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Catalyst-Free Halogenation of α-Diazocarbonyl Compounds with *N*-Halosuccinimides: Synthesis of 3-Halooxindoles or Vinyl Halides

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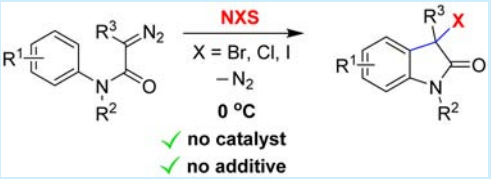
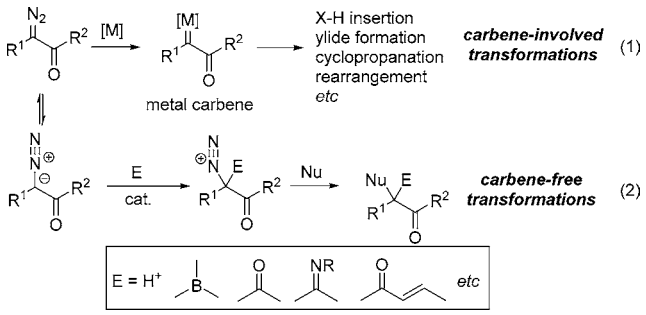
Supporting Information

ABSTRACT: A novel catalyst-free halogenative cyclization of *N*-aryl diazoamides with *N*-halosuccinimides (NXS) is reported for the synthesis of 3-halooxindoles through a carbene-free mechanism. *N*-Aryl diazoamides reacted with NXS under mild and catalyst-free conditions to afford the corresponding 3-halooxindoles in good yields. This transformation is proposed to proceed through diazonium ion formation followed by intramolecular Friedel−Crafts alkylation.



α-Diazocarbonyl compounds have been extensively used as metal carbene precursors in a variety of transition-metal-catalyzed transformations, such as X−H insertion (X = C, N, O, Si and S), ylide formation, cyclopropanation, rearrangement, etc. (Scheme 1, eq 1).[1] On the other hand, thanks to the

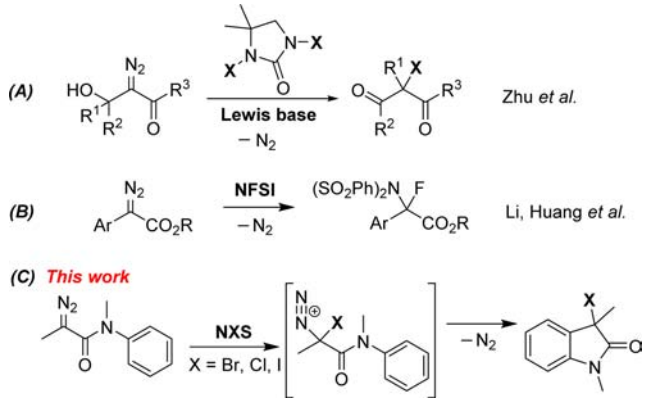
Scheme 1. General Reaction Pathways of α-Diazocarbonyl Compounds



electron-rich character of the diazo carbon from its resonance structure, α-diazocarbonyl compounds react readily with electron-deficient species through carbene-free mechanisms without the aid of transition metal catalysts.[2] The resulting diazonium ion intermediates can be further intercepted by electron-rich species in either an inter- or intramolecular manner to give different types of products. Within this context, proton sources such as carboxylic acids, alcohols or water,[3] organoboron compounds,[2c,4] carbonyl groups,[5] imines,[6] or α,β-unsaturated carbonyl compounds[7] have been extensively utilized as electron-deficient sources for such types of transformations (Scheme 1, eq 2). Given these advantages, the introduction of new types of electrophilic-deficient species that will allow the establishment of novel carbene-free transformations from α-diazocarbonyl compounds is still highly desirable.

