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Process Optimization in the Synthesis of 9-[2-(Diethylphosphonomethoxy)ethyl]adenine: Replacement of Sodium Hydride with Sodium *tert*-Butoxide as the Base for Oxygen Alkylation

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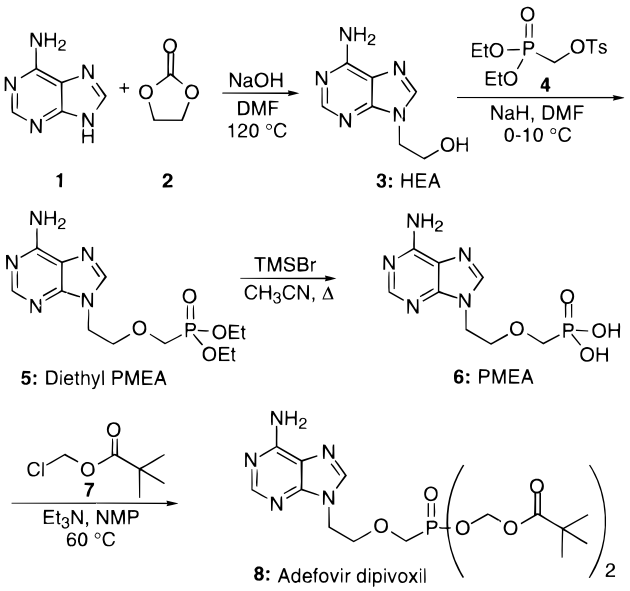
Abstract:

9-[2-(Diethylphosphonomethoxy)ethyl]adenine (diethyl-PMEA), a key intermediate in the production of the antiviral drug adefovir dipivoxil, was originally produced via a process utilizing sodium hydride (NaH) to couple hydroxyethyl adenine with diethyl *p*-toluenesulfonyloxymethanephosphonate. The use of NaH presented safety and consistency problems. It was found that sodium *tert*-butoxide (NaO^{t}Bu) was a suitable replacement for NaH as the base to effect the coupling reaction. Optimization of reagent stoichiometry and introduction of a simplified filtration workup procedure led to a robust process affording diethyl-PMEA in consistent yields and purities. The modifications and process improvements were scaled-up successfully to batch sizes of >100 kg.

Introduction

Adefovir dipivoxil (9-[2-bis(pivaloyloxymethyl)phosphonomethoxyethyl]adenine (**8**), Scheme 1)[1,2a] is an orally bioavailable prodrug of 9-[2-(phosphonomethoxy)ethyl]adenine [PMEA (**6**)], a nucleotide analogue with activity against the human immunodeficiency virus, hepatitis B virus, herpes simplex virus, cytomegalovirus, Epstein−Barr virus, and other DNA viruses.[1b,2−4] Adefovir dipivoxil is currently in late-phase clinical trials[5] for the treatment of HIV and in early-phase clinical trials for the treatment of hepatitis B virus.

Scheme 1. **Synthesis of adefovir dipivoxil from adenine**



The supply of adefovir dipivoxil for these programs depends on a four-step synthetic process (Scheme 1). In the first step, adenine (**1**) is condensed with ethylene carbonate (**2**) in hot DMF to afford the intermediate 9-(2-hydroxyethyl)-adenine [HEA (**3**)] in 83−95% yield after crystallization from toluene. This step scaled-up well and was reproducible at the 100−200-kg scale. Similarly, the third step, phosphonate ester cleavage with bromotrimethylsilane, worked well at production scale to afford **6**, as did the final esterification of the phosphonate to append the pivaloyloxymethyl groups.

The second step, the synthesis of 9-[2-(diethylphosphonomethoxy)ethyl]adenine [diethyl-PMEA (**5**)] (**3** → **5**), which at the outset of this investigation was derived from the laboratory procedure initially described by Holý and Rosenberg,[6] was problematic on large scale. In this step, the alkylation of **3** was performed using diethyl *p*-toluenesulfo-

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(1) (a) Starrett, J. E., Jr.; Tortolani, D. R.; Russell, J.; Hitchcock, M. J. M.; Whiterock, V.; Martin, J. C.; Mansuri, M. M. *J. Med. Chem.* **1994**, *37*, 1857−1864. (b) Starrett, J. E., Jr.; Tortolani, D. R.; Hitchcock, M. J. M.; Martin, J. C.; Mansuri, M. M. *Antiviral Res.* **1992**, *19*, 267−273.

