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Direct N-*sec*-Alkylation of Amides by Reaction of α-Halohydroxamates and Sulfonylindoles: An Approach to 3-Indolyl Methanamines

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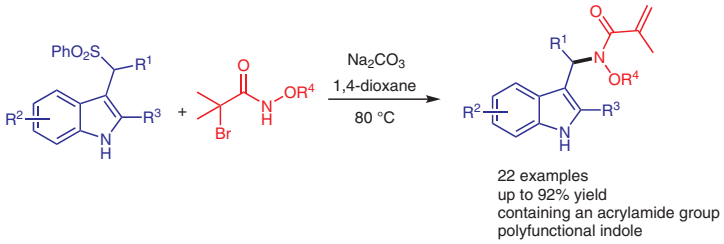

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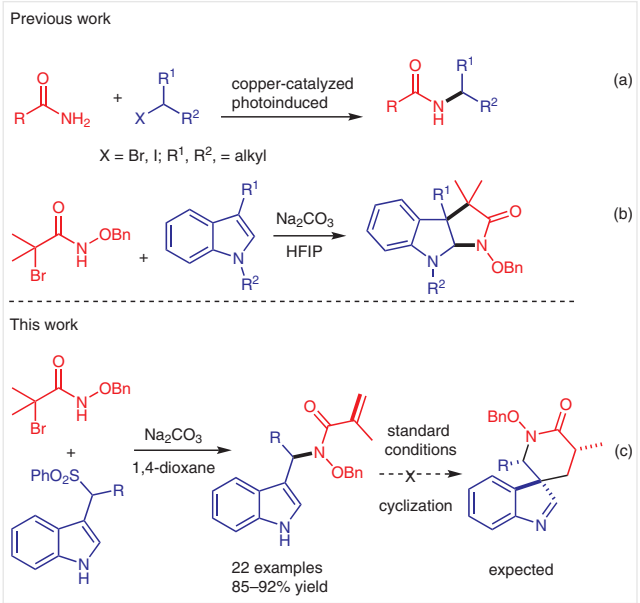
Abstract A catalyst-free, base-mediated N-*sec*-alkylation of amides by reaction of sulfonylindoles and α-halohydroxamates has been developed. The N-*sec*-alkylation of amides reaction is based on an intermolecular nucleophilic addition of vinylogous imine with *N*-(benzyloxy)meth-acrylamide/azaoxyallyl cations formed in situ and represents a simple way to give polyfunctionalized 3-indolyl methanamines in good to excellent yields.

Key words 3-indolyl methanamines, azaoxyallyl cations, vinylogous imine, sulfonylindoles, α-halohydroxamates

3-Indolyl methanamine derivatives are widely found in many natural and unnatural products with unique biological activities.[1] They are also important building blocks for constructing complex molecules.[1] Thus, the synthesis of 3-indolyl methanamine derivatives has attracted attention during the past years.[2] The most prominent approach to 3-indolyl methanamine relies on the Lewis or Brønsted acid catalyzed Friedel–Crafts reaction of imines with indoles.[3] However, alkyl imine is usually ineffective for this Friedel–Crafts reaction because it can tautomerize to the corresponding enamine.[3] Frequently, the competing bisindole by-product limits the versatility of these strategies.[3] Therefore, the development of an efficient method to synthesize 3-indolyl methanamines is of importance.

During recent years, metal-catalyzed methods for C–N bond formation, such as Buchwald–Hartwig couplings,[4] olefin hydroamination and reductive amination,[5] have been fully developed. However, there are few reports of N-*sec*-alkylation of amides with electrophiles. The N-alkylation reaction (formation of a Csp^3–N bond) between an amide and an alkyl halide is a classic method for providing functional amides through a substitution process (S_N2). Although primary halides could provide amides in good yields, the yields of the desired amides are very poor when inactivated secondary halides are used as substrate.[6] In 2014, a breakthrough study was reported by Peters, Fu and co-workers, in which a copper-catalyzed coupling of amides with secondary alkyl bromides and iodides provided N-*sec*-alkylation amides in good yield (Scheme 1a).[7] Therefore, the development of an efficient method to give N-*sec*-alkylation of amide is a worthwhile objective.[7]



