EurJOC European Journal of Organic Chemistry

SHORT COMMUNICATION

DOI: 10.1002/ejoc.201301512

A Metal-Free Route to CF_3-Containing Oxindoles by $PhI(OAc)_2$-Mediated Trifluoromethylation of *N*-Arylacrylamides with $TMSCF_3$

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Keywords: Synthetic methods / Amides / Fluorine / Iodine / Heterocycles

A mild and efficient $PhI(OAc)_2$-mediated trifluoromethylation reaction of *N*-arylacrylamides with $TMSCF_3$ under metal-free conditions was developed. This method provides convenient access to a variety of useful CF_3-containing oxindoles in moderate to good yields.

Introduction

The trifluoromethyl moiety is one of the key structural units found in pharmaceuticals, agrochemicals, and functional materials mainly because of its excellent metabolic stability, elevated electronegativity, and extremely high lipophilicity.[1,2] Consequently, extensive efforts have been devoted to incorporating the trifluoromethyl group into a series of skeletal structures. Transition-metal-catalyzed trifluoromethylation reactions starting from aryl halides,[3] boronic acids,[4] arenes substituted with directing groups,[5] alkynes,[6] and alkenes[7] have been recognized as powerful methods for the preparation of CF_3-containing compounds. Effective transition-metal catalysts are mainly based on palladium, copper, and others. However, the use of expensive metal catalysts and the problems involved in removing the residual metals from the final products, which is usually a difficult and tedious process, limits the practical applications of this strategy. Hence, the development of alternative metal-free, direct trifluoromethylation reactions performed under milder conditions are highly desirable.[8]

The oxindole unit is a ubiquitous structural motif frequently found in many natural products and synthetic molecules with varied bioactivities.[9] In particular, CF_3-containing oxindoles are of significant interest because the trifluoromethyl group enhances the biological and therapeutic activities of organic compounds. In 2012, Liu and co-workers reported the intramolecular oxidative aryltrifluoromethylation of *N*-arylacrylamides by using $TMSCF_3$ in the presence of $Pd(OAc)_2$ (Scheme 1).[10] Another efficient strategy to build the oxindole scaffold was based on Cu- and Ru-catalyzed trifluoromethylation of *N*-arylacrylamides with Togni's reagent developed by the groups of Sodeoka[11] and Zhu,[12] respectively. More recently, Nevado and co-workers described the first example of a copper-promoted trifluoromethylation/aryl migration/desulfonylation and $C(sp^2)$–N bond formation of conjugated tosyl amides by using Togni's reagent as the radical trifluoromethylthiolating reagent.[13] Although these methods are advantageous for the synthesis of the trifluoromethylated oxindole scaffold, these methods do require transition-metal catalysts or expensive Togni's reagent.

Recently, the metal-free hypervalent iodine promoted trifluoromethylation of arenes and alkenes was developed.[14] For instance, Shibata reported an efficient oxidative trifluoromethylation of arenes by using a simple combination of trifluoromethanesulfinate and phenyliodine bis(trifluoroacetate).[15] Zhou et al. also described the intermolecular phenyliodine diacetate (PIDA)-mediated trifluoromethylation of 2-isocyanobiphenyls with CF_3SiMe_3 for the synthesis of 6-(trifluoromethyl)phenanthridines.[16] Encouraged by these results and in our continuing efforts to develop new and efficient strategies towards CF_3-containing heterocycles and related libraries,[17] we envisaged that this metal-free strategy could be applied as a general approach for the synthesis of CF_3-containing oxindoles starting from readily available *N*-arylacrylamides. Given that hypervalent iodine(III) promoted trifluoromethylation is generally performed at ambient temperature, a wider substrate scope and higher reaction yields were expected.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201301512.

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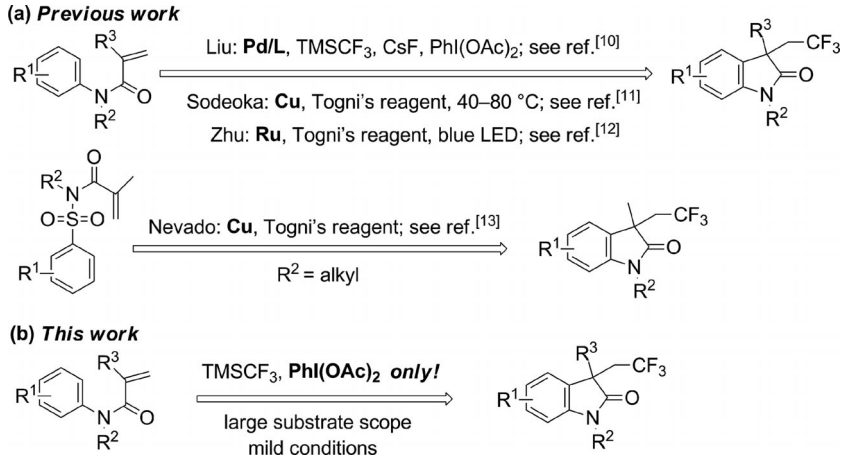
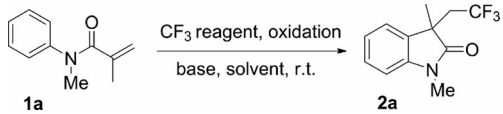


Scheme 1. The main approaches to CF_3-containing oxindoles.

