Tetrahedron Letters 51 (2010) 2464–2466

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of (purin-6-yl)methylphosphonate bases and nucleosides

Zbyněk Hasník, Radek Pohl, Michal Hocek *

Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Gilead Sciences & IOCB Research Center, Flemingovo nam. 2, CZ-16610 Prague 6, Czech Republic

ARTICLE INFO

Article history:
Received 10 December 2009
Revised 13 February 2010
Accepted 26 February 2010
Available online 3 March 2010

Keywords:
Purines
Nucleosides
Phosphonates
Cross-coupling reactions

ABSTRACT

Three approaches to the synthesis of the title (purin-6-yl)methylphosphonates were investigated and compared. While, the Arbuzov reaction of 6-(iodomethyl)purines with triethyl phosphite did not work, Michaelis–Becker alkylation of the sodium salt of diethyl phosphonate with 6-(mesyloxymethyl)purines gave the desired products in good yields. The best method was based on Rh- or Pd-catalyzed cross-coupling reactions of 6-iodopurines with (diisopropoxyphosphorylmethyl)zinc bromide. In this way a small series of 6-(diisopropoxyphosphorylmethyl)purine bases and nucleosides was prepared in high yields.

Purine is an important and extensively investigated heterocycle. However, purines bearing functionalized C-substituents at position 6 have only recently been systematically studied. We have developed syntheses of many subtypes of these compounds, mostly based on the cross-coupling reactions of halopurines with functionalized organometallics followed by further functional group transformations[1,2] or by additions and cycloadditions to 6-vinyl- and 6-ethynylpurines.[3] Ribonucleosides derived from 6-hydroxymethyl-,[1] 6-(di/tri)fluoromethyl-, 6-(aminomethyl)-,[2] 6-(2-aminovinyl)-, and 6-(2-aminoethyl)purines[3] were shown to possess interesting cytostatic and anti-HCV activities. Purin-6-yl acetates were recently prepared[4] by the Pd-catalyzed cross-couplings of halopurines with the Reformatsky reagent and were further converted into carboxamides and 6-(2-hydroxyethyl)purines. Herein, we report on the synthesis of hitherto unknown 6-(phosphonomethyl)purine bases and nucleosides which are phosphorous analogues of the acetates. Acyclic nucleoside phosphonates of purines are clinical antivirals of paramount importance,[5] however the methylphosphonate moiety was never directly connected to the purine. The only known related examples were phosphonopurines (with a direct P–C linkage to purine).[6]

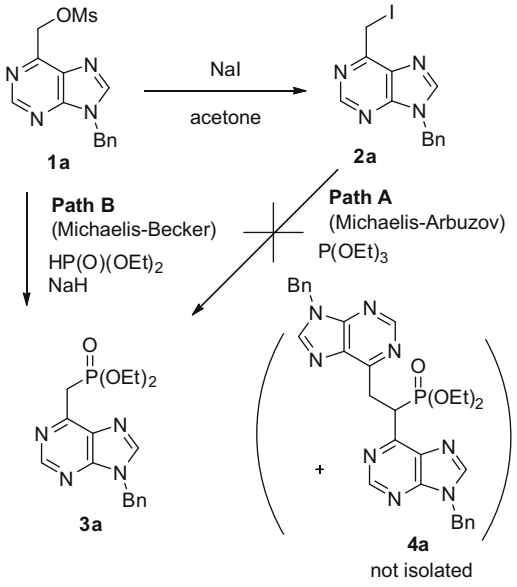
Three approaches for the synthesis of the title (purin-6-yl)methylphosphonates have been investigated: (i) Michaelis–Arbuzov reaction[7] of 6-(iodomethyl)purines with trialkyl phosphites, (ii) Michaelis–Becker[8] alkylation of sodium diethyl phosphonate, and (iii) cross-coupling of (diisopropoxylphosphonylmethyl)zinc iodide[9] with 6-halopurines.

