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Synthesis of 3,3-Dihalo-2-oxindoles from 2-Substituted Indoles *via* Halogenation–Decarboxylation/Desulfonamidation–Oxidation Process

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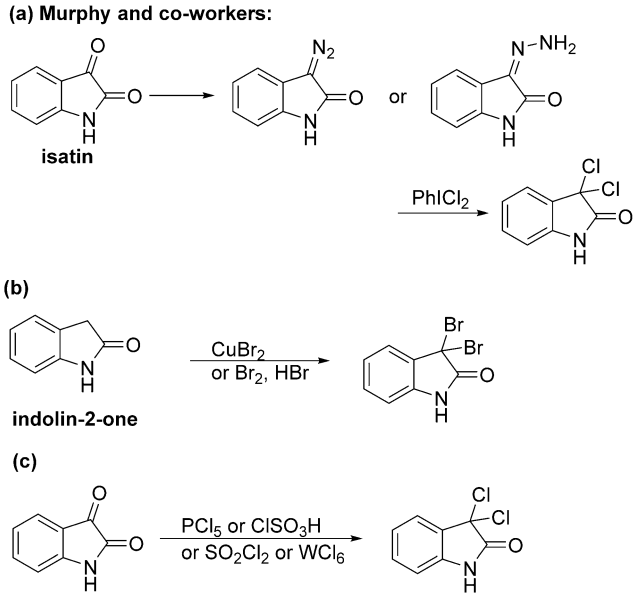
Abstract: A novel one-pot reaction which combines halogenation, decarboxylation/desulfonamidation with oxidation has been developed. Diverse valuable 3,3-dihalo-2-oxindole compounds can be produced rapidly and safely with isolated yields of up to 98% under mild conditions.

Keywords: decarboxylation; desulfonamidation; 3,3-dihalo-2-oxindoles; halogenation; oxidation

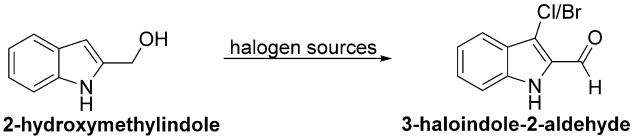
Synthesis of the 3,3-dihalo-2-oxindole unit is of critical importance in organic, medicinal, and material chemistry.[1] The use of hypervalent iodine reagents has proven to be a helpful strategy for the synthesis of highly valued 3,3-dihalo-2-oxindoles.[2] For example, Murphy and co-workers reported a production of 3,3-dichloro-2-oxindole from the toxic and explosive 3-diazo-2-oxindole intermediate and preformed hydrazone using $PhICl_2$ (Scheme 1a).[2a,b]

Strategies applying metal halides or bromine to generate the 3,3-dihalo-2-oxindoles are useful as well.[1g,3] As shown in Scheme 1b, 3,3-dibromo-2-oxindole can be accomplished by bromination of the corresponding indolin-2-one. Other methods, such as deoxygenation of isatin using PCl_5,[1e,4] $ClSO_3H$,[5] SO_2Cl_2,[6] and WCl_6[7] have also been documented (Scheme 1c).

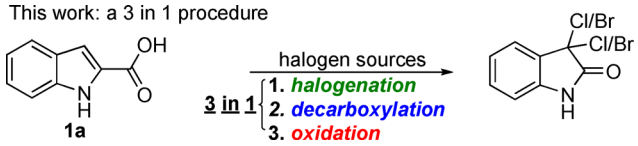
Halogen sources (E^+ sources), such as *N*-chlorosuccinimide (NCS) and *N*-bromosuccinimide (NBS) have oxidative[8,9] and decarboxylative[10] properties besides being well-known halogenation reagents. We have previously disclosed a halogenation–oxidation process in a one-pot manner.[11] Reactions in Scheme 2 demonstrate that 2-hydroxymethylindole can be converted into 3-haloindole-2-aldehyde in the presence of halogen sources such as NCS and NBS. As such, the halogenation and oxidation activities of halogen sources can be realized in a one-pot reaction. We reasoned that it might be possible to combine the decarboxyla-



Scheme 1. Previous pathways for the generation of 3,3-dihalo-2-oxindoles.



