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Palladium-Catalyzed Synthesis of 9-(2-Cyclopentenyl) Guanine

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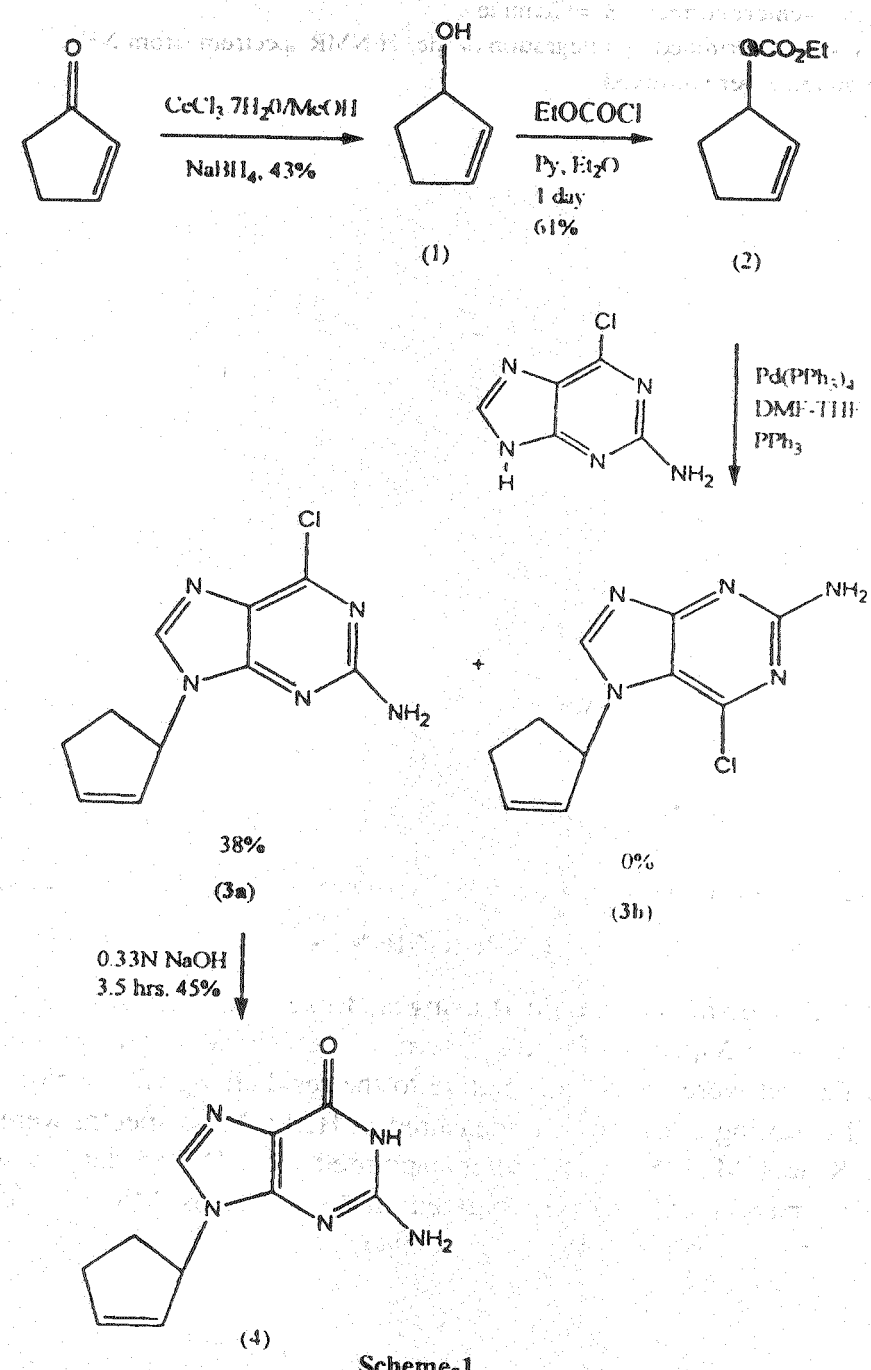
The racemic synthesis of the 9-(2-cyclopentenyl) guanine (**4**) from 2-cyclopentenon was prepared in 4 steps with a good yield (43%) and excellent selectivity (N9-isomer). The syntheses were achieved in a convergent and direct manner *via* palladium(0) catalysed coupling between 2-amino-6-chloropurine and 2-cyclopentene-1-ethylcarbonate (**2**). Compounds **2–4** have been characterized by high resolution MS, ^{1}H NMR and IR.