Scheme 1 Reaction of amide with alkyl halide or indole derivatives

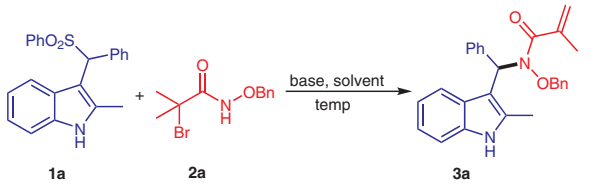
As a versatile 1,3-dipole, the azaoxyallyl cation generated in situ from α-bromohydroxamate has been widely applied to synthesize various heterocycles.[8,9] Jeffrey,[8a] Wu,[8b] and Liao[8c] realized [3+2] cycloaddition reactions between

electron-rich 3-substituted indoles and azaoxyallyl cations to construct pyrroloindolines, respectively (Scheme 1b). Jeffrey's group developed aza-[4+3] annulation of azaoxyallyl cation intermediates with electron-rich dienes for synthesizing seven-membered heterocycles.[9a–d] Chen realized [3+1] or [3+2] cycloaddition reactions between azaoxyallyl cations and electron-rich sulfur ylides for the synthesis of β-lactams and γ-lactams.[9f] Wu and Xia also described a base-mediated [3+3] cycloaddition reaction of azaoxyallyl cations with electron-rich isoquinoline N-oxides.[9g] Very recently, Huang and Lin reported that a new [3+3] cycloaddition reaction between azaoxyallyl cations and electron-rich 2-alkenylindoles provided tetrahydro-β-carbolinones in good yields.[9h]

Cycloaddition reactions between the electron-deficient reactants and azaoxyallyl cations have also been reported during recent years. In 2016, the groups of Lin[10a] and Jeffrey,[10b] respectively, reported a [3+2] cycloaddition reaction of the electron-deficient carbonyl reactant with azaoxyallyl cations. In 2018, the group of Jiang and Zhu reported a palladium-catalyzed coupling reaction between N-tosylhydrazones and electron-deficient benzo-1,2-quinones leading to the formation of two C–O bonds on the carbenic carbon.[10c] The electron-deficient vinylogous imines are usually generated in situ from sulfonylindoles by leaving the sulfonyl group in situ under basic conditions, and has intriguing potential for organic synthesis.[11] We envisioned that a cycloaddition reaction of vinylogous imines with azaoxyallyl cations might occur to provide 3,3-spiroindolines (for a possible mechanism, see Scheme 4 below). To our disappointment, the reaction of α-bromohydroxamates with sulfonylindoles stopped at the aza-Michael step, and only 3-indolyl methanamines were obtained in the course of the experiment (Scheme 1c). The development of new cyclization strategies making use of the 3-indolyl methanamines is ongoing in our laboratory. To our knowledge, the azaoxyallyl cations being employed as a nucleophile reagent has not been reported to date. Herein, we report a metal-free N-alkylation reaction between α-bromohydroxamates and sulfonylindoles to synthesize 3-indolyl methanamines bearing an acrylamide group, which could be used for diverse transformation in organic synthesis.[12]

At the outset of this project, a model reaction of 2-methyl substituted sulfonylindole **1a** (1.0 equiv) with α-bromohydroxamate **2a** (1.5 equiv) at room temperature was initially studied under Föhlisch's,[13] Jeffrey's,[8a] and Wu's[8b] conditions {[Et_3N, trifluoroethanol (TFE)] or [Na_2CO_3, hexafluoroisopropanol (HFIP)]}. Only the 3-indolyl methanamine **3a** containing an acrylamide group was obtained in very low yield (Table 1, entries 1 and 2, <15% yield), and the pyrroloindoline products reported in the previous works[8] were not observed. Increasing the reaction temperature from 25 to 60 °C, using Na_2CO_3 as base in TFE or HFIP, the 3-indolyl methanamine **3a** was obtained in 20%

