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doi.org/10.1002/slct.202002864

Organic & Supramolecular Chemistry

Microwave-Assisted Tandem Kornblum Oxidation and Biginelli Reaction for the Synthesis of Dihydropyrimidones

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A simple and straightforward approach for the synthesis of dihydropyrimidones via sequential Kornblum oxidation/Biginelli reaction has been developed. The protocol involves an in situ oxidation of benzyl halides which serve as a carbonyl equivalents followed by cyclocondensation with (thio) urea and ethylacetoacetate to furnish dihydropyrimidones under catalyst and base free conditions in a one-pot tandem manner under microwave irradiation. Further, the product purification using aqueous recrystallization avoids large quantities of volatile and a toxic organic solvent usually required for work-up and very less time required for this process makes the method environmental- and nature-friendly.

Introduction

Dihydropyrimidones (DHPMs) and related heterocyclic compounds have emerged as useful drug candidates because of their wide range of pharmacological activities such as anticancer,[3] antibacterial,[4] antifungal,[5] antitubercular,[6] antimalarial,[7] antiviral and anti-inflammatory.[8,9] Dihydropyrimidone moiety also represents a key structural unit in some marine natural alkaloids such as Betzallidine A and B known to inhibit the binding of HIV gp-120 to CD_4 cells.[10] Some derivatives such as monastrol,[11] L-771688,[12] SQ 32926[13] with dihydropyrimidone moiety as a key pharmacophore have also been developed, (Figure 1).[16]

Owing to their diverse therapeutics applications, there has been a continued interest from synthetic and medicinal organic chemists to development newer, more efficient methodologies for the synthesis of DHPMs. Among these methods, Biginelli and related reactions which involve the condensation of an aldehyde, (thio) urea and enolizable carbonyl offers the robust procedures for the construction of DHMP scaffolds, scheme 1.[1,2] Recent advances involve the use of catalysts of different nature such as Brønsted acid or base,[14,15] metal based Lewis acids,[16,17] organocatalysts,[18] and heterogeneous catalysts.[19–21] Nonconventional techniques, such as the use of microwave, ultrasound, high pressure and grindstone chemistry have also been developed for the synthesis of DHPMs.[22–25] The scope of Biginelli reaction in these methods is limited to aldehyde substrate only. Numerous efforts have been dedicated to broaden the substrate scope to construct new and more useful DHMPs of therapeutic importance. Although benzyl alcohols, as well as a number of enolizable carbonyl counterparts of β-ketoester substrates have been explored,[26] however, none of the studies have incorporated benzyl halides in their substrate scope. Further, most of developed methods although efficient require expensive catalysts, prolonged reaction time and often require tedious work-up and column purification which ultimately reduce the reaction yield. Therefore, the development of a new and milder Biginelli-like reactions employing new carbonyl component to construct DHMPs is highly desirable.[2]

In continuation of our research work on designing novel and green synthesis,[27–30] herein we have explored the two-step synthesis of dihydropyrimidones from benzyl halides in a one-pot tandem approach. The method involves in situ generation of benzaldehydes from benzyl halides under catalyst-free conditions which are subsequently converted into dihydropyrimidones in a one-pot manner under microwave irradiation using dimethyl sulfoxide (DMSO) as an oxidant/catalyst, scheme I.

Result and discussion

Conventional heating for organic synthesis usually needs longer heating time, tedious apparatus setup which results in a higher cost of the process, and excessive use of solvents/reagents are health hazardous and cause environmental pollution. In contrast, microwave assisted synthesis offers an economical approach for the construction of a large number of organic molecules and has emerged as a new and green tool in organic transformations. Important advantages of this technology include their competency to minimize reaction time, the number of steps, energy consumption, waste production, and to maximize synthetic efficiency and environmental benignity.[31]

Towards this rationale, we propose a one-pot scheme involving oxidation of benzyl halides to benzaldehydes generated in situ followed by Biginelli reaction under microwave irradiation for the synthesis dihydropyrimidones. This route thus extends the applicability of the Biginelli reaction by not limiting one of the substrates to being an aldehyde.

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/slct.202002864