Organic LETTERS

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Photoredox-Catalyzed Tandem Radical Cyclization of *N*-Arylacrylamides: General Methods To Construct Fluorinated 3,3-Disubstituted 2-Oxindoles Using Fluoroalkylsulfonyl Chlorides

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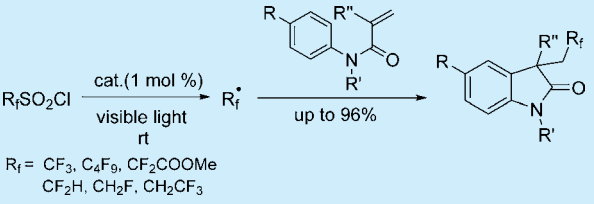
Supporting Information

ABSTRACT: Fluorinated radicals were generated from R_fSO_2Cl by photoredox catalysis under mild conditions, where R_f = *n*-C_4F_9, CF_3, CF_2H, CH_2F, CH_2CF_3, and CF_2CO_2Me. This method provided a general way to construct fluorinated 2-oxindoles from reaction with *N*-arylacrylamides via a proposed tandem radical cyclization process.



The discovery of isatin in the early 19th century has led to extensive investigation of the reactivity and synthesis of indole containing motifs.[1] In particular, 3,3-disubstituted 2-oxindoles, an isatin derivative, have attracted much attention due to the stereogenic center located at C_3 and because of the increased bioavailability of pharmaceuticals containing these moieties.[2] Therefore, these structural entities continue to be an attractive synthetic target. It is also well-known that the introduction of fluorinated substituents can significantly alter the physical, chemical, and biological properties of the parent compound.[3] Thus, incorporation of fluorinated substituents into potential pharmaceuticals and agrochemical agents continues to attract considerable attention from synthetic chemists. When introduced into pharmaceuticals, a fluorinated substituent can enhance membrane permeability, bioavailability, binding affinity, and lipophilicity.[4]

Recently, 3,3-disubstituted 2-oxindoles bearing the CF_3 group have been synthesized using the Togni reagent,[5] $TMSCF_3$,[6] or CF_3SO_2Na.[7] However, increasing the diversity of available methodology in this area remains of considerable interest. Thus far, the reported methods have been limited to introduction of the CF_3 moiety. Therefore, there is an incentive to broaden the methodology to apply to other fluorinated groups with respect to preparation of 3,3-disubstituted 2-oxindole systems. Among the various methods available to prepare 3,3-disubstituted 2-oxindole compounds, perhaps the most efficient route involves the cyclization reactions of *N*-arylacrylamides.[8] These reactions can be initiated by the reaction of radicals with C−C double bonds followed by intramolecular radical cyclization onto the aryl substituent. Consistent with these findings, we hypothesized similar reactions could be carried out using a large variety of fluorinated radicals to construct a diverse series of fluorinated 2-oxindoles. Fluorinated radicals can be generated in many ways,[9] but the reduction of R_fX (X = I, Br, Cl) using reductive reagents such as $Na_2S_2O_4$[10] or transition metals[11] or oxidation of R_fSO_2M (M = Zn or Na)[12] are two preferred methods. Various fluoroalkylsulfonyl chlorides, R_fSO_2Cl, are commercially available or may be readily prepared from inexpensive starting materials. Our current work was conceived with the knowledge that Baran's R_fSO_2M reagents were prepared from their respective sulfonyl chlorides,[12b] and our hypothesis was that it might therefore prove advantageous if one could use these sulfonyl chlorides directly for radical formation.[13] The results outlined in this current communication represent our efforts to demonstrate that sulfonyl chlorides can be effectively used as synthetic sources of a variety of fluoroalkyl radicals. We believe that the direct use of these sulfonyl chlorides constitutes a viable alternative to the previous mentioned methods. Although photosensitized approaches to the generation of fluorinated radicals from R_fI have recently received much attention due to the excellent reductive ability of a photocatalyst in the excited state under mild conditions,[14] to the best of our knowledge, the only fluoroalkylsulfonyl chloride that has thus far been reportedly used for R_f radical generation has been CF_3SO_2Cl.[15] In general, fluoroalkylsulfonyl chlorides have more positive reductive potentials, lower volatility, and a higher boiling point compared to the respective fluoroalkyl iodides,[16] so they should be better candidates for photosensitized radical generation than the analogous iodides. Thus, in this paper we describe the photocatalyzed reaction of a number of fluoroalkylsulfonyl chlorides (R_fSO_2Cl) with *N*-arylacrylamides, reactions which prove to be effective for the construction of the respective fluorinated 2-oxindoles.

