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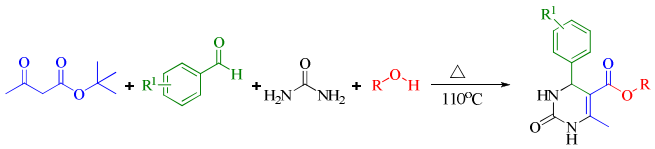
Graphical Abstract

Greener and expeditious one-pot synthesis of dihydropyrimidinone derivatives using non-commercial β-ketoesters *via* Biginelli reaction

G. B. Dharma Rao,* B. Anjaneyulu, M. P. Kaushik.*



An expeditious synthesis of novel 3,4-dihydropyrimidin-2(1*H*)-one derivatives has been developed using a multi-component reaction involving the in situ generation of non-commercial β-ketoesters *via* transesterification of *tert*-butyl β-ketoester with corresponding alcohol followed by Biginelli reaction with arylaldehyde and urea in one-pot at 110˚C under greener conditions.

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Paper

Greener and expeditious one-pot synthesis of dihydropyrimidinone derivatives using non-commercial β-ketoesters *via* Biginelli reaction†

G. B. Dharma Rao,* B. Anjaneyulu and M. P. Kaushik*

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An expeditious synthesis of novel 3,4-dihydropyrimidin-2(1*H*)-one derivatives has been developed using a multi-component reaction involving the in situ generation of non-commercial β-ketoesters *via* transesterification of *tert*-butyl β-ketoester with corresponding alcohol followed by Biginelli reaction with arylaldehyde and urea in one-pot at 110˚C under greener conditions.

Multi-component reactions[1] (MCRs) emerged as a versatile synthetic tool for the construction of multi-functionalized and structurally diverse drug-like chemical entities as well as miscellaneous libraries of small molecules. Besides this, it offers a substantial advantage over conventional linear-type synthesis in terms of speed, diversity and efficiency. The MCRs gained great importance, since these processes form a network of elementary reactions involving the different precursors towards one specific type of target product, thus making the process efficient and free of bi-products. One such outstanding MCR that produces a motivating class of nitrogen heterocycle is the venerable Biginelli reaction established by Italian chemist Pietro Biginelli (University of Florence) in 1893[2] for the synthesis of 3,4-dihydropyrimidinones (DHPMs) under strong acidic conditions. However, the yields of the products were modest.

3,4-Dihydropyrimidinones appear to be a class of honoured organic compounds and extensively explored in the bygone decades triggered by their different biological and therapeutic activities.[3] Some of which have antitumor, antihypertensive, calcium channel blocker, α_{1a}-antagonist, neuropeptide Y (NPY) antagonist, antibacterial, and anti-inflammatory activities. DHPM-derived scaffolds are also existing in the skeleton of several natural marine polycyclic guanidine alkaloids such as crambine, batzelladine B (potent HIV gp-120CD4 inhibitors), and ptilomycalin alkaloids.[4]

In over 120 years of study of the Biginelli reaction, only slight structural deviations in its three building blocks have been reported.[5] However, to the best of our awareness, most of the literature precedents restricted only to β-ketoester which are commercially accessible as an active methylene building block in Biginelli reaction. Herein, we report the first example of the Biginelli reaction employing the in situ generation of non-commercial β-ketoester *via* transesterification of *tert*-butyl β-ketoester with corresponding alcohol followed by Biginelli reaction with arylaldehyde and urea in one-pot at 110˚C under greener conditions.

Transesterification[6] is a paramount organic transformation and provides an essential synthon for number of complex natural products, pheromones and additives for paints.[7] In addition, transesterification alteration has also occupied a prominent position in industrial laboratories.[8] The chemistry elaborated in transesterification is the interchange of alkoxy moiety in ester with alcohol to form a new ester.

Our own overview of the related literature has led to the conclusion that, in addition we found insignificant amount of reports for the construction of dihydropyrimidinone C5 ester derivatives. Desai et. al has reported[9] that the synthesis of dihydropyrimidinones C5 ester derivatives is considerably long *i.e* three step process and experienced from various downsides such as the prerequisite of drastic reaction conditions, prolonged reaction time, requirement of unusual experimental apparatus, use of toxic/expensive catalysts and tedious work-up procedure. Obviously, the stated protocol by Desai et. al not at all acceptable in the context of green synthesis. With an objective to develop a greener protocol recently we reported the dihydropyrimidinone C5 ester derivative synthesis using a two-step sequence.[10]

The current emphasis on improvement of sustainable chemical process has provided an emerging mission to those who applied chemistry in industry and academic research. The construction of chemical compounds or protocols by avoiding relatively volatile toxic solvents and perilous catalysts is essential in the present scenario of green synthesis.[11,12] However, there is a growing

