Some 5-Aryl-6-arylmethyl-2, 4-diaminopyrimidines

BERNARD E. ROSENKRANTZ,[1] LOUIS CITAREL,[2] GEORGE E. HEINSOHN,[3] and ERNEST I. BECKER
Polytechnic Institute of Brooklyn, Brooklyn 1, N. Y.

A CONTINUING EFFORT is being made in these laboratories to synthesize potential medicinal agents. A recent review article (*7*) discusses some 5-aryl-6-alkyl-2, 4-diaminopyrimidines. Hitchings and Russell (*3*) have published an apparently general route for the preparation. In this method α-acylphenylacetonitriles are converted by reaction with diazomethane (*3*), or by reflux with isobutyl alcohol and *p*-toluenesulfonic acid to their enol ethers (*4*), and then condensed with guanidine to give the 5-phenyl-6-alkyl-2,4-diaminopyrimidines in good yield. The present article describes the extension of this procedure to the synthesis of 5-aryl-6-arylmethyl-2,4-diaminopyrimidines containing Cl, F, and CF_3 groups in the aryl rings with emphasis on the fluorine derivatives because of current interest in the biological activity of such compounds.

The synthesis of the pyrimidines required the prior preparation of the appropriate α,γ-diarylacetoacetonitriles. these were conveniently synthesized (*1*) by the base-catalyzed condensation of an ethyl arylacetate with an arylacetonitrile (Equation 1). New intermediates for III, namely,

$$ArCH_2CO_2C_2H_5 + Ar'CH_2CN \xrightarrow{C_2H_5ONa} ArCH_2COCH(CN)Ar' + C_2H_5OH \quad (1)$$

I: Ar = *p*-$CH_3C_6H_4$-, Ar' = C_6H_5-
II: = *p*-FC_6H_4-, = *p*-FC_6H_4-
III: = *m*-$CF_3C_6H_4$-, = *m*-$CF_3C_6H_4$-

m-trofluoromethylphenylacetonitrile and ethyl *m*-trifluoromethylphenylacetate were prepared according to standard procedures (Equation 2). *m*-Trifluoromethylbenzyl bromide reacted smoothly with potassium cyanide in ethanol to give *m*-trifluoromethylphenylacetonitrile, which in turn was directly converted

$$m\text{-}CF_3C_6H_4CH_2Br \xrightarrow[C_2H_5OH]{KCN} m\text{-}CF_3C_6H_4CH_2CN \xrightarrow[H_2SO_4]{C_2H_5OH} m\text{-}CF_3C_6H_4CH_2CO_2C_2H_5 \quad (2)$$

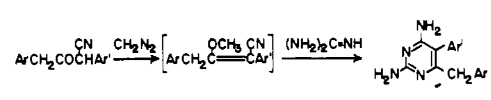
to ethyl *m*-trifluoromethylphenylacetate by reaction with ethanol and sulfuric acid.

[1] Present address, Hoffman-La Roche, Summitt, N. J.
[2] Present address, Thiokol Corp., Trenton, N. J.
[3] Present address, General Tire & Rubber Co., Akron, Ohio.

Attempts to prepare α,γ-bis(*p*-trifluoromethylphenyl) acetoacetonitrile failed. Fluoride ion appeared in the reaction mixture; furthermore, fluoride ion appeared when either *p*-trifluoromethylphenylacetonitrile or ethyl *p*-trifluoromethylphenylacetate was refluxed in alcoholic sodium ethoxide solutions. Such marked difference from the *m*-compounds was unexpected, although it is well-known (*2*, *5*) that the nature and position of other nuclear substituents has an effect on the hydrolytic stability of a CF_3 group on an aromatic ring. "No-bond" resonance is apparently an important phenomenon in these systems (*6*). Such electrical effects would be expected to labilize the fluorine atoms in the *p*-CF_3 group, but not the *m*-CF_3 group, and thus prevent the desired condensation.

On the other hand, concentrated aqueous alkali hydrolyzed ethyl *p*-trifluoromethylphenylacetate to *p*-trifluoromethylphenylacetic acid in 80% yield. Since the ester was not soluble in the base, it is likely that aqueous hydroxide ion under the conditions of the experiment was not strong enough to form the anion at the α-carbon atom. Of course, once the aryl-acetate anion had been formed by hydrolysis, the attack of another molecule of hydroxide would be unlikely.

