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Metal-Free Synthesis of 3,3-Disubstituted Oxoindoles by Iodine(III)-Catalyzed Bromocarbocyclizations

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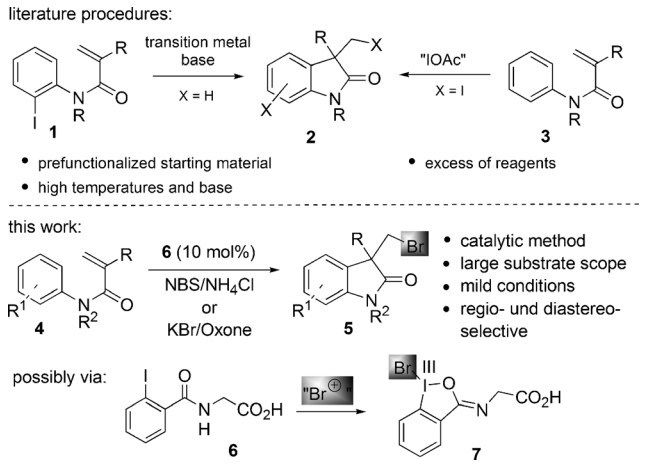
Dedicated to Professor Dr. Dr. h.c. Gerhard Bringmann on the occasion of his 60th birthday

The oxoindole structural motif constitutes a central unit in a multitude of pharmaceutically relevant natural products and synthetic lead structures.[1] The often at the C-3 position disubstituted heterocycle is most of the times responsible for the excellent bioactivities of these compounds. Furthermore, oxoindoles are valuable building blocks towards other nitrogen-containing ring systems, such as indolines, that have a quaternary center at C-3.[2] The most commonly used methods for the construction of indoline-2-on derivatives **2** are metal-catalyzed intramolecular cyclizations (Scheme 1, top).[1a,f,3] Despite first successful attempts on transition-metal-promoted CH-activation/ring-closing reactions,[4] the intramolecular Heck reaction of anilides containing a halogen atom in *ortho* position still constitutes the method of choice for the generation of oxoindoles.[3a] The introduction of the required leaving group at the aromatic ring, however, represents not only an additional step in the synthetic sequence, but is often laborious or even impossible owing to the poor regioselectivity encountered in aromatic substitutions, leading to time-consuming and costly separations of the formed isomers. For these reasons, the development of efficient, selective, and environmentally benign organocatalytic methods to these interesting targets is of great importance.



Scheme 1. Ring-closing reactions towards 3,3-disubstituted oxoindoles and putative formation of the iodine(III) species **7**.

Halocarbocyclization provides an elegant approach for the metal-free synthesis of heterocycles.[5] Although this research field has been growing rapidly in the last years, generally applicable and efficient methods are still rare. Studies recently published by Zhu and co-workers[6] reported on the conversion of methacrylamides **3** into iodo oxoindoles **2** by using iodoacetic acid ("IOAc", Scheme 1, top). A disadvantage of this strategy certainly is the overstoichiometric amounts of $PhI(OAc)_2$ and I_2 that are used for the in situ generation of IOAc,[7] combined with the acidic conditions needed. This work, however, demonstrated that the use of electron-deficient olefins in halocarbocyclization is indeed possible. Thus, the exploration of a first organocatalytic method for the synthesis of the oxoindole framework **5** by using a bromocarbocyclization seemed very promising to us (Scheme 1, bottom). Herein, we describe the development of the first catalytic, metal-free, halonium-induced C,C coupling reaction of substrates bearing electron-poor double bonds. The feasibility to access a multitude of structurally different indolones **5**, also on a gram scale, with complete selectivity for the five-membered ring under mild and practical conditions is shown for 25 different examples. The obtained heterocycles **5** with their exocyclic bromide substituent constitute versatile building blocks that can be transformed easily into structurally complex targets. This is exemplarily proven by the short formal total synthesis of the alkaloid physostigmine (**11**, Scheme 3).

