One-Flow Synthesis of Heterocyclic Thioquinazolinones through Serial Microreactions with Two Organolithium Intermediates

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The synthesis of pharmaceutical compounds via short-lived intermediates in a microreactor is attractive, because of the fast flow and high throughput. Additionally, intermediates can be utilized sequentially to efficiently build up a library in a short time. Here we present an integrated microfluidic synthesis of biologically active thioquinazolinone libraries. Generation of o-lithiophenyl isothiocyanate and subsequent reaction with aryl isocyanate is optimized by controlling the residence time in the microreactor to 16 ms at room temperature. Various S-benzylic thioquinazolinone derivatives are synthesized within 10 s in high yields (75–98%) at room temperature. These three-step reactions involve two organolithium intermediates, an isothiocyanate-functionalized aryllithium intermediate, and a subsequent lithium thiolate intermediate. We also demonstrate the gram-scale synthesis of a multifunctionalized thioquinazolinone in the microfluidic device with a high yield (91%) and productivity(1.25 g in 5 min)