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POWER-VARIABLE TRIFLUOROMETHYLATING AGENTS, (TRIFLUOROMETHYL)DIBENZOTHIO- AND -SELENOPHENIUM SALT SYSTEM

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(Trifluoromethyl)dibenzothio- and -selenophenium triflates and their nitro derivatives differing in trifluoromethylating power were developed as a new system of electrophilic trifluoromethylating agents.

Trifluoromethylated organic compounds are of importance in the development of new or more effective medicines because of the unique character of the trifluoromethyl substituent.[1] However, methods for introducing a trifluoromethyl group into an organic compound have proven unsatisfactory so far.[2] In particular, the lack of a good electrophilic reagent has been cited as the reason for the scarcity of reports on electrophilic trifluoromethylation. Yagupol'skii *et al.* indicated (trifluoromethyl)diarylsulfonium salts to react with sodium *p*-nitrobenzenethiolate to give *p*-nitro(trifluoromethylthio)benzene.[3] We wish to report on (trifluoromethyl)-dibenzothio- and -selenophenium triflates **1** and **2** and their derivatives **3-5** as a new system of electrophilic trifluoromethylating agents, the trifluoromethylating power-variable reagents.

(Trifluoromethyl)dibenzothiophenium triflate (**1**) was synthesized in 75% yield by treatment of **8** with an equivalent amount of triflic anhydride in 1,1,2-trichlorotrifluoroethane[4] at room temperature for 2 d. Triflate **1** appeared as white precipitates as the reaction proceeded. Selenium analog **2** was obtained more readily by similar treatment of **9** (0°C→room temperature, 2 h, 94% yield). Sulfoxide **8** and selenoxide **9** were prepared in 98 and 96% yields by oxidation of sulfide **6**[5] and selenide **7**[6] with m-chloroperbenzoic acid, respectively. Triflate **1** was also synthesized in 57% yield from **6** by treatment with 1.2 equivalent amounts of molecular fluorine diluted with nitrogen (F_2/N_2=1/9) in trichlorofluoromethane at -78°C, followed by treatment with an equivalent amount of triflic acid at -78°C to room temperature for *ca.* 1 h. Mononitro derivative **3** was synthesized in 76% yield by nitration of **1** with 1.3 equivalent amounts of nitronium triflate, which was prepared *in situ* from 94% nitric acid and a slight excess of triflic anhydride, in nitromethane at room temperature overnight. Dinitro derivatives **4** and **5** were obtained in 85 and 83% yields by treatment of **1** and **2** with 3 equivalent amounts of nitronium triflate, prepared as above, at room temperature for 3 d and 3 h, respectively, with no added nitromethane solvent. Triflates **1-5** were stable, nonhygroscopic crystals,[7] but the most reactive **4** decomposed slowly in solution at room temperature.

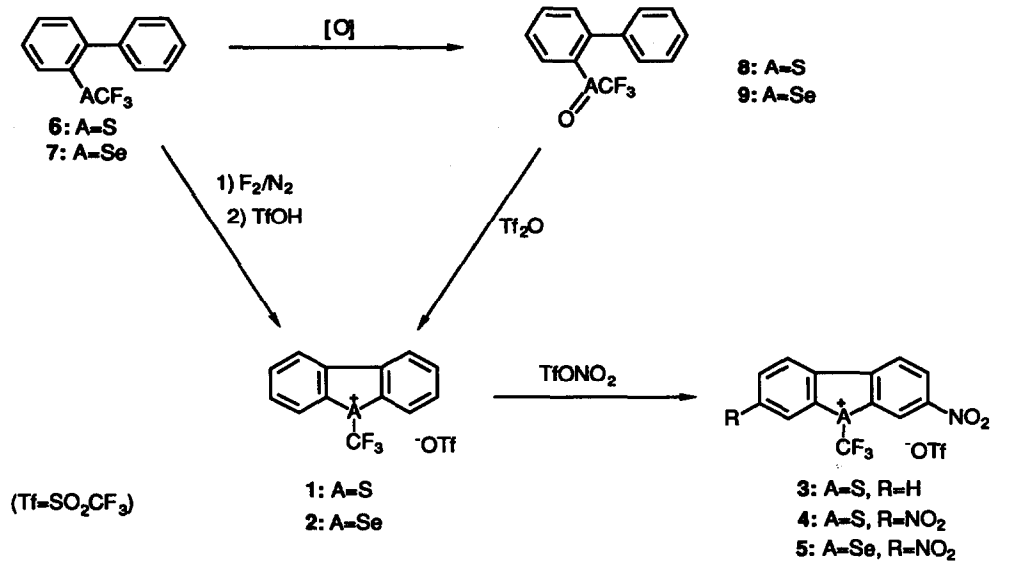
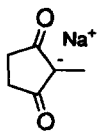
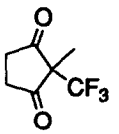
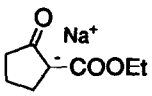
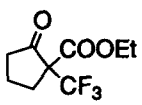
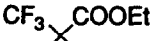
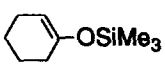
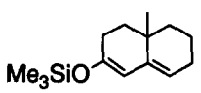
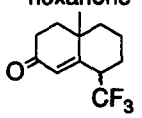
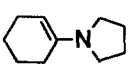


