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 monohdyrate. 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.

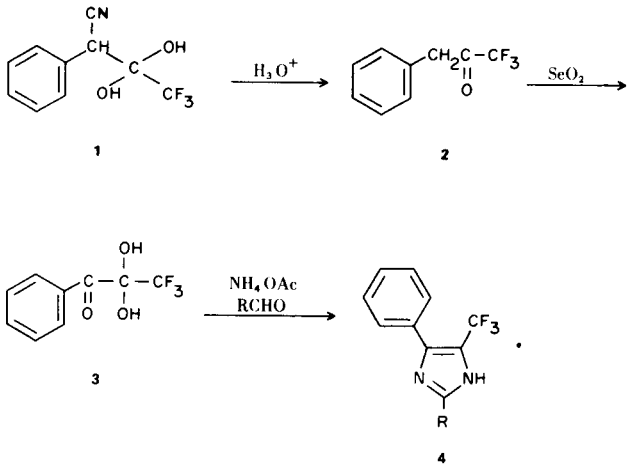


Figure 1

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

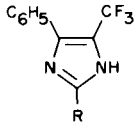
Melting points were determined on a Thomas-Hoover melting point apparatus in open capillaries and are uncorrected. Ir spectra were determined in potassium bromide pellets and mass spectra were measured on a Hitachi Perkin-Elmer Model RMU-6E. Potentiometric titrations were carried out in 2:1 dioxane-water (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_6H_5	47	I-W	231-232	$C_{16}H_{11}F_3N_2$ (c)	66.7	3.85	9.73	66.49	3.97	9.50
6	4-$CH_3OC_6H_4$	28	B	253-255	$C_{17}H_{13}F_3N_2O$	64.1	4.12	8.81	63.92	4.08	8.71
7	4-BrC_6H_4	42	B	260-263	$C_{16}H_{10}BrF_3N_2$ (d)	52.3	2.73	7.63	52.64	2.88	7.72
8	2-pyridyl	35	B	237-238	$C_{15}H_{10}F_3N_3$	62.3	3.50	14.5	61.96	3.63	14.34
9	4-ClC_6H_4	10	B-H	245 dec.	$C_{16}H_{10}ClF_3N_2$	59.7	3.12	8.67	59.99	3.31	8.73
10	4-$CH_3SC_6H_4$	15	B-H	228-230	$C_{17}H_{13}F_3N_2S$	61.2	3.93	8.38	61.48	4.15	8.23
11	CF_3 (e)	46	H	164 dec.	$C_{11}H_6F_6N_2$	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 (-CF_2). (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 (CF_3), 13.86 μ (C_6H_5); mass spectrum: m/e (Calcd. 202) no parent ion was observed; 105 (C_6H_5CO), 77 (C_6H_5), 69 (CF_3).

Anal. Calcd. for $C_9H_7O_3F_3$: 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 *p*H 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 CH_3); ir: 2.9 (NH), 7.93 (OCH_3), 11.95 μ (C_6H_4). 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 *p*H 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 (CF_3), 13.10 and 14.45 μ (C_6H_5); 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 *p*H ½ = 8.12. See Table I.

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