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Exploration of the Synthetic Potential of Electrophilic Trifluoromethylthiolating and Difluoromethylthiolating Reagents

Jingjing Zhang,+ Jin-Dong Yang,+ Hanliang Zheng, Xiao-Song Xue*, Herbert Mayr*, Jin-Pei Cheng

Abstract: Electrophilicity parameters (E) of some popular trifluoromethylthiolating and difluoromethylthiolating reagents were determined by following the kinetics of their reactions with a series of enamines and carbanions with known nucleophilicity parameters (N, s_N), using the linear free-energy relationship log $k_2 = s_N(N + E)$. The electrophilic reactivities of these reagents cover a range of 17 orders of magnitude, with Shen and Lu's reagent **1a** being the most reactive and Billard's reagent **1h** the least reactive electrophile. While the observed electrophilic reactivities (E) of the amido-derived trifluoromethylthiolating reagents correlate well with the calculated Gibbs energies of the heterolytic cleavage of the X-SCF₃ bonds (Tt'DA), the cumol-derived reagents **1f** and **1g** are more reactive than expected from the thermodynamics of the O-S cleavage. The E parameters of tri(di)fluoromethylthiolating reagents derived in this work provide an ordering principle for their use in synthesis.

Recently, there has been growing interest in trifluoromethylthio (-SCF₃) and difluoromethylthio (-SCF₂H) groups. Due to their unique properties, such as high lipophilicity and strong electronwithdrawing ability, they may strongly improve the pharmacokinetic properties of lead compounds.^[1] Consequently, a number of shelf-stable electrophilic trifluoromethylthiolating^[2,3,4] and difluoromethylthiolating reagents^[5] that allow efficient incorporation of these groups under mild conditions have been developed by several groups, such as the teams of Billard, [3c-e, g] Shen and Lu,^[3f, h-i, m, 5] and Shibata^[6]. One notable question has remained open, however. That is, can the synthetic potential of these synthetically important reagents be predicted?



Figure 1. Popular electrophilic SCF3 and SCF2H reagents.

We herein report on the quantification of the electrophilicities of some popular tri(di)fluoromethylthiolating reagents (Fig. 1) utilizing the linear free energy relationship (1), where s_N and N

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are solvent-dependent nucleophile-specific parameters, and *E* is an electrophile-specific parameter. Since its introduction in 1994,^[7] eq. (1) has widely been applied for characterizing the electrophilic reactivities of carbocations, Michael acceptors, imines, quinones, and other π -systems.^[8]

$$\log k_2(20 \ ^{\circ}\text{C}) = s_N(N + E)$$
 (1)

We now report on the determination of the electrophilicities of various SCF₃ and SCF₂H reagents **1a-i** by investigating the kinetics of their reactions with enamines (**2a-b**) or carbanions (**2c-g**), whose N and s_N parameters are listed in Table 1.

Table 1. Enamines and carbanions used as reference nucleophiles in this work. $^{[9]}$

Nucleophile ^[a]			N (S _N) ^[b]	λ _{max} [nm]
Ph		2a	8.78 (0.83)	306
	$X = NO_2$	2b-NO ₂	10.42 (0.82)	465
X	X = CN	2b-CN	10.63 (0.84)	375
	X = H	2b-H	11.66 (0.82)	317
	X = OMe	2b-OMe	11.99 (0.84)	296
		2c	14.94 (0.96)	538
0 ₂ N				
×	X = NO ₂	2d-NO ₂	13.91 (0.76)	360
e e	X = COMe	2d-COMe	16.03 (0.86)	340
	X = CN	2d-CN	16.55 (0.78)	328
	$X = SO_2Ph$	2d-SO₂Ph	17.19 (0.56)	325
	X = COPh	2d-COPh	17.46 (0.65)	370
	X = CO ₂ Et	2d-CO₂Et	17.52 (0.74)	327
×	X = CN	2e-CN	19.67 (0.68)	539
0 ₂ N	X = CO ₂ Et	2e-CO₂Et	20.00 (0.71)	550
⊖ O S ^S Ph		2f	22.60 (0.57)	375
NC				

The reactions of the fluoromethylating reagents 1 with the nucleophiles 2 gave the tri(di)fluoromethylthiolated products in 71–91% yield after aqueous workup (Scheme 1 and Table 3, see SI for details). Since analogous reactions can be expected for the combination of 1 with other nucleophiles, product studies have not been performed for all reactions that have been studied kinetically.

