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A SILICON-MEDIATED SYNTHESIS OF NOVEL 5-SUBSTITUTED 2,4-DIMETHOXYPYRIMIDINES AND 5-SUBSTITUTED URACILS[1]

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Summary: A highly efficient and general method for the synthesis of 5-(2-acylethynyl)-2,4-dimethoxypyrimidines starting from 2,4-dimethoxy-5-/2-(trimethylsilyl)ethynyl/ pyrimidine is described. The 5-(2-acylethynyl)-2,4-dimethoxypyrimidines have been converted to 5-(2-acyl-1-iodovinyl) uracils and 5-(2-acylethynyl) uracils.

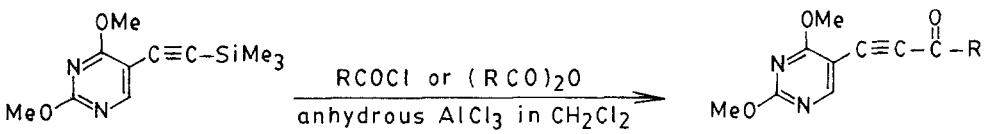
5-Substituted derivatives of uracil have been of great importance because of their biological activity. 5-Fluorouracil (FU) and the corresponding 2'-deoxyribonucleoside (FUdR) are extensively used in the treatment of patients suffering from metastatic cancers[2]. 5-Trifluoromethyl-2'-deoxyuridine (F_3TdR) is highly effective against ocular herpes keratitis[3]. Various 5-alkyl substituted derivatives of uracil have been synthesized for both anticancer and antiviral properties[2-4]. Notable amongst them is (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU) which has been found to be one of the most potent drugs effective against herpes simplex virus type I, (HSV-I)[5]. Recently some 5-substituted derivatives of uracil, e.g. azidothymidine and CS-85, are being tested as anti-AIDS drugs[6].

The present methods for the synthesis of 5-substituted derivatives of uracil are usually targeted to the synthesis of a particular 5-substituted uracil[4,7]. Only a few methods attempt to synthesize 5-substituted uracils or the corresponding nucleosides by a general procedure. Some of them involve expensive palladium reagents[8]. Organo-lithium derivatives of pyrimidine bases and nucleosides have also been utilized for synthesis of C_5 and C_6 substituted uracil derivatives[9]. A photochemical approach for the synthesis of C_5 and C_6-substituted uracils has also been reported[10].

In view of our interest to develop inhibitors of thymidylate synthetase and dihydroorotate dehydrogenase, essential enzymes required for the growth of cells, we have sought methods for the synthesis of various 5-and 6-substituted derivatives of uracil[11,12] and dihydro uracil[13]. We felt that a uracil molecule with an ethynyl side chain at C_5-position, which is further conjugated with an acyl group (e.g., a C_5-substituent like -C≡C-COR) could act (after being converted to the corresponding 2'-deoxy ribonucleosides) as potent inhibitors of thymidylate synthetase. The present letter reports on a general method for the synthesis of 5-(2-acylethynyl)-2,4-dimethoxypyrimidines and their conversion to 5-(2-acylethynyl) uracils.

Silylated acetylenes have been useful intermediates for the synthesis of conjugated acetylenic ketones[14]. However, surprisingly, the use of C-silylated intermediates for the synthesis of 5-substituted pyrimidines is lacking. Recently, we have reported[12] the synthesis of a C-silylated pyrimidine, e.g., 2,4-dimethoxy-5-/2-(trimethylsilyl)ethynyl/ pyrimidine (1). When a mixture of compound 1 and an acid chloride or, anhydride is treated with anhydrous aluminum chloride in dichloromethane, the corresponding acetylenic ketones (2-10) were obtained, as shown in Scheme-1.

Scheme 1



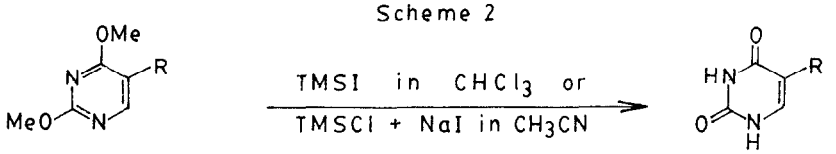
1 2-10

The reaction proved to be highly efficacious and a number of 5-(2-acylethynyl)-2,4-dimethoxypyrimidines were synthesized in extremely high yield (see Table-I). This is the first report of the synthesis of 5-substituted pyrimidines where the 5-substituent has been elongated through a silicon-intermediate. A typical experimental procedure follows.

