A new palladium-catalyzed coupling reaction of vinylic and allylic triflates with pyrimidine nucleosides

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Vinylic trifluoromethane sulfonates (triflates) form palladium intermediates that react with pyrimidine nucleosides to produce C-5 alkyl substituted nucleosides after hydrogenation of the vinylic coupling products with hydrogen and Pd/C in methanol. The reaction, which is run under mild conditions, appears to be a general one since both mono- and disubstituted vinylic triflates, as well as the cyclic ones, gave high yields of the corresponding C-5 alkyl-substituted nucleoside. The reaction with allyl triflate requires the use of the 5-chloromercurinucleoside.

Key words: nucleosides, triflates, palladium catalysis.

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Les trifluorométhanesulfonates vinyliques forment des intermédiaires vinyliques que réagissent avec les nucléosides de pyrimidine pour conduire, après hydrogénation des produits de couplage vinyliques à l'aide d'hydrogène et de Pd/C, à des nucléosides substitués en position 5 par des groupements alkyles. Il semble que cette réaction, qui est réalisée dans des conditions douces, est générale puisque des triflates vinyliques mono- ou di-substitués, aliphatiques ou cycliques, donnent des rendements élevés des nucléosides correspondants, substitués en position 5 par des groupements alkyles. La réaction avec le triflate d'allyle nécessite l'utilisation du 5-chloromercurinucléoside.

Mots clés : nucléosides, triflates, catalyse par palladium.

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Introduction

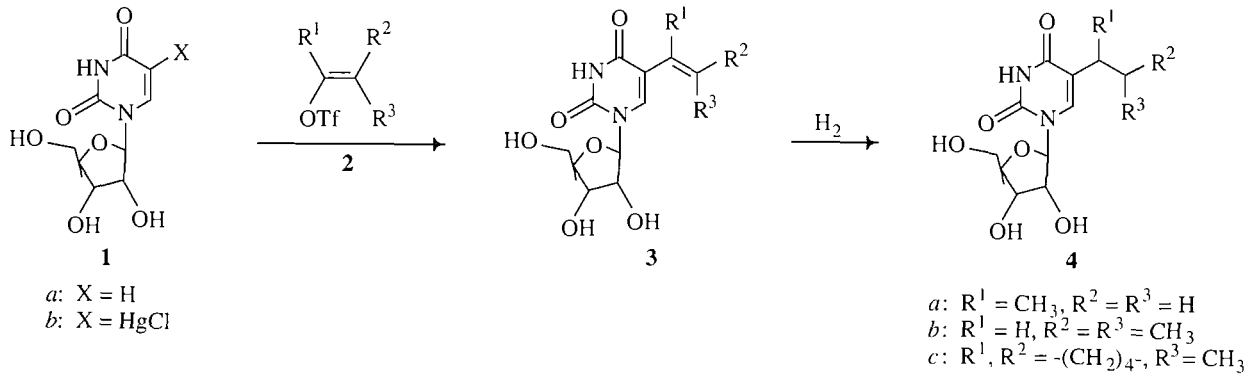
The direct synthesis of 5-alkyl substituted pyrimidine nucleosides has been reported by two routes (1, 2). A photochemical approach through the generation of an initial reactive species from either a haloalkyl or 5-iodouridine derivative has been reported (1). Alternatively, an approach employing the palladium-catalyzed olefination reaction of 5-chloromercuriuridine derivatives (2) is a useful synthetic procedure, which allows for ready access to these potential antiviral and anticancer agents (3). However, the reaction of C-5 mercurated nucleosides with simple monosubstituted alkenes generally leads to complex product mixtures and in some instances is complicated by the formation of substantial amounts of C-5 methoxyalkyl nucleosides (2). While the palladium-catalyzed reaction of alkenes with vinyl halides has been practically limited to the reactions of vinylic bromides and iodides (4), the ease of preparation of vinylic trifluoromethanesulfonate (triflates) in high regioselective purity persuaded us to investigate the palladium-catalyzed coupling reaction of pyrimidine nucleosides with vinyl triflates.

When uridine **1***a* was refluxed for 48 h in tetrahydrofuran under nitrogen with 2-propenyl triflate (5) **2***a* in the presence of tetrakis(triphenylphosphine)palladium(0) and 3 equivalents of lithium chloride, the expected modified nucleoside 5-(2-propenyl)uridine **3***a* was isolated in a moderate yield (54%). The structure of **3***a* was established based on its ^{1}H NMR, mass spectrum, and its catalytic hydrogenation to 5-(2-propyl)uridine **4***a* (2). While alkyl substituted olefins are usually inert in the Heck olefination reaction (6), we observed that both mono- and dialkyl substituted vinyl triflate derivatives react well under these reaction conditions. Therefore, the reaction between uridine **1***a* and 2-methyl-1-propenyl triflate **2***b* (7) afforded 5-(2-methyl-1-propenyl)uridine **3***b* in 43% yield. Catalytic hydrogenation of **3***b* gave 5-(2-methyl-1-propyl)uridine **4***b*. The reaction also was extended to the coupling of uridine **1***a* with cyclic vinylic triflates. 5-(6-Methylcyclohexen-1-yl)uridine **3***c* was obtained from the reaction of **1***a* with 6-methylcyclohexen-1-yl-triflate **2***c* (8).

