ORGANIC LETTERS

2013
Vol. 15, No. 19
5036–5039

S-, N-, and Se-Difluoromethylation Using Sodium Chlorodifluoroacetate

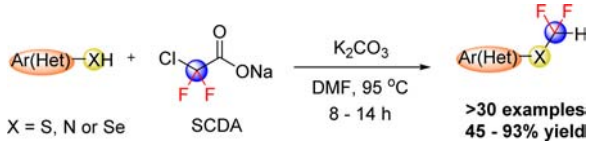
Vaibhav P. Mehta and Michael F. Greaney*

School of Chemistry, University of Manchester, Oxford Road, Manchester M13 9PL, U.K.

Michael.Greaney@manchester.ac.uk

Received August 18, 2013

ABSTRACT



A simple protocol for the difluoromethylation of thiols is reported using chlorodifluoroacetate as the difluoromethylating agent. This cheap reagent undergoes smooth decarboxylation at 95 °C to afford difluorocarbene, which can be trapped with a variety of aromatic and heteroaromatic thiols. The reaction is also effective for the difluoromethylation of heterocyclic nitrogen compounds and phenylselenol.

Selective fluorination is an important method for controlling molecular function and properties. Biological activities such as potency, log D, and metabolic stability can frequently be modulated through the selective incorporation of fluorine-containing groups,[1] creating great demand for mild, selective, and cost-effective fluorination strategies.[2] Impressive progress in reaction development has been made in recent years, particularly in the areas of tri- and difluoromethylation.[3] The cost, however, of many fluorinating and per-fluorinating agents is recognized as a major barrier to translating these reactions to industrial processes.[4] There is a clear requirement for cheaper reagents to accomplish selective per-fluoromethylation in the context of process chemistry. Our interest in decarboxylative C−C bond formation[5] stimulated us to examine fluoroacetate derivatives in this regard. Trifluoroacetic acid and its salts are bulk chemicals that can be sourced at low cost and have demonstrated utility in selective trifluoromethylations.[6] We were interested in the related compound sodium chlorodifluoroacetate (SCDA), **1**. Costing *ca.* 15% of the commonly used $TMSCF_3$ reagent, and available in bulk as a crystalline solid, it has great potential as a cheap, atom economical di- and trifluoromethylation reagent.The ability of SCDA to act as a difluorocarbene precursor was first noted by Haszeldine, who demonstrated difluorocarbene generation and trapping with alkenes by thermal decarboxylation (Scheme 1).[7] Subsequent work from Chen[8] and Burton[9] showed that decarboxylation in the presence of fluoride and

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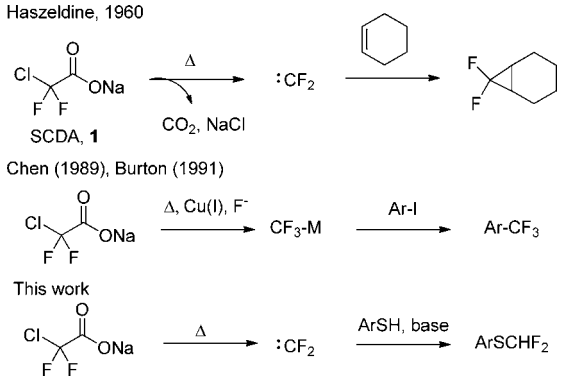
10.1021/ol402370f
Published on Web 09/23/2013

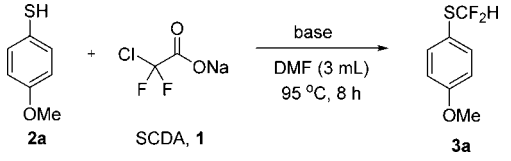
Cu salts generated $CuCF_3$ species, which could be harnessed in C- and O-trifluoromethylations.[4,10] In contrast to TFA, which requires temperatures in excess of 150 °C and a metal catalyst to decarboxylate, SCDA is reported to undergo loss of CO_2 at lower temperatures and in the absence of metals.

