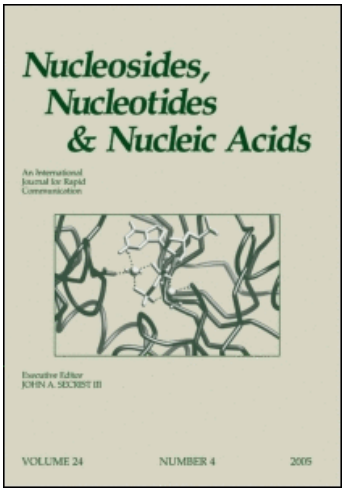

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

A New Regio-Defined Synthesis of PMEA

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To cite this Article Dang, Qun , Liu, Van and Erion, Mark D.(1998) 'A New Regio-Defined Synthesis of PMEA', Nucleosides, Nucleotides and Nucleic Acids, 17: 8, 1445 — 1451
To link to this Article: DOI: 10.1080/07328319808003479
URL: http://dx.doi.org/10.1080/07328319808003479

NUCLEOSIDES & NUCLEOTIDES, 17(8), 1445-1451 (1998)

A NEW REGIO-DEFINED SYNTHESIS OF PMEA

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ABSTRACT: A new regio-defined synthesis of PMEA was developed suitable for gram-scale synthesis. Key to this synthesis was the early introduction of the phosphonomethoxy ethyl moiety and subsequent cyclization for the construction of the purine ring. This synthesis is regiospecific when compared to the commonly used adenine alkylation methods.

INTRODUCTION

9-(2-Phosphonomethoxyethyl)adenine (PMEA) has been the subject of many antiviral studies, and consequently the synthesis of PMEA and its analogs has been well studied.[1] However, most synthetic routes rely on the alkylation of adenine with electrophiles as a key step, and the alkylation reaction generally suffers poor regioselectivity at N-9 and N-7 positions. One way to alleviate this problem is to regioselectively introduce the phosphonomethoxyethyl moiety in PMEA at an early stage. Even though this type of synthesis entails more reaction steps than Holy's original synthesis,[1a] it is considered advantageous to avoid the difficult separation of the N-9 and N-7 alkylated adenine derivatives, which could be problematic for large scale synthesis.[2]

The well known three-step sequence, developed by Montgomery[3] for the construction of purines from 5-amino-4,6-dichloropyrimidine, has been used to synthesize many adenine derivatives, and we envisioned that this method could be used for the regiospecific introduction of the N-9 substituent in PMEA, scheme 1. Herein, the preliminary results of studies toward a new regio-defined synthesis of PMEA are reported.

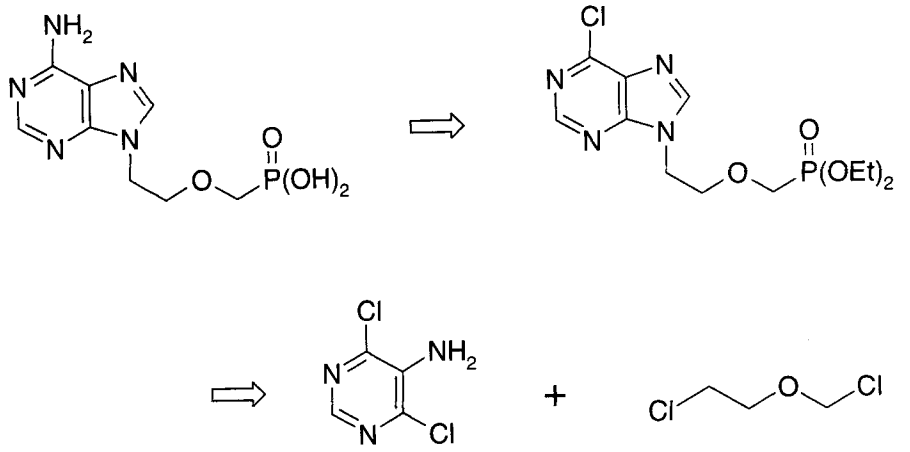
RESULTS AND DISCUSSION

In order to apply Montgomery's purine synthesis to PMEA, diethyl 2-aminoethoxymethylphosphonate (**3**) needed to be prepared. Amine **3** was envisioned to be readily accessible from the reported diethyl 2-chloroethoxymethylphophonate, and its synthesis is described in scheme 2. According to Holy's procedure[4] diethyl 2-chloroethoxymethylphosphonate was prepared from chloromethyl 2-chloroethylether on 100 g scale (90 %, distilled). Conversion of the chloro group to an amino group was conducted using the conventional phthalimide two-step procedure to give amine **3** in the presence of the phosphonate diethyl ester functionality.

