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Nucleophilic Reactions on 1-Trifluoromethanesulfonylpyridinium Trifluoromethanesulfonate (Triflylpyridinium Triflate, TPT). Ring-Opening and “Unexpected” 1,4-Dihydropyridine Reaction Products[1]

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The reaction products of 1-trifluoromethanesulfonylpyridinium trifluoromethanesulfonate (TPT) with secondary amines have been thoroughly examined by spectroscopic and X-ray diffraction methods. The products include the normal ones expected for a ring-opening reaction (1-azahexatriene and cyanine) in addition to the “unexpected” formation of a 4-substituted 1,4-dihydropyridine. Tandem reactions —ring-opening, nucleophilic addition— on the pyridinium ring seems to be the most probable pathway to the 1,4-dihydropyridine compounds. Preliminary tests on the compounds revealed significant anti-microbial activity against Gram-positive bacteria, with moderate specificity towards *Enterococcus faecalis*.

Key words pyridinium salt; pyridinium ring-opening; 1-azahexatriene; 1,4-dihydropyridine

It is well known that the treatment of pyridinium compounds with nucleophiles results in an isolable ring-opened product[4] or the formation of dihydropyridines.[5] The most important condition for a successful pyridine ring-opening is the presence of an electrophilic substituent at the pyridine nitrogen, as in the classical Zincke,[6] Köning,[7] and Baumgarten[8] ring-opening reactions. Nucleophiles other than hydroxide, such as ammonia, compounds containing active methylenes or an amine, have also been used to promote the opening of the pyridine ring.

In connection with studies upon the coordination ability of $Fe_2(CO)_9$ towards conjugated systems, we have achieved the synthesis of 1-azahexatrienes and the product of a γ-addition to the pyridinium ring by utilizing trifluoromethanesulfonylpyridinium trifluoromethanesulfonate (TPT).

Results and Discussion

We have found that TPT (**1**), which is readily accessible from the trifluoromethanesulfonic anhydride $(CF_3SO_2)_2O$ and pyridine (see Experimental), is attacked at the α-carbon by secondary amines. As usual, the primary product (**2**) undergoes ring-opening to give the 1-azahexatriene (**3**) (Chart 1).

When gaseous dimethylamine was bubbled into a CH_2Cl_2 suspension of TPT, the 1,5-bis(dimethylamino)-pentamethinium trifluoromethanesulfonate **4a** and the 1,4-dihydropyridine **5a** were obtained as the only products. In a second run, the bubbling rate was reduced (visually evaluated) to the minimum, and again the only products were **4a** and **5a**, although the yield of the latter was increased. Likewise, when the nucleophilic agent was changed to diethylamine, stoichiometric quantities were used and the addition rate of nucleophile and reaction

