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A NOVEL ROUTE TO 5-FLUOROURACILS FROM CHLOROTRIFLUOROETHENE

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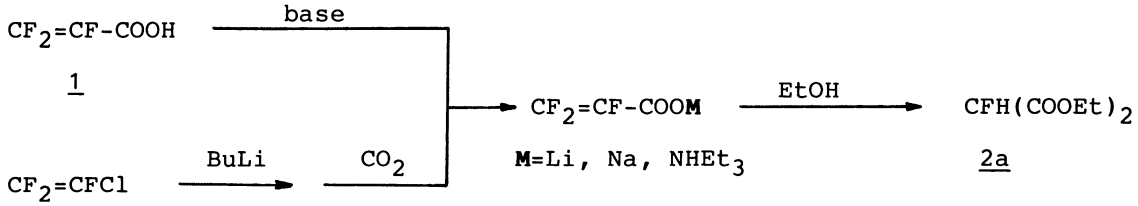
Diethyl fluoromalonate was prepared in one-pot from chlorotrifluoroethene via trifluoroacrylic acid lithium salt in 79% yield. Diethyl fluoromalonate was easily converted to 5-fluoro-6-chlorouracils, reductions of which gave 5-fluorouracils in good yields.

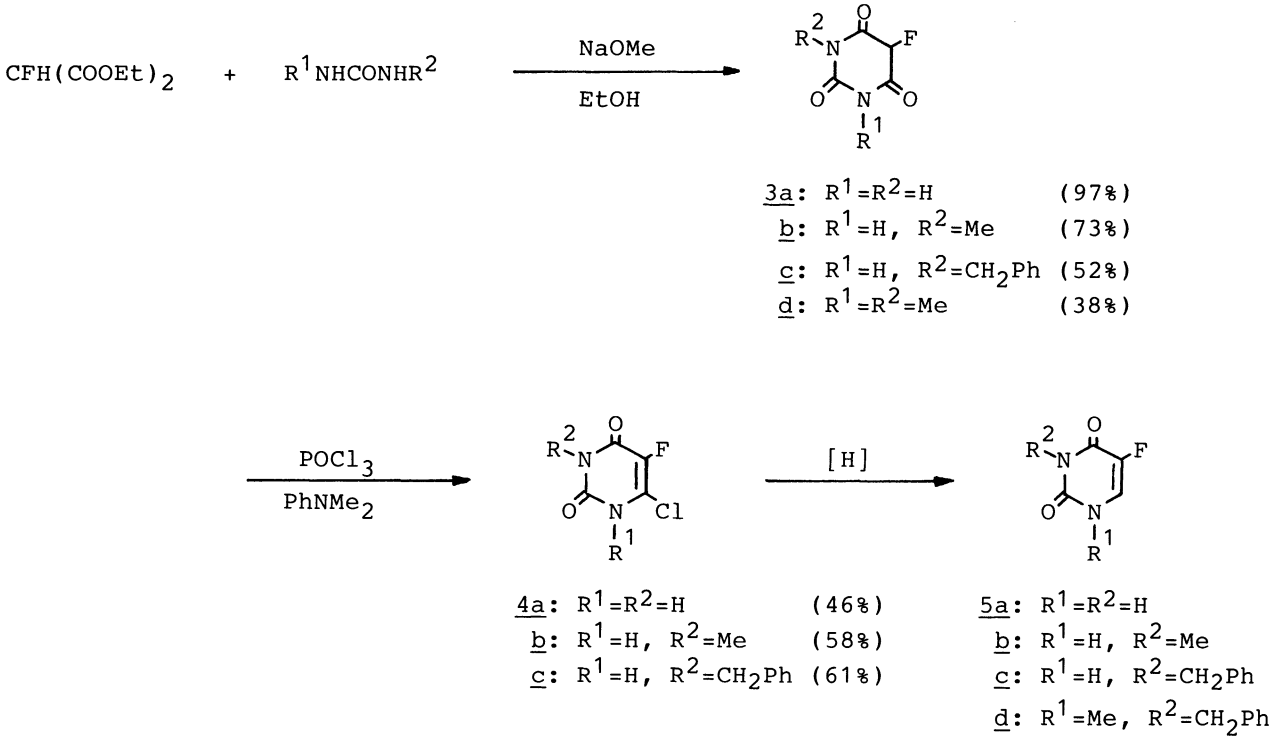
Recently, remarkable attentions have been focused on fluorine-containing nucleic acids such as 5-fluoro- and 5-trifluoromethyluracils for their unique biological properties such as antitumour and/or antiherpes activities.[1] In the course of our studies on functionalization of fluorine-containing olefins,[2] we have already found and reported a convenient synthesis of 5-trifluoromethyluracils via 5-trifluoromethyl-5,6-dihydrouracils prepared by ureidocarbonylation of 2-bromo-3,3,3-trifluoropropene[3] or by cyclization of α-trifluoromethylacrylic acid with ureas in acetic anhydride.[4] On the other hands, preparation of 5-fluorouracils reported up-to-date are very dangerous because of explosiveness of fluorinating reagents[5] or toxicity of starting materials such as fluoroacetamide[6] or ethyl fluoroacetate.[7] In this paper, we wish to report a convenient route to 5-fluorouracils starting from chlorotrifluoroethene.