N-Halosuccinimides (NXS) have been extensively used as electrophilic halogenating agents in organic synthesis. However, there are no examples where NXS has been used as an electron-deficient species to react with α-diazocarbonyl compounds via carbene-free pathways.[8] In 2014, Zhu and co-workers utilized relatively active 1,3-dihalo-5,5-dimethylhydantoin as the halogenating agents to react with α-diazocarbonyl compounds for a sequential halogenation/semipinacol rearrangement under Lewis base catalysis (Scheme 2A).[9] Very recently, Li, Huang

Scheme 2. Reaction Pathways for NXS-Involved Transformations of α-Diazocarbonyl Compounds via Carbene-Free Transformations



and co-workers developed a *gem*-aminofluorination of diazocarbonyl compounds with *N*-fluorobenzenesulfonimide (NFSI) under catalyst-free conditions (Scheme 2B).[10] As part of our ongoing research interest in exploring novel transformations with an *N*-aryl diazoamide,[11] we envisioned that NXS would react with the *N*-aryl diazoamide to give the corresponding

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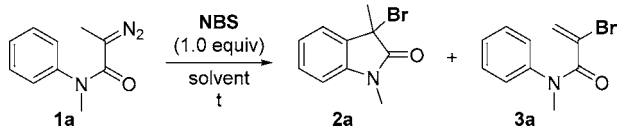
diazonium ion, which would further undergo intramolecular Friedel–Crafts alkylation with concomitant extrusion of N_2 gas to afford 3-halooxindoles (Scheme 2C). We hoped that the intramolecular Friedel–Crafts alkylation pathway would provide a favorable driving force for the proposed transformation to proceed under mild and catalyst-free conditions. The produced 3-halooxindoles are important building blocks for constructing 3,3-disubstituted oxindoles, which are common structural motifs found in a number of natural products and pharmaceuticals.[12,13] Therefore, the current method would provide a convenient and efficient alternative for rapidly accessing a variety of 3-halooxindole moieties.

We initiated our exploration by investigating the reaction of *N*-methyl-*N*-phenyl diazoacetamide (**1a**) with *N*-bromosuccinimide (NBS). Without the addition of any catalysts or additives, a clear gas release was observed when a solution of **1a** in CH_2Cl_2 was added dropwise to a solution of NBS in CH_2Cl_2. After completion of the addition, 3-bromooxindole **2a** and the *β*-H elimination product **3a** were obtained in 92% combined yield and an 88:12 ratio (Table 1, entry 1). In order to improve

Table 1. Optimization of the Reaction Conditions[a]



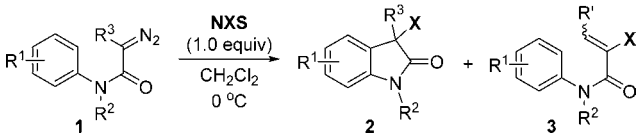
entry	solvent	*t* (°C)	yield of **2a** (%)[b]	ratio (**2a**:**3a**)[c]
1	CH_2Cl_2	25	81	88:12
2	toluene	25	39	48:52
3	Et_2O	25	57	67:33
4	THF	25	40	50:50
5	EtOH	25	37	42:58
6	EtOAc	25	59	75:25
7	$CHCl_3$	25	77	85:15
8	CH_2Cl_2	0	88	93:7

[a]Reaction conditions: **1a** (0.1 mmol) in 0.5 mL of the corresponding solvent was added to a mixture of NBS (0.1 mmol) in 0.5 mL of the corresponding solvent in a dropwise manner. [b]Isolated yield of **2a**. [c]Determined by crude ^{1}H NMR.

the chemoselectivity of the desired Friedel–Crafts alkylation product over the undesired *β*–H elimination product, a series of condition optimizations was conducted. Among different solvents being tested, CH_2Cl_2 gave the highest chemoselectivity (Table 1, entries 2–7). With CH_2Cl_2 as the solvent, reducing the reaction temperature to 0 °C improved chemoselectivity to 93:7 while the yield remained unaffected (Table 1, entry 8). Further reducing the reaction temperature to −10 °C led to a very slow decomposition of **1a** as observed by the reduced gas evolution from the reaction mixture.

With the readily obtained optimization conditions in hand, we further investigated the substrate scope for this catalyst-free halogenative Friedel–Crafts reaction. *N*-Chlorosuccinimide (NCS) and *N*-iodosuccinimide (NIS) both reacted with **1a** smoothly to afford the corresponding 3-halooxindoles in excellent yields with excellent chemoselectivities (>95:5) (Table 2, entries 2 and 3). Utilizing NBS as the halogenating agent, various substituted diazoamides were then investigated. Diazoamides containing both electron-donating and -withdrawing groups on the aryl ring generally gave the desired cyclizing products in high yields. The electron propensity of the