Table 1 Optimization of Reaction Conditions[a]



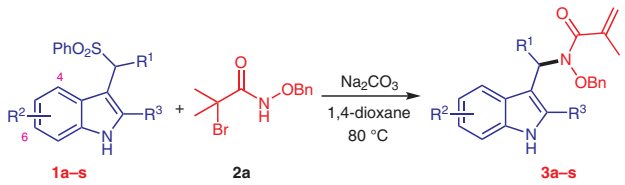
Entry	Base	Solvent	*T* (°C)	Yield (%)[b]
1	Et_3N	TFE	25	10
2	Na_2CO_3	HFIP	25	15
3	Na_2CO_3	TFE	60	20
4	Na_2CO_3	HFIP	60	26
5	Na_2CO_3	isopropanol	60	35
6	Na_2CO_3	MeCN	60	41
7	Na_2CO_3	toluene	60	47
8	Na_2CO_3	1,4-dioxane	60	62
9	K_2CO_3	1,4-dioxane	60	55
10	Cs_2CO_3	1,4-dioxane	60	46
11	NaO^{t}Bu	1,4-dioxane	60	27
12	Na_2CO_3	1,4-dioxane	80	91

[a] Reaction conditions: **1a** (0.1 mmol, 1.0 equiv), **2a** (0.15 mmol, 1.5 equiv), base (0.3 mmol, 3.0 equiv) in solvent (1 mL) for 8 h.
[b] Isolated yield.

and 26% yields, respectively (entries 3 and 4). Better results (35–62% yield of **3a**) were obtained when the solvent was changed to isopropanol, MeCN, toluene, or 1,4-dioxane (entries 5–8). The best choice was 1,4-dioxane (62% yield, entry 8). When the base Na_2CO_3 was replaced with K_2CO_3, Cs_2CO_3 or NaO^{t}Bu in 1,4-dioxane solvent, no better results were obtained (entries 9–11). To our delight, the best result (91% yield of **3a**) was obtained by increasing the temperature from 60 to 80 °C for 8 hours (entry 12).

With the optimized conditions in hand, a range of sulfonylindoles **1** were examined. The results are summarized in Table 2. Generally, in these 2-methyl substituted sulfonylindoles **1a–l**, R^1 could be different substituents with aryl and alkyl groups (entries 1–12).[14] Those substrates with electron-withdrawing (CN, NO_2) and electron-donating (MeO) group at the 4-position of the substituted phenyl ring (R^1) had no effect on this transformation, and the products **3b–d** were obtained in good to excellent yields (89–90%, entries 2–4). Both *ortho*- and *meta*-substituted phenyl (R^1) were well tolerated to give the products **3e–i** in good yields (87–92% yield, entries 5–9). Notably, substrates with heteroaromatic groups (R^1), such as 2-thienyl and 3-pyridyl, could also provide the desired products **3j**, **3k** in 87% and 90% yields (entries 10 and 11). Fortunately, alkyl substituted (R^1) sulfonylindole was also tolerated, giving **3l** in satisfactory yield (entry 12). In addition, the R^2 group with various electronic nature (Cl, Br, Me or MeO) at different positions

Table 2 Reactions of Sulfonylindoles with α-Bromohydroxamate **2a**[a]



Entry	R^1	R^2	R^3	3	Yield (%)[b]
1	Ph	H	Me	**3a**	91
2	4-CNC_6H_4	H	Me	**3b**	90
3	4-$NO_2C_6H_4$	H	Me	**3c**	89
4	4-$OMeC_6H_4$	H	Me	**3d**	90
5	3-ClC_6H_4	H	Me	**3e**	89
6	3-MeC_6H_4	H	Me	**3f**	92
7	2-ClC_6H_4	H	Me	**3g**	92
8	2-CNC_6H_4	H	Me	**3h**	90
9	3,4,5-$(OMe)_3$ C_6H_2	H	Me	**3i**	87
10	2-thienyl	H	Me	**3j**	87
11	3-pyridyl	H	Me	**3k**	90
12	propyl	H	Me	**3l**	87
13	Ph	4-Cl	H	**3m**	85
14	Ph	5-Br	H	**3n**	86
15	Ph	6-Cl	H	**3o**	91
16	Ph	7-Br	H	**3p**	86
17	Ph	7-Me	H	**3q**	86
18	Ph	4-Br	Me	**3r**	91
19	Ph	5-OMe	Me	**3s**	89