The methods were tested on model 9-benzylpurines. The Michaelis–Arbuzov reaction is the most common method for the preparation of diverse alkylphosphonates,[7] and was the first approach tried in the synthesis of the title compounds (Scheme 1, Path A). 9-Benzyl-6-(mesyloxymethyl)purine (**1a**) was converted into the more reactive 6-(iodomethyl)purine (**2a**) which was subjected to reaction with triethyl phosphite under standard conditions. However, heating **2a** in the presence of excess triethyl phosphite resulted only in decomposition of the starting material and no traces of the desired product. Therefore, we focused on the alternative Michaelis–Becker approach (Scheme 1, Path B). The mesylate **1a** was reacted with the in situ-generated sodium salt of diethyl phosphonate under various conditions (Table 1). Performing this reaction at −20 °C gave the desired diethyl 6-(phosphonomethyl)purine **3a** in a mixture with **4a** (not isolated in pure form; it was identified by NMR from the mixture with **3a**) as a side-product of its alkylation with a second equivalent of **1a** (entry 1). The selectivity of the substitution was significantly increased by lowering the reaction temperature to −78 °C to give the phosphonate **3a** in a good yield of 79% (entry 2). When the amount of sodium diethyl phosphonate was increased to 4 equiv, the yield of the desired 6-(phosphonomethyl)purine **3a** increased to 84% (entry 3).

Since the Michaelis–Becker approach required very efficient cooling to prevent side reactions, we decided to investigate a direct introduction of the phosphonomethyl group by cross-coupling with an appropriate phoshonomethylzinc reagent. The only known example[9] of such coupling was the Rh-catalyzed reaction of aryl halides with (diethoxyphosphonylmethyl)zinc iodide. Related cross-couplings of (phosphonodifluoromethyl)zinc were de-

* Corresponding author. Tel.: +420 220183324; fax: +420 220183559.
E-mail address: hocek@uochb.cas.cz (M. Hocek).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.02.167



Scheme 1. Michaelis–Arbuzov (Path A) and Michaelis–Becker (Path B) approaches to the title 6-phosphonomethylpurines.

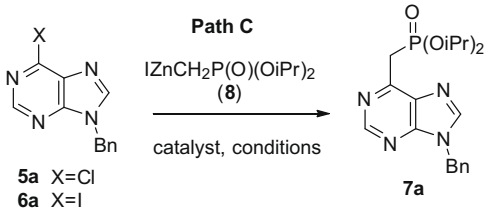
Table 1
Michaelis–Becker synthesis of **3a**

Entry	Conditions	*T* (°C)	Yield of **3a** (%)
1	$HP(O)(OEt)_2$ (2 equiv)/NaH	−20	59[a]
2	$HP(O)(OEt)_2$ (2 equiv)/NaH	−78	79
3	$HP(O)(OEt)_2$ (4 equiv)/NaH	−78	84

[a] Unseparable mixture containing 29% of **4a** (2:1).

scribed[10] earlier using Cu-catalysis. We have prepared a new organozinc reagent, (diisopropoxyphosphonylmethyl)zinc iodide (**8**) to avoid possible problems with alkyl transfer from diethyl phosphonates. The organozinc **8** was prepared by the reaction of diisopropyl iodomethylphosphonate with zinc dust preactivated using TMSCl and 1,2-dibromoethane in analogy with our previous procedure used for the generation of the Reformatsky reagent.[4] The organozinc **8** was tested in reactions with 9-benzyl-6-chloro-(**5a**) and -6-iodopurine (**6a**) with Rh or Pd-catalysis under different conditions (Scheme 2). 6-Chloropurine **5a** was found to be completely unreactive with all the tested catalytic systems even at high temperatures. Therefore, only 6-iodopurine **6a** was used for the optimization (Table 2). The Rh-catalyzed[9] (10 mol % $Rh(COD)Cl_2$ with dppf) reaction of **6a** with 4 equiv of **8** at rt gave only low conversion, while heating at 60 °C gave the desired 6-(phosphonomethyl)purine **7a** in an excellent yield of 94% (entries 1 and 2). When using cheaper $Pd(PPh_3)_4$ as the catalyst (10 mol %), the reaction at rt did not proceed. However, at 60 °C the reaction proceeded smoothly to give **7a** in nearly quantitative yield (entry 4). Further experiments (entries 5–8) were performed to decrease the excess of the organozinc **8** and the loading of the catalyst. Thus, the optimized conditions required 2 equiv of **8** and 5 mol % of $Pd(PPh_3)_4$ to give an almost quantitative conversion to **7a** (entry 8).

