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Full Paper

Continuous Flow

Fast and Efficient Continuous Flow Method for the Synthesis of Ynones and Pyrazoles

Mohanraj Kandasamy,[a] Balaji Ganesan,[a] Min-Yuan Hung,[b] and Wei-Yu Lin*[a,c]

Abstract: In this study, we developed a convenient and efficient two-step method for the synthesis of ynones in a flow reactor, through the generation of lithium acetylide and its subsequent reactions with acid chlorides. Using this approach, we obtained the ynones in moderate to good yields at room temperature. Moreover, we transformed the ynones into pyrazole derivatives through coupling with hydrazines. This transition metal-free process, mild reaction conditions, and broad functional group tolerance are all attractive features in comparison with conventional bench-top methods.

Introduction

Ynones are used widely as building blocks in the synthesis of many bioactive heterocycles and natural products with pharmaceutical applications.[1] The three main routes[2] that are commonly used to synthesize ynones are (i) the addition of a metal acetylide (Li, Zn, Cu, Al, In, Sn, Ag, MgBr, Si)[3] to an anhydride, aldehyde, or acyl chloride; (ii) the transition metal–catalyzed cross-coupling of an aryl halide, carbon monoxide, and an alkyne;[4] and (iii) the direct oxidation of alkynes to ynones using SeO_2/TBHP,[5] CrO_3/TBHP,[6] or $CuCl_2$/TBHP.[7] The first of these methods is typically the simplest because of the ease of preparation and the broad availability of carbonyl compounds. Nevertheless, the syntheses of ynones can still require multiple steps, harsh conditions, or additional additives[8] to prevent over-addition to the carbonyl group. Thus, it can be challenging to synthesize ynones in a simple, precise, reagent-controllable,[4c,9] and economical manner.

Ynones are versatile intermediates for the syntheses of many important N-heterocyclic compounds, including pyrazoles, quinolones, quinolines, diazepines, triazoles, pyrimidines, indoles, isoxazoles, oxazepines, and oxazines.[3d,10] Pyrazoles five-membered-ring compounds having two adjacent nitrogen atoms are particularly interesting because of their wide physiological activities;[11] for example, cyenopyrafen and pyrazolynate are pesticides[12] and celecoxib is a nonsteroidal anti-inflammatory agent.[13] The general synthetic method for accessing a pyrazole ring is through [3+2] cycloaddition of a 1,3-dielectrophile[14] derivative (an α,β-unsaturated aldehyde/ketone, an allenic ketone, or a β-alkynyl ketone) with hydrazine.[15] Because of their wide biological activity,[16] the challenge remains to develop new synthetic routes for the rapid and regioselective[17] assembly of substituted pyrazoles from simple and readily available starting materials.[18] In this context, when compared with batch techniques, continuous flow chemistry has many attractive features: enhancing mass- and heat-transfer, minimizing reaction volumes, and improving the degrees of sample- and reagent-mixing.[19] Furthermore, the residence time in a microreactor can be controlled precisely to achieve the maximum yield and reaction-selectivity.[20] These features have made flow-microreactor systems an excellent alternatives to traditional batch reaction systems when preparing unstable and highly reactive organometallic intermediates (e.g., aryllithiums, oxiranyllithiums).[21] In addition, the reaction intermediates can be trapped through precise control of various reaction parameters (e.g., residence time, temperature) in a flow-microreactor.[19a]

To date, only a few processes have been reported for the synthesis of ynones[22] and pyrazoles through flow chemistry.[23] Ley and co-workers developed a transition metal–catalyzed process to synthesize ynones and pyrazoles: first coupling a terminal acetylene with an acyl chloride in the presence of a palladium catalyst and then reacting the ynone with hydrazine to afford a pyrazole with overall reaction times of 30 and 60 min, respectively.[24] The same group subsequently reported a metal-free multi-step continuous flow process for the generation of *N*-aryl pyrazoles using amine-redox chemistry.[25] Recently, Jamison and co-workers reported[23j,26] a rapid (within 0.6–60 min) and modular continuous flow synthesis of therapeutic agents, containing highly functionalized fluorinate pyrazole units, for the treatment of measles. Unfortunately, applying their method for the synthesis of ynones and pyrazoles required specific reagents and harsh reaction conditions (high temperatures, long reaction times). Herein, we describe a simple, convenient, and highly efficient method for the synthesis of ynones and pyrazoles in a continuous flow reactor. By reacting terminal

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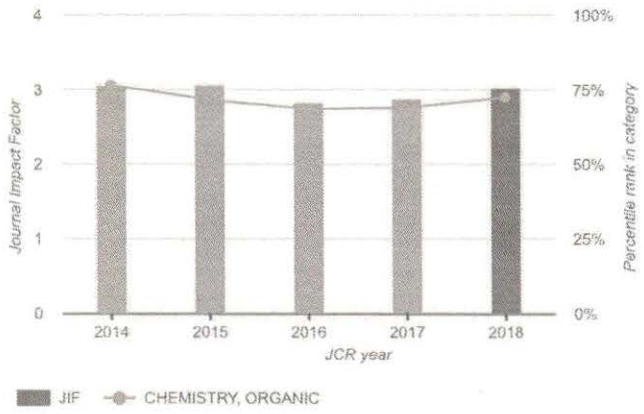

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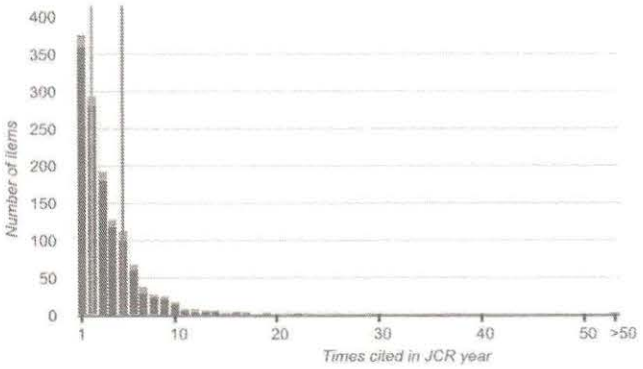

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