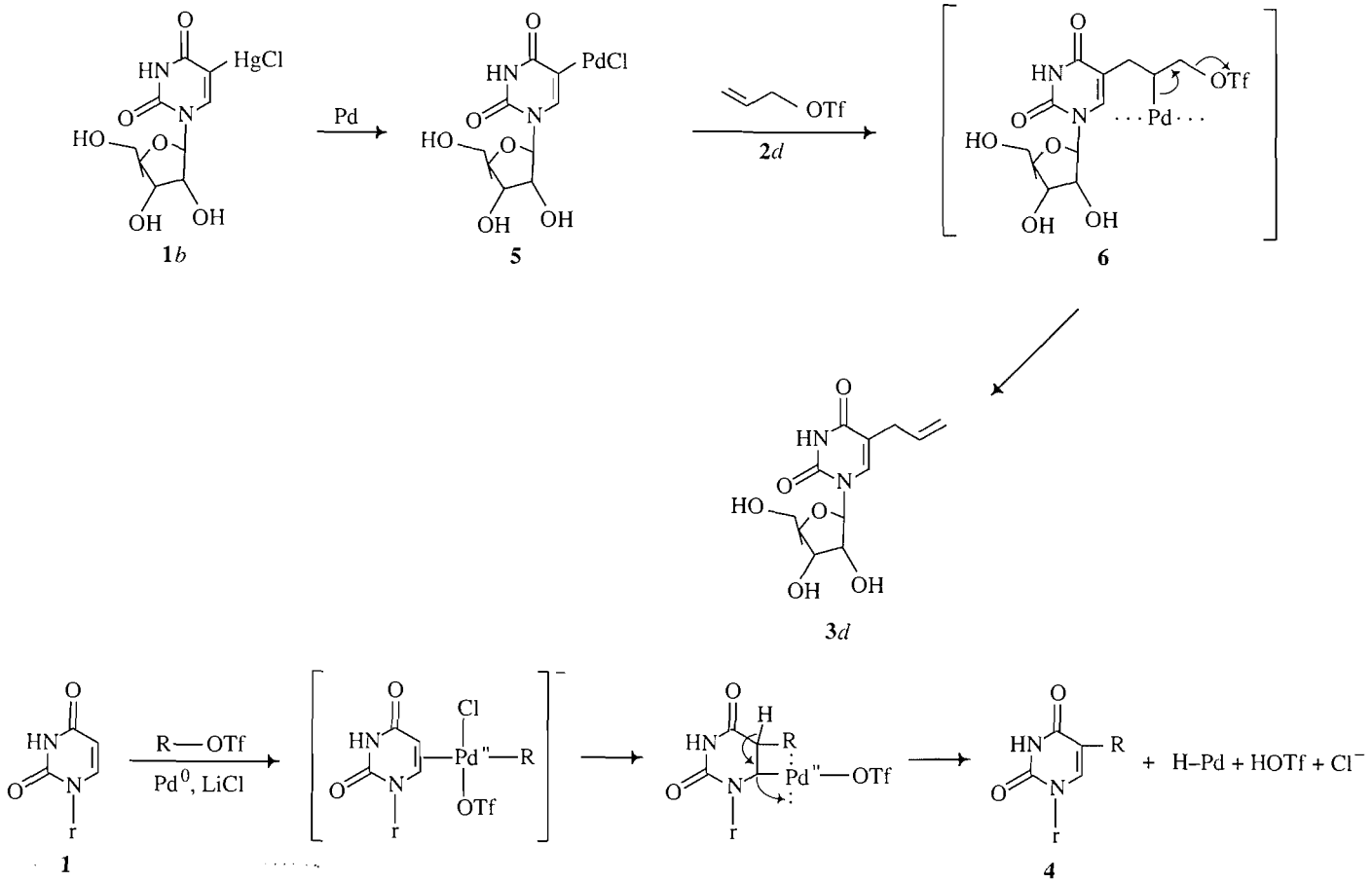
In an attempt to increase the yield of these reactions, we activated the nucleoside by its conversion to the 5-chloromercuri derivative **1***b*, prior to coupling with **2**. This, however, led to a complicated product mixture. Catalytic hydrogenation of the product mixture obtained from the reaction of **1***b* with **2***a* afforded 5-(2-propyl)uridine **4***a*, with identical melting point and ^{1}H NMR to that obtained from the hydrogenation of **3***a*. In the absence of lithium chloride or when bis(triphenylphosphine)palladium(II) dichloride was used instead of tetrakis palladium(0), a remarkable yield depression was observed. This may indicate that the vinylpalladium(II) triflate, which resulted from the oxidative addition of triflates to palladium, is incapable of entering a catalytic cycle as in the Heck olefination reaction (6). In the presence of lithium chloride, apparently a vinylpalladium(II) chloride complex is generated, which is then capable of undergoing further reaction with the nucleoside **1***a* to afford the coupled product and generate a palladium(0) species (Scheme 2).