The kinetics of the reactions of **1a-i** with enamines **2a-b** or carbanions **2c-g** were studied in CH₃CN or DMSO solution at 20 °C by following the disappearance of the UV/Vis absorptions of the reference nucleophiles **2** under pseudo-first-order conditions ([**1**]₀/[**2**]₀ > 10). The first-order rate constants k_{obs} (s⁻¹) were derived by least-squares fitting of the exponential function $Abs = Abs_0 \cdot \exp(-k_{obs}t) + C$ to the observed time-dependent absorbances. Plots of k_{obs} versus the concentrations of the nucleophiles gave straight lines as shown for one example in Fig. 2 and for all other reactions in the SI. The slopes of these plots correspond to the second-order rate constants k_2 (M⁻¹ s⁻¹) which are summarized in Table 2.





Scheme 1. Reactions of SCF₃/SCF₂H reagents with enamines and carbanions. [a] Yields of isolated products after purification by column chromatography.

Plots of $(\log k_2)/s_N$ vs N for the reactions of **1a,b** with the enamines 2a,b were linear with slopes close to 1.0, showing that these reactions follow eq. 1 (Figure 3a), thus providing the E parameters for 1a,b. Much poorer correlations were found for the analogous reactions of 1c-i with carbanions as illustrated by Figure 3b. Approximate E parameters for 1c-i were, therefore, obtained by enforcing a unity slope in the $(\log k_2)/s_N$ vs N correlations (Fig. 3b). Comparison of the experimental rate constants k_2^{exp} with those calculated by eq. (1) from the *E* values in Table 2 and N and s_N from Table 1 shows agreement within a factor of 30 (right column of Table 2), i. e., within the tolerance limit of eq. (1). Because of the significant scatter in these plots, we did not attempt to improve the correlations by including an electrophile-specific sensitivity parameter s_E.^[10] It has to be admitted, however, that the comparison of k_2^{exp} and k_2^{calcd} in Table 2 may not be representative, because all reaction series in Table 2 refer to reactions with either enamines or carbanions. If there were electrophiles which can be studied with both classes of nucleophiles, larger deviations can be expected.



Figure 2. Monoexponential decay of the absorbance Abs (at 390 nm) with time for the reaction of **2b-CN** (5.62 × 10⁻⁵ M) with 1a (2.55 × 10⁻³ M) in CH₃CN at 20 °C. Inset: Correlation of kobs with the concentrations of 1a.



Figure 3. Plots of $(\log k_2)/s_N$ for the reactions of enamines 2a-b with 1a (a) and carbanions 2c-d with 1d (b) against the nucleophilicity parameters N (see the SI for other reagents).

The graphical presentation of the E parameters in the right part of Fig. 4 indicates the ranking 1a,b >> 1c,d,e > 1f,g >> 1h, in agreement with previous qualitative observations. Shen and Lu's reagent 1a^[3k] (E: -6.06), is the most electrophilic SCF₃ reagent of this series, slightly more reactive than Shen's Ntrifluoromethyl-thiosaccharin 1b^[3h] (E: -6.48). The electrophilicity of Haas' reagent 1d (E: -12.56)[3a] is similar to those of Munavalli's 1c (E: -11.92)^[3b] and Billard's second generation