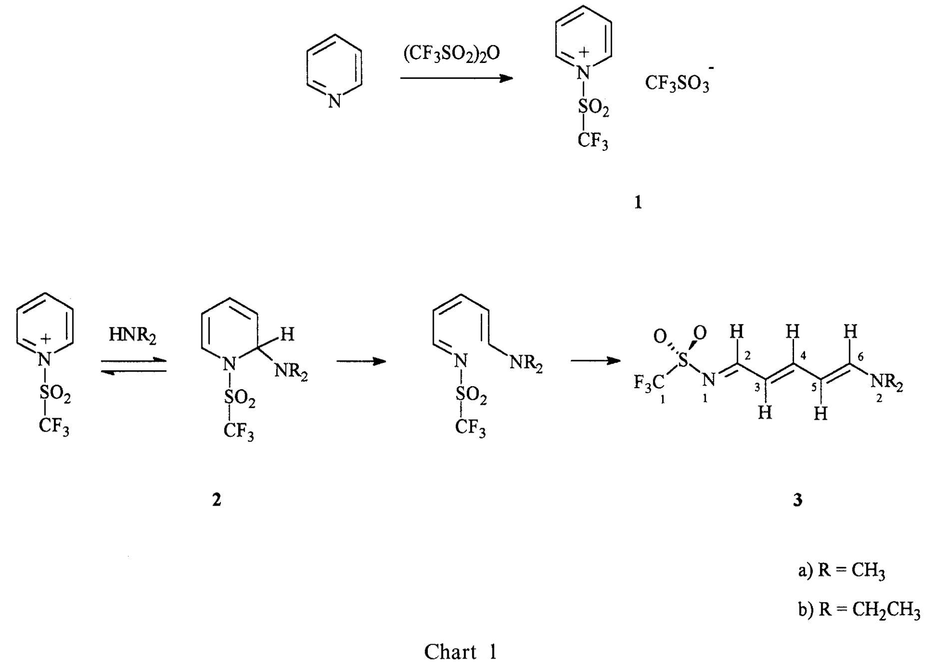

Chart 1

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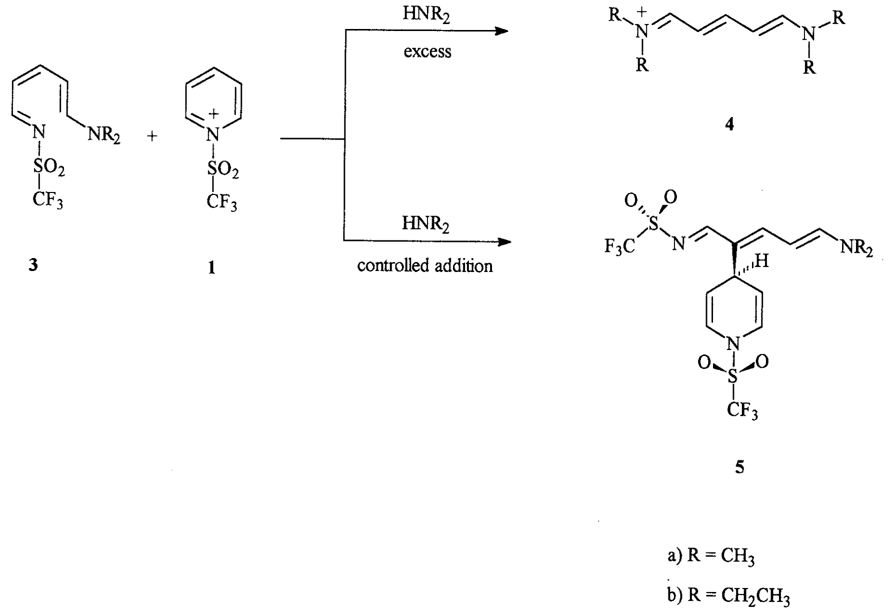

Chart 2

Table 1. ^{13}C and ^{19}F-NMR Data for Compounds in This Paper (in $CDCl_3$)

	3b	4a	5a	5b
C-1[a]	120.03 (J=321 Hz)	120.30 (J=319 Hz)	119.92 (J=319 Hz)	119.92 (J=321 Hz)
C-2	172.21	103.30	170.42	171.13
C-3	114.22	163.84	123.14	123.38
C-4	165.95	161.99	165.60	165.37
C-5	103.66	same as C-3	102.12	101.26
C-6	159.39	same as C-2	162.82	159.33
C-7	44.05[b]	38.00	38.41	44.55[b]
C-8	12.18[c]	46.13	46.62	11.90[c]
C-9	51.88[b]	same as C-7	—	52.18[b]
C-10	14.35[c]	same as C-8	—	14.41[c]
C-4′	—	—	35.88	20.37
C-3′	—	—	112.47	112.32
C-2′	—	—	121.37	121.09
C-1′[a]	—	—	119.87 (J=325 Hz)	119.57 (J=323 Hz)
F[d]	−80.0	−86.01	−79.60 −80.50	−81.55 −85.21

a) Quartet. b, c) May be interchanged in each column. d) Relative to C_6F_6.

