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## [2+2+2]-Co-cyclotrimerization 6-alkynylpurines with diynes: a method for preparation of 6-arylpurines

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Abstract—A novel approach to 6-arylpurines based on [2+2+2]-co-cyclotrimerization of 6-alkynylpurines with various  $\alpha,\omega$ -diynes is described. Co-cyclotrimerization is catalyzed by Ni- and Co-phosphine catalysts and their choice depends on the substitution pattern of the both reactants. © 2003 Elsevier Science Ltd. All rights reserved.

6-Arylpurine derivatives were recently found to exhibit diverse types of biological activity: some substituted 6-arylpurine bases are antagonists of corticotropinreleasing hormone<sup>1</sup> or possess antimycobacterial and antibacterial activity,<sup>2</sup> while 6-arylpurine ribonucleosides are potent cytostatics.<sup>3</sup> Moreover, 6-arylpurines were used as unnatural nucleobases in artificial base-pairs<sup>4</sup> and as covalent base-pair analogues.<sup>5</sup> So far, biological activity screening was limited to easily available purines bearing simple aryl groups, while those bearing highly substituted and/or functionalized aryl moieties still remain to be explored. 6-Arylpurines have been efficiently prepared by crosscoupling reactions of 6-halopurines with various organometallics.<sup>6</sup> However, these methods are limited by availability, reactivity and stability of the corresponding aryl-organometallic reagent. Therefore, it is still of general interest to develop alternative methods for the preparation of some (in particular highly substituted) 6-arylpurines. One such hitherto unexplored and [2+2+2]-copotentially interesting strategy is cyclotrimerization of 6-alkynylpurines with other alkynes or diynes. Herein we report on a novel approach to the synthesis of 6-arylpurines based on transition-metal



## Scheme 1.

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catalyzed co-cyclotrimerizations of 6-alkynylpurines 1 with  $\alpha, \omega$ -diynes 2.

Although cyclotrimerization can be affected by a number of transition metal complexes, often the proper choice of a catalyst determines the successful course of the reaction. Generally speaking, alkynylpurines as a class of compounds has been prepared only recently, and because of that there is no information concerning their reactivity with other alkynes in the presence of transition metal catalysts. The only exception is the recent report of homocyclotrimerization of 6-ethynylpurine into tris(purin-6-yl)benzenes.7 The above mentioned reasons prompted us to study cyclotrimerization of alkynylpurines  $1^{7b}$  and diynes 2 to arylpurines 3 (Scheme 1) in the presence of various transition metal complexes such as RhCl(PPh<sub>3</sub>)<sub>3</sub> (Wilkinson's catalyst),<sup>8</sup> catalytic systems composed of NiX<sub>2</sub>(L)<sub>n</sub> (L=PPh<sub>3</sub>,<sup>9</sup> dppe<sup>10</sup>) and a reductant (Zn), and rarely used  $CoBr(PPh_3)_3$ .<sup>11</sup> Some representative results are summarized in Table 1. The reactions were usually carried out on a 0.1 mmol scale in the presence of 10–20 mol% of the transition metal catalyst. The best results were obtained when the Rh- and Co-catalyzed reactions were carried out in toluene and those with the Ni-catalysts in MeCN.

The use of Wilkinson's catalyst, which is known to catalyze co-cyclotrimerization of various alkynes with  $\alpha, \omega$ -diynes was not very efficient. In comparison with Ni and Co catalysts its superiority was demonstrated only in the reaction of ethynylpurine **1a** with diyne **2b** that

Table 1. Co-cyclotrimerization of alkynylpurines 1 with  $\alpha,\omega$ -diynes 2 into 3 catalyzed by various TM-complexes

1	2	Catalyst <sup>a</sup>	t (h) <sup>c</sup>	Product	Yield (%) <sup>f</sup>
1a	2b	A	24 <sup>d</sup>	3ab	10
		В	72	3ab	7
		D	72	3ab	0
1a	2d	С	96	3ad	12
		D	96	3ad	7
		Е	72	3ad	55
1a	2e	D	96	3ae	7
1b	2a	В	96	3ba	11
		Е	96	3ba	0
1b	2b	А	24 <sup>d</sup>	3bb	10
		В	72	3bb	48
		D	72	3bb	35
1b	2c	В	96	3bc	13
1b	2d	С	120	3bd	5
		D	120	3bd	18
		Е	72	3bd	55
1c	2b	D	20	3cb	64
		$\mathbf{D}^{\mathbf{b}}$	20	3cb	61
1c	2d	С	96	3cd	5
		D	72 <sup>e</sup>	3cd	87
		Е	16	3cd	88

