Nature of Invention: Chemical molecule and synthesis route

Applicant: PetroProtons Pvt. Ltd.

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Chemical Formula: $(C_2H_4O)_nCH_4O$

Chemical Name: Methoxy polyethylene glycol (mPEG)

Preparation of MPEG at Lab Scale –

Polyethylene glycol monomethyl ether (general term for family of mPEGs) can be produced by anionic ring opening polymerization of ethylene oxide using a microflow system with a tubular reactor.

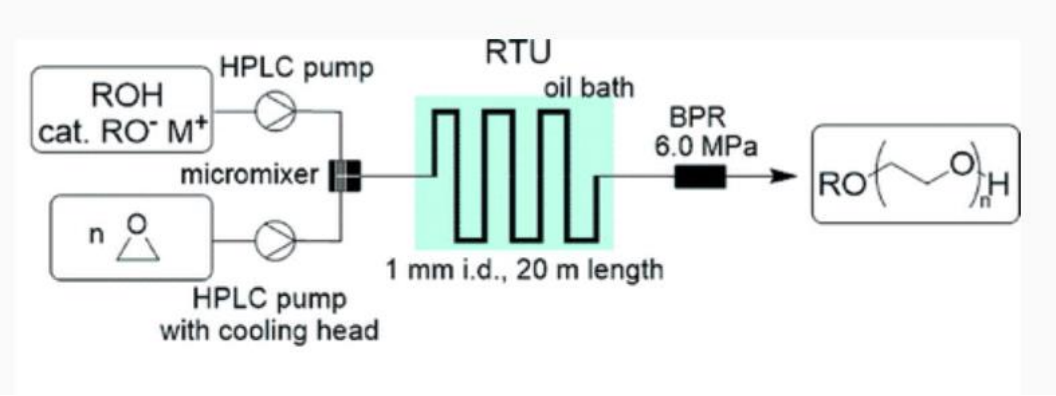
Reactants Needed - Methanol and Ethylene oxide.

Catalysts Used – Sodium methoxide (MeONa)

Solvent Used - Methanol

Reaction Conditions – 30 min, 6 MPa, 150 °C

Monoalkyl-ether terminated PEGs were obtained within 30 mins. of residence time by the microfluidic system when using alkoxy anions as an initiator. For obtaining high yields, use of a suitable micromixer is important.



Reaction steps are as follows for the “flow” process used–

1. Place methanol (9.57 g) and 28% MeONa in MeOH (0.973 g) in a 20 mL flask under argon atmosphere and pump (flow rate = 0.02 mL/min) by a HPLC pump.
2. Supply the ethylene oxide (flow rate = 0.50 mL/min) through a HPLC pump under pressurized N_2 atmosphere (0.4 MPa).
3. Mix the solution and EO using a β150 micromixer.

4. Pass the mixture through a stainless-steel tube (1.0 mm inner diameter, 20 m long) as a residence time unit (RTU) for 30 min residence time, under 150 °C.
5. Add methanol (1.0 mL/min) through the T-shaped mixer (500 µm i.d) and connect a pressure relief valve (6 MPa) to the outlet.
6. Collect the reaction mixture for 30 min in glass flask and filter through an alumina silica-gel pad and wash with methanol.
7. Concentrate the solution to afford the product.

%Yield and Purity -

The Yield Percentage depends on a number of factors as depicted below[1]:

a. The % Yield varied with different micromixers and hence choosing an appropriate micromixer is important. β150 micromixer gives the maximum yield of 97%. Table depicting reaction of EO with methanol for mPEG having M_n 400 (calc.) using several micromixers:

Entry	Micromixer	Yield (%)	M_n[b)]	PDI[b)]
1	α600	76	600	1.41
2	α200	95	120	1.88
3	β150	97	320	1.62

b. The Yield% also depends on the type of system(flow and batch) and on the catalysts and catalyst mol% used as depicted below for the synthesis of mPEG having M_n (calc.) of 1000:

Entry	System	Catalyst (mol%)	Temp (°C)	Time (min)	Yield (%)	M_n[b)]	PDI[b)]
1	flow	MeONa(1)	150	30	45	450	1.99
2	flow	MeONa(2)	150	30	96	1070	1.33
3	flow	MeONa(3)	150	30	99	920	1.14
4	flow	MeONa(3)	160	30	99	1130	1.24
5	batch[c)]	MeONa(3)	150	300	90	820	1.18
6	flow	MeOK(2)	150	20	96	1140	1.29
7	flow	MeOK(2)	120	30	90	940	1.16
8	flow	MeOCs(2)	120	30	93	920	1.12

Concentration of the final solution gave mPEG in a 99% yield.

Purity [2]:

Since living anionic polymerization can be killed by protonation or reactions with unexpected terminating species such as trace of moisture, oxygen, or other impurities, the mPEG obtained contains a considerable amount of diol PEG because of the

presence of trace amount of water during polymerization. Moreover, it has been reported that decomposition reaction of mPEG might occur as well to produce a low molecular vinyl compound depending on the reaction temperature and the amount of catalyst.

Normally, low molecular weight mPEG (Mn = 2–5 kDa) without diol PEG, whose purity was 96.8%–99.4%, could be prepared in a sealed glass ampoule by the anionic polymerization of ethylene oxide at 70°C, in which alcoholate of methyl ether of Tri ethylene glycol acted as the initiating centre.