Scheme 1. Decarboxylative Trifluoromethylation



We were interested in exploring the potential of SCDA for S-difluoromethylation, an application that has thus far been restricted to isolated reports in the patent literature.[11] The $SCHF_2$ group is valued in medicinal and agrochemistry for its lipophilic and H-bonding characteristics,[12,13] and is classically installed with chlorodifluoromethane gas,[14] an ozone-depleting reagent that is subject to environmental regulation. Alternative reagents for S-difluoromethylation have recently been introduced, such as $BrF_2CPO(OEt)_2$,[15] $FSO_2CF_2CO_2TMS$,[16] $PhCOCF_2Cl$,[17] $ArSONRCF_2H$,[18] $Ar_2SCHF_2^+BF_4^-$,[19] $Zn(SO_2CF_2H)_2/^tBuOOH$,[20] CHF_2OTf,[21] $TMSCHF_2$,[22] and CHF_3/KOH,[23] but limitations such as lack of commercial availability and expense, the requirement for strongly basic reaction conditions, and/or poor atom economy mean there is still scope for developing an inexpensive, mild, and atom economical S-difluoromethylation method.

Table 1. Optimization Study for Difluoromethylation of Thiol **2a**[a]



entry	base	solvent	SDCA (equiv)	yield[b] (%)
1	K_2CO_3	DMF	1	50
2	K_2CO_3	DMF	1.5	78
3	K_2CO_3	DMF	2	>99(93)
4	Na_2CO_3	DMF	2	92
5	LiOH	DMF	2	94
6	Cs_2CO_3	DMF	2	97
7	KF	DMF	2	<5
8	$NaHCO_3$	DMF	2	<2
9	NEt_3	DMF	2	<1
10	DBU	DMF	2	42
11	K_2CO_3	NMP	2	>95
12	K_2CO_3	DMSO	2	60
13	K_2CO_3	solvents[c]	2	<2
14[d]	K_2CO_3	DMF	2	75(62)
15[e]	K_2CO_3	DMF	2	<1
16	no base	DMF	2	n.d.[f]

[a] Reaction conditions: In an oven-dried 25 mL screw capped reaction vial containing a stir bar were added base (0.75 mmol, 1.50 equiv) and **1** (1.00 mmol, 2.00 equiv), and the vial was evacuated and filled with argon (3 times). Then solvent (3 mL) was added followed by **2a** (0.50 mmol, 1.00 equiv) under argon. The vial was tightly sealed and stirred for 8 h. [b] ^{19}F NMR yield (value in parentheses indicates isolated yield). [c] 1,4-Dioxane, DCE, MeCN, and THF failed to give the desired conversion. [d] Reaction temperature 65 °C. [e] Room temperature. [f] n.d. = no desired product observed in ^{19}F NMR spectra.

We began our investigations with *p*-methoxythiophenol, **2a**, and were pleased to observe successful difluoromethylation in the presence of 1 equiv of SCDA and K_2CO_3 at 95 °C (Table 1, entry 1). Raising the equivalents of SCDA enhanced the reaction, with 2 equiv providing a 93% isolated yield of **3a** (entry 3). The reaction was equally effective for Na_2CO_3, LiOH, and Cs_2CO_3 (entries 4–6), but the weaker bases NEt_3 and $NaHCO_3$ gave little if any decarboxylation (entries 8 and 9). A polar solvent such as DMF, NMP (entry 11) or DMSO (entry 12) was needed in the reaction, with alternative solvents being completely ineffective (entry 13). Reducing the reaction temperature maintained efficiency (62%) at 65 °C (entry 14), but lower temperatures shut the reaction down (entry 15). Finally, in the absence of base no difluoromethylated product could be isolated.