Key Words: Carbocyclic nucleosides, Carbovir, Purines.

INTRODUCTION

Carbocyclic nucleosides are considered nucleoside analogues in which the furanose ring is replaced by a cyclopentane ring and their analogues have found potential as anti-tumour, anti-HSV and anti-HIV agents[1–3]. Because of this biological activity, the research for new general methods for the synthesis of carbocyclic nucleoside such as carbovir is a potential drug for the treatment of AIDS by selective inhibition of HIV-1[4]. Several methods have been discussed for the preparation of carbocyclic nucleosides[5, 7]. The palladium mediated coupling reaction seemed to be a good method for synthesis of carbocyclic nucleosides analogues[8, 9]. We report here one route to racemic synthesis of 9-(2-cyclopentenyl) guanine by the palladium mediated coupling reaction. Commercially available 2-cyclopentenone was reduced using Luche's method[10] and gave exclusively 1,2-reduction of alcohol (**1**) in 43% yield (**Scheme-1**). Alcohol (**1**) was reacted with ethylchloroformate in pyridine to give 2-cyclopentene-1-ethylcarbonate (**2**) in 61% yield. The coupling reaction of carbonate (**2**) with purines was investigated as shown in Table-1. The coupling reaction of carbonate (**2**) with 2-amino-6-chloropurine was investigated in several solvents (Table-1). The best solvent found using DMF-THF solvent mixtures gave excellent selectivity (only N-9 isomer was obtained) in 38% yield. Using DMSO-THF gave poor selectivity (83 : 17) N-9 (**3a**) and N-7 (**3b**) isomer of the 2-(cyclopentenyl)-6-chloropurine. It was found that base was not effective for the coupling reaction. Without base (**3a**) was obtained in good yield (38%) and excellent selectivity (entry 3). The π-allylpalladium carbonate (**2**) reacted with guanine and no

product (4) was obtained (Table-4, entry 4). This was presumably due to the insolubility of guanine. The N-9 product (3a) was readily hydrolyzed[11] to carbocyclic nucleosides (4) in 45% yield (Scheme-1)[12]. The reaction of nucleophiles with carbonate (2) without addition of base can be explained in the following mechanism (Scheme-2). Oxidative addition of Pd(0) to carbonate (2) gives (π -allyl) palladium carbonate (5). The carbonate anion of (5) undergoes decarboxylation to give the (π-allyl) palladium alkoxide (6). The alkoxide anion generated *in situ* picks up the active hydrogen of the nucleophile to produce an anionic nucleophile. Nucleophilic attack of the anion on the π-allyl palladium gives the allylated compound (3a) and Pd(0)-phosphine complex is regenerated[13].

