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Silver(I)-mediated oxidation/cyclization of acrylamides with alkyl trifluoroborates

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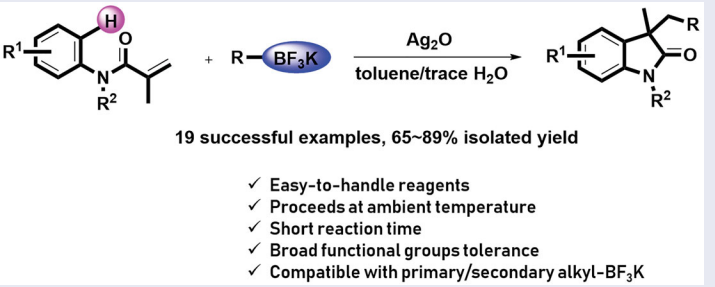
ABSTRACT

A mild silver-mediated oxidative cyclization of acrylamides has been developed by using alkyl trifluoroborates as radical precursors. It proceeds through a tandem radical addition/cyclization process, in which two new carbon-carbon bonds were formed. This protocol allows reliable and practical access to build the skeleton of 3,3-disubstituted oxindoles in moderate yields, the readily available starting reagents, broad substrate scope and mild reaction conditions are the characteristic features of this protocol.

GRAPHICAL ABSTRACT



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3,3-disubstituted oxindole;
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Introduction

3,3-Disubstituted oxindoles, privileged structural motifs, are attractive targets in various bioactive natural products and pharmacological componds.[1] Specifically, the difference in substitutes at the 3-position significantly affects biological activities. Therefore, numerous strategies have been devised to create the skeleton structure of 3,3-disubstituted oxindoles. After an in-depth study of their synthetic methods, the tandem radical addition/cyclization of *N*-arylacrylamide with various radical precursors is the principal strategy for constructing these types of heterocycles.[2] Common mechanisms

