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NUCLEIC ACID RELATED COMPOUNDS. 31. SMOOTH AND EFFICIENT PALLADIUM-COPPER CATALYZED COUPLING OF TERMINAL ALKYNES WITH 5-IODOURACIL NUCLEOSIDES[1]

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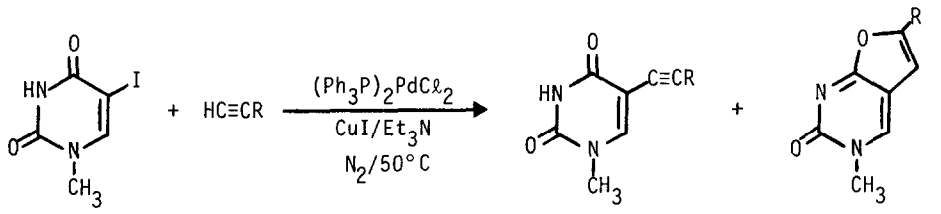
Coupling of terminal alkynes with protected 5-iodouracil nucleosides in the presence of dichlorobis(triphenylphosphine)palladium and copper(I) iodide in triethylamine gives the corresponding 5-(alkyn-1-yl)uracil nucleosides in 72-92% yields.

Considerable interest in the development of 5-substituted pyrimidine deoxynucleosides as potential inhibitors of thymidylate synthetase[3] and as putative antiviral agents[4] exists at present. Recently several groups have described methods for the palladium-catalyzed coupling of olefins with 5-mercurated or 5-iodo derivatives of uracil based on the pioneering studies of Heck.[5] Bergstrom[6] was the first to report useful procedures for this carbon-carbon bond formation at C-5. Daves[7], Jones and Walker[8], and Mertes[9] and their co-workers have described C-5 couplings based on these precedents.

We have been seeking an efficient procedure for coupling a versatile and easily functionalizable carbon chain to C-5 of uracil nucleosides. The acetylene grouping appeared attractive since it is readily subject to functional elaboration. In addition, 5-ethynyl-2'-deoxyuridine[10] has potent biological activity per se and its 5'-monophosphate is a strong inhibitor of thymidylate synthetase.[11]

Bergstrom had noted that attempts to couple 5-chloromercuri- or 5-iodouridine with phenylacetylene employing Heck's methods gave uridine or a complex mixture of products.[6b] A modified procedure for coupling terminal alkynes with aryl and vinyl halides using palladium plus copper catalysis was reported by Sonogashira et al.[12] This mild general method was applied recently to substituted pyrimidines and quinazoline by Edo et al.[13] We now wish to report the smooth coupling of terminal alkynes, including phenylacetylene, with 5-iodouracil compounds using a modification of this procedure.

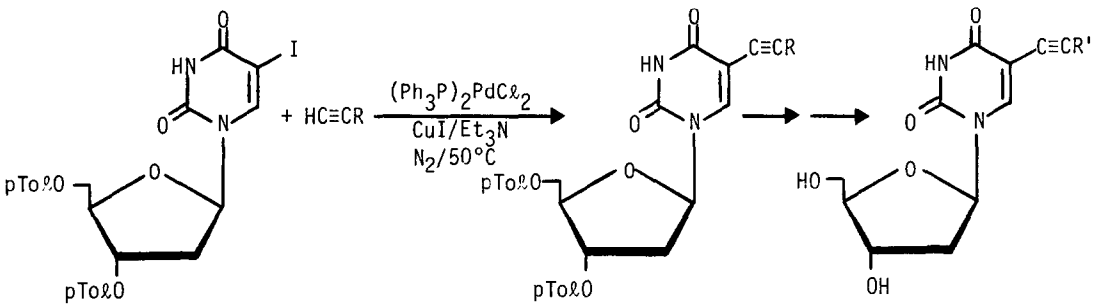
Treatment of 5-iodo-1-methyluracil[14] (1) with 1-hexyne in degassed triethylamine at 50°C in the presence of catalytic quantities of $(Ph_3P)_2PdCl_2$ and CuI under a nitrogen atmosphere gave 5-hexynyl-1-methyluracil (2a) in 84% isolated yield plus a minor quantity (9%) of the fluorescent 6-n-butyl-3-methylfurano[2,3-d]pyrimidin-2-one (3a). The by-product furanopyrimidine (3a) was obtained in 92% yield upon treatment of isolated 2a with CuI in refluxing triethylamine/methanol. Analogous coupling of 1 and 4-(p-toluyloxy)butyne gave the corresponding 5-alkynyl-1-methyluracil 2b in 85% isolated yield with only a trace of fluorescent (presumably cyclized) by-product.



