PALLADIUM CATALYZED COUPLING OF 5-HYDROXYURACIL TRIFLUOROMETHANE-SULFONATES (TRIFLATES) WITH ALKENES AND ALKYNES

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Abstract - Cross coupling of 5-hydroxyuracil triflates (1) with alkenes and alkynes in the presence of a palladium catalyst and triphenylphosphine affords 5-vinyluracils (2) and 5-alkynyluracils (3), respectively, in good yields. Coupling of the triflate (1a) with organocopper reagents [$R_2Cu(CN)Li_2$] is also described.

The palladium catalyzed reaction of vinyl or aryl triflates has been extensively studied as one of the efficient approach to carbon-carbon bond formation.[1] To our best knowledge, no example of palladium catalyzed vinylation and alkynylation of heterocyclic triflates has been appeared in the literatures.[1,2] We attempted the application of this type of reaction to 5-hydroxyuracil triflates because some 5-carbon substituted uracil derivatives have interesting biological activities.[3] The present result provides a novel method[4] for the preparation of uracil derivatives possessing the carbon functional groups at the 5-position, which is the first demonstration of the C-C coupling of heterocyclic triflates.

The 5-hydroxyuracil triflates (**1a** and **1b**),[5] employed here as starting materials, were prepared in 99% and 54% yields, respectively, upon treatment of the corresponding 5-hydroxyuracils[6] with trifluoromethanesulfonic anhydride in dry pyridine under ice cooling.

A mixture of the triflate (**1a**)[1 mM], methyl acrylate [1.5 mM], triethylamine [2 mM], palladium chloride [0.02 mM], and triphenylphosphine [0.04 mM] in dry dimethylformamide was heated at 60-70 °C for 6 h. After removal of the solvent, the residue was triturated with water. The mixture thus obtained was extracted with chloroform to obtain 5-(2-E-methoxycarbonyl)vinyl-1,3-dimethyluracil (**2a**) in 76% yield. No formation of other products (e.g. (Z)-isomer of **2a**) in this reaction was shown by T.L.C. analysis of the reaction mixture and ^{1}H-NMR spectrum of

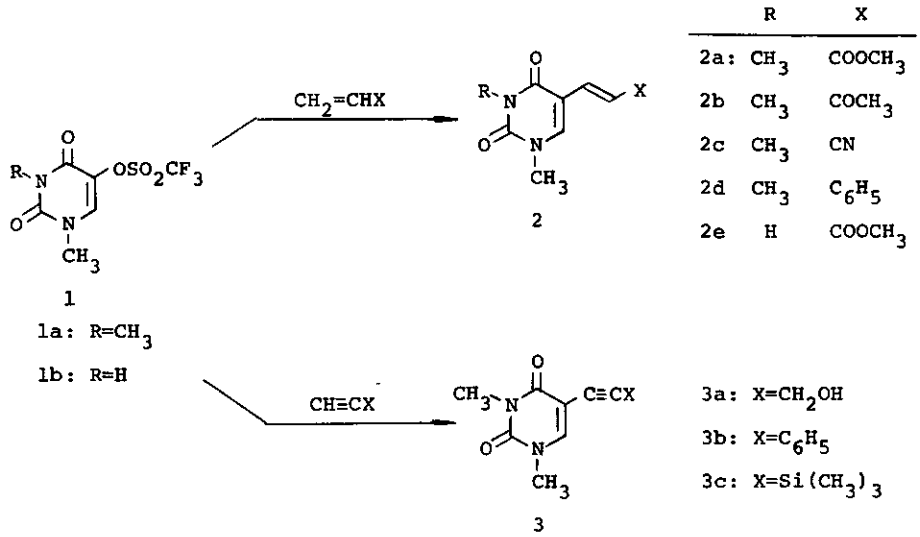


Table. Formation of 5-Vinyluracils (2) and 5-Alkynyluracils (3)

Starting material	Alkene or alkyne	Reaction time (h)	Product	mp (°C) (Recryst. solvent)	Yield(%)*
1a	CH_2=CH·CO_2CH_3	6	2a	165-167 (CH_3OH)	76
1a	CH_2=CH·$COCH_3$	12	2b	164-166 (C_2H_5OH)	96
1a	CH_2=CH·CN	5	2c	165-166 (C_2H_5OH)	93
1a	CH_2=CH·C_6H_5	5	2d	144-146 (C_2H_5OH)	95
1b	CH_2=CH·CO_2CH_3	5	2e	272-274 (CH_3OH)	88
1a	CH≡C·CH_2OH	3	3a	201-203 (C_2H_5OH)	72
1a	CH≡C·C_6H_5	3	3b	157-158 (C_2H_5OH)	83
1a	CH≡C·$Si(CH_3)_3$	2.5	3c	160-162 (C_2H_5OH)	59

* Isolated yields.

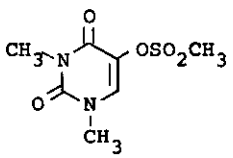
the crude product. The coupling reaction did not proceed in the absence of palladium chloride and triphenylphosphine.

Analogous coupling reaction of 1a with other alkenes such as methyl vinyl ketone,

acrylonitrile, and styrene gave the corresponding 5-vinyluracils (**2b–2d**) in high yields. The 5-hydroxy-1-methyluracil triflate (**1b**), which possesses no substituent at the 3-position, also reacted with methyl acrylate to give a coupling product (**2e**). All results of the vinylation of **1a** and **1b** are summarized in Table. The trans configuration of the vinyl group of **2a-e** was determined on the basis of a large coupling constant (16 Hz) in the ^{1}H-NMR spectrum.

When the methanesulfonate (**4**) of 5-hydroxy-1,3-dimethyluracil was used instead of the triflates (**1**) in the palladium-catalyzed coupling reaction, the sulfonate (**4**) was recovered unchanged. This result indicates that the O-triflate function is an excellent leaving group for the palladium catalyzed C-C coupling reaction.

Treatment of **1a** with alkynes such as 2-propyn-1-ol, phenylacetylene, and trimethylsilylacetylene in the presence of palladium acetate,[7] triphenylphosphine, triethylamine, and copper iodide[8] resulted in the formation of the 5-alkynyluracils (**3a-c**) in good yields (see Table).



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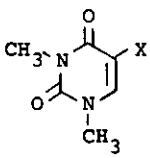

5a: X=CH_3

5b: X=C_4H_9

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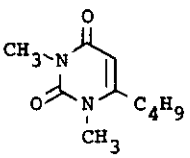

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Direct introduction of an alkyl group into the 5-position of uracil derivatives has been scarcely investigated.[9] Thus, coupling of the triflate (**1a**) with organocuprate [$R_2Cu(CN)Li_2$][10] in the absence of a palladium catalyst was examined. When the triflate (**1a**) was treated with $Me_2Cu(CN)Li_2$ in tetrahydrofuran under argon atmosphere, the expected thymine derivative (**5a**)[11] was obtained in 71% yield. On the other hand, analogous coupling of **1a** with $Bu_2Cu(CN)Li_2$ led to the formation of 5-butyl-1,3-dimethyluracil (**5b**),[12] 6-butyl-1,3-dimethyluracil (**6**), and 1,3-dimethyluracil in 20%, 10%, and 29% yields, respectively.

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Received, 16th October, 1986