A New General Synthesis of Bistetrafluoroborates of 2,3,4,5-Tetrasubstituted 1,3,4-Thiadiazoliums

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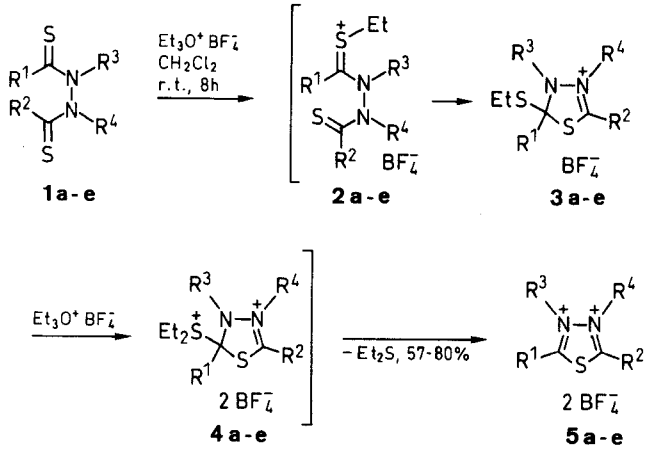
A new preparative method for the synthesis of bistetrafluoroborates of 2,3,4,5-tetrasubstituted 1,3,4-thiadiazoliums **5a–e** from *N,N*-dialkyl-*N,N*-dithioacylhydrazines **1a–e** is reported. This reaction is extended to the synthesis of bistetrafluoroborate of 3,5-bis(*N,N*-dimethyliminium)-1,2,4-trithiolane (**7**) starting from tetramethylthiuram disulfide (**6**). The mechanism of the reaction is discussed.

The derivatives of 1,3,4-thiadiazoles are of considerable importance in pharmacology and in the synthesis of dyes.[1] The main route to 1,3,4-thiadiazoles is the cyclization of the unit S=C–N–N–C=S,[1] which was regarded as 1,5-electrocyclization by Huisgen.[2] This method affords the neutral heterocycle as well as the monoquaternized form.[3] The only way to obtain diquaternary salts is to treat 1,3,4-thiadiazoles with a strong alkylating agent such as trimethyloxonium tetrafluoroborate.[4] However, use of tetraethyloxonium tetrafluoroborate affords only the monoquaternary salt.

In connection with our study on *N,N'*-dialkyl-*N,N'*-diacylhydrazines,[5] we report here a new synthesis of bistetrafluoroborates of 2,3,4,5-tetrasubstituted 1,3,4-thiadiazoliums **5** from *N,N'*-dialkyl-*N,N'*-dithioacylhydrazines **1**.



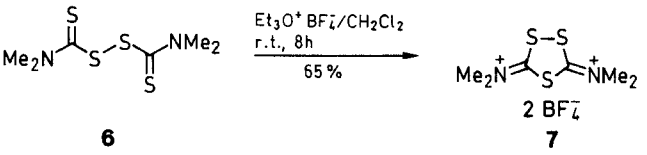
1–5	R^1	R^2	R^3	R^4
a	Me	Me	Me	Me
b	Ph	Ph	Me	Me
c	4-$MeOC_6H_4$	4-$MeOC_6H_4$	Me	Me
d	Me	Me	Ph	Ph
e	1-naphthylmethyl	Me	Me	Me

Scheme 1

Treatment of **1** with two equivalents of triethyloxonium tetrafluoroborate in dichloromethane gave the thiadiazolium salts **2** in good yields (Scheme 1 and Table 2). An attempt to run the cyclization using a Lewis acid (3 equivalents of boron trifluoride) led to inferior results.

We believe that cyclization of **1** to **5** involves the following steps: (i) monoalkylation of **1**; (ii) 1,5-electrocyclization of cation **2** into **3**; (iii) second alkylation of **3** on the most nucleophilic center leading to dication **4**; (iv) elimination of diethyl sulfide with the formation of **5** (Scheme 1).

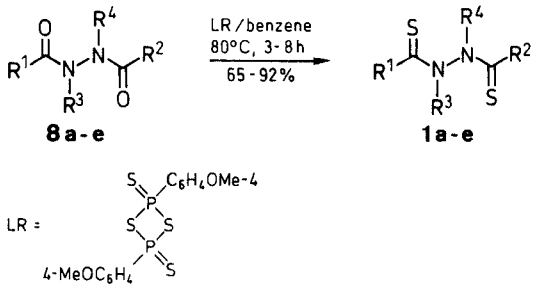
The present method of cyclization of thiocarbonyl compounds may be of more general use. Thus, tetramethylthiuram disulfide (**6**) was converted under the same conditions into 3,5-bis(*N,N*-dimethyliminium)1,2,4-trithiolane (**7**) in good yield.



Scheme 2

The above reactions are the first example of 1,5-electrocyclization leading to dicationic heterocycles. Due to the accessibility of compounds **1** with different R^1-R^4, our synthesis of **5** is general.

The starting compounds **1a–e** have not been previously described and were synthesized by thionation of *N,N'*-dialkyl-*N,N'*-diacylhydrazines **8** with Lawesson reagent (LR) (Scheme 3, Table 1).



Scheme 3

Tetramethylthiuram disulfide (**6**) was purchased from Aldrich. CH_2Cl_2 was dried over molecular sieves (4Å). Lawesson reagent,[6] hydrazines **8a**,[7] **8b**,[8] **8d**,[5d] and **8e**[5b] were synthesized according to literature. Hydrazine **8c** was prepared adopting the procedure reported in Ref. 5d. The compounds were purified by chromatography on L 100/400 and L 5/40 silica gel.