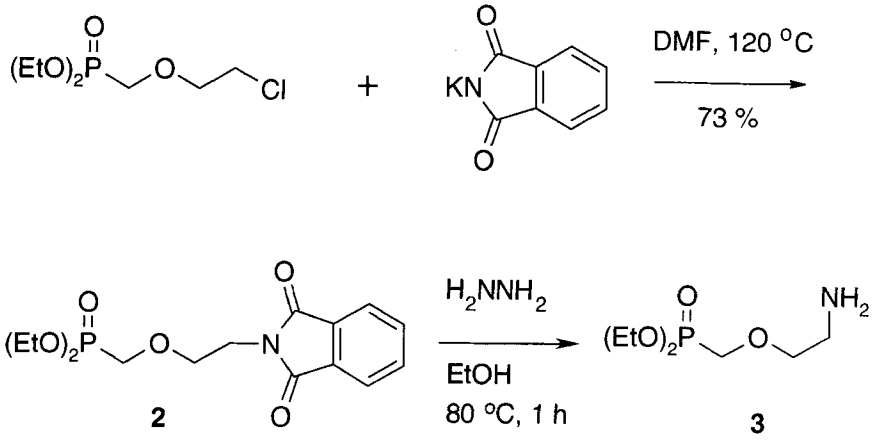
Diethyl 2-chloroethoxymethylphosphonate was treated with potassium phthalimide in DMF to give compound **2** (20 g scale, 73 %), and subsequent deprotection of the phthalimide group under hydrazine deprotection condition gave amine **3** leaving the phosphonate diethyl ester group undisturbed. The attachment of amine **3** to the pyrimidine nucleus, and the application of Montgomery's purine synthesis are outlined in scheme 3.

5-Amino-4,6-dichloropyrimidine was substituted by amine **3** in the presence of triethylamine with ethanol as the solvent, and the resulting compound **4** was purified by filtration through a short silica gel column (10 g scale, 70 % with 15 % of unreacted 5-amino-4,6-dichloropyrimidine being recovered). Cyclization of compound **4** was achieved using Montgomery's procedure to give compound **5**, and the 6-amino group was introduced under careful amination reaction conditions in the presence of the phosphonate diethyl ester moiety to afford PMEA diethyl ester (**6**, 80 %, two steps). Final deprotection of PMEA diethyl ester was conducted following Holy's original TMSBr reaction conditions[1a] to give PMEA (**1**, 95 %).

In summary a new regio-defined synthesis of PMEA was developed employing regioselective introduction of the phosphonomethoxyethyl moiety to a pyrimidine nucleus,

