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Synthesis and Reactivity of 3,3-Diazidooxindoles

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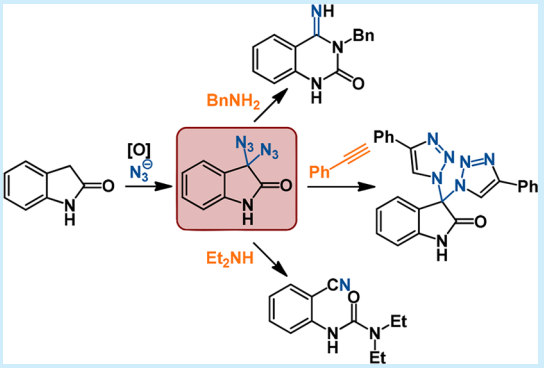
Supporting Information

ABSTRACT: The synthesis of previously unknown 3,3-diazidooxindoles as synthetically useful derivatives of isatins was accomplished through the direct oxidative diazidation of 2-oxindoles. The method yielded the diazido compounds from the starting oxindoles under mild and simple conditions with NaN_3 and iodine, in good yields. The notable reactivity of this new class of compounds toward primary and secondary nucleophilic amines is also described, which gives access to either 4-imino-3,4-dihydroquinazolin-2(1*H*)-one derivatives or cyanophenylureas.



Isatin **A** (Figure 1) and its derivatives constitute a class of heterocyclic compounds that are found in countless natural products, drugs, and biologically active compounds.[1] The versatile reactivity of isatins makes them valuable building blocks for the synthesis of a large variety of other heterocycles, such as indoles, quinolones, 2-oxindoles, and many others, as summarized in several reviews regarding their syntheses and reactivities.[2] Besides the classical methods,[3] there are several new synthetic strategies, which give mild and easy access to the isatin scaffold.[4] For example, the oxidation of indole derivatives with hypervalent iodine compounds[5] or the metal catalyzed cyclization of aminoacetophenones is easily possible,[6] to name just a few. The reactivity of isatins **A** is mostly based on the highly reactive C-3 carbonyl group. As a habitual result, one of the most used applications of isatins is the transformation into 3,3-disubstituted 2-oxindole derivatives **B**, which are also of tremendous interest because of their biological activities and occurrence in natural products (Figure 1).[7,8] Many variants of the isatin-derived core **B** with X = C, O, N, S, etc., and in particular spirocyclic structures with this motif, exist, and their synthesis is of ongoing interest.[9] Our literature search revealed, however, that the kindred diazido core **C** was fully unknown, although one might expect a range of new and valuable reactions with this building block. From a strategic point of view, diazide **C** may become accessible from isatin **A** in a straightforward and redox-neutral manner. Alternatively, the azidation of 2-oxindole **D** may also provide the diazido target, under oxidative conditions.

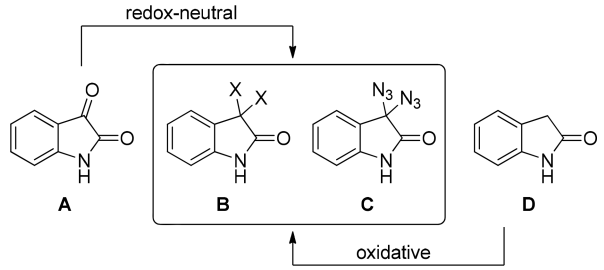


Figure 1. Structures of isatin **A**, 3,3-disubstituted oxindoles **B**, 3,3-diazidooxindoles **C**, and 2-oxindoles **D**.

We recently started a research project aimed at the synthesis and reactivity of small molecules with geminal diazido units.[10] In this context, the synthesis of 3,3-diazidooxindoles and subsequent studies on their fundamental reactivities became primary targets of our research. Herein, we report our early results on the diazidation of oxindoles and on novel reactions with diazidated oxindoles. At the beginning of our studies, we tested the direct access of diazides **C** from the isatin core **A**. This endeavor based on addition and substitution reactions failed with every attempt, and so we then focused on direct oxidative diazidations, starting with 2-oxindole **D**. To our delight, it was easily possible to access **C** from the less-oxidized 2-oxindole core by use of standard azidation conditions[10c] (NaN_3, I_2, DMSO/H_2O, room temperature). The 3,3-diazidooxindole **2a** could be synthesized from oxindole **1a** by use of this operationally simple method in 86% isolated yield, and no further optimization of the reaction conditions was required (Scheme 1).[11] Diazides of type **C** must be considered potentially hazardous and should be handled with care: TGA-DSC curves show that decomposition of diazide **2a** starts at around 100 °C (see SI); **2a** also had a marked impact sensitivity of 5 J.