reference nucleophiles 2 in CH ₃ CN or DMSO at 20 °C							
Electrophile ^[a]	Nucleophile	k ₂ ^{exp} [M ⁻¹ s ⁻¹]	k ₂ ^{calcd} [M ⁻¹ s ⁻¹]	k_2^{exp}/k_2^{calcd}			
Ph ^S N ^S Ph	2a	$(1.62 \pm 0.09) \times 10^2$	1.81 × 10 ²	0.90			
SCF3	2b-H	$(4.17 \pm 0.41) \times 10^4$	3.91 × 10 ⁴	1.07			
	2b-NO ₂	$(5.23 \pm 0.22) \times 10^3$	3.76 × 10 ³	1.39			
E = -0.00	2b-CN	$(7.63 \pm 0.19) \times 10^3$ 6.90×10^3		1.11			
	2b-OMe	$(6.78 \pm 0.35) \times 10^4$	9.58 × 10 ⁴	0.71			
	2a	$(6.38 \pm 0.66) \times 10^{1}$	8.11 × 10 ¹	0.79			
S N-SCF3	2b-H	$(1.96 \pm 0.21) \times 10^4$	1.77 × 10 ⁴	1.11			
0 Ŭ 1b	2b-NO ₂	$(2.42 \pm 0.06) \times 10^3$	1.70 × 10 ³	1.42			
E = -6.48	2b-CN	$(4.13 \pm 0.08) \times 10^3$	3.06×10^{3}	1.35			
	2b-OMe	$(2.61 \pm 0.08) \times 10^4$	4.25 × 10 ⁴	0.61			
	2d-NO ₂	8.06 ± 0.17	3.25×10^{1}	0.25			
N-SCF3	2c	$(4.62 \pm 0.15) \times 10^{1}$	7.93 × 10 ²	0.06			
0 1c	2d-COMe	$(1.16 \pm 0.05) \times 10^4$	3.42 × 10 ³	3.39			
	2d-CN	$(1.49 \pm 0.10) \times 10^4$	4.09 × 10 ³	3.64			
<i>E</i> = -11.92	2d-SO₂Ph	$(1.98 \pm 0.11) \times 10^3$	8.94 × 10 ²	2.21			
	2d-COPh	$(1.89 \pm 0.09) \times 10^3$	3.99 × 10 ³	0.47			
	2d-CO ₂ Et	(2.77 ± 0.18) × 10 ⁴	1.39 × 10 ⁴	1.99			
- N-SCE	2d-NO ₂	2.03 ± 0.08	1.06 × 10 ¹	0.19			
YN-SCF3	2c	$(1.26 \pm 0.05) \times 10^{1}$	1.93 × 10 ²	0.07			
1d	2d-COMe	$(3.28 \pm 0.03) \times 10^3$	9.64 × 10 ²	3.40			
<i>E</i> = -12.56	2d-CN	$(3.48 \pm 0.04) \times 10^3$	1.29 × 10 ³	2.70			
	2d-CO₂Et	$(1.54 \pm 0.02) \times 10^4$	4.68 × 10 ³	3.29			
Me Me	2d-NO ₂	0.71 ± 0.03	2.28	0.31			
0 ⁰ 0 1e	2c	0.94 ± 0.04	2.75 × 10 ¹	0.03			
<i>E</i> = -13.44	2d-COMe	$(5.54 \pm 0.30) \times 10^2$	1.69 × 10 ²	3.28			
	2d-CN	$(6.38 \pm 0.30) \times 10^2$	2.67 × 10 ²	2.39			
	2d-CO₂Et	$(4.14 \pm 0.14) \times 10^3$	1.05 × 10 ³	3.94			
Me Me	2e-CN	$(5.41 \pm 0.12) \times 10^3$	1.03 × 10 ⁴	0.53			
1f	2e-CO₂Et	$(1.11 \pm 0.07) \times 10^4$	2.65 × 10 ⁴	0.42			
E = -13.77	2f	$(3.16 \pm 0.06) \times 10^5$	1.08 × 10⁵	2.93			
OSCF ₃	2d-CO₂Et	$(2.63 \pm 0.13) \times 10^2$	1.66 × 10 ²	1.58			
Me	2e-CN	$(4.45 \pm 0.43) \times 10^2$	3.18 × 10 ³	0.14			
^{1g} E	2e-CO₂Et	$(1.88 \pm 0.09) \times 10^3$	7.78 × 10 ³	0.24			
= -14.52	2f	(3.56 ± 0.13) × 10 ⁵	4.03 × 10 ⁴	8.83			
Me		, <i>i</i>					
Ph ^{/''`} SCF ₃ 1h	2g	$(2.56 \pm 0.17) \times 10^{2[b]}$	identical	-			
<i>E</i> = -23.32	-	,					
0	2d-NO ₂	$(1.76 \pm 0.04) \times 10^{1}$	3.61 × 10 ¹	0.49			
N-SCF ₂ H	2c	$(1.19 \pm 0.03) \times 10^2$	9.05 × 10 ²	0.13			
	2d-COMe	$(1.53 \pm 0.05) \times 10^4$	3.86 × 10 ³	3.96			
1i	2d-CN	(1.36 ± 0.13) × 10 ⁴	4.55 × 10 ³	2.99			
E= -11.86	2d-COPh	$(1.51 \pm 0.11) \times 10^4$	4.37 × 10 ³	3.46			
2- 11.00				-			

2e-CN $(5.46 \pm 0.37) \times 10^4$ 2.05 × 10⁵ [a] Electrophilicity parameters E were derived according to Equation (1), and 1a and 1b were measured in CH₃CN, other reagents were measured in DMSO. [b] Only one k_2^{exp} value was used for the determination of E.

reagent 1e (E: -13.44)^[3g]. The electrophilicities of Shen and Lu's first- (1g)^[3f] and second- (1f)^[3i] generation O-SCF₃ reagents are very close to each other, in line with Shen and Lu's report that cumyl trifluoromethanesulfenates with or without substituent at the aromatic ring show similar reactivity toward a variety of nucleophiles.^[3i] Billard's first generation reagent 1h^[3c] (E: -23.32), is by far the least electrophilic reagent studied, but can efficiently be activated by Brønsted and Lewis acids. [1c,1]] Shen and Lu's difluoromethylthiolating reagent 1i^[5] (E: -11.86) is only slightly more electrophilic than its SCF₃ analog 1c, suggesting

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that replacement of one F by H might also have little effect on the electrophilicities of the other SCF_3 reagents listed in Fig. 4.



