Registry No. CH_2Br_2, 74-95-3; cyclohexene, 110-83-8; bicyclo[4.1.0]heptane, 286-08-8; cyclooctene, 931-88-4; bicyclo[6.1.0]nonane, 286-60-2; α-pinene, 80-56-8; 2,7,7-trimethyltricyclo[4.1.1.$0^{2,4}$]octane, 32549-17-0; β-pinene, 127-91-3; 6′,6′-dimethylspiro[cyclopropane-1,2′-norpinane], 35117-81-8; 1-hexene, 592-41-6; butylcyclopropane, 930-57-4; 1-octene, 111-66-0; hexylcyclopropane, 4468-61-5; 3,4-dihydropyran, 110-87-2; 2-oxabicyclo[4.1.0]heptane, 286-16-8; *trans*-crotyl alcohol, 504-61-0; *trans*-2-methylcyclopropylcarbinol, 21003-36-1.

Condensation with Trifluoroacetonitrile: A Simple One Step Synthesis of 5-Cyano-6-(trifluoromethyl)uracil

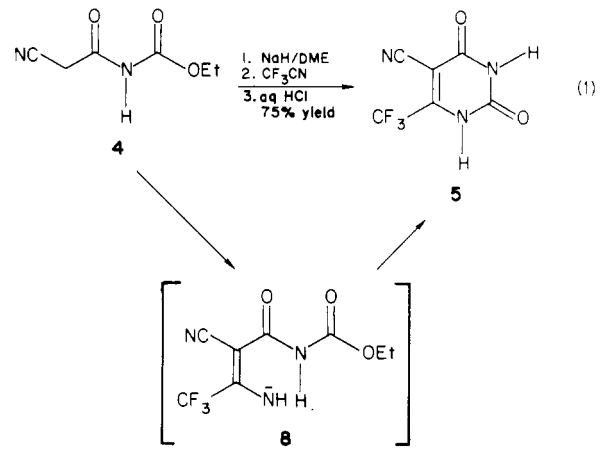
Y. Larry Sing* and Len F. Lee

Research Division, Monsanto Agricultural Products Company, St. Louis, Missouri 63167

Received April 19, 1985

A number of fluorine-substituted uracil derivatives show interesting biological activity. For example, 5-fluorouracil derivatives are useful as antitumor agents, and 5-(trifluoromethyl)deoxyuridine shows marked antiviral activity.[1,2] The binding of 6-substituted uracil to thymidine phosphorylase has been studied. The 6-trifluoromethyl derivative has been reported to bind to this enzyme sevenfold better than the 6-methyl analogue. Presumably the increased activity was due to the increased acidity of the uracil.[3] The 3-substituted-6-(trifluoromethyl)uracils have also been reported as herbicides.[4]

It is noteworthy that the existing synthetic routes to the 6-(trifluoromethyl)uracils do not allow a facile derivation at the 5-position,[3-5] which is needed for the synthesis of various analogues for biological evaluations. An acid function such as a cyano group at the 5-position is highly desirable, since it would offer increased opportunities for derivation. However, the 5-cyano derivative was hitherto unknown. It has been reported that an active methylene compound reacted with trifluoroacetonitrile to give the corresponding 2-trifluoromethyl enamine.[6] By employing an active methylene compound with a γ-ester function, such as *N*-(cyanoacetyl)urethane (**4**), one should be able to prepare the corresponding uracil in one step. In fact, treatment of **4** with sodium hydride followed by reaction of the resulting anion with trifluoroacetonitrile gave 5-cyano-6-(trifluoromethyl)uracil (**5**) in 75% yield (eq 1). Presumably the reaction intermediate was enamine **6**, though it was not isolated. The structural assignment of **5** was supported by its spectral properties and combustion analysis. Trifluoroacetonitrile has been condensed with enamines or ynamines to give the corresponding 2,4-bis(trifluoromethyl)pyrimidine.[7] However, trifluoroacetonitrile has not been used for the synthesis of uracils.