(2) (a) Benzaria, S.; Pélicano, H.; Johnson, R.; Maury, G.; Imbach, J.-L.; Aubertin, A.-M.; Obert, G.; Gosselin, G. *J. Med. Chem.* **1996**, *39*, 4958−4965. (b) Bronson, J. J.; Ghazzouli, I.; Hitchcock, M. J. M.; Russell, J. W.; Klunk, L. J.; Kern, E. R.; Martin, J. C. *Abstracts of Papers*, 5th International Conference on AIDS, Montreal, Canada, 1989; Abstract MCP74. (c) Naesens, L.; Neyts, J.; Balzarini, J.; Bischofberger, N.; De Clercq, E. *Antiviral Res.* **1995**, *26*, A276. (d) Naesens, L.; Neyts, J.; Balzarini, J.; Bischofberger, N.; De Clercq, E. *Antiviral Res.* **1995**, *26*, A277. (e) Naesens, L.; Neyts, J.; Balzarini, J.; Bischofberger, N.; De Clercq, E. *Nucleosides Nucleotides* **1995**, *14*, 767−770. (f) Naesens, L.; Balzarini, J.; Bischofberger, N.; De Clercq, E. *Antimicrob. Agents Chemother.* **1996**, *40*, 22−28. (g) Srinivas, R. V.; Robbins, B. L.; Connelly, M. C.; Gong, Y. F.; Bischofberger, N.; Fridland, A. *Antimicrob. Agents Chemother.* **1993**, *37*, 2247−2250. (h) Cundy, K. C.; Fishback, J. A.; Shaw, J.-P.; Lee, M. L.; Soike, K. F.; Visor, G. C.; Lee, W. A. *Pharm. Res.* **1994**, *11*, 839−843.

(3) Naesens, L.; Balzarini, J.; De Clercq. E. *Rev. Med. Virol.* **1994**, *4*, 147−159.

(4) De Clercq, E. *Biochem. Pharmacol.* **1991**, *42*, 963−972.

(5) (a) Walker, R. E.; Vogel, S. E.; Jaffe, H. S.; Polis, M. A.; Kovacs, J. A.; Faloon, J.; Davey, R. T.; Ebeling, D.; Cundy, K.; Paar, D.; Markowitz, N.; Masur, H.; Lane, H. C. 1st National Conference on Human Retroviruses and Related Infections, Washington, DC, 1993; Abstract 522. (b) *Antiviral Agents Bull.* **1994**, *7*, 232−233. (c) Barditch-Crovo, P. A.; Toole, J.; Burgee, H.; Wachsman, M.; Ebeling, D.; Cundy, K. C.; Jaffe, H. S.; Lietmand, P. S. *Antiviral Res.* **1995**, *26*, A229.

(6) Holý, A.; Rosenberg, I. *Collect. Czech. Chem. Commun.* **1987**, *52*, 2801−2809.

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nyloxymethanephosphonate (**4**) and 3.0 equiv of sodium hydride in DMF. The heterogeneity of the reaction mixture, in which both NaH and **3** were virtually insoluble, coupled with a strong, delayed onset exotherm led to large variations in product purities (83−96%) and yields (17−44%) at production scale (Table 2). Furthermore, the hydrogen evolution during the reaction and during the acetic acid quench of the excess NaH at the end of the reaction caused safety and operational difficulties. At 200-kg scale (1116 mol of **3**), the NaH process generated 7.51×10^4 L of hydrogen gas. Dilution of this hydrogen to below the 4% hydrogen flammability limit required 1.80×10^6 L of nitrogen (2.25 metric tons).[7] Additionally, concentrated mixtures of NaH in DMF can also result in runaway decomposition.[8]

A continuous extraction procedure using methylene chloride to isolate the partially water soluble diethyl-PMEA (**5**) worked well in the pilot plant facility; however, further scale-up proved arduous, necessitating replacement with a tedious batch extraction procedure. In addition, the removal of the sodium tosylate byproduct was variable using this extractive workup method. Finally, the mineral oil in which the NaH was dispersed required an additional hexane extraction step for its removal. Because of these process weaknesses and concerns with the use of NaH, an effort was initiated to improve the chemistry associated with this step.

Results and Discussion

Reaction Modifications and Optimization. The modification of the diethyl-PMEA process focused on replacing NaH with alternative bases while maintaining a reaction profile similar to that of the NaH process. Lithium *tert*-butoxide (LiO^tBu), which previously was found to be effective for the synthesis of the related compound, PMPA,[9] afforded a thick suspension of the lithium salt of **3** in DMF which hindered agitation and reaction progress. In contrast, the related base, sodium *tert*-butoxide (NaO^tBu), afforded a homogeneous mixture on reaction with **3** in DMF. In some instances, the sodium salt of **3** precipitated out of solution as a viscous resin as the reaction progressed. Counterintuitively, the viscous resin did not dissolve as more solvent was added. It was discovered that, at high concentration (1.5 M), the sodium salt of **3** was soluble, affording a homogeneous solution throughout the coupling reaction, whereas at lower concentration (0.8−1.0 M), the mixture became heterogeneous as the sodium salt of **3** precipitated. Aside from this concentration issue, it was observed in some runs that large clumps of starting **3** did not react with NaO^tBu and thus remained as floating particulates in the reaction mixture. To circumvent this issue, an initial digestion at 125−135 °C in DMF, followed by fast cooling, fully dissolved and reprecipitated **3** as a fine solid. Once performed, addition of NaO^tBu reliably gave a homogeneous solution.

