A CONVENIENT AND FACILE SYNTHESIS OF 5-TRIFLUOROMETHYL-1,2,4-TRIAZINE DERIVATIVES

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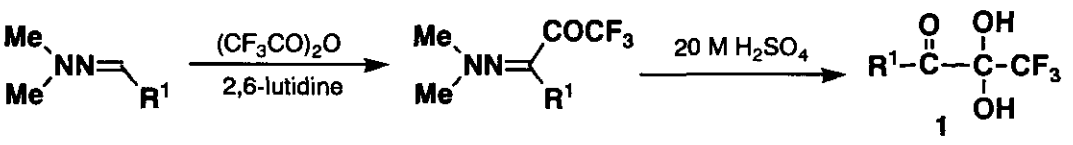
Abstract - 3-Hydrazono-1,1,1-trifluoroalkan-2-ones (**2**) and 3-methylhydrazono-1,1,1-trifluoroalkan-2-ones (**3**) prepared from 1,1,1-trifluoroalkane-2,3-diones (**1**) reacted with several aldehydes in the presence of aq. NH_4OH to afford 5-trifluoromethyl-2,3-dihydro-1,2,4-triazines (**4** and **5**) of which oxidation gave 5-trifluoromethyl-1,2,4-triazines (**6**) and 5-trifluoromethyl-2,5-dihydro-5-hydroxy-1,2,4-triazines (**7**). Thermal reaction of **5** afforded 1-amino-4-trifluoromethylimidazoles (**8**).

Triazine derivatives are of special interest owing to their potentially high pharmacological properties applicable to cardiotonics, antihypertensives etc.[1-3] In particular, fluorine-containing triazine derivatives may be fascinating target for many organic synthetic chemists.[4] 1,1,1-Trifluoroalkane-2,3-dione monohydrates (**1**) which are readily obtainable from a varieties of aldehydes by our three-steps method[5] may be one of the most useful intermediates accessible to fluorine-containing 1,2,4-triazine derivatives. This prompted us to try synthesis of 5-trifluoromethyl-1,2,4-triazine derivatives from **1**. Now we wish to report the results.

By usual method,[5] trifluoroacetylation of aldehyde dimethylhydrazones with the use of



trifluoroacetic anhydride gave 3-dimethylhydrazono-1,1,1-trifluoroalkan-2-ones, which were hydrolyzed with hot 10M H_2SO_4 affording **1** as monohydrates. Thus obtained **1** was treated with hydrazine hydrate in MeOH affording 1,1,1-trifluoro-3-hydrazonoalkan-2-ones (**2**) in good yields. Similarly **1** reacted with methylhydrazone in AcOH to give 1,1,1-trifluoro-3-methylhydrazonoalkan-2-ones (**3**) in high yields. A mixture of **2** and various aldehydes dissolved in MeOH reacted for 24 h with 28% aq. NH_4OH. The reaction mixture was treated with 1M HCl to afford 5-trifluoromethyl-2,3-dihydro-1,2,4-triazine (**4**). Similarly, 2-methyl derivatives (**5**) could be obtained. When we omitted above treatment with 1 M HCl, 5-trifluoromethyl-2,3,4,5-tetrahydro-5-hydroxy-1,2,4-triazines (**4'** or **5'**) [6] could be obtained, in some cases of **5'**, together with small amounts of **5**. Apparently dil. HCl catalyzes dehydration of **4'** and **5'** to the corresponding **4** and **5**, respectively. Purification by silica gel column chromatography also completely converted **4'** and **5'** to **4** and **5**, respectively. Results are summarized in Table 1. Dihydrotriazines (**4**) and (**5**) are fairly stable compounds but **5** was gradually oxidized under atmosphere to 5-trifluoromethyl-2,5-dihydro-5-

