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Green Synthesis Improvement of Tenofovir Disoproxil

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Polyethylene glycol, known as 'Green Chemical', is a catalyst for the synthesis of tenofovir disoproxil. Some technological parameters were discussed by adoptting *via* single-factor experiments. Through the catalytic reaction, not only tenofovir disoproxil yield was improved but also by-products was reduced obviously. The results showed that the optimal conditions were as follows: 0.6 equiv PEG-600, 4.0 equiv triethylamine, 6.0 equiv *N*-methyl-2-pyrrolidone and temperature at 50 °C for 16 h with a yield of 65.12 %.

Keywords: Polyethylene glycol, Tenofovir Disoproxil, Tenofovir, Alkylation.

INTRODUCTION

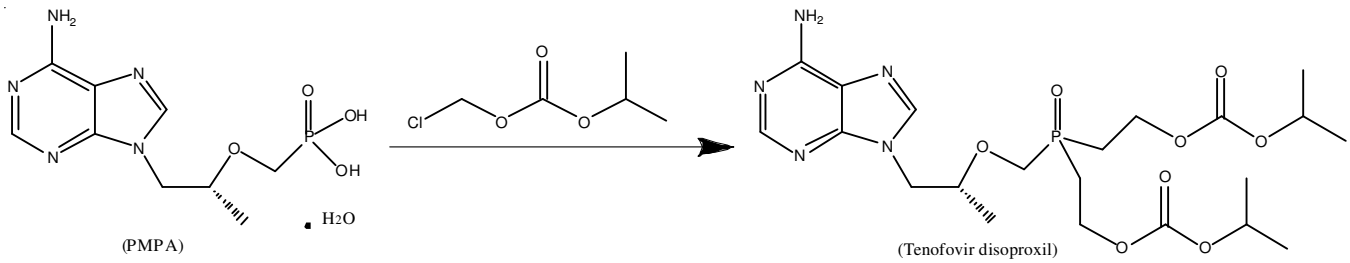
Tenofovir disoproxil (TD) is a key intermediate in the preparation of tenofovir disoproxil fumarate (TDF) which is a prodrug of tenofovir (known as PMPA)[1] and a nucleoside analogue reverse transcriptase inhibitor (nRTI) that is used to treat HIV/AIDS and hepatitis B.1[2]. PMPA was converted into tenofovir disoproxil based on promotting alkylation and chloromethyl isopropyl carbonate (CIC) was used to adopte as alkylation reagents.

However, the conversion of PMPA into tenofovir disoproxil with excess chloromethyl isopropyl carbonate is accompanied by the generation of some by-products[3]. Due to the hydrolysis of PMPA and its salts, the reaction must be run in a polar and aprotic solvent[4]. But chloromethyl isopropyl carbonate has poor solubility in the solvent. In order to increase the solubility of chloromethyl isopropyl carbonate and improve yield, we considered to add phase transfer catalyst in chemical reaction. Polyethylene glycol (PEG) has high thermal stability, low toxicity, difficult to volatile, non-flammable, low cost, *etc.*[5]. Now polyethylene glycol is widely used in organic synthesis reaction as a green solvent and phase transfer catalys[6].

In the light of the advantages and disadvantages of various phase transfer catalyst, polyethylene glycol was adopted as phase transfer catalyst in the experiment. *Via* singl-factor experiments and some technological parameters were discussed and the best reaction conditions were established.

EXPERIMENTAL

Polyethylene glycol was heated at 80 °C under vacuum for 0.5 h before use to remove traces of moisture. ^{1}H NMR spectra in $CDCl_3$ on a Bruker Avance DPX instrument (400 MHz). Tenofovir was purchased from Xian ShuaiDi biotechnology co., LTD. Polyethylene glycol , *N*-methyl-2-pyrrolidone, cyclohexane, triethylamine and ethyl acetate were purchased from Chengdu kelon chemical reagent co., Ltd All organic reagents and solvents were of reagent grade purity. Products were characterized by comparison of their physical data, High performance liquid chromatography and ^{1}H NMR spectra with known samples.