Scheme 2. Halogenation–oxidation reaction.



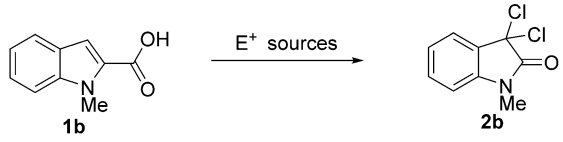
Scheme 3. A single-step procedure.

tion process with the current successful halogenation–oxidation procedure in a single step. As depicted in Scheme 3, treatment of indole-2-carboxylic acid **1a** with halogen sources such as NCS or NBS has indeed afforded the desired 3,3-dichloro/bromo-2-oxindole compounds in a single step procedure.

Interestingly, we discovered that a sulfonamide group could be removed by halogen sources as well. Herein, we report a convenient method to rapidly synthesize useful 3,3-dihalo-2-oxindole compounds from various indole-2-carboxylic acids and indole-2-sulfonamides *via* a halogenation–decarboxylation/desulfonamidation–oxidation process in a one-pot reaction.

We began our study by using indole-2-carboxylic acid **1b** as a model and the results are shown in Table 1. Only a trace amount of the desired 3,3-dichloro-2-oxindole product **2b** was obtained when 1.0 equiv. of NCS was used (Table 1, entry 1). We found that a dominant amount of 3-chloro-substituted indolecarboxylic acid compound was formed, indicating that the chlorination process is the primary step

Table 1. Optimization of substrate **1b**.



Entry[a]	Solvent	E^+ sources	Temp. [°C]	Yield [%][c]
1	EtOAc	NCS (1.0 equiv.)	r.t.	<5
2	EtOAc	NCS (2.0 equiv.)	r.t.	50
3	EtOAc	NCS (3.0 equiv.)	r.t.	70
4	EtOAc	DCDMH[b]	r.t.	93
5	EtOAc	DCDMH[b]	0	88
6	$CHCl_3$	DCDMH[b]	r.t.	60
7	DCM	DCDMH[b]	r.t.	40
8	DCE	DCDMH[b]	r.t.	46
9	PhMe	DCDMH[b]	r.t.	84
10	Me_2CO	DCDMH[b]	r.t.	46
11	THF	DCDMH[b]	r.t.	54
12	MeCN	DCDMH[b]	r.t.	40
13	Et_2O	DCDMH[b]	r.t.	52
14	hexane	DCDMH[b]	r.t.	27

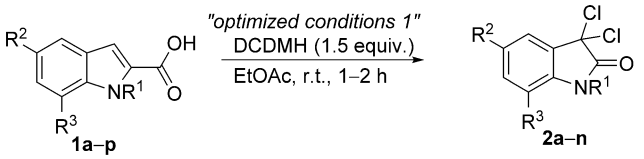
[a] All reactions were carried out at 0.2 mmol scale in 8 mL of solvent.
[b] 1.5 equivalents of E^+ source were used.
[c] Isolated yields.

of this transformation. Product **2b** was obtained with an isolated yield of 50% when 2.0 equiv. of NCS were applied (Table 1, entry 2). Since we observed a certain amount of starting material **1b** preserved in this reaction, we suspected that the subsequent decarboxylation–oxidation process might occur simultaneously. The yield increased substantially when 3.0 equiv. of NCS were used (Table 1, entry 3), suggesting that the whole halogenation–decarboxylation–oxidation process consumes three equiv. of the halogen source. Because 1 equiv. of 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) can provide 2 equiv. of chlorine source, 1.5 equiv. of DCDMH were sufficient for this reaction. A yield of up to 93% of product **2b** was obtained when ethyl acetate was used as solvent at room temperature (Table 1, entry 4). The yield decreased slightly when the temperature was reduced to 0 °C (Table 1, entry 5). Ethyl acetate proved to be a suitable solvent for this process as other solvents, such as $CHCl_3$, DCM, DCE, PhMe, Me_2CO, THF, MeCN, and Et_2O failed to deliver higher yields (Table 1, entries 6–13). The very low yield of product **2b** was probably due to the poor solubility of carboxylic acid substrate **1b** in hexane (Table 1, entry 14).