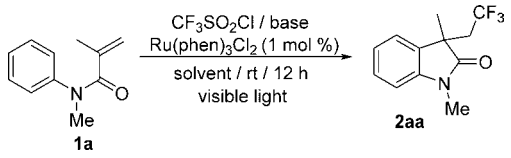
In our preliminary experiments, *N*-methyl-*N*-phenylmethacrylamide, **1a**, and CF_3SO_2Cl were selected as model substrates. An initial experiment using 1 mol % $Ru(phen)_3Cl_2$ as the catalyst, MeCN as the solvent, and K_2HPO_4 as an added base led to formation of the expected product **2aa** in 68% yield, as determined by ^{19}F NMR: (δ −62.0, t, J = 11.0

Received: July 22, 2014
Published: August 19, 2014

   dx.doi.org/10.1021/ol502163f | *Org. Lett.* 2014, 16, 4594−4597

Hz). Under these initial conditions, 38% of byproducts were observed (singlets at −61.2, −62.1, and −62.2 ppm), and these peaks were attributed to products obtained from direct trifluoromethylation of the phenyl ring.[15a] Results from optimization experiments are provided in Table 1. With

Table 1. Optimizations of Reaction Conditions



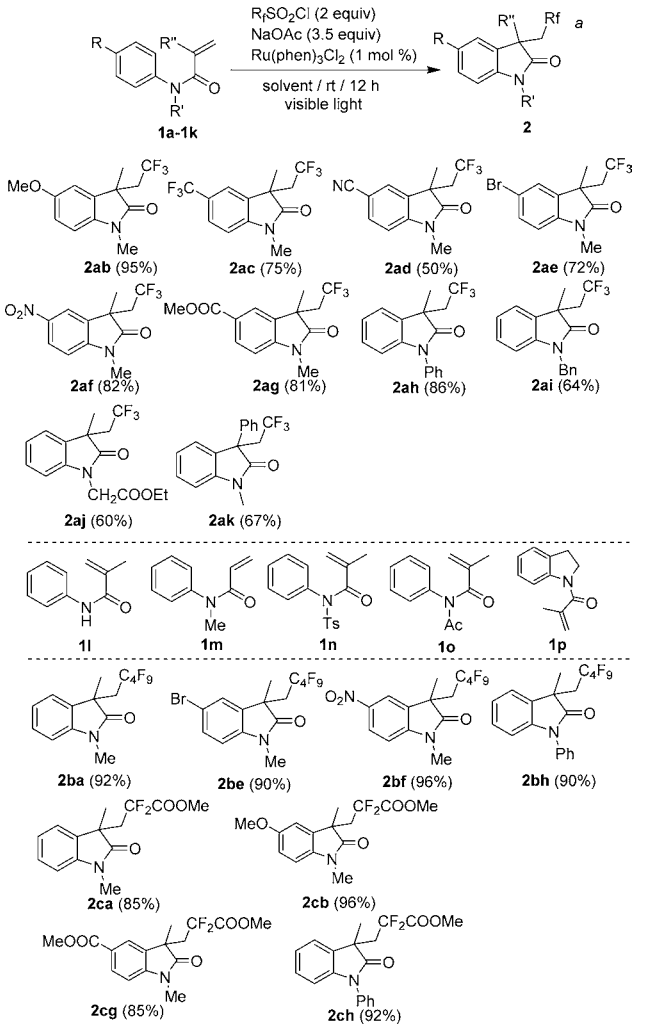
entry	solvent	base	yield[a]
1	MeCN	K_2HPO_4	68%
2	MeCN	Na_2CO_3	40%
3	MeCN	K_3PO_4	20%
4	MeCN	$NaHCO_3$	15%
5	MeCN	K_2CO_3	67%
6	MeCN	NaOAc	74%
7	DCM	NaOAc	60%
8	DMF	NaOAc	54%
9	acetone	NaOAc	35%
10	DMAc	NaOAc	24%
11	HOAc	NaOAc	84%
12	HOAc	NaOAc[b]	92% (88%[c])
13	HOAc	no base	49%
14	MeCN	no base	48%