(PMPA) (Tenofovir disoproxil)

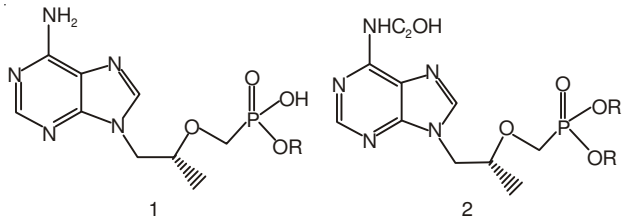
Preparation of tenofovir disoproxil: PMPA (25 g), dry *N*-methyl-2-pyrrolidone (NMP, 6.0 equiv, 50 mL) and cyclohexane (120 mL) were charged to a reactor vessel and agitated with a magnetic stirrer (500 rpm) at 50 °C. PMPA was dried in advance at about 80 °C under vacuum for 24 h. Cyclohexane was removed in advance by distillation twice under reduced pressure at 50 °C. When the reaction was cooled to 45 °C, triethylamine (35.2 g, 4.0 equiv) and PEG-600 (31.3 g, 0.6 equiv, water content < 1 %) were added. Precipitation of triethylamine salts of PMPA was caused. The reaction mixture was heated to 50 °C and chloromethyl isopropyl carbonate (66.4 g, 5.0 equiv) was added at this temperature. The reaction was monitored for completion at 16 h and the initially thick suspension was almost clear. The reaction samples were analyzed by HPLC (purity 88.7 %) which was performed on a liquid chromatograph (Shimadzu, Japan, 10 Atvp) with Shimadzu DAD detectoran and ACQUITY BEH C18 column (2.1 mm × 150 mm, 1.7 um). The binary mobile phase was composed of water and methanol in proportion 40/60 (v/v). The flow rate was 0.6 mL/min.

Product isolation: The reaction mixture was cooled to 25-30 °C and ethyl acetate (250 mL) and water (120 mL) were added. The mixture was stirred for 10 min and phases were clearly separated from each other. The aqueous phase was successively separated twice with ethyl acetate (70 mL each). The organic phases were combined and washed three times with water (150 mL each) and aqueous solution of 10 % NaCl. The organic phase was dried with solid sodium sulfate and evaporated in vacuum. The residue was cooled at 5 °C and provided solid mass of 29.4 g (65.12 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz), δ: 8.38 (s, 1H, N = CHN), 7.94 (s, 1H, N = CHN), 5.54 (m, 4H, 2 × OCH_2O), 4.86-4.91 [m, 2H, 2 × $CH(CH_3)_2$], 4.35 (dd, *J* = 3.0,13.8 Hz,1H, NCH_2), 4.23 (dd, *J* = 7.1, 14.0 H, 1H, NCH_2), 3.86-3.90 (m, 2H, OCH_2P), 3.76-3.79 (dd, *J* = 9.2, 13.2 Hz, 1H, CH_2CHO), 1.31 [d, *J* = 14.3 Hz, 12H, 2 × CH $(CH_3)_2$], 1.26 (d, *J* = 7. 1 Hz, 3H, CH_3).

RESULTS AND DISCUSSION

Several key impurities included reaction intermediate (1) and *N*-hydroxymethylated impurities (2), which leads to reduction of product[7]. It might be that *N*-methyl-2-pyrrolidone brought water into the reaction and the presence of triethylamine produced a basic water layer (pH 10) to promote reaction hydrolysis. In addition, chloromethyl isopropyl carbonate is sparingly soluble in the polar and aprotic solvent.

Therefore, improving conversion fully and product stability must be intensive to investigate. Addition of phase-transfer reagents were identified to affect mainly tenofovir disoproxil yield. Other critical processing parameters include base concentration, reaction concentration, reaction mixture and reaction temperature.