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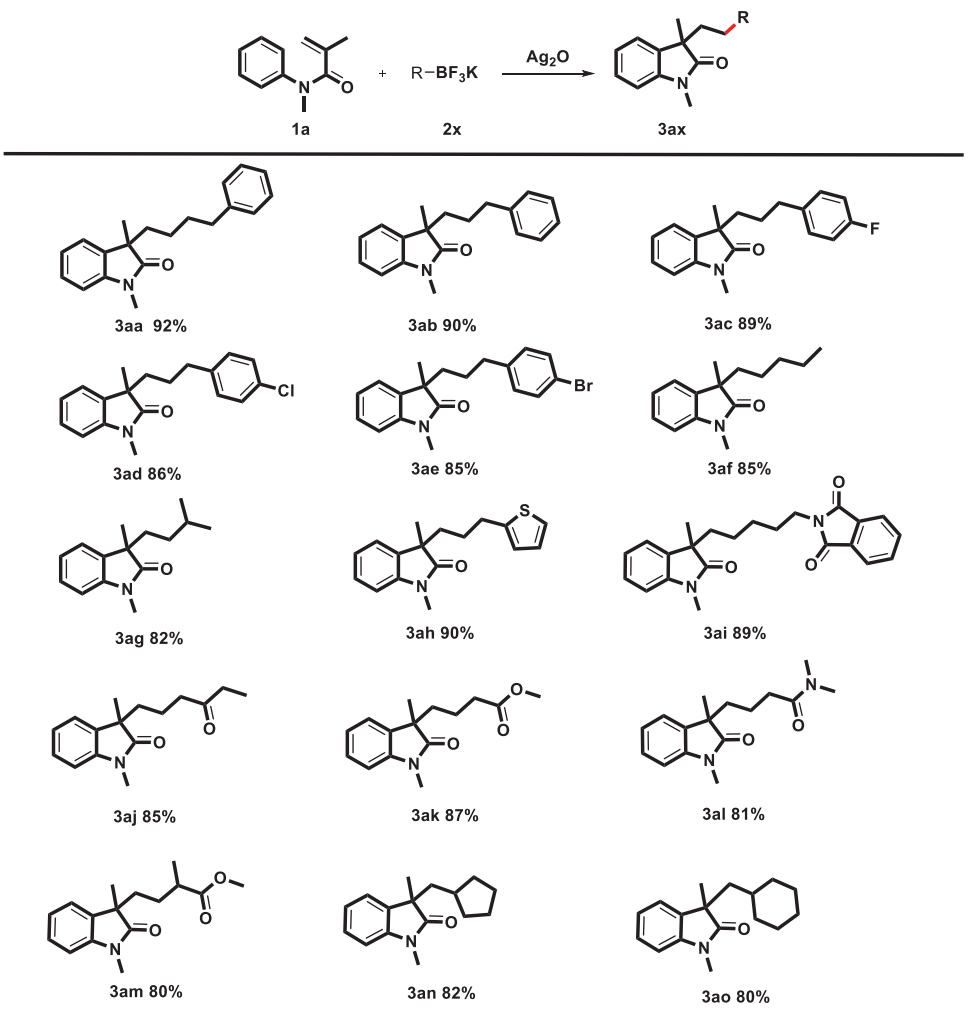
involved the intramolecular addition of radicals to the unsaturated bond, followed by the intramolecular radical cyclization to afford the skeleton. Among these strategies, various compounds can be converted to their corresponding alkyl radicals under specific conditions. Liu et al. summarized an organocatalytic method using [bis(pivaloyloxy)iodo]benzene as the alkyl precursor with calcium carbonate.[3] Zhu et al. provided efficient access to alkyl radicals using aliphatic carboxylic acids under visible light photocatalysis conditions.[4] Cheng group reported a catalytic reaction system of $FeCl_2$,[5a] moreover, Liu and coworkers developed a similar CuBr system[5b] using di-tert-butyl peroxide (DTBP) and dicumyl peroxide (DCP) as methyl radical precursor respectively. And then, Liu group invented a strategy using catalytic amounts of $IrCl_3$ with DTBP or DCP as radical initiators. Under this condition, phenylethane and cumene can be transformed into their corresponding alkyl radicals.[6] Almost at the same time, Duan and his coworkers found another way making use of Cu_2O together with tert-butyl peroxybenzoate (TBPB) to obtain the benzylic radical.[7] Compared with active C-H bonds in the benzyl position, Liu group developed an efficient and convenient Cu_2O catalyzed path using simple alkanes as the starting materials.[8] For the first time, Li and coworkers provided a $FeCl_3$ catalyzed system to various ethers that can be served as alkyl radicals.[9] Furthermore, Duan and Guo group explored using stoichiometric amounts of tert-butyl hydroperoxide to obtain α-hydroxycarbon radicals and then to complete the cyclization reaction.[10] 1,3-dicarbonyl compounds can be transformed into their corresponding radicals by $AgNO_3$ and potassium persulfate, which was invented by Duan group.[11] The above methods have some disadvantages, such as long reaction time and high reaction temperatures. However, alkyl-boron compounds for this synthesis have not been established. Herein, we report a novel tandem oxidative cyclization reaction of acrylamides with alkyl trifluoroborates (Figure 1). This approach would provide a new entry to more valuable high-efficiency 3,3-disubstituted oxindoles.