[a]Reactions were run with 0.5 mmol of **1a**, 1 mmol of CF_3SO_2Cl, 1.5 mmol of base, and 0.01 mmol of $Ru(phen)_3Cl_2$ in 5 mL of solvent. All yields were based on **1a** using $PhCF_3$ as the internal standard. [b]1.75 mmol (3.5 equiv) of NaOAc was used. [c]Isolated yield based on **1a**.

continued use of CH_3CN as solvent, other bases were tested including Na_2CO_3, K_3PO_4, and $NaHCO_3$, all which gave poor yields of **2aa**. When K_2CO_3 or NaOAc was used as the base, improved yields were obtained, and the Ar−CF_3 products were suppressed (<5%). Variation of the solvent led to the discovery that acetic acid was an excellent solvent for this reaction, when used in conjunction with the buffer base, NaOAc (entries 11 and 12). As shown by the last two entries, the presence of a base is definitely advantageous, its role most likely being the removal of coproduct HCl from the reaction. One would expect the phen ligand of $Ru(phen)_3Cl_2$ to be sensitive to the presence of HCl.

Using these optimized reaction conditions, the cyclization reactions of CF_3SO_2Cl with various *N*-arylacrylamides were explored. As shown in Scheme 1, various functional groups were well tolerated, and substrates with both electron-donating and -withdrawing substituents performed well under the reaction conditions. For acrylamides **1l**, **1n**, and **1o**, the lack of substitution on the amide, or replacement of the methyl by either a carbonyl or sulfonyl substituent, shut down the cyclization process completely, as did the lack of a substituent at the α-position of the acrylamide **1m**. The lack of reactivity of compounds **1l**, **1m**, and **1p** is perhaps best understood in terms of conformational effects. All of the substrates, except **1l**, **1m**, and **1p**, are sterically hindered from maintaining a ground-state planar conformation for the acrylamide. Thus, the vinyl group for all reactive substrates is likely not well conjugated with the carbonyl function, which should enhance these substrates' reactivities with the

Scheme 1. Substrate Scope Catalyzed by $Ru(phen)_3Cl_2$[a]



[a]0.1 M acrylamindes in 0.5 mmol scale, isolated yield based on **1**.

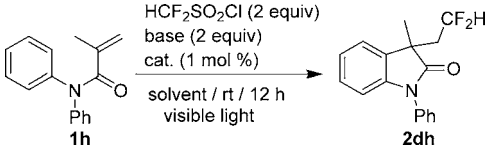
inherently reactive, but electron-deficient trifluoromethyl radical.

The lack of reactivity of the *N*-acyl and *N*-sulfonyl amides, **1n** and **1o**, is probably an indication of the need for some electron donation into the aryl group by the amide nitrogen in order to stabilize the cyclized radical intermediate and/or to foster oxidation of this radical to its respective carbocation. Moreover, our initial experiments using fluorinated sulfonyl chlorides other than CF_3SO_2Cl involved the use of *n*-$C_4F_9SO_2Cl$ and $MeO_2CCF_2SO_2Cl$, which proved to have high reactivity under the prescribed conditions.