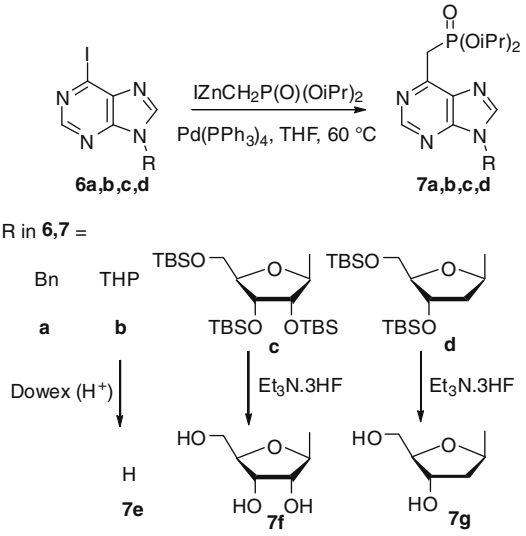
These optimized conditions were applied to the preparation of other purine derivatives with protecting groups at position 9 of the purine moiety (Scheme 3, Table 3). All the starting compounds **6b–d** reacted readily and gave full conversion to the corresponding phosphonates **7**. THP-protected purine **6b** showed good stability toward this cross-coupling reaction and gave the desired phosphonomethylpurine **7b** in 93% yield (entry 2). Both silyl-protected iodopurine nucleosides **6c** and **6d** were also excellent substrates for this cross-coupling reaction and gave the desired phosphonate



Scheme 2. Cross-coupling of 6-halopurines with organozinc **8** (Path C).

Table 2
Optimization of the cross-coupling of **6a** with **8**

Entry	Catalyst (mol %)	8 (equiv)	*T* (°C)	Yield of **7a** (%)
1	$Rh(COD)Cl_2$/dppf (10)	4	rt	34
2	$Rh(COD)Cl_2$/dppf (10)	4	60	94
3	$Pd(PPh_3)_4$ (10)	4	rt	0
4	$Pd(PPh_3)_4$ (10)	4	60	95
5	$Pd(PPh_3)_4$ (10)	2	60	94
6	$Pd(PPh_3)_4$ (10)	2	50	91
7	$Pd(PPh_3)_4$ (5)	2	50	85
8	$Pd(PPh_3)_4$ (5)	2	60	94



Scheme 3. Synthesis of 6-(diisopropoxyphosphorylmethyl)purine bases and nucleosides.

Table 3
Synthesis of 6-(diisopropoxyphosphorylmethyl)purine bases and nucleosides

Entry	Substrate	Cross-coupling product (yield)	Deprotection product (yield)
1	**6a**	**7a** (94%)	–
2	**6b**	**7b** (93%)	**7e** (55%)
3	**6c**	**7c** (97%)	**7f** (63%)
4	**6d**	**7d** (93%)	**7g** (62%)

nucleosides **7c** and **7d** in almost quantitative yields (entries 3 and 4). The protecting groups were removed by standard procedures giving the free purine base and nucleosides. The THP-protecting group in **7b** was cleaved using Dowex 50 (H^+ form)[11] in ethanol at 70 °C yielding 55% of the free purine base **7e**. Deprotection of the TBS groups in nucleosides **7c,d** was performed using a small excess of $Et_3N{\cdot}3HF$ in THF[12] overnight to give the desired free nucleosides **7f,g** in good yields.

In conclusion, a novel and efficient approach to (purin-6-yl)methylphosphonates was developed based on cross-coupling

reactions of 6-iodopurines with (diisopropoxyphosphonylmethyl)zinc iodide. For the first time, these reactions were successfully performed under Pd-catalysis. The resulting purine-phosphonates can potentially be used for other synthetic transformations (alkylations, Horner–Emmons reactions, etc.).

