Process Development of an Energetic Bromoacetylene and Kilogram-Scale Production of LpxC Inhibitor ACT-1003-3570

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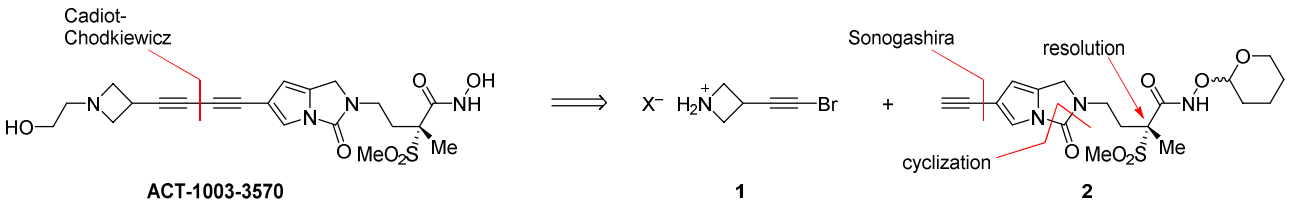

During the anti-infective program at Idorsia, LpxC inhibitor ACT-1003-3570 was identified as a potential agent against Gram-negative bacteria.[1] It was envisioned to form its unusual 1,3-butadiyne structure through Cadiot-Chodkiewicz coupling of a suitable bromoalkyne precursor **1** with primary alkyne **2**.[2] The route used in the multi-kilogram production of **2** encompassed chiral resolution by crystallization, cyclization to construct the pyrroloimidazolone core, and Sonogashira coupling. This set the stage for the Cadiot-Chodkiewicz coupling and the final steps towards kilogram quantities of the API. On the side of bromoalkyne **1**, a safe and scalable synthesis was developed at Dottikon. Highlights included an iron-catalyzed substitution with an alkynyl-Grignard reagent,[3] as well as selection of a suitable counterion X^- in view of the energetic properties and quality aspects of **1**.[4]

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[2] P. Cadiot, W. Chodkiewicz, in *Chemistry of Acetylenes*, H. G. Viehe, Ed.; Marcel Dekker: New York, **1969**; pp 597−647.
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