Table 1 shows the results of trifluormethylation of various substrates with 1-5. Triflates 1 and 2 readily reacted with sodium salts of active methylene compounds in dimethylformamide (DMF) to give the trifluoromethylated products. With an β-diketone, the yield was high, but it decreased on going to a β-keto ester and to a malonate. The yields obtained by thiophenium salt 1 were slightly higher than those by selenophenium salt 2. In contrast, with a hard carbanion, PhC≡CLi, 2 trifluoromethylated the carbanion in better yield than 1 (Runs 6 and 7). Attempts to trifluoromethylate *n*-$C_{12}H_{25}MgBr$, PhMrBr, and *n*-C_4H_9Li failed at the present stage of our research. Trifluoromethylation of enol trimethylsilyl ethers of a ketone and an α,β-unsaturated ketone was accomplished by heating with 1 at 80°C in DMF in the presence of an equivalent amount of pyridine as a base, giving an α-trifluoromethyl ketone and a γ-trifluoromethyl-α,β-unsaturated ketone, respectively (Runs 8 and 9). Treatment of an active enamine with 1 in the presence of 4-(dimethylamino)pyridine (1 eq), followed by acidic hydrolysis, gave a mixture of mono- and bistrifluoromethyl ketones (Run 10). Triflate 4 readily reacted with aniline, an activated aromatic, at room temperature to give a 2.2:1 mixture of *o*- and *p*-(trifluoromethyl)anilines in 83% yield (Run 11), while 1 reacted very slowly as seen in Table 2. The reaction of 2 with sodium salt of an alkanethiol produced a trifluoromethylthioalkane in high yield, while 1 gave 47% of the product along with 30% of a nonfluoro disulfide as a byproduct (Runs 13 and 14). Triflate 1 reacted with sodium iodide to give trifluoromethyl iodide in 70% yield. The reaction with sodium iodide was found to be accelerated by light.

As evident from the results of controlled experiments shown in Table 2, 1-5 had different trifluoromethylating power and the order was 2<1<3<5<4. Thus, the power increased on going from unsubstituted salts to mononitro and to dinitro salts and from selenium salts to thiophenium salts. Each order in the thio- and selenophenium salt series is in agreement with the order of ^{19}F NMR chemical shifts of the trifluoromethyl groups, which may reflect electron-

Table 1. Trifluoromethylations with Thio- and Selenophenium Triflates **1-5**.

Run	Substrate[a]	"CF_3^+"	Solv.	Temp(°C)	Time[b]	Product[c]	Y(%)[d]	^{19}F-NMR[e]
1		1	DMF	-65 → R.t.	O.n.		83	69.8 (s)
2		2	DMF	-65 → R.t.	3 h		74	69.8 (s)
3		1	DMF	-65 → R.t.	2.5 h		67	69.0 (s)
4		1	DMF	-65 → R.t.	5 h		38	70.9 (s)
5		2	DMF	-65 → R.t.	3 h		26	70.9 (s)
6	PhC≡CLi	1	THF	-78 → R.t.	O.n.	$PhC{\equiv}CCF_3$	30	49.7 (s)
7	PhC≡CLi	2	THF	-78 → R.t.	O.n.	$PhC{\equiv}CCF_3$	46	49.7 (s)
8[f]		1	DMF	80	O.n.	2-CF_3-cyclo-hexanone	65	69.2 (d)[j]
9[f]		1	DMF	100	O.n.		54 15	68.3 (dd)[k] 66.6 (d)[l]
10[g]		1	DMF	0	2 h	2-CF_3-cyclo-hexanone 2,6-Di(CF_3)-cyclo-hexanone	49 26	69.2 (d)[j] 69.8 (d)[m]
11	Aniline	4	DMF	R.t.	2 h	*o*-CF_3-aniline *p*-CF_3-aniline	57 26	— —
12	*n*-$C_{12}H_{25}SNa$	1	THF	R.t.	0.5 h	*n*-$C_{12}H_{25}SCF_3$	47[h]	41.5 (s)
13	*n*-$C_{12}H_{25}SNa$	2	THF	R.t.	0.5 h	*n*-$C_{12}H_{25}SCF_3$	87	41.5 (s)
14	NaI	1	DMF	R.t.	3 d	CF_3I	70	–
15	Ph_3P	3	CH_3CN	R.t.[i]	5 d	$Ph_3(CF_3)P^+{}^-OTf$	58	58.3 (d)[n]
16	Ph_3P	4	CH_3CN	R.t.[i]	1 d	$Ph_3(CF_3)P^+{}^-OTf$	70	58.3 (d)[n]
17	Ph_3P	5	CH_3CN	R.t.[i]	4 d	$Ph_3(CF_3)P^+{}^-OTf$	22	58.3 (d)[n]