Our studies on the bromonium-induced intramolecular carbocyclization commenced with the treatment of model substrate **4a** with common bromination agents, such as NBS (Table 1, entry 1). Even after the addition of strong Brønsted acids, neutral hydrogen-bond donors, or Lewis bases, like for example, TsOH, Schreiner's catalyst, and DMA (entries 2–5),[8] no conversion of **4a** was observed. In the next step, the application of catalytic amounts of hypervalent λ^3-iodanes was tested. In the last years, these compounds proved themselves as valuable reagents not only in tradi-

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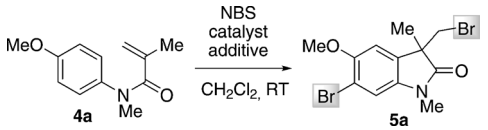
Table 1. Optimization of the conditions for the bromocarbocyclization using NBS.



Entry	NBS [equiv]	Catalyst [mol%]	Additive [mol%]	t [h]	Conversion [%][b]	Yield [%][c]
1	1.2	–	–	24	–	n.d.
2	1.2	–	*p*-TsOH (120)	24	–	n.d.
3	1.2	SC (10)	–	24	–	n.d.
4	1.2	SC (10)	*p*-TsOH (10)	24	<5	3
5	1.2	–	DMA	24	–	n.d.
6	1.2	**6** (10)	–	24	–	n.d.
7	1.2	**6** (10)	TFA (10)	3	52	41[d]
8	2.4	**6** (10)	TFA (10)	3	>99	83
9	2.4	**6** (10)	H_3PO_4 (10)	3	>99	90
10	2.4	**6** (10)	*p*-TsOH (10)	3	83	74
11	2.4	**6** (10)	HOAc (10)	3	36	30
12	2.4	**6** (10)	NH_4Cl (10)	3	>99	94
13	2.4	–	NH_4Cl (10)	24	–	n.d.

[a] Methacrylamide **4a** (0.3 mmol), catalyst (10 mol%), and additive (10 mol%) were dissolved in CH_2Cl_2 (3.0 mL). NBS was added at RT and the mixture was stirred for the given time in the dark. DMA = *N*,*N*-dimethylaniline, n.d. = not determined, NBS = *N*-bromosuccinimide, SC = Schreiner's catalyst, TsOH = *p*-toluenesulfonic acid, TFA = trifluoroacetic acid. [b] Determined by GC using nitrobenzene as an internal standard. [c] Isolated yield. [d] Compound **4a** was reisolated in 40% yield.