Table 2. Substrate Scope[a]



entry	NXS	**1**	R^1	R^2	R^3	yield of **2** (%)[b]	ratio (**2**:**3**)[c]
1	NBS	**1a**	H	Me	Me	88	93:7
2	NCS	**1a**	H	Me	Me	85	>95:5
3	NIS	**1a**	H	Me	Me	96	>95:5
4	NBS	**1b**	*p*-Me	Me	Me	92	>95:5
5	NBS	**1c**	*p*-MeO	Me	Me	85	94:6
6	NBS	**1d**	*p*-F	Me	Me	69	74:26
7	NBS	**1e**	*p*-Cl	Me	Me	63	67:33
8	NBS	**1f**	*p*-Br	Me	Me	60	64:36
9	NBS	**1g**	*o*-Me	Me	Me	60	75:25
10[d]	NBS	**1h**	*o*-Br	Me	Me	95	<5:95
11[d]	NBS	**1i**	2,6-Cl_2	Me	Me	92	<5:95
12	NBS	**1j**	*m*-Me	Me	Me	72	>95:5
13	NBS	**1k**	H	Me	Et	89	>95:5
14	NBS	**1l**	H	Me	Bn	86	>95:5
15	NBS	**1m**	H	Bn	Me	81	90:10

[a]Reaction conditions: **1a** (0.1 mmol) dissolved in 1.0 mL of CH_2Cl_2 was added to a stirred solution of NXS (0.2 mmol) in 1.0 mL of CH_2Cl_2 in a dropwise manner. [b]Isolated yield of **2**. [c]Detected by crude ^{1}H NMR. [d]Isolated yield of **3**.

substituent groups had a profound effect on the chemoselectivity between the Friedel–Craft alkylation product **2** and the *β*-H elimination product **3**. For substrates bearing *para*-substituents, electron-donating groups provided high chemoselectivity (up to >95:5) while electron-withdrawing ones gave only moderate chemoselectivity (Table 2, entries 4 and 5 vs entries 6–8). An *ortho*-methyl substituted substrate (**1g**) gave poor chemoselectivity despite its electron-donating nature, probably owing to its steric effect for the alkylation step (Table 2, entry 9). When an *ortho*-bromo substituted substrate (**1h**) was used, the chemoselectivity was completely switched to *β*-H elimination product **3h** (Table 2, entry 10). A 2,6-dichloro substituted substrate (**1i**) also gave the corresponding vinyl bromide product in good yield (Table 2, entry 11). With a *meta*-methyl substituted substrate (**1j**), the cyclization occurred exclusively at the *para*-position of the methyl group, affording the desired product in 72% yield with excellent chemoselectivity (Table 2, entry 12). Diazoamides with ethyl or benzyl substituents at the diazo carbon also gave corresponding 3-bromooxindoles in high yields with excellent chemoselectivities (Table 2, entries 13–14). However, the substrate bearing a phenyl substituent at the diazo carbon failed to give the desired cyclization product. *N*-Benzyl protected diazoamide (**1m**) also yielded the desired 3-bromooxindole in good yield with high chemoselectivity (Table 2, entry 15). With tetrahydroquinoline-derived diazoamide (**1n**) as the substrate, the corresponding tricyclic 3-bromooxindole product (**2n**) and the vinyl bromide product (**3n**) were obtained in high yields with a 1:1 ratio (Scheme 3).

We further tried to apply the current halogenating/Friedel–Craft alkylation strategy to the synthesis of 3-fluorooxindoles. By employing selectfluor as the fluorinating reagent under standard reaction conditions, the desired 3-fluorooxindole product was not observed. However, with the addition of 1 equiv of K_2CO_3 and MeCN as the solvent, the corresponding

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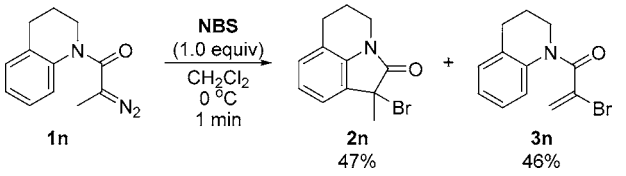
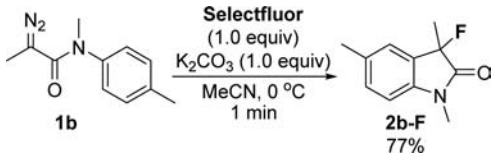
Scheme 3. Bromination of Tetrahydroquinoline-Derived Diazoamide 1n



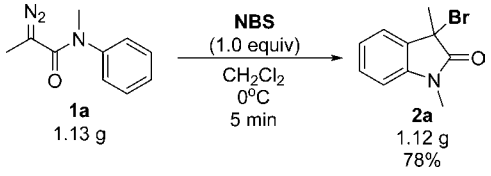
3-fluorooxindole product **2b-F** was afforded exclusively in 77% yield (Scheme 4).