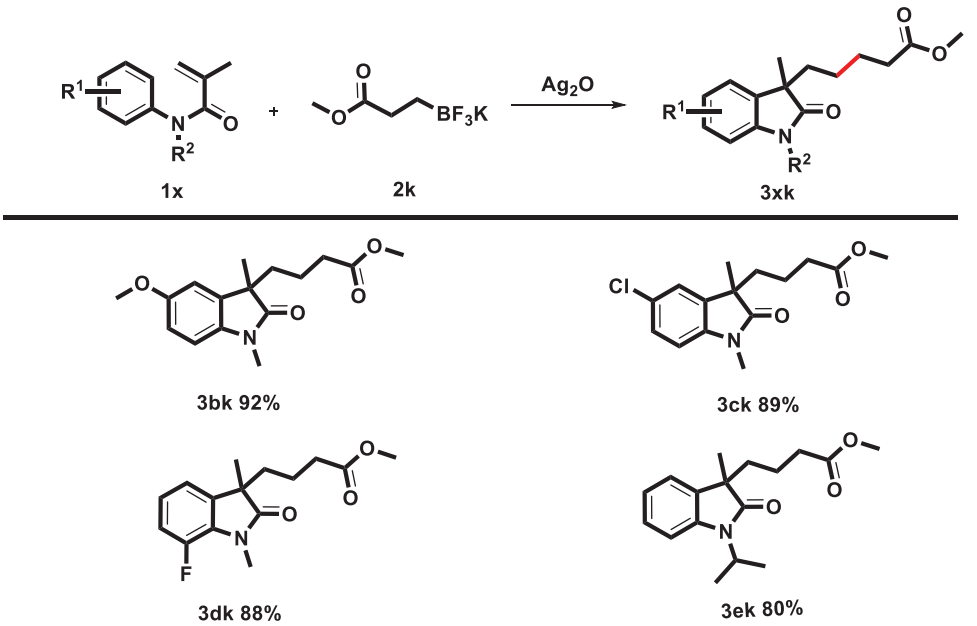
Results and discussion

Based on our earlier studies, we devised and developed a rapid and highly efficient method for radical formation using potassium alkyl trifluoroborates as a radical precursor, that conducts under relatively mild conditions using silver(I) as the oxidant.[12] The generated alkyl radicals can be trapped immediately with TEMPO, providing critical evidence for the existence of the radical intermediate. For making this method useful, we must find its application. Currently, the successful application of this new radical formation strategy is in the boron-selective oxidative cross-coupling reaction[13] using arylboronic acids and alkyl trifluoroborates as coupling partners. Encouraged by the preliminary results, we explored meaningful application from the synthetic point. Arylisonitrile is another well-established radical acceptor, which is isoelectronic with carbon monoxide, and they can undergo insertion reaction to provide nitrogen-containing heterocycles that are important substrate present in many natural products with varying biological activities.[14] Our ongoing interest in the construction of diversely functionalized oxindoles prompted us to develop an effective method for these valuable heterocycles.



Scheme 1. Scope of potassium alkyl trifluoroborates. [a]Reaction conditions: the potassium alkyltrifluoroborate **2k** (0.2 mmol, 1.0 equiv.), Ag_2O (0.2 mmol, 1.0 equiv.) and acrylamide **1x** (0.21 mmol, 1.05 equiv.), toluene (2.0 mL) and distilled water (40 μL), stirred at room temperature for 10 min.

With the above consideration in mind, we embarked on our investigation with *N*-methyl-*N*-phenyl-2-methylacrylamide **1a** and phenylpropyl trifluoroborate **2a** as the model substrates, of which the reaction was easily monitored by GC-MS and TLC. Gratifyingly, we found that the desired product **3aa** could be isolated in moderate yield involving the use of Ag_2O as an oxidant. The combination of toluene and a trace of water was found to be the best solvent system, which can afford the target product **3aa** in 82%. It is worth emphasizing that the presence of trace amounts of distilled water is critical to ensuring a successful transformation. When other solvents, such as protic, polar and nonpolar solvents were used instead of toluene, the yields were significantly lower. Further screening different reaction temperatures, both elevated and decreased reaction temperatures are unfavorable for this conversion. A slight modification on the ratio of **1a** and **2a** (from 1.0/1.0 to 1.05/1.0) could produce a better result with a 92% yield of the target product. Notably, the reaction must be conducted in an inert

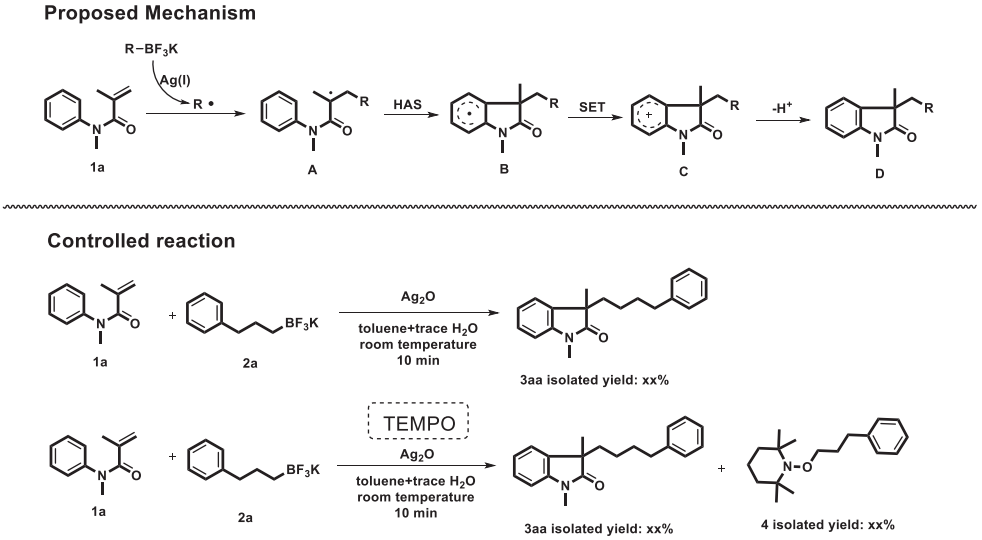


Scheme 2. Scope of acrylamides. [a]Reaction conditions: the potassium alkyltrifluoroborate **2x** (0.2 mmol, 1.0 equiv.), Ag_2O (0.2 mmol, 1.0 equiv.) and acrylamide **1a** (0.21 mmol, 1.05 equiv.), toluene (2.0 mL) and distilled water (40 μL), stirred at room temperature for 10 min.

atmosphere because air and oxygen were unsuitable for this transformation. From the above studies, we summarize that the optimized reaction should be performed using a dosage of alkyl trifluoroborates and *N*-methyl-*N*-phenyl-2-methylacrylamide (1:1.05) at room temperature in the presence of 1.0 equivalent Ag_2O under N_2.