[a] Reaction conditions: **1** (0.1 mmol, 1.0 equiv), **2a** (0.15 mmol, 1.5 equiv), Na_2CO_3 (0.3 mmol, 3.0 equiv) in 1, 4-dioxane (1 mL) at 80 °C for 8–12 h.
[b] Isolated yield.

(4, 5, 6 and 7) of the indole core had no apparent effect on the yield of **3m–s** (85–91% yields, entries 13–19), irrespective of R^3 being a hydrogen or methyl group. The relative configuration of **3g** was determined unambiguously by X-ray crystallography (Figure 1, see Supporting Information).[15]

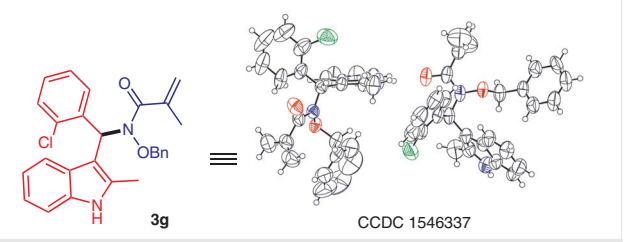
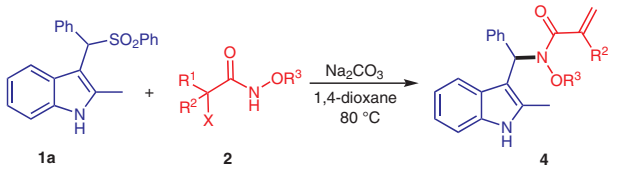
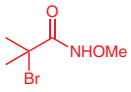
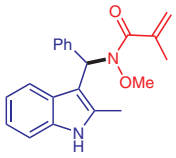
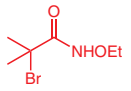
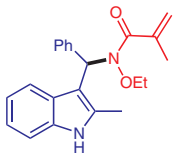
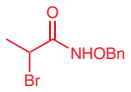
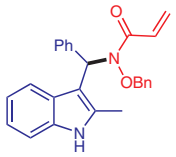


Figure 1 Relative configuration of compound **3g**

We explored the scope of the reaction with α-halohydroxamates **2** (Table 3). Replacing the benzyl group with methyl or ethyl groups (**2b**, **2c**), the desired 3-indolyl methanamines **4a** and **4b** were delivered in 89% and 88% yield, respectively. The α-bromohydroxamate with a methyl group (**2d**) also provided **4c** in 90% yield.

Table 3 Substrate Scope of the Reaction with α-Halohydroxamate **2**[a]

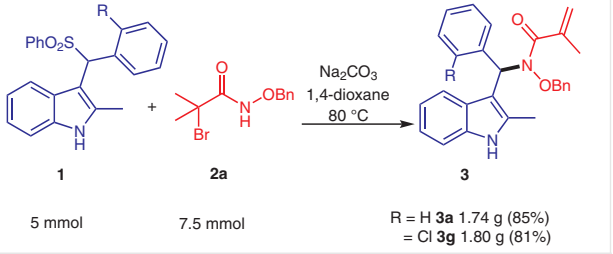


α-Halohydroxamate **2**	Product	Yield (%)[b]
		