With the optimized conditions chosen (Table 2, entry 4), a variety of indole-2-carboxylic acids **1** were subjected to investigation. In general, good to excellent reaction yields were achieved under the "optimized conditions" in 1–2 hours reaction time (Table 2). Up to a 98% isolated yield of product **2a** was obtained when an indolic hydrogen was present (Table 2, entry 1). Diverse *N*-substituents were well tolerated in this chlorination–decarboxylation–oxidation process. For instance, *N*-substituents containing alkyl, aryl, allyl, and cyanide groups appeared to be able to deliver excellent yields (Table 2, entries 2–7 and 9). However, a propargyl substituent only returned a moderate yield (Table 2, entry 8). We suspect that the alkyne moiety might trigger the substitution side reactions, leading to a lower yield. For the substrates with electron-deficient R^2 and R^3 substituents, good yields could be achieved (Table 2, entries 10, 11 and 13, 14). When a substrate with R^2 as the 5-OMe group was subjected to the reaction, only a moderate yield could be obtained (Table 2, entry 12), indicating that an electron-rich Ar system of the indole ring could induce the substitution side reactions. Surprisingly, *N*-substituents containing halide moieties, such as Br, and Cl somehow failed to return the desired 3,3-dichloro-2-oxindole products (Table 2, entries 15 and 16).

Although we had identified the optimal conditions for the chlorination–decarboxylation–oxidation process, the bromination–decarboxylation–oxidation process of indole-2-carboxylic acids was less efficient. We investigated several substrates in the bromination–decarboxylation–oxidation process under "optimized

Table 2. Chlorination–decarboxylation–oxidation of **1**.



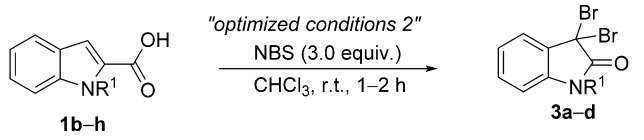
Entry[a]		R^1	R^2	R^3	Product	Yield [%][b]
1	**1a**	H	H	H	**2a**	98
2	**1b**	Me	H	H	**2b**	93
3	**1c**	Ph	H	H	**2c**	92
4	**1d**	Bn	H	H	**2d**	95
5	**1e**	$NC(CH_2)_3$	H	H	**2e**	83
6	**1f**	*i*-Pr	H	H	**2f**	92
7	**1g**	allyl	H	H	**2g**	90
8	**1h**	progargyl	H	H	**2h**	62
9	**1i**		H	H	**2i**	82
10	**1j**	H	F	H	**2j**	89[c]
11	**1k**	H	Cl	H	**2k**	85[c]
12	**1l**	H	OMe	H	**2l**	63
13	**1m**	H	Br	H	**2m**	86[c]
14	**1n**	H	H	Br	**2n**	78[c]
15	**1o**	$Cl(CH_2)_3$	H	H	–	<5
16	**1p**	$Br(CH_2)_2$	H	H	–	<5

[a] All reactions were carried out at a 0.2 mmol scale of **1** in EtOAc (8 mL) in the presence of 1.5 equivalents of DCDMH.
[b] Isolated yields.
[c] Reactions were run under reflux conditions for 4 h.

conditions 2".[12] As demonstrated in Table 3, only low to moderate yields could be achieved in the presence of 3.0 equiv. of NBS in $CHCl_3$ (Table 3, entries 1–4).

The disappointing results of this bromination–decarboxylation–oxidation procedure urged us to try different functional groups in place of the carboxylic acid group. Gratifyingly, we discovered that a sulfonamide group worked effectively for both the chlorination–desulfonamidation–oxidation and bromination–desulfonamidation–oxidation processes, affording the desired 3,3-dichloro/bromo-2-oxindole products with high yields.

Table 3. Bromination–decarboxylation–oxidation of **1**.



