Green Chemistry

Cite this: *Green Chem.*, 2011, **13**, 1009

www.rsc.org/greenchem

PAPER

Efficient synthesis of 3,4-dihydropyrimidin-2-ones in low melting tartaric acid–urea mixtures†

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Received 3rd January 2011, Accepted 7th February 2011
DOI: 10.1039/c1gc00009h

A general, efficient and green method for the synthesis of dihydropyrimidinones is described under mild conditions employing low melting mixtures of *L*-(+)-tartaric acid and urea derivatives as a novel reaction medium. The melt plays a triple role: as solvent, as catalyst and as reactant, furnishing highly functionalized dihydropyrimidinones in good to excellent yields.

Introduction

Dihydropyrimidinones (DHPMs) are important substructures present in a wide variety of biologically active natural products.[1] In recent years, dihydropyrimidinones and their derivatives have been used as calcium channel blockers and antihypertensive agents.[2a–d] Numerous marine alkaloids containing the dihydropyrimidinone skeleton have interesting biological properties, such as batzelladine alkaloids that are potent HIV gp-120-CD4 inhibitors.[2a–d] Monastrol, a thio derivative of DHPM, acts as a cell-permeable molecule to block mitosis by specifically inhibiting the motor activity of the mitotic kinesis Eg5 and is thus considered as a lead molecule for the development of new anticancer drugs.[3a] In addition, (*R*)-SQ 32926 acts as a antihypertensive agent with potent oral activity,[3b] whereas Mon-97 shows promising anticancer activity (Fig. 1).[3c]

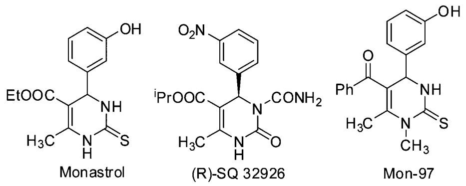

Fig. 1 Pharmacologically active DHPMs.

One-pot multicomponent condensation reactions represent an efficient tool to perform efficient synthesis, because they allow the assembly of complex molecules with maximum simplicity and brevity.[4] Pietro Biginelli reported more than one century ago a one-pot multicomponent approach for the synthesis of DHPMs by multicomponent reaction of urea, aldehydes and β-ketoesters under strong acidic conditions.[5]

The unique biological significance of the DHPM skeleton stimulated several research groups to develop new synthetic procedures based on the Biginelli reaction.[6] Thus, various improved protocols for the synthesis of DHPMs based on the use of Lewis acids such as $BF_3{\cdot}OEt_2$,[7a] strong protic acids like HCl[7b] and H_2SO_4,[7c] metal triflates,[7d–f] zeolites,[7g] as well as microwave[7h] and ultrasonic assisted methods[7i,j] have been reported in the literature. However, many of these methods are not environmentally friendly[8,9] and suffer from several drawbacks such as harsh or sensitive reaction conditions, low yields, use of expensive or hazardous reagents and lack of substrate scope. Moreover, most of these methods employ organic solvents as reaction medium.

Recently, we have established low melting mixtures consisting of urea, carbohydrates and inorganic salts as new alternative renewable solvents for organic transformations.[10] The stable melts of these mixtures are environmentally benign, as they are easily biodegradable, and available from bulk renewable resources without any further modification. The reaction medium consists of only nontoxic materials and has very low vapour pressure like ionic liquids. Moreover, the polarity of these melts is very high.[11] Our continued interest in the exploration of low melting mixtures as novel and green reaction media resulted in the development of several environmentally benign organic transformations such as cycloaddition reactions,[10,11] coupling reactions[11–13] and synthesis of glycosyl ureas.[14]

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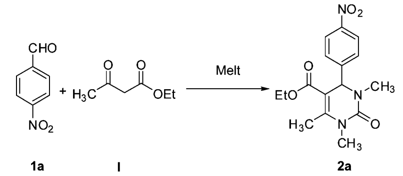
† Electronic supplementary information (ESI) available: Synthetic procedures, characterization data and copies of NMR spectra. See DOI: 10.1039/c1gc00009h

Table 1 Biginelli reaction of 4-nitrobenzaldehyde, ethylacetoacetate and DMU in various melts[a]



Entry	Melt	Temp (° C)	Time (h)	Yield (%)[b]
1	Citric acid–DMU 40 : 60	65	17	90
2	**L-(+)-Tartaric acid–DMU 30 : 70**	**70**	**12**	**96**
3	D-(−)-Fructose–DMU 70 : 30	71	33	42
4	Sorbitol–DMU–NH_4Cl 70 : 20 : 10	67	19	80
5	D-(+)-Mannose–DMU 30 : 70	75	30	54

[a] Reaction conditions: 4-nitrobenzaldehyde (1 mmol), ethyl acetoacetate (1 mmol) in melt (1.5 g). [b] Isolated yield.

Herein, we report a facile and environmentally benign synthesis of dihydropyrimidinones in low melting mixtures under mild conditions.

