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Topoisomerase Inhibitors Addressing Fluoroquinolone Resistance in Gram-Negative Bacteria
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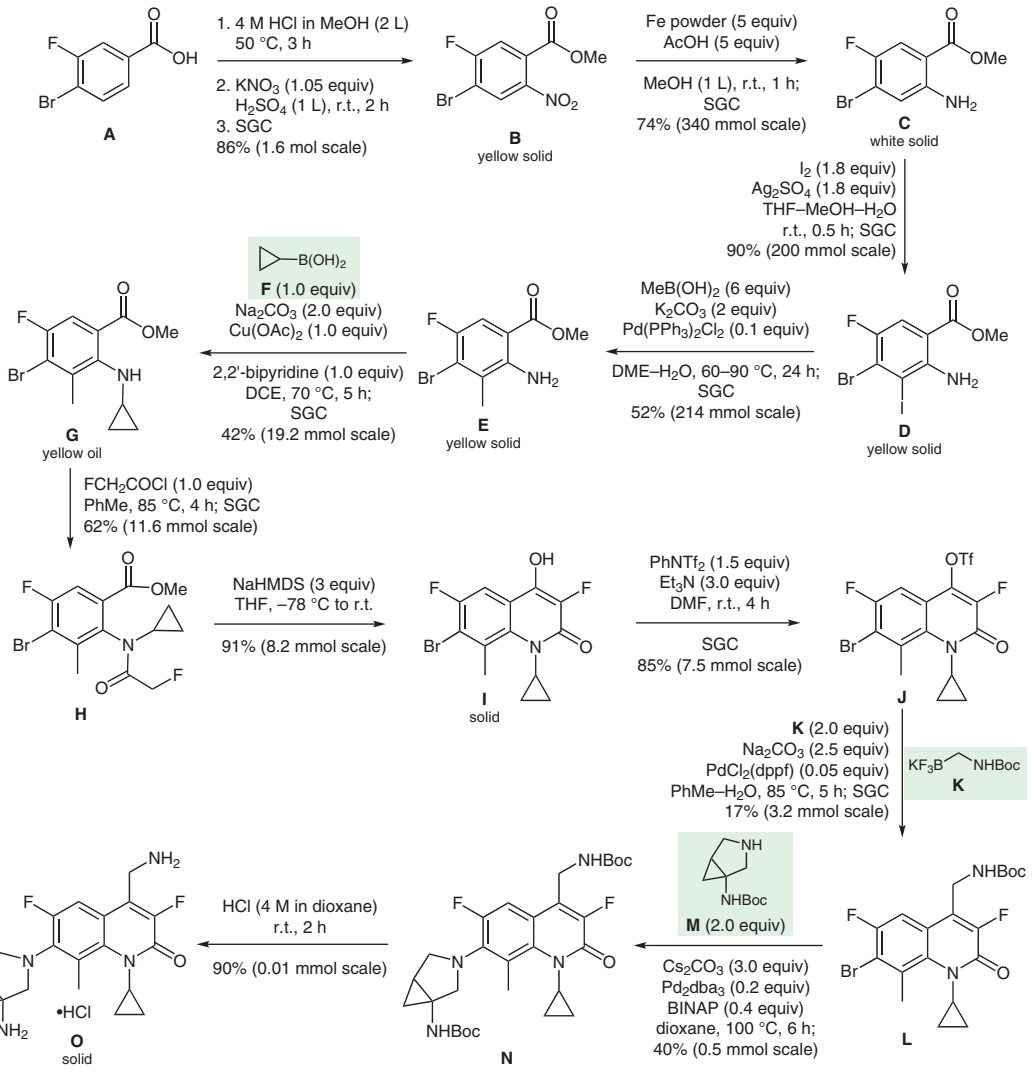
Synthesis of 4-(Aminomethyl)quinolin-2(1*H*)-ones



Significance: Compound **O** is one of a series of 4-(aminomethyl)quinolin-2(1*H*)-ones that inhibits bacterial DNA gyrase and topoisomerase IV, and displays potent activity against ciprofloxacin-resistant Gram-negative pathogens. Unfortunately, a number of in vitro safety issues were identified that, together with severe loss of antibacterial potency at pH 5.8, led to termination of the project.

Comment: Noteworthy steps in the synthesis of **O** are (1) the appendage of the cyclopropyl ring to the aniline via a Chan–Lam coupling; (2) construction of the quinolin-2(1*H*)-one core by base-mediated Claisen condensation (**H** → **I**); appendage of the aminomethyl group via Suzuki reaction (**J** → **L**); and Buchwald–Hartwig coupling of the pyrrolidine fragment **M** and enol triflate **J**.

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Category

Synthesis of Natural Products and Potential Drugs

Key words

topisomerase IV inhibitor

DNA gyrase inhibitor

fluoroquinolones

Chan–Lam coupling

Suzuki coupling

Buchwald–Hartwig coupling