Selection of base: Bases included both inorganic bases and organic bases. Inorganic bases produced insoluble phosphonic acid salts, which affect the tenofovir disoproxil yield[7]. Therefore, several organic bases were selected and compared about the affection of the yield, such as triethylamine (TEA), *N*,*N*-diisopropylethylamine (*N*,*N*- DEM), tetramethylguanidine (TMG) and 2,6-lutidine. As shown in Fig. 1, triethylamine provided the best performance among organic bases in the reaction.

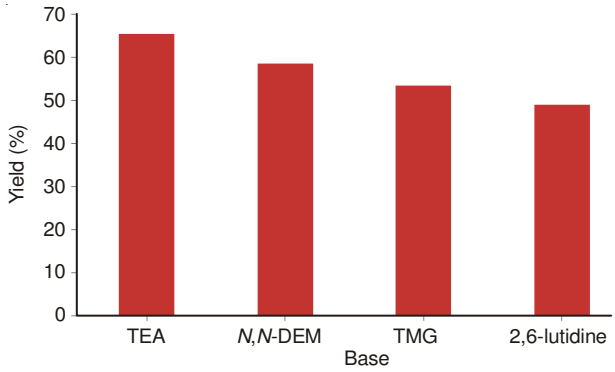


Fig. 1. Selection of base. PMPA, 25 g; PEG-600, 0.6 equiv; *N*-methyl-2-pyrrolidone, 6.0 equiv; temperature, 50 °C reaction time, 16 h

Selection of triethylamine concentration: As depicted in Fig. 2, with the increase of triethylamine concentration, the yield was improved continuously. When the base exceeded 4.0 equiv, the yield was almost no obvious change. By considering the experiment economic, 4.0 equiv triethylamine was adopted.

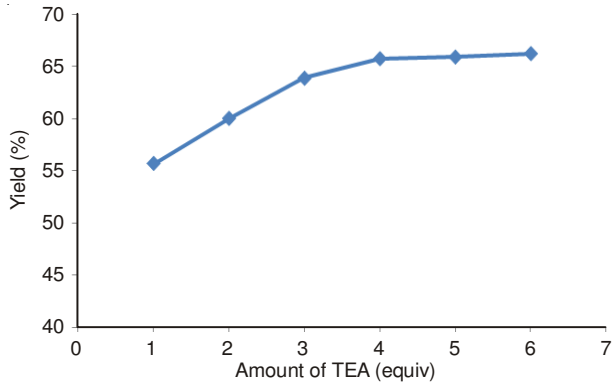


Fig. 2. Selection of triethylamine parameter. PMPA, 25 g; PEG-600, 0.6 equiv; *N*-methyl-2-pyrrolidone, 6.0 equiv; temperature, 50 °C; reaction time, 16 h

Selection of polyethylene glycol type: The triethylamine salt of PMPA originally formed was sparingly soluble in *N*-methyl-2-pyrrolidone and leaded to heterogeneous in the reaction. Thus, a phase-transfer catalyst was adopted to enhance the dissolution rate and conversion in the reaction. In order to identify this, a number of polyethylene glycol additives were tested in the reaction. PEG600 was best among the catalyst in the experiment (Fig. 3).

Selection of PEG 600 concentration: As illustrated by the results in Fig. 4, when PEG600 exceeded 0.6 equiv, with the increase of PEG 600 concentration, the tenofovir disoproxil yield has little change. According to the experimental economics and security, 0.6 equiv PEG 600 was adopted.