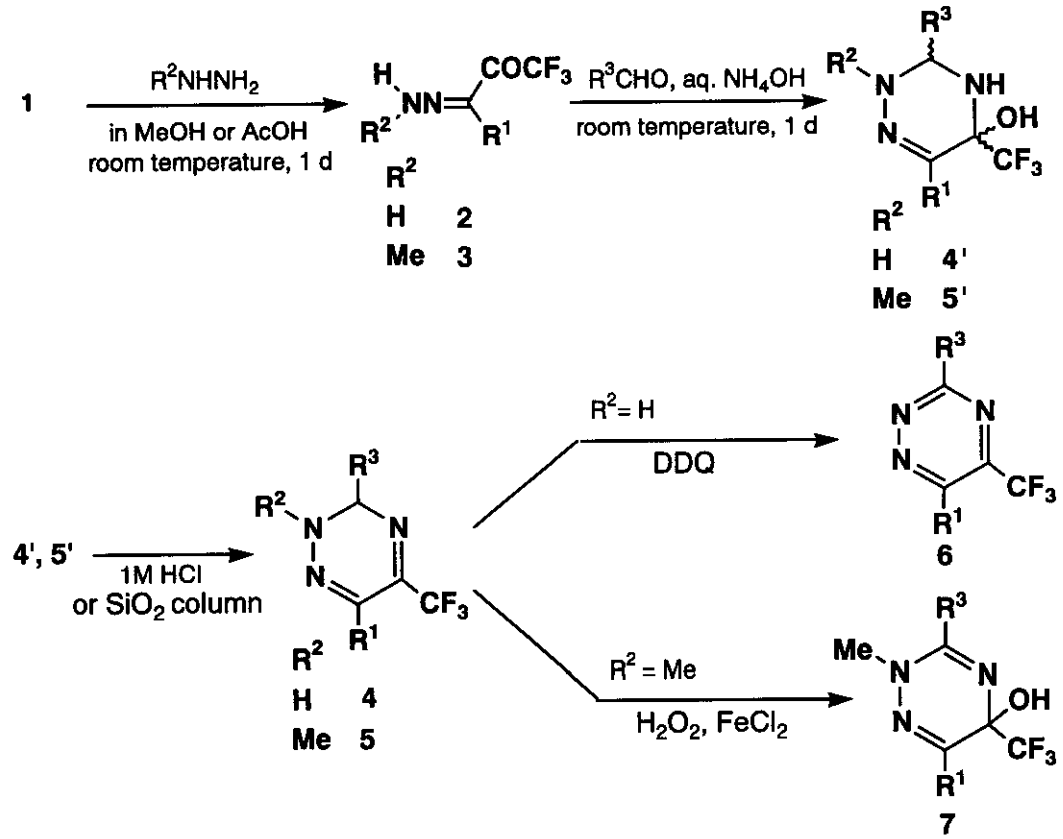


Table 1. Synthesis of 5-Trifluoromethyl-2,3-dihydro-1,2,4-triazines (**4** and **5**).

