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Synthesis of fused dihydropyrido[*e*]purines via ring closing metathesis

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ABSTRACT

Ring closing metathesis (RCM) of 8,9-diallylpurines or 9-butenyl-8-vinylpurines with the Grubbs 2nd generation catalyst resulted in fused 6,9- or 8,9-dihydropyrido[*e*]purines, respectively. The 8,9-dialkenylpurines were prepared from 8-bromopurines after 9-alkenylation and subsequent Stille coupling at C-8 with alkenylstannanes in the presence of $Pd(PPh_3)_4$ or $Pd(PPh_3)_2Cl_2$.

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Nucleosides represent a class of compounds that possess very interesting biological activities,[1–4] especially antiviral and anticancer. Such activities also appear in cyclonucleosides[5,6] bearing a linkage between the heterocyclic ring and the sugar moiety. Fused purine derivatives also display a wide range of biological effects, for example, anti-inflammatory, antihypertensive, anxiolytic, antitumor, antiviral, and vasodilation activity.[7–9]

Three different strategies have been applied for the preparation of fused purine derivatives.[10,11] The first method involves the radical[6,12–16] or ionic[9,11,17–20] cyclization of substituted purines (9-substituted for fused [*e*]purines). The second method starts from a functionalized pyrimidine where the imidazole ring is formed by a cyclocondensation.[7,8,10,11] The third method involves construction of the pyrimidine ring by heterocyclization of an appropriately substituted fused imidazole derivative.[21–25] Recently, ring closing metathesis (RCM) was used for the synthesis of asmarines (fused diazepino[*g*,*h*]purines).[26]

In continuation of our studies on modified nucleosides,[27] and in connection with our efforts on the application of RCM metathesis for the synthesis of heterocycles,[28,29] we report here the use of RCM[30,31] for the synthesis of fused dihydropyrido[*e*]purines. The fused [*e*]purines may intercalate to DNA or bind to adenine binding sites of enzymes as the ring fusion preserves the base-pairing characteristics of the purine ring.[18,32] The reactions studied and the products obtained are depicted in Schemes 1 and 2.

Allylation of 8-bromo-6-(piperidin-1-yl)-9*H*-purine (**2a**) [prepared by bromination of 6-(piperidin-1-yl)-9*H*-purine (**1a**)[27] (97%) with Br_2 in glacial CH_3COOH[33,34]] with allyl bromide in DMF,[35] in the presence of K_2CO_3, gave the 9-allylpurine derivative **3a** (35%) and the corresponding 3-allylpurine derivative **4a** (58%) (Scheme 1). The structures of the allyl derivatives **3a** and **4a** were determined by ^{1}H NMR comparisons with 9-allyladenine and 3-allyladenine[36] and by NOE experiments (a 12% correlation between $NC\mathbf{H}_2CH{=}CH_2$ and H-2 for **4a**). The ratio of the allylated products **3a** and **4a** was analogous to the benzylated products prepared from 8-bromoadenine.[37] Stille[38–40] coupling of the 9-allyl-8-bromopurine derivative **3a** with allyltributyltin in the presence of a catalytic amount of $Pd(PPh_3)_4$ in dry DMF under N_2 at 95 °C afforded the 8,9-diallylpurine derivative **5a** (71%), the 7-allylpurine derivative **6a** (14%) and the debromination product, 9-allyl-6-(piperidin-1-yl)-9*H*-purine[27] (10%). In NOE studies of the 7-allylpurine **6a**, 5% or 3% correlations between the β,γ-C**H**$_2$ or the α-C**H**$_2$ of the piperidine ring with the $NCH_2C\mathbf{H}{=}CH_2$ unit were recorded. Derivative **6a** is probably formed by isomerization of starting material **3a**. On using $Pd(PPh_3)_2Cl_2$ as the catalyst at 80 °C, the yields of the diallylated product **5a** and the isomerization product **6a** were only 21% and 5%, while 55% of the starting material remained unchanged. RCM of the 8,9-diallylpurine **5a** using the Grubbs 2nd generation catalyst **7** (19 mol %) in CH_2Cl_2 at rt for 2 days gave 4-(piperidin-1-yl)-6,9-dihydropyrido[1,2-*e*]purine (**8a**) in 97% yield (Scheme 1).