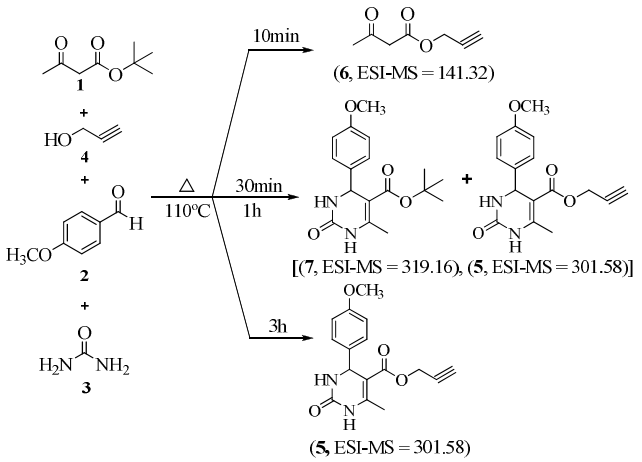
**Discovery Centre, Process Technology Development Division, Defence R&D Establishment, Jhansi Road, Gwalior–474002, M.P., India.* Tel.:+91-751-2343972; fax: +91-751-2340042. e-mail address: gbdharmarao@gmail.com (G. B. Dharma Rao) mpkaushik@rediffmail.com (M.P. Kaushik).

†Electronic Supplementary Information (ESI) available: General details, Experimental procedures, characterisation data, and copies of ^{1}H and ^{13}C NMR for selected compounds. See DOI: 10.1039/b000000x

awareness in finding processes that would provide well-organized alternatives to traditional Biginelli reaction and result in more economical and environmentally benign procedure.

tert-Butyl β-ketoester readily underwent transesterification transformation with alcohol to form the corresponding new β-ketoester in presence of toluene/xylene as solvent under catalyst-free condition[13] due to presence of better leaving group. By taking the benefit of bulkier group of *tert*-butyl β-ketoester herein, we knock a viable protocol exceeds the boundaries associated with formerly occurred processes for the synthesis of dihydropyrimidin-2(1*H*)-one C5 ester derivatives (**5**) using in situ generation of non-commercial β-ketoester *via* transesterification of *tert*-butyl β-ketoester (**1**) with corresponding alcohol (**4**) followed by Biginelli reaction with arylaldehyde (**2**) and urea (**3**) in one-pot at 110˚C under greener circumstances.

In continuation of our preceding work,[14] there was a need to synthesize a large library of diversified dihydropyrimidinone derivatives with reducing time, excellent yields and outstanding biological activities. The finest conditions for the 3,4-dihydropyrimidin-2(1*H*)-one C5 ester derivatives were examined by making use of 4-methoxy benzaldehyde, *tert*-butyl β-ketoester, urea and propargyl alcohol were taken as model substrates under greener conditions. It was found that when *tert*-butyl β-ketoester, arylaldehyde, urea and propagyl alcohol were used in the ratio of 1: 1: 1.2: 1.5 under solvent and catalyst free conditions at 110˚C gave best result towards the formation of title product (Table 1, entry 7). The use of increased quantity of propargyl alcohol did not enhance the desired product yield, whereas lower amount of propargyl alcohol gave the modest yield due to the equilibrium of transesterification. With the curiosity in finding the reaction pathway, we analyzed the reaction mixture of model reactants with time intervals of 10min, 30min, 1h, 2h and 3h using ESI-MS technique. From the above experiments we observed propargyl β-ketoester (Scheme 1, **6**, ESI-MS = 141.32, M+1) after 10min, the products *i.e* dihydropyrimidinones with both propargyl β-ketoester and *tert*-butyl β-ketoester **(**Scheme 1, **5&7**, ESI-MS = 301.58 & 319.16, M+1) after 1h and finally obtained the desired dihydropyrimidinones with propargyl β-ketoester (Scheme 1, **5**,



Scheme 1: Reaction mixture is analyzed at different time intervals using ESI-MS technique.

ESI-MS = 301.58, M+1) after 3hr of reaction. On the basis of above observations, it can be concluded that the reaction of four components in one-pot follows two reaction pathways (transesterification followed by Biginelli reaction or Biginelli reaction followed by transesterification) simultaneously towards the construction of desired title product. This is essentially because both the synthon species (propargyl β-ketoester and *tert*-butyl β-ketoester) were willingly participated in Biginelli reaction with arylaldehyde (**2**) and urea (**3**).

