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# Synthesis of Deoxy Analogs of HEPT involving a Palladium (0) Catalyzed Coupling

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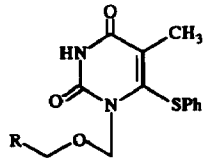
Abstract : *Deoxy analogs of HEPT (4-7) were prepared by Pd(0) catalyzed coupling between 6-(phenylthio)thymine and cinnamyl acetate or 3-(heteroaryl) allyl acetates.*

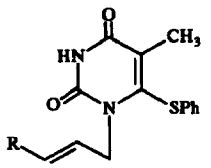
Subsequent to the discovery of 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio) thymine **1** (or HEPT)[1] as a novel potent and selective inhibitor of HIV-1, it has been found that the hydroxy function at the end of the side chain was not necessary for antiviral activity[2]. For example, compounds **2** (EPT) and **3** (BPT) having a terminal ethoxymethyl or benzyloxymethyl group, respectively, are more potent inhibitor of HIV-1 replication than HEPT. Numerous other modifications have also been described.[3-6] However, at the outset of our program, no work on N-1-alkyl analogs of HEPT had been reported.[7] In order to contribute to a better understanding[8] of the structure-activity relationships of deoxy analogs of HEPT, we have undertaken the synthesis of compounds **4a-7a** and their corresponding saturated analogs **4b-7b.**



**1** R = $CH_2OH$

**2** R = $CH_3$

**3** R = Ph

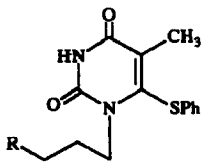


**4a** R = Ph

**5a** R = 3-pyridinyl

**6a** R = 2-furyl

**7a** R = 2-thienyl



**4b** R = Ph

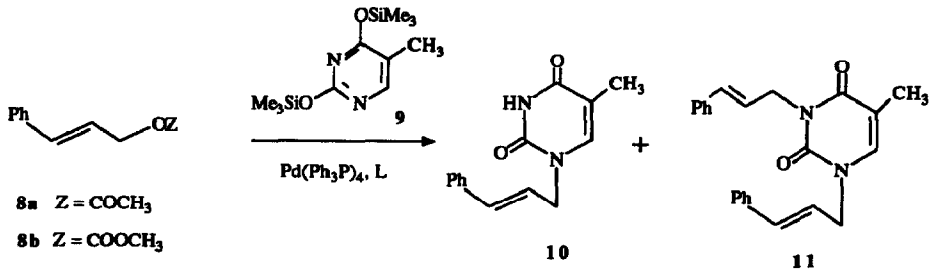
**5b** R = 3-pyridinyl

**6b** R = 2-furyl

**7b** R = 2-thienyl

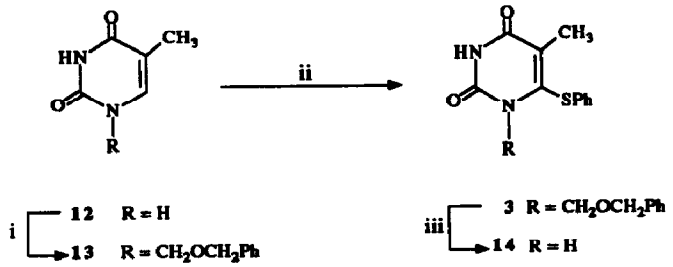
As reported for carbocyclic nucleoside analogs such as carbovir[9], perhaps one of the simplest routes for preparing compounds **4a-7a** involves Pd(0) catalyzed coupling between heterocyclic bases and suitable allylic acetates. In preliminary experiments, 3-phenyl-2-propenol acetate [(E)-cinnamyl acetate] **8a** was reacted with 2,4-bis[(trimethylsilyl)oxy]thymine **9** and tetrakis (triphenylphosphine) palladium(0) as catalyst. Although there are two ambident anionic centers for alkylation, only the N-1 monoalkylated derivative[10] **10** and the N-1, N-3 bisalkylated derivative **11**, both with (E) configuration were formed. This suggests that N-1 alkylation is faster than reaction at the N-3 position.[11]

The overall yield (60-70%) and the ratio of **10/11** (5:5 to 6:4) were not significantly modified by changing the solvent ($CH_3CN$, THF or DMF) , or by using the allylic carbonate **8b** usually more reactive than the corresponding acetate[12] nor by the addition of mono or bidentate phosphines ($Ph_3P$ or $(Ph_2P)_2Pr$).