<sup>a</sup> A = RhCl(PPh<sub>3</sub>)<sub>3</sub>, B = NiI<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>/Zn, C = NiBr<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>/Zn, D = NiBr<sub>2</sub>(dppe)<sub>2</sub>/Zn, E = CoBr(PPh<sub>3</sub>)<sub>3</sub>.

<sup>b</sup> In THF.

f Isolated yields.

resulted in the formation of arylpurine **3ab** in a low yield of 10% after 24 h at 80°C. In this instance the use of other catalysts gave inferior results. Also, its efficiency in the co-cyclotrimerization of hexynylpurine **1b** with diyne **2b** to give arylpurine **3bb** was of the same magnitude (yield 10%). When a stoichiometric amount was used product **3bb** was isolated in 67% yield. In further experiments the use of Wilkinson's catalyst was abandoned because of its high price and our interest focused to other catalytic systems.

The most promising catalytic system seems to be the one based on Ni(0)–phosphine complexes, because Ni(cod)<sub>2</sub>/ 2PPh<sub>3</sub> was the only catalyst able to homocyclotrimerize **1a**.<sup>7</sup> To avoid manipulation with rather unstable Ni(cod)<sub>2</sub>, which is sensitive to oxygen and protic solvents, we decided to generate Ni(0) compounds in situ by the reduction of Ni(II)–phosphine complexes with excess of Zn powder. It is noteworthy that the ligation around the nickel atom played a crucial role in the catalytic activity of the complexes.

Two Ni(II) complexes were tested as potential catalysts:  $NiX_2(PPh_3)_2$  (X = Br or I) and  $NiBr_2(dppe)$ . The best result with the former catalyst was obtained in cocyclotrimerization of hexynylpurine 1b with diyne 2b, which resulted in the formation of arylpurine **3bb** in 48%. In comparison with other catalysts its use gave superior results for co-cyclotrimerizations of ethynylpurine 1a with divne 2e to give anylpurine 3ae, and hexynylpurine 1b with divines 2a and 2c to furnish arylpurines 3ba and **3bc**, respectively, albeit in low yields. The latter showed highest activity for co-cyclotrimerization of hexynylpurine 1b with diyne 2d that afforded arylpurine 3bd in 55% yield, and for the reaction of phenylethynylpurine 1c with diynes 2b and 2d to give arylpurines 3cb<sup>12</sup> and 3cd in 64 and 87%, respectively. The reaction of phenylethynylpurine 1c with diyne 2b was also carried out in THF under the same conditions with a similar result (61% yield). It is important to note that when  $Ni(PPh_3)_4$ complex was prepared from Cp<sub>2</sub>Ni and 4PPh<sub>3</sub><sup>13</sup> no cyclotrimerization of ethynylpurine **1a** with divne **2b**, or hexynylpurine 1b with diynes 2a,b,c was observed.

Cyclopentadienylcobalt complexes are very efficient catalysts for cyclotrimerization of alkynes, however, the use of high reaction temperatures for a successful reaction is required. Recently, it was shown that the cobalt analogue of Wilkinson's catalyst CoBr(PPh<sub>3</sub>)<sub>3</sub> can cyclotrimerize alkynes to benzene derivatives in some cases even at room temperature.<sup>11</sup> This fact sparked our interest to apply this complex for co-cyclotrimerization of alkynylpurines 1 with divnes 2. Indeed, its use enabled us to achieve the reaction even in some cases where other catalysts failed to give any products. The cobalt catalyst was very efficient in co-cyclotrimerization of alkynylpurines **1a**,**b**, and c with divnes 2d and afforded arylpurines 3ad, 3bd and **3cd**<sup>14</sup> in 55, 55, and 88% yields, respectively. For comparison, the reaction of ethynylpurine 1a with divne 2d catalyzed by  $NiI_2(PPh_3)_2$  gave the product in 12% yield, and the reaction of hexynylpurine **1b** with diyne **2d** catalyzed by NiBr<sub>2</sub>(dppe) gave the product in 18% yield. The structure of arylpurine 3ad was confirmed by a single-crystal X-ray analysis (Fig. 1).<sup>15</sup>

<sup>&</sup>lt;sup>c</sup> At 60°C unless otherwise mentioned.

