Title: Minimizing HCN in DIC/Oxyma mediated amide bond forming reactions

Name: Marion ERNY
PolyPeptide Group, France

Abstract:
Diisopropylcarbodiimide (DIC) and ethyl (hydroxyimino)cyanoacetate (Oxyma) are the most widely used coupling reagents in peptide synthesis. McFarland et al. recently discovered the reaction between DIC and Oxyma, which forms hydrogen cyanide (HCN). Controling the formation of toxic side products is crucial for advancing protocols for safer and environmentally sensible peptide synthesis. HCN is formed during amino acid activation but also during amide bond forming reactions mediated by DIC and Oxyma. The linear DIC/Oxyma adduct rearranges to form the oxadiazole and HCN in a 1:1 ratio. This ratio changes depending on the concentration of DIC and Oxyma. At low concentration, the majority of HCN formed stays in the solution but not at higher concentration. We have shown that the amount of HCN can be minimized in two ways: by quenching the formed HCN and by decreasing HCN formation. First, the concept of in situ scavenging of the HCN formed was evaluated by using dimethyl trisulfide (DMTS), which transforms the HCN into the less hazardous methyl thiocyanate. DMTS can be used as HCN scavenger during the amination without disturbing the reaction. Secondly, screening different solvents allowed to replace *N*,*N*-dimethylformamide (DMF) with a greener solvent mixture such as *N*-Butyl-2-pyrrolidone (NBP)/ethyl acetate (EtOAc) (1:4). In those conditions amidation kinetic rates are increased and HCN amount is reduced, because the linear DIC/Oxyma adduct is more stable and therefore HCN formation is minimized.

Biography
Marion ERNY studied in Rennes (France) and Stuttgart (Germany), where she received respectively a degree in engineering and an MSc in chemistry in 2017. After a first professional experience in Germany, she joined the Innovation team of PolyPeptide Group as R&D Chemical Engineer in 2019. She is currently performing a PhD thesis at PolyPeptide, under the supervision of Dr. Frédéric Bihel (University of Strasbourg) and Dr. Olivier Ludemann-Hombourger (PolyPeptide Group). She is working on the development of green strategies for peptide manufacturing.

Presenting author details
Full name: Marion ERNY
Contact number: -
Twitter account: -
Linked In account: https://fr.linkedin.com/in/marion-erny-27997283
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