

## 2-Trifluoromethylperimidines with electron-withdrawing groups at the 6(7)-position: a case of extremely hindered annular prototropy

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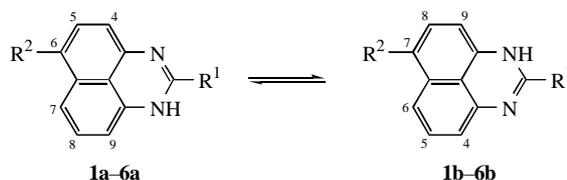
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In solutions of 6(7)-formyl-, 6(7)-acetyl- and 6(7)-*p*-toluenesulfonyl-2-trifluoromethylperimidines in non-polar solvents, both of the NH tautomers were detected using <sup>1</sup>H NMR spectroscopy even on heating up to 130 °C.

It is well known that annular tautomerism in NH azoles is a very fast process in the NMR time scale, which can be normally frozen only at rather low temperatures.<sup>1,2</sup> Here, we report amidine-like NH heterocycles, in which annular prototropy is hindered so that distinct tautomers are observed not only under ordinary conditions but also on heating above 100 °C. We found that in the <sup>1</sup>H NMR spectra of 6(7)-formyl-, 6(7)-acetyl- and 6(7)-*p*-toluenesulfonyl-2-trifluoromethylperimidines<sup>†</sup> in non-polar solvents (CDCl<sub>3</sub>, CDCl<sub>2</sub>CDCl<sub>2</sub> and C<sub>6</sub>D<sub>6</sub>) at room temperature all signals are duplicated showing the presence of both possible annular tautomers **1a–3a** and **1b–3b** [Figure 1(a)].<sup>‡</sup> The individual tau-



**1** R<sup>1</sup> = CF<sub>3</sub>, R<sup>2</sup> = CHO

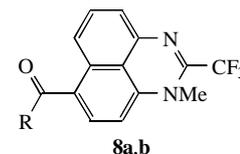
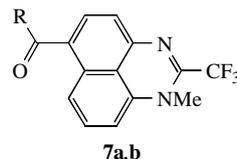
**2** R<sup>1</sup> = CF<sub>3</sub>, R<sup>2</sup> = COMe

**3** R<sup>1</sup> = CF<sub>3</sub>, R<sup>2</sup> = 4-MeC<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>

**4** R<sup>1</sup> = CF<sub>3</sub>, R<sup>2</sup> = H

**5** R<sup>1</sup> = Me, R<sup>2</sup> = H

**6** R<sup>1</sup> = H, R<sup>2</sup> = COMe



**7, 8:** **a** R = H  
**b** R = Me

<sup>†</sup> Compounds **1**, **4** and **6** were prepared in accordance with procedures described in refs. 3, 4 and 5, respectively. New compounds **2** and **3** gave satisfactory elemental analyses. The synthesis of compounds **7** and **8** will be described elsewhere. The <sup>1</sup>H NMR spectra were recorded on a Bruker-250 spectrometer. Because of fast prototropy in [2H<sub>6</sub>]DMSO, the atoms in compounds **1–3** were numbered arbitrarily.

For **1**: <sup>1</sup>H NMR ([2H<sub>6</sub>]DMSO) δ: 6.75 (br. d, 1H, 9-H), 7.03 (br. dd, 1H, 4-H), 7.55 (dd, 1H, 5-H, <sup>3</sup>J<sub>5,4</sub> 7.9 Hz, <sup>3</sup>J<sub>5,6</sub> 8.2 Hz), 7.85 (d, 1H, 8-H, <sup>3</sup>J<sub>8,9</sub> 8.0 Hz), 8.64 (br. d, 1H, 6-H, <sup>3</sup>J<sub>6,5</sub> 8.5 Hz), 9.89 (s, 1H, CHO), 12.40 (br. s, 1H, NH).

For **1a**: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 6.66 (dd, 1H, 9-H, <sup>3</sup>J<sub>9,8</sub> 7.1 Hz, <sup>4</sup>J<sub>9,7</sub> 0.7 Hz), 7.04 (d, 1H, 4-H, <sup>3</sup>J<sub>4,5</sub> 7.8 Hz), 7.46 (dd, 1H, 8-H, <sup>3</sup>J<sub>8,9</sub> 7.1 Hz, <sup>3</sup>J<sub>8,7</sub> 8.9 Hz), 7.79 (d, 1H, 5-H, <sup>3</sup>J<sub>5,4</sub> 7.8 Hz), 8.23 (br. s, 1H, NH), 8.77 (dd, 1H, 7-H, <sup>3</sup>J<sub>7,8</sub> 8.9 Hz, <sup>4</sup>J<sub>7,9</sub> 0.7 Hz), 10.04 (s, 1H, 6-CHO).