Table 2. Crystal Data and Structure Refinements

Compound	3b	5a	5b
Crystal dimensions, mm	0.60 × 0.20 × 0.02	0.40 × 0.24 × 0.12	0.70 × 0.24 × 0.04
Formula weight	284.30	467.41	495.46
Crystal system	Monoclinic	Orthorhombic	Monoclinic
a, Å	12.450 (1)	11.144 (1)	12.311 (2)
b, Å	9.044 (2)	16.023 (1)	17.221 (4)
c, Å	12.468 (2)	22.995 (3)	10.286 (3)
β°	102.45 (1)	—	91.04 (3)
Cell volume, Å^3	1370.9 (4)	4106.0 (7)	2180.5 (9)
Space group	$P2_1/c$	$Pbca$	$P2_1/c$
Formula units	4	8	4
D_{calc}, g cm^{-3}	1.378	1.512	1.509
μ_{calc}, mm^{-1}	2.430	3.104	2.956
2θ range, deg	3.0 to 105	3.0 to 113.5	3.0 to 105
Reflns./parameters	1565/164	2745/263	2496/290
R, wR_2	0.0621, 0.159	0.065, 0.1546	0.0769, 0.2154
S	1.032	1.031	1.055
Min., max. residuals eÅ^{-3}	−0.23, 0.26	−0.31, 0.23	−0.57, 0.30

time were carefully controlled, we were able to isolate the new crystalline solids **3b** and **5b**. These observations are consistent with the initial formation of 1-azahexatriene (**3**), which, in the presence of TPT, competes with the secondary amine to give 4-substituted 1,4-dihydropyridine (Chart 2). This reaction pathway was supported by the quantitative conversion of **3b** into **5b** under the same reaction conditions but in the absence of amine.

Although classical[6-8] or modified[9] pyridine ring-opening reactions have been widely studied or applied as synthetic methods, to our knowledge this is the first report of a pyridinium ring alkylation by a reagent self-produced by the substrate. The factors favoring α- or γ-attack of nucleophiles on pyridinium salts are still unclear,[10] though Klopman[11] has suggested a correlation of attack at the 2 and 4 positions in pyridines with the hardness and softness, respectively, of the nucleophile.

Structure Determination of Products Practical separation of the products was achieved by column chromatography on silica gel. In all cases the presence of a triflyl group was firmly established by its infrared absorptions and ^{19}F resonance, and the all-*trans* conformations for the 1-azahexatriene and pentamethinium moieties were proposed on the basis of the ^1H-NMR spectra. Individual assignments of proton and carbon resonances (Table 1) were obtained from heteronuclear multiple quantum coherence (HMQC) and heteronuclear multiple bond correlation (HMBC) experiments and the proposed structures were confirmed by single crystal X-ray analysis[12] (Table 2 and Figs. 1 to 3). The simplicity of the NMR spectra of compound **4a** implies a highly symmetric structure. Thus, the structure can grossly be represented as the resonance hybrid depicted in Chart 3. The crystal structures reveal that the 1-azahexatriene moiety is essentially planar with an all-*trans* conformation in all

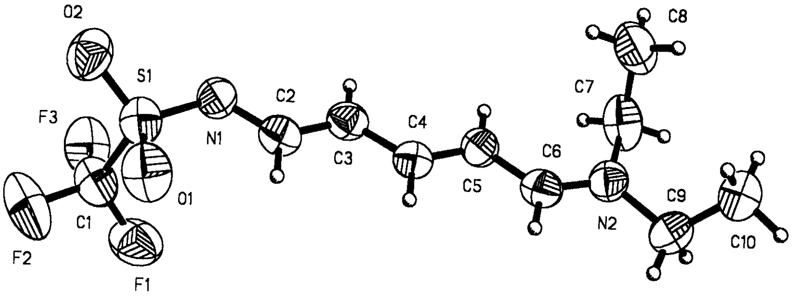

Fig. 1. ORTEP-Type Drawing of Compound **3b**
Thermal ellipsoids at 30% probability level.

