

# 2-lodoisatogens: Versatile Intermediates for the Synthesis of Nitrogen Heterocycles

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**(5)** Supporting Information

**ABSTRACT:** A Cu-promoted cyclization of 2-nitrophenyl iodoacetylenes provides a direct route to a range of 2-iodoisatogens. These compounds represent useful intermediates for the late-stage elaboration of the C–I bond to furnish isatins and a range of alternative heterocyclic products.

ipolar compounds represent an important class of intermediate in organic synthesis, largely because of their potential to undergo cycloaddition reactions toward complex functionalized molecules.<sup>1</sup> Recent studies in our laboratories have focused on the chemistry of sydnones, as these stable mesoionic compounds are easily functionalized and represent useful precursors for the synthesis of pyrazoles.<sup>2</sup> In this context, and in connection with our general research effort in the chemistry of dipolar compounds, we became interested in the chemistry of indolone N-oxides (isatogens). Isatogens were first prepared by Baeyer<sup>3</sup> and have subsequently been shown to display a range of useful biological properties.<sup>4</sup> These compounds are traditionally generated from 2-nitrophenylacetylenes under acid or base conditions.<sup>5</sup> However, these methods have largely been superseded by transition-metalcatalyzed variants based on Pd<sup>6</sup> and Au.

Söderberg and co-workers recently highlighted that 2nitrophenyl haloacetylenes form isatins under Pd catalysis. However, only in two cases, the corresponding 2-bromoisatogen could be isolated in high yield (Scheme 1).<sup>8</sup> We were



intrigued by this report as 2-haloisatogens have not previously been reported, and so their chemistry is unexplored. Accordingly, we set out to develop a general set of conditions for the synthesis of 2-haloisatogens and to explore their uses in organic synthesis. We were particularly keen to establish a method for the late-stage elaboration of isatogen derivatives.

At the outset of the project, we had the opportunity to focus our studies on the cyclization of bromo- or iodoethynyl 2-



nitrobenzenes in an effort to generate the corresponding 2haloisatogens. Looking forward to the proposed product functionalization studies, we decided to focus our attention on the iodide series, expecting that the chemistry of the corresponding products would be more straightforward. Accordingly, we prepared 1-(2-iodoethynyl)-2-nitrobenzene 1a and set about exploring the cyclization of this substrate; our results are depicted in Table 1. We began by conducting

Table 1. Transition-Metal-Catalyzed Cyclization Reactions

	NO2 16 h	O ⊕ N O	O N H	=0
	1a	2a	3a	
entry	catalyst	solvent	2a (%)	3a (%)
1	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> (5 mol	%) acetone	0	46
2	CuI (10 mol %)	acetone	0	27
3	CuCl <sub>2</sub> (10 mol %)	acetone	0	22
4	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> (5 mol	%) THF	0	55
5	CuBr.DMS (10 mol %	5) THF	66	16
6	CuBr.DMS (25 mol 9	%) THF	89	8
7	CuBr.DMS (50 mol %	5) THF	73	13
8	CuBr.DMS (100 mol	%) THF	0	60

the reaction under conditions similar to those reported by Söderberg, and were able to generate isatin **3a**, with no detectable quantity of the corresponding iodoisatogen **2a**. Cu salts also promoted the cyclization reaction, but in much lower yield. In the case of the Pd-catalyzed cyclization, we noted that the reaction medium became very acidic over time and that the crude reaction mixtures were often rather complex. We speculated that products derived from acid-catalyzed aldol condensation of the acetone solvent could cause formation of

Received: December 3, 2014

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unwanted byproducts and so switched to THF. This provided a marginal improvement in the yield of isatin, but again no isatogen was observed. Surprisingly, on changing to CuBr-DMS catalyst, we observed a good yield of the iodoisatogen 2a, together with a small amount of isatin 3a. Further optimization highlighted that 2a could be generated in excellent yield with 25 mol % of catalyst and that increasing the loading of Cu salt above this led to lower yields as 2a was converted to isatin 3a over the course of the reaction.

