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Mild Chlorodifluoroacylation of Indoles via Self-Activation of Sodium Chlorodifluoroacetate

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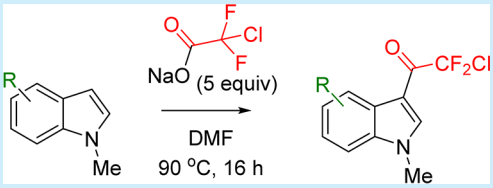
Supporting Information

ABSTRACT: A mild acylation of *N*-alkylindoles is reported using sodium chlorodifluoroacetate (SCDA) to synthesize useful chlorodifluoroketones. Friedel–Crafts reactivity of carboxylate salts is unusual and is not observed in similar electron-deficient acetate salts such as sodium trifluoroacetate. Mechanistic experiments indicate that the characteristic ability of SCDA to generate difluorocarbene is responsible for the reaction pathway via self-activation to form the active ester.



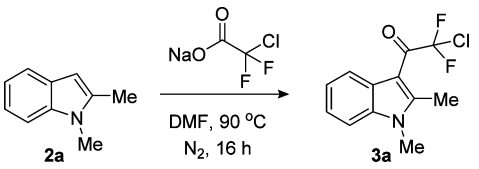
There is considerable interest in the development of new methods for selective incorporation of fluorine into organic compounds. Fluorine-containing compounds play a central role in pharmaceuticals (e.g., best-selling drugs rosuvastatin, Advair, and sitagliptin), agrochemicals (e.g., fungicides epoxiconazole and flusilazole), and medical imaging agents (^{18}F positron emission tomography), with introduction of the fluoro or perfluoro group frequently being the key determinant to a viable synthesis.[1]

Sodium chlorodifluoroacetate (SCDA, **1**) is a versatile reagent for introducing CF_2 and CF_3 groups in this regard. The reagent undergoes decarboxylation at moderate temperatures (ca. 90 °C) to form difluorocarbene.[2] This highly reactive and transient intermediate can then be used in situ for di- and (in the presence of fluoride base) trifluoromethylations.[3,4] Unlike many common perfluoromethylating agents, SCDA is an inexpensive, crystalline solid which is stable at ambient temperature and in air.[5] These factors have brought the reagent into focus as a potential solution to process-scale di- and trifluoromethylation.

We have recently reported *S*-, *N*-, and *Se*-difluoromethylation methodologies using SCDA.[6] In the course of these studies, we uncovered a surprising result upon treatment of indole derivatives with SCDA. Reaction of 1,2-dimethylindole **2a** with SDCA and CsF in DMF at 90 °C afforded the unexpected chlorodifluoro*acylated* product **3a** with moderate conversion (Table 1). The connectivity of this product was confirmed by 2D NMR spectroscopy and XRD crystallographic studies (Figure 1) on a subsequent derivative (vide infra). Trace quantities of dimethylindole-3-carboxaldehyde were also observed, presumably from the reaction of indole and DMF in a Vilsmeier–Haack-type process.[7]

Although Freidel–Crafts acylation of indoles at the 3-position is well-known, it generally requires strong electrophiles (anhydrides or acid chlorides) in combination with reactive Lewis acids.[8] Carboxylate salts are generally not considered to be effective electrophiles, and to our knowledge, this is the only example both of acylation of an indole with such a reagent and of SCDA behaving in this reaction mode. These considerations, combined with the synthetic utility of chlorodifluoroketones[9−11] and chlorodifluoroalkylindoles,[12] encouraged us to investigate the reaction further.

Table 1. Chlorodifluoroacylation of 1,2-Dimethylindole



entry	salt (equiv)	base	yield of **3**[a] (%)
1	2	CsF	51
2	2	NaF	50
3	0.5		7
4	1		18
5	2		69 (57)
6	5		95 (81)
7[b]	2		34
8[c]	2		0
9[d]	2	NEt_3	91
10[e]	2		0
11[f]	2	NEt_3	0

[a]NMR yields calculated by ^{1}H NMR spectroscopy. Isolated yields in parentheses. [b]Reaction performed in NMP solvent at 130 °C. [c]Reaction performed with chlorodifluoroacetic acid (CDA). [d]Reaction performed with CDA in the presence of triethylamine base (2 equiv). [e]Reaction performed with TFA. [f]Reaction performed with TFA in the presence of triethylamine base (2 equiv).