<sup>&</sup>lt;sup>d</sup> 80°C.

<sup>° 20°</sup>C.



Figure 1. View of molecular structure 3ad with the atom numbering scheme. The thermal ellipsoids are drawn at 50% probability level.

Interestingly, for some combinations the use of any of the catalysts did not result in the formation of benzene derivatives. This prompted us to compare some results with the reactions carried with a stoichiometric amount of a catalyst. For that purpose  $NiI_2(PPh_3)_2$  was chosen because of its low cost. The results are summarized in Table 2. Reactions of hexynylpurine 1b with diynes 2a and 2c under stoichiometric conditions gave higher yields of the corresponding products 3ba and 3bc than under catalytic conditions. It is notable that the reaction of ethynylpurine 1a with diynes 2b and hexynylpurine **1b** with 1,7-octadiyne **2f** afforded arylpurines 3ab and 3bf in 9 and 39% yields, respectively. Under catalytic conditions the formation of neither of these products was detected. Reaction of hexynylpurine 1b with divne 2b gave arylpurine 3ab in

Table 2. Co-cyclotrimerization of 1 with 2 in the presence of a stoichiometric amount of  $NiI_2(PPh_3)_2$ 

1	2	<i>t</i> (h) <sup>a</sup>	Product	Yield (%) <sup>b</sup>
1a	2b	72	3ab	9
1b	2a	48	3ba	29
1b	2b	48	3bb	52
1b	2c	24	3bc	53
1b	2f	24	3bf	39
1c	2b	48	3cb	22

<sup>a</sup> At 60°C.

<sup>b</sup> Isolated yields.



comparable yield (52%) to the catalytic reaction. Finally, the reaction of phenylethynylpurine **1c** with diyne **2b** gave arylpurine **3cb** in inferior yield (22%).

In order to check compatibility of the reaction conditions with respect to purine nucleosides, tri-O-acetyl protected 6-phenylethynylpurine nucleoside **4** was cocyclotrimerized with **2b** and **2d** in the presence of a catalytic amount of Ni(dppe)Br<sub>2</sub>/Zn catalyst (20 mol%,  $60^{\circ}$ C, 72 h) to give the corresponding arylpurines **5a** and **5b** in yields of 35 and 47%, respectively (Scheme 2).

This study showed that the [2+2+2]-co-cyclotrimerization of alkynylpurines with diynes into arylpurines could be successfully catalyzed by Ni and Co phosphine complexes under mild and simple conditions.<sup>12,14</sup> The yields varied from moderate to good and were strongly dependent on the combination of substituents R and linkers X and on the nature of catalytic system or stoichiometric reagent. So far, no generally applicable conditions were found but, for most combinations of starting compounds, either Ni or Co catalysts could be efficiently used. Some intriguing aspects of this reaction still remain unclear: (i) the effect of ligation around the central atom in the case of nickel catalysis; (ii) effect of substitution of the linker in diynes.

In conclusion, this first application of [2+2+2]-cocyclotrimerization methodology to purine systems allows an efficient preparation of highly substituted 6-phenylpurines (in particular purines bearing 2,4,5trisubstituted phenyl moieties) that would not be easily accessible by standard cross-coupling reactions. Further extension of this methodology to the synthesis of a large series of purine bases and nucleosides, and biological activity screening of these product is underway.