Figure 4. Predicting the scope of non-catalyzed reactions of SCF₃/SCF₂H reagents 1a-i with carbon-centered nucleophiles. – N parameters from. Ref. 8.

How can synthetic chemists make use of the *E* parameters determined in this work? The left part of Fig. 4 lists carboncentered nucleophiles with increasing reactivities from top to bottom. Both scales are arranged in a way, that systems at the same level (E + N = -3) should react with a rate constant of 10^{-3} M⁻¹s⁻¹ (from eq (1) for $s_N = 1.0$ at 20 °C), which corresponds to a half reaction time of somewhat more than 1 h for 0.2 M solutions. Thus, one can expect that at room temperature the tri(di)fluoromethylthiolating agents 1 should react with nucleophiles on the same level or located lower in Fig. 4.

In order to examine this prediction, we have selected a representative electrophile from each of the four groups and determined the yields of their reactions with typical nucleophiles at 20 °C. Table 3 shows that **1b** was the only reagent which underwent non-catalyzed reactions with the indoles listed in Fig. 4. In agreement with this observation, Shen, Lu, and co-workers reported that in the absence of any additive, reagent **1a** which has a similar *E* value as **1b** could trifluoromethylthiolate indoles and pyrroles under mild conditions.^[3k] The same paper stated, however, that also styrene (*N* = 0.78) reacted with **1a** at 20 °C though styrene is above **1a** in Fig. 4, and eq. (1) predicts a rate constant of 10⁻⁵ M⁻¹s⁻¹, which corresponds to a half reaction time of 2 days at the given conditions. This example indicates one of

Table 3. Reactions of SCF₃ reagents with pyrroles, indoles, enamines and carbanions in CH₃CN.^[a]

Nucleophile	N	1b ^[e]	1d ^[f]	1g ^[f]	1h ^[f]	Product
	5.55 ^[b]	100%	0	0	_[1]	SCF3
Me	5.75 ^[b]	100%	0	0	_[]	SCF3
	6.91 ^[c]	100%	0	0	_[i]	$\bigcup_{SCF_3}^{H}$
	10.67 ^[c]	100%	55%	0	_[i]	F ₃ CS
MeO Ph	11.99 ^[c]	85% ^[k]	60% ^[g]	44% ^[g]	0	F ₃ CS Ph MeO
C" O	14.91 ^[c]	55% ^[g,h]	81% ^[g]	76% ^[g]	0	SCF3
	16.03 ^[d]	+0	82% ^[k]	+0	0	
Ph CO ₂ Et	17.52 ^[d]	+0	72% ^[k]	+0	0	Ph CO ₂ Et
O2N CN	19.67 ^[d]	+01	+0	83% ^[k]	0	

[a] Yields were determined by ¹H NMR using CH₂Br₂ as the internal standard. [b] Measured in CH₂Cl₂. [c] Measured in CH₃CN. [d] Measured in DMSO. [e] Reaction conditions: SCF₃ reagent (0.2 mmol), nucleophiles (0.2 mmol), CH₃CN (1 mL), 20 °C, 3 h. [f] Reaction conditions: SCF₃ reagents (0.2 mmol), nucleophiles (0.2 mmol), CH₃CN (1 mL), 20 °C, 8 h. [g] Yields were determined by ¹H NMR after hydrolysis. [h] With some not identified side products. [i] Not tested, because **1h** did not even react with stronger nucleophiles. [j] Reaction expected, but not tested. [k] Isolated yields.

the limitations of eq. (1): Since eq. (1) is calibrated for reactions in which only one new σ -bond is formed in the rate-limiting step, it is not applicable to reactions with bridging electrophiles. The suggested intermediacy of episulfonium ions from **1a** and styrenes^[3k] is thus supported by the fact that these reactions proceed faster than calculated by eq. (1). Nucleophilic assistance by the solvent DMF through stabilizing the developing positive charge at the benzylic carbon may also accelerate the electrophilic attack of **1a** at CC-double bonds in this solvent. Surprisingly, **1b** did not react with 3-aryl-substituted furans in DMF at 90 °C, but good yields were obtained when NaCl was present.^[11]

Whereas the electrophilicity of **1d** is not sufficient for attack at the indoles depicted in Fig. 4, Table 3 shows its reaction with 2,4-dimethylpyrrole as well as with enamines and carbanions, which are positioned lower in Fig. 4. In line with these findings, agent **1c**, which is slightly more electrophilic than **1d**, has previously been reported to trifluoromethylthiolate enamines at room temperature.^[3b]

Lu and Shen's reagent **1g**, which did not react with 2,4dimethylpyrrole under the conditions of Table 3, was found to react with enamines, including those which are only slightly more nucleophilic than 2,4-dimethylpyrrole.

