Water-based amide coupling with sustainable xylose acetals as co-solvents: A novel organic base-free strategy

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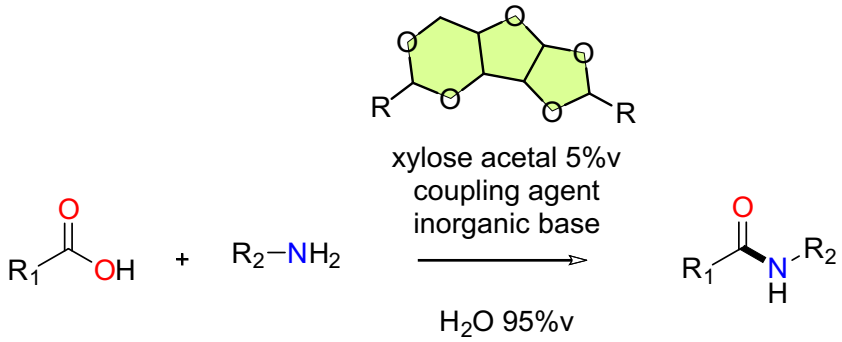
Amide bond formation is one of the most fundamental and widely used chemical transformations, playing a crucial role in the synthesis of pharmaceuticals, agrochemicals, and bulk chemicals. Despite its industrial significance, traditional amide coupling methodologies often require highly polar, petroleum-derived solvents such as N,N-dimethylformamide (DMF), acetonitrile, or N-methyl-2-pyrrolidone (NMP) to efficiently solubilize polar coupling reagents,[1] which are essential for activating carboxylic acids toward nucleophilic attack by amines. These solvents are not only derived from non-renewable resources but are also associated with significant environmental and human health concerns, including reprotoxicity.

To address these issues, aqueous reaction media supplemented with surfactants have been explored as a more sustainable alternative. However, these methodologies still rely on toxic and hazardous non-renewable organic bases such as pyridine, 2,6-lutidine, or triethylamine, which are often used in excess and, in turn, act as co-solvents.[2,3] A major challenge in developing greener alternatives lies in maintaining efficient solubilization of all reagents in a strictly aqueous medium while ensuring high reactivity and selectivity. Inorganic bases offer a more sustainable alternative, yet they often lead to lower reactivity and reduced selectivity in amide bond formation due to their weaker solubilization and buffering capabilities.



This work presents a novel organic base-free amide coupling strategy that leverages biomass-derived xylose acetals as key additives.[4] By utilizing these renewable sugar-based compounds, we aim to improve the solubility and reactivity of coupling agents in aqueous media, thereby reducing reliance on hazardous polar aprotic solvents and organic bases. Additionally, xylose acetals play a crucial role in counterbalancing the intrinsic lower reactivity and selectivity induced by inorganic bases, offering an efficient and more sustainable approach to amide bond formation.

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[3] S. Sharma, N. W. Buchbinder, W. M. Braje and S. Handa, *Org. Lett.*, **2020**, *22*, 5737–5740.
[4] A. O. Komarova, C. M. Warne, H. Pétremand, L. König-Mattern, J. Stöckelmaier, C. Oostenbrink, G. M. Guebitz, J. Luterbacher and A. Pellis, *ChemSusChem*, **2024**, e202401877.