8c; yield: 70%; mp 98–99°C.

$C_{18}H_{20}N_2O_4$	calc.	C 65.8	H 6.14	N 8.53
(328.4)	found	65.48	6.00	8.36

^{1}H NMR (CD_3CN/TMS): δ = 3.20 (s, 6H, NCH_3), 3.80 (s, 6H, OCH_3), 7.00 (d, 4H_{arom}, J = 9.4 Hz), 8.15 (d, 4H_{arom}, J = 9.4 Hz).

The following instruments were used: 1H NMR: Bruker WM-250 (250 MHz) and VXR-Varian-400 (400 MHz) spectrometers.

Table 1. Compounds **1** Prepared

Product[a]	Yield (%)	mp (°C)	Molecular Formula[b]	^{1}H NMR (CD_3CN/TMS) δ			
				R^1	R^2	R^3	R^4
1a	65	111–112	$C_6H_{12}N_2S_2$ (176.3)	2.45 (s), 2.47 (s)	2.51 (s)(6H)	3.51 (s), 3.53 (s)	3.59 (s, 6H)
1b	92	159–160	$C_{16}H_{16}N_2S_2$ (300.4)	7.20–7.50 (m, 10H)		3.23 (s), 3.49 (s)	3.84 (s, 6H)
1c	85	149–150	$C_{18}H_{20}N_2O_2S_2$ (360.5)	3.83 (s), 3.88 (s) 6.90–7.50 (m, 8H)	3.89 (s) (6H)	3.26 (s), 3.53 (s)	3.81 (s, 6H)
1d	67	152–153	$C_{16}H_{16}N_2S_2$ (300.4)	2.39 (s, 6H)		7.20–7.58 (m, 10H)	
1e[c]	73	97–98	$C_{16}H_{18}N_2S_2$ (302.4)	4.37 (s), 4.66 (s) (2H, CH_2) 7.35–8.15 (m, 7H)	2.01 (s), 2.65 (s) (3H, CH_3)	3.68 (s), 3.62 (s) (3H, CH_3)	3.51 (s), 3.54 (s) (3H, CH_3)

[a] Thiohydrazides **1a–c** exist in solution in three geometric isomers cis/cis, cis/trans, trans/trans with respect to the thioamide group.
[b] Satisfactory microanalyses obtained: C ± 0.42, H ± 0.17, N ± 0.38, S ± 0.34.
[c] ^{1}H NMR spectrum was recorded in DMSO-d_6. Compound **1e** exists in two isomers.

Table 2. Compounds **5** Prepared

Product	Yield (%)	mp (°C)	Molecular Formula[a]	^{1}H NMR (CF_3CO_2D/TMS) δ, J (Hz)
5a	80	98–100	$C_6H_{12}B_2F_8N_2S$ (317.9)	3.42 (s, 6H, 2, 5-CH_3), 4.67 (s, 6H, 3, 4-CH_3)
5b	68	170–172	$C_{16}H_{16}B_2F_8N_2S$ (442.0)	4.98 (s, 6H, 3, 4-CH_3), 8.01–8.28 (m, 10H, 2, 5-C_6H_5)
5c	71	157–158	$C_{18}H_{20}B_2F_8N_2O_2S$ (502.0)	4.09 (s, 6H, s, 6H, 2 × Ar-OCH_3), 4.76 (s, 6H, 3, 4-CH_3), 7.39 (d, 4H_{arom}, J = 8.4), 8.01 (d, 4H_{arom}, J = 8.4)
5d	57	148–149	$C_{16}H_{16}B_2F_8N_2S$ (442.0)	3.43 (s, 6H, 2,5-CH_3), 7.81–7.98 (m, 10H, 3,4-C_6H_5)
5e	75	180–182	$C_{16}H_{18}B_2F_8N_2S$ (444.0)	3.32 (s, 3H, 2-CH_3), 4.82 (s, 3H 3-CH_3), 5.04 (s, 3H, 4-CH_3), 5.49 (s, 2H, CH_2), 7.70–8.30 (m, 7H_{arom})
7	65	188–190	$C_6H_{12}B_2F_8N_2S_3$ (382.0)	3.85, 3.98 [s, N $(CH_3)_2$]

[a] Satisfactory microanalyses obtained: C ± 0.35, H ± 0.35, N ± 0.43, S ± 0.31.

***N,N'*-Dialkyl-*N,N'*-dithioacylhydrazines 1a–e; General Procedure:**
A solution of **8a–e** (10 mmol) and Lawesson Reagent (4.4 g, 10 mmol) in anhydr. benzene (75 mL) was refluxed for 3–8 h. The benzene was removed by evaporation in vacuo and the residue was purified by column chromatography on silica gel (benzene/acetone, 10:1). Recrystallization from EtOH gave compounds **1a–e** (Table 1).

Bistetrafluorborates of 2,3,4,5-Tetrasubstituted 1,3,4-Thiadiazolium 5a–e and 3,5-Bis(*N,N*-dimethyliminium)-1,2,4-trithione (7); General Procedure:
A solution of **1a–e** [or tetramethylthiuram disulfide (**6**)] (1 mmol) and $Et_3O^+BF_4^-$ (2 mmol) in anhydr. CH_2Cl_2 (10 mL) was stirred in an atmosphere of Ar at r.t. for 8 h. The precipitate was filtered, washed with anhydr. CH_2Cl_2 and dried (P_2O_5) (Table 2). The compounds were stored in a vacuum desiccator over P_2O_5.

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