Whereas **1d** and **1g** reacted smoothly with the stabilized carbanions shown in Table 3, Fig. 4 indicates that the electrophilicity of **1h** is so low that it does not even react with carbanions of N < 20. In order to determine its electrophilicity we investigated its reaction with **2g**, the anion derived from ethyl phenylacetate, which is so nucleophilic (N = 27.54) that it did not even fit in Fig.4. The nitrogen of **1h** is rather basic, however, that it can easily be activated by Brønsted and Lewis acids to form reagents which even react with ordinary alkenes^[3d] and

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moderately activated arenes.^[4] Since PhNHSCF₃ (**1h**') can be expected not to differ too much in reactivity from its methylated analog **1h**, its failure to undergo non-catalyzed reactions with allylsilanes is also in line with Fig. 4. The reaction proceeds with good yields, however, when **1h'** is activated by acetyl chloride.^[12]

Please note that Fig. 4 includes only carbon nucleophiles. Since the *N* and s_N parameters have been derived from reactions with C-electrophiles, and *E* parameters have been derived from reactions with C-nucleophiles, eq. (1) can only be applied to reactions where at least one of the reaction centers is carbon. One can assume, however, that the relative reactivities of electrophiles **1a-i** also hold with respect to other types of nucleophiles, and Cahard and coworkers have recently shown that allylic alcohols react with the highly electrophilic **1b** in the presence of base to give trifluoromethyl sulfoxides after [2,3]-sigmatropic rearrangement.^[13]

In line with a recent analysis of the electrophilic reactivities of Michael acceptors^[14], Fig. S1 shows that there is no significant correlation between the electrophilic reactivities E of SCF₃ reagents and their LUMO energies. A good linear correlation of electrophilic reactivities E of N-SCF₃ reagents with their calculated Tt⁺DA parameters^[15] was observed, however (Fig. 5a). positive deviation of 1f,g from this so-called The Bell-Evans-Polanyi correlation line^[16] for N-SCF₃ reagents indicates that O-SCF₃ compounds react via lower intrinsic barriers, in line with Hoz' rule^[17] that in nucleophilic substitutions. the intrinsic barriers are the lower, the further right nucleophiles and nucleofuges are in the periodic table. The even better correlation between the electrophilic reactivities E and the pK_a values of the corresponding X-H acids in water is probably due to the fact that the lower intrinsic barriers for the reactions of the O-SCF₃ reagents are compensated by a larger difference between O-H and O-S bond energies than between N-H and N-S bond energies (Fig. 5b). These correlations allow a quick estimation of electrophilic reactivities for new reagents from thermodynamic data.



Figure 5. Plots of measured electrophilicities *E* against (a) the corresponding Tt^{*}DA values taken from ref. 15 (not including **1f** and **1g**), and (b) experimental pK_a values of corresponding X-H acids (in water)^[18].

In summary, the second-order rate constants of **1a-i** with enamines and carbanions have been used to derive the empirical electrophilicity parameters *E* of the most common tri(di)fluoromethylthiolating reagents. The rule of thumb that uncatalyzed reactions of the tri(di)fluoromethylthiolating reagents **1a-i** will take place with those nucleophiles positioned below themselves in Fig. 4 (i.e., when E + N > -3) has been demonstrated to be a good guide for the design of tri(di)fluoromethylthiolating reactions by the product studies in Table 3 and many examples reported in the literature.

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COMMUNICATION

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COMMUNICATION



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Exploration of the Synthetic Potential of Electrophilic Trifluoromethylthiolating and Difluoromethylthiolating Reagents

Electrophilicities (E) of some popular trifluoromethylthiolating and difluoromethylthiolating reagents were investigated by following the kinetics of their reactions with a series of enamines and carbanions with known nucleophilicity parameters (N, s_N) using the linear free-energy relationship log $k_2 = s_N(N + E)$. The electrophilicity parameters for these reagents thus derived cover a reactivity range of 17 orders of magnitude. The definition of the E parameters of tri(di)fluoromethylthiolating reagents offers an expeditious means of predicting unprecedented reactions.