An initial screen of reaction parameters established that base was not required for the reaction but that SCDA stoichiometry was very important (Table 1, entries 1–5). A minimum of 2 equiv was required for good yields (entry 5), with 5 equiv providing an 81% isolated yield of **3a** (entry 6). Substituting SCDA for the protonated chlorodifluoroacetic acid shut down

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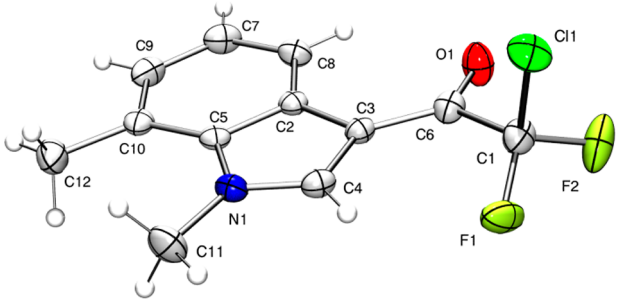
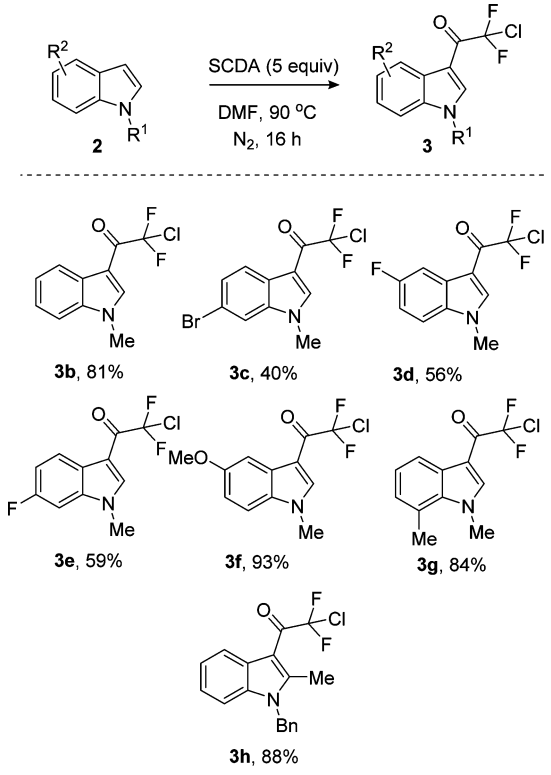


Figure 1. XRD crystallographic structure for **3g** (thermal elipsoids set at 50%).

the reaction completely (entry 8), but on addition of triethylamine the reaction proceeded to full conversion (entry 9). Finally, a control reaction using trifluoroacetic acid showed no reactivity for both the acid and carboxylate (entries 10–11). Additional control experiments with sodium trifluoroacetate, pivalate, and acetate also gave no reaction.

With an optimized procedure in hand, we elected to first examine the substrate scope of the process (Scheme 1). The

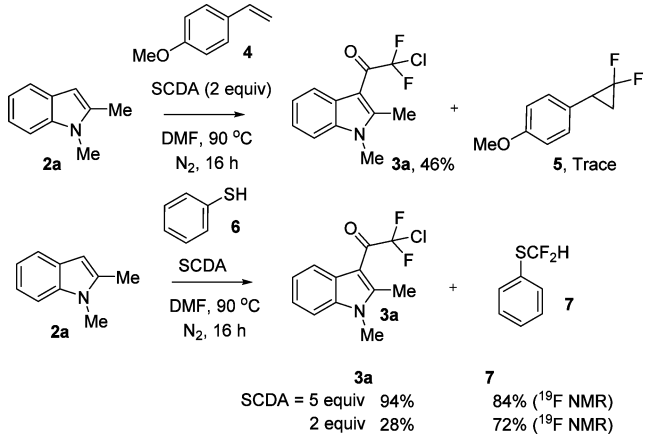
Scheme 1. Substrate Scope



reaction was found to be entirely selective for the indole 3-position when the 2-methyl group was removed (**3b**).[13] Electron-donating substitution on the benzo-fused ring generally gave good to excellent yields of the acylated products (**3f,g**).[14] Electron-withdrawing substituents, by contrast, were poorly tolerated in the reaction, e.g., 1-methyl-5-nitroindole was entirely unreactive. Similarly, attenuation of the indole nucleophilicity at the *N*-position in the form of Ts or Boc groups shut down the reaction. However, an electron-donating *N*-benzyl group gave the product in excellent yield (**3h**).

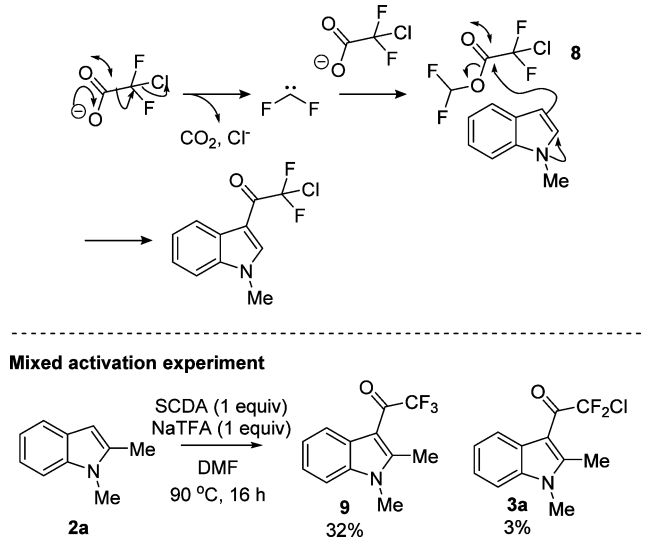
The unusual acylation reactivity of SCDA when compared with other, similar, acetates rules out a simple electrophilic substitution mechanism. Rather, the unique facility of SCDA to generate difluorocarbene is likely implicated in the reaction pathway. To investigate this possibility, we conducted the reaction in the presence of the carbene traps 1-methoxy-4-vinylbenzene[15] and thiophenol (Scheme 2). The first reaction