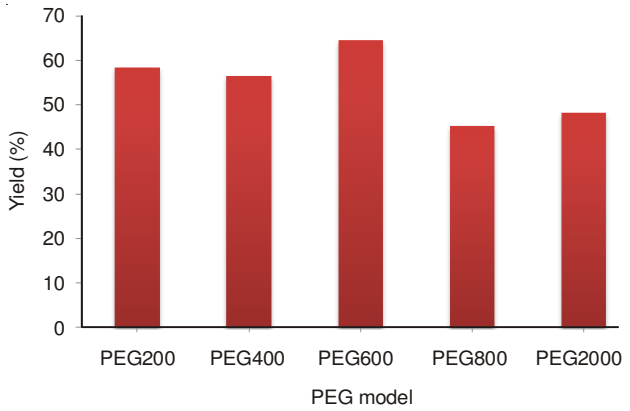


Fig. 3. Selection of polyethylene glycol model. PMPA, 25g; triethylamine, 4.0 equiv; *N*-methyl-2-pyrrolidone, 6.0 equiv; temperature, 50 °C; reaction time, 16 h

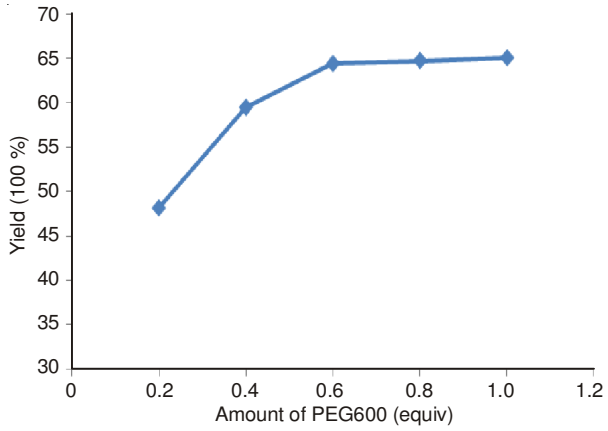


Fig. 4. Selection of the PEG600 parameter. PMPA, 25 g; triethylamine, 4.0 equiv; *N*-methyl-2-pyrrolidone, 6.0 equiv; temperature, 50 °C; reaction time, 16 h

Temperature: The tenofovir disoproxil yield was improved continuously with the increase of reaction temperature. When reaction temperature reached 50 °C, the tenofovir disoproxil yield was maximum (63.08 %). But with the reaction temperature rise, the tenofovir disoproxil yield began to reduced slowly. It might be the increase of reaction by-products. Thus, temperature 50 °C was adopted (Fig. 5).

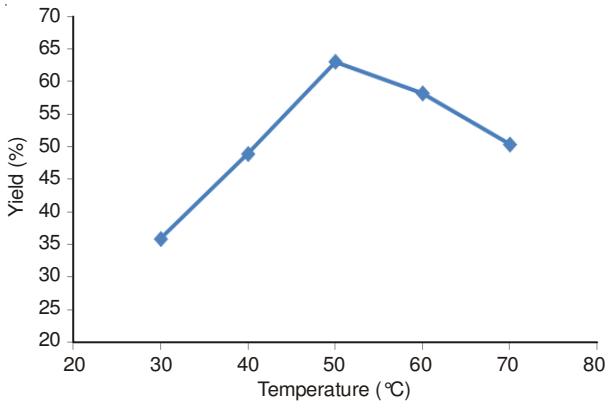


Fig. 5. Selection of temperature. PMPA, 25 g; PEG-600, 0.6 equiv; *N*-methyl-2-pyrrolidone, 6.0 equiv; triethylamine, 4.0 equiv; reaction time, 16 h

Solvent: A polar aprotic solvent is necessary for the alkylation reaction, as a solvent of the starting material[4]. In order to improve the yield, A cursory examination of several polar aprotic solvent selection was studied. As Fig. 6 shown *N*-methyl-2-pyrrolidone was confirmed as the optimal solvent for the reaction.