2b	**4a**	89
		
2c	**4b**	88
		
2d	**4c**	90

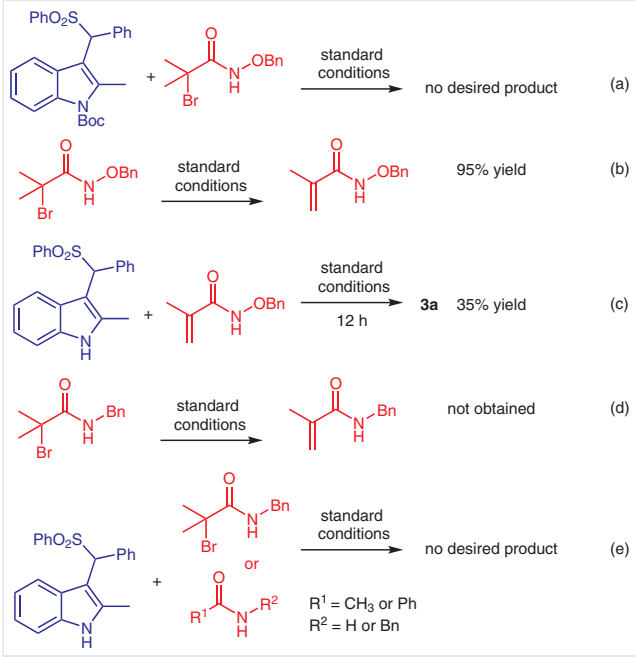
[a] Reaction conditions: sulfonylindole **1a** (0.1 mmol, 1.0 equiv), α-halohydroxamate **2** (0.15 mmol, 1.5 equiv), Na_2CO_3 (0.3 mmol, 3.0 equiv) in 1,4-dioxane (1 mL) at 80 °C for 8–12 h.
[b] Isolated yield.

This reaction could be carried out on a multigram scale. The product **3a** (1.74 g) and **3g** (1.80 g) were afforded in 85% and 81% yield, respectively (Scheme 2, see the Supporting Information for details).

To gain insight into the mechanism, a number of control experiments were carried out (Scheme 3). No desired product was detected when the N-Boc protected arenesulfonylindole was employed under the standard conditions (Scheme 3a), which suggested that the reaction mechanism is not an S_N2 substitution process. Although the α-halohydroxamates can be transformed into the corresponding product *N*-(benzyloxy)methacrylamide in 95% yield under the standard conditions (Scheme 3b), the aza-Michael addition reaction between the *N*-(benzyloxy)methacrylamide



