Pergamon

Tetrahedron Letters 41 (2000) 1695–1697

TETRAHEDRON LETTERS

C6 substitution of inosine using hexamethylphosphorous triamide in conjunction with carbon tetrahalide or *N*-halosuccinimide†

Eduardo A. Véliz and Peter A. Beal *

Department of Chemistry, University of Utah, Salt Lake City, Utah 84112, USA

Received 22 November 1999; accepted 30 December 1999

Abstract

Herein we report the facile conversion of 2′,3′,5′-tri-*O*-acetylinosine to three different nucleoside analogs via reaction of hexamethylphosphorous triamide and an organic halide. Acetyl-protected 6-bromopurine riboside, 6-chloropurine riboside and N^6,N^6-dimethyladenosine can each be prepared in good yield from 2′,3′,5′-tri-*O*-acetylinosine, HMPT and halide. The major product of the reaction is determined by the identity of the halide used and the reaction temperature. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: halogenation; inosine; HMPT; 6-halopurine.

Nucleoside analogs substituted on the purine ring have potential impact in a number of research areas including understanding the biological effects of DNA damaging reagents,[1] mechanistic analysis of nucleoside metabolizing enzymes,[2] and in the development of antibacterial or antiviral chemotherapeutics.[3] We became interested in the preparation of these compounds in our ongoing studies of RNA-editing adenosine deaminases, where the use of purine analogs will be valuable in helping to define the deamination reaction mechanism.[4]

Purine derivatives halogenated at C6 are useful intermediates in the synthesis of a variety of nucleoside analogs via substitution or cross coupling reactions of the halopurine.[5] Herein, we wish to report a new, simple and efficient procedure for the preparation of 6-bromopurine riboside (**2**), 6-chloropurine riboside (**3**) and N^6,N^6-dimethyladenosine (**4**) from the reaction of 2′,3′,5′-tri-*O*-acetylinosine (**1**) and hexamethylphosphorous triamide (HMPT) in conjunction with either carbon tetrahalide or *N*-halosuccinimide.

The Appel protocol (Ph_3P/CCl_4) and its variations (Ph_3P/Y, Y=CBr_4, Br_2, I_2, NBS) have been widely used in the generation of alkyl halides from alcohols and are well documented in the literature.[6,7] Furthermore, these protocols have been applied to the synthesis of iminoyl halides from secondary amides and γ-lactams.[7,8] Thus, we believed that regioselective halogenation of the purine ring may be possible using this approach and a ribose-protected inosine as the starting material. Our primary

* Corresponding author. Tel: (801) 585-9719; e-mail: beal@chemistry.chem.utah.edu (P. A. Beal)

† Dedicated to the memory of Angela Chanis P.

0040-4039/00/$ - see front matter © 2000 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(00)00051-4

motivation was the investigation of new methods to prepare 6-bromopurine riboside, given the well-documented reactivity of bromides in metal-catalyzed coupling reactions using Pd, Zn or Cu. However, when we attempted to prepare this compound using PPh_3/CBr_4 and inosine **1**, only starting material was recovered. This lack of reactivity was observed with either acetonitrile (ACN) or dichloromethane (DCM) as solvent at room temperature or reflux. Recently, Sugimoto et al. reported the halogenation of hydroxyheterocycles by the action of PPh_3 and *N*-halosuccinimide.[9] When we applied this procedure, however, again only unreacted starting material was recovered.

We reasoned that a more nucleophilic phosphine might be required for the formation of the intermediate phosphonium species from inosine. Therefore, the reaction was carried out with HMPT. A rapid disappearance of inosine **1** was observed upon addition of HMPT and CBr_4 at room temperature. Analysis of the reaction mixture by ^{31}P NMR indicated that HMPT had been converted to a new compound with a chemical shift consistent with an aryloxyphosphonium salt.[10] When the phosphonium salt formed from inosine **1**/HMPT/CBr_4 was treated with 5 equiv. of LiBr at 70°C for 5 h, the bromo derivative **2** was isolated in 65% yield. LiBr was more effective as an external halide source than tetrabutylammonium bromide (TBAB), as addition of TBAB led to a more modest yield (Fig. 1). We also found that if NBS was used instead of CBr_4 (2.5 equiv. HMPT, 3.0 equiv. NBS), the reaction proceeded to product in higher yield (79%) with fewer colored by-products, simplifying purification.

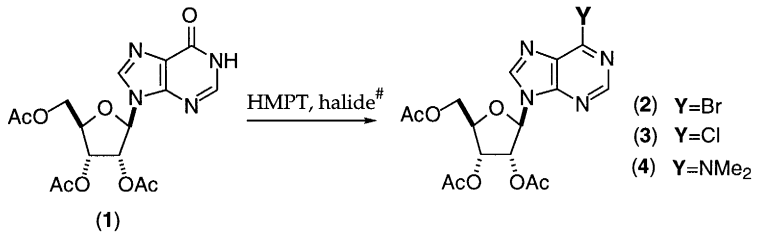

Fig. 1. Formation of C6-substituted purine analogs[11]

We attempted a similar procedure to prepare the 6-chloropurine **3**. Inosine **1** was allowed to react with HMPT/CCl_4 in ACN or DCM. Again, the starting material was rapidly consumed and after heating at reflux, the 6-chloro derivative **3** was isolated in 96% yield. Interestingly, when this reaction was repeated at room temperature using 2.0 equiv. of HMPT and 1.1 equiv. of either CBr_4 or CCl_4, N^6,N^6-dimethyladenosine **4** was formed as the major product in good yield. Products arising from reaction of dimethylamine liberated from HMPT have been observed previously.[12]

Because of its ease of formation and apparent reactivity at higher temperatures to external nucleophiles, the inosine oxyphosphonium salt may provide a new route to purine analogs and these experiments are underway in our laboratories.

