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## A green chemistry approach for the stepwise synthesis of mono-disperse PEGs

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The Problem: Polyethylene glycol (PEG) and derivatives have wide applications including as linkers in organic synthesis, as coating L agents to stabilize nanoparticles, and as drug PEGylation agents. They are mostly synthesized by random polymerization of ethylene oxide, which gives complex mixtures of multi-disperse PEGs. However, for many applications, the purer mono-disperse PEGs are needed. Currently, short mono-disperse PEGs (less than 50 ethylene glycol units) can be synthesized via stepwise organic synthesis. However, the methods require multiple chromatographies, generate large volumes of harmful wastes and are highly expensive. Purpose: The aim of the project is to develop a green chemistry approach for the stepwise synthesis of mono-disperse short PEGs. Methodology: A solid phase synthesis technology has been developed. The cheap tetraethylene glycol monomer, which contains a tosyl group at one end and a DMTr group at the other, was added to the Wang resin repeatedly. Each addition consisted of three steps - deprotection, deprotonation, and coupling. For all steps, excess reagents and other impurities were simply washed away leaving only the desired product on the resin. There was no need of reaction workout and chromatography. Findings: mono-disperse PEGs with 12 ethylene glycol units or less could be reliably synthesized using the technology. Longer PEGs can be synthesized but more research is needed. The PEGs and their derivatives are highly pure as determined by MS analysis. The yields were quantitative. Conclusion & Significance: A greener technology for the synthesis of PEGs have been successfully developed. The method avoids tedious reaction workout and chromatography after each step of a multiple step process. It drastically reduces the use of harmful solvents and other materials. We expect that the PEGs synthesized with the new technology will be significantly cheaper and purer, and therefore many areas will benefit from the new technology.

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