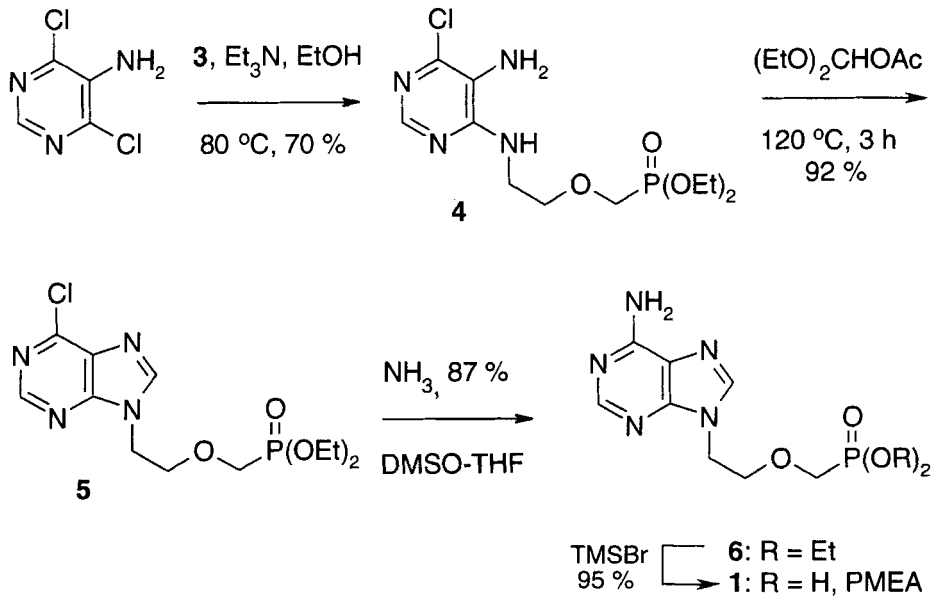


Scheme 1



Scheme 2

and subsequent cyclization to construct the purine ring system. This synthesis required only short silica column filtration as the purification method, and the crystallization of PMEA diethyl ester was facilitated by the absence of the N-7 alkylated regio isomer. The overall yield[5] for the synthesis of PMEA is 35 % from the commercially available chloride. Amine **3** was obtained as a liquid and it can potentially be purified via distillation which should allow generation of amine **3** in large quantities without chromatography, therefore it is noteworthy that overall yield is higher from 5-amino-4,6-dichloropyrimidine (53 %).



Scheme 3

The easy accessibility of compound **5** should also allow rapid synthesis of 6-substituted PMEA analogs, some of which have been reported to exhibit potent inhibitory effects of murine lymphocyte proliferation.[6]

EXPERIMENTAL SECTION

General. Glassware was oven dried (125 °C, 12 h) and all reactions were performed with magnetic stirring under dry nitrogen. Ethanol and DMF were dried over activated 4 Å molecular sieves. Triethylamine was dried over sodium hydroxide. 2-Chloroethyl chloromethyl ether was purchased from TCI America, 5-Amino-4,6-dichloropyrimidine was purchased from Aldrich and these materials were used as received. Silica gel filtrations were done with the aid of vacuum using 60 Å silica gel (230 - 400 mesh). Silica gel GF analytical TLC plates (0.25 mm) were purchased from VWR and were visualized at 254 nM or with ninhydrin stain purchased from Aldrich. Melting points were uncorrected. ^{1}H NMR spectra were obtained at 200 MHz, and J values are given in Hertz. Electrospray mass spectra were obtained from Mass Consortium, San Diego, CA.

5-Amino-4-chloro-6-(diethylphophonomethoxyethylamino)pyrimidine (4) A solution of diethyl 2-chloroethoxymethylphosphonate (20 g, 86.79 mmol, 1.0 equiv) in anhydrous DMF (85 mL) was treated with potassium phthalimide (17.23 g, 93.02 mmol, 1.1 equiv) at 25 °C under nitrogen, and the resulting mixture was heated at 120 °C for 7 h. The cooled reaction mixture was concentrated and the residue was partitioned between EtOAc (250 mL) and saturated sodium bicarbonate (100 mL) + water (100 mL). The layers were separated, and the organic phase was washed with water (3 x 200 mL), brine (100 mL), dried ($MgSO_4$), and evaporated to give compound **2** as a yellow syrup (21.7 g, 73 %). ^1H NMR analysis confirmed it was the desired product.

A solution of compound **2** (21.7 g, 63.61 mmol, 1.0 equiv) in ethanol (200 mL) was treated with hydrazine (4.08 g, 127.22, 2.0 equiv), and the resulting solution was heated at reflux under nitrogen. After 1 h the reaction mixture (white solid formed) was cooled, diluted with EtOAc (300 mL), and filtered (washed with EtOAc, 3 x 20 mL). The filtrate was evaporated to dryness and the residue was diluted with CH_2Cl_2 (100 mL). The suspension was filtered (washed with CH_2Cl_2, 3 x 10 mL), and the filtrate was evaporated to give compound **3** as a clear light brown oil. ^1H NMR analysis confirmed it was the desired product.