By analogous reaction sequences from the 6-(morpholin-1-yl)-9*H*-purine (**1b**)[27] or the 6-(pyrrolidin-1-yl)-9*H*-purine (**1c**),[27] 8-bromo-6-(morpholin-1-yl)-9*H*-purine (**2b**)[33,34] (85%) and 8-bromo-6-(pyrrolidin-1-yl)-9*H*-purine (**2c**)[34] (98%) were prepared. These were allylated to give the corresponding 9-allyl derivatives **3b** (34%) and **3c** (33%), the 3-allylpurine derivatives **4b** (61%) or **4c** (54%) being the major products. Stille coupling of the 9-allyl derivatives **3b** or **3c** with allyltributyltin in the presence of $Pd(PPh_3)_4$ at 95 °C afforded the 8,9-diallyl derivatives **5b** (73%) or

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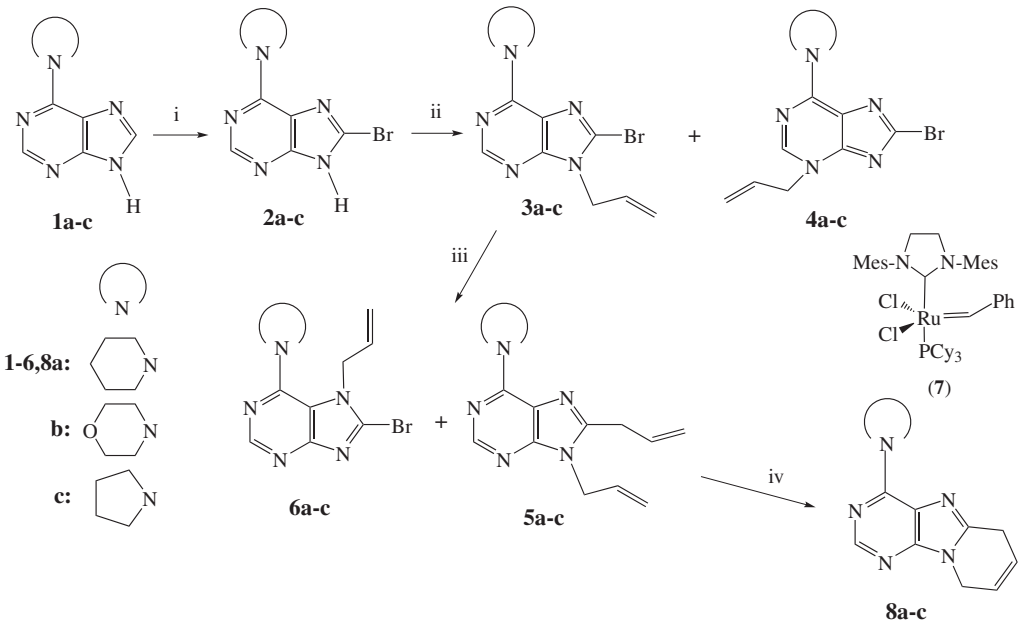
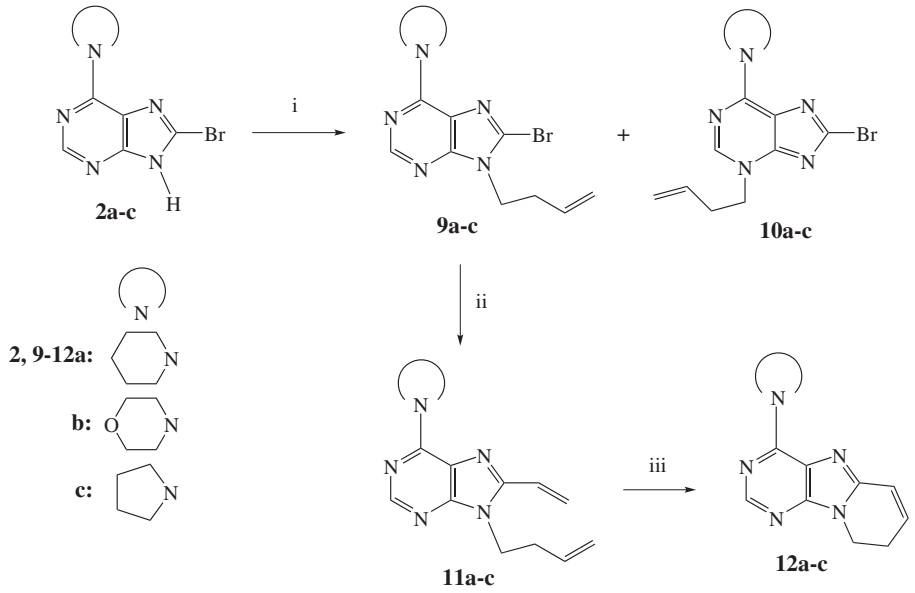


Scheme 1. Reagents and conditions: (i) Br_2, CH_3COOH, CH_3COONa, 80 °C, 3 h. (ii) Allyl bromide, K_2CO_3, DMF (dry), rt, 24 h. (iii) Allyltributyltin, $Pd(PPh_3)_4$, DMF (dry), N_2, 95 °C, 15 h. (iv) Catalyst **7** (19 mol %), CH_2Cl_2 (dry), argon, rt, 2 days.