Synthesis of **3a** *by Michaelis–Becker reaction*: To a suspension of NaH (20 mg, 0.5 mmol) in 2 ml of THF was added dropwise diethyl phosphonate (79 mg, 64 μl, 0.5 mmol) at 0 °C and the mixture was allowed to warm to room temperature. After 2 h the solution was cooled to −78 °C and transferred to a mixture of mesylate **1a** (80 mg, 0.25 mmol) in 2 ml of THF at −78 °C. The mixture was allowed to warm to room temperature overnight, then quenched with H_2O, and extracted with $CHCl_3$ (3 × 15 ml). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated. The residue was chromatographed on silica gel (hexane/EtOAc 10:1–1:1) to give pure **3a** as a yellowish oil in 84% yield. MS (ESI): 383 (100, M+Na), 361 (25, M+H). HRMS (ESI): calcd for $C_{17}H_{21}N_4O_3PNa$: 383.1243, found: 383.1244. ^1H NMR (600.1 MHz, $CDCl_3$): 1.28 (td, 6H, J_{vic} = 7.1, $J_{H,P}$ = 0.4, CH_3CH_2); 3.85 (d, 2H, $J_{H,P}$ = 22.7, CH_2P); 4.17 (m, 4H, CH_2CH_3); 5.44 (s, 2H, CH_2N); 7.32 (m, 2H, H-*o*-Ph); 7.35 (m, 1H, H-*p*-Ph); 7.36 (m, 2H, H-*o*-Ph); 8.04 (d, 1H, $J_{H,P}$ = 1.0, H-8); 8.96 (d, 1H, $J_{H,P}$ = 0.6, H-2). ^{13}C NMR (150.9 MHz, $CDCl_3$): 16.29 (d, $J_{C,P}$ = 6.3, CH_3CH_2); 31.74 (d, $J_{C,P}$ = 134.1, CH_2P); 47.36 (CH_2N); 62.55 (d, $J_{C,P}$ = 6.3, CH_2CH_3); 127.92 (CH-*o*-Ph); 128.66 (CH-*p*-Ph); 129.16 (CH-*m*-Ph); 133.05 (d, $J_{C,P}$ = 5.6, C-5); 134.90 (C-*i*-Ph); 144.23 (CH-8); 151.16 (d, $J_{C,P}$ = 1.1, C-4); 152.53 (d, $J_{C,P}$ = 2.6, CH-2); 153.38 (d, $J_{C,P}$ = 9.4, C-6). $^{31}P\{^1H\}$ NMR (202.3 MHz, $CDCl_3$): 23.35. IR (CCl_4): 3439, 2983, 1595, 1333, 1245, 1030.

Synthesis of **7a** *via Pd-catalyzed cross-coupling*: A solution of diisopropyl iodomethylphosphonate (673 mg, 463 μl, 2.2 mmol) in THF (2 ml) under argon was added at room temperature to an argon-purged flask containing a suspension of zinc dust (196 mg, 3 mmol) in THF (1 ml), which had been preactivated with 1,2-dibromoethane and trimethylsilyl chloride (10 μl). The suspension was stirred for 1 h, the zinc was allowed to settle, and the supernatant was transferred through a septum to a mixture of 6-iodopurine **6a** (336 mg, 1 mmol), $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) in THF (2 ml) under argon. The reaction mixture was stirred at 60 °C for 12 h, cooled to room temperature, and then the reaction was quenched with 1 M NH_4Cl (30 ml) and extracted with $CHCl_3$ (3 × 30 ml). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated. The residue was chromatographed on silica gel ($CHCl_3$/MeOH 1:0–4:1) to give **7a** as a colorless oil in 94% yield. MS (ESI): 411 (100, M+Na), 389 (25, M+H). HRMS (ESI): calcd for $C_{19}H_{25}N_4O_3PNa$: 411.1556, found: 411.1558. ^1H NMR (500.0 MHz, $CDCl_3$): 1.19, 1.26 (2 × d, 2 × 6H, J_{vic} = 6.2, $(CH_3)_2CH$); 3.78 (d, 2H, $J_{H,P}$ = 22.9, CH_2P); 4.69 (dhept, 2H, $J_{H,P}$ = 7.8, J_{vic} = 6.2, $CH(CH_3)_2$); 5.40 (s, 2H, CH_2N); 7.26 (m, 2H, H-*o*-Ph); 7.30 (m, 1H, H-*p*-Ph); 7.32 (m, 2H, H-*o*-Ph); 8.02 (d, 1H, $J_{H,P}$ = 1.0, H-8); 8.91 (d, 1H, $J_{H,P}$ = 0.6, H-2). ^{13}C NMR (125.7 MHz, $CDCl_3$): 23.66 (d, $J_{C,P}$ = 5.3, $(CH_3)_2CH$); 23.95 (d, $J_{C,P}$ = 3.6, $(CH_3)_2CH$); 32.86 (d, $J_{C,P}$ = 135.8, CH_2P); 47.23 (CH_2N); 71.13 (d, $J_{C,P}$ = 6.7, $CH(CH_3)_2$); 127.75 (CH-*o*-Ph); 128.52 (CH-*p*-Ph); 129.04 (CH-*m*-Ph); 132.97 (d, $J_{C,P}$ = 5.8, C-5); 134.90 (C-*i*-Ph); 144.17 (CH-8); 151.03 (d, $J_{C,P}$ = 1.2, C-4); 152.31 (d, $J_{C,P}$ = 2.7, CH-2); 153.57 (d, $J_{C,P}$ = 9.4, C-6). ^{31}P NMR (202.3 MHz, $CDCl_3$): 21.16. IR (CCl_4): 3436, 2980, 1595, 1333, 1243, 994. Anal. Calcd for $C_{19}H_{25}N_4O_3P{\cdot}3/4H_2O$ (401.9): C, 56.78; H, 6.65; N, 13.94. Found: C, 56.57; H, 6.94; N, 13.42.

