. Bull.*, **25**, 3110 (1977).

[11] E. Ziegler and Th. Kappe, *Monatsh. Chem.*, **94**, 736 (1963).

[12] A. A. Santilli and T. S. Osdene, *J. Org. Chem.*, **29**, 2717 (1964).

[13] M. R. Bell. A. W. Zalay, R. Oesterlin, P. Schane, and G. O. Potts, *J. Med. Chem.*, **13**, 664 (1970).

[14] R. K. Smalley, H. Suschitzky, and E. M. Tanner, *Tetrahedron Letters*, 3465 (1966).

[15] J. G. Archer, A. J. Baker, and R. K. Smalley, *J. Chem. Soc., Perkin Trans I.*, 1169 (1973).