On the other way, the purity of mPEG (Mn = 2–5 kDa) could rise from 75% to around 99% through the silica gel column chromatographic purification of commercial mPEG.

Recently, one of the most common used initiator systems in anionic polymerization, potassium naphthalene, was used in the synthesis of some heterotelechelic poly (ethylene glycol) derivatives by anionic solution polymerization. With the new initiating system, anionic solution homopolymerization of EO at ambient temperature under normal pressure led to good yields of mPEG almost without diol PEG.

Purification using Chromatographic Approach [3]:

A chromatographic approach to purify polyethylene glycol derivatives at a preparative scale which is based on the polystyrene-divinylbenzene beads with ethanol/water as eluants. The validity of this method was verified with the reaction mixture of mPEG-Glu and mPEG propionaldehyde diethylacetal (ALD-PEG) as the model. The target products were one-step achieved with the purity of >99% on the polymer resins column at gram scale.

Alternate Synthesis Route –

Preparation using Macrocyclization of Oligo (ethylene glycols)[4].

Reactants - 3,6,9,12,15,18,21,24-Octaoxapentacosan-1-ol

1,3-Dioxa-2-thiacyclotetradecane, 2-oxide

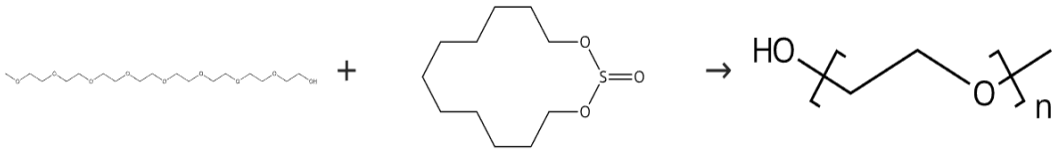
Reagents - Sodium hydride, Sulfuric acid, Sodium bicarbonate

Solvents used – Water, Tetrahydrofuran

Reaction steps are as follows ->

1. Add a solution of Octa(ethylene glycol) monomethyl ether (12.02 mmol) in THF (20 mL) to a suspension of NaH (0.72 g, 60% dispersed in mineral oil, 18.03 mmol, in 80 mL THF) at 0 °C, under the atmosphere of Argon.

2. Stir the reaction mixture for 30 minutes.
3. Add a solution of MCS (18.03 mmol) in THF (50 mL) at this temperature.
4. Stir the resulting mixture for 5 hours at room temperature.
5. Concentrate the resulting mixture under vacuum.
6. Dissolve the resulting residue in water (50 mL).
7. Extract the resulting residue with CH_2Cl_2 (50 mL, three times). Concentrate the water layer.
8. Dissolve the water layer in THF (100 mL). Add water (0.43 mL, 24.04 mmol) and H_2SO_4 (0.60 mL, 12.02 mmol) to the reaction mixture.
9. Stir the resulting mixture for 3 hours at room temperature.
10. Quench the reaction mixture with saturated $NaHCO_3$ solution and extract the reaction mixture with CH_2Cl_2.
11. Combine the organic layers.
12. Dry the organic layers over anhydrous Na_2SO_4.
13. Concentrate the organic layers under vacuum.
14. Purify the organic layers flash chromatography on silica gel with MeOH/CH_2Cl_2 (1/30) as eluents.



%Yield and Purity -

The %Yield of the reaction is 85%.

As for the purification, all the intermediates can be purified by flash chromatography on silica gel with methanol and CH_2Cl_2 as eluents.

Most impurities can be removed by selectively extracting sodium sulfate intermediates into water and leaving most impurities in the organic phase. The rest impurities can be easily removed by flash chromatography after hydrolysis of the intermediates. In this way, excess MCS in this reaction were also recovered. With this strategy, many biopharmaceutically useful M-PEGs and derivatives which are difficult to synthesize with established methods can be conveniently prepared within minimal synthetic steps from the corresponding OEGs and MCS.

References:

[1] Efficient Anionic Ring Opening Polymerization of Ethylene Oxide under Microfluidic Conditions | Bulletin of the Chemical Society of Japan (csj.jp)

[2] Synthesis of monomethoxy poly(ethylene glycol) without diol poly(ethylene glycol) - Zhang - 2007 - Journal of Applied Polymer Science - Wiley Online Library

[3] Preparative purification of polyethylene glycol derivatives with polystyrene-divinylbenzene beads as chromatographic packing - ScienceDirect

[4] Highly Efficient Synthesis of Monodisperse Poly(ethylene glycols) and Derivatives through Macrocyclization of Oligo(ethylene glycols) - Zhang - 2015 - Angewandte Chemie International Edition - Wiley Online Library

List the contributions of each author:

- Author 1 and 3 carried out the literature search for method 1. They found out the reaction steps along with the product yield depending on different factors.
- Author 1 and 2 found out literature on the different ways to purify the product as well as the entry on Purification using Chromatographic Approach to achieve desired product purity.
- Author 1 and 2 carried out the search for the alternate method along with the yield and purification.

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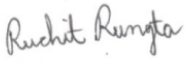
Author 1: Ruchit Rungta	210878	
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