R^1	R^2	R^3	**4'** : **4**[a] **5'** : **5**	product[b] / Yield[c] %	^{1}H nmr ($CDCl_3$/TMS) δ
p-MeC_6H_4	H	Et	**4a'**:**4a** (1 : 0)	**4a** / 65	1.05 (t, *J* = 5.0 Hz, 3H, CH_2Me), 1.78 (m, 2H, CH_2Me), 2.30 (s, 3H, Me), 3.24 (s, 3H, NMe), 4.40 (t, *J* = 6.0 Hz, 1H, CH), 7.01, 7.21 (d, *J* = 8.0 Hz, 4H, ArH)
p-MeC_6H_4	H	*i*-Pr	**4b'**:**4b** (1 : 0)	**4b** / 99	1.08 (d, *J* = 6.0 Hz, 6H, CHMe), 1.90-2.33 (m, 1H, CHMe), 2.33 (s, 3H, Me), 3.87 (br, d, *J* = 5.0 Hz,1H, NCH), 6.70-6.90 (br, 1H, NH), 6.90-7.35 (AA'BB'q, *J* = 8.0 Hz, 4H, ArH)
p-MeC_6H_4	H	*o*-MeC_6H_4	**4c'**:**4c** (1 : 0)	**4c** / 73	2.37 (s, 6H, Me), 5.10 (br, 1H, CH), 6.43-6.64 (br, 1H, NH), 6.96-7.73 (m, 8H, ArH)
n-C_6H_{13}	H	*i*-Pr	**4d'**:**4d** (1 : 0)	**4d** / 83	0.33-1.83, 1.03 (m and d, *J* = 6.2 Hz, 17H, *n*-C_5H_{11} and CHMe), 1.83-2.83 (m, 3H, =CCH_2 and CHMe), 6.00-7.00 (br, 1H, NH)
n-C_6H_{13}	H	*p*-MeC_6H_4	**4e'**:**4e** (1 : 0)	**4e** / 99	0.70-1.93 (m, 11H, *n*-C_5H_{11}), 2.18-2.90, 2.33 (m and s, 5H, =CCH_2 and Me), 4.87 (s, 1H, NCH), 6.84-3.34, 6.70-7.70 (AA'BB'q and br, *J* = 8.0 Hz, 5H, ArH)
p-MeC_6H_4	Me	*i*-Pr	**5a'**:**5a** (1 : 0)	**5a** / 83	1.01 (d, *J* = 6.6 Hz, 6H, CHMe), 2.24 (m, 1H, CHMe), 2.30 (s, 3H, Me), 3.24 (s, 3H, NMe), 4.42 (d, *J* = 6.4 Hz, 1H, NCH),7.06, 7.29 (d, *J* = 9.0 Hz, 4H, ArH)
p-$MeOC_6H_4$	Me	*i*-Pr	**5b'**:**5b** (1 :1.5)	**5b** / 35	1.05 (d, *J* = 6.6 Hz, 6H, CHMe), 1.63-2.66 (m, 1H, CHMe), 3.33 (s, 3H, NMe), 3.77 (s, 3H, OMe), 4.48 (d, *J* = 6.0 Hz, 1H, NCH), 6.81, 7.29 (d, *J* = 9.0 Hz, 4H, ArH)
p-$O_2NC_6H_4$	Me	*i*-Pr	**5c'**:**5c** (1 : 0)	**5c** / 31	1.06 (d, *J* = 7.0 Hz, 6H, CHMe), 1.98-2.58 (m, 1H, CHMe), 3.45 (s, 3H, NMe), 4.68(d, *J* = 7.8 Hz, 1H, NCH), 7.63, 8.24 (d, *J* = 8.4 Hz, 4H, ArH)
p-MeC_6H_4	Me	*p*-MeC_6H_4	**5d'**:**5d** (1 : 0)	**5d** / 97	2.37 (s, 6H, Me), 3.11 (s, 3H, NMe), 5.29 (s, 1H, CH), 7.05-7.53 (AA'BB'q x 2, J = 8.0 Hz, 8H, ArH)

a) Products ratio before washing with 1M HCl . b) Product obtained after washing with 1M HCl. c) Yellow syrupy oil was obtained after purification by silica gel column chromatography.

Table 2. Oxidation of **4** and **5** to **6** and **7**, respectively.