With an optimized protocol in hand, we assayed the reaction against a number of substituted thiophenols (Scheme 2). Yields of difluoromethylated products were good to excellent for a range of substitution patterns, being largely independent

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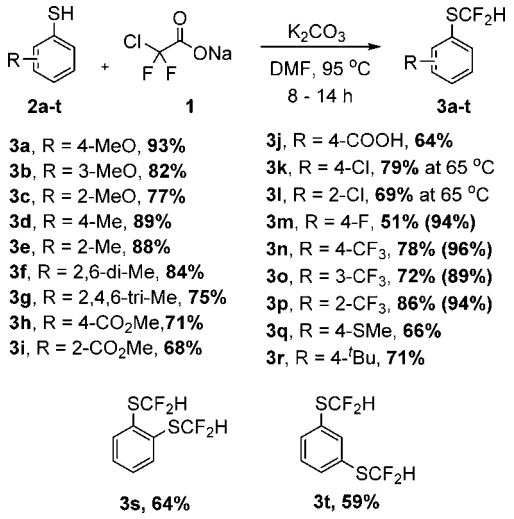
of the electronic character of the aromatic ring (**3a**−**3r**). Steric hindrance in terms of *ortho*-substitution was also tolerated, with *o*-MeO, Me, CO_2Me, Cl, and CF_3 groups all undergoing smooth conversion. Surprisingly, the carboxylic acid group was tolerated in the reaction, with compound **3j** being formed in 64% yield from the acid substrate.

Scheme 2. Difluoromethylation of Thiophenols[a]



[a] Reactions were carried out on a 1.00 mmol scale. Isolated yields (values in parentheses indicates ^{19}F NMR yield).

Double difluoromethylation was also possible, with 1,2- and 1,3-dithiophenols affording the adducts **3s** and **3t** in reasonable yield. The method was not successful for alkyl thiols, which gave intractable mixtures. The difluoromethylation of 4-methoxythiophenol was scaled up to 10 mmol, affording an 86% yield of **3a**. A small amount of disulfide was isolated from this reaction, suggesting that disulfides do not undergo reaction with SCDA.

We next expanded the protocol to nitrogenous heteroaromatic thiols, of the type more commonly found in medicinal and agrochemistry discovery programs (Scheme 3). These ambident nucleophiles can react on sulfur or nitrogen to produce dearomatized products. Difluoromethylation of 1-substituted 5-sulfanyltetrazoles gave clean N-difluoromethylation under the reaction conditions (δ_f (CHF_2) = −102.95), forming thiones **5a** and **5b** in high yield (structure **5b** confirmed by X-ray crystallography). Yagupol'skii has studied the difluoromethylation of these, and related azolemercaptan compounds, with gaseous chlorodifluoromethane/KOH and identified S-difluoromethylation as the kinetic product at low temperature, with formation of the more stable N-difluoromethylated species observed at higher temperature (100−120 °C).[24]

For azinemercaptans, the $SCHF_2$ products were preferred for 2-thiopyridines and pyrimidines (**5c**, **5d**, **5f**, and **5g**), but 4-thiopyridine gave the thione **5e** as a single product

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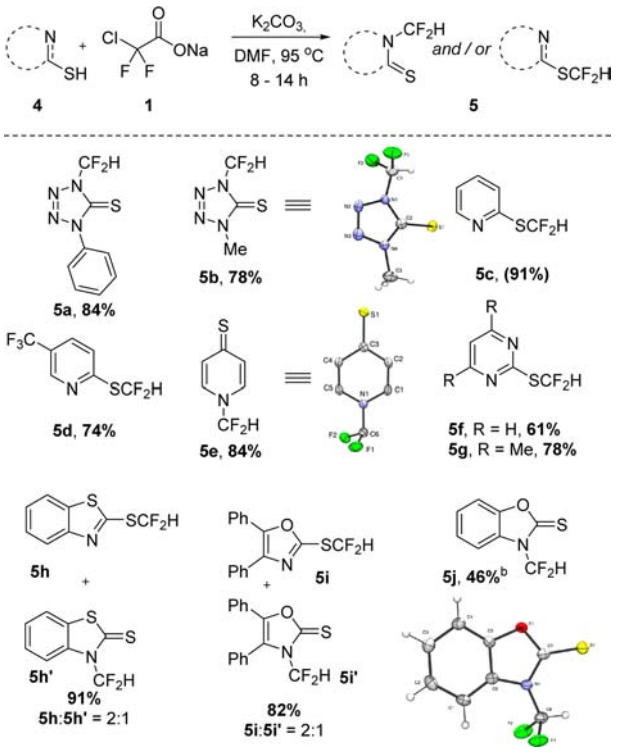
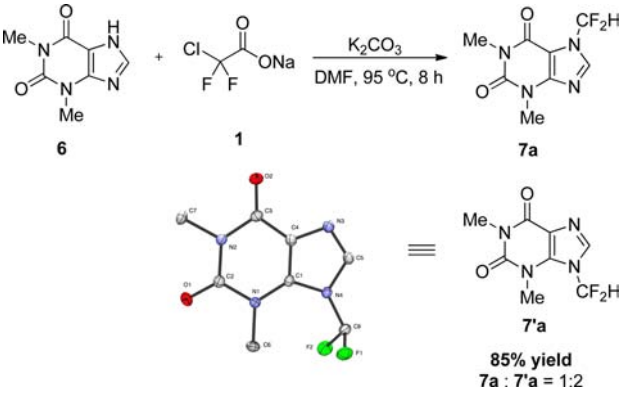
Scheme 3. Difluoromethylation of Heteroaromatic Thiols[a]