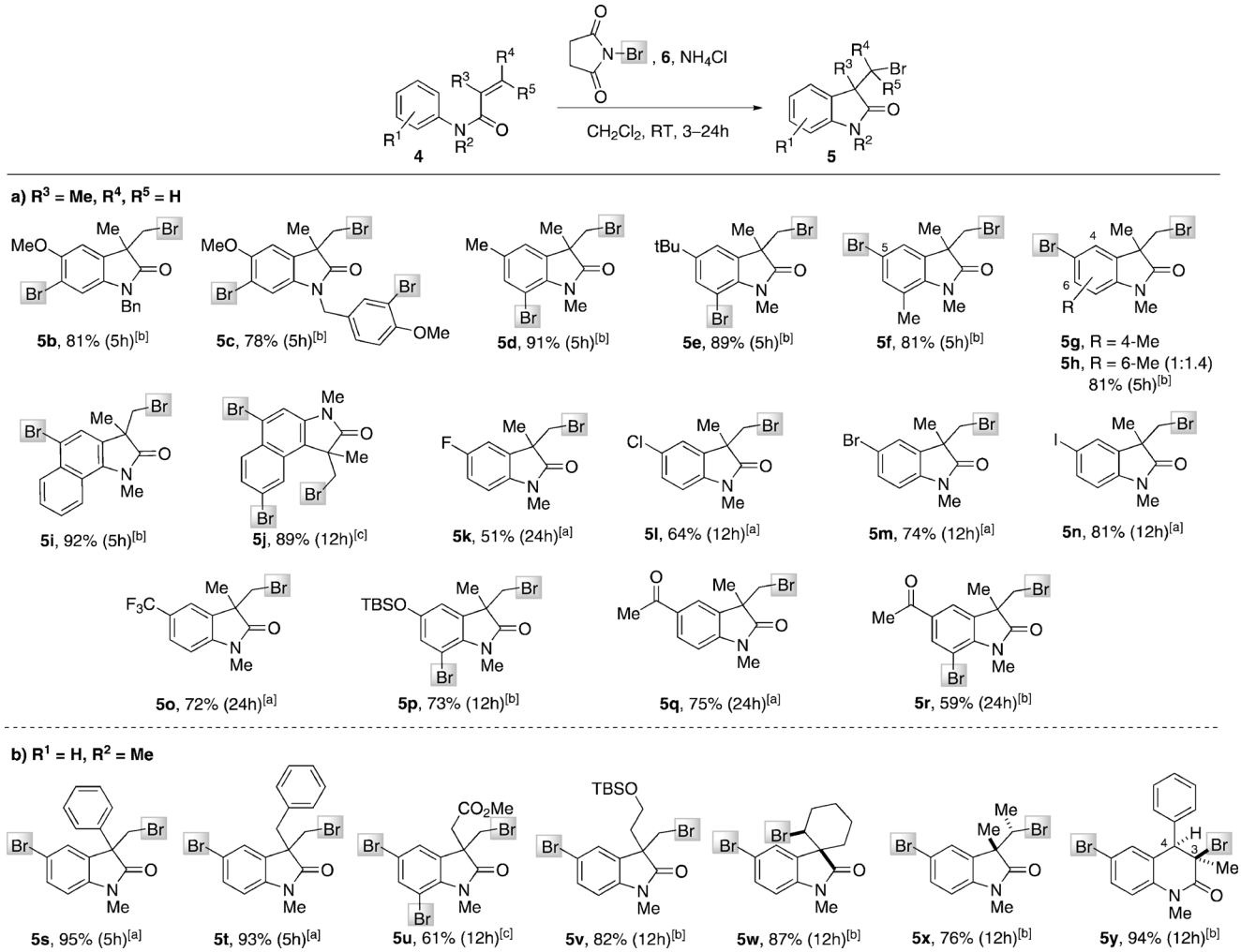
tional oxidation reactions, but also in heteroatom-transfer reactions.[9] The application of bromoiodinanes for the bromination of electron-rich arenes and alkenes was described by Martin[10] already in 1979 and later refined by Braddock, who showed that the halogen-transferring bromo-iodo(III) compounds can, in principle, also be generated in situ.[11] Therefore, we treated starting material **4a** with 1.2 equivalents of NBS and 10 mol% of *o*-iodobenzamide **6**, which unfortunately did not result in the formation of the desired product **5a** (Table 1, entry 6). The isolation of oxoindole **5a** (41%, entry 7), together with nonconverted starting material **4a** (40%), was not possible until the addition of Brønsted acids, such as TFA (10 mol%), to the reaction mixture. Increasing the amount of NBS then selectively delivered the 5-*exo*-trig compound **5a** in good 83% yield. The observed acceleration of catalyst activity is in accordance to other iodine(III)-promoted transformations, in which a strong acid, such as TFA, is decisive to achieve high turnover numbers.[12] Here, variations of the acid additive clearly revealed a similar trend, since a correlation between the acid strength and the amount of isolated product **5a** (entries 8–11) was obvious. One exception was the use of NH_4Cl, which gave **5a** in excellent yield within 3 h (94%, entry 12). It is speculated that, in this case, activation of **7** may occur through noncovalent interactions, like for example, hydrogen bonding, thus, resulting in the good conversion of **4a**. Control experiments without iodobenzamide **6** showed no formation of the desired product **5a** (entry 13), pointing at the decisive role of **6** in this transformation.