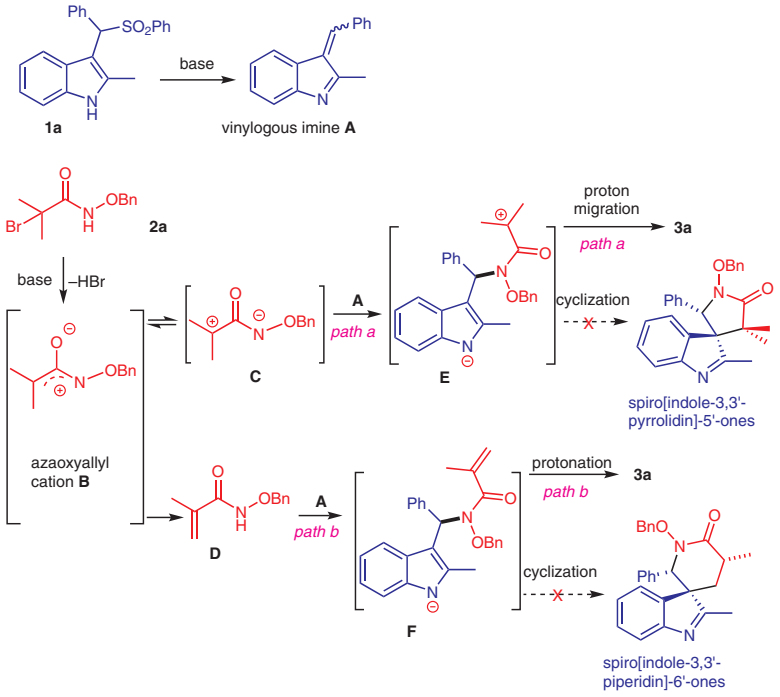
Scheme 2 Gram-scale experiments



Scheme 3 Control experiments

and arenesulfonylindole **1a** resulted in the 3-indolyl methanamine **3a** only in 35% yield under the standard conditions (Scheme 3c). The α-bromohydroxamate with an electron-donating group (-OBn) replacing a benzyl (-Bn) group failed to transform the corresponding *N*-benzylmethacrylamide (Scheme 3d) and failed to react with the arenesulfonylindole (Scheme 3e). Using acetamide, *N*-methylacetamide, benzamide, and N-methylbenzamide as substrates, it was found that they failed to react with α-halohydroxamates under the standard conditions (Scheme 3e). The reactions (Scheme 3b–e) indicate that the electron-donating group (-OBn) plays a key role in realizing this aza-Michael addition reaction.

Based on the previous work,[8,11] a plausible mechanism is proposed as illustrated in Scheme 4. The sulfonyl group of **1a** acts as a leaving group under basic conditions, which enables the formation of vinylogous imines intermediates **A**. The azaoxyallyl cation **B** is formed from α-bromohydroxamate **2a** under the basic conditions. Subsequently, from **B**, two pathways are possible: (a) a zwitterionic intermediate **C**, which is generated from **B**, reacts with vinylogous imines



Scheme 4 Possible mechanism for the cycloaddition reaction.

A to give the intermediate **E** through an aza-Michael addition process, subsequently affording **3a** by a proton migration. (b) An aza-Michael addition reaction between the *N*-(benzyloxy)methacrylamide **D**, formed from azaoxyallyl cation **B** in situ, and vinylogous imines **A** occurs to give intermediate **F**, affording **3a** through a protonation process. Unfortunately, the cyclization of intermediate **E** or **F** to provide 3,3-spiroindolines such as spiro[indole-3,3′-pyrrolidin]-5′-ones or spiro[indole-3,3′-piperidin]-6′-ones did not occur under the standard conditions. Development of new cyclization strategies making use of these 3-indolyl methanamines is ongoing in our laboratory.

In conclusion, a new procedure involving an N-*sec*-alkylation of amides using sulfonylindoles and α-halohydroxamates has been successfully developed. This protocol paves the way to synthesize 3-indolyl methanamines bearing an acrylamide group, which could be transformed into a diverse array of products via different chemoselective processes[12] in good to excellent yields. We believe that this N-*sec*-alkylation of amides will be widely used in organic synthesis.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611754.

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(14) **Typical procedure and characterization data for 3a:** To a solution of sulfonylindole **1a** (0.1 mmol) in 1,4-dioxane (1.0 mL) was added α-halohydroxamates **2a** (0.15 mmol) and Na_2CO_3 (0.3 mmol). The reaction mixture was stirred at 80 °C until the starting material sulfonylindole was consumed (monitored by TLC). After cooling to room temperature, the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel [flash column chromatography eluent, petroleum ether/ethyl acetate (6:1–4:1, v/v)] to give the pure product **3a** (37 mg, 91% yield) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.34 (m, 3 H), 7.30–7.27 (m, 3 H), 7.23–7.21 (m, 1 H), 7.16–7.13 (m, 3 H), 7.11–7.08 (m, 1 H), 6.96–6.92 (m, 1 H), 6.77 (d, *J* = 6.94 Hz, 2 H), 5.48 (s, 1 H), 5.35 (s, 1 H), 4.95 (s, 1 H), 4.59 (d, *J* = 8.68 Hz, 1 H), 3.96 (d, *J* = 8.70 Hz, 1 H), 2.20 (s, 3 H), 2.06 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171. 4, 141.1, 139.9, 135.1, 134.9, 134.4, 129.5, 129.3, 128.6, 128.5, 128.4, 128.3, 128.1, 127.0, 126.8, 121.3, 119.8, 119.7, 117.3, 110.3, 108.7, 78.6, 57.4, 20.4, 12.5. HRMS: *m*/*z* [M+H]$^+$ calcd for $C_{27}H_{26}N_2O_2$: 410.2013; found: 410.2016.

(15) CCDC 1546337 (**3g**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.