Scheme 2. Reagents and conditions: (i) 4-bromo-1-butene, K_2CO_3, DMF (dry), rt, 24 h. (ii) Vinyltributyltin, $Pd(PPh_3)_2Cl_2$, DMF (dry), N_2, 80 °C, 15 h. (iii) Catalyst **7** (6 mol %), CH_2Cl_2 (dry), argon, rt, 24 h.

5c (72%) (Scheme 1), along with the isomerization products, the 7-allylpurine derivatives **6b** (26%) and **6c** (13%), and the debromination products, 9-allyl-6-(morpholin-1-yl)-9*H*-purine[27] (1%) and 9-allyl-6-(pyrrolidin-1-yl)-9*H*-purine[27] (12%). Finally, RCM reactions of the diallyl intermediates **5b** or **5c** with the 2nd generation Grubbs catalyst **7** gave 4-(morpholin-1-yl)-6,9-dihydropyrido[1,2-*e*]-purine (**8b**) (82%) and 4-(pyrrolidin-1-yl)-6,9-dihydropyrido[1,2-*e*]purine (**8c**) (84%).

Butenylation of purine **2a** with 4-bromo-1-butene in DMF in the presence of K_2CO_3 led to the 9-but-3-en-1-ylpurine derivative **9a** (31%) and the 3-(but-3-en-1-yl)purine derivative **10a** (57%) (Scheme 2). The structures of these products were established by NOE experiments (e.g., an 18% correlation between $NCH_2CH_2CH{=}CH_2$ and H-2 was observed for **10a**). Stille coupling of the 8-bromo-9-(but-3-en-1-yl)purine derivative **9a** with vinyltributyltin in the presence of a catalytic amount of $Pd(PPh_3)_2Cl_2$ in dry DMF under N_2 at 80 °C afforded the 9-(but-3-en-1-yl)-8-vinylpurine derivative **11a** (52%). RCM of the latter with catalyst **7** (6 mol %) in CH_2Cl_2 at rt over 24 h gave the 4-(piperidin-1-yl)-8,9-dihydropyrido[1,2-*e*]purine (**12a**) in 93% yield.

The 9-(but-3-en-1-yl) purine derivatives **9b** (30%) and **9c** (35%) and the 3-(but-3-en-1-yl)purine derivatives **10b** (51%) and **10c** (41%) were isolated from analogous butenylation reactions of the bromo-compounds **2b** and **2c**. The Stille coupling reactions of the 8-bromo-9-(but-3-en-1-yl) derivatives **9b** and **9c** with vinyltributyltin in the presence of a catalytic amount of $Pd(PPh_3)_2Cl_2$ in dry

DMF under N_2 at 80 °C resulted in the 9-(but-3-en-1-yl)-8-vinylpurine derivatives **11b** (51%) and **11c** (59%). When $Pd(PPh_3)_4$ was used for the synthesis of compound **11c** instead of $Pd(PPh_3)_2Cl_2$, the results were almost the same (58% yield). Vinyl compounds **11a–c** appeared to polymerize after evaporation of the solvent in air, and so were stored under argon in a refrigerator. RCM of compounds **11b** and **c** with catalyst **7** (6 mol %) afforded 4-(morpholin-1-yl)-8,9-dihydropyrido[1,2-*e*]purine (**12b**) (90%) and 4-(pyrrolidin-1-yl)-8,9-dihydropyrido[1,2-*e*]purine (**12c**) (85%).

In conclusion, dihydropyrido[*e*]purine derivatives have been synthesized by RCM reactions in good yields for the final step.

Supplementary data

Supplementary data (general procedures, spectral, and analytical data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.008.