Results and Discussion

We commenced the investigation with *N*-arylacrylamide **1a** as a model substrate under various conditions, and the results are summarized in Table 1. The trifluoromethylation reagent CF_3SO_2Na was first attempted with PIFA [phenyliodine bis(trifluoroacetate)], but no desired product was formed (Table 1, entry 1). To our delight, **1a** reacted with $TMSCF_3$ (4.0 equiv.) and $PhI(OAc)_2$ (2.0 equiv.) as the oxidant in the presence of K_2CO_3 at room temperature to give trifluoromethylated **2a** in 54% yield (Table 1, entry 2). Among the inorganic bases examined, NaOAc was best, and K_2CO_3 and Cs_2CO_3 were less effective (Table 1, entries 2–4). The use of 6.0 equiv. of $TMSCF_3$ gave a good yield, but if the amount of $TMSCF_3$ was increased to 8.0 equiv., the yield of **2a** did not increase further (Table 1, entries 5 and 6). The reaction proceeded well in *N*-methylpyrrolidone (NMP), and DMF provided a slightly lower yield of the product, whereas other solvents such as CH_3CN and CH_2Cl_2 were found to be less effective in this reaction (Table 1, entries 7–9).

Table 1. Optimization of the reaction conditions for **2a**.[a]



Entry	CF_3 reagent (equiv.)	Oxidant	Solvent	Base	Yield[b] [%]
1	CF_3SO_2Na (2.0)	PIFA	HFIP	–	0
2	$TMSCF_3$ (4.0)	PIDA	NMP	K_2CO_3	54
3	$TMSCF_3$ (4.0)	PIDA	NMP	NaOAc	65
4	$TMSCF_3$ (4.0)	PIDA	NMP	Cs_2CO_3	51
5	$TMSCF_3$ (6.0)	PIDA	NMP	NaOAc	78
6	$TMSCF_3$ (8.0)	PIDA	NMP	NaOAc	79
7	$TMSCF_3$ (6.0)	PIDA	DMF	NaOAc	60
8	$TMSCF_3$ (6.0)	PIDA	CH_3CN	NaOAc	25
9	$TMSCF_3$ (6.0)	PIDA	CH_2Cl_2	NaOAc	trace

[a] Reaction conditions: **1a** (0.3 mmol) and oxidant (2.0 equiv.) in solvent (1.0 mL) at room temperature for 12 h. [b] Isolated yield.

With the optimized reaction conditions in hand, we further explored the scope of the trifluoromethylation reaction with a variety of *N*-arylacrylamides (Scheme 2). It was found that substrates containing various *N*-protecting groups, such as isopropyl, butyl, benzyl, and phenyl, were tolerated in this transformation (Scheme 2, see **2b**–**f**). However, the use of *N*-free *N*-arylacrylamides resulted in no reaction (Scheme 2, see **2g**). Subsequently, the effect of substituents on the *N*-aryl moiety was examined. Both electron-donating and electron-withdrawing groups located in the *para* and *ortho* positions of the aromatic rings were found to be tolerated in this reaction, and these substrates furnished the corresponding CF_3-containing oxindoles in moderate to good yields (Scheme 2, see **2h**–**p**). *N*-Arylacrylamides possessing electron-donating groups (see **2h** and **2i**) gave the desired products in higher yields than substrates bearing electron-withdrawing groups (see **2j**–**n**). Moreover, the procedure seemed sensitive to steric effects. Generally, reactions with substrates possessing substituents in the *para* position on the benzene ring proceeded well. In comparison, *ortho* substituents on the benzene ring reduced the yields of the products (see **2o** and **2p**). Cyclization of *meta*-methyl-substituted substrates resulted in a mixture of regioisomers **2r** in a 2:1 ratio. 3,5-Disubstituted *N*-arylacrylamide **1q** was also transformed into desired product **2q** in 81% yield. However, upon using bulky 1-naphthyl-substitued **1t**, desired product **2s** was obtained in low yield. Additionally, good results were obtained with tetrahydroquinoline derivative **1t** as the substrate. The molecular structure of representative product **2n** was determined by X-ray crystallography (see the Supporting Information).[18]

On the basis of the above results and related literature,[9c–9g,12,16] a plausible reaction mechanism is depicted in Scheme 3. Initially, PIDA reacts with $TMSCF_3$ to give intermediate **A** upon release of TMSOAc. The following homolysis generates hypervalent iodine(III) centered radical **B** and the $^{\cdot}CF_3$ radical. Subsequently, the addition of the $^{\cdot}CF_3$ radical to *N*-arylacrylamide **1** generates alkyl radical **C**, followed by an intramolecular radical cyclization to give

