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# A FACILE CONVERSION OF 5-TRIFLUOROMETHYL-5,6-DIHYDROURACILS TO 5-TRIFLUOROMETHYLURACILS

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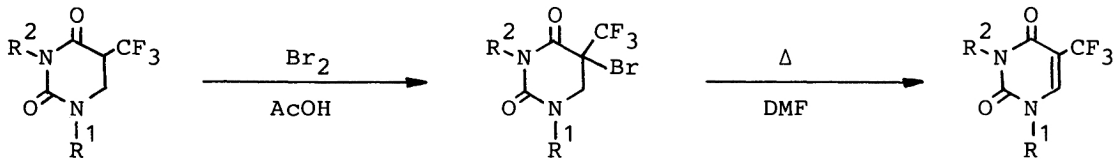
5-Trifluoromethyl-5,6-dihydrouracils were directly converted to the corresponding 5-trifluoromethyluracils by the reaction with copper(II) bromide in dimethylformamide/water or dimethylformamide/acetic acid in good to excellent yields.

Among recent physiological interest in organofluorine compounds, fluorine-containing nucleic acids are one of the most attractive drugs for their unique biological activities.[1] Some of 5-trifluoromethyluracil derivatives have shown potent antitumour activity and cytotoxicity, and undergone critical evaluation as topical agents against clinical herpes and adenovirus eye infections.[2] Though numerous 5-fluorouracil derivatives have been actively synthesized and tested in their biological properties, little systematic study has been examined for 5-trifluoromethyluracils because of difficulties in their preparations.[3] In the course of our studies on functionalization of fluorine-containing olefins,[4] we have found a convenient synthesis of 5-trifluoromethyl-5,6-dihydrouracils, which we have also found to exhibit considerable antitumour activity toward the tumour cells of ascitic mastocarcinoma MM2 of inbred mice, by palladium-complex catalyzed ureidocarbonylation of 2-bromo-3,3,3-trifluoropropene[5] or by cyclization of α-trifluoromethylacrylic acid with ureas in acetic anhydride.[6] We would like to report here a facile method to convert 5-trifluoromethyl-5,6-dihydrouracils to 5-trifluoromethyluracils using copper(II) bromide in one-step.

5-Trifluoromethyl-5,6-dihydrouracil (1a) was reported to be converted to 5-trifluoromethyluracil (3a) via 5-bromo-5-trifluoromethyl-5,6-dihydrouracil (2a) by

the action of bromine in acetic acid followed by heating in N,N-dimethylformamide (DMF) in 66%.[3a] However, when we employed this method in the reaction of N-alkyl-substituted derivatives (1b and e), excess amounts of bromine were required for the complete consumption of the dihydrouracils. Moreover, no or little desired uracil (2c) was obtained in the case of phenyl-substituted one, 3-phenyl-5-trifluoromethyl-5,6-dihydrouracil (1c), because bromination occurred predominantly on phenyl ring. From these results, we realized the necessity to develop a novel and general method for conversion of 1 to 3.



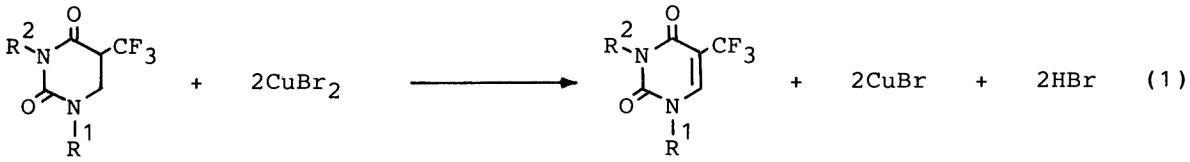

1 2 3

Attempts of dehydrogenation of 5-trifluoromethyldihydrouracil 1a by using dicyanodichlorobenzoquinone (DDQ) or by using Pd/C or Rh complex as catalyst was unsuccessful and compound 1a was quantitatively recovered. Though anodic oxidation of 1a showed the formation of some amounts of uracil 3a, 5-bromo-5-trifluoromethyl-6-hydrouracil (2a) was obtained as main product, in addition to considerable amounts of decomposition products.[7] We found that copper(II) bromide is an effective reagent to oxidize dihydrouracil 1a to uracil 3a. In this method, a sort of solvents and reaction temperature are essencial factors for the product yields: For example, almost no reaction occurred at 100 °C in DMF, AcOEt, MeOH-$H_2O$ or AcOEt-$CHCl_3$, or 5-bromo-5-trifluoromethyl-5,6-dihydrouracil (2a) was obtained as main product in a solvent such as AcOH, AcOH-$H_2O$, DMF-AcOEt, DMF-EtOH and DMF-$CHCl_3$, where high reaction temperature (130 °C) affoded a considerable amount of decomposition products with some of 3a. While reaction in DMF-$H_2O$ (1:1) at 100 °C or in DMF-AcOH (1:1) at 115 °C gave 5-trifluoromethyluracil (3a) directly in good yield. It is of interest to note that in these conditions only a trace amount of 5-bromo derivative (2a) was detected by $^{19}F$ NMR analysis even at initial stage of the reaction. This result may be rationalized in terms that dehydrobromination from 5-bromo derivatives initially formed could be fasten in these mixed solvent systems, though addition of base such as lithium hydroxide or potassium carbonate