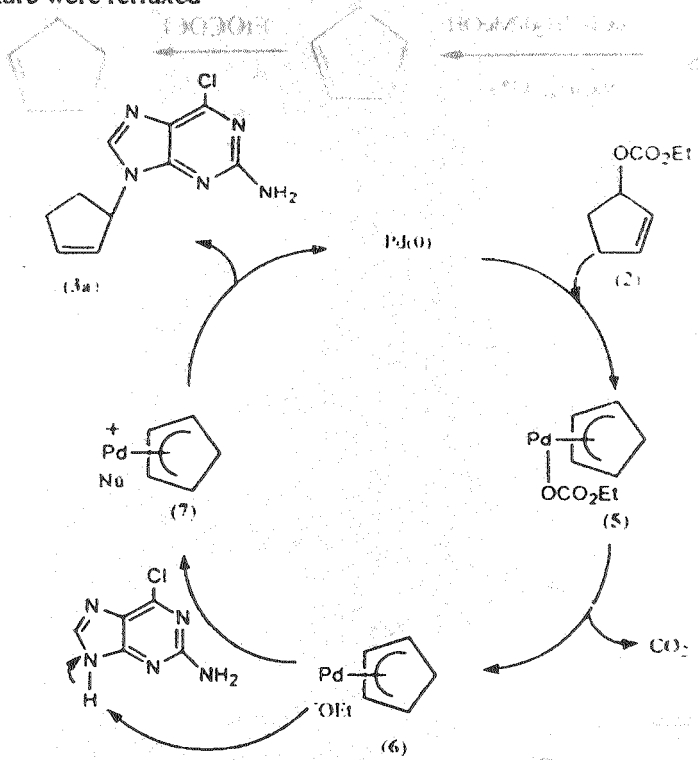


Scheme-1

TABLE-1
PALLADIUM-MEDIATED REACTION OF 2-CYCLOPENTENE-1-ETHYLCARBONATE (2) WITH PURINES

Entry	Purine	Base	$Pd(PPh_3)_4$	Yield (3a : 3b)	Ratio (3a : 3b)	Reaction time	Solvents
1	A	NaH	0.5	27 : 0	100 : 0	1 d	DMF-THF
2	A	NaH	0.3	11 : 0	83 : 17	1 d	DMSO-THF
3	A	—	0.3	38 : 0	100 : 0	8 d	DMF-THF
4	B	—	0.3	0	0	8 d	DMF-THF

A = 2-amino 6-chloropurine, B = Guanine.
[a]The ratios were determined by integration of the ^1H NMR spectrum (from NH_2)
[b]Reaction mixture were refluxed



Scheme-2. Palladium-mediated reaction of 2-cyclopentene-1-ethylcarbonate (2) with purines

EXPERIMENTAL

^1H NMR spectra was recorded using a Bruker ACF-250 spectrophotometer supported by an Aspect 4000 data system. The chemical shifts were recorded on the δ scale and were measured relative to the residual signal of chloroform at δ 7.25. All coupling constants are measured in Hertz. Mass spectra were obtained using a Kratos MS 25 spectrometer supported by a DS 55 data system. High resolution mass spectra were obtained using a Kratos MS 80 spectrometer supported by a DS 90 data system operating in E.I. Melting points were determined using a Kofler hot stage apparatus. Infrared spectra were recorded in the range 4000–600 cm^{-1} using a Perkin-Elmer 157 G spectrophotometer. Solid samples were recorded using potassium bromide discs, whilst liquid samples were

recorded as thin films. $Pd(PPh_3)_4$ was prepared by literature method[13]. Dry DMF methanol, 2-cyclopenten-1-one, 2-amino-6-chloropurine and guanine are commercially available.

2-Cyclopenten-1-ol (1)

2-cyclopenten-1-one (2.0 g, 24.0 mmol) was dissolved in a solution of $CeCl_3 \cdot 7H_2O$ (9.1 g, 24.0 mmol) in methanol (15 cm^3). $NaBH_4$ (0.9 g, 24.0 mmol) was slowly added with stirring. The mixture was allowed to react for 5 min after which saturated ammonium chloride (50 cm^3) was added and extracted with CH_2Cl_2 (4 × 50 cm^3). The solvent was removed under reduced pressure. The title compound was obtained as a colourless oil (892 mg, 43%). R_f 0.3 [acetone/petrol (30 : 70)]. ν_{max} (thin film/cm^{-1}) 1453 ν(C=C), 2939–2853 ν(CH), 3333 ν(OH); δ_H (250 MHz; $CDCl_3$) 1.6 (IH, m, 4-H_a), 2.2 (2H, m, 5-H_2), 2.45 (IH, m, 4-H_b), 3.25 (IH, br s, OH), 4.75 (IH, m, 1-H), 5.7 (IH, m, 2-H), 5.85 (IH, m, 3-H); m/z (EI) 84(M^+, 55%), 83 (100), 66 (20), 55 (14); (Found: M^+, 84.0575; C_5H_8O requires m/z 84.0577).

2-Cyclopenten-1-ethylcarbonate (2)

To a solution of alcohol (**1**) (675 mg, 8.0 mmol) and pyridine (2 cm^3) in ether (2 cm^3) under nitrogen atmosphere was added ethyl chloroformate (2 cm^3, 20 mmol). The reaction mixture was left to stir overnight and neutralized with 1 M HCl. The reaction mixture was extracted with ether and dried. Purification on silica gel using acetone/petrol (30 : 70) as an eluent gave the title compound as a colourless oil (764 mg, 61%). R_f 0.8 [acetone/petrol (30 : 70)]. ν_{max} (cm^{-1}) 2981–2856 ν(CH), 1741 ν(C=O); δ_H (250 MHz; $CDCl_3$) 1.25 (3H, t, *J* 3.0, —OCH_2CH_3), 1.85 (1H, m, 4-H_a), 2.25 (2H, m, 5-H_2), 2.45 (1H, m, 4-H_b), 4.2 (2H, m, —OCH_2CH_3), 5.6 (1H, m, 1-H), 5.85 (1H, m, 2-H), 6.1 (1H, m, 3-H); δ_C (63 MHz; $CDCl_3$); 14.2 (CH_3), 29.6 (C4), 31.0 (C5), 63.6 (CH_2), 83.9 (C1), 128.7 (C3), 138.4 (C2), 154.9 (C=O); (Found: C, 61.78; H, 8.01, $C_8H_{12}O_3$ requires C, 61.5; H, 7.69%); m/z (EI) 156 (M^+, 10%), 83 (100), 67 (82), 55 (15).