Powdered anhydrous aluminum chloride (0.23 g, 1.73 mmol) was added in portions to an ice-cold solution of 2,4-dimethoxy-5-/2-(trimethylsilyl)ethynyl/ pyrimidine, 1, (0.1 g, 0.42 mmol) and acetyl chloride (0.06 g, 0.76 mmol) in methylene chloride (15 ml). The mixture was stirred at 25°C for 6 hours and poured on ice-hydrochloric acid mixture. The organic layer was separated, washed with water and dried. On removal of solvent, a solid (0.09 g) was obtained which was crystallized from petroleum-ether (b.p. 40-60°C) into white needle shaped crystals of 2.

The 5-(2-acylethynyl)-2,4-dimethoxypyrimidines can be easily reduced catalytically (Pd/C 10%) to the corresponding saturated ketones and by partial reduction to the corresponding vinylic ketones[15]. Deblocking of the blocked pyrimidines with iodotrimethylsilane or with chlorotrimethylsilane and sodium iodide readily affords the corresponding 5-substituted uracil derivatives[16] (Table-II) according to Scheme-2.

Scheme 2

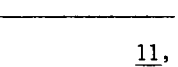


2,4-7 11 - 16

TABLE-I. Synthesis of 5-(2-acylethynyl)-2,4-dimethoxypyrimidines (2-10) (Scheme-1)

Electrophile (mmol equivalent)		Reaction Time (Hrs)	Products[17]	M.P(°C)	Yield (%)
CH_3COCl	(1.8)	6.0	2, R=CH_3	94-96	99
$(CH_3CO)_2O$	(1.5)	6.0	2, R=CH_3	94-96	89
C_2H_5COCl	(3.0)	12.0	3, R=C_2H_5	78-80	99
$(C_2H_5CO)_2O$	(1.0)	6.0	3, R=C_2H_5	78-80	54
$(n\text{-}C_3H_7CO)_2O$	(2.0)	21.0	4, R=n-C_3H_7	gum	90
C_6H_5COCl	(1.25)	5.0	5, R=C_6H_5	122-125	82
(p)CH_3-C_6H_4COCl	(1.0)	6.0	6, R=-C_6H_4-CH_3(p)	150-151	84
(o)Cl-C_6H_4-COCl	(1.2)	6.0	7, R=-C_6H_4-Cl(o)	118-120	95
(p)O_2N-C_6H_4-COCl	(1.2)	5.0	8, R=-C_6H_4-NO_2(p)	190-192	83
(p)MeO-C_6H_4-COCl	(1.2)	6.0	9, R=-C_6H_4-OMe(p)	124-125	73
Succinic anhydride	(1.0)	20.0	10, R=-CH_2-CH_2CO_2H	> 300	90

TABLE-II. Conversion of 2,4-dimethoxy-5-substituted pyrimidines to 5-substituted uracils (Scheme-2)

Substrates (R=)	Reagents, Reaction Conditions[18]	Products[19,20] (R=)	Yield (%)
2, -C≡C-$COCH_3$	A	11, 	67
4, -C≡C-CO$(CH_2)_2$-CH_3	A	12, 	78
6, -C≡C-CO-C_6H_4-CH_3(p)	B	13, 	44
5, -C≡C-CO-C_6H_5	C	14, -C≡C-CO-C_6H_5	45
7, -C≡C-CO-C_6H_4-Cl(o)	C	15, -C≡C-CO-C_6H_4-Cl(o)	49
6, -C≡C-CO-C_6H_4-CH_3(p)	D	16, -C≡C-CO-C_6H_4-CH_3(p)	27