The conversion of the α,γ-diarylacetoacetonitriles to their enol ethers by means of diazomethane and finally condensation with guanidine to give the 2,4-diaminopyrimidines proceeded without difficulty (Equation 3). The new pyrimidines are listed in Table I.



(3)

IV-IX

Parenthetically, the infrared spectra of the α,γ-diarylacetoacetonitriles gave some indication as to their structures. A broad band. of medium intensity at 3120 $cm.^{-1}$, and a medium strong band at 1630 $cm.^{-1}$ suggest an enol-rather than a keto-nitrile,

$$Ph\text{-}CH_2\text{—}\overset{\overset{\displaystyle OH}{|}}{C}=(CN)Ph$$

despite the improbability of forming a 6-membered chelate ring.

Table I. Physical Properties of 5-Aryl-6-arylmethyl-2,4-diaminopyrimidines

Compd. No.	Ar	Ar′	M.P., °C.	Yield, %	Empirical Formula	Analyses C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
IV	C_6H_5-	C_6H_5-	217.5–218.0[a]	73	$C_{17}H_{16}N_4$	73.89	73.74	5.84	5.80	20.28	20.19
V	C_6H_5-	p-$CH_3C_6H_4$-	190.5–191.5	67	$C_{18}H_{18}N_4$	74.45	74.38	6.25	6.38	19.30	19.23
VI	p-ClC_6H_4-	C_6H_5-	234.5–235.0[b]	62	$C_{17}H_{15}ClN_4$	65.70	65.54	4.86	4.98	18.03	18.09
VII	p-FC_6H_4-	C_6H_5-	208.5–209.3	74	$C_{17}H_{15}FN_4$	69.37	69.43	5.13	5.28	19.04	19.02
VIII	p-FC_6H_4-	p-FC_6H_4-	214.5–215.2	32	$C_{17}H_{14}F_2N_4$	65.38	65.44	4.52	4.66	17.94	18.10
IX	m-$CF_3C_6H_4$-	m-$CF_3C_6H_4$-	143.0–144.0	56	$C_{19}H_{14}F_6N_4$	55.34	54.94	3.42	3.34	13.58	13.91

[a] Reported (4), m.p. 213–215°.
[b] Reported (4), m.p. 235–236°.

EXPERIMENTAL

***m*- and *p*-Trifluoromethylphenylacetonitriles.** A solution of 7.5 grams (0.031 mole) of *p*-trifluoromethylbenzyl bromide in 30 ml. of ethanol was added to 4.1 grams (0.63 mole) of potassium cyanide in 10 ml. of water, and the mixture was stirred at room temperature overnight. The yellow reaction mixture was filtered with suction, and the solvents were removed in vacuo. The residue was dissolved in ether, dried over magnesium sulfate, and distilled to give 3.8 grams (66%) of colorless product, b.p. 98–100° (7 mm.), solidifying upon cooling, m.p. 40–41°.

Anal. Calcd. for $C_9H_6F_3N$: C, 58.38; H, 3.26; N, 7.56. Found: C, 58.48; H, 3.23; N, 7.56.

m-Trifluoromethylphenylacetonitrile was prepared in 85% yield by refluxing the corresponding benzyl bromide (95.6 grams, 0.40 mole) with potassium cyanide (32.5 grams 0.50 mole) in 80% ethanol. The product distilled at 92°–93° (4 mm.), n_D^{21} 1.4582.

Anal. Calcd. for $C_9H_6F_3N$: C, 58.38; H, 3.26; N, 7.56. Found: C, 58.62; H, 3.42; N, 7.61.

***m*- and *p*-Trifluoromethylphenylacetic Esters.** The ethyl esters were prepared from the corresponding phenylacetonitriles by the usual ethanol-sulfuric acid method. A mixture of 35.1 grams (0.10 mole) of *m*-trifluoromethylphenylacetonitrile, 75 ml. of ethanol, 25 ml. of concentrated sulfuric acid, and 5 ml. of water was refluxed for 10 hours. The reaction mixture was cooled and poured into 150 ml. of water and the lower layer separated. After extracting the aqueous phase twice with 50-ml. portions of ether, the ether extracts were combined with the organic layer and washed successively with saturated sodium bicarbonate solution and twice with water. After drying the ether solution over anhydrous magnesium sulfate, the solvent was distilled, and the product twice distilled, to give 34.0 grams (80%) of colorless ester, b.p. 87–88° (4 mm.) n_D^{21} 1.4770.