to these systems resulted in decrease in the product yields because of increase of decomposition products.

Typical procedure is as follows: A solution of 5-trifluoromethyl-5,6-dihydrouracil (1a) (91 mg, 0.5 mmol) and copper(II) bromide (223.4 mg, 1.0 mmol) in DMF (1 ml) and acetic acid (1 ml) was heated at 115 °C for 14 h with stirring. After the solvent was removed, the residue was purified by column chromatography on silica gel (AcOEt) to give 74 mg (82%) of 5-trifluoromethyluracil (3a).

The present method can be widely applicable to the compounds having substituents on N atom, for being free from bromination on phenyl ring. Thus, 3-phenyl- and 3-benzyl-5-trifluoromethyluracil (3c and 3d) were obtained in 73 and 96%




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

3a: $R^1=R^2=H$
b: $R^1=H$, $R^2=Me$
c: $R^1=H$, $R^2=Ph$
d: $R^1=H$, $R^2=CH_2Ph$
e: $R^1=R^2=Me$

Table 1. Conversion of 5-Trifluoromethyl-5,6-dihydrouracils (1) to 5-Trifluoromethyluracils (3)

| | $R^1$ | $R^2$ | Solvent | Temp °C | Time h | Product (Yield/%) |
|---|---|---|---|---|---|---|
| 1a | H | H | DMF-$H_2O$ | 100 | 10 | 3a (76) |
| | | | DMF-AcOH | 110 | 14 | 3a (70) |
| | | | DMF-AcOH | 115 | 14 | 3a (82) |
| | | | DMF-AcOH | 120 | 12 | 3a (80) |
| | | | DMF-AcOH | 130 | 10 | 3a (50) |
| 1b | H | Me | DMF-$H_2O$ | 100 | 13 | 3b (75) |
| | | | DMF-AcOH | 115 | 13 | 3b (88) |
| 1c | H | Ph | DMF-AcOH | 115 | 16 | 3c (73) |
| 1d | H | $CH_2Ph$ | DMF-AcOH | 115 | 15 | 3d (96) |
| 1e | Me | Me | DMF-$H_2O$ | 100 | 12 | 3e (96) |
| | | | DMF-AcOH | 115 | 13 | 3e (88) |
| | | | DMF-AcOH[a)] | 115 | 80 | 3e (56) |

a) Reaction was run in DMF and 25% HBr solution in acetic acid in the presence of 12 mol% of $CuBr_2$ under oxygen atmosphere.

yields from 1c and 1d, respectively. Results are summarized in Table 1. From the fact that two equivalents of copper(II) bromide was always required for the complete conversion of 1 under nitrogen atmosphere, stoichiometry of these reactions should be as shown in Eq. 1. As copper(I) salts are well known to be reoxidize to copper(II) salts in acidic media under oxygen atmosphere, copper(II) bromide should act as catalyst in the present reaction. In fact, reaction of 1e in mixed solvent of DMF and 25% HBr solution in acetic acid in the presence of 12 mol% of copper(II) bromide under oxygen at 115 °C for 80 h gave 3e in 56% yield.

Recently, many attempts to diminish harmful side-effects for antitumour activities of 5-trifluoromethyluracils by modifying substituents on N atoms have been actively studied. So, present reaction should offer a novel methodology for preparing biological active fluorine-containing nucleic acids. Further studies on the application of this reaction are now underway.

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7) For example, constant-current electrolysis of 1a (0.5 mmol) with a current of 54 mA for 1 h (4 F/mol) in the presence of KBr (1 mmol) as electrolyte in DMF(5 ml)-$H_2O$(0.5 ml) using platinum electrodes (1 cm x 1 cm) in an undivided cell gave 2a (43%) and 3a (9%).

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