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NEW AND DIRECT ROUTE TO 5-TRIFLUOROMETHYL-5,6-DIHYDROURACILS BY MEANS OF PALLADIUM COMPLEX CATALYZED "UREIDOCARBONYLATION" OF 2-BROMO-3,3,3-TRIFLUOROPROPENE

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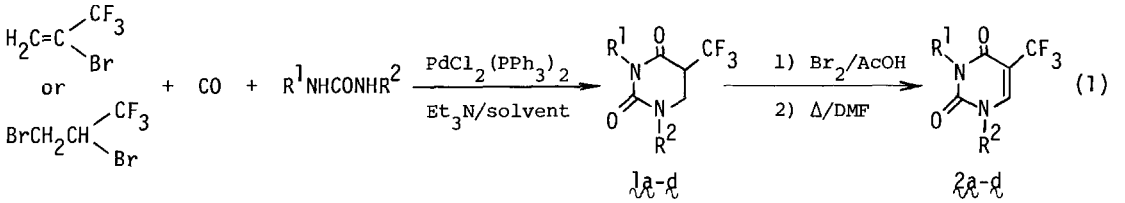
Summary *Palladium complex catalyzed carbonylation of 2-bromo-3,3,3-trifluoropropene (2-Br-TFP) with ureas afforded 5-trifluoromethyl-5,6-dihydrouracils in moderate to good yields, which were converted into 5-trifluoromethyluracils in nearly quantitative yields.*

It has been shown that the palladium complex catalyzed amidation of vinyl halides is a convenient method for the synthesis of α,β-unsaturated amides [1] Recently, this method was successfully applied to the synthesis of a 3-methylidene-β-lactam, which was a key-intermediate of nocardicin, by using an intramolecular amidation [2] We wish to report here a novel one-step synthesis of 5-trifluoromethyl-5,6-dihydrouracils by means of the palladium complex catalyzed "ureidocarbonylation" of 2-Br-TFP[3] accompanied by cyclization



(1)

A general scheme of the present novel reaction is shown in eq 1 Typical procedure for the synthesis of 1,3-dimethyl-5-trifluoromethyl-5,6-dihydrouracil (1a) is as follows A mixture of $PdCl_2(PPh_3)_2$ (70 mg, 0 1 mmol), 2-Br-TFP (1 75 g, 10 mmol), 1,3-dimethylurea (0 88 g, 10 mmol), and triethylamine (1 31 g, 13 mmol) in 10 ml of dimethylformamide (DMF) in a 50 ml stainless steel autoclave was heated at 100°C for 10 hr under carbon monoxide pressure (40 atm) with stirring Then, the reaction mixture was poured into water (20 ml), extracted with chloroform (20 ml x 3), and the extract was dried over anhydrous sodium sulfate After the solvent was evaporated, the resulting crude product was submitted to a column chromatography on silica gel to give 1a in 70% yield (1 47 g)

In a similar manner, 2-Br-TFP was allowed to react with methylurea to give a mixture of 3-methyl-5-trifluoromethyldihydrouracil (1b) and 1-methyl-5-trifluoromethyldihydrouracil (1c), which were readily separated by a column chromatography on silica gel to afford 1b and 1c in 51% and 9% yields, respectively When unsubstituted urea was employed, the yield of 5-trifluoro-

methyldihydrouracil (1d) was lower than those of the substituted ones although the reaction conditions were not optimized It was found that 2,3-dibromo-1,1,1-trifluoropropane[4] could be used instead of 2-Br-TFP The results are summarized in Table 1 [7]

Table 1 Synthesis of 5-Trifluoromethyl-5,6-dihydrouracils

R^1	R^2	Cat (mol%)	solvent	CO (atm)	Temp (°C)	Time (hr)	Product[a] (Yield, %)
Me	Me	1	DMF	40	100	10	1a(70)
Me	Me[b]	1	THF	45	100	15	1a(58)
Me	H	5	DMF	45	100	1	1b(51), 1c(9)
Me	H[b]	1	DMF	45	100	16	1b(27), 1c(4)
H	H	1	DMF	45	60	18	1d(26)
H	H[b]	2	DMF	45	60	21	1d(24)

a Isolated yield *b* 2,3-Dibromo-1,1,1-trifluoropropane was used

5-Trifluoromethyl-5,6-dihydrouracils (1) thus obtained were readily converted to the corresponding 5-trifluoromethyluracils (2a-d) by treating with bromine[6d] in nearly quantitative yields (eq 1) The present reaction may involve 2-trifluoromethylpropenoylpalladium intermediate, which further reacts with a urea in a manner of the amidation of the intermediate to form 2-trifluoromethylpropenoylurea followed by intramolecular Michael addition to give 1 As even a trace of 2-trifluoromethylpropenoylurea was not detected in the reaction mixture in every case examined, it is strongly suggested that the cyclization step is very fast

As 5-trifluoromethyluracil derivatives such as 5-trifluoromethyluridine have been found to have antitumor and anti-viral activities[5] and the effective routes to these compounds are still to be explored in spite of the extensive synthetic studies,[6] our novel ureidocarbonylation of 2-Br-TFP may serve as efficient new synthetic route to the analogs of these compounds

Further studies on the application and extension of the present ureidocarbonylation to the synthesis of various trifluoromethyl-containing heterocycles is now actively underway

References and Notes

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7. All new compounds obtained here gave satisfactory elemental analyses and spectral data.

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