With these mild reaction conditions in hand, we investigated the substrate scope of this carbocyclization starting with methacrylamides **4**, which differ in the aryl portion and the substituent at the nitrogen (Scheme 2a). Reduction- and oxidation-prone moieties at the nitrogen (R^2), such as benzyl and *p*-methoxybenzyl, were well tolerated. An alternative cyclization mode that employs the benzyl fragments in **4b** and **c** as nucleophiles, leading to the corresponding isoquinolones, was not observed. In general, the use of starting materials with electron-donating groups at the aryl ring gave the cyclized products **5** in good yields, like the C-5-alkyl-substituted oxoindoles **5d** and **e** (89–91%). The *o*-tolyl derivate **4f** was also successfully converted into a single product **5f**, while treatment of the corresponding *m*-methyl analogue **4g** yielded a 1:1.4 mixture of regioisomers **5g** and **h** in favor of the 6-methyl compound. Naphthalene compounds were also transformed easily into the corresponding products **5i** and **j**.

The ring-closure of starting materials with electron-withdrawing groups at the phenyl ring proceeded smoothly under the developed reaction conditions, but needed, as expected, longer reaction times (up to 24 h) to achieve good yields. The outcome of oxoindoles **5k–o** was highly dependent on the kind of halogen atom present (51–81%) and systematically increased, as anticipated, with decreasing −I effect. Because of the mild reaction conditions, substrates bearing chemically sensitive functional groups, like for example, silyl ethers or ketones, were well accepted, giving the heterocycles **5p–r** in good yields. It is worth noting that aromatic bromination of substrates with deactivated aryl moieties was avoided by using 1.2 equivalents of NBS. Increasing the amount of NBS, however, resulted in additional bromination at the phenyl ring, as exemplified for the benzophenones **5q** and **r**.

In the next step, substrates with different substituents at the α-position of the Michael-acceptor unit were tested (Scheme 2b). Like for the formation of **5b** and **c**, only the aromatic residue of the anilide moiety in **4s–v** acted as a nucleophile, forming oxoindoles **5s–v** in 61–95% yield. Aromatic halogenation at the α-phenyl and α-benzyl fragment was not observed likewise. Compounds comprising ester groups and acid-labile silyl ethers were also accepted, owing to the mild reaction conditions. α,β-Substituted amides **4w–y** were readily transferred into the heterocyclic compounds **5w–y** in good yields. Only the ring closure of (*E*)-α-methylcinnamic acid amide **4y** did not take place following the 5-*exo*-trig mode, as observed in all other examples before, but resulted exclusively in the formation of the six-membered ring product, the quinolone **5y** (94% yield). All cyclizations described here proceeded under complete stereocontrol, affording one single diastereomer. The relative configuration of the C-3 methyl and C-4 phenyl unit in **5y** was assigned to *trans*, as expected for a carbocyclization via an intermediate bromonium ion.

One disadvantage of the presented method, especially in the context of the development of modern, environmentally friendly, and sustainable synthetic methods, is the poor atom



Scheme 2. Substrate scope for the metal-free bromocarbocyclization. [a] 1.2 equivalents of NBS were used. [b] 2.4 equivalents of NBS were used. [c] 3.6 equivalents of NBS were used.

