

Synthesis of 2-Aryl-4-phenyl-5-trifluoromethylimidazoles

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Several 2-aryl-4-phenyl-5-trifluoromethylimidazoles have been made from the previously unknown 1-phenyl-3,3,3-trifluoro-1,2-propanedione monohydrate. One analog, 4-phenyl-2,5-bis(trifluoromethyl)imidazole, is quite acidic, exhibiting pK_a 8.1.

Although 2-trifluoromethylbenzimidazoles are well known (1-3), little has been reported about trifluoromethylimidazoles. Since antiinflammatory activity was found (4) for certain 2-trifluoromethylimidazoles, the effect on activity of moving the CF_3 substituent from the 2 to the 4 position was investigated.

The synthesis route to the title compounds 4 is outlined in Figure 1.

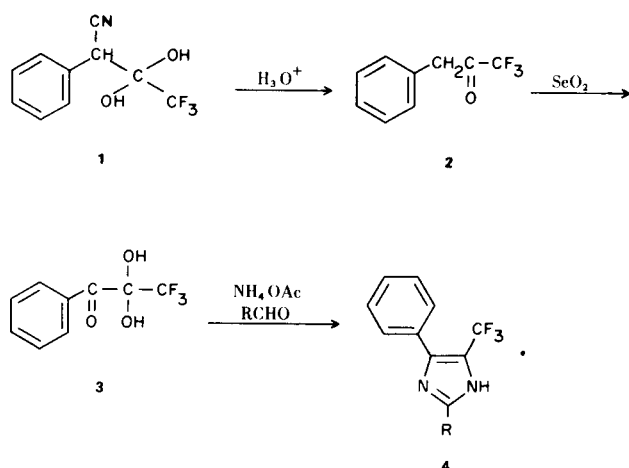


Figure 1

Compounds 1 and 2 were prepared by the method of Nes and Burger (5) except that a much longer distillation time was found necessary for the preparation of 2. Selenium dioxide oxidation of 2 in acetic acid solution produced a crystalline diketone monohydrate (3) which was then combined with various aldehydes in the presence of ammonium acetate (6) to produce the desired 4. Table I summarizes the analogs of 4. Although the water present in 3 was very likely detrimental to the imidazole preparation (7), all attempts to dehydrate 3 were unsuccessful. Trifluoroacetaldehyde ethyl hemiacetal was used in excess in the last synthetic step in order to prepare 11 (4, $R = CF_3$).

Compound 5 (Table I) failed to titrate with sodium hydroxide to a discernible end-point. Compound 11, however, was titrated in 2:1 dioxane-water and exhibited pK_a 8.1 making it considerably more acidic than imidazole or simple arylimidazoles which have (8) pK_a 12.5-14.5. Others have reported enhanced acidity for various substituted imidazoles. For example, in 1:1 ethanol-water 2,4,5-tribromoimidazole and 2,4,5-triiodoimidazole have pK_a 6.9 and 8.0, respectively (3), while 2-trifluoromethylbenzimidazole has a pK_a of 8.8 in water (2).

Several of the analogs of 4 exhibited antiinflammatory activity in the carrageenin rat-foot edema test (9). For example, compounds 6 and 7 produce 20% and 49%, respectively, inhibition of edema when administered orally to six rats at a dose of 10 mg./kg.

EXPERIMENTAL

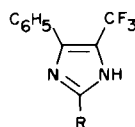
Melting points were determined on a Thomas-Hoover melting point apparatus in open capillaries and are uncorrected. IR spectra were determined in potassium bromide pellets and mass spectra were measured on a Hitachi Perkin-Elmer Model RMU-6E. Potentiometric titrations were carried out in 2:1 dioxane-water (v/v) solvent using a Metrohm Automatic titrator Model 436 and 0.5 N sodium hydroxide. Analyses were carried out by the Physical Measurements Laboratory of Pfizer Inc.

Trifluoroacetaldehyde ethyl hemiacetal was purchased from Pierce Chemical Co. and 4-methylthiobenzaldehyde was prepared from 4-chlorobenzaldehyde and methanethiol by the method of Gregory and Kreuchunas (10). All other aldehydes were commercially available and used as received.

1-Phenyl-3,3,3-trifluoro-1,2-propanedione Monohydrate (3).