When it was attempted to extend the work to the addition of the CF_2H radical, it was found that under the conditions that were optimal for CF_3SO_2Cl, HCF_2SO_2Cl only yielded trace amounts of the desired product, with substrate **1h** being essentially completely recovered (Table 2, entry 1). Since the reductive potential of HCF_2SO_2Cl should be more negative than that of CF_3SO_2Cl, the $Ru(phen)_3Cl_2$ ($E_{1/2}^{III/*II}$ = −0.87 V vs SCE in MeCN) catalyst might not be effective in reducing HCF_2SO_2Cl to provide the CF_2H radical. Consistent with this assumption, similarly poor results were obtained when $Ru(bpy)_3Cl_2$ ($E_{1/2}^{III/*II}$ = −0.81 V vs SCE in MeCN) was used as the catalyst. In contrast, when *fac*-$Ir(ppy)_3$ ($E_{1/2}^{IV/*III}$ = −1.73 V vs SCE in MeCN)[17] was used as the

dx.doi.org/10.1021/ol502163f | Org. Lett. 2014, 16, 4594−4597

Table 2. Optimization of Conditions for the Reaction of HCF_2SO_2Cl



entry	cat.	solvent	base	yield[a]
1	$Ru(phen)_3Cl_2$	HOAc	NaOAc	<1%
2	$Ru(bpy)_3Cl_2$	HOAc	NaOAc	<1%
3	*fac*-Ir(ppy)$_3$	HOAc	NaOAc	59%
4	*fac*-Ir(ppy)$_3$	MeCN	NaOAc	41%
5	*fac*-Ir(ppy)$_3$	HOAc	K_2HPO_4	52%
6	*fac*-Ir(ppy)$_3$	MeCN	K_2HPO_4	80% (77%[b])
7	*fac*-Ir(ppy)$_3$	MeCN	K_2HPO_4[c]	75%

[a]Reactions were run with 0.5 mmol of **1h**, 1 mmol of HCF_2SO_2Cl, and 0.005 mmol of catalyst in 5 mL of solvent. All yields were based on **1h** using $PhCF_3$ as the internal standard. [b]Isolated yield based on **1h**. [c]1.5 mmol (3 equiv) of K_2HPO_4 was used.

catalyst, generation of the CF_2H radical was observed, with formation of 59% of product **2dh**. In optimizing the use of this catalyst, it was found that a combination of K_2HPO_4 as the base and acetonitrile as the solvent provided the best results (Table 2, entry 6), with the desired cyclized product being formed in 80% yield. It should also be noted that no byproducts from addition of the CF_2H radical directly to the aryl group were detected under these conditions.

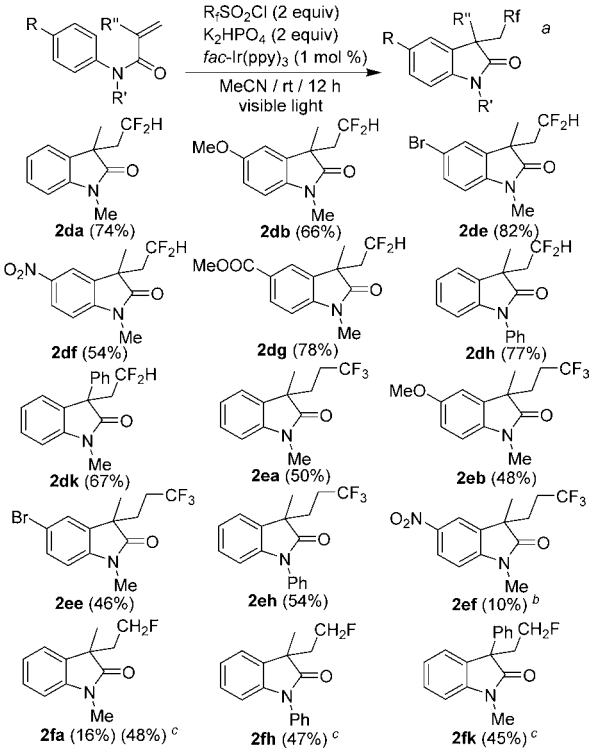
It was found that the 2,2,2-trifluoroethyl radical could also be effectively generated from $CF_3CH_2SO_2Cl$ by the use of this same Ir catalyst, although the yields were more modest for this radical. The results obtained for these two fluorinated sulfonyl chlorides in reacting with a variety of *N*-arylacrylamides are given in Scheme 2. Good yields (55−82%) were obtained when using CF_2HSO_2Cl, but $CF_3CH_2SO_2Cl$ provided only 46−54% yields of the desired, cyclized products. Yields were not improved by using longer reaction times. In attempts to use H_2CFSO_2Cl as a source of the CH_2F radical in the reaction with *N*-methyl-*N*-phenylmethacrylamide **1a**, only a 16% yield of desired product **2fa** could be obtained under the reaction conditions of Table 2. The yields of cyclized products (**2fa**, **2fh**, and **2fk**) were improved to 45−48% when the reactions were run at 105 °C using DCE instead of MeCN as the solvent. It is apparently even more difficult to reduce CH_2FSO_2Cl than in the cases of HCF_2SO_2Cl and $CF_3CH_2SO_2Cl$.