substrate	method[a]	product[b] yield, %	bp or mp[c] °C (solvent)	^{1}H nmr ($CDCl_3$/TMS) δ
4 a	A	**6 a** 77	100/3 torr[d]	1.50 (t, J = 7.8 Hz, 3H, $CH_2\underline{Me}$), 2.32 (s, 3H, Me), 3.24 (q, J = 7.8 Hz, 2H, CH_2), 7.14, 7.40 (d, J = 8.0 Hz, 4H, ArH)
4 b	A	**6 b** 71	90/1 torr[d]	1.49 (d, J = 6.4 Hz, 6H, CH$\underline{Me}$), 2.40 (s, 3H, Me), 3.56 (hept, J = 6.4 Hz, 1H, C$\underline{H}$Me), 7.17, 7.44 (d, J = 8.0 Hz, 4H, ArH)
4 C	A	**6 c** 89	150/1 torr[d]	2.44 (s, 3H, *p*-Me), 2.70 (s, 3H, OMe), 7.14-7.50 (m, 6H, ArH), 7.57 (d, J = 8.0 Hz, 2H, ArH)
4 d	A	**6 d** 59	70/3 torr[d]	0.63-2.53, 1.42 (m and d, J = 6.2 Hz, 17H, *n*-C_5H_{11} and CH$\underline{Me}$), 2.90-3.37 (m, 3H, ($C\underline{H}_2$)C_5H_{11}-*n* and C$\underline{H}$Me)
4 e	A	**6 e** 71	48 (*c*-hexane)	0.67-2.23 (m, 11H, *n*-C_5H_{11}), 2.40 (s, 3H, Me), 2.87-3.33 (m, 2H, ($C\underline{H}_2$)C_5H_{11}-*n*), 7.16, 8.40 (d, J = 8.0 Hz, 4H, ArH)
5 a	B	**7 a** 56	143 (*n*-hexane)	1.20 (d, J = 6.6 Hz, 6H, CH$\underline{Me}$), 2.32 (s, 3H, Me), 2.76 (hept, J = 6.6 Hz, 1H, C$\underline{H}$Me), 3.51 (s, 3H, NMe), 3.77-4.06 (br, 1H, OH), 7.04, 7.73 (d, J = 8.4 Hz, 4H, ArH)
5 b	B	**7 b** 46	154 (*n*-hexane)	1.20 (d, J = 6.4 Hz, 6H, CH$\underline{Me}$), 2.82-3.15 (br, 1H, CH), 3.52 (s, 3H, NMe), 3.75 (s, 3H, OMe), 5.80-6.00 (br, 1H, OH), 6.76, 7.81 (d, J = 9.0 Hz, 4H, ArH)
5 d	B	**7 d** 31	180 (benzene)	2.33 (s, 3H, Me), 2.37 (s, 3H, Me), 3.37 (s, 3H, NMe), 4.23 (s, 1H, OH), 7.21 (s, 4H , ArH), 7.28, 7.73 (d, J = 7.6 Hz, 4H, ArH)

a) Method A: Substrate (1 mmol), DDQ(1.1 mmol) and MeCN (5 ml) were used, and the reaction was carried out at ambient temperature for 1 h. Method B: Substrate (1 mmol), H_2O_2 (2 mmol) in the cases of **5 a** and **5 b**, H_2O_2 (5 mmol) in the case of **5 d**, $FeCl_2$ (0.5 mmol) in the cases of **5 a** and **5 d**, and $FeCl_2$ (0.2 mmol) in the case of **5 b** were used. MeCN (5 ml) was used in all cases. Reaction was carried out at ambient temperature for 2 d. b) Yields refer to pure isolated compounds. c) Uncorrected. d) Oven temperature.

hydroxy-1,2,4-triazine (**7**), and after a week about half of **5** were oxidized to **7**. However 5-trifluoromethyl-2,3-dihydro-3-hydroxy-1,2,4-triazine, a isomer of **7**, was not detected in the mixture at all. Aromatization of **4** to 5-trifluoromethyl-1,2,4-triazines (**6**) proceeded very easily and cleanly by a

treatment with DDQ. On the other hand, oxidation of **5** with H_2O_2 in the presence of $FeCl_2$ in MeCN afforded **7**, and in this case too, none of 5-trifluoromethyl-2,3-dihydro-3-hydroxy-1,2,4-triazine was obtained. These results are listed in Table 2.[7]

Interestingly, thermal reaction of **5** afforded *N*-aminoimidazoles (**8**)[8] in excellent yields (Table 3). For instance, **5 a** was maintained at 100°C for a day to give **8 a** in 99% yield. As is illustrated in Scheme 1, electrocyclic ring opening of **5** and subsequent recyclization by nucleophilic attack of azo nitrogen atom to azomethine carbon atom followed by prototropy are one of the most

