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2-Iodoisatogens: Versatile Intermediates for the Synthesis of Nitrogen Heterocycles

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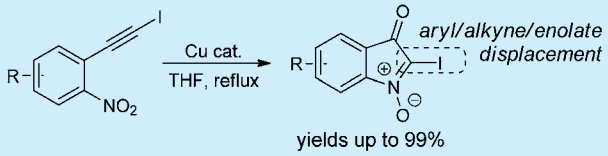
Supporting Information

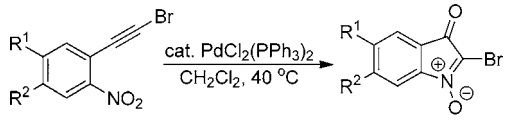
ABSTRACT: A Cu-promoted cyclization of 2-nitrophenyl iodoacetylenes provides a direct route to a range of 2-iodoisatogens. These compounds represent useful intermediates for the late-stage elaboration of the C−I bond to furnish isatins and a range of alternative heterocyclic products.



Dipolar compounds represent an important class of intermediate in organic synthesis, largely because of their potential to undergo cycloaddition reactions toward complex functionalized molecules.[1] 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.[2] 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[3] and have subsequently been shown to display a range of useful biological properties.[4] These compounds are traditionally generated from 2-nitrophenylacetylenes under acid or base conditions.[5] However, these methods have largely been superseded by transition-metal-catalyzed variants based on Pd[6] and Au.[7]

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

Scheme 1. Söderberg's Synthesis of 2-Bromoisatogens

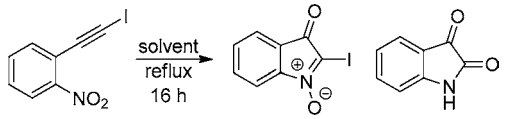


R^1,R^2:H; 87%
R^1,R^2:OCH_2O; 78%

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 2-haloisatogens. 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



1a **2a** **3a**

entry	catalyst	solvent	**2a** (%)	**3a** (%)
1	$PdCl_2(PPh_3)_2$ (5 mol %)	acetone	0	46
2	CuI (10 mol %)	acetone	0	27
3	$CuCl_2$ (10 mol %)	acetone	0	22
4	$PdCl_2(PPh_3)_2$ (5 mol %)	THF	0	55
5	CuBr.DMS (10 mol %)	THF	66	16
6	**CuBr.DMS (25 mol %)**	**THF**	**89**	**8**
7	CuBr.DMS (50 mol %)	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

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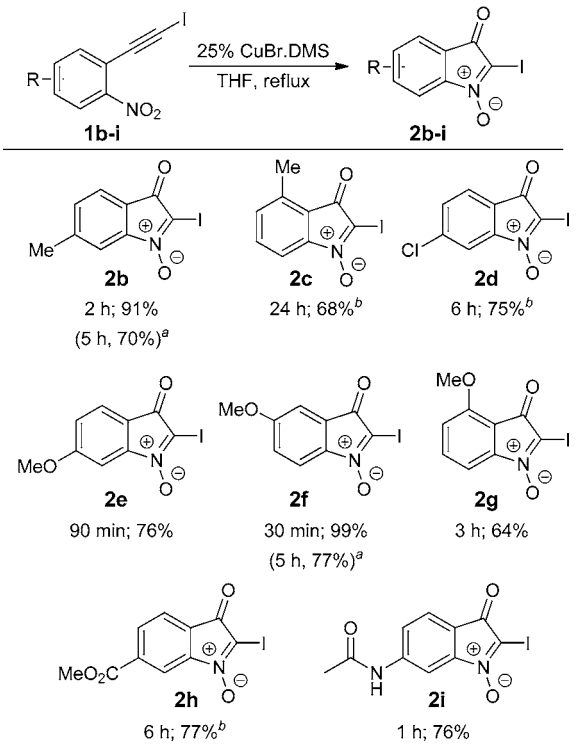
unwanted byproducts and so switched to THF. This provided a marginal improvement in the yield of isatin, but again no isatogen was observed. Surprisingly, on changing to CuBr·DMS catalyst, we observed a good yield of the iodoisatogen **2a**, together with a small amount of isatin **3a**. Further optimization 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