Scheme 4. Fluorination of Diazocarbonyl Compound 1b



To demonstrate the synthetic efficiency of this transformation, we explored a gram scale synthesis of 3-bromooxindole **2a**. The reaction was complete after the slow addition of diazoamide **1a** over 5 min. When the reaction was finished, simply washing the reaction mixture with water and further recrystallization from Et_2O afforded **2a** in 78% yield (Scheme 5).

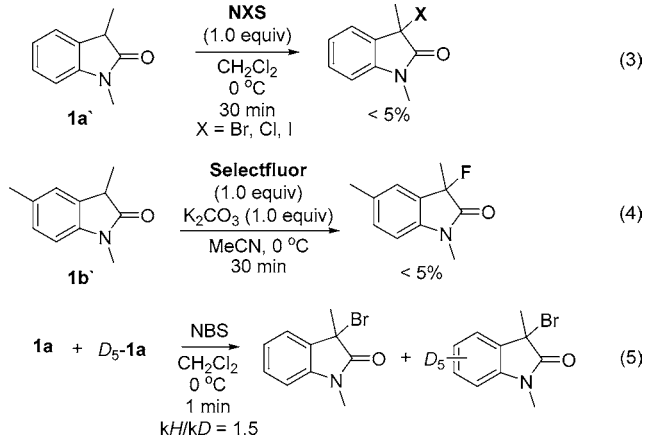
Scheme 5. Gram-Scale Synthesis of 2a



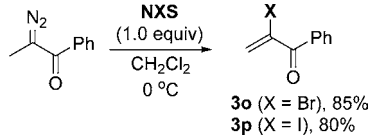
After the completion of the NBS-involved transformation, the C−H insertion product was not detected. Nonetheless, to preclude the possibility of a rapid transformation involving a stepwise C−H insertion followed by direct halogenation. Several control experiments were conducted. Under standard reaction conditions, the C−H insertion product **1a′** from **1a** gave no 3-halooxindole products (Scheme 6, eq 3). For the fluorination reaction, since 1 equiv of K_2CO_3 was required, it was more likely to undergo a stepwise pathway. However, subjecting oxindole **1b′** to the standard reaction conditions also gave no desired product (Scheme 6, eq 4). These results partially indicated that this transformation proceeded through a halogenation/Friedel−Craft type alkylation pathway. To further gain some insight into the mechanism of this transformation, an intermolecular kinetic isotope effect (KIE) experiment was conducted. The KIE (k_H/k_D = 1.5) indicated that the C−H bond cleavage should not be the rate-determining step (Scheme 6, eq 5). This transformation proceeded smoothly in the presence of 2 equiv of TEMPO, indicating that a radical process was unlikely involved.

The formation of β-H elimination products inspired us to develop a practical method for the synthesis of vinyl halides. For example, under the mild and catalyst-free conditions, 2-diazo-1-phenylpropan-1-one **4** was smoothly converted into the vinyl bromide or vinyl iodide in high yields (Scheme 7). Vinyl bromides have generally been utilized as useful reagents in a

Scheme 6. Control Experiments and Intermolecular KIE Experiment



Scheme 7. Synthesis of Vinyl Halide Compounds



number of cross-coupling reactions.[14] Therefore, the current method offers a very convenient and easily executed method for the synthesis of such compounds.

In summary, we have developed a highly convenient and efficient method for the synthesis of 3-halooxindoles starting from *N*-aryl diazoamides under catalyst-free conditions. This transformation is proposed to proceed through the formation of a halogenated diazonium ion from NXS and *N*-aryl diazoamide via a carbene-free pathway. The generated diazonium ion intermediate further underwent intramolecular Friedel−Craft alkylation with concomitant extrusion of N_2 gas to give a variety of 3-halooxindoles. Also, when starting from suitable α-diazocarbonyl substrates, the halogenated diazonium ion intermediate could also undergo efficient β-H elimination to produce vinyl halide products in high yields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01346.

Experimental procedures and full spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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