When the above mentioned reaction conditions were applied to the methyl β-ketoester, ethyl β-ketoester, isobutyl β-ketoester instead of *tert*-butyl β-ketoester with propargyl alcohol for Biginelli four component reaction and we observed that the dihydropyrimidinones with methyl, ethyl, isobutyl β-ketoesters (Figure 1, **8**, **9, 10**). At this point propargyl alcohol behaved as a solvent but not as a precursor in novel four component cascade reaction owing to the existence of equilibrium. inesant

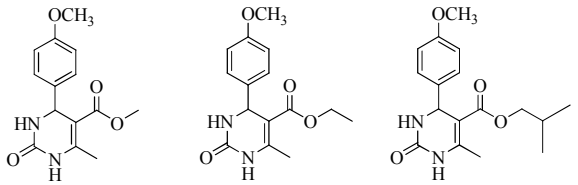


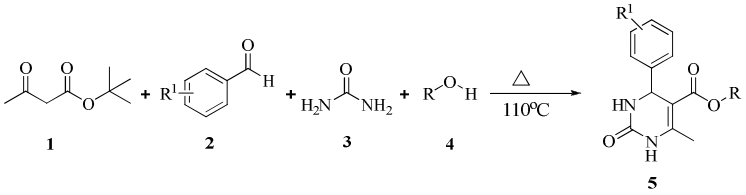
Figure 1: Dihydropyrimidinones of methyl/ethyl/isobutyl β-ketoesters (ESI-MS = 277.18, 291.62, 319.38, M+1).

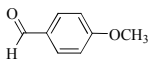
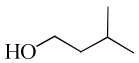
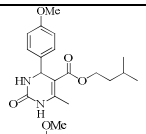
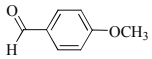
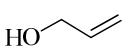
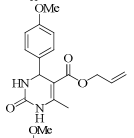
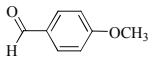
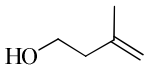
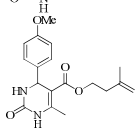
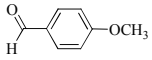
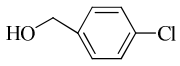
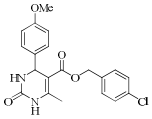
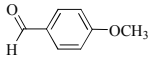
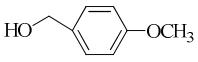
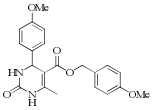
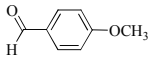
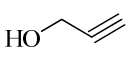
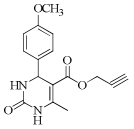
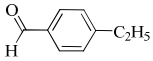
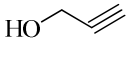
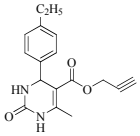
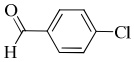
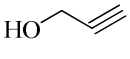
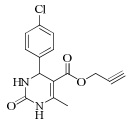
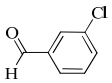
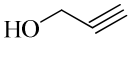
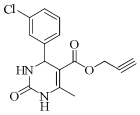
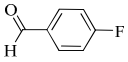
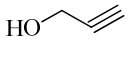
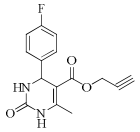
The applicability of these optimized reaction conditions and usefulness of this protocol has also been extended to diversified arylaldehydes with various functional substitutions and variety of alcohols. The protocol seems to be tolerant with both electron donating and electron withdrawing substituents on arylaldehyde and accessible with different alcohol provide the corresponding anticipated dihydropyrimidin-2(1*H*)-one C5 ester in high yield and all the results were appended in Table 1.

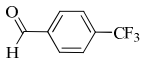
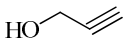
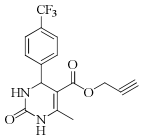
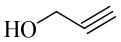
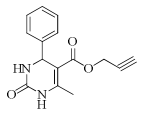
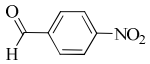
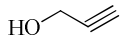
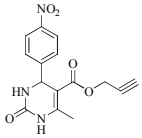
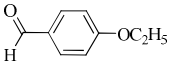
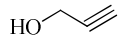
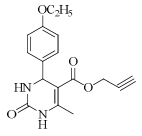
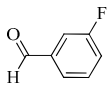
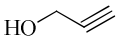
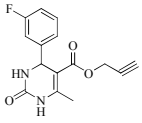
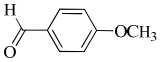
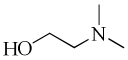
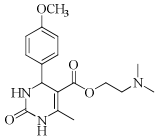
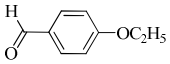
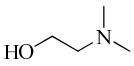
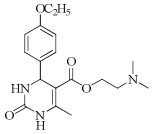
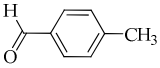
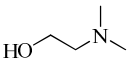
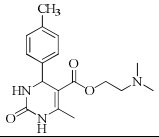
The newly advanced protocol (method-A) is also compared with earlier adjusted bang[10] (method-B) and we found that relatively comparable yields in both protocols. The novel four component one-pot Biginelli reaction towards the construction of dihydropyrimidin-2(1*H*)-one C5 ester is offers more advantages than compare with previously reported two step reaction in terms of shorter reaction time, mild reaction conditions, cost-effectiveness, atom economy and diminish the synthetic reaction steps from two to one.