9-(2-Cyclopentenyl)-6-chloropurine (3a : 3b)

A mixture of 2-amino-6-chloropurine (126 mg, 0.7 mmol) in dry DMF (3 cm^3), 2-cyclopentene-1-ethylcarbonate (**2**) (106 mg, 0.7 mmol) in THF (2 cm^3), palladium tetrakis (triphenylphosphine) (196 mg, 0.2 mmol) and triphenylphosphine (45 mg, 0.2 mmol) were refluxed for 5 d under nitrogen. Methanol (10 cm^3) was added to the residue and the mixture filtered and the filtrate evaporated. The product was purified by flash chromatography using [acetone/petrol (40 : 60)] to give the title compound as a white solid (60 mg, 38% of N-9 isomer). m.p. = 166.0–166.7°C; R_f 0.2 [acetone/petrol (30 : 70)]. ν_{max} (cm^{-1}) 3316–3199 ν(NH_2), 2926–2846 ν(CH); δ_H (250 MHz; $CDCl_3$) 1.8 (1H, m, 4′-H_a), 2.5 (3H, m, 5′-H_2 and 4′-H_b), 5.3 (2H, br s, NH_2), 5.5 (1H, m, 1′-H), 5.8 (1H, m, 2′-H), 6.25 (1H, m, 3′-H), 7.75 (1H, s, 8-H); m/z (EI) 237 ($^{37}M^+$, 10%), 235 ($^{35}M^+$, 37%), 169 (100), 134 (43); (Found: M^+, 235.0624; $C_{10}H_{10}N_5{}^{35}Cl$ requires m/z, 235.0626). Repeating the reaction in DMSO for 5 d gave a 83 : 17 ratio of **3a** and **3b** as a white solid. The N-7 isomer had: δ_H (250 MHz; $CDCl_3$) 1.8 (1H, m,

4′-H_a), 2.5 (3H, m, 5′-H_2 and 4′-H_b), 5.0 (2H, br s, NH_2), 5.5 (1H, m, 1′-H), 5.8 (1H, m, 2′-H), 6.25 (1H, m, 3′-H), 7.51 (1H, s, 8-H).

9-(2-Cyclopentenyl)quanine (4)

A solution of 9-(2-cyclopentenyl)-6-chloropurine (**3a**) (32 mg, 0.1 mmol) in 1.8 cm^3 of a 0.33 M NaOH solution was heated at reflux for 3.5 h. After cooling to room temperature, the solution was neutralized with 1 cm^3 0.5 M HCl solution. The solvents were removed under reduced pressure. MeOH (5 cm^3) was added to the mixture and the filtrate evaporated. The product was purified by flash chromatography using acetone/MeOH (90 : 10) and gave the title compound as a white solid (13 mg, 45%), R_f 0.5 in [acetone/EtOAc (40 : 60)]. δ_H (250 MHz; $CDCl_3$) 1.8 (1H, m, 4′-H_a), 2.5 (3H, m, 5′-H_2 and 4′-H_b), 5.4 (1M, m, 1′-H), 5.85 (1H, dd, 5.0 and 1.5, 2′-H), 6.25 (1H, dd, *J* 5.0 and 1.5, 3′-H), 7.0 (2H, br s, NH_2), 8.0 (1H, s, 8-H), 11.23 (1H, br s, NH); m/z (EI) 217 (M^+, 14%), 151 (35), 66 (100); (Found: M^+, 217.0963. $C_{10}H_{11}N_5O_1$).

In conclusion, we report here a versatile method for synthesis of racemic carbocyclic nucleosides (**4**) in four steps using π-allyl palladium chemistry in the key step. This process should be a useful method for the preparation of potential antiviral and anti-tumour agents.

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