A solution of compound **3** (63.61 mmol, 1.0 equiv), 5-amino-4,6-dichloropyrimidine (10.43 g, 63.61 mmol, 1.0 equiv), and triethylamine (7.72 g, 76.33 mmol, 1.2 equiv) in anhydrous ethanol (100 mL) was heated at reflux under nitrogen. After 20 h the cooled reaction mixture was concentrated in vacuo, and the residue was partitioned between CH_2Cl_2 (100 mL) and saturated sodium bicarbonate (50 mL) + water (50 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (5 x 50 mL). The combined organic extracts were dried ($MgSO_4$), and evaporated to give a yellow solid. The product was adsorbed onto silica gel (150 mL), loaded onto a short silica column (7 x 7 cm), and eluted with 50, 80, 100 % EtOAc-Hexane (1 l each, gradient) to give compound **4** as a yellow solid (14.12 g, 66 % for the two steps). ^1H NMR (200 MHz, $CDCl_3$) δ 7.96 (1H, s), 6.49 (2H, bs), 4.24-3.64 (11H, m), 1.37-1.30 (6H, m); Mass spectrum (electrospray) for $C_{11}H_{20}N_4O_4PCl$: *m/z* 339/341 (M + H).

6-Chloro-N^9-(2-diethylphosphonomethoxyethyl)purine (5). A suspension of compound **4** (9.38 g, 27.71 mmol, 1.0 equiv) in diethoxymethyl acetate (45

mL, 10 equiv) was heated at 120 °C under nitrogen for 3 h. The cooled reaction mixture was concentrated and the residue was adsorbed onto silica gel (200 mL), loaded onto a short silica column (7 x 9 cm), and eluted with EtOAc (3 x 1l), 5 % MeOH-CH_2Cl_2 (3 x 500 mL) to give compound **5** as a clear yellow oil (8.89 g, 92 %).^{1}H NMR (200 MHz, $CDCl_3$) δ 8.73 (1H, s), 8.28 (1H, s), 4.50 (2H, t, J = 4.8 Hz), 4.15-3.94 (6H, m), 3.77 (2H, d, J = 8.2 Hz), 1.28 (6H, t, J = 6.8 Hz); Mass spectrum (electrospray) for $C_{12}H_{18}N_4O_4PCl$: *m/z* 349/351 (M + H).

N^9-(2-diethylphosphonomethoxyethyl)adenine (6). A solution of compound **5** (1.51 g, 4.33 mmol, 1.0 equiv) in THF - DMSO (1:1, 20 mL) was cooled to -78 °C in a steel bomb, and treated with liquid ammonia (ca. 10 mL, excess). The bomb was sealed and stirred at 25 °C for 24 h. The reaction mixture was evaporated to dryness and purified by flash chromatography (SiO_2, 3 x 9 cm, 5 % MeOH-CH_2Cl_2) to give the desired product as a white solid (1.25 g, 87 %). mp 135 - 136 °C (white flakes, crystallized from EtOAc-EtOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.73 (1H, s), 8.28 (1H, s), 4.50 (2H, t, J = 4.8 Hz), 4.15-3.94 (6H, m), 3.77 (2H, d, J = 8.2 Hz), 1.28 (6H, t, J = 6.8 Hz); Mass spectrum (electrospray) for $C_{12}H_{20}N_5O_4P$: *m/z* 330 (M + H).

Anal. Calcd. for $C_{12}H_{20}N_5O_4P$: C: 43.77, H: 6.12, N: 21.27. Found: C: 43.67, H: 6.08, N: 20.98.

N^9-(2-phosphonomethoxyethyl)adenine (1). The reaction was conducted following Holy's procedure[1a] to give PMEA as a white powder. mp > 250 °C; ^{1}H NMR (200 MHz, D_2O - NaOD) δ 8.02 (1H, s), 7.95 (1H, s), 4.19 (2H, t, J = 4.8 Hz), 3.72 (2H, t, J = 4.8 Hz), 3.26 (2H, d, J = 8.4 Hz).

Anal. Calcd. for $C_8H_{12}N_5O_4P$ + 0.85 H_2O: C: 33.31, H: 4.79, N: 24.28. Found: C: 33.02, H: 4.73, N: 23.94.

ACKNOWLEDGEMENT

We wish to thank Drs. Mike Matelich and David Bullough for helpful discussions during the preparation of this manuscript.

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2. During our initial PMEA synthesis according to Holy's procedure,[1a] we experienced problem with the purification of PMEA diethyl ester. The reported crystallization protocol could not be reproduced in our hand. We speculated that the unreacted adenine and the presence of N-7 isomer could be hindering the product crystallization, which prompted us to look for alternative PMEA synthesis.

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Received 12/3/97
Accepted 3/6/98