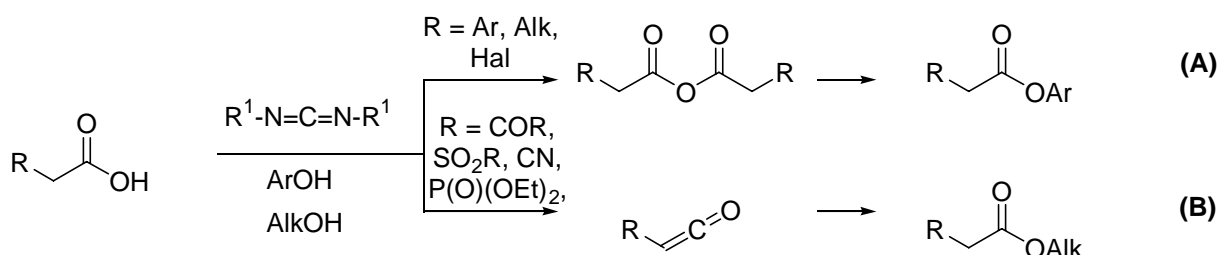


Chemoselective Esterification through Carbodiimide Couplings

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The reactivity in the carbodiimide driven esterifications of carboxylic acids was investigated by competition kinetics.¹ The chemoselectivity of the reaction is determined by the electronic properties of the substituents in the alpha position to the carboxylic group.



Carboxylic acids possessing alkyl, aryl, or halogen substituents in the alpha position react with O-, and S-nucleophiles with reaction rates increasing with the acidity of nucleophile (pathway **A**). Phenols and thiols can be acylated chemoselectively in the presence of aliphatic hydroxy groups. With the use of water-soluble carbodiimide the acylation of acidic phenols can be done in water solutions. The mechanism of the esterification involves the formation of a symmetric anhydride on the first stage of the reaction, followed by a nucleophilic attack of a phenolate anion on the symmetric anhydride and the conversion of the released carboxylic acid back into a symmetric anhydride.

Carboxylic acids possessing strong electron-withdrawing groups in the alpha position upon reaction with a carbodiimide undergo elimination producing the corresponding ketenes (pathway **B**). The resulting ketene intermediates were found to be highly efficient species capable of acylating a variety of aliphatic alcohols including chemically sensitive tertiary alcohols that cannot be acylated by conventional reagents. The chemoselectivity in the acylation through ketene intermediates is opposite to the esterification through pathway **A**, enabling the selective acylation of aliphatic hydroxy groups in the presence of aromatic ones.

¹ (a) Nahmany, M.; Melman, A. *Org. Lett.* **2001**, *3*, 3733-3735. (b) Shelkov, R.; Nahmany, M.; Melman, A.; *J. Org. Chem.* **2002**, *67*, 8975-8982. (c) Shelkov, R. Nahmany, M. Melman, A. *Org. & Biomol. Chem.*, *in press*.