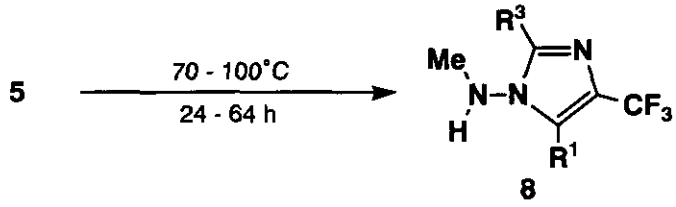


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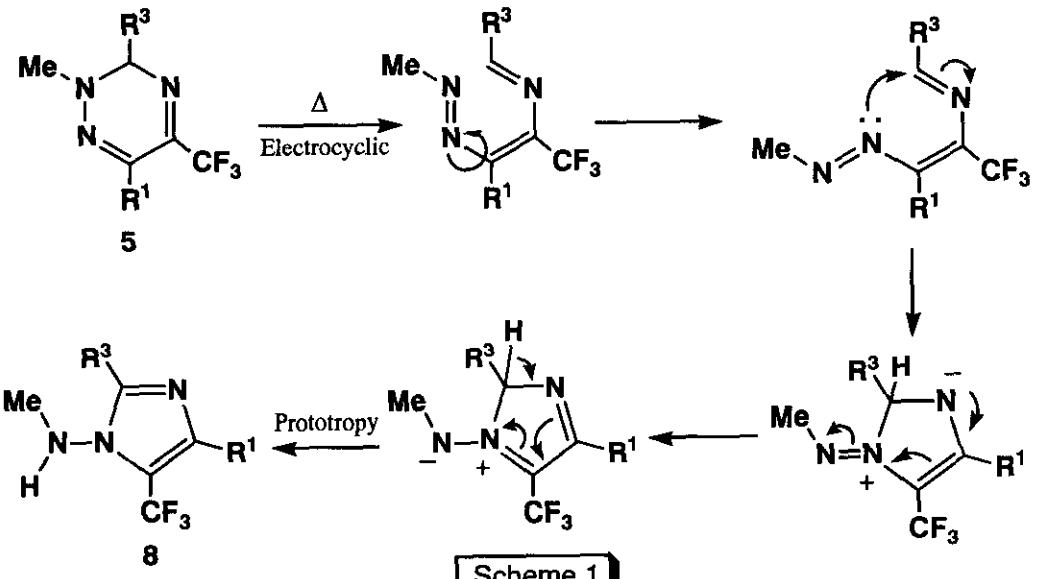
Table 3. Thermal Conversion of **5** to **8**.

substrate	product	yield[a] / bp[b] % °C/torr	^{1}H nmr ($CDCl_3$/TMS)
5 a	**8 a**	99 / 150/2	1.34 (d, *J* = 6.4 Hz, CHMe), 2.37 (s, 3H, Me), 2.40 (d, *J* = 5.8 Hz, 3H, NMe), 3.24 (hept, *J* = 5.4 Hz, 1H, CHMe), 3.51 (q, *J* = 5.8 Hz, 1H, NH),3.77-4.06 (br, 1H, OH), 7.16 (s, 4H, ArH)
5 b	**8 b**	52 / 150/3	1.35 (d, *J* = 6.4 Hz, 6H, CHMe), 2.46 (d, *J* = 4 Hz, 3H, NMe), 3.19 (hept, *J* = 6.4 Hz, 1H, CHMe), 3.80 (s, 3H,OMe), 4.40-4.90 (br, 1H, NH), 7.25, 6.90 (d, *J* = 8.0 Hz, 4H, ArH)
5 c	**8 c**	53 / 190/3	1.60 (d, *J* = 6.4 Hz, 6H, CHMe), 3.40, 3.43 (hept and s, *J* = 6.4 Hz, 4H, CHMe and NMe), 6.70-7.25 (br, 1H, NH), 7.48, 8.08 (d, *J* = 8.0 Hz, 4H, ArH)
5 d	**8 d**	72 / 121[c] (*c*-hexane)	2.37 (s, 3H, Me), 2.40 (s, 3H, Me), 4.70-5.15 (br, 1H, NH), 7.13, 7.20 (d and s, *J* = 8.0 Hz, 3H, ArH), 7.89 (d, *J* = 8.0 Hz, 2H, ArH)

a) Yields refer to pure isolated compounds. b) Oven temperature of Kugelrohr distillation. c) Mp *uncorrected*.

reasonable reaction path from **5** to **8**.