We further investigated the substrate scope of the method and found that a good variety of substituted 2-oxindoles could

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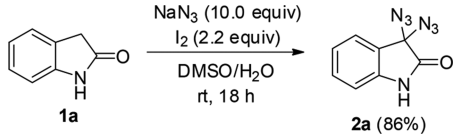
Scheme 1. Synthesis of 3,3-Diazidooxindole 2a



be transformed into the corresponding 3,3-diazidooxindoles in moderate to good yields, employing the exact conditions detailed in Scheme 1. As Figure 2 shows, several substituents in

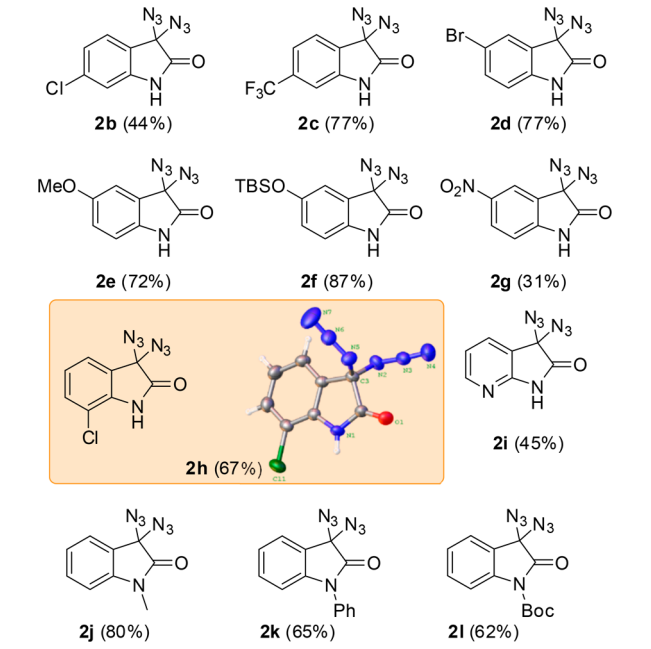
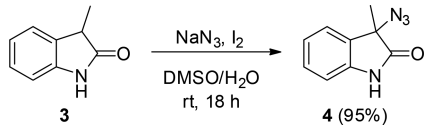


Figure 2. Scope of the diazidation of 2-oxindoles.

the positions 1, 5, 6, and 7 of the oxindole parent structure were well tolerated in the diazidation reaction. 3,3-Diazido-6-chloro-2-oxindole **2b** and 3,3-diazido-6-trifluoromethyl-2-oxindole **2c** were isolated in 44% and 77% yields. Bromo, methoxy, and *tert*-butyldimethylsilyloxy substituents in position 5 were accepted as demonstrated with the examples **2d**–**2f** (72–87%), whereas a nitro group in the same position gave the corresponding diazide **2g** in a diminished yield of 31%. The 3,3-diazido-7-chloro-2-oxindole **2h** was obtained in 67% yield, and the structure was unequivocally evidenced by X-ray crystallography. A suitable single crystal of **2h** was grown from $CDCl_3$; the azido groups are attached at the tetrahedral carbon atom C3 as one should expect. When using a pyrrolopyridinone, diazide **2i** was isolated in a moderate yield of 45%. As demonstrated by the formation of **2j** in 80% yield, **2k** in 65% yield, and **2l** in 62% yield, *N*-substituted oxindoles were tolerant of the reaction conditions as well.

Apart from the above diazidation of 2-oxindoles, further studies revealed that the method could also be used for the monoazidation of 3-methyl-2-oxindole **3** (Scheme 2): our protocol furnished the 3-azido-3-methyl-2-oxindole **4** in an excellent yield of 95%. We point out that the number of alternative methods for the monoazidation of 3-substituted oxindoles is rather limited. For example, Jioa and co-workers reported the copper-catalyzed monoazidation of 3-methyl-2-oxindole **3** by using a hypevalent iodine reagent as an azide source and $Cu(acac)_2$ under argon.[12] More recently, the

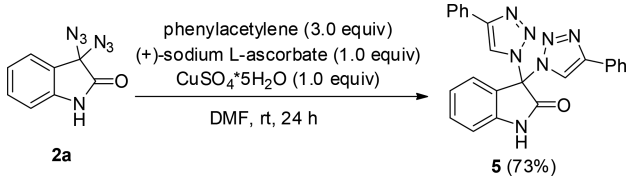
Scheme 2. Monoazidation of 3-Methyl-2-oxindole 3



monoazidation of 2-oxindoles has also been reported under metal-free conditions with $TMSN_3$.[13] In the latter case, oxindole **3** was one of the examples that was not reactive, thus highlighting the value of our current method for the conversion of **3** → **4**.