For **1b**: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 6.49 (d, 1H, 9-H, <sup>3</sup>J<sub>9,8</sub> 7.9 Hz), 7.25 (dd, 1H, 4-H, <sup>3</sup>J<sub>4,5</sub> 7.6 Hz, <sup>4</sup>J<sub>4,6</sub> 0.7 Hz), 7.62 (dd, 1H, 5-H, <sup>3</sup>J<sub>5,4</sub> 7.6 Hz, <sup>3</sup>J<sub>5,6</sub> 8.7 Hz), 7.68 (d, 1H, 8-H, <sup>3</sup>J<sub>8,9</sub> 7.9 Hz), 8.23 (br. s, 1H, NH), 8.82 (dd, 1H, 6-H, <sup>3</sup>J<sub>6,5</sub> 8.7 Hz, <sup>4</sup>J<sub>6,4</sub> 0.7 Hz), 9.97 (s, 1H, 7-CHO).

For **2**: A mixture of compound **4** (2 mmol), AcOH (3 mmol) and polyphosphoric acid (6 g, 84% P<sub>2</sub>O<sub>5</sub>) was stirred at 65 °C for 4 h and then poured into water (100 ml). The subsequent basification with NH<sub>4</sub>OH to pH 3–4, extraction with ethyl acetate (3×20 ml) and column chromatography on silica gel gave **2** (in the second fraction) as orange crystals with mp 218–219 °C (decane), 76% yield. <sup>1</sup>H NMR ([2H<sub>6</sub>]DMSO) δ: 2.57 (s, 3H, Me), 6.69 (br. d, 1H, 9-H, <sup>3</sup>J<sub>9,8</sub> 8.0 Hz), 6.96 (br. dd, 1H, 4-H), 7.48 (dd, 1H, 5-H, <sup>3</sup>J<sub>5,4</sub> 7.6 Hz, <sup>3</sup>J<sub>5,6</sub> 8.7 Hz), 8.07 (d, 1H, 8-H, <sup>3</sup>J<sub>8,9</sub> 8.1 Hz), 8.57 (br. dd, 1H, 6-H), 12.20 (br. s, 1H, NH). IR, (Vaseline oil, ν/cm<sup>-1</sup>): 3180–3 090 (NH), 1633 (C=O), 1613, 1580 (ring).

For **2a**: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 2.63 (s, 3H, Me), 6.55 (dd, 1H, 9-H, <sup>3</sup>J<sub>9,8</sub> 7.6 Hz, <sup>4</sup>J<sub>9,7</sub> 0.7 Hz), 6.92 (d, 1H, 4-H, <sup>3</sup>J<sub>4,5</sub> 8.0 Hz), 7.35 (dd, 1H, 8-H, <sup>3</sup>J<sub>8,9</sub> 8.9 Hz, <sup>3</sup>J<sub>8,7</sub> 8.9 Hz), 7.92 (d, 1H, 5-H, <sup>3</sup>J<sub>5,4</sub> 8.0 Hz), 8.10 (br. s, 1H, NH), 8.55 (dd, 1H, 7-H, <sup>3</sup>J<sub>7,8</sub> 8.9 Hz, <sup>4</sup>J<sub>7,9</sub> 0.7 Hz).

For **2b**: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 2.60 (s, 3H, Me), 6.35 (d, 1H, 9-H, <sup>3</sup>J<sub>9,8</sub> 8.0 Hz), 7.16 (dd, 1H, 4-H, <sup>3</sup>J<sub>4,5</sub> 7.5 Hz, <sup>4</sup>J<sub>4,6</sub> 0.8 Hz), 7.52 (dd, 1H, 5-H, <sup>3</sup>J<sub>5,4</sub> 7.5 Hz, <sup>3</sup>J<sub>5,6</sub> 8.8 Hz), 7.83 (d, 1H, 8-H, <sup>3</sup>J<sub>8,9</sub> 8.0 Hz), 8.10 (br. s, 1H, NH), 8.72 (dd, 1H, 6-H, <sup>3</sup>J<sub>6,5</sub> 8.8 Hz, <sup>4</sup>J<sub>6,4</sub> 0.8 Hz).