It was reported that trifluoroacrylic acid (1) is thermally unstable and a violent reaction normally occurred during product distillation with the simultaneous evolution of hydrogen fluoride,[8] however no detail analysis of the product



has been examined. We found that diethyl fluoromalonate (2a) was formed in 54 to 65% yield, when 1 was heated in ethanol in the presence of base such as triethylamine, sodium ethoxide or lithium hydroxide. A similar reaction of 1 with sodium methoxide in methanol afforded dimethyl fluoromalonate (2b)[9] in 34%. Compound 2a was successfully synthesized in one-pot via trifluoroacrylic acid lithium salt prepared from chlorotrifluoroethene, buthyllithium and carbon dioxide,[10] followed by heating in added ethanol in 79%. Diethyl fluoromalonate reacted with substituted ureas such as methylurea, 1,3-dimethylurea or benzylurea in the presence of sodium methoxide in ethanol under similar conditions employed with unsubstituted urea[9,11] to give N-substituted 5-fluorobarbituric acids (3b-d), while we failed to obtain the desired product in the reaction with phenylurea.

When 5-fluorobarbituric acid (3a) was heated with excess of phosphorus oxychloride in the presence of 2 equiv. of *dimethylaniline* at 100 °C for 10 min, 5-fluoro-6-chlorouracil (4a) was obtained in 46% yield.[12] Similar reactions of 3b and 3c gave the corresponding 5-fluoro-6-chlorouracils (4b and 4c) in 58 and 61% yields, respectively. It is of interest to note that 3-substituted isomers were exclusively formed in these reactions. Though our attempt to obtain 1,3-disubstituted 5-fluoro-6-chlorouracil from 1,3-dimethyl-5-fluorobarbituric acid (3d) was



3a: $R^1=R^2=H$ (97%)
b: $R^1=H$, $R^2=Me$ (73%)
c: $R^1=H$, $R^2=CH_2Ph$ (52%)
d: $R^1=R^2=Me$ (38%)

4a: $R^1=R^2=H$ (46%)
b: $R^1=H$, $R^2=Me$ (58%)
c: $R^1=H$, $R^2=CH_2Ph$ (61%)

5a: $R^1=R^2=H$
b: $R^1=H$, $R^2=Me$
c: $R^1=H$, $R^2=CH_2Ph$
d: $R^1=Me$, $R^2=CH_2Ph$

unsuccessful under the same reaction conditions, we were able to synthesized 1,3-disubstituted derivative, 1-methyl-3-benzyl-5-fluoro-6-chlorouracil (4d), by methylation of 4c with methyl iodide in 79%.

Hydrogenolysis of 4a catalyzed by palladium on carbon in 1 M sodium hydroxide solution under atmosphilic pressure of hydrogen at room temperature gave 5-fluorouracil selectively, though long period of reaction time or use of large amounts of catalyst afforded uracil as main product.[14] In a similar way, the reduction of N-substituted derivatives (4b-d) to 5-fluorouracils (5b-d) was carried out in 1 M sodium hydroxide solution or in ethanol or ethanol-tetrahydrofuran (THF) in the presence of equimolar amount of triethylamine in 87 to 99% yields. The conversion of 5-fluoro-6-chlorouracils (4) to 5-fluorouracils (5) was also performed by zinc reduction. Thus, heating of 4a with zinc powder in acetic acid at 100 °C for 5 h gave 5a in 91%.

It is so difficult in general to introduce a substituent selectively at the desired position, especially at 3-position, of uracil or 5-fluorouracil that this method may make offer a new methodology not only for safety preparation of 5-

Table 1. Reduction of 5-fluoro-6-chlorouracils (4)

R^1	R^2	Method[a]	Pd/C ($\times 10^{-2}$ equiv.)	Solvent(base)	Time / h	Product (Yield/%)
H	H	A	3.9	1 M NaOH aq.	4	5a (73)
H	H	A	10.0	1 M NaOH aq.	4	—— b)
H	H	B	3.5	EtOH (Et_3N)	3	5a (84)
H	H	C	——	AcOH	5	5a (91)
H	Me	A	3.7	1 M NaOH aq.	4	5b (91)
H	CH_2Ph	A	5.6	1 M NaOH aq.	4	5c (87)
Me	CH_2Ph	B	6.1	EtOH-THF (Et_3N)	9	5d (99)
Me	CH_2Ph	B	6.1	THF (Et_3N)	3.5	—— c)

a) Method A: Reactions were run with 4 (0.25 mmol) and Pd/C in 2.5 ml of 1 M sodium hydroxide solution under atmosphilic pressure of hydrogen at room temperature. Method B: Reactions were run with 4 (0.25 mmol), triethylamine (0.25 mmol) and Pd/C in ethanol (1 ml) or ethanol(1 ml)-THF(1 ml) under atmosphilic pressure of hydrogen at room temperature. Method C: Reaction was run with 4 (0.4 mmol) and zinc powder (1.5 mg-atom) in 2 ml of acetic acid at 100 °C. b) Uracil was obtained in 80% yield. c) No reaction was occurred and starting 4d was recovered unchanged quantitatively.

fluorouracils but also for development of novel physiological active fluorine-containing nucleic acids. Further studies on the application of this reaction are now underway.

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12) German patent[13] has claimed that the reaction of 5-fluorobarbituric acids with phosphorous oxycloride in the presence of *water* gave 5-fluoro-6-chloro-uracils, however we could obtain no or little desired product under the same reaction conditions.
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