To a suspension of 8.8 g. (0.079 mole) of selenium dioxide in 300 ml. of acetic acid at 80° under nitrogen was slowly added a solution of 13.7 g. (0.072 mole) of benzyl trifluoromethyl ketone (5) in 40 ml. of acetic acid. After 2 hours at 80° , the reaction was cooled, filtered and the filtrate added to 1500 ml. of iced water. After extraction (twice) with ether, the ether extracts were washed six times with 10% sodium bicarbonate and twice with water. Drying (calcium sulfate) and evaporation of the ether gave a green-yellow semi-solid which was recrystallized from

TABLE I (a)



No.	R	Yield, %	Recrystn. Solvent (b)	M.p. °C	Formula	Analyses, %					
						Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
5	C ₆ H ₅	47	I-W	231-232	C ₁₆ H ₁₁ F ₃ N ₂ (c)	66.7	3.85	9.73	66.49	3.97	9.50
6	4-CH ₃ OC ₆ H ₄	28	B	253-255	C ₁₇ H ₁₃ F ₃ N ₂ O	64.1	4.12	8.81	63.92	4.08	8.71
7	4-BrC ₆ H ₄	42	B	260-263	C ₁₆ H ₁₀ BrF ₃ N ₂ (d)	52.3	2.73	7.63	52.64	2.88	7.72
8	2-pyridyl	35	B	237-238	C ₁₅ H ₁₀ F ₃ N ₃	62.3	3.50	14.5	61.96	3.63	14.34
9	4-ClC ₆ H ₄	10	B-H	245 dec.	C ₁₆ H ₁₀ ClF ₃ N ₂	59.7	3.12	8.67	59.99	3.31	8.73
10	4-CH ₃ SC ₆ H ₄	15	B-H	228-230	C ₁₇ H ₁₃ F ₃ N ₂ S	61.2	3.93	8.38	61.48	4.15	8.23
11	CF ₃ (e)	46	H	164 dec.	C ₁₁ H ₆ F ₆ N ₂	47.2	2.16	10.0	47.47	2.45	9.88

(a) All of these compounds were prepared by the method illustrated in the Experimental section for **6**. (b) I = isopropyl alcohol; W = water; B = benzene; H = hexane. (c) Mass spectrum: *m/e* 288 (Calcd. 288), 269 (-F), 219 (-CF₂). (d) Mass spectrum: *m/e* 367 (Calcd. 367) with typical Br isotope; 288 (loss of Br). (e) See Experimental section.

petroleum ether to give 5.2 g. (36%) of **3** in two crops, m.p. 83-85°; ir: 2.95 (OH), 5.92 (C=O), 7.98 (CF₃), 13.86 μ (C₆H₅); mass spectrum: *m/e* (Calcd. 202) no parent ion was observed; 105 (C₆H₅CO), 77 (C₆H₅), 69 (CF₃).

Anal. Calcd. for C₉H₇O₃F₃: C, 49.2; H, 3.20. Found: C, 48.87; H, 3.22.

2-(4-Methoxyphenyl)-4-phenyl-5-trifluoromethylimidazole (**6**).

A solution of 1.0 g. (0.0045 mole) of 1-phenyl-3,3,3-trifluoro-1,2-propanedione monohydrate (**3**), 2.0 g. of ammonium acetate and 0.736 g. (0.0054 mole) of *p*-anisaldehyde in 35 ml. of acetic acid was stirred at room temperature for ¼ hour and then heated to reflux. After 18 hours at reflux, the clear yellow solution was slowly poured into 250 ml. of water and the pH of the resulting suspension adjusted to 7.0 using ammonium hydroxide. Filtration and recrystallization (benzene) of the white solid gave 0.40 g. (28%) of **6**, m.p. 253-255°; mass spectrum: *m/e* 318 (Calcd. 318), 303 (loss of CH₃); ir: 2.9 (NH), 7.93 (OCH₃), 11.95 μ (C₆H₄). See Table I.

Certain reactions (e.g. to prepare **5**, **8** and **10**) required less than 18 hours of reflux to complete. In all cases, thin-layer chromatography was used to monitor the course of the reaction.

4-Phenyl-2,5-bis(trifluoromethyl)imidazole (**11**).

To a stirred solution of 1.0 g. (0.0045 mole) of **3** and 2.0 g. of ammonium acetate in 25 ml. of acetic acid was slowly added a solution of 0.78 g. (0.0054 mole) of trifluoroacetaldehyde ethyl hemiacetal in 10 ml. of acetic acid. The resulting solution was stirred at room temperature for ½ hour and then heated to reflux. After 1½ hours, another 0.78 g. of hemiacetal was added and the reaction refluxed another 2 hours. The yellow solution was poured into 200 ml. of water and the pH adjusted to 7.0 using ammonium hydroxide. Extraction with ethyl acetate, drying of the extracts (sodium sulfate) and evaporation yielded a viscous oil which slowly crystallized. Recrystallization from hexane gave

0.59 g. (46%) of **11**, m.p. 164° dec.; ir: 3.05 (NH), 7.85 (CF₃), 13.10 and 14.45 μ (C₆H₅); mass spectrum: *m/e* 280 (Calcd. 280); 261 (-F). Titration of **11** with sodium hydroxide in 2:1 dioxane-water indicated neut. equivalent 297 and pH ½ = 8.12. See Table I.

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