Interestingly, it was found that use of an unambiguous thermal free radical initiator, dilauryl peroxide (DLP), in reactions of **1a** with CF_3SO_2Cl, HCF_2SO_2Cl, or H_2CFSO_2Cl gave rise to the corresponding cyclized products with yields of 63%, 54%, and 70%, respectively (Scheme 3).

Although authors reporting the similar preparations of CF_3-containing 2-oxindoles by the use of Togni reagent/CuCl[5c] or $TMSCF_3/Pd(OAc)_2$[6b] invoked mechanisms involving cyclization of carbocations, based on the results of Scheme 3, we believe that a radical cyclization mechanism, followed by oxidation of a cyclized radical intermediate is more credible for our reactions of fluorinated sulfonyl chlorides (Scheme 4).

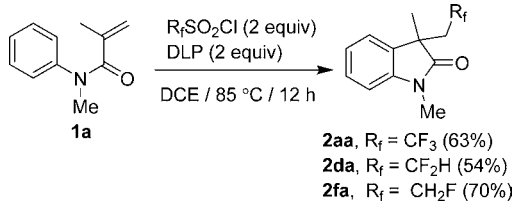
In summary, a general way of generating fluorinated radicals from fluorinated sulfonyl chlorides via photoredox catalysis under mild conditions has been reported. This method can be used to generate CF_3, CF_2CO_2Me, and n-C_4F_9 radicals, but it also has been modified to allow the generation of other fluorinated radicals such as CF_2H, CH_2F, and CF_3CH_2. The utility of this process has been demonstrated through the preparation of a variety of fluorinated 3,3-disubstituted 2-oxindoles. Additional applications for the use of these new fluoroalkylation reagents are currently under investigation.

Scheme 2. Substrate Scope Catalyzed by *fac*-Ir(ppy)$_3$

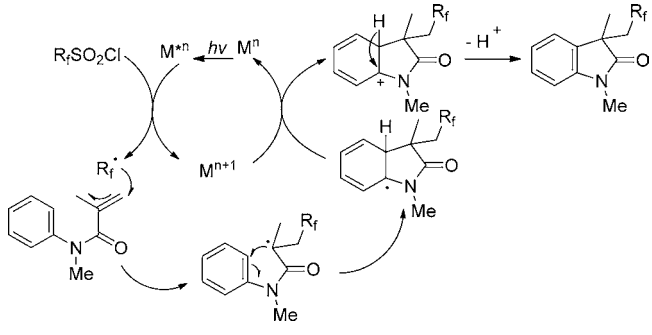


[a]0.1 M acrylamindes in 0.5 mmol scale, isolated yield. [b] ^{19}F NMR yield; this product was not isolated due to low yield. [c] Reactions were run at 105 °C in DCE.

Scheme 3. DLP-Initiated Radical Cyclization Reactions



Scheme 4. Proposed Radical Cyclization Mechanism for Photocatalyzed Reactions



dx.doi.org/10.1021/ol502163f | Org. Lett. 2014, 16, 4594−4597

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization, and NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Support of this research by a grant from Syngenta Crop Protection is gratefully acknowledged.

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