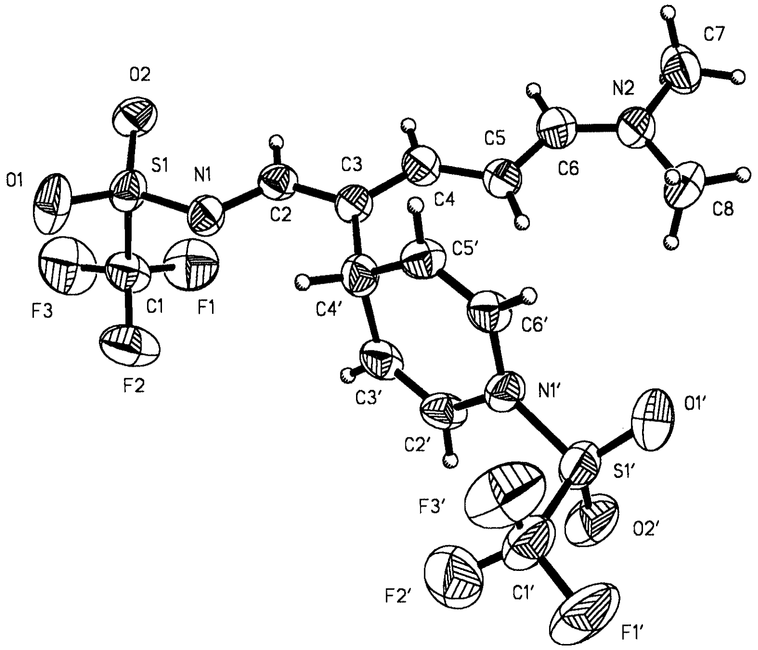

Fig. 2. ORTEP-Type Drawing of Compound **5a**
Thermal ellipsoids at 30% probability level.

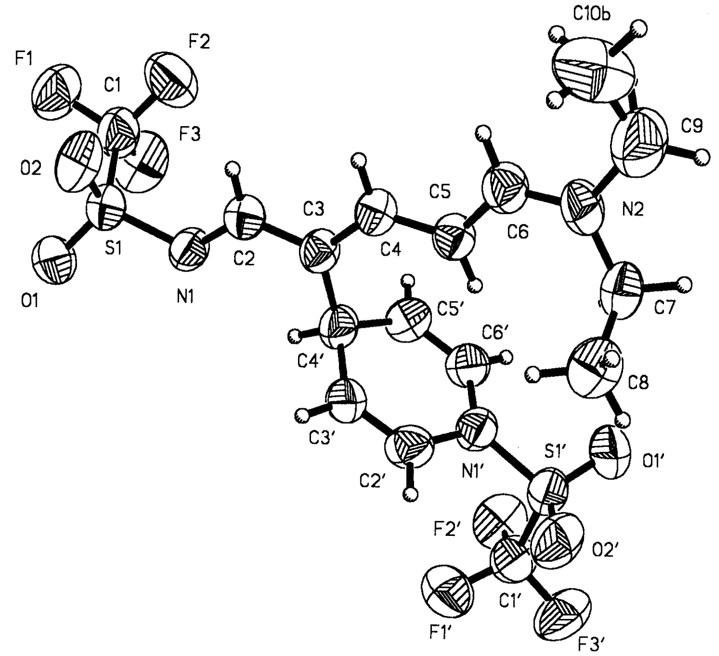

Fig. 3. ORTEP-Type Drawing of Compound **5b**
Thermal ellipsoids at 30% probability level.