*In a typical experiment a mixture of 8b ( 192 mg, 1 mmol), $Pd(Ph_3P)_4$ (58 mg, 0.05 eq.) and $PPh_3$ (53 mg, 0.2 eq.) was stirred for 15 min. at room temperature under argon atmosphere before addition of 9 [prepared from thymine (126 mg, 1 mmol), hexamethyldisilazane (1.5 mL) and pyridine (0.6 mL) ] in THF (3 mL). After heating at 60°C for 2h, evaporation followed by flash chromatography (cyclohexane-EtOAc, 8:2 --> 1:1) succcessively afforded 11 (87 mg, 24%) and 10 (110 mg, 45%).*

The subsequent step required introduction of a 6-phenylthio group on **10** . This was first attempted using the general conditions (LDA, PhSSPh) reported for the preparation of HEPT nucleosides[2]. Unfortunatly under these conditions the desired derivative **4a** was obtained in low yield (<10 %), probably due to the lack of oxygen atom on the $N_1$-chain which stabilize the lithio derivative . Therefore we decided to reexplore a new route which involves introduction of the 6-phenylthio residue prior to the Pd(0) catalyzed coupling. As depicted in the following scheme, the 6-(phenylthio)thymine **14** was elaborated[13] from thymine **12** ( 60 % overall yield) by preparation of **13**[5], introduction of the 6-phenylthio residue to afford **3** and finally hydrolysis of **3** in the presence of $BCl_3$.




Reagents : i and ii according ref.5; iii: $BCl_3$, $CH_2Cl_2$, - 78°C --> RT

Pd(0) catalyzed alkylation of **14** with allylic acetates **8a**, **15**-**17**[14] afforded the expected unsaturated compounds **4a-7a**[15] along with the corresponding bis-alkylated products in the range of 75-80% overall yield (see table ). Hydrogenation[16] of compounds **4a-7a** in MeOH (10% Pd/C) led to the corresponding deoxy HEPT analogs **4b-7b** (45-65%), along with small amounts of products resulting from hydrogenolysis of the C-S bond.

| Entry | R | [a] | Solvent | Ligand (0.2 eq.) | Overall yield [b] % | Monoalkyl derivatives | Ratio Mono / Bis |
|---|---|---|---|---|---|---|---|
| 1 | Ph | 8a | THF | $Ph_3P$ | 80 | 4a | 6 / 4 |
| 2 | Ph | 8a | DMF | - | 70 | 4a | 5 /5 |
| 3 |  | 15 | THF | $Ph_3P$ | 75 | 5a | 7 / 3 |
| 4 |  | 16 | THF | $Ph_3P$ | 80 | 6a | 5 / 5 |
| 5 |  | 17 | THF | $Ph_3P$ | 80 | 7a | 5 / 5 |

[a] 1mmol of allylic substrate, silylated 14 (1 mmol) , 0.05 eq. of $Pd(PPh_3)_4$ in 6 mL of solvent, 60°C, 3h; [b] determined after isolation by chromatography.

Antiviral activity of the new compounds will be reported elsewhere.

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7. During completion of this work, several $N_1$-alkyl 6-(phenylthio)thymine derivatives (methyl, ethyl, and butyl ) have been reported in ref.5 and it has been shown that introduction of an ethyl or butyl group into the N-1 position, significantly contributes to an anti-HIV-1 activity.
8. It should be also of great interest to ascertain if these new compounds retain marked activity against HIV-1 mutant strains that are resistant to other HIV-1 specific inhibitors as pointed out for HEPT derivatives themselves in: Balzarini, J. ; Karlsson, A. ; De Clercq, E. *Molecular Pharmacol.* **1993**, *44*, 694-701.
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10. $N_1$ alkylation was based on comparison of the UV spectra in neutral *vs* 0.1 N NaOH (Baker, B.R.; Kawazu, M. ; Santi, D.V. ; Schwan, T.J. *J. Med. Chem.*, **1967**, *10*, 304-311) which shows less than a 2-mμ shift.
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12. Tsuji, J. *Synthesis*, **1990**, 739-749.
13. Spectroscopic data for **14** are in agreement with those reported by Tanaka *et al.*[5]
14. Acetates **15-17** were prepared from the corresponding acrylic acid derivatives through reduction of the mixed carbonic anhydrides by sodium borohydride according to: Soai, K.; Yokohama, S.; Mochida, K. *Synthesis* **1987**, 647-648.
15. All new compounds gave satisfactory microanalytical and spectroscopic data. Data for representative compound **4a** : Mp 195 °C; IR ($CHCl_3$) ν 3391, 3171, 3031, 1675, 1451 $cm^{-1}$; UV (EtOH 95 %) λ max 248 nm (ε = 27.000), UV (0.1 M NaOH) λ max 247 nm; $^1$H-NMR (250 MHz, $CDCl_3$) δ 2.14 (s, 3H, 5-Me), 4.86 (d, 2H, *J* = 6 Hz, 1'-$CH_2$), 6.15 (dt, 1H, *J* = 6 and 16 Hz, 2'-H), 6.52 (d, 1H, *J* =16 Hz, 3'-H), 7.20 -7.34 (m, 10H, 2 Ar), 8.90 (br s, 1H, NH); MS (DCI/$NH_3$) m/z 350 $(M + H)^+$; Anal. calcd for $C_{20}H_{18}N_2O_2S$ : C, 68.55; H, 5.18; N, 7.99 . Found : C, 68.60; H, 5.24; N, 8.17.
16. Catalyst poisoning interfered with the hydrogenation of the C=C bond in compounds **4a-7a** necessitating a change in catalyst part way through the experiment.


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