Scheme 2. CuBr-Catalyzed Cyclization

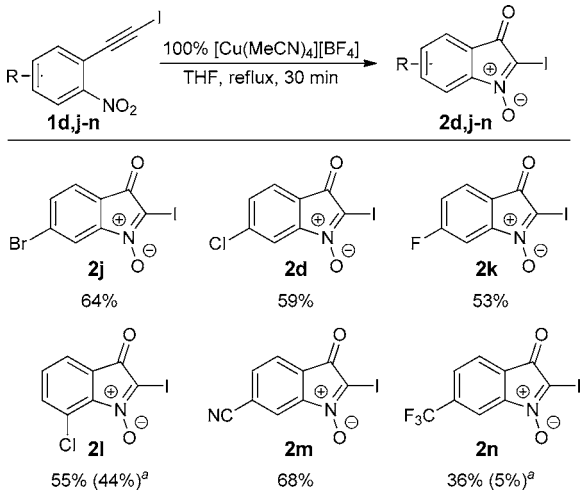


a10 mol % CuBr·DMS used. b100 mol % CuBr·DMS used.

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, 6-bromo-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

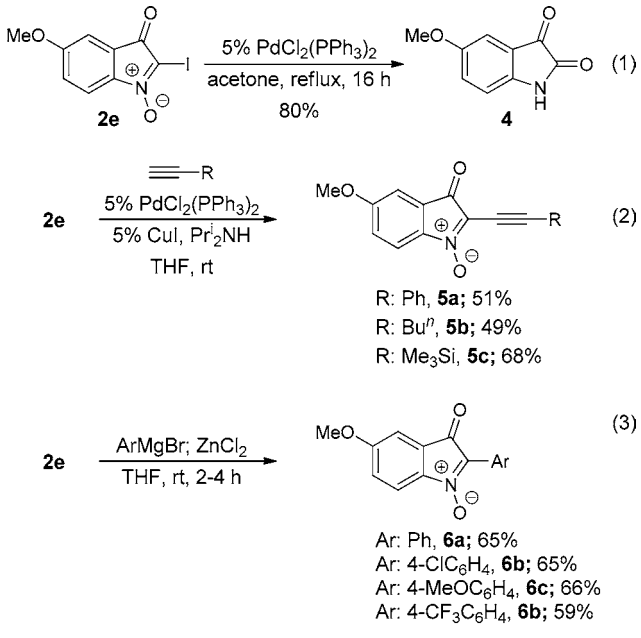


a100 mol % of CuBr·DMS used.

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.[9]

Having developed a general method for the synthesis of 2-iodoisatogens, 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[8] 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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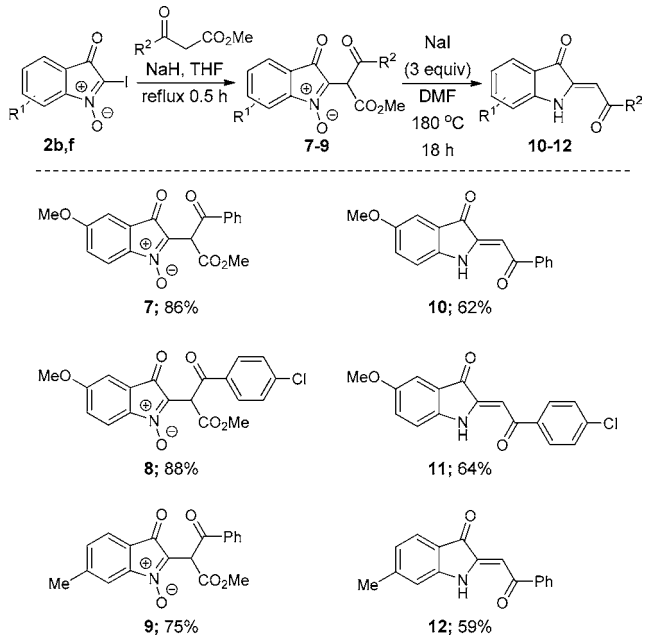
aromatic groups, we explored Negishi coupling reactions but found these gave the corresponding products in low yield. Interestingly, however, a selection of in situ generated arylzinc chlorides underwent relatively clean substitution to provide products **6a−d** in the absence of Pd catalyst. Notably, this latter class of compounds has been shown to undergo bioreduction in red blood cells thereby exhibiting potent antiplasmodial activity.[10]

Finally, in relation to our recent interest in the synthesis and spectroscopic properties of 3-acylidene 2-oxindoles,[11] 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.[12] 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 β-keto esters with iodides **2b,f** proceeded smoothly to generate isatogens **7−9** in high yield.[13] Pleasingly, Krapcho decarboxylation took place with concomitant reduction of the N−O bond to produce the corresponding 2-acylidene 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.[14] 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 2-iodoisatogens. 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

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.

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(14) The supplementary crystallographic data for compound **12** has been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 1029181. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.CCDC.

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