For **3**: A mixture of compound **4** (2 mmol), 4-MeC<sub>6</sub>H<sub>4</sub>SO<sub>3</sub>H·H<sub>2</sub>O (3 mmol) and polyphosphoric acid (5 g, 84% P<sub>2</sub>O<sub>5</sub>) was stirred at 140–145 °C for 1 h and then poured into water (50 ml). The subsequent basification with NH<sub>4</sub>OH to pH 4–5 gave a solid, which was filtered off, washed with water and dried. After column chromatography on silica gel, firstly, with benzene to separate 4(9)-*p*-toluenesulfonyl-2-trifluoromethylperimidines (14%, yellowish crystals, mp 253–254 °C) and then with benzene-ethyl acetate (10:1) gave **3** as yellow-green crystals with

mp 259–260 °C (benzene), 44% yield. <sup>1</sup>H NMR ([2H<sub>6</sub>]DMSO) δ: 2.33 (s, 3H, Me), 6.80 (br. d, 1H, 9-H), 6.97 (br. dd, 1H, 4-H), 7.37 (d, 2H, 4-MeC<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>, 3'-H and 5'-H, J<sub>0</sub> 8.1 Hz), 7.46 (br. dd, 1H, 5-H), 7.77 (m, 3H, 6-H, 4-MeC<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>, 2'-H and 6'-H, J<sub>0</sub> 8.1 Hz), 8.14 (d, 1H, 8-H, <sup>3</sup>J<sub>8,9</sub> 8.9 Hz), 12.30 (br. s, 1H, NH).

For **3a**: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 2.35 (s, 3H, Me), 6.53 (dd, 1H, 9-H, <sup>3</sup>J<sub>9,8</sub> 7.3 Hz, <sup>4</sup>J<sub>9,7</sub> 0.7 Hz), 6.99 (d, 1H, 4-H, <sup>3</sup>J<sub>4,5</sub> 7.8 Hz), 7.22 (d, 2H, 4-MeC<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>, 3'-H and 5'-H, J<sub>0</sub> 8.4 Hz), 7.25 (m, 1H, 8-H), 7.78 (d, 2H, 4-MeC<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>, 2'-H and 6'-H, J<sub>0</sub> 8.4 Hz), 7.85 (dd, 1H, 7-H, <sup>3</sup>J<sub>8,9</sub> 8.7 Hz), 8.26 (d, 1H, 5-H, <sup>3</sup>J<sub>5,4</sub> 7.8 Hz), 8.43 (br. s, 1H, NH).

For **3b**: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 2.35 (s, 3H, Me), 6.45 (d, 1H, 9-H, <sup>3</sup>J<sub>9,8</sub> 8.1 Hz), 7.07 (dd, 1H, 4-H, <sup>3</sup>J<sub>4,5</sub> 7.5 Hz, <sup>4</sup>J<sub>4,6</sub> 0.7 Hz), 7.21 (d, 2H, 4-MeC<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>, 3'-H and 5'-H, J<sub>0</sub> 8.4 Hz), 7.40 (dd, 1H, 5-H, <sup>3</sup>J<sub>5,4</sub> 7.5 Hz, <sup>3</sup>J<sub>5,6</sub> 8.7 Hz), 7.77 (d, 2H, 4-MeC<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>, 2'-H and 6'-H, J<sub>0</sub> 8.4 Hz), 7.90 (dd, 1H, 6-H, <sup>3</sup>J<sub>6,5</sub> 8.7 Hz, <sup>4</sup>J<sub>6,4</sub> 0.7 Hz), 8.13 (d, 1H, 8-H, <sup>3</sup>J<sub>8,9</sub> 8.1 Hz), 8.60 (br. s, 1H, NH).

<sup>‡</sup> Preliminary <sup>19</sup>F and <sup>13</sup>C NMR examinations of compounds **1–3** led to the same conclusions.