1 2 3

a, R = n-C_4H_9; b, R = $CH_2CH_2OCOC_6H_4CH_3$ (p)

The protected ribonucleoside 5-iodo-2',3',5'-tri-O-p-toluyluridine[14] was coupled with 4-(p-toluyloxy)butyne to give the fully protected 5-alkynyl nucleoside in 92% yield. Similar coupling of 5-iodo-3',5'-di-O-p-toluyl-2'-deoxyuridine[14] (4) with the alkynes listed gave the corresponding protected derivatives (5a-k) with near quantitative conversions. These products were deprotected to provide the 5-alkynyl-2'-deoxyuridine compounds (6a-j). In each case the



4 5 6

Coupling Reaction Time (hours)	R	Isolated Yield of 5 (%)		6	R'
10	C_2H_5	a	91	a	C_2H_5
3	n-C_3H_7	b	85	b	n-C_3H_7
4	n-C_4H_9	c	89	c	n-C_4H_9
3	n-C_5H_{11}	d	77	d	n-C_5H_{11}
12	$C(CH_3)_3$	e	89	e	$C(CH_3)_3$
18	$Si(CH_3)_3$	f	85	f	H
1	C_6H_5	g	91	g	C_6H_5
2	CH_2OTHP	h	72	h	CH_2OH
5	n-C_2H_4OTHP	i	85	i	n-C_2H_4OH
2.5	n-C_2H_4OpTol	j	85		
4	n-C_3H_6OpTol	k	87	j	n-C_3H_6OH

protected derivatives 5a-k were isolated by thorough evaporation of volatile materials in vacuo. The residue was dissolved in chloroform and this solution was washed with 5% aqueous EDTA solution, water, and dried over Na_2SO_4. The mixture was filtered and the filtrate evaporated to a small volume. (When necessary, this solution was purified further by passage through a short column of neutral silica gel, using $CHCl_3$/MeOH (9:1) for elution.) Addition of 5 volumes of methanol then usually resulted in precipitation of a colorless product. The precipitated products were recrystallized from $CHCl_3$/MeOH.

Deprotection of 5h and 5i necessitated acid-catalyzed removal of the tetrahydropyranyl group using CF_3CO_2H/MeOH/CH_2Cl_2 (5:10:15) for 1.5 hours at room temperature. The p-toluyl ester protecting groups were removed from 5a-k using NaOMe/MeOH. This treatment with methoxide also removed the trimethylsilyl function from 5f to yield the known 5-ethynyl-2'-deoxyuridine[10] (6f) directly.

It may be noted that coupling of 4 with trimethylsilylacetylene followed by deprotection with NaOMe/MeOH provides a straightforward and convenient synthesis of 6f. Such direct modification of naturally occurring nucleosides avoids the diastereochemical separation and β-anomer yield problems associated with base, sugar coupling routes.[10] This supports the view that preformed nucleoside transformations are extremely useful for high-yield syntheses of pure compounds of unambiguous structure.[15]

Functional modification of the alkynyl side chains and extension of this facile coupling to other nucleoside systems are currently under investigation. Experimental details[16] and results of biological studies will be reported.

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