It has been reported (9) that the organopalladium(II) complex formed from the transmetalation of the 5-chloromercurinucleoside and palladium chloride undergoes reaction with variously substituted allylic chlorides regioselectively and requires only catalytic amounts of palladium chloride. The difficulty in synthesizing and purifying the allylic chlorides limits this approach. Other allylic derivatives afforded poor yields and (or) additional side products (9). When allyl triflate **2***d* (10) was allowed to react with uridine **1***a* under the above conditions, only starting material was recovered. However, treatment of allyl triflate with 5-chloromercuriuridine **1***b* afforded the expected allylic uridine derivative **3***d* (52% yield). It seems that in this latter case the palladium exchanges initially for the nucleoside mercury to give the transient organopalladium intermediate **5**, which then forms another intermediate **6** with the allylic triflate. This then collapses to 5-allyluridine **3***d*.

Finally, we attempted to extend this reaction to the attachment of a simple unsubstituted alkyl side chain at C-5 of the pyrimidine nucleoside. In all cases these attempts were unsuc-



SCHEME 1



SCHEME 2

cessful. Upon treatment of nucleosides **1***a* or **1***b* with ethyl or propyl triflates (1, 2) under similar conditions, no alkyl substituted nucleoside could be detected. Most probably alkyl palladium triflates containing an sp^3 hydrogen β to the carbon bearing the palladium undergo a facile β-hydride elimination in preference to alkene insertion. It is also quite possible that this type of triflates does not undergo oxidative addition in the first place.

Experimental

Melting points were taken on a Fisher–Johns melting point apparatus and are uncorrected. IR spectra were measured with a Unicam S.P. 2006, and UV spectra with a Perkin–Elmer 554 recording spectrophotometer. ^{1}H NMR spectra were obtained on a Varian 56/69 A and mass spectra on a Varian CH5 mass spectrometer. Unless indicated, C, H, N analyses were ±0.4% of the calculated values, and were performed at the Microanalytical Center, Cairo University. High pressure liquid chromatography was performed using Partisile PXS 10/25 ODS-II, and preparative, Partisile M9-10/50 ODS-2 columns.

5-(2-Propenyl)uridine **3**a *and 5-(2-propyl)uridine* **4**a

Method A

To a stirred suspension of 2-propenyl triflate **2***a* (5) (836 mg, 4.4 mmol), lithium chloride (542 mg, 13 mmol), and $Pd(PPh_3)_4$ (110 mg, 4.4 mol %) in 50 mL of tetrahydrofuran, was added 500 mg of uridine **1***a* (2.05 mmol). The reaction mixture was refluxed under

nitrogen for 48 h, cooled, and filtered through a Celite pad. It was washed with 10% ammonium hydroxide solution (3 × 25 mL), then with water (2 × 25 mL), dried over magnesium sulfate, and the resulting solution was concentrated under vacuum. The residue was chromatographed (silica gel; 15% methanol in chloroform) to afford 5-(2-propenyl)uridine **3***a* (314 mg, 54% yield) as white crystals after crystallization from CH_3CN, mp 143°C. ^1H NMR (D_2O), δ: 1.91 (3H, s, Me), 3.89 (2H, m), 4.28 (3H, m), 5.30 (1H, d, J = 11 Hz), 5.36 (1H, d, J = 11 Hz), 6.21 (1H, m, anomeric proton), 7.80 (1H, s, C6 proton). Anal. calcd. for $C_{12}H_{16}N_2O_6$: C 50, 70, H 5.63, N 9.86; found: C 50.89, H 5.76, N 9.58.