**Table 1** Ratio between tautomers at 25 °C.

Compound	Solvent	Content (%)		Equilibrium constant $K_T = \frac{[\text{form a}]}{[\text{form b}]}$
		6-COR (1a–3a)	7-COR (1b–3b)	
1	CDCl <sub>3</sub>	37	63	0.59
	CDCl <sub>2</sub> CDCl <sub>2</sub>	34	66	0.52
	C <sub>6</sub> D <sub>6</sub>	38	62	0.62
	[ <sup>2</sup> H <sub>6</sub> ]DMSO	33 <sup>a</sup>	67 <sup>a</sup>	0.50 <sup>a</sup>
	CD <sub>3</sub> CN	38 <sup>a</sup>	62 <sup>a</sup>	0.61 <sup>a</sup>
2	CDCl <sub>3</sub>	40	60	0.67
	CDCl <sub>2</sub> CDCl <sub>2</sub>	38	62	0.61
	C <sub>6</sub> D <sub>6</sub>	47	53	0.89
	[ <sup>2</sup> H <sub>6</sub> ]DMSO	49 <sup>a</sup>	51 <sup>a</sup>	0.96 <sup>a</sup>
	CD <sub>3</sub> CN	68 <sup>a</sup>	32 <sup>a</sup>	2.12 <sup>a</sup>
3	CDCl <sub>3</sub>	33	67	0.49
	CDCl <sub>2</sub> CDCl <sub>2</sub>	36	64	0.56

<sup>a</sup>Fast equilibrium.

its 6-R counterpart ( $\mu = 1.05$  D).<sup>†</sup> This can result in more effective stabilisation of the 7-R form in a crystalline state and, to a certain extent, in solution because of stronger dipole-dipole interactions.

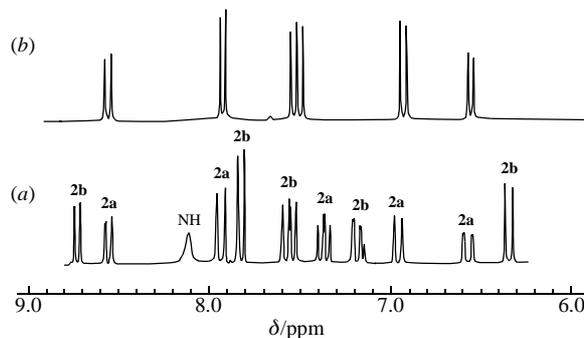
We failed to reach a coalescence temperature for signals of both of the tautomeric forms in the non-polar solvents used. Upon heating a solution of aldehyde **1** or ketone **2** in C<sub>6</sub>D<sub>6</sub> up to 70 °C or in CDCl<sub>2</sub>CDCl<sub>2</sub> up to 130 °C, only slight broadening of the indicator peaks was observed. Judging from these observations, we can suggest that the value of  $\Delta G^\ddagger$  for the tautomerisation of compounds **1** and **2** in non-polar media may be higher than 20 kcal mol<sup>-1</sup>. To the best of our knowledge, this is an unprecedentedly high value for annular tautomerism in azole systems (cf. refs. 1 and 2).

At the same time, the coalescence does occur when a drop of D<sub>2</sub>O is added to a solution of **1–3** in CDCl<sub>2</sub>CDCl<sub>2</sub>.<sup>‡</sup> Moreover, fast tautomerisation with averaging signals of both of the forms takes place at room temperature in solutions of **1–3** in polar solvents, e.g., CD<sub>3</sub>CN and [<sup>2</sup>H<sub>6</sub>]DMSO [Figure 1(b)]. In this instance, the percentage of tautomers in an equilibrium mixture was calculated for compounds **1** and **2** using the equation<sup>§</sup>