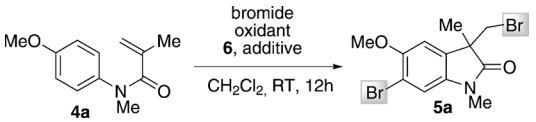
economy[12,13] of the brominating reagent. In situ generation of the desired electrophilic Br^+ species by oxidation of the bromide by applying an external oxidant would avoid the use of NBS and thus, highly improve the efficiency of the reaction.[14] To realize such an organocatalytic oxidative bromocyclization, we tested different inorganic bromide salts in combination with various oxidants for the conversion of model substrate **4a** into oxoindole **5a** (Table 2). The use of common oxidants, such as peroxides, peracids, N-oxides, or hypochlorides, turned out not to be successful. These oxidants either reacted directly with **4a**, delivering the corresponding epoxide (entries 1 and 3), or no conversion was detected (entry 2 and entries 4–6). The desired reaction was finally accomplished with Oxone, yielding oxoindole **5a** in 92% yield (entry 7).[15–19] Here, the addition of NH_4Cl was obsolete (entry 8), which can be attributed to the acidic character of Oxone. Variation of the applied bromide salt did not result in any improvement (entries 9 and 10).

By using this optimized NBS-free method, we converted a variety of structurally different substrates with electron-donating (**4d–f** and **4i**) and electron-withdrawing (**4k–o**) substituents at the aryl ring selectively into the respective oxoindoles (see the Supporting Information). To achieve complete conversion, extended reaction times (up to 24 h) compared to the procedure using NBS were necessary, but the yields were similar to those described in Scheme 2.

The practicability of our method was demonstrated by the formal total synthesis of the acetylcholinesterase inhibitor physostigmine (**11**, Scheme 3).[20] This alkaloid, which originates from the African calabar bean, is clinically used as an antidote and miotic agent, as well as for the treatment of glaucoma and Alzheimer's disease.[21] Starting from methacrylamide **4z**, oxoindole **5m** was obtained in excellent yield (95–97%). Both reaction conditions **A** and **B** were similarly successful and applicable on a gram scale.

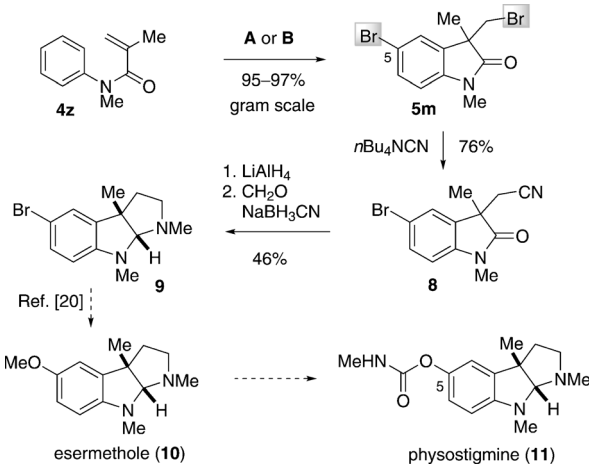
The bromo substituent at the C-5 position, which is necessary for the introduction of the methylcarbamate functionality in the final product, was already installed during the bromocarbocyclization, thus avoiding additional steps within the synthetic sequence. Substitution of the exocyclic bromo

Table 2. Evaluation of the reaction conditions for the bromocarbocyclization using an in situ generated electrophilic bromination agent.



Entry	Bromide	Oxidant	Additive [mol%]	Yield [%]
1	KBr	H_2O_2	NH_4Cl	n.d.[b]
2	KBr	TBHP	NH_4Cl	n.d.
3	KBr	*m*CPBA	NH_4Cl	n.d.[b]
4	KBr	Urea-H_2O_2	NH_4Cl	traces
5	KBr	NMO	NH_4Cl	n.d.
6	KBr	NaOCl	NH_4Cl	n.d.
7	KBr	Oxone	NH_4Cl	92
8	KBr	Oxone	–	93
9	NaBr	Oxone	–	62
10	NH_4Br	Oxone	–	23

[a] Methacrylamide **4a** (0.3 mmol), bromide (0.72 mmol), **6** (10 mol%), and NH_4Cl (10 mol%) were suspended in CH_2Cl_2 (3.0 mL). The oxidant (0.72 mmol) was added at RT and the mixture was stirred for 12 h in the dark. [b] Formation of the corresponding epoxide.



