



Cyclotrimerization of 6-ethynylpurines. Synthesis of 1,2,4- and 1,3,5-tris(purin-6-yl)benzenes as novel Hoogsteen-triplet analogues

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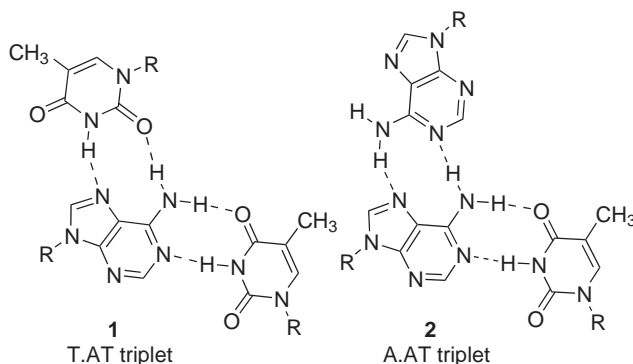
Abstract—Cyclotrimerization reactions of the 9-protected 6-ethynylpurines **4a,b** in the presence of various transition metal catalysts were studied. The best results were obtained with $\text{Ni}(\text{COD})_2$ or $\text{Ni}(\text{COD})_2/\text{PPh}_3$ to obtain the 1,2,4- and 1,3,5-tris(purin-6-yl)benzenes **5a,b** and **6a,b** in moderate to good yields (in a 4:1 to 10:1 ratio). This method is suitable for the practical synthesis of the unsymmetrical 1,2,4-tris(purin-6-yl)benzenes **5a–c**, while the symmetrical 1,3,5-tris(purin-6-yl)benzenes **6a,b** are generally formed as minor products. © 2001 Elsevier Science Ltd. All rights reserved.

Two main hydrogen bonding motifs exist in DNA: the Watson–Crick motif in duplexes and the Hoogsteen motif in triplexes. Numerous covalently bound purine and pyrimidine derivatives representing Watson–Crick base-pair models have been prepared¹ and their properties as DNA cross-links, intercalators or fluorescent probes have been studied. By contrast, no synthetic models of covalent Hoogsteen-type triplets **1** or **2** have been reported so far with the only exception being the tris(purin-6-yl)amines described very recently.²

As significant biological activity has been found in diverse 6-arylpurine derivatives, i.e. the cytostatic activity³ of substituted 6-phenylpurines and the antimy-

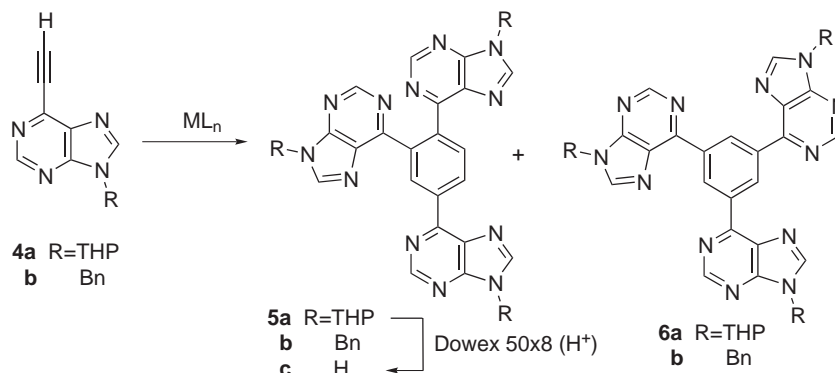
cobacterial activity⁴ of 6-aryl-9-benzylpurines, we have devised novel nucleic base triplet analogues **3** consisting of three purine bases linked by a benzene moiety. Such compounds might be expected to intercalate into DNA and, accordingly, to affect important biological processes (e.g. triplex formation).