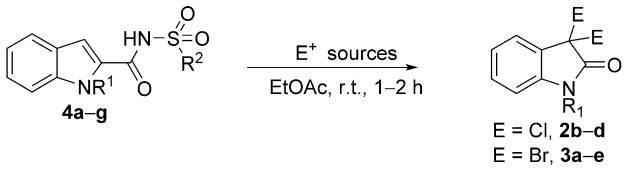
Entry[a]		R^1	Product	Yield [%][b]
1	**1b**	Me	**3a**	59
2	**1d**	Bn	**3b**	25
3	**1e**	$NC(CH_2)_3$	**3c**	35
4	**1h**	propargyl	**3d**	15

[a] All reactions were carried out at the 0.2 mmol scale of **1** in EtOAc (8 mL) in the presence of 3.0 equivalents of NBS.
[b] Isolated yields.

As shown in Table 4, indole-2-toluenesulfonamide, indole-2-*p*-methoxybenzenesulfonamide, and indole-2-methanesulfonamide substrates afforded the desired 3,3-dichloro-2-oxindole products **2** with good to excellent yields (Table 4, entries 1–3, 5, 6, and 8). However, the 4-nitrobenzenesulfonamide **4d** was somehow less effective compared to the other sulfonamide substrates (Table 4, entry 4). It is important to note that the bromination–desulfonamidation–oxidation procedure worked satisfactory for the indole-2-sulfonamide substrate **4**. As we can see from Table 4, excellent yields were obtained when indole-2-toluenesulfonamide and indole-2-methanesulfonamide substrates were used (Table 4, entries 9, 12–14). Exceptional cases, including the indole-2-*p*-methoxybenzenesulfonamide and indole-2-*p*-nitrobenzenesulfonamide substrates, retuned moderate to low yields (Table 4, entries 10 and 11).

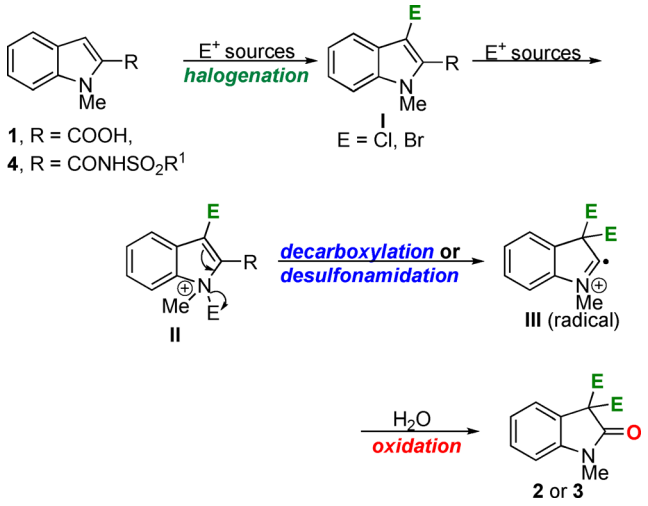
For the mechanistic study, we believed that halogenation of the C-3 position of the indole ring was the primary step in this transformation because we recovered a dominant amount of 3-haloindole inter-

Table 4. Substrate scope of **4**.



Entry[a]	R^1, R^2	E^+ sources	Product	Yield [%][d]
1	**4a**, H, 4-MeC_6H_4	DCDMH[b]	**2a**	70
2	**4b**, Me, 4-MeC_6H_4	DCDMH[b]	**2b**	90
3	**4c**, Me, Me	DCDMH[b]	**2b**	90
4	**4d**, Me, 4-$NO_2C_6H_4$	DCDMH[b]	**2b**	50
5	**4e**, Me, 4-$MeOC_6H_4$	DCDMH[b]	**2b**	80
6	**4f**, Bn, 4-MeC_6H_4	DCDMH[b]	**2d**	95
7	**4g**, Ph, 4-MeC_6H_4	DCDMH[b]	**2c**	40
8	**4h**, *i*-Pr, 4-MeC_6H_4	DCDMH[b]	**2f**	70
9	**4b**	NBS[c]	**3a**	90
10	**4d**	NBS[c]	**3a**	60
11	**4e**	NBS[c]	**3a**	30
12	**4c**	NBS[c]	**3a**	90
13	**4f**	NBS[c]	**3b**	93
14	**4g**	NBS[c]	**3e**	90

[a] All reactions were carried out at the 0.2 mmol scale in EtOAc (8 mL).
[b] 1.5 equivalents of DCDMH were used.
[c] 3.0 equivalents of NBS were used.
[d] Isolated yields.