Anal. Calcd. for $C_{11}H_{11}F_3O_2$: C, 56.90; H, 4.78. Found: C, 56.89; H, 4.78.

From 12.5 grams (0.67 mole) of *p*-trifluoromethylphenylacetonitrile was obtained 12.7 grams (80%) of product, b.p. 104°–105° (7 mm.), solidifying upon cooling, m.p. 34°–35°.

Anal. Calcd. for $C_{11}H_{11}F_3O_2$: C, 56.90; H, 4.78. Found: C, 57.14; H, 4.94.

α,γ-Diarylacetoacetonitriles. The intermediary ketonitriles were prepared according to previously reported methods (*1*).

α,γ-Bis(*m*-trifluoromethylphenyl)acetoacetonitrile. To a stirred and refluxing solution of sodium ethoxide prepared by dissolving 1.15 grams (0.050 gram-atoms) of sodium in 20 ml. of absolute ethanol was added a mixture of 4.6 grams (0.025 mole) of *m*-trifluoromethylphenylacetonitrile and 5.8 grams (0.025 mole) of ethyl *m*-trifluoromethylphenylacetate over a period of 0.5 hour. The mixture was stirred and refluxed for 12 hours, cooled poured onto 60 ml. of ice water, and extracted twice with 25-ml. portions of benzene. The alkaline aqueous layer was acidified with cold 2*N* HCl and extracted thrice with 50-ml. portions of ether. The combined ether extracts were washed twice with 10-ml. portions of saturated sodium bicarbonate solution, twice with water, and dried over anhydrous sodium sulfate. Distillation of the solvent gave 5.0 grams (52%) of an oil which crystallized on cooling, m.p. 62°–66°. Recrystallization from a 2 to 1 hexane-benzene mixture raised the melting point to 68.4°–69.2°, in 74% yield on the recrystallization.

Anal. Calcd. for $C_{18}H_{11}F_6NO$: C, 58.22; H, 2.98; N, 3.77. Found: C, 58.22; H, 3.24; H, 4.15.

5-Phenyl-6-benzyl-2,4-diaminopyrimidines. In a typical procedure, an ethereal solution of diazomethane (prepared from N-nitrosomethylurea) was added to 2.35 grams (0.010 mole) of α,γ-diphenylacetoacetonitrile until a yellow color persisted. After standing overnight the solution was distilled to dryness and to the residue was added an alcoholic solution of guanidine prepared from 1.00 gram of guanidinium chloride and 0.540 gram of sodium methoxide in 50 ml. of methanol. The alcoholic solution was evaporated to dryness, the residue taken up in 30% acetic acid, heated to boiling with charcoal, and filtered hot. Basifying with 25% potassium hydroxide precipitated a white solid which was recrystallized from 50% alcoholic solution, affording 2.0 grams (73%) of white needles. The physical properties of this and other pyrimidines are given in the Table I.

LITERATURE CITED

(1) Coan, S.B., Becker, E.I., *J. Am. Chem. Soc.* **76**, 501 (1954); *Org. Syn.* **35**, 30 (1955).
(2) Fillar, R., Novar, H., *Chem. & Ind.* (London) **1960**, p. 1273.
(3) Hitchings, G.H., Russell, P.B., *J. Am. Chem. Soc.* **73**, 3767 (1951).
(4) Hitchings, G.H., Russell, P.B. (to Burroughs Wellcome) U. S. Patent **2,767,183**, (October 16, 1956).
(5) Jones, R., *J. Am. Chem. Soc.* **69**, 2346 (1947).
(6) Roberts, J.D., Webb, R.L., and McElhill, E.A., *J. Am. Chem. Soc.* **72**, 408 (1950)
(7) Roy, D., Ghosh, S., and Guha, B.C., *Arch. Biochem. Biophys.* **92**, 366 (1961)

RECEIVED for review July 13, 1962. Accepted September 28, 1962. Taken from the M.S. theses of B.E. Rosenkrantz, 1962; Louis Citarel, 1956; and B.S. thesis of G.E. Heinsohn, 1962.