With the established conditions, we subsequently explored the scope of the cyclization reaction, varying in substitutes of alkyl trifluoroborates **2x**, using *N*-methyl-*N*-phenyl-2-methylacrylamide **1a** as the model substrate, and the results are summarized in Scheme 1. Encouragingly, in all cases, the desired cyclized product **3aa–3ao** were observed as the predominant isolable products under the standard condition. The halogen atoms (F, Cl, Br) remained intact during the process, confirming the truth of the mild nature of the reaction condition. In general, the alkyl trifluoroborates with ester (**2k** and **2m**), ketone (**2j**), even amides (**2i** and **2l**) groups gave good to high yields, whereas the heteroarene groups (**2h** and **2i**) were also compatible in the system. Surprisingly, the branched alkyl trifluoroborates (**2g** and **2m**) worked well to deliver the corresponding oxindoles (**3ag** and **3am**), and this outcome gave us a hint that the conversion was insensitive to the steric hindrance. Furthermore, the secondary alkyl boron compounds (**2n** and **2o**) can also be effectively oxidized to form the relevant radicals, eventually forming the corresponding oxindoles **3an** in 82% and **3ao** in 80% respectively.

We next investigated the substitute effects on acrylamide substrates, which was shown in Scheme 2. Again, the reaction showed satisfactory transformation, providing the desired products in moderate yield. Both electron-donating and electron-withdrawing substituents at the para position of the aniline moiety were compatible with this conversion (**3bk** and **3ck**) upon treatment under the standard condition. The ortho-fluoro-



Scheme 3. Proposed mechanism and controlled reaction.

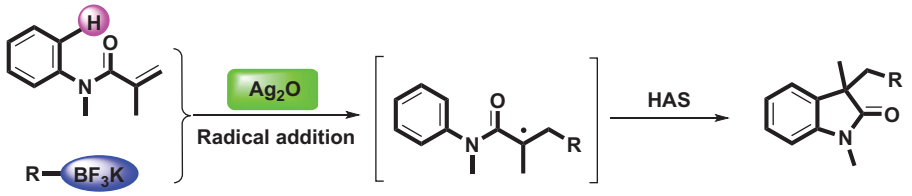


Figure 1. Our work using potassium alkyl trifluoroborates as the alkyl precursors.

substituted acrylamide **1d** reacted smoothly to give the corresponding product **3dk** in satisfactory yield. Notably, the steric effect of ortho-substituents had no significant effect on this reaction. Additionally, we examined using a different substituent with larger steric hindrance (an isopropyl group) in place of the methyl group on the *N* tether, remarkably again, the corresponding oxindole **3ek** could be readily obtained in a little lower yield.

The mechanism of this reaction process was clarified by performing one competition experiment (Scheme 3). First, *N*-methyl-*N*-phenyl-methacylamide **1a**, phenylpropyl trifluoroborate **2a** and TEMPO (2,2,6,6-tetramethyl-1-piperdinoxyl, a radical scavenger) was subjected to the standard reaction conditions, the original reaction was suppressed, providing the TEMPO-adduct as the major product. This clearly indicated that the reaction proceeded through a free-radical addition which was similar to the mechanism proposed in our previous reports.[12–14] Taking into account all these observations, a proposed mechanism for the formation of the cyclization products is put forward in Scheme 3. The alkyl radical (R·) is formed via single electron transfer process of phenylpropyl trifluoroborate **2a** in the presence of Ag_2O. Subsequently, a radical addition with *N*-methyl-*N*-phenyl-methacylamide **1a** to generate the intermediate A, followed by

intramolecular homolytic aromatic substitution (HAS), forming the intermediate radical B, which was proposed as a common step in the radical cyclization reaction. Subsequently, another single-electron transfer (SET) step was occurred to afford cation C followed by deprotonating aromatization to get the final product D.