Scheme 4. Proposed mechanism for the halogenation–decarboxylation/desulfonamidation–oxidation process.

mediate **I** in the presence of 1.0 equiv. of the E^+ source, such as NCS as discussed before. The nitrogen atom in substrate **1** or **4** could contribute to the halogenation to give an iminium ion intermediate **II** (Scheme 4). The cation intermediate **II** initiated the decarboxylative or desulfonamidative process to formed a radical intermediate **III**. Subsequent oxidation with a trace amount of water in the media furnished the desired quaternary 3,3-dihalo-2-oxindole products **2** or **3**. We also suspected that the decarboxylation process might be a radical process which might couple to the process of the second halogenation. This hypothesis was partially supported by several reported halodecarboxylation literature reports.[10]

In summary, we have successfully merged three procedures, including halogenation, decarboxylation/desulfonamidation, and oxidation into a single reaction. A novel one-pot reaction therefore has been discovered. This novel strategy allows for the rapid synthesis of diverse valuable 3,3-dichloro/bromo-2-oxindole compounds under mild conditions. An isolated yield of up to 98% of the desired 3,3-dichloro/bromo-2-oxindole products can be achieved using inexpensive and safe indole-2-carboxylic acid or indole-2-sulfonamide substrates in the presence of inexpensive halogen sources.

Experimental Section

General Procedure for Chlorination–Decarboxylation–Oxidation

To a solution of indole-2-carboxylic acid **1** (0.2 mmol, 1.0 equiv.) in ethyl acetate (8 mL) was added 1,3-dichloro-5,5-dimethylhydantoin (DCDMH, 59.1 mg, 0.3 mmol, 1.5 equiv.) in one portion. The reaction mixture was stirred at room temperature and was monitored by TLC. After removing the solvent under vacuum, the residue was purified by flash column chromatography (hexanes/EtOAc = 3:1) to yield the corresponding 3,3-dichloro-2-oxindole compounds **2**.

General Procedure for Bromination–Decarboxylation–Oxidation

To a solution of indole-2-carboxylic acid **1** (0.2 mmol, 1.0 equiv.) in chloroform (8 mL) was added *N*-bromosuccinimide (NBS, 106.8 mg, 0.6 mmol, 3.0 equiv.) in one portion. The reaction mixture was stirred at room temperature and was monitored by TLC. After removing the solvent under vacuum, the residue was purified by flash column chromatography (hexanes/EtOAc = 3:1) to yield the corresponding 3,3-dibromo-2-oxindole compounds **3**.

General Procedure for Chlorination–Desulfonamidation–Oxidation

To a solution of indole-2-sulfonamide **4** (0.2 mmol, 1.0 equiv.) in ethyl acetate (8 mL) was added 1,3-dichloro-5,5-dimethylhydantoin (DCDMH, 59.1 mg, 0.3 mmol, 1.5 equiv.) in one portion. The reaction mixture was stirred at room temperature and was monitored by TLC. After removing the solvent under vacuum, the residue was purified by flash column chromatography (hexanes/EtOAc = 3:1) to yield the corresponding 3,3-dichloro-2-oxindole compounds **2**.

General Procedure for Bromination–Desulfonamidation–Oxidation

To a solution of indole-2-sulfonamide **4** (0.2 mmol, 1.0 equiv.) in ethyl acetate (8 mL) was added *N*-bromosuccinimide (NBS, 106.8 mg, 0.6 mmol, 3.0 equiv.) in one portion. The reaction mixture was stirred at room temperature and was monitored by TLC. After removing the solvent under vacuum, the residue was purified by flash column chromatography (hexanes/EtOAc = 3:1) to yield the corresponding 3,3-dibromo-2-oxindole compounds **3**.

Acknowledgements

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[12] For the optimization of the bromination–decarboxylation–oxidation, please see the Supporting Information.