$$p_t = \chi_a p_7 + \chi_b p_8, \quad (1)$$

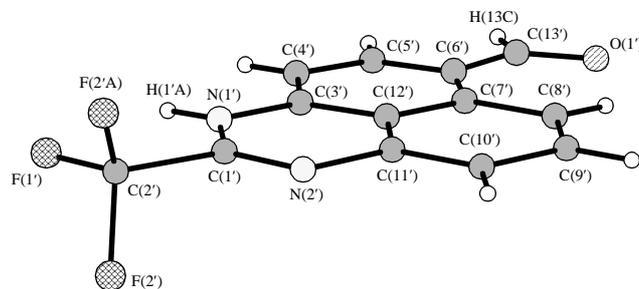
<sup>§</sup> Crystals of **1** suitable for X-ray analysis were obtained by slow evaporation of a solution of **1** in acetylacetone. A red single crystal (0.50 × 0.25 × 0.20 mm) containing 0.5 molecules of acetylacetone per molecule of **1** was chosen (C<sub>13</sub>H<sub>7</sub>F<sub>3</sub>N<sub>2</sub>O·0.5C<sub>5</sub>H<sub>8</sub>O<sub>2</sub>,  $M = 314.26$ ). The crystals are orthorhombic,  $a = 6.9420(14)$  Å,  $b = 16.340(3)$  Å,  $c = 24.776(5)$  Å,  $V = 2810.4(10)$  Å<sup>3</sup>,  $d_{\text{calc}} = 1.485$  g cm<sup>-3</sup>,  $Z = 8$ , space group  $Pmc2_1$ ,  $\mu(\text{MoK}\alpha) = 1.26$  cm<sup>-1</sup>,  $F(000) = 1288$ . Intensities of 3645 reflections were measured on an Enraf-Nonius CAD4 diffractometer at 293 K (graphite-monochromated MoK $\alpha$  radiation,  $\theta/5/3\theta$  scan technique,  $\theta \leq 26.96^\circ$ ) and 3306 independent reflections ( $R_{\text{int}} = 0.0518$ ) were used in further calculations and refinement. The structure was solved by a direct method and refined by a full-matrix least-squares technique against  $F^2$  in an anisotropic approximation for non-hydrogen atoms. All hydrogen atoms were placed in the geometrically calculated positions and included in the refinement using the riding model approximation with  $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{C}_i)$  and  $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C}_j)$ , where  $\text{C}_i$  and  $\text{C}_j$  are the carbon atoms to which the corresponding hydrogen atoms are attached in methyl groups and benzene rings, respectively. The refinement was converged to  $wR_2 = 0.1515$  and  $\text{GOOF} = 0.936$  for all independent reflections [ $R_1 = 0.0438$  is calculated against  $F$  for the 1183 independent reflections with  $I > 2\sigma(I)$ ]. The number of the refined parameters was 547. All calculations were performed using SHELXL PLUS 5.0 on an IBM computer. Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2000. Any request to the CCDC for data should quote the full literature citation and the reference number 1135/67.

<sup>†</sup> The dipole moments were calculated by the PM3 method for conformations in which a carbonyl oxygen atom is directed towards the peri-proton. The occurrence of such conformations was confirmed by X-ray diffraction data (for **1**) and <sup>1</sup>H NMR spectra showing strong deshielding of peri-protons for both of the tautomers.

**Figure 1** <sup>1</sup>H NMR spectra (250 MHz, 30 °C) of compound **2** in (a) CDCl<sub>3</sub> and (b) [<sup>2</sup>H<sub>6</sub>]DMSO.

where  $p_t$  is the difference between the chemical shifts of 4-H and 9-H atoms for compound **1** or **2**,  $p_7$  and  $p_8$  are the analogous differences for fixed forms **7** and **8** (Table 2),  $\chi_a$  and  $\chi_b$  are the molar fractions of tautomers **1a,2a** and **1b,2b**, respectively. As can be seen in Table 1, the ratio between both of the forms for aldehyde **1** and ketone **2** in non-polar and polar solvents differs little; the only exception is compound **2** in CD<sub>3</sub>CN, for which the 6-COR form becomes somewhat predominant.

A pronounced influence of perfluoroalkyl groups on prototropy in NH-containing heterocycles was reported.<sup>9</sup> In 2-perfluoropropylimidazole, a stabilisation of annular prototropy was observed as thought because of intramolecular hydrogen bonding between NH protons and terminal fluorine atoms in the *n*-C<sub>3</sub>F<sub>7</sub> substituent.<sup>10</sup> Obviously, a similar explanation is not valid in our case because (i) no stabilisation of prototropy was noticed for 2-CF<sub>3</sub>- and 2-C<sub>2</sub>F<sub>5</sub>-imidazoles<sup>10</sup> and (ii) X-ray diffraction data did not indicate the existence of similar intramolecular hydrogen bonding for **1**. We believe that the main reason for the very slow tautomerism of compounds **1–3** in non-polar media consists in their very low basicity<sup>‡</sup> and insufficient NH acidity to ensure fast proton interchange between different molecules of the hetero-

**Figure 2** Molecular structure of compound **1** (one of four independent molecules is shown; the acetylacetone molecule is omitted for clarity; the atom numbering does not correspond to the IUPAC nomenclature). Selected bond lengths and distances (Å): N(1')–C(1') 1.39(2), N(2')–C(1') 1.29(2), N(1')–C(3') 1.34(2), N(2')–C(11') 1.40(2), C(6')–C(13') 1.45(2), O(1')–C(13') 1.27(2), O(1')...H(8'A) 2.38(0.02), O(1')...C(8') 3.00(0.02); selected bond angles (°): C(3')–N(1')–C(1') 115(1), C(1')–N(2')–C(11') 116(1), N(2')–C(1')–N(1') 127(1), N(2')–C(1')–C(2') 119(1), N(1')–C(1')–C(2') 113(1), N(1')–C(3')–C(12') 123(1), N(1')–C(3')–C(4') 117(1), C(5')–C(6')–C(13') 112(1), C(6')–C(7')–C(8') 121(1), O(1')–C(13')–C(6') 124(2).