[a] Reactions were carried out on a 1.00 mmol scale. Isolated yields (values in parentheses indicates ^{19}F NMR yield). [b] Minor amounts of an unidentified difluoromethylated compound were isolated as a side product.

Scheme 4. Difluoromethylation of Theophylline[a]

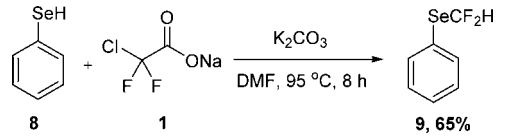


[a] Reaction was carried out on 1.00 mmol scale. Isolated yield.

in high yield (X-ray).[25] Azole compounds gave mixtures of N- and S-difluoromethylation in excellent overall yield,[18a] indicating smaller differences in stability between the two products (**5h**/**5h′** and **5i**/**5i′**). This product ratio was temperature dependent; difluoromethylation of

(25) CCDC 956096, 953257, 956095, and 948730 contains the crystallographic data for **5b**, **5e**, **5j**, and **7a′**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Scheme 5. Difluoromethylation of Phenylselenol[a]



[a] Reaction was carried out on 1.00 mmol scale. Isolated yield.

2-mercaptobenzothiazole **4h** at the higher temperature of 120 °C altered the ratio from 2:1 in favor of $SCHF_2$ (95 °C) to 1:1. 2-Mercaptobenzoxazole **4j** was somewhat anomalous as a substrate, affording the expected $NCHF_2$ compound **5j** in 46% isolated yield (confirmed by X-ray), along with minor amounts of impure difluoromethylated material that did not correspond to the $SCHF_2$ compound (see Supporting Information).

The N-difluoromethylation reaction pathway could be extended to theophylline, **6**, a non-sulfur-containing substrate,[10f] with difluoromethylation being observed at both imidazole nitrogen centers in high overall yield (**7a**:**7a′** = 1:2). An X-ray structure of the major regioisomer characterized it as the 9-$NCHF_2$ regioisomer (Scheme 4).

Finally, we were able to synthesize (difluoromethyl)(phenyl)selane (**9**) from phenylselenol in 65% yield using SCDA (Scheme 5). This compound has recently been shown by Hu to undergo deprotonation and subsequent C–C bond formation, making it a versatile fluorinated synthon for further functionalization.[26]

In conclusion, we have developed a simple and cost-effective protocol for the difluoromethylation of aromatic and heteroaromatic thiols using inexpensive sodium chlorodifluoroacetate. The cost-effectiveness of the transformation is matched by the simplicity of the reaction conditions; K_2CO_3 at 95 °C is sufficient to decarboxylate SCDA in the absence of any transition metal catalyst systems, and the difluorocarbene generated effectively captures a variety of S, N, and Se nucleophiles in generally high yield.

Acknowledgment. We thank the EPSRC for funding (postdoctoral fellowship to V.P.M., Leadership Fellowship to M.F.G.). Dr. James Raftery and Dr. Thomas Storr (University of Manchester) are thanked for X-ray crystallography. Mr. Gareth Smith (University of Manchester) is thanked for mass spectrometry.

Supporting Information Available. Experimental procedures and characterization data for all new compounds is available in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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