Results and discussion

Since the Biginelli reaction works well under acidic conditions, initially, we focused on the melt systems consisting of an organic acid as one of the melt components. Thus, the citric acid–dimethylurea (DMU) (40 : 60) melt (65 °C) was chosen as a catalyst as well as reaction medium for the Biginelli reaction. To test the feasibility of this melt system, initially the Biginelli reaction of 4-nitrobenzaldehyde, ethylacetoacetate and dimethylurea, which is one of the melt components, was carried out at 65 °C. To our delight, the corresponding DHPM derivative was obtained in good yield. In order to improve the efficiency of this method, the Biginelli reaction was performed in various low melting mixtures and the results are summarized in Table 1.

The Biginelli reaction proceeds faster (12 h) in *L*-(+)-tartaric acid–DMU melt and the corresponding DHPM is isolated in excellent yield (96%) (entry 2, Table 1). Similarly, a Biginelli reaction involving urea as one of the components in an *L*-(+)-tartaric acid–urea melt at 90 °C gives the corresponding DHPMs in good yield.[15,16]

Once the reaction conditions were established, the scope of the multicomponent reaction was investigated with different aldehydes and β-ketoesters yielding a variety of highly functionalized DHPMs. The results are summarized in Tables 2, 3 and 4. The reaction proceeds smoothly with aromatic and aliphatic aldehydes to provide a wide spectrum of DHPMs. Interestingly, α,β-unsaturated aldehydes such as cinnamaldehyde gave the corresponding DHPM in 72% yield without isomerization of the double bond (entry 8, Table 2). Aromatic aldehydes having both electron donating as well as electron withdrawing substituents gave the corresponding dihydropyrimidinones in excellent yield. Since the reaction conditions are very mild, several acid sensitive functional groups such as olefins, ether, ester and cyano groups remain unaffected under the reaction conditions.

Since thiopyrimidinones are important pharmacophores, our next objective was to develop an efficient procedure for their synthesis using thiourea as one of the melt components. However, all our efforts towards the formation of a clear melt of *L*-(+)-tartaric acid–thiourea were futile. Interestingly, *L*-(+)-tartaric acid–choline chloride (50 : 50) formed a clear melt at 90 °C which was used as a medium for the synthesis of thiopyrimidinones using thiourea as one of the reactants. 3-Hydroxybenzaldehyde on treatment with thiourea in *L*-(+)-tartaric acid–choline chloride melt smoothly furnished the anticancer drug monastrol (**18a**) in good yield (entry 11, Table 2).

The reaction works equally well with various 1,3 dicarbonyl compounds such as benzoyl acetone (**23a**), allyl acetoacetate (**19a**), ethyl benzoyl acetate (**21a**) and methyl acetoacetate (**25a**). In all the cases the corresponding DHPMs were obtained in good to excellent yields. Under the reaction conditions, the less reactive simple ketone such as cyclohexanone also furnished the corresponding DHPM in moderate yield (entry 5, Table 3).

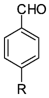
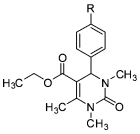
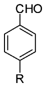
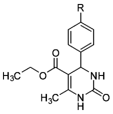
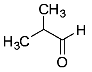
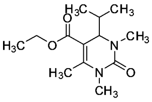
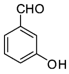
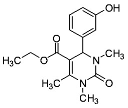
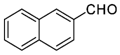
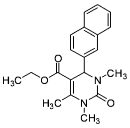
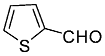
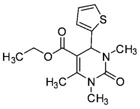
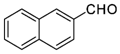
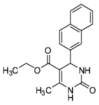
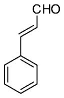
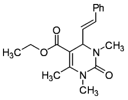
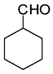
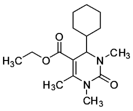
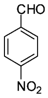
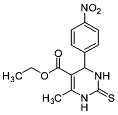
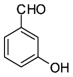
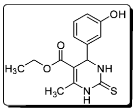
For the first time, masked aldehydes are successfully used in the Biginelli reaction. The masked aldehydes such as dihydropyran and dihydrofuran reacted readily under the reaction conditions to give corresponding functionalized dihydropyrimidinone derivatives in excellent yields (Table 4).

It is important to note that the DHPM synthesis in a melt requires neither tedious work up procedure nor column chromatographic purification. The DHPMs are obtained by quenching of the reaction mixture with water and recrystallization of the precipitated solid from ethanol to yield analytically pure products.

Conclusion

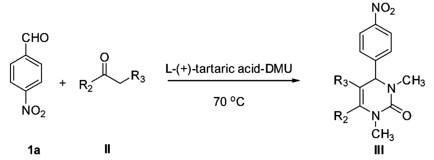
In summary, we have developed an environmentally benign method for the preparation of DHPMs under mild and additive free conditions using low melting mixtures as a novel and green reaction medium. For the first time, masked aldehydes have been used as substrates in the Biginelli reaction to give functionalized DHPM derivatives. The melt medium plays a triple role: as solvent, as catalyst and as reactant. Moreover, the method does not require any tedious work up procedure and the DHPMs are isolated in excellent yields and high purity.