Herein we report an original approach to the nucleic base triplets **3** that relies on cyclotrimerization⁵ of properly functionalized alkynes. The protected 6-ethynylpurines **4a,b**, readily accessible by the Sonogashira coupling of 6-halopurines with alkynes,⁶ were used as key substrates⁷ for a series of cyclotrimerization experiments varying transition metal catalysts and reac-



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Scheme 1.

tion conditions according to literature protocols (Scheme 1, Table 1).^{8–13} While TaCl₅ in benzene, the Grubbs catalyst PhCH= Ru(PCy₃)Cl₂ in dichloromethane, Pd(PPh₃)₄ or Ni(CO)₂(PPh₃)₂ in tetrahydrofuran, and the Wilkinson catalyst RhCl(PPh₃)₃ in ethanol left the starting alkynes **4a,b** untouched even under reflux for a prolonged reaction period, the use of CpCo(CO)₂ in decane at 140°C with the concomitant visible light irradiation led to a very complex mixture containing only traces of the target products **5** or **6** (according to the MS analysis of the crude reaction mixture). The observed low reactivity of these alkynes towards cyclotrimerization might be explained in terms of a substantial decrease of the electron density at the triple bond due to the presence of the electron-deficient purine moiety.

The situation dramatically changed when applying a highly reactive Ni(COD)₂ complex to enforce the nucleic base triplet formation. The THP-protected **4a** with a catalytic amount of Ni(COD)₂ and PPh₃ afforded¹⁴ an 8:1 mixture of tris(purin-9-yl)benzenes **5a** and **6a** in good yield (74%). Both regioisomers were successfully separated by column chromatography. The use of a stoichiometric amount of Ni(COD)₂ (1/3 equiv.) without PPh₃ as a stabilizing ligand gave a 4:1 mixture of **5a** and **6a** in moderate yield (41%). Analogously, the reaction of the Bn-protected derivative **4b** with Ni(COD)₂ and PPh₃ afforded the unsymmetrical 1,2,4-tris(purin-9-yl)benzene **5b** in 50% yield, while the symmetrical

product **6b** could not be isolated in a pure form. Finally, compound **5a** was deprotected by means of wet Dowex 50×8 (H⁺ form) in methanol¹⁵ to give the free purine derivative **5c** in 70% yield.

While the NMR spectra of the 1,3,5-trisubstituted benzenes **6a** and **6b** displayed very simple patterns due to their high symmetry, the spectra of the 1,2,4-trisubstituted derivatives **5a–c** contained distinct sets of signals belonging to each purine ring. Possessing chirality centers at the THP protecting groups, the compounds **5a** and **6a** have to occur as mixtures of diastereoisomers. In spite of this, these materials were chromatographically homogeneous. Although in the ¹H and ¹³C NMR spectra of **5a** some signals of proximal purines were split, the spectra of **6a** exhibited a perfect symmetry again. Furthermore, no hindered rotation was observed in dynamic NMR experiments with compounds **5b,c** and **6a** even at low temperatures (up to –70°C), indicating that these compounds could easily adopt a planar conformation that is necessary for intercalation into DNA.

In conclusion, the Ni(COD)₂/PPh₃-catalyzed cyclotrimerization of 6-ethynylpurines provided the unsymmetrical (major) and symmetrical (minor) tris(purin-6-yl)benzenes **5** and **6** as the novel Hoogsteen-triplet analogues. The application of this reaction to nucleoside and nucleotide derivatives, as well as biological activity studies will be the subject of further investigation.

Table 1. Cyclotrimerization of 6-ethynylpurines **4a,b**

Starting compound	Catalyst/ligand (mol %)	Solvent	Conditions	Yield (%)	
				5	6
4a	CpCo(CO) ₂ (40) PPh ₃ (80)	Decane	140°C, hv	Complex mixture	
4a	Ni(COD) ₂ (20) PPh ₃ (50)	THF	Rt	66 ^a	8 ^a
4a	Ni(COD) ₂ (33)	THF	Rt	33 ^a	8 ^a
4b	Ni(COD) ₂ (20) PPh ₃ (50)	THF	Rt	50 ^a	5 ^b

^a Isolated yields of pure compounds (characterized by NMR and HR MS).

^b Compound **6b** was not isolated in a pure form (yield estimated from ¹H NMR of the crude reaction mixture).