We could present new convenient synthetic method accessible to fluorine-containing 1,2,4-triazine derivatives (**4**, **5**, **6**, and **7**) and *N*-aminoimidazoles (**8**) bearing CF_3 group.



5 **8**

Scheme 1

EXPERIMENTAL

^1H Nmr and ^{13}C nmr spectra were recorded at 60 MHz on a JEOL PMX 60SI and at 22.5 MHz on a JOEL FX90Q, respectively. Ir spectra were taken with a Hitachi model G3. Distillation was performed by Kugelrohr. Mp was measured with Mitamura Riken model 7-12 apparatus.

5-Trifluoromethyl-2,3-dihydro-1,2,4-triazine (4 and 5). General Procedure:

To a mixture of **2** (or **3**,1 mmol) and aldehyde (1.2 mmol) dissolved in MeOH (5 ml) was added 28% aq. NH_4OH (2 ml), and the mixture was stirred for 24 h at ambient temperature. To the mixture was added CH_2Cl_2 (50 ml) and the whole was washed with 1M HCl and with water. The organic layer was dried over Na_2SO_4 and the solvent was removed to afford 5-trifluoromethyl-2,3-dihydro-1,2,4-triazine (**4** and **5**).

5-Trifluoromethyl-1,2,4-triazines (6) and 5-Trifluoromethyl-2,5-dihydro-5-hydroxy-2-methyl-1,2,4-triazine (7). General Procedure:

Method A: A mixture of **4** (1 mmol) and DDQ (249.7 mg, 1.1 mmol) in MeCN (5 ml) was stirred for 1 h at ambient temperature. The solvent was removed and CH_2Cl_2 (50 ml) was added. Insoluble

materials were filtered off and filtrate was washed with 1M aq. NaOH. The organic layer was dried over Na_2SO_4 and the solvent was removed to afford 5-trifluoromethyl-1,2,4-triazines (**6**).

Method B: To a mixture of **5** (1 mmol) and H_2O_2 (2 - 5 mmol) in MeCN (5 ml) was added $FeCl_2$ (0.2 - 0.5 mmol) and the mixture was stirred for 2 d at ambient temperature. The reaction mixture was poured onto saturated aq. $NaHSO_3$ and extracted with CH_2Cl_2 (50 ml x 3). The combined extracts were dried over Na_2SO_4 and the solvent was removed to afforded 5-hydroxy-2-methyl-5-trifluoromethyl-2,5-dihydro-1,2,4-triazine (**7**).

4-Trifluoromethy-1-methylaminolimidazole (**8**). General Procedure:

Dihydrotriazine (**5**) was heated for 24 h at 100°C and the crude product was purified by Kugelrohr distillation or recrystallization to afford pure 4-trifluoromethyl-1-methylaminoimidazole (**8**).

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6. For instance, **4 a'**: pale yellow syrupy oil; ^{1}H nmr ($CDCl_3$/TMS) δ 0.97 (t, *J* = 6.2 Hz, 3H, CH_2Me), 1.30-1.86 (m, 2H, CH_2), 2.29 (s, 3H, Me), 3.55-4.02 (m, 1H, CH), 6.00-6.50 (br, 3H, NH and OH), 7.02, 7.47 (d, *J* = 8.0 Hz, 4H, ArH); ir (KBr) 3280 (s), 2500-3200 (br), 1507 (m), 1456 (m), 1295 (s), 1278 (s), 1252 (m), 1205 (s), 1160 (s), 1123 (s), 1060 (s), 822 (s). **5 a'**: yellow syrupy oil; ^{1}H nmr ($CDCl_3$/TMS) δ 1.04, 0.95 (d, *J* = 6.9 Hz, 6H, CHMe), 2.27 (m, 1H, CHMe), 2.32 (s, 3H, Me), 2.37 (br, 2H, NH and OH), 2.96 (s, 3H, NMe), 3.46 (d of d, *J* = 7.4 Hz and 2.3 Hz, 1H, NCH), 7.12, 7.59 (d, *J* = 8.3 Hz, 4H, ArH); ^{13}C nmr ($CDCl_3$/TMS) δ 13.9,18.4