Acknowledgments

This work is part of the research project Z4 055 0506 of the Academy of Sciences of the Czech Republic. It was supported by the Ministry of Education, Youth and Sports (1M0508), and by Gilead Sciences, Inc. (Foster City, CA, USA).

Supplementary data

Supplementary data (complete experimental details and characterization data of all compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.167.

References and notes

1. (a) Šilhár, P.; Pohl, R.; Votruba, I.; Hocek, M. *Org. Lett.* **2004**, *6*, 3225–3228; (b) Šilhár, P.; Pohl, R.; Votruba, I.; Hocek, M. *Collect. Czech. Chem. Commun.* **2005**, *70*, 1669–1695.
2. (a) Šilhár, P.; Pohl, R.; Votruba, I.; Hocek, M. *Org. Biomol. Chem.* **2005**, *3*, 3001–3007; (b) Šilhár, P.; Pohl, R.; Votruba, I.; Hocek, M. *Synthesis* **2006**, 1848–1852; (c) Hocková, D.; Hocek, M.; Dvořáková, H.; Votruba, I. *Tetrahedron* **1999**, *55*, 11109–11118; (d) Šilhár, P.; Hocek, M.; Pohl, R.; Votruba, I.; Shih, I.-h.; Mabery, E.; Mackman, R. *Bioorg. Med. Chem.* **2008**, *16*, 2329–2366.
3. (a) Kuchař, M.; Hocek, M.; Pohl, R.; Votruba, I.; Shih, I.-h.; Mabery, E.; Mackman, R. *Bioorg. Med. Chem.* **2008**, *16*, 1400–1424; (b) Kuchař, M.; Pohl, R.; Klepetářová, B.; Votruba, I.; Hocek, M. *Org. Biomol. Chem.* **2008**, *6*, 2377–2387; (c) Kuchař, M.; Pohl, R.; Klepetářová, B.; Hocek, M. *Tetrahedron* **2008**, *64*, 10355–10364.
4. (a) Hasník, Z.; Šilhár, P.; Hocek, M. *Tetrahedron Lett.* **2007**, *48*, 5589–5592; (b) Hasník, Z.; Pohl, R.; Klepetářová, B.; Hocek, M. *Collect. Czech. Chem. Commun.* **2009**, *74*, 1035–1059; For an alternative approach to these compounds, see: (c) Qu, G.-R.; Mao, Z.-J.; Niu, H.-Y.; Wang, D.-C.; Xia, C.; Guo, H.-M. *Org. Lett.* **2009**, *11*, 1745–1748.
5. For reviews, see: (a) Holý, A. *Curr. Pharm. Design* **2003**, *9*, 2567–2592; (b) DeClercq, E.; Holý, A. *Nat. Rev. Drug. Disc.* **2005**, *4*, 928–940.
6. (a) Honjo, M.; Maruyama, T.; Horikawa, M.; DeClercq, E. *Chem. Pharm. Bull.* **1987**, *35*, 3227–3234; (b) Maruyama, T.; Honjo, M. *Nucleosides Nucleotides* **1988**, *7*, 203–211; (c) Qu, G. R.; Xia, R.; Yang, X. N.; Li, J. G.; Wang, D. C.; Guo, H. M. *J. Org. Chem.* **2008**, *73*, 2416–2419.
7. Battacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415–430.
8. For examples, see: (a) Kem, K. M.; Nguyen, N. V.; Cross, D. J. *J. Org. Chem.* **1981**, *46*, 5188–5192; (b) Meziane, D.; Hardouin, J.; Elias, A.; Guenin, E.; Lecouvey, M. *Heteroat. Chem.* **2009**, *20*, 369–377.
9. Takahashi, H.; Inagaki, S.; Yoshii, N.; Gao, F.; Nishihara, Y.; Takagi, K. *J. Org. Chem.* **2009**, *74*, 2794–2797.
10. Yokomatsu, T.; Murano, T.; Suemune, K.; Shiubuya, S. *Tetrahedron* **1997**, *53*, 815–822.
11. Hocek, M.; Holý, A. *Collect. Czech. Chem. Commun.* **1995**, *60*, 1386–1389.
12. Čapek, P.; Pohl, R.; Hocek, M. *J. Org. Chem.* **2005**, *70*, 8001–8008.