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34. Selected data (the data for other procedures and compounds are provided as Supplementary data):
    (a) *General procedure for the Stille coupling of 9-allyl-8-bromo-6-N-substituted purines with Pd(PPh$_3$)$_4$.* Allyltributyltin (64 mg, 0.06 ml, 0.197 mmol) was added to a stirred solution of compound **3a** (50 mg, 0.155 mmol) and $Pd(PPh_3)_4$ (8 mg, 0.0069 mmol) in dry DMF (3 ml) under N_2 and heated at 95 °C for 12 h. Additional $Pd(PPh_3)_4$ (10%) (5 mol % in total) and allyltributyltin (0.217 mmol in total) were added and the mixture heated at 95 °C for a further 3 h. The resulting precipitate was removed by filtration, the filtrate evaporated and the residue chromatographed [silica gel, hexane/EtOAc (2:1)] to give, from the faster moving band, *8,9-diallyl-6-(piperidin-1-yl)-9H-purine* (**5a**) (71% yield), oil, IR (neat): 3050, 2910, 2840, 1570 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.65–1.80 (m, 6H), 3.61 (dt, 2H, J_1 = 1.6 Hz, J_2 = 6.2 Hz), 4.17–4.34 (m, 4H), 4.77 (dt, 2H, J_1 = 1.7 Hz, J_2 = 5.0 Hz), 4.96 (ddt, 1H, J_1 = 0.7 Hz, J_2 = 1.7 Hz, J_3 = 17.2 Hz), 5.15 (dq, 1H, J_1 = 1.6 Hz, J_2 = 17.4 Hz), 5.17–5.23 (m, 2H), 5.87–6.12 (m, 2H), 8.29 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.9, 26.1, 32.5, 44.2, 46.4, 117.1, 117.7, 119.0, 132.4, 132.7, 147.8, 151.9, 152.0, 153.5. MS (ESI): 283 $[M]^+$. Anal. Calcd for $C_{16}H_{21}N_5$: C, 67.82; H, 7.47; N, 24.71. Found: C, 67.93; H, 7.58; N, 24.46.
    (b) *General procedure for the RCM reactions of 8,9-diallylpurines.* Catalyst **7** [26 mg (in 4 portions each after 2 h), 0.0306 mmol, 19 mol %] was added to a degassed solution of compound **5a** (45 mg, 0.158 mmol) in dry CH_2Cl_2 (25 ml) and the solution stirred at rt for 48 h. After evaporation of the solvent, the residue was purified by column chromatography [silica gel, hexane/EtOAc (2:1)] to give *4-(piperidin-1-yl)-6,9-dihydropyrido[1,2-e]purine* (**8a**) (97% yield), mp 113–115 °C (hexane/EtOAc), IR (KBr): 3016, 2927, 2847, 1588 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.63–1.81 (m, 6H), 3.59–3.68 (m, 2H), 4.17–4.28 (m, 4H), 4.66–4.74 (m, 2H), 6.00–6.12 (m, 2H), 8.30 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.0, 24.9, 25.6, 42.1, 46.4, 119.4, 120.0, 122.2, 143.9, 150.7, 151.6, 153.3. MS (ESI): 256 $[M+H]^+$. Anal. Calcd for $C_{14}H_{17}N_5$: C, 65.86; H, 6.71; N, 27.43. Found: C, 66.11; H, 6.65; N, 27.25.
    (c) *General procedure for the RCM reactions of 9-(but-3-en-1-yl)-8-vinylpurines.* The catalyst **7** [10 mg (in 4 potions each after 2 h), 0.0118 mmol, 6 mol %] was added to a degassed solution of compound **11a** (60 mg, 0.31 mmol) in dry CH_2Cl_2 (30 ml), and the solution was stirred at rt for 24 h. After evaporation of the solvent, the residue was purified by column chromatography [silica gel, hexane/EtOAc (1:1)] to give *4-(piperidin-1-yl)-8,9-dihydropyrido[1,2-e]purine* (**12a**) (93% yield), mp 75–77 °C (hexane/EtOAc), IR (KBr): 3018, 2925, 2852, 1587 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.59–1.80 (m, 6H), 2.64–2.75 (m, 2H), 4.15–4.29 (m, 6H), 6.41 (dt, 1H, J_1 = 4.4 Hz, J_2 = 10.0 Hz), 6.63 (dt, 1H, J_1 = 1.7 Hz, J_2 = 10.0 Hz), 8.30 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.3, 24.8, 26.1, 38.6, 46.3, 119.6, 120.3, 132.3, 144.0, 150.8, 152.2, 153.4. MS (ESI): 256 $[M+H]^+$, 278 $[M+Na]^+$. Anal. Calcd for $C_{14}H_{17}N_5$: C, 65.86; H, 6.71; N, 27.43. Found: C, 65.95; H, 6.86; N, 27.32.
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