<sup>‡</sup> Unlike **1** and **2**, prototropy in **3** is extremely sensitive to moisture traces. Thus, in three different commercial batches of CDCl<sub>3</sub>, only the average spectrum of **3** was observed, whereas in each of these cases compounds **1** and **2** demonstrated separate signals of both tautomers. Tautomers **3a** and **3b** could be observed only in a carefully dried sample of CDCl<sub>3</sub>. Indirectly, these data indicate that the tautomerisation of **1–3** most likely proceeds through a mesomeric N anion rather than the perimidinium cation. Indeed, the NH acidity of **3** should be greater than that of **1** and **2** because the 4-MeC<sub>6</sub>H<sub>4</sub>SO<sub>2</sub> group ( $\sigma_p = 0.67$ ) is a stronger electron acceptor than CHO ( $\sigma_p = 0.22$ ) and COMe ( $\sigma_p = 0.50$ ).<sup>7</sup>

<sup>§</sup> In accordance with published data,<sup>11</sup> the value of  $pK_a$  for 1-methyl-2-trifluoromethylperimidine in MeCN is equal to 6.64. Extrapolation to an aqueous solution results in  $pK_a$  within the limits from -1.0 to -0.5. Obviously, the basicity of compounds **1–3** should be even lower.

**Table 2** Chemical shifts of 4-H and 9-H protons in polar solvents.

Compound	Solvent	$\delta(9\text{-H})^a/$ ppm	$\delta(4\text{-H})^a/$ ppm	$p = \delta(4\text{-H}) - \delta(9\text{-H})/$ ppm
<b>1</b>	[ <sup>2</sup> H <sub>6</sub> ]DMSO	6.75	7.03	0.28
	CD <sub>3</sub> CN	6.75	7.05	0.30
<b>2</b>	[ <sup>2</sup> H <sub>6</sub> ]DMSO	6.69	6.96	0.27
	CD <sub>3</sub> CN	6.65	6.95	0.30
<b>7a</b>	[ <sup>2</sup> H <sub>6</sub> ]DMSO	7.00	7.04	0.04
	CD <sub>3</sub> CN	6.85	7.00	0.15
<b>7b</b>	[ <sup>2</sup> H <sub>6</sub> ]DMSO	6.88	6.95	0.07
	CD <sub>3</sub> CN	6.76	6.93	0.17
<b>8a</b>	[ <sup>2</sup> H <sub>6</sub> ]DMSO	6.83	7.23	0.40
	CD <sub>3</sub> CN	6.65	7.20	0.55
<b>8b</b>	[ <sup>2</sup> H <sub>6</sub> ]DMSO	6.68	7.14	0.46
	CD <sub>3</sub> CN	6.55	7.13	0.58

<sup>a</sup>The atom numbering in compounds **1** and **2** is arbitrary.

cyclic compounds (conjugated cations or anions are known to be ordinary prototropy intermediates in NH heterocycles).<sup>1</sup> This view is substantiated by the fact that 2-trifluoromethyl- and 2-methylperimidines **4** and **5**, respectively, as well as 6(7)-acetylperimidine **6**, exhibit only average spectra even in non-polar solvents (see also ref. 12).<sup>§§</sup> It follows from the above discussion that the specificity of compounds **1–3** consists in a cooperative electron acceptor effect of the 2-CF<sub>3</sub> group and a substituent at the 6(7)-position, which creates an optimal balance of the basicity and NH acidity making prototropy in non-polar media extremely hindered.

<sup>§§</sup> It is noteworthy that in compound **4**, unlike **5**, the average 4-H and 9-H signal is considerably broadened even at room temperature. Thus, the 2-CF<sub>3</sub> group alone slows down prototropy, though to a lesser extent than both substituents in compounds **1–3**.

## References

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