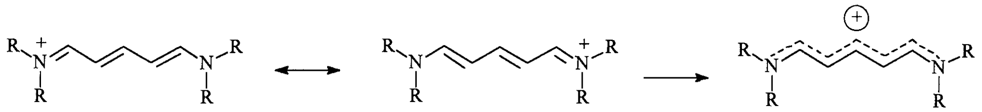

Chart 3

Table 3. Final Atomic Coordinates and Equivalent Temperature Factor

Compd.	Atom	x	y	z	U_{eq}
3b	S(1)	2120 (1)	1933 (2)	9644 (1)	98 (1)
	F(1)	3688 (3)	1720 (5)	8574 (4)	146 (2)
	F(2)	4243 (3)	1970 (5)	10305 (4)	166 (2)
	F(3)	3608 (3)	−108 (5)	9626 (3)	139 (1)
	O(1)	2155 (3)	3512 (4)	9525 (3)	123 (1)
	O(2)	2034 (3)	1342 (5)	10676 (3)	123 (1)
	N(1)	1327 (3)	1088 (4)	8701 (4)	89 (1)
	C(1)	3473 (5)	1351 (9)	9528 (6)	115 (2)
	C(2)	912 (4)	1847 (6)	7781 (5)	86 (1)
	C(3)	183 (4)	1294 (6)	6900 (5)	86 (1)
	C(4)	−263 (4)	2166 (6)	5989 (4)	82 (1)
	C(5)	−1024 (4)	1751 (6)	5102 (4)	84 (1)
	C(6)	−1415 (4)	2721 (6)	4262 (5)	92 (2)
	N(2)	−2170 (3)	2508 (5)	3371 (4)	92 (1)
	C(7)	−2744 (5)	1090 (7)	3197 (5)	119 (2)
	C(8)	−3640 (5)	942 (7)	3796 (6)	149 (3)
	C(9)	−2471 (5)	3641 (8)	2508 (5)	120 (2)
	C(10)	−3627 (5)	4123 (7)	2288 (5)	124 (2)
5a	S(1)	859 (2)	8857 (1)	1454 (1)	71 (1)
	F(1)	1241 (5)	9984 (3)	2248 (2)	133 (2)
	F(2)	2837 (4)	9526 (3)	1853 (3)	130 (2)
	F(3)	1716 (6)	10364 (3)	1392 (3)	158 (2)
	O(1)	1462 (5)	8663 (3)	923 (2)	108 (2)
	O(2)	−340 (4)	9165 (3)	1421 (2)	86 (1)
	N(1)	1110 (4)	8162 (3)	1917 (2)	68 (1)
	N(2)	−1653 (5)	6804 (3)	4605 (2)	77 (2)
	C(1)	1727 (7)	9735 (5)	1746 (4)	91 (2)
	C(2)	325 (5)	8095 (3)	2360 (3)	65 (2)
	C(3)	491 (5)	7572 (4)	2824 (3)	62 (2)
	C(4)	−384 (6)	7574 (4)	3261 (3)	70 (2)
	C(5)	−415 (6)	7163 (4)	3772 (3)	72 (2)
	C(6)	−1439 (6)	7203 (4)	4123 (3)	73 (2)
	C(7)	−2802 (7)	6892 (5)	4906 (3)	103 (2)
	C(8)	−786 (7)	6236 (6)	4863 (3)	115 (3)
	S(1′)	3629 (2)	5783 (1)	4312 (1)	89 (1)
	F(1′)	5641 (5)	4969 (4)	4247 (2)	164 (2)
	F(2′)	5463 (5)	5958 (5)	3638 (3)	157 (2)
	F(3′)	4525 (6)	4832 8 4)	3510 (3)	164 (3)
	O(1′)	2971 (6)	5092 (4)	4516 (2)	127 (2)
	O(2′)	4142 (5)	6385 (4)	4694 (2)	117 (2)
	N(1′)	2833 (5)	6249 (3)	3825 (2)	72 (1)
	C(1′)	4894 (9)	5363 (7)	3909 (4)	109 (3)
	C(2′)	3087 (6)	7103 (4)	3674 (3)	75 (2)
	C(3′)	2547 (5)	7461 (4)	3243 (3)	77 (2)
	C(4′)	1640 (6)	7059 (4)	2853 (3)	71 (2)
	C(5′)	1486 (6)	6165 (4)	3030 (3)	69 (2)
	C(6′)	2019 (5)	5804 (4)	3461 (3)	68 (2)
5b	S(1)	6581 (2)	1249 (1)	2350 (3)	98 (1)
	F(1)	8607 (4)	1353 (3)	3054 (7)	150 (2)
	F(2)	7885 (4)	2415 (3)	2492 (7)	166 (2)
	F(3)	7542 (5)	1926 (4)	4319 (8)	170 (3)
	O(1)	6445 (4)	601 (3)	3190 (6)	123 (2)
	O(2)	6920 (5)	1115 (4)	1038 (7)	132 (2)
	N(1)	5587 (4)	1820 (3)	2526 (6)	92 (2)
	N(2)	2971 (6)	4846 (4)	−1204 (7)	109 (2)
	C(1)	7702 (7)	1749 (5)	3101 (15)	120 (3)
	C(2)	5430 (5)	2365 (4)	1606 (8)	88 (2)
	C(3)	4576 (5)	2875 (4)	1655 (8)	83 (2)
	C(4)	4482 (5)	3404 (4)	625 (8)	86 (2)
	C(5)	3672 (5)	3917 (4)	338 (8)	86 (2)
	C(6)	3717 (7)	4381 (4)	−764 (9)	102 (2)
	C(7)	1918 (6)	4919 (4)	−577 (9)	104 (3)
	C(8)	1151 (7)	4288 (5)	−947 (9)	124 (3)
	C(9)	3138 (14)	5351 (9)	−2373 (15)	173 (6)
	C(10A)	2971 (32)	5003 (14)	−3320 (35)	203 (19)
	C(10B)	3948 (21)	5091 (20)	−3320 (30)	186 (14)
	S(1′)	485 (2)	3970 (1)	3066 (3)	109 (1)
	F(1′)	34 (4)	2774 (3)	4481 (6)	149 (2)
	F(2′)	676 (5)	3722 (4)	5543 (7)	151 (2)
	F(3′)	−960 (4)	3757 (4)	4827 (7)	167 (3)
	O(1′)	616 (5)	4767 (3)	3349 (8)	150 (3)
	O(2′)	−248 (5)	3682 (4)	2091 (7)	136 (2)
	N(1′)	1663 (4)	3598 (3)	2864 (7)	92 (2)
	C(1′)	20 (8)	3536 (6)	4560 (11)	120 (3)
	C(2′)	1767 (6)	2854 (4)	2275 (8)	103 (3)
	C(3′)	2694 (6)	1500 (4)	2198 (9)	106 (3)
	C(4′)	3744 (5)	2821 (4)	2703 (8)	94 (2)
	C(5′)	3541 (6)	3568 (4)	3399 (8)	97 (2)
	C(6′)	2606 (6)	3904 (4)	3469 (9)	97 (2)