Conclusion

In summary, we have developed a facile synthetic method for the oxindoles using acrylamides with alkyl trifluoroborates as starting materials. The method was successful because of the simultaneous control of the formation of alkyl radicals and the corresponding cycloaddition step. The silver-mediated oxidation of alkyl trifluoroborates. Provides an expedient approach for the synthesis of 3,3-disubstituted oxindoles. Considering the broad substrate scope with various functional groups, good to excellent yield and simple reaction operations, this work may provide a basis for further development of the preparation of these and related challenging molecules.

Experimental

General

Unless otherwise noted, all reactions were carried out in a flame-dried, sealed Schlenk reaction tube under an atmosphere of nitrogen. Analytical thin-layer chromatography was performed on glass plates coated with 0.25 mm 230–400 mesh silica gel containing a fluorescent indicator (Merck). Visualization was accomplished by exposure to a UV lamp, and/or treatment with a solution of $KMnO_4$ or a solution of Phosphomolybdic Acid (PMA) followed by brief heating with a heating gun. Most of the products in this article are compatible with standard silica gel chromatography. Column chromatography was performed on silica gel 60 N (spherical and neutral, 140–325 mesh) using standard methods.

Structural analysis

NMR spectra were measured on a Bruker Avance-400 spectrometer and chemical shifts (δ) are reported in parts per million (ppm). ^{1}H NMR spectra were recorded at 400 MHz in NMR solvents ($CDCl_3$, Acetone-d_6, DMSO-d_6) and referenced internally to corresponding solvent resonance, and ^{13}C NMR spectra were recorded at 100 MHz and referenced to corresponding solvent resonance, Coupling constants are reported in Hz with multiplicities denoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). High resolution mass spectra (HRMS) were obtained on a Q-TOF microspectrometer.

Materials

Commercial reagents were purchased from J&K, Energy, Sigma-Aldrich, Alfa Aesar, Acros Organics, Strem Chemicals, TCI and used as received unless otherwise stated. Hexane, THF, Et_2O, toluene were purified by distillation over sodium and stored under N_2.

General procedure

In air, the potassium alkyltrifluoroborate (0.2 mmol, 1.0 equiv.), Ag_2O (0.2 mmol, 1.0 equiv.) and acrylamide (0.21 mmol, 1.05 equiv.) were sequentially weighed and added to a screw-capped Schenk tube containing a magnetic stir bar. The vessel was evacuated and refilled with nitrogen for three times. toluene (2.0 mL) and distilled water (40 μL) were added in turn under N_2 atmosphere using syringes through a septum which was temporarily used to replace the screw cap. The reaction mixture was then vigorously stirred at room temperature for the indicated time. The resulting mixture was filtered through a pad of Celite®, and the filter cake was washed with ethyl acetate (3 mL × 2). The combined filtrate was evaporated under vacuum to dryness and the residue was purified by column chromatography to yield the desired product.

Selected spectral data

1,3-Dimethyl-3-(4-phenylbutyl)indolin-2-one (3aa)

The general procedure was followed using *N*-methyl-*N*-phenyl-methacylamide **1a** (33.8 mg, 0.21 mmol, 1.05 equiv.), phenylpropyl trifluoroborate **2a** (45.2 mg, 0.2 mmol, 1.0 equiv.) and Ag_2O (46.2 mg, 0.2 mmol, 1.0 equiv.) as the starting materials, the desired product 1,3-dimethyl-3-(4-phenylbutyl)indolin-2-one **3aa** was obtained as white solid (53.9 mg, yield 92%).(CAS: 1159803-53-8).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 5H), 7.07 (m, 3H), 6.84 (d, $J = 7.8$ Hz, 1H), 3.21 (s, 3H), 2.46 (t, $J = 8.0$ Hz, 2H), 1.93 (td, $J = 12.7$, 4.8 Hz, 1H), 1.77 (td, $J = 12.7$, 4.5 Hz, 1H), 1.47 (m, 2H), 1.35 (s, 3H), 1.06 (m, 1H), 0.92 (m, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 180.8, 143.3, 142.5, 134.2, 128.3, 128.2, 128.2, 127.6, 125.6, 122.5, 122.4, 107.9, 48.4, 38.3, 35.6, 31.7, 26.1, 24.3, 23.8;

HRMS (ESI) calcd for C20H23NNaO $[M + Na]^+$: 316.1677, found: 316.1673.

Full experimental details and ^{1}HNMR, ^{13}CNMR, and HRMS for all compounds can be found in the Supplementary Content section which can be accessed through the article's web page.

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