a) Mol ratios of substrate/"CF_3^+" were 1 except for Runs 6, 7, and 11. Mol ratios were *ca.* 1.35 in Runs 6 and 7, and 2 in Run 11. b) O.n.= overnight. c) Satisfactory elemental analyses were obtained for new compounds. d) Yields were determined by ^{19}F NMR of the reaction mixtures except for Run 12 (an isolated yield). e) ppm, upfield from CCl_3F as an internal standard in $CDCl_3$. In Runs 6 and 7, THF was used as a solvent. f) This reaction was done in the presence of pyridine (1 eq). g) This reaction was done in the presence of 4-(dimethylamino)pyridine (1 eq). The following hydrolysis was carried out by adding conc. HCl to the reaction mixture and stirring at r.t. overnight. h) (*n*-$C_{12}H_{25}S)_2$ was isolated in 30% yield as a byproduct. i) Ph_3P was mixed with **3**, **4**, or **5** in DMF at -45°C. Then the mixture was warmed to r.t. in *ca.* 2 h and the stirring was continued at r.t. for the time shown in this table. j) J=8.5 Hz. k) J=9.0, 2.5 Hz. l) J=11.3 Hz. m) J=8 Hz. n) J=*ca.* 90 Hz.

Table 2. Controlled Trifluoromethylation of Aniline with 1-5[1)]

Run	"CF_3^+"	Temp	Time (h)	Yields of CF_3-Aniline		Remaining "CF_3^+"
				o-CF_3	*p*-CF_3	
1	1	R.t.	0.5	0%	0%	100%
		R.t.	20	14	6	63
2	1	80°C	5	37	15	0
3	2	R.t.	0.5	0	0	100
		R.t.	20	7	4	83
4	3	R.t.	0.5	18	11	71
5	4	R.t.	0.5	54	20	5
6	5	R.t.	0.5	39	16	30

1) Mol ratio; aniline/"CF_3^+"=2. Solv.; DMF. Each of the reaction mixtures was traced by ^{19}F NMR, and yields of CF_3-anilines and the remainder of **1-5** were determined by internal standard method.

deficiency at the cationic sulfur or selenium atoms induced by the electron-withdrawing nitro group; **1** (52.9 ppm in CD_3CN)[8)] < **3** (50.3) < **4** (48.8); **2** (45.5) < **5** (42.0). A great difference in power between nitro salts (**3**, **4**, and **5**) and unsubstituted salts (**1** and **2**) was observed in the reactions with triphenylphosphine to give (trifluoromethyl)triphenylphosphonium triflate. Thus, **4**, **5**, and **3** reacted with it at room temperature at different rates (Runs 15-17 in Table 1), while neither **1** nor **2** reacted. **1** did not react even at 100°C, but **1** itself decomposed.

Alkaline hydrolysis of **1**, **3**, and **4** provided interesting information regarding the trifluoromethylation mechanism. Thus, **1** and **3** gave the corresponding dibenzothiophene S-oxide only, while **4** gave a 1:4 mixture of 2,7-dinitrodibenzothiophene and its S-oxide. This suggests that a great difference in the reaction mechanism may exist between **4** and **1** or **3**.

To our knowledge, there have been no reports so far on trifluoromethylation of carbanions, enol silyl ethers, a phosphine, and an iodide anion as mentioned above. Thus, the power-variable thio- and selenophenium salt system is expected to serve as widely applicable reagents for electrophilic trifluoromethylation.

References and Notes

1) "Biomedicinal Aspects of Fluorine Chemistry," ed by R.Filler and Y.Kobayashi, Kodansha Ltd., Tokyo (1982). 2) The latest review and papers: J.T.Welch, *Tetrahedron*, **43**, 3123 (1987); K. Uneyama and K.Ueda, *Chem. Lett.*, **1988**, 853; G.K.S.Prakash, R.Krishnamurti, and G.A.Olah, *J. Am. Chem. Soc.*, **111**, 393 (1989); Q.-Y.Chen and S.-W.Wu, *J. Chem. Soc., Chem. Commun.*, **1989**, 705; G.Pawelke, *J. Fluorine Chem.*, **42**, 429 (1989); G.P.Stahly and D.R. Bell, *J. Org. Chem.*, **54**, 2873 (1989). 3) L.M.Yagupol'skii, N.V.Kondratenko, and G.N.Timofeeva, *J. Org. Chem. USSR*, **20**, 103 (1984). 4) Dichloromethane can be used instead of the trichlorotrifluoroethane. 5) **6** was prepared in 88% yield by reaction of sodium salt of 2-mercaptobiphenyl with trifluoromethyl bromide in DMF at 0°C under irradiation with high pressure Hg lamp. **6**: oil, ^{19}F NMR (in $CDCl_3$)[8)] 42.5 (s). 6) **7** was prepared in 67% overall yield from 2-selenocyanatobiphenyl by reduction with sodium borohydride in DMF at -30°C followed by treatment with trifluoromethyl iodide at -30°C → room temperature. **7**: mp 44-45°C, ^{19}F NMR (in $CDCl_3$)[8)] 36.0 (s). 7) Mp (°C): **1**, 155; **2**, 170-172; **3**, 153; **4**, 130-135 (dec.); **5**, 198-200 (dec.). 8) Upfield from CCl_3F as an internal standard.

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