With a range of diazidated oxindoles easily available, we then focused on the reactivity of this class of compounds, of which nothing was known. First, we tested a protocol for the copper-catalyzed azide–alkyne cycloaddition (CuAAC) and obtained the expected bistriazole **5** in a good yield of 73% (Scheme 3).[14]

Scheme 3. Synthesis of Bistriazole 5



Next, the reactivity of the 3,3-diazido-2-oxindoles with nucleophilic primary and secondary amines was studied, following our previous studies on the reactivity of geminal diazides with amines.[15] Hence, we began with the conversion of the 3,3-diazido-2-oxindole **2a** in the presence of benzylamine under basic conditions, obtaining the corresponding 3-benzyl-4-imino-3,4-dihydroquinazolin-2(1*H*)-one **6a** (Scheme 4).

Among the broad array of nitrogen-containing heterocycles, quinazoline and quinazolinone derivatives represent an important class of compounds having many applications in pharmaceuticals, agrochemicals, polymers, dyes, and organic electronics, as intensively reviewed.[16] Previous methods for the synthesis of 4-imino-3,4-dihydroquinazolin-2-(1*H*)-ones include, among others,[20] the aza-Wittig reaction of iminophosphoranes,[17] the reductive cyclization of 2-(2-nitrophenyl)-1*H*-imidazoles with isocyanates,[18] and the simple conversion of 2-aminobenzonitrile with isocyanates or isothiocyanates.[19] To our knowledge, the direct transformation of the isatin core into imino-3,4-dihydroquinazolin-2-(1*H*)-ones was not previously described. Due to the definite synthetic value of the transformation **2** → **6**, the reaction conditions were further optimized, and best results were obtained in DMF as solvent at a temperature of 50 °C in the presence of Cs_2CO_3. As summarized in Scheme 4, several 3,3-diazido-2-oxindoles gave the corresponding 4-imino-3,4-dihydroquinazolinones in moderate to good yields (31–72%) when treated with benzylamine. Substituents at the aromatic core (**6a**–**6f**) as well as the pyrrolopyridinone **6g** were tolerated, while *N*-substituted 3,3-diazidooxindoles (**6h**, **6i**) did not show any conversion under the presented reaction conditions.

The methodology was also briefly evaluated with respect to a number of selected primary amines (Scheme 5): Starting with **2a**, the expected heterocycles **7a**–**e** were in all cases easily isolated in yields between 61% and 72%. Of note, the dimer **7f**

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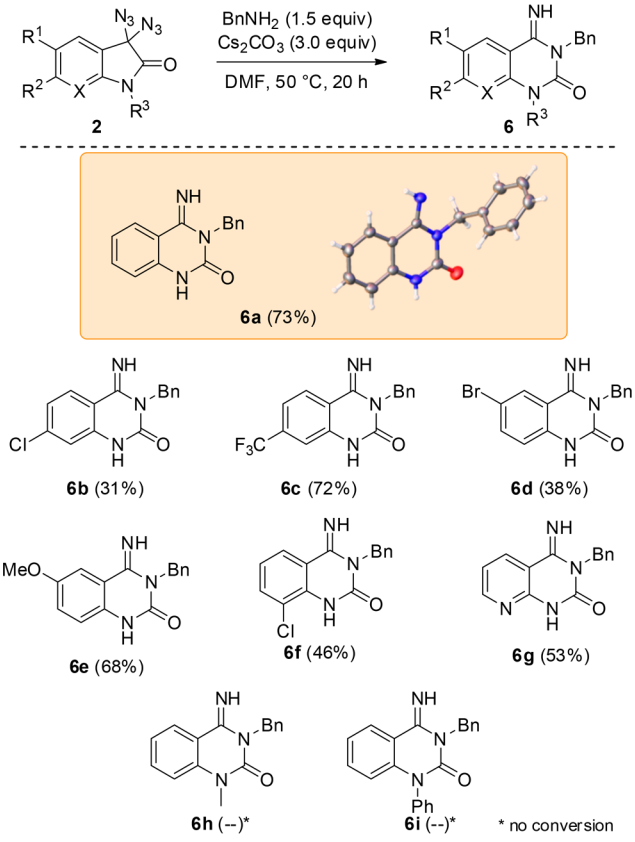
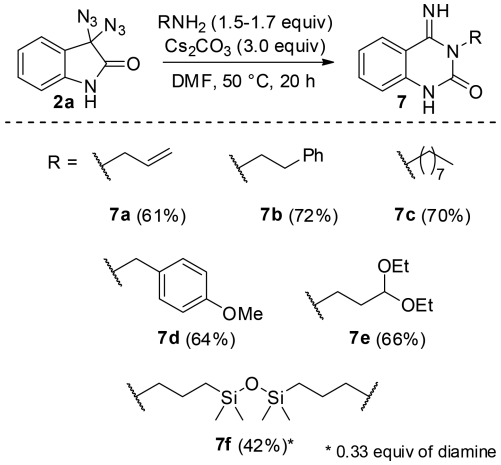
Scheme 4. Formation of 3-Benzyl-4-imino-3,4-dihydroquinazolin-2(1*H*)-ones 6