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- Typical experiment—cyclotrimerization of 4a*: A solution of Ni(COD)₂ in THF (0.065 M, 6 ml, 0.4 mmol) was added dropwise through a septum to a stirred solution of **4a** (500 mg, 2 mmol) and PPh₃ (262 mg, 1 mmol) in THF (10 ml) under argon (*CAUTION!* exothermic reaction). The mixture was stirred at ambient temperature for 5 h and then the solvent was evaporated. Column chromatography of the residue on silica gel [50 g, light petroleum–ethyl acetate–methanol (1:1:0→0:1:0→0:9:1)] afforded compound **6a** (40 mg, 8%) followed by compound **5a** (330 mg, 66%). *Selected data*: 1,3,5-Tris[9-(tetrahydropyran-2-yl)purin-6-yl]benzene (**6a**): yellow amorphous solid; FAB MS, *m/z* (rel. %): 685 (27) [M+H], 601 (12) [M+H-THP], 517 (13) [M+2H-2THP], 433 (100) [M+3H-3THP]. ¹H NMR (400 MHz, CDCl₃): 1.65–2.22 (m, 18H, CH₂); 3.84 (dt, 3H, *J*=2.2, 11.5, CH₂Oa); 4.22 (d, 3H, *J*=11.3, CH₂Ob); 5.90 (dd, 3H, *J*=10.2, 2.4, OCHN); 8.43 (s, 3H, H-8-Pu); 9.15 (s, 3H, H-2-Pu); 10.36 (s, 3H, H-benzene). ¹³C NMR (100 MHz, APT, CDCl₃): 23.54, 25.64 and 32.65 (3×CH₂); 69.55 (CH₂O); 82.77 (OCHN); 132.21 (C-5-Pu); 134.51 (CH-benzene); 137.51 (C-benzene); 143.29 (C-8-Pu); 152.62 (C-6-Pu); 153.33 (C-2-Pu); 155.13 (C-4-Pu). Exact mass (FAB HR MS): 685.3135; C₃₆H₃₇N₁₂O₃ [M+H] requires: 685.3112. 1,2,4-Tris[9-(tetrahydropyran-2-yl)purin-6-yl]benzene (**5a**): yellow amorphous solid; FAB MS, *m/z* (rel. %): 685 (9) [M+H], 601 (3) [M+H-THP], 517 (7) [M+2H-2THP], 433 (100) [M+3H-3THP]; 85 (42) [THP]. ¹H NMR (500 MHz, CDCl₃, particular purine rings designated as A, B and C): 1.60–2.20 (m, 18H, CH₂); 3.80 and 4.19 (2×m, 6H, CH₂O); 5.79 (d, 2H, *J*=9.6, OCHN); 5.88 (d, 1H, *J*=9.9, OCHN); 8.14 (s, 1/2H), 8.16 (s, 1H) and 8.19 (s, 1/2H, H-8-PuA,B); 8.36 (s, 1H, H-8-PuC); 8.46 (d, 1H, *J*=8.2, H-6-benzene); 8.68, 8.70, 8.72 and 8.74 (4×s, 4×1/2H, H-2-PuA,B); 9.07 (s, 1H, H-2-PuC); 9.21 (d, 1H, *J*=8.2, H-5-benzene); 9.60 (s, 1H, H-3-benzene). ¹³C NMR (100 MHz, APT, CDCl₃): 23.51, 25.60, 32.43 and 32.58 (4×CH₂); 69.48 (CH₂O); 82.60, 82.67 and 82.76 (OCHN); 131.87 (C-5-benzene); 132.25 and 132.81 (C-5-PuA,B,C); 133.37 (C-6-benzene); 134.11 (C-3-benzene); 136.88 (C-2-benzene); 137.67 (C-4-benzene); 138.54 (C-1-benzene); 142.84, 142.90 and 143.12 (C-8-PuA,B,C); 151.79 (C-4-PuA,B,C); 152.58 (C-2-PuA,B); 153.13 (C-2-PuC); 154.36 (C-6-PuC); 158.13 (C-6-PuA); 158.77 (C-6-PuB). Exact mass (FAB HR MS): 685.3128; C₃₆H₃₇N₁₂O₃ [M+H] requires: 685.3112.
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