With optimal conditions for the synthesis of 2-iodoisatogens in hand, we next studied the scope of the cyclization reaction. As shown in Scheme 2, 2-iodoisatogen **2b** could be prepared in





<sup>a</sup>10 mol % CuBr·DMS used. <sup>b</sup>100 mol % CuBr·DMS used.

excellent yield under the optimized conditions, the product could also be generated using lower catalyst loading but in reduced yield. Isomeric 4-methylisatogen 2c was found to undergo relatively slow cyclization and required stoichiometric quantities of Cu salt, as did the formation of 6-Cl derivative 2d. Substrates bearing a MeO group were found to perform well, giving the corresponding products 2e-g in high yield, and finally ester and acetamido substituents were also found to be compatible with the cyclization process giving 2h and 2i in good yields.

Our preliminary studies highlighted that substrates bearing an electron-deficient group undergo slow cyclization requiring stoichiometric quantities of the Cu catalyst for success (cf. compounds 2d,h, Scheme 2). In order to develop conditions that were compatible with these more demanding substrates, we undertook further catalyst screening and found tetrakis-(acetonitrile)copper trifluoroborate performed well in these cases; our results are shown in Scheme 3. For example, 6bromo-substituted isatogen 2j could not be generated cleanly when CuBr·DMS was employed but was produced in 64% yield Scheme 3. Cyclization of Electron-Deficient Substrates



in the presence of the copper tetrafluoroborate salt. This chemistry was extended to Cl- and F-substituted analogues 2d and 2k and 7-Cl-isatogen 2l. Finally, substrates bearing cyano-(2m) and trifluoromethyl (2n) groups were also prepared under these conditions, although the latter product was isolated in low yield.<sup>9</sup>

Having developed a general method for the synthesis of 2iodoisatogens, we wanted to assess the potential of these compounds to access new heterocyclic products through elaboration of the C–I bond. Our first thoughts were to employ Pd-catalyzed cross-coupling reactions, but the apparent proclivity of palladium to reduce these compounds to isatins<sup>8</sup> suggested that this could be problematic. Indeed, as shown in Scheme 4, **2e** underwent efficient hydrolytic reduction to generate isatin **4** (eq 1). Nonetheless, we were able to conduct Sonogashira coupling of **2e** at rt which provided a selection of 2-alkynylisatogens **5a–c** (eq 2). In an effort to incorporate

#### Scheme 4. Pd-Catalyzed Cross-Coupling



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aromatic groups, we explored Negishi coupling reactions but found these gave the corresponding products in low yield. Interestingly, however, a selection of in situ generated arylzinc chlorides underwent relatively clean substitution to provide products 6a-d in the absence of Pd catalyst. Notably, this latter class of compounds has been shown to undergo bioreduction in red blood cells thereby exhibiting potent antiplasmodial activity.<sup>10</sup>

Finally, in relation to our recent interest in the synthesis and spectroscopic properties of 3-acylidene 2-oxindoles,<sup>11</sup> our observation that displacement of the iodide could be quite facile (Scheme 4, eq 3) suggested that 2-iodoisatogens could in fact offer a facile strategy for the synthesis of the isomeric 2-acylidene 3-oxindoles. These compounds are relatively rare and have been far less studied with respect to their biological activity or cycloaddition chemistry as compared to the 2-oxindole isomers. Moreover, current methods for generating these compounds are rather limited and generally low yielding.<sup>12</sup> We therefore investigated a two-step displacement-decarboxylation sequence toward these products, and our results are summarized in Scheme 5.

#### Scheme 5. Synthesis of 2-Acylidene 3-oxindoles



Reaction of  $\beta$ -keto esters with iodides **2b**,**f** proceeded smoothly to generate isatogens 7–9 in high yield.<sup>13</sup> Pleasingly, Krapcho decarboxylation took place with concomitant reduction of the N–O bond to produce the corresponding 2acylidene 3-oxindoles **10–12**. These compounds were isolated as single olefin isomers and compound **12** was confirmed as having the Z-configuration by X-ray crystallography.<sup>14</sup> Compounds **10** and **11** are tentatively assigned as Z by analogy.

In conclusion, we have developed a Cu-promoted cyclization of 2-nitrophenyl haloacetylenes that generates a range of 2iodoisatogens. These compounds represent useful intermediates that can be elaborated to isatins or to a range of alternative heterocyclic products through subsequent displacement of the iodide.

### ASSOCIATED CONTENT

#### **S** Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http:// pubs.acs.org.

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#### Notes

The authors declare no competing financial interest.

#### ACKNOWLEDGMENTS

We gratefully acknowledge GlaxoSmithKline and the EPSRC for financial support.

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