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Three component condensations catalyzed by iodine–alumina for the synthesis of substituted 3,4-dihydropyrimidin-2(1*H*)-ones under microwave irradiation and solvent-free conditions

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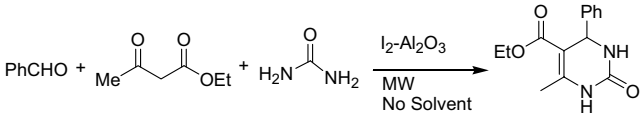
Abstract—Condensation of an aldehyde, ethyl acetoacetate and urea or thiourea under microwave irradiation in the presence of 10% iodine adsorbed on neutral alumina gives substituted 3,4-dihydropyrimidin-2(1*H*)-ones in excellent yields.

4-Substituted 3,4-dihydropyrimidin-2(1*H*)-ones are of interest due to their wide range of biological activities.[1] They have a similar pharmacological profile to that of classical dihydropyridine based calcium channel modulators.[2] Some recently isolated marine alkaloids also show biological activity due to the presence of the dihydropyrimidine moiety.[3] 4-Aryl substituted dihydropyrimidones are generally referred to as Biginelli compounds because Pietro Biginelli first synthesized such compounds in 1893 through the acid catalyzed condensation of ethyl acetoacetate, benzaldehyde and urea.[4] Due to the strongly acidic conditions and low yields in the cases of substituted aromatic and aliphatic aldehydes, the original Biginelli condensation is unsuitable for compounds with sensitive functional groups. Several improvements in the process using Lewis acids such as $BF_3{\cdot}OEt_2$, $FeCl_3$, $LaCl_3$, $La(OTf)_3$, $Yb(OTf)_3$, InX_3, $ZrCl_4$, $BiCl_3$, $Mn(OAc)_3$, $LiClO_4$ or a combination of Lewis acids with transition metal salts, clays, etc. have been reported.[5] Recently Baruah et al.[6] as well as Maiti et al.[7] reported LiBr catalyzed one-pot syntheses of Biginelli compounds. More recently the transition metal salt, vanadium(III) chloride was reported as a catalyst for this condensation by Sabitha et al.[8] while Paraskar et al.[5] described $Cu(OTf)_2$ as a reusable catalyst for the high yield synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones. Salehi et al.[9] on the other hand had introduced silica–sulfuric acid as an efficient and reusable catalyst for the one-pot synthesis of the same compounds.

As part of our on going interest[10] in the use of cheap and commercially available catalysts along with microwave irradiation for important organic transformations, we had the opportunity to look into the Biginelli condensation. Microwave activation, as a nonconventional energy source has become an important method in organic synthesis.[11] Moreover many reactions under microwave irradiation can be performed without using any solvent.[12]



Here we report a quick and efficient one-pot method for the three component condensation of an aldehyde, urea/thiourea and a 1,3-dicarbonyl compound to synthesize 3,4-dihydropyrimidin-2(1*H*)-ones using iodine–alumina as the catalyst under microwave irradiation. When a mixture of an aldehyde, ethyl acetoacetate and urea (or thiourea) was heated for one minute under microwave irradiation in the presence of a catalytic amount (10 mol%) of iodine adsorbed on neutral alumina, a substituted pyrimidone was formed in high yield. A number of aromatic, substituted aromatic and heterocyclic aldehydes were used with ethyl acetoacetate and urea or thiourea to illustrate the generality of the condensation. The results are summarized in Table 1.

In a typical reaction, 2 mmol of benzaldehyde, 2 mmol of ethyl acetoacetate, 2 mmol of urea and 0.2 mmol of

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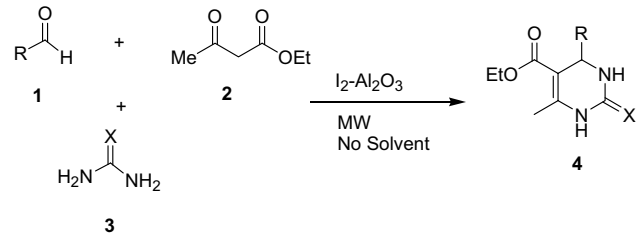
Table 1. Iodine catalyzed three component condensations under microwave irradiation



Entry	R	X	Yield[a] (%)	Mp (observed/reported[ref]) (°C)
1	C_6H_5	O	90	199–201/200–202[5]
2	C_6H_5	S	65	192–194/199–200[13]
3	4-(MeO)C_6H_4	O	74	200–201/200–201[5]
4	4-(MeO)C_6H_4	S	58	130–131/131–132[13]
5	4-(NO_2)C_6H_4	O	85	207–208/207–209[5]
6	4-FC_6H_4	O	78	177–179/182–184[9]
7	4-ClC_6H_4	O	87	214–215/213–215[14]
8	4-ClC_6H_4	S	59	176–177/—[7]
9	Cinnamyl	O	73	155–156/—[6]
10	Furyl	O	71	210–212/203–205[5]

[a] Yields are of isolated pure compounds. Products were characterized by spectral (IR, ^{1}H NMR, MS) analysis and by comparison of mp's. Mp's are uncorrected.

iodine adsorbed on 0.5 g of neutral alumina[10a] were mixed thoroughly and irradiated in a Prolabo fixed focus microwave reactor at a temperature of 90 °C for 1 min. On completion, the mixture was cooled, diluted with ethyl acetate, filtered and the residue was washed with ethyl acetate. The ethyl acetate layer was further washed with a dilute solution of sodium thiosulfate followed by water and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure left a residue, which on crystallization from ethanol yielded a crystalline product.

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