Table 1. **Effects of stoichiometry on product purity and reaction efficiency**

		reaction			HPLC assay	
entry	scale (g)	NaO^tBu (equiv)	tosylate (equiv)	time (h)	HEA + major impurities (area %)	product (area %)
1	35.8	1.10	1.20	26.0	21.7	46.6
2	35.8	1.30	1.20	23.0	17.5	58.7
3	50.0	1.50	1.40	20.0	18.5	56.8
4	100.0	1.50	1.40	20.0	17.8	57.6
5	35.8	1.50	1.20	11.0	14.7	56.0
6	35.8	1.75	1.25	7.5	13.4	63.6
7	239.0	1.75	1.25	7.5	12.9	55.1
8	35.8	2.00	1.25	10.0	11.8	60.4
9	35.8	3.00	1.25	30.0	>27.0	na

Previously, NaH (3.0 equiv) was added portion-wise and concurrently with a solution of tosylate **4** in DMF at less than 10 °C to minimize the side reaction of NaH with **4**. Sodium *tert*-butoxide proved more selective and milder, requiring only 1.5 equiv to effect the coupling reaction. Furthermore, the entire amount of base could be charged in one portion without degradation of **4**.

Ranging studies (Table 1) established that the best stoichiometry was 1.50−2.00 equiv of NaO^tBu and 1.20−1.25 equiv of **4.** A final adjustment to 1.75 equiv of NaO^tBu and 1.25 equiv of **4** afforded a completed reaction (<3% HEA) in under 8 h with yields and purities superior to those of the NaH process. The use of NaO^tBu in the optimized stoichiometry eliminated the flammability hazards and the mineral oil associated with the use of NaH, offered a milder quench with acetic acid, and reduced the amount of NaOTs and NaOAc generated, simplifying the purification procedures.

Workup Optimization. The workup optimization centered on the removal of the salt byproducts in the product mixture. In the NaH process workup procedure, the salt byproducts were removed by dissolving the concentrated reaction mixture in water, extracting with hexanes to remove the mineral oil from NaH, followed by numerous batch extractions (>12) with methylene chloride to recover the product from the aqueous phase.

In the new workup, the use of NaO^tBu eliminated the need for a hexane extraction and an extensive aqueous workup. After the initial concentration of the reaction mixture, the semisolid product mixture was diluted with methylene chloride to precipitate the majority of the sodium tosylate and sodium acetate salts. Filtration of this mixture efficiently removed the salts, provided that the DMF level after distillation was <20 wt %[10] to limit the solubility of the salts. Above this level, the salts became soluble, and the filtration was slowed considerably. A final 9:1 (CH_2Cl_2/H_2O, w/w) partition of the reconcentrated filtrate was incorporated to entirely remove trace amounts of dissolved salts and residual DMF. This ratio of solvents afforded the best separation with the minimum amount of product retained in the water.

(7) Perry, R. H.; Green, D. W.; Maloney, J. O. *Perry's Chemical Engineers' Handbook*, 7th ed.; McGraw-Hill: New York, 1997; pp 11−107.
(8) (a) Buckley, J.; Lee, R.; Laird, T.; Ward, R. J. *Chem. Eng. News* **1982**, *60* (28), 5. (b) DeWall, G. *Chem. Eng. News* **1982**, *60* (37), 5 and 43.
(9) Schultze, L. M.; Chapman, H. H.; Dubree, N. J. P.; Jones, R. J.; Kent, K. M.; Lee, T. T.; Louie, M. S.; Postich, M. J.; Prisbe, E. J.; Rohloff, J. C.; Yu, R. H. *Tetrahedron Lett.* **1998**, *39*, 1853−1856.
(10) A representative sample was obtained after addition of methylene chloride. The level of DMF was determined by ^{1}H NMR comparing by wt % of DMF versus NaOTs, NaOAc, and diethyl-PMEA.

Table 2. **Comparison of large scale results using NaH and NaO^{t}Bu**

reaction			results			
			purity (HPLC area %)		yield (% theory)	
base used	no. of batches	scale (kg of HEA, **3**)	av	range	av	range
NaH	10	5−249	92.6	82.7−96.1	29.0	17.5−43.7
NaO^{t}Bu	4	200	95.0	94.6−95.3	41.0	39.4−43.7

The isolation of **3** involved concentration of the methylene chloride layer, a coevaporation with toluene to remove water, and crystallization from toluene. The isolated laboratory yields of the NaO^{t}Bu procedure were 35−45%, with purities of 88−95%. On production scale, the yields and purities (Table 2) were impressively consistent compared to the NaH process.