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- Typical experimental procedure for nickel-complex catalyzed reaction.
  9-Benzyl-6-[6-phenyl-2,2-bis(ethoxycarbonyl)indan-5-yl]-9H-purine 3cb. In an argon purged glass vial a mixture of an alkynylpurine 1c (0.1 mmol), a diyne 2b (0.1 mmol), a Ni(dppe)Br<sub>2</sub> (12 mg, 0.02 mmol), and Zn powder (32 mg, 0.05 mmol) in MeCN (2 mL) was

heated to 60°C for 20 h. Column chromatography on silica gel (1/1 hexane/EtOAc) afforded 35 mg (64%) of an yellow oil: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.27 (t, *J*=7.2 Hz, 6H), 3.70 (s, 2H), 3.72 (s, 2H), 4.23 (q, *J*=7.2 Hz, 2H), 5.37 (s, 2H), 7.06–7.14 (m, 5H), 7.14–7.18 (m, 2H), 7.28–7.36 (m, 3H), 7.38 (s, 1H), 7.62 (s, 1H), 7.82 (s, 1H), 8.87 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  13.96, 40.14, 40.36, 46.99, 60.57, 61.74, 126.21, 126.40, 127.44, 127.61, 128.38, 128.99, 129.15, 132.03, 133.39, 135.15, 139.28, 141.12, 141.31, 142.18, 144.03, 151.39, 152.34, 159.20, 171.36; IR (CHCl<sub>3</sub>) *v* 3037, 3025, 2987, 1731, 1588, 1499, 1447, 1369, 1329, 1230, 1217, 1214, 1196, 1159, 1069, 907 cm<sup>-1</sup>; *m*/*z* (EI) 545 (M<sup>+</sup>, 22), 473 (6), 399 (6), 91 (100); HR-MS calcd for C<sub>33</sub>H<sub>30</sub>N<sub>4</sub>O<sub>4</sub> 546.2267, found 546.2274. *R*<sub>f</sub> (1/2 hexane/EtOAc)=0.40.

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- 14. Typical experimental procedure for the cobalt-complex catalyzed reaction. 9-Benzyl-6-(6-phenyl-1,3-dihydroisobenzofuran-5-yl)-9H-purine 3cd. In an argon purged glass vial a mixture of an alkynylpurine 1c (0.1 mmol), a diyne 2d (0.1 mmol), and CoBr(PPh<sub>3</sub>)<sub>3</sub> (18 mg, 0.02 mmol) in toluene (2 mL) was heated to 60°C for 16 h. Column chromatography on silica gel (1/4 hexane/ EtOAc) afforded 36 mg (88%) of a yellow oil: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.22 (s, 4H), 5.40 (s, 2H), 7.08–7.16 (m, 5H), 7.16-7.22 (m, 2H), 7.32-7.38 (m, 3H), 7.41 (s, 1H), 7.66 (s, 1H), 7.86 (s, 1H), 8.89 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) & 47.12, 73.39, 73.46, 123.19, 123.32, 126.48, 127.55, 127.75, 128.50, 129.07, 129.21, 132.12, 133.83, 135.09, 138.37, 141.09, 141.16, 141.68, 144.26, 151.49, 152.39, 158.95; IR (CHCl<sub>3</sub>) v 3021, 2989, 2859, 1589, 1499, 1455, 1438, 1332, 1216, 1213, 1121, 1048, 902, 855 cm<sup>-1</sup>; m/z (EI) 404 (M<sup>+</sup>, 6), 403 (11), 277 (100), 201 (24), 183 (20), 91 (25), 77 (44), 59 (58); HR-MS calcd for  $C_{26}H_{20}N_4O$  404.1637, found 404.1614.  $R_f$  (EtOAc) = 0.32.
- 15. Crystal structure determination for 3ad. Single crystals were grown from hexane. Crystal data:  $C_{20}H_{16}N_4O$ , M =328.37, monoclinic; space group  $P2_1/n$ ; a=9.3510(2), b=c = 13.9450(3)Å;  $\beta = 100.9640(14)^{\circ};$ 12.4700(3), U=1596.40(6) Å<sup>3</sup>, T=150 K, Z=4,  $\mu$ (Mo K $\alpha$ )=0.088 mm<sup>-1</sup>; 23987 diffractions collected, 3646 unique diffractions ( $R_{int} = 0.026$ ) used in all calculations, final  $R(F^2) =$ 0.0433 (for observed diffractions with  $I > 2\sigma(I)$ ) and  $wR(F^2) = 0.1173$  (for all data). Crystallographic data (excluding structure factors) for the structures in this paper, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 192707. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).