Scheme 2. Carbene Trapping Experiments



reduced the reaction conversion to 46%, but only trace quantities of difluorocyclopropane **5** were observed by ^{19}F NMR spectroscopy. The second reaction, however, showed suppression of acylation and a 72% conversion (determined by ^{19}F NMR spectroscopy) to $PhSCF_2H$ (**7**) with 2 equiv of SCDA.[6,16] Taken with the stoichiometric requirement for two equivalents of SCDA in the reaction, we propose the self-activating mechanism shown in Scheme 3. Decomposition of

Scheme 3. Proposed Mechanism



SCDA generates difluorocarbene, which may be trapped by a molecule of the starting carboxylate. The activated ester **8** then enables Friedel–Crafts acylation of indole in the usual manner.

To test this hypothesis, we carried out a mixed activation experiment. As discussed above, substituting SCDA with NaTFA does not give the corresponding trifluoroacylindole product, as NaTFA cannot decompose to give difluorocarbene

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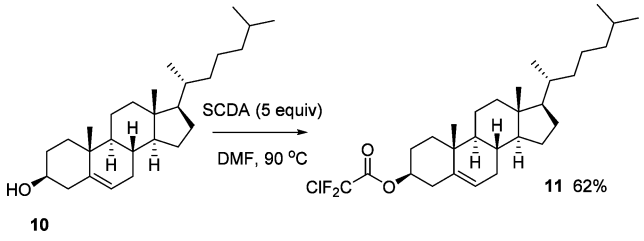
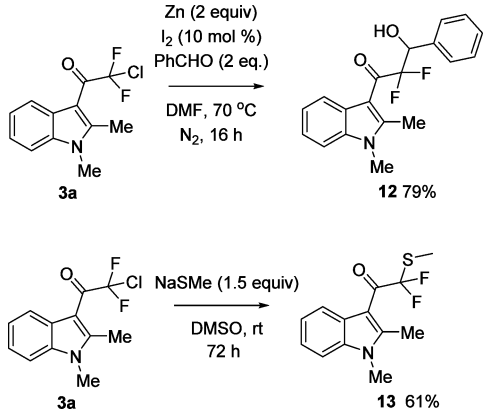
and hence cannot generate an active ester of type **8**. However, in the presence of SCDA (i.e., a reaction regime which can produce difluorocarbene and ester **8**) 32% of **9** is observed, along with a trace quantity of **3a**.

The chlorodifluoroacyl group is a valuable synthon for the construction of *vic*-difluorinated molecules. To demonstrate the potential of this simple chlorodifluoroacylation method for the synthesis of more complex fluoro-organics, we carried out a selection of transformations shown in Schemes 4 and 5.

Scheme 4. Reaction with *O*-Nucleophiles



Scheme 5. Further Transformations of CF_2Cl



First, we demonstrated that the self-activation reaction mode can accommodate *O*-nucleophiles. Cholesterol (**10**) gave a 62% yield of chlorodifluoroacetyl cholesterol ester **11** when subjected to the standard reaction conditions.[17] Second, we could exemplify some Reformatski chemistry by reacting **3a** with activated zinc in the presence of benzaldehyde. The reaction proceeded in 79% yield to give the hydroxyketone **12**.[18] Treatment of **3a** with NaSMe in DMSO resulted in $S_{RN}1$ substitution of Cl to give **13** (61% yield by ^{1}H NMR).[19,20] The use of these compounds as a starting point for biologically relevant fluorinated compounds is currently under investigation.

In conclusion, we have developed a simple method for the chlorodifluoroacylation of *N*-methylindoles using inexpensive SCDA. The method is mild, eschewing activation with anhydrides, acyl chlorides or strong Lewis acids. Mechanistic investigations indicate active ester formation via difluorocarbene, an unprecedented pathway for this valuable perfluorination reagent. We are currently exploring the utility of this reaction in the development of biologically relevant molecules.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all 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.

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(13) 3-Substituted indoles were also found to be unreactive at the 2-position.
(14) CCDC 1007557 contains the crystallographic data for **3i**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. ORTEP-3 was used to produce the thermal ellipsoid plots: Farrugia, L. J. *J. Appl. Crystallogr.* **1997**, *30*, 565.
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(20) It proved impossible to separate product from starting material by column chromatography. Raising reaction the temperature to 60 °C and using 5 equiv of NaSMe resulted in a complex reaction mixture with trace product.

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