Experimental Section

Starting material **3** was prepared according to the literature procedure.[11] Compound **4** was prepared using a method similar to the literature description[12] and was used as a ∼90% concentrated toluene solution adjusted for purity. NaO^{t}Bu and acetic acid were commercially available and were used as received. All reactions were performed under a dry nitrogen atmosphere. Proton nuclear magnetic resonance spectra were obtained on a Varian spectrometer (300 MHz). The ^{1}H NMR chemical shifts are expressed in parts per million (δ) relative to the protio form of the solvent used. Cooling baths (for laboratory scale) used are as follows: −10 °C (ice/methanol), 0 °C (ice/water/salt). HPLC analyses were performed on a Rainin Dynamax HPLC system using an Alltech Alltima 5 μm, reversed-phase column with 5% MeOH in water as eluent.

9-[2-(Diethylphosphonomethoxy)ethyl]adenine (5). A suspension of **3** (200.2 kg, 1117 mol) in *N*,*N*-dimethylformamide (DMF) (960 kg, 1.10 M) was heated at 125−135 °C for 30 min. Upon reaching 130 °C, solution was achieved. The contents were rapidly cooled to 20−30 °C to reprecipitate **3** as a fine suspension in DMF. NaO^{t}Bu (188.0 kg, 1956 mol) was charged slowly to the suspension with cooling so as to maintain the content temperature at 20−30 °C. The resulting solution was then held at 20−30 °C for 30 min before being cooled to −10 °C. A solution of **4** (508.4 kg, 1577 mol) in DMF (241 kg) was slowly added to the reaction mixture with cooling so as to maintain the content temperature at −10 to 0 °C. After completion of addition, the mixture was stirred for an additional 1.5 h.

Acetic acid (134.5 kg, 2240 mol) was charged to the reaction mixture while the temperature was kept <20 °C. After the mixture was stirred for 15 min, the contents were concentrated in vacuo (maximum temperature of 80 °C with minimum vacuum of 25 mmHg) to remove DMF and residual solvents until the distillation stopped at a maximum pot temperature of 80 °C. The concentrate was cooled to 40 °C, diluted with methylene chloride (3201 kg), and charged with Celite (100.3 kg) before filtration. The solids containing NaOTs and NaOAc salts were removed by filtration and rinsed with methylene chloride (3 × 80 kg). The combined filtrate was concentrated in vacuo until distillation halted at a maximum pot temperature of 80 °C. The concentrate was cooled to 40 °C, diluted with methylene chloride (1000 kg), and reconcentrated in vacuo until distillation halted at a maximum pot temperature of 80 °C. The concentrate was cooled to 40 °C, diluted again with methylene chloride (1388 kg) to dissolve all solids, and washed once with water (163.3 kg). The aqueous washing was back-extracted twice with methylene chloride (300 kg each back-extraction). The methylene chloride phases were combined and concentrated in vacuo until distillation halted at a maximum pot temperature of 80 °C. The resulting oil was diluted with toluene (600 kg) and reconcentrated in vacuo until distillation halted at a maximum pot temperature of 80 °C. The concentrate was again diluted with toluene (600 kg) and then warmed to 80 °C for 30 min with moderate agitation. The solution was cooled slowly to 30 °C over 90 min and then to 0 °C, where it was maintained for 12 h with slow agitation. The white solid product was isolated by filtration, washed with cold toluene (3 × 35 kg), and dried in vacuo at 50 °C, yielding 151.6 kg (41.52%) of **5**. Purity by HPLC assay was 93−96% by area. Characterization and ^{1}H NMR data were consistent with literature values.[6]

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(11) (a) Ueda, N.; Kondo, K.; Kono, M.; Takemoto, K.; Imoto, M. *Makromol. Chem.* **1968**, *120*, 13. (b) Raic, S.; Pongracic, M.; Vorkapic-Furac, J.; Vikic-Topic, D.; Hergold-Brundic, A.; Nagl, A.; Mintas, M. *Nucleosides Nucleotides* **1996**, *15*, 937−960.

(12) Holý, A.; Rosenberg, I. *Collect. Czech. Chem. Commun.* **1982**, *47*, 3447−3463. Other methods: (a) Farrington, G. K.; Kumar, A.; Wedler, F. C. *J. Med. Chem.* **1985**, *28*, 1668−1673. (b) Merlo, V.; Roberts, S. M.; Storer, R.; Bethell, R. C. *J. Chem. Soc., Perkin Trans. 1* **1994**, *11*, 1477−1481.