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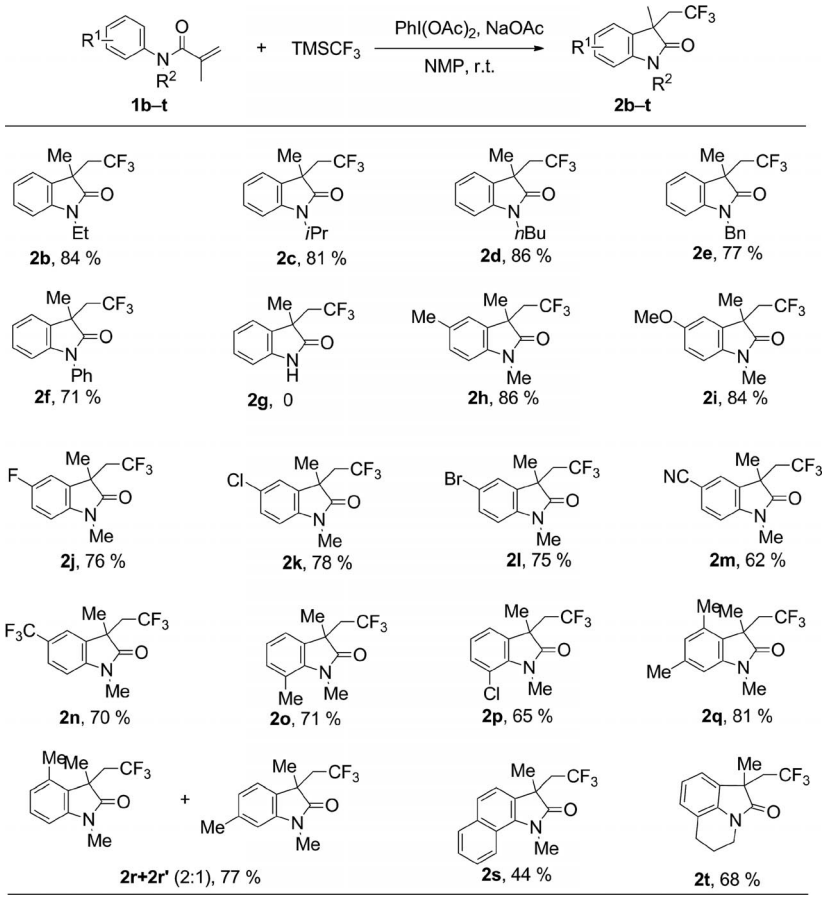
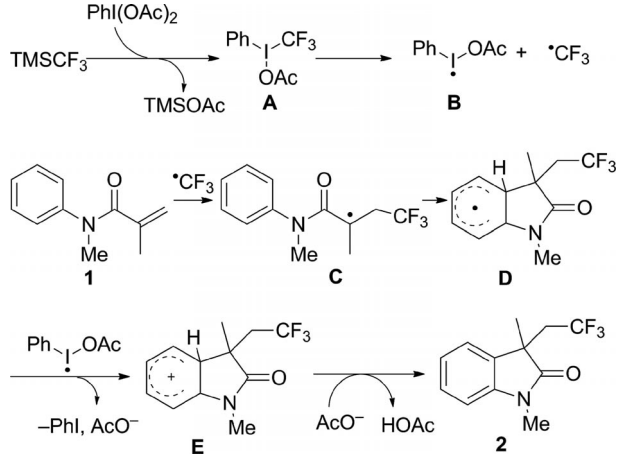


Scheme 2. Scope of the *N*-arylacrylamides. *Reaction conditions: N*-arylacrylamide **1** (0.3 mmol), $TMSCF_3$ (1.8 mol), NaOAc (0.6 mmol), and $PhI(OAc)_2$ (0.6 mol) in NMP (1.0 mL) at room temperature for 12 h.

cyclized radical intermediate **D**. A single-electron oxidation of intermediate **D** by intermediate **B** forms cyclohexadienyl cation **E**, which undergoes dehydrogenation to give product **2**.



Scheme 3. Plausible reaction mechanism.

Conclusions

In conclusion, we have developed a mild and efficient method for the construction of oxindoles bearing a trifluoromethyl group through oxidative aryltrifluoromethylation of *N*-arylacrylamides with the use of $TMSCF_3$ under metal-free conditions. The process showed considerable synthetic advantages in terms of the functional group tolerance, substrate scope, the simplicity of the reaction procedure, and mild reaction conditions.

Experimental Section

General Procedure for the Aryltrifluoromethylation of *N*-Arylacrylamides: $TMSCF_3$ (1.8 mmol) was added to a mixture of *N*-arylacrylamide **1** (0.30 mmol), $PhI(OAc)_2$ (0.6 mmol), and NaOAc (0.6 mmol) in NMP (1.0 mL). After stirring at room temperature for 12 h, the reaction mixture was diluted by adding EtOAc and brine. The aqueous layer was extracted with EtOAc. The combined organic layer was dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel to give desired oxindole **2**.

Supporting Information (see footnote on the first page of this article): Synthesis, characterization data, and copies of the ^1H NMR and ^{13}C NMR spectra.

Acknowledgments

The authors are grateful to the National Natural Science Foundation of China (NSFC) (project numbers U1204205, 21202078, and 21272110)

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[18] CCDC-963690 (for **2n**) 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.

Received: October 5, 2013
Published Online: December 19, 2013

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