(CH<u>Me</u>), 21.2 (Me), 27.6 (<u>C</u>HMe), 40.4 (NMe), 70.9 (NCH), 79.5 (q, $^2J_{CF}$ = 30.4 Hz, <u>C</u>CF_3), 123.6 (q, $^1J_{CF}$ = 288.6 Hz, CF_3) , 128.0, 128.5, 133.9, 137.7 (Ar), 139.6 (N=C); ir (KBr) 2090-3680 (br), 1621 (s), 1586 (m), 1467 (m), 1308 (m), 1290 (m), 1257 (s), 1185 (s), 1174 (s), 1132 (s), 1000 (m), 926 (m), 827 (m), 630 (m) cm^{-1}.

7. For instances, **4 d**: yellow syrupy oil; ir (KBr) 3200 (br), 2895 (s), 1530 (m), 1450 (m), 1357 (m), 1180 (s), 1131 (s), 1030 (s), 715 (w) cm^{-1}. **5 a**: yellow syrupy oil; ^{13}C nmr ($CDCl_3$/TMS) δ 16.8,19.0 (CH<u>Me</u>), 21.2 (Me), 27.4 (<u>C</u>HMe), 43.6 (NMe), 78.7 (NCH), 123.0 ($^1J_{CF}$ = 277.6 Hz, CF_3), 127.3, 129.0, 131.5, 138.1 (Ar), 137.7 (N=C), 147.0 ($^2J_{CF}$ = 34.0 Hz, <u>C</u>CF_3); ir (KBr) 2980 (m), 1465 (m), 1372 (m), 1201 (s), 1145 (s), 1030 (s), 826 (s), 767 (m), 724 (m) cm^{-1}. **6 b**: pale yellow oil; ir (KBr) 2950 (m), 1606 (m),1460 (m), 1398 (s), 1370 (s), 1305 (s), 1261 (s), 1189 (s), 1140 (s), 1104 (s), 1060 (m), 1027 (m), 1008 (m), 903 (m), 825 (m), 804 (s), 731 (m) cm^{-1}. Anal. Calcd for $C_{14}H_{14}N_3F_3$: C, 59.78; H, 5.02. Found C, 59.64; H, 4.89. **7 a**: pale yellow crystal; ^{13}C nmr ($CDCl_3$/TMS) δ 19.2,20.3 (CH<u>Me</u>), 21.3 (Me), 30.0 (<u>C</u>HMe), 40.4 (NMe), 79.3 ($^2J_{CF}$ = 32.9 Hz, <u>C</u>CF_3), 123.7 ($^1J_{CF}$ = 291.2 Hz, CF_3), 128.7, 129.5, 130.5, 139.8 (Ar), 138.9 (N=C); ir (KBr) 3600-2100 (br), 1611 (s), 1578 (s), 1459 (s), 1421 (m), 1388 (m), 1368 (m), 1318 (m), 1300 (s), 1284 (s), 1268 (s), 1169 (s), 1126 (s), 1015 (s), 984 (s), 921 (m), 873 (m), 820 (m), 718 (m) cm^{-1}. Anal. Calcd for $C_{15}H_{18}N_3OF_3$: C, 57.50; H, 5.79; N, 13.41. Found C, 57.65; H, 5.77; N, 13.24.
8. For instance, **8 a**: pale yellow oil; ir (KBr) 3330 (w), 2970 (m), 2925 (m), 1508 (m), 1490 (m), 1392 (m), 1299 (m), 1183 (s), 1146 (s), 1095 (s), 963 (m), 807 (m) cm^{-1}. Anal. Calcd for $C_{15}H_{18}N_3F_3$: C, 60.60; H, 6.10; N, 14.13. Found C, 60.50; H, 6.16; N, 13.89.

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