Table 4. Selected Bond Lengths for Compounds in This Work

Bond	Compound **3b**	Compound **5a**	Compound **5b**
S(1)–N(1)	1.561 (4)	1.566 (5)	1.583 (5)
N(1)–C(2)	1.341 (6)	1.347 (7)	1.345 (8)
C(2)–C(3)	1.361 (6)	1.371 (8)	1.370 (9)
C(3)–C(4)	1.396 (6)	1.399 (8)	1.400 (9)
C(4)–C(5)	1.345 (6)	1.348 (8)	1.361 (9)
C(5)–C(6)	1.373 (6)	1.398 (9)	1.389 (10)
C(6)–N(2)	1.306 (6)	1.302 (8)	1.293 (9)

three cases. The 1,4-dihydropyridine ring in compounds **5a** and **5b** adopts a planar conformation that is almost perfectly bisected by the plane of 1-azahexatriene.

In the three crystal structures, the canonical form depicted in Charts 1 and 2 for the 1-azahexatriene moiety (imino-amine, for N1, N2 respectively) does not exist. Instead, an "amine–imine" tautomer resulting from the "push–pull" effect due to the conjugated double bonds is found, with lengthening of the N1–C2 bond and shortening of the S1–N1 and C6–N2 bonds as compared with closely related molecules such as sulfathiazole[13)] and sulphapyridine[14)] (Table 4). This finding prompted us to test compounds **3** and **5** for biological activity.[15)] Preliminary tests revealed significant anti-microbial activity against Gram-positive bacteria with moderate specificity towards *Enterococcus faecalis*.

Hence, we have established that TPT is an excellent substrate for nucleophilic attack by secondary amines, and the yields of the reaction products can be modified by manipulation of the nucleophile addition and reaction time. The corresponding carbonyl iron complexes have already been obtained, as will be reported elsewhere.