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REFERENCES AND NOTES

1. Part 10 of the series on Studies on Uracil Derivatives and Analogues.
2. Heidelberger, C., Pyrimidine and Pyrimidine Nucleoside Antimetabolites , in Cancer Medicine, Eds. Holland, J.F., and Frei, E., Lea and Febiger, Philadelphia, 1984, 801-824.
3. Heidelberger, C., and King, D.H., in Antiviral Agents, D. Shugar, Ed., Pharmacology and Therapeutics, Vol.6, Pergamon Press, Oxford, England, 1979, p.427.
4. Bergstrom, D.E., Ruth, J.L.,Reddy, P.A., DeClercq, E., J. Med. Chem.,1981, 27, 410; Herdewijn, P., DeClerq, E., Balzarini, J., Vanderhaeghe, H., J. Med. Chem., 1985, 28, 550.
5. DeClercq, E., Descamps, J., DeSomer, P., Barr, P.J., Jones, A.S., Walker, R.T., Proc. Natl. Acad. Sci. (USA), 1979, 76, 2947.
6. Dagani, R., Chem. and Eng. News, 1986, 64, 7; DeClercq, E., J. Med. Chem., 1986, 29, 1561.
7. Perman, J., Sharma, R.A., and Bobek, M., Tetrahedron Letters, 1976, 2427; Jones, A.S., Verhelst, G., and Walker, R.T., ibid, 1979, 4415.
8. Edo, K. Sakamoto, T., and Yamanaka, H., Chem. Pharm. Bull., 1978, 26, 3843; Bergstrom, D.E., and Ogawa, M.K., J. Am. Chem. Soc., 1978, 100, 8106; Bigge, C.F., Kalaritis, P., Deck, J.R., and Mertes, M.P., J. Am. Chem. Soc., 1980, 102, 2033; Robins, M.J., and Barr, P.J., J. Org. Chem., 1983, 46, 1854.
9. Tanaka, H., Havakawa, J., Obi, K. and Miyasaka, T., Tetrahedron, 1986, 42, 4187.
10. Saito, I., Ikehira, H., and Matsuura, T., J. Org. Chem., 1986, 51, 5148.
11. Bhatt, R.S., Kundu, N.G., Chwang, T.L., and Heidelberger, C., J. Heterocycl. Chem., 1981, 18, 771.
12. Kundu, N.G., and Schmitz, S.A., J. Heterocycl. Chem., 1982, 19, 463.
13. Kundu, N.G., Sikdar, S., Hertzberg, R.P., Schmitz, S.A., Khatri, S.G., J. Chem. Soc. Perkin Trans.I, 1985, 1293.
14. Birkofer, L., Ritter, A., and Uhlenbrauck, H., Chem. Ber., 1963, 96, 3280.
15. Smith, III, A.B., Levenberg, P.A., and Suits, J.Z., Synthesis, 1986, 184.
16. A typical deblocking procedure - Synthesis of 5-(2-p-toluoylethynyl) uracil (16) : A mixture of 2,4-dimethoxy-5-(2-p-toluoylethynyl) pyrimidine, 6 (500 mg, 1.77 mmol) and iodotrimethylsilane (0.78 ml) in chloroform (40 ml) was stirred at rt under N_2-atmosphere for 24 hr. After removal of solvent the residue was treated with water and CH_3OH. The solid was filtered and crystallized from CH_3OH to yield an yellow powder (300 mg, 44%) of compound 13, mp 250-254°C. A mixture of compound 13 (100 mg, 0.26 mmol) and KOH (1.1 ml, 2M) in dioxane (3 ml) was stirred at rt for 7 hr and heated at 90°C for 20 min. After adjustment to pH 6-7 the mixture was cooled and filtered to yield 40 mg (61%) of 5-(2-p-toluoylethynyl) uracil (16), mp > 290°C.
17. All new compounds had elemental analyses and spectra data consistent with assigned structures. Some typical NMR (100 MHz) data (δ) are as follows - compound 6, 2.44 (s, 3H, CH_3-Ar), 4.04 (s, 3H, OCH_3), 4.12 (s, 3H, OCH_3), 7.32 (d, 2H, J=8 Hz, Ar-H_m), 8.13 (d, 2H, J=8 Hz, Ar-H_o), 8.56 (bs, 1H, C_6-H); compound 9, 3.88 (s, 3H, OCH_3), 4.04(s, 3H,OCH_3) 4.10 (s, 3H, OCH_3), 6.98 (d, 2H, J=8 Hz, Ar-H_m), 8.2 (d, 2H, J=8 Hz, Ar-H_o), 8.54 (s, 1H, C_6-H). All the products, 2-10, showed a stromg band at 2200cm^{-1} (C≡C) in the infra-red.
18. A, TMSCl (3.2 eq), NaI (3.1 eq) in CH_3CN, rt, 24 hr; B, TMSI (3.2 eq), rt, 26 hr; C,(i), TMSCl (3.2 eq), NaI (3.1 eq) in CH_3CN, rt, 22 hr; (ii), KOH in dioxane (2M, 8.0 eq) on crystallized material from (i), rt, 7 hr; D,(i), TMSI (3.2 eq), rt, 24 hr, (ii),As in C.
19. Satisfactory spectroscopic data were obtained for all the new compounds.
20. Compound 14 and 16 led to 100% inhibition of growth of Ehrlich Ascites Carcinoma Cells in Swiss Albino mice, Compound 16 was also active against CCRF-CEM cells in vitro, the IC_{50} value being 4.5 μmol . The biological properties of other compounds are being studied.

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