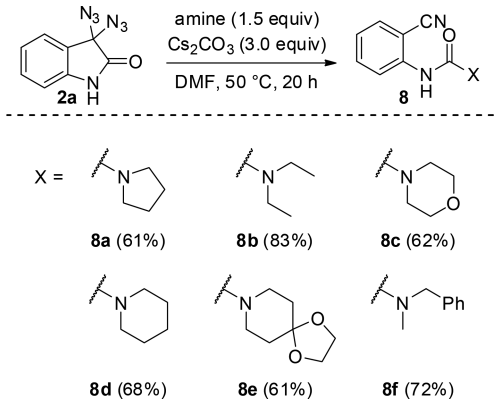
Scheme 5. Scope of the Reaction with Primary Amines



was readily accessible when using 1,3-bis(3-aminopropyl)-tetramethyldisiloxane as the nucleophile.

Regarding a plausible mechanism for the formation of the quinazolinone products **6** and **7**, we fully relied on our previous studies with geminal diazides:[15] It is assumed that a ring opening of the diazidated 2-oxindole through nucleophilic attack of the amine triggers the degradation of the diazido leaving group into a nitrile[15e] through loss of both nitrogen and an azide anion. The resulting cyanophenylurea should be the key intermediate, which finally undergoes a ring closure to form the 4-imino-3,4-dihydroquinazolin-2(1*H*)-one products **6** and **7**. The latter ring closure is one of the standard routes to access 4-imino-3,4-dihydroquinazolin-2(1*H*)-one derivatives; this cyclization was reported to proceed under basic conditions[21,22] and under thermal treatment.[23,24] To obtain evidence for the occurrence of cyanophenylurea intermediates in the course of the transformation of **2** into **6** (or **7**), 3,3-diazido-2-oxindole **2a** was treated with several secondary amines. It was expected that the cyanophenylureas were formed in those cases through ring opening of the diazidooxindole and subsequent fragmentation while cyclization to the quinazoline core was no longer possible. Indeed, the reaction of diazidated oxindole **2a** with pyrrolidine gave the *N*-(2-cyanophenyl)-pyrrolidine-1-carboxamide **8a** in 61% isolated yield (Scheme 6). Other secondary amines were also successfully employed furnishing the corresponding cyanophenylureas **8b**–**8f** in good yields between 61% and 83%.

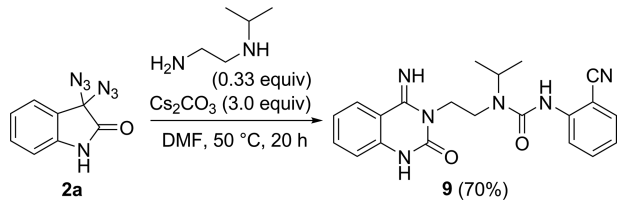
Scheme 6. Reaction of 3,3-Diazido-2-oxindole 2a with Secondary Amines



Of importance, this observation of cyanophenylurea products may be taken as direct proof that geminal diazide units undergo degradation into cyanides through loss of nitrogen and azide. Moreover, the feasibility of the reaction **2** → **8** supports our previously postulated mechanism regarding the fragmentation of diazido acetates where we also assumed the existence of cyanide intermediates, mostly based on theoretical calculations.[15e]

An interesting variant is shown in Scheme 7: when using *N*-isopropylethylenediamine as the nucleophilic component, a

Scheme 7. Formation of 9



substrate containing both a primary and a secondary amine function, the reaction with 3,3-diazidooxindole **2a** provided the mixed compound **9** with a quinazoline and a cyanophenylurea moiety, in 70% yield.

In conclusion, we have reported a mild method for the synthesis of novel 3,3-diazido-2-oxindoles through the direct oxidative diazidation of 2-oxindoles. Preliminary studies on the reactivity of the diazidated oxindoles resulted in the development of a couple of new reactions: A straightforward entry to

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the corresponding bistriazoles and, more importantly, to 4-imino-3,4-dihydroquinazolin-2(1*H*)-ones and cyanophenylurea derivatives through simple treatment with nucleophilic amines was presented. In due course, we will report the synthesis and reactivity of geminal diazides derived from other heterocycles to further expand the knowledge on the fascinating chemistry of geminal diazides.[25]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03013.

Experimental and spectral details for all new compounds and all reactions (PDF)

Accession Codes

CCDC 1841281 and 1866908 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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