Experimental

Unless otherwise stated, the following procedures were adopted. Melting points were determined on a Mel-Temp II melting point apparatus and are uncorrected. IR spectra were taken on a Nicolet FTIR Magna 750 spectrophotometer and the data are given in cm^{-1}. NMR spectra were measured on Varian Gemini 200 and Unity Plus (200 MHz for ^1H and 500 MHz for ^{13}C and ^{19}F) spectrometers with tetramethylsilane as an internal standard and the chemical shifts are given in δ values. Mass spectra (MS) and high-resolution MS (HRMS) were taken with a JEOL JMS-SX102A at 70 eV and M^+ are indicated as m/z (%). Column chromatography was performed on silica gel (Merck, 70—230 mesh). Yields are expressed in percent (mol/mol) referred to the quantity of pyridine used.

1-Trifluoromethanesulfonylpyridinium Trifluoromethanesulfonate (TPT) (1) Trifluoromethanesulfonic anhydride (2 ml, 12 mmol) was added dropwise to a stirred solution of pyridine (1 ml, 12 mmol) in methylene chloride (CH_2Cl_2) (40 ml) at $-25\,°C$ under a nitrogen atmosphere. Stable, crystalline, albeit very hygroscopic TPT was obtained in excellent yields. The product was used without further purification.

Preparation of the Reaction Products of TPT and Dimethylamine In a three-necked round-bottomed flask equipped with an inlet, outlet and mechanical stirring, gaseous dimethylamine was bubbled into a continuously stirred suspension of freshly prepared TPT in methylene chloride at $-30\,°C$ during 45 min. The reaction mixture changed from colorless to yellow and finally deep red. The reaction mixture was separated by elution through a silica gel column (50 : 50 ethyl acetate and acetone) affording **4a** (34.2%) and **5a** (13.3%).

Preparation of the Reaction Products of TPT and Diethylamine In a similar system to that used for the reaction with dimethylamine, an addition funnel replaced the inlet–outlet gas pipes and a stoichiometric amount of diethylamine was added dropwise to the continuously stirred suspension of freshly prepared TPT in methylene chloride at $-30\,°C$ during 45 min to give **3b** in 14.7% yield and **5b** in 21.8% yield. Work-up of the reaction mixture followed the same procedure outlined above.

Conversion of 3b to 5b Equimolar quantities of **1** and **3b** were allowed to react under the same general conditions (*vide supra*), just excluding the presence of diethylamine. The course of the reaction and the identity of the sole product formed were monitored by TLC.

X-Ray Crystal Analysis Single crystals of compounds were obtained from CH_2Cl_2 solutions by slow evaporation. Crystal data, structure solution and refinement details are summarized in Table 2. Intensities collected at room temperature (20 °C) on a Siemens P4/PC diffractometer were corrected for Lorentz and polarization effects, and an empirical absorption correction using XABS2[16] was also employed. The structures were determined by direct methods (program SIR92[17]) and refined by least-squares (program SHELXL93[18]) using anisotropic temperature factors for non-H atoms. Ideal positions for H atoms were calculated and included in the structure factor calculations. The function $\Sigma w(F_O^2 - F_C^2)^2$ was minimized in each case. For refinement the present discrepancy indexes $R = \Sigma \| F_O | - | F_C \| / \Sigma | F_O |$, $wR_2 = [\Sigma(w(F_O^2 - F_C^2)^2)/(\Sigma w(F_O^2)^2]^{1/2}$ and $S = [\Sigma(w(F_O^2 - F_C^2)^2]/(M - N)]^{1/2}$, where M = no. of reflections and N = no. of variables, were used. The final parameters and ORTEP-type drawings of the molecules are given in Table 3 and Figs. 1—3.[19]

1,5-Bis(dimethylamino)pentamethinium Trifluoromethanesulfonate (4a) Light-orange crystals from CH_2Cl_2, mp 108—110 °C. IR (KBr): 1610, 1550, 1271, 1182, 1111. ^1H-NMR ($CDCl_3$) δ: 3.10 (6H, s, $NCH_3 \times 2$), 3.33 (6H, s, $NCH_3 \times 2$), 5.65 (2H, dd, $J = 11.9$, 11.9 Hz, C_3-H and C_5-H), 7.59 (2H, d, $J = 11.7$ Hz, C_2-H and C_6-H), 7.60 (1H, t, $J = 12.7$ Hz, C_4-H). FAB-MS m/z: 148.9516 (Calcd for SO_3CF_3: 148.9520). FAB-MS m/z: 153 (pentamethinium).

