# Category

**Innovative Drug** Discovery and Development

#### **Key words**

homologation carboxylic acids radical decarboxylation one-pot reaction



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Homologation of Carboxylic Acids Using a Radical-Polar Conjunctive Reagent J. Am. Chem. Soc. 2024, 146, 32919-32924, DOI: 10.1021/jacs.4c13687

# One-Pot Homologation of Aliphatic Carboxylic Acids

### Arndt-Eistert homologation:

# Alexanian's one-pot homologation of carboxylic acids:

### Examples of homologated drugs and natural products:

**Significance:** Carboxylic acids are omnipresent, decorating natural products as well as drug and building block libraries. They are involved in the most fundamental and well-developed reactions, such as the amide or ester bond coupling. In contrast, a simple one-carbon extension of carboxylic acids remains a challenging three-step transformation (Arndt-Eistert reaction). In collaboration with Abbvie, Alexanian's group reports a novel one-pot homologation of aliphatic carboxylic acids to form the corresponding one-carbon-extended carboxylic acid derivatives. The new methodology is operationally simpler and safer than the Arndt–Eistert procedure.

**Comment:** The Arndt–Eistert homologation strategy is based on the stereospecific Wolff rearrangement. Conceptually independent, Alexanian's approach relies on a HAT-induced radical decarboxylation (mediated by 2), followed by a diastereoselective radical capture with the twocarbon unit 1, to form activated carboxylic acid derivative 3 (an acyl phosphonate). Subsequent capture by a nucleophile in one pot furnishes the homologated products. However, whereas the Arndt-Eistert method is precedented for both aliphatic and aromatic carboxylic acids, the authors of this manuscript do not comment on the reaction outcomes with aromatic carboxylic acids.

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