In summary, this study provides a simple, efficient procedure to prepare the important synthetic intermediates 6-bromopurine riboside and 6-chloropurine riboside from inosine. In addition, minor modifications of the reaction conditions leads to the formation of 2′,3′,5′-tri-*O*-acetyl-N^6,N^6-dimethyladenosine in good yield. Further refinements and extensions of this protocol are being investigated and will be reported as events merit.

Typical procedure: To a cold (−20°C) solution of **1** and CBr_4 (or NBS) in dry ACN, HMPT was added dropwise. After addition, the cold bath was removed and the reaction mixture stirred at rt for 0.5 h. Then, LiBr was added and the mixture was heated (see Table 1) for 5 h. The mixture was concentrated under

reduced pressure and then purified by flash column chromatography (2% MeOH:$CHCl_3$) to afford the halogenated product.

Table 1

Entry	Halogenating Reagent (eq)	HMPT eq	Solvent	T(°C)	External Nucleophile	Product	Yield (%)
1	CBr_4(1.25)	1.1	ACN	70	LiBr (5 eq)	**2**	65
2	CBr_4 (1.25)	1.1	ACN	70	TBAB (5 eq)	**2**	21
3	CCl_4 (1.25)	1.1	ACN	70	-	**3**	96
4	NBS (3.0)	2.5	ACN	70	LiBr (5 eq)	**2**	79
5	CBr_4 (1.1)	2.0	ACN	RT	-	**4**	77
6	CCl_4 (1.1)	2.0	ACN	RT	-	**4**	72

References

1. Wallace, S. S.; Van Houten, B. V.; Kow, Y. W. *Ann. New York Acad. Sci.* **1994**, *726*, 1.
2. Kati, W. M.; Acheson, S. A.; Wolfenden, R. *Biochemistry* **1992**, *31*, 7356.
3. Suhadolnik, R. J. *Nucleosides as Biological Probes*; Wiley: New York, 1979.
4. Yi-Brunozzi, H. Y.; Easterwood, L. M.; Kamilar, G. M.; Beal, P. A. *Nucleic Acids Res.* **1999**, *27*, 2912.
5. For substitution reactions, see: (a) Trivedi, B. K. In *Nucleic Acid Chemistry. Part 4*; Townsend, L. B.; Tipson, R. S., Eds.; Wiley: New York, 1991; pp. 269–273. (b) Bridges, A. J. *ibid* pp. 230–239. (c) Robins, M. J.; Basom, G. L. *Can. J. Chem.* **1973**, *51*, 3161 and references cited therein. Coupling reactions: (1) Cu-catalyzed: Hocek, M.; Holy, A. *Collect. Czech. Chem. Commun.* **1999**, *64*, 229 and references cited therein. (2) Pd-catalyzed: Lakshman, M. K.; Keeler, J. C.; Hilmer, J. H.; Martin, J. Q. *J. Am. Chem. Soc.* **1999**, *121*, 6090. (3) Zn-catalyzed: (a) Stevenson, T. M.; Prasad, A. S. B.; Citineni, J. B.; Knochel, P. *Tetrahedron Lett.* **1996**, *37*, 8375. (b) Prasad. A. S. B.; Stevenson, T. M.; Citineni, J. B.; Nyzam, V.; Knochel, P. *Tetrahedron* **1997**, *53*, 7237. (c) Véliz, E. A.; Beal, P. A. Unpublished results.
6. Castro, B. R. *Org. React.* **1983**, *29*, 1 and references cited therein.
7. Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801 and references cited therein.
8. He, F.; Snider, B. B. *J. Org. Chem.* **1999**, *64*, 1397 and references cited therein.
9. Sugimoto, O.; Mori, M.; Tanji, K. *Tetrahedron Lett.* **1999**, *40*, 7477.
10. For salt formation, the mixture was stirred at rt for 0.5 h. ^{31}P NMR (121 MHz, CH_3CN, 85% H_3PO_4 as external standard) resonances: (a) HMPT: 25.33 ppm; (b) HMPT+CBr_4: 48.51 ppm; (c) HMPT+CBr_4+**1**: 35.37 ppm. ^{31}P NMR resonance reported for an aryloxyphosphonium salt: 38.5 ppm, Ramirez, F.; Patwardhan, A. V.; Smith, C. P. *J. Am. Chem. Soc.* **1965**, *87*, 4973.
11. Compounds **2** and **3** gave spectroscopic data as reported values.[13] Compound **4** gave satisfactory analytical spectroscopic data (^1H and ^{13}C NMR, MS, and HRMS).
12. Hans, J. J.; Driver, R. W.; Burke, S. D. *J. Org. Chem.* **1999**, *64*, 1430 and references cited therein.
13. Nair, V.; Richardson, S. G. *J. Org. Chem.* **1980**, *45*, 3969.