Based on literature precedents, a plausible reaction mechanism for the observed dihydropyrimidin-2(1*H*)-one C5 ester derivatives is depicted in Scheme 2. In trans-acetoacetylation (transesterification) transformation, *tert*-butyl β-ketoester (**1**) underwent *trans*-acetoacetylation through acetylketene intermediate[13] to form new β-ketoester (**6**) with alcohol (**4**). In the Biginelli reaction, the imine intermediate (**11**) was formed by the

Table 1: Synthesis of dihydropyrimidin-2(1*H*)-one derivatives[15] using non-commercial β-ketoesters under greener conditions[a]

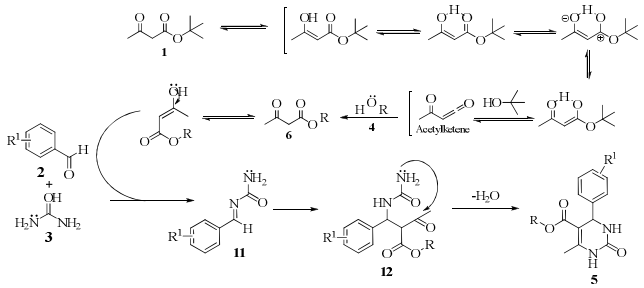


Entry	Aldehyde (**2**)	Alcohol (**4**)	Product (**5**)	M.P (°C)	(%)Yield[b, ref]	
					Method-A (1 step/3hr)	Method-B (2 steps/6hr)
1				148-150	92	86
2				152-154	92	90[10]
3				128-130	90	87[10]
4				200-202	92	90[10]
5				178-180	90	92[10]
6				194-196	90	85[10]
7				150-152	92	89
8				174-176	90	83
9				156-158	87	78
10				172-174	91	85

11				166-168	94	89
12				182-184	92	86
13				180-182	87	78
14				196-198	91	83
15				184-186	89	83
16				158-160	90	82[10]
17				178-180	72	58
18				168-170	81	62

[a]Reaction conditions: *tert*-Butyl β-ketoester (1.0 mmol), arylaldehyde (1.0 mmol), urea (1.2 mmol) and alcohol (1.5 mmol) under solvent and catalyst free conditions at 110˚C.
[b]Isolated yields

combination of arylaldehyde (**2**) and urea (**3**) which is interacted with keto-enol form of new β-ketoester (**6**) to form the adduct product (**12**). The cyclisation followed by dehydration occurred during the course of final desired dihydropyrimidin-2(1*H*)-one C5 ester derivative (**5**) with corresponding aldehyde and alcohol.



Scheme 4: proposed reaction pathway for dihydropyrimidin-2(1*H*)-one C5 ester derivatives.

In conclusion, we have established a simple, environmentally benign and straight forward one-pot protocol for the efficient synthesis of dihydropyrimidin-2(1*H*)-ones C5 ester derivatives through in situ generation of new β-ketoester (transesterification) followed by Biginelli reaction using available laboratory reagents under solvent and catalyst free conditions at 110˚C. This method is endowed with outstanding features such as, simple operation, mild reaction conditions, easy work-up procedure, short reaction time, no hazardous catalysts and solvents. This protocol is also environmentally benign and commercially viable.

Experimental Section:

An oven-dried 25ml round bottomed flask equipped with a refluxed condenser was charged with arylaldehyde (1.0 mmol) and urea (1.2 mmol). The precursors were finely powdered and mixed together and allowed to mechanical stirring for 30min at room temperature. The *tert*-butyl β-ketoester (1.0 mmol) and an alcohol (1.5 mmol) were added to above mixture subsequently. The resulting reaction mixture was heated for 3hr at 110˚C (oil bath) with constant stirring till the reaction was completed. The progress of reaction was monitored by TLC. After completion of

reaction as indicated on TLC, the contents of reaction mixture was cooled to room temperature and the crude reaction mixture was crushed and washed with chilled water (15ml x 3), filtered and dried under vacuum. For analytically pure products, the final solid mass was washed with diethyl ether (10ml x 3) to remove the un-reacted reactants to afford the pure product in 85-94% yield.

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