The nucleoside **3***a* (284 mg, 1 mmol) in 100 mL of methanol was treated with 50 mg of 10% Pd/C and stirred under 24 psi of hydrogen for 10 h (1 psi = 6.9 kPa). The catalyst was removed by filtration and the filtrate evaporated under reduced pressure. The residue was chromatographed over silica gel, using 10% methanol in chloroform as eluent, to give 5-(2-propyl)uridine **4***a* (224 mg, 78.4% yield), mp 192°C (lit. (2) mp 191–193°C). ^1H NMR (D_2O), δ: 1.1 (6H, d, J = 6.2 Hz, 2Me), 2.78 (1H, m, Me-C*H*-Me), 3.9 (2H, s), 4.25 (3H, m), 6.1 (1H, d, J = 3 Hz, anomeric H), 7.8 (1H, s, C6 proton).

Method B

A mixture of 2-propenyl triflate **2***a* (836 mg, 4.4 mmol), lithium chloride (542 mg, 13 mmol), Pd $(PPh_3)_4$ (110 mg, 4.4 mol%), and 5-chloromercuriuridine **1***b* (980 mg, 2.0 mmol) was refluxed in THF under nitrogen for 48 h. Work-up as described above afforded a complicated mixture of vinylic uridines, as proved by ^1H NMR spectroscopy. However, catalytic hydrogenation of this mixture under the same conditions described for hydrogenation of **3***a* gave 5-(2-propyl)uridine **4***a* having a melting point and NMR identical to the product of method A.

5-(2-Methyl-1-propenyl)uridine **3**b

Uridine **1***a* (500 mg, 205 mmol) was added to a stirred mixture of 2-methyl-1-propenyl triflate **2***b* (7) (898 mg, 4.4 mmol), lithium chloride (542 mg, 13 mmol), and Pd $(PPh_3)_4$ (110 mg, 4.4 mmol%) in THF and refluxed under nitrogen for 48 h. Work-up as above afforded **3***b*, crystallizing from CH_3CN as white crystals, mp 168°C (264 g, 43% yield). ^1H NMR (D_2O), δ: 1.83 (6H, s, 2Me), 3.95 (2H, m), 4.20 (2H, m), 4.25 (1H, m), (1H, s, olefinic proton). Anal. calcd. for $C_{13}H_{18}N_2O_6$: C 52.35, H 6.04, N 9.40; found: C 52.29, H 6.26, N 9.63.

5-Isobutyluridine **4**b

Catalytic hydrogenation of 5-(2-methyl-1-propenyl)uridine **3***b*, prepared as in the previous synthesis, gave 5-isobutyluridine **4***b* (74% yield) as white crystals, mp 171°C. ^1H NMR (D_2O), δ: 1.2 (6H, d, 2Me), 1.67 (1H, m, Me-CH-Me), 2.3 (2H, t), 3.91 (2H, m), 4.32 (3H, m), 6.1 (1H, m, anomeric proton), 7.70 (1H, s, C6 proton). Anal. calcd. for $C_{13}H_{20}N_2O_6$: C 5.20, H 6.67, N 9.33; found: C 51.83, H 6.9, N 9.57.

5-(6-Methylcyclohexen-1-yl)uridine **3**c

6-Methylcyclohexen-1-yl triflate (8) (1.70 g, 4.4 mmol) was dissolved in THF (50 mL) and treated successively with lithium chloride (542 mg, 13 mmol), Pd $(PPh_3)_4$ (110 mg, 4.4 mol%), and uridine **1***a* (500 mg, 2.05 mmol) and refluxed under nitrogen for 48 h. Work-up as above afforded **3***c* (316 mg, 45.7% yield), mp 162°C. ^1H NMR (D_2O), δ: 1.89 (d, 3H, Me), 1.61 (4H, m), 2.1 (2H, m), 2.5 (1H, m), 3.9 (2H, m), 4.23 (3H, m), 5.96 (1H, m, anomeric proton), 6.09 (1H, t, J = 4.2 Hz), 7.82 (1H, s, C6 proton). Anal. calcd. for $C_{16}H_{22}N_2O_6$: C 56.80, H 6.50, N 8.28; found: C 56.55, H 6.23, N 8.40.

5-Allyluridine **3**d

5-Chloromercuriuridine, **1***b* (980 mg, 2.0 mmol), was added to a stirred mixture of allyl triflate (**2***d*, 863 mg, 4.4 mmol), Pd $(PPh_3)_4$ (110 mg, 4.4 mol%), and lithium chloride (542 mg, 13 mmol) in tetrahydrofuran and refluxed for 48 h. Work-up as above gave 5-allyluridine **3***d*, as white crystals, mp 176°C (lit. (13) mp 175–176°C) (295 mg, 52% yield). ^1H NMR (D_2O), δ: 3.1 (2H, d, J = 6 Hz), 3.9 (2H, m), 4.25 (3H, m), 5.19 (1H, d, J = 17 Hz), 5.21 (1H, d, J = 11 Hz), 5.95 (2H, m), 7.7 (1H, s).

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