1-Trifluoromethanesulfonyl-3-(4-(1-trifluoromethanesulfonyl)-1,4-dihydropyridinyl)-6-(dimethylamino)-1-azahexa-1,3,5-triene (5a) Yellow laminar crystals from CH_2Cl_2, mp 121—123 °C. IR (KBr): 1640, 1582, 1522, 1229, 1189, 1113. ^1H-NMR ($CDCl_3$) δ: 3.07 (3H, s, NCH_3), 3.24 (3H, s, NCH_3), 4.83 (1H, br d, $C_{4'}$-H), 4.99 (2H, dd, $J = 8.25$, 3.8 Hz, $C_{3',5'}$-H), 5.89 (1H, t, $J = 12.8$ Hz, C_5-H), 6.52 (2H, d, $J = 7.5$ Hz, $C_{2',6'}$-H), 7.21 (1H, d, $J = 13.0$ Hz, C_6-H), 7.25 (1H, d, $J = 12.5$ Hz, C_4-H), 8.06 (1H, s, C_2-H). MS m/z: 467 (M^+, 6), 334 ($M^+ - SO_2CF_3$, 28), 290 (14), 212 (100), 157 (77).

1-Trifluoromethanesulfonyl-6-(diethylamino)-1-azahexa-1,3,5-triene (3b) Yellow laminar crystals from CH_2Cl_2, mp 144—146 °C. IR (KBr): 1645, 1587, 1544, 1263, 1183, 1112. ^1H-NMR ($CDCl_3$) δ: 1.29 (3H, t, $J = 7.4$ Hz, CH_3), 1.34 (3H, t, $J = 7.2$ Hz, CH_3), 3.46 (2H, q, $J = 7.3$ Hz, NCH_2), 3.51 (2H, q, $J = 7.4$ Hz, NCH_2), 5.76 (1H, t, $J = 12.3$ Hz, C_5-H), 6.16 (1H, t, $J = 12.0$ Hz, C_3-H), 7.38 (1H, d, $J = 11.7$ Hz, C_6-H), 7.43 (1H, t, $J = 12.8$ Hz, C_4-H), 8.15 (1H, d, $J = 11.4$ Hz, C_2-H). MS m/z: 284 (M^+, 48), 212 ($M^+ - NEt_2$, 62), 151 ($M^+ - SO_2CF_3$, 100).

1-Trifluoromethanesulfonyl-3-(4-(1-trifluoromethanesulfonyl)-1,4-dihydropyridinyl)-6-(diethylamino)-1-azahexa-1,3,5-triene (5b) Yellow laminar crystals from CH_2Cl_2, mp 125—127 °C. IR (KBr): 1630, 1584, 1525, 1242, 1184, 1115. ^1H-NMR ($CDCl_3$) δ: 1.29 (3H, t, $J = 7.5$ Hz, CH_3), 1.36 (3H, t, $J = 7.2$ Hz, CH_3), 3.43 (2H, q, $J = 7.2$ Hz, NCH_2), 3.51 (2H, q, $J = 7.2$ Hz, NCH_2), 4.85 (1H, br d, $C_{4'}$-H), 5.02 (2H, dd, $J = 8.4$, 3.3 Hz, $C_{3',5'}$-H), 6.01 (1H, t, $J = 13.4$, 12.2 Hz, C_5-H), 6.52 (2H, d, $J = 8.4$ Hz, $C_{2',6'}$-H), 7.3 (1H, d, $J = 13.4$ Hz, C_4-H), 7.28 (1H, d, $J = 12.2$ Hz, C_6-H), 8.02 (1H, s, C_2-H). MS m/z: 495 (M^+, 3), 362 ($M^+ - SO_2CF_3$, 63), 290 (7), 212 (57), 157 (100).

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References and Notes

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