(1)

Experimental Section

Melting points are uncorrected. ^{19}F NMR spectra were obtained on a Varian EM-360 spectrometer. ^1H NMR spectra were obtained on a Varian XL-300 spectrometer. ^{13}C NMR spectra were recorded on a JEOL FX-100 spectrometer. Signals are reported in parts per million downfield from tetramethylsilane. Infrared spectra were obtained on a Perkin-Elmer Model 727B infrared spectrophotometer. Mass spectra were obtained on a Finnigan MAT CH7A mass spectrometer. Elemental microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

5-Cyano-6-(trifluoromethyl)uracil (5). To a solution of *N*-(cyanoacetyl)urethane (**4**) (100 g, 0.64 mol, Aldrich Co.) in 700 mL of anhydrous 1,2-dimethoxyethane under an atmosphere of nitrogen was added 34 g (0.7 mol) of sodium hydride (50% oil dispersion). The temperature of the exothermic reaction was kept below 45 °C by a water bath. The resulting muddy gray suspension was stirred for 30 min. After the exothermic reaction subsided, it was warmed to 35 °C by external heating. To this mixture, a stream of trifluroacetonitrile (Fairfield Co.) was added in slowly. At the end of 5.5 h, the uptake of trifluoroacetonitrile became very slow, and an excess amount of trifluoroacetonitrile was used. The resulting brown solution was poured into cold 6 N aqueous hydrochloric acid and extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$), and concentrated to give a solid. It was washed with chloroform/acetonitrile to give 97 g of a cream color solid (75% yield) as **5**: mp 245–253 °C; IR (Nujol) 2250 (m, C≡N), 1703 (s), 1630 (s) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 12.1 (s, N_4H, 1 H), 9.9 (br s, N_1H, 1 H; chemical shift and integration varied with the amount of moisture in Me_2SO-d_6); ^{13}C NMR (Me_2SO-d_6) δ 160.4 (C_4), 149.6 (C_2), 148.9 (C_6, q, J = 35.9 Hz), 118.3 (CF_3, q, J = 278.1 Hz), 111.6 (CN), 86.9 (C_5, q, J = 1.4 Hz); ^{19}F NMR (Me_2SO-d_6, CCl_3F) δ −67.53; mass spectrum, *m/e* (relative intensity) 205 (M^+, 40.3), 162 (40.0), 96 (12.3), 93 (59.9), 28 (100.0).

Anal. Calcd for $C_6H_2F_3N_3O_2$: C, 35.14; H, 0.98; N, 20.49. Found: C, 35.14; H, 0.92; N, 20.48.

Registry No. **4**, 6629-04-5; **5**, 98577-47-0; trifluoroacetonitrile, 353-85-5.

Synthesis and Fluorescence Spectra of Structural Analogues of Potential Benzo[*b*]fluoranthene-DNA Adducts[1,2]

Shantu Amin,* George Balanikas, Keith Huie, Nalband Hussain, J. Edgar Geddie, and Stephen S. Hecht

Division of Chemical Carcinogenesis, Naylor Dana Institute for Disease Prevention, American Health Foundation, Valhalla, New York 10595

Received March 26, 1985

Benzo[*b*]fluoranthene (**1**), an environmental carcinogen[3-7] interacts in vivo with the DNA of mouse epidermis

(1) (a) Heidelberger, C.; Parsons, D. G.; Remy, D. C. *J. Am. Chem. Soc.* **1962**, *84*, 3597. (b) Heidelberger, C.; Parsons, D. G.; Remy, D. C. *J. Med. Chem.* **1964**, *7*, 1. (c) Ryan, K. J.; Acton, E. M; Goodmann, L. *J. Org. Chem.* **1966**, *31*, 1181.

(2) Heidelberger, C. *Cancer Res.* **1970**, *30*, 1549.

(3) Baker, B. R.; Kanazu, M.; McClure, J. D. *J. Pharm. Sci.* **1967**, *56*, (9), 1081.

(4) Lutz, A. W.; Trotto, S. H. *J. Heterocycl. Chem.* **1972**, *9*, 513.

(5) Fuchikami, T.; Ojima, I. *Tetrahedron Lett.* **1982**, 4099.

(6) (a) Bodnarchuk, N. D.; Momot, V. V.; Gavrilenko, B. B. *J. Gen. Chem. USSR (Engl. Transl.)* **1975**, *45*, 873. (b) Bodnarchuk, N. D.; Gavrilenko, B. B.; Derkach, G. I. *J. Org. Chem. USSR (Engl. Transl.)* **1968**, *4*, 1645.

(7) (a) Burger, K.; Hein, F.; Wassmuth, U.; Krist, H. *Synthesis* **1981**, 904. (b) Burger, K.; Wassmuth, U.; Hein, F.; Rottegger, S. *Liebigs Ann. Chem.* **1984**, 991.

0022-3263/85/1950-4642$01.50/0