Scheme 3. Formal synthesis of physostigmine (**11**). **A**: NBS (2.4 equiv), **6** (10 mol%), NH_4Cl (10 mol%), 97%; **B**: KBr (2.4 equiv), oxone (2.4 equiv), **6** (10 mol%), 95%.

atom by a cyano group gave compound **8**, which was converted into pyrrolidinindole **9** by reductive cyclization, followed by N-methylation. The key intermediate **9**, which was obtained solely as the *cis*-configured diastereomer,[22] can then be transformed into target compound **11** via the natural product esermethole (**10**) in two further steps following literature-known procedures.[23] By using this short and efficient route, **11** becomes available in only six synthetic steps.

In summary, we have developed the first organocatalytic bromocarbocyclization utilized in an effective transition-metal-free method for the synthesis of C-3-disubstituted oxoindoles **5**. A prefunctionalization of the aryl moiety, as indispensable for most of the metal-catalyzed strategies to heterocycles **5**, was not necessary. The ring-closing reaction occurred with complete diastereoselectivity in all cases, except one, following a 5-*exo*-trig mode, which is unusual for 1,5 dienes. Chemically sensitive functionalities, such as ketones or silyl ethers, were well tolerated under these mild reaction conditions and afforded the desired products **5** in good yields. Furthermore, this intramolecular carbocyclization is experimentally easy to perform, since no oxygen-free or anhydrous conditions are needed for this metal-free process. The organocatalytic method presented here was further extended by applying an in situ umpolung of the bromide into an electrophilic Br^+. With the use of non-toxic Oxone as oxidant, an atom economic and environmentally benign approach to oxoindoles **5** became available, producing only water and K_2SO_4 as stoichiometric waste.

The exploration of the potential of the presented iodine(III)-catalyzed halocyclization strategy, for example, for the direct access to different substrate categories, as well as the development of a stereoselective method to oxoindoles combined with in-depth mechanistic studies, especially on the postulated intermediate **7**, are part of ongoing research in our group.

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Keywords: bromocarbocyclization · heterocycles · natural products · organocatalysis · oxoindoles

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[16] It cannot be excluded that **6** is transformed to its corresponding iodine(III) compound, which then acts as the oxidant to generate Br^+ from bromide. For similar reactions, please confer: D. C. Braddock, G. Cansell, S. A. Hermitage, *Synlett* **2004**, 461–464.

[17] A reaction mechanism including an iodine(V) intermediate, which could possibly be produced in situ from **6** and Oxone, seems unlikely, because experiments employing catalytic amounts of iodine(V) reagents, like for example, 2-iodoxybenzoic acid (IBX), did not form **5a**.

[18] Control experiments without **6** by only employing KBr and Oxone as reagents did not afford oxoindole **5a**.

[19] The reaction proceeding through a radical mechanism, as suggested by one of the reviewers, is unlikely, because the transformation is conducted in the dark and retains its reactivity in the presence of radical scavengers, like for example, 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO).

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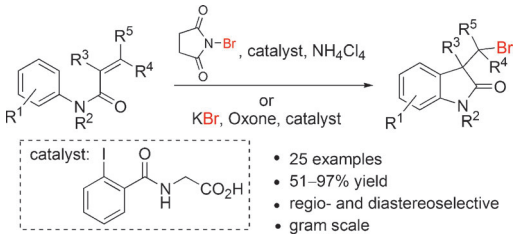
Carbocyclization



"I" did it: An iodine(III)-mediated bromocarbocyclization was elaborated as an efficient tool for the synthesis of oxoindoles. This method is applicable to a variety of structurally different substrates, also with chemically sensitive groups, and gives access to the heterocycles in a regio- and stereoselective fashion (see scheme). The indole-2-ones obtained can be converted easily into structurally complex target compounds, such as the alkaloid physostigmine.