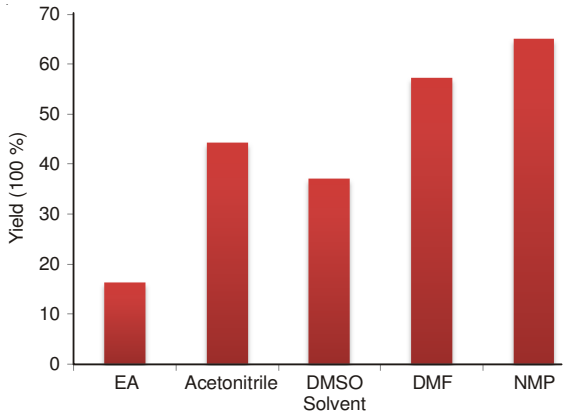


Fig. 6. Selection of solvent. PMPA, 25 g; PEG-600, 0.6 equiv; triethylamine, 4.0 equiv; temperature, 50 °C; reaction time, 16 h

***N*-Methyl-2-pyrrolidone concentration:** As depicted in Fig. 7, when *N*-methyl-2-pyrrolidone exceeded 6.0 equiv, with the increase of *N*-methyl-2-pyrrolidone concentration, the tenofovir disoproxil yield has almost little change. According to the experimental economics and security, 6.0 equiv *N*-methyl-2-pyrrolidone was adopted as the optimum.

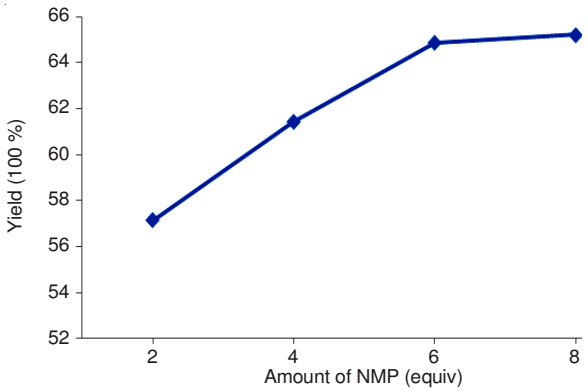


Fig. 7. Investigate of solvent consumption. PMPA, 25 g; PEG-600, 0.6 equiv; triethylamine, 4.0 equiv; temperature, 50 °C; reaction time, 16 h

Reaction time: As illustrated by the results in Fig. 8, with the increase of reaction time, the tenofovir disoproxil yield

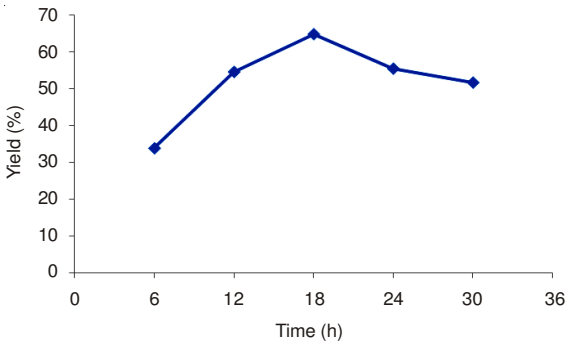


Fig. 8. Selection of reaction time. PMPA, 25 g; PEG-600, 0.6 equiv; triethylamine, 4.0 equiv; temperature, 50 °C; *N*-methyl-2-pyrrolidone, 6.0 equiv

rise initially soon. When the reaction time was 16 h, the tenofovir disoproxil yield was maximum (64.72 %). But with the increase of reaction time, the tenofovir disoproxil yield was reduced slowly. It maight be the increase of reaction by-products. The reaction time 16 h was adopted as the optimum.

Conclusion

In the presence of PEG600 as phase-transfer catalyst, the results of study show that Tenofovir disoproxil could be obtained in high yields. In addition, polyethylene glycols are welcome phase-transfer catalyst, particularly in base conditions. The optimal reaction conditions were: 0.6 equiv PEG-600, 4.0 equiv triethylamine, 6.0 equiv *N*-methyl-2-pyrrolidone, reaction temperature of 50 °C and reaction time of 16 h. The yield of tenofovir disoproxil was 65.12 %.

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