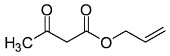
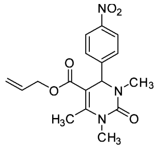
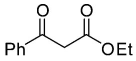
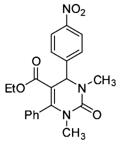
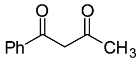
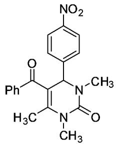
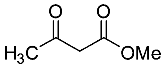
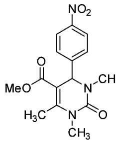
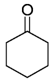
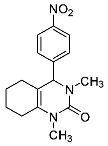
Table 2 Synthesis of dihydropyrimidinones in low melting mixtures[a]

Entry	Aldehydes	Time (h)	Product	Yield (%)[b]
1				
	R = NO_2: **1a**	12	R = NO_2: **2a**	96
	Cl: **1b**	20	Cl: **2b**	90
	CN: **1c**	15	CN: **2c**	97
	Br: **1d**	15	Br: **2d**	84
	OMe: **1e**	14	OMe: **2e**	98
	H: **1f**	24	H: **2f**	97
2				
	R = NO_2: **1a**	11	R = NO_2: **3a**	91[c]
	Cl: **1b**	13	Cl: **3b**	83[c]
3	 **4a**	14	 **5a**	98
4	 **6a**	16	 **7a**	92
5	 **8a**	22	 **9a**	93
6	 **10a**	21	 **11a**	99
7	 **8a**	12	 **12a**	70[c]
8	 **13a**	18	 **14a**	72
9	 **15a**	15	 **16a**	95
10	 **1a**	8	 **17a**	85[d]
11	 **6a**	13	 **18a**	86[d]

[a] Reaction conditions: aldehyde (1 mmol), ethyl acetoacetate (1 mmol) in *L*-(+)- tartaric acid–DMU melt (1.5 g) at 70 °C. [b] Isolated yield. [c] At 90 °C in *L*-(+)- tartaric acid–urea melt. [d] Thiourea (2 mmol) was used in *L*-(+)- tartaric acid–choline chloride melt at 90 °C.

Table 3 Synthesis of DHPMs from various carbonyl compounds[a]



Entry	Carbonyl compound	Time (h)	Product	Yield (%)[b]
1	 **19a**	13	 **20a**	83
2	 **21a**	10	 **22a**	94
3	 **23a**	10	 **24a**	95
4	 **25a**	8	 **26a**	97
5	 **27a**	48	 **28a**	70

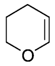
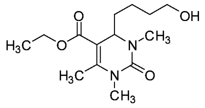
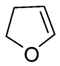
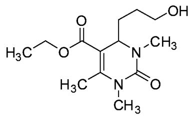
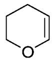
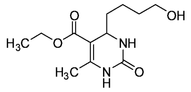
[a] Reaction conditions: 4-NO_2-benzaldehyde (1 mmol), carbonyl compound (1 mmol) in *L*-(+)-tartaric acid-DMU melt (1.5 g) at 70 °C. [b] Isolated yield.

Experimental

General procedure for the synthesis of DHPMs in low melting mixtures

All chemicals were purchased from Aldrich and were used without any further purification. In a typical experiment, 1.5 g of *L*-(+)-tartaric acid–DMU (30 : 70) was heated to 70 °C to obtain a clear melt. To this melt, 1 mmol of aldehyde and 1 mmol of ethyl acetoacetate were added at 70 °C. The reaction was monitored by thin layer chromatography. The reaction mixture was quenched by adding water while still hot, cooled to room temperature and the separated solid was filtered off, washed with water (3 × 5 mL), dried in vacuum and recrystallized from ethanol to afford the pure product.

Table 4 Masked aldehydes as novel substrates for the Biginelli reaction[a]

Entry	Aldehydes	Time (h)	Product	Yield[b](%)
1	 **29a**	13	 **30a**	97
2	 **31a**	15	 **32a**	94
3	 **29a**	16	 **33a**	87[c]

[a] Reaction conditions: masked aldehyde (1 mmol), ethyl acetoacetate (1 mmol) in *L*-(+)-tartaric acid–DMU melt (1.5 g) at 70 °C. [b] Isolated yield. [c] Reaction was carried out at 90 °C by using *L*-(+)-tartaric acid–urea melt.

Acknowledgements

SG thanks Dr Petra Hilgers for her help in the INDIGO exchange programme. We thank CSIR and DST (New Delhi) for financial support and DST-FIST (New Delhi) for NMR facility. SG (SRF) thanks IIT Madras, INDIGO (Indian-German exchange programme of the German Academic Exchange Service, DAAD) and BASF for research fellowships. We thank University of Regensburg for providing infrastructure facility.

Notes and references

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