

A novel one pot synthesis of nitrogen containing heterocycles: an alternate methodology to the Biginelli and Hantzsch reactions †

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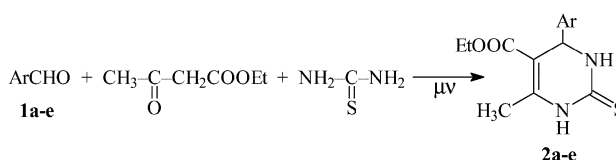
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Modified Biginelli and Hantzsch reactions were carried using environmentally benign processes. Neat reactants subjected to microwave radiation gave the required products more quickly and in better yields in comparison to traditional methodologies. The observed yields and enhancement in reaction rates are due to the solvent free conditions coupled with the use of microwave radiation.

Environmental concerns in research and industry are increasing¹ with the increasing pressure to reduce the amount of pollutants produced, including organic solvents whose recovery is mandated by ever more strict laws. Hence the challenge for a sustainable environment calls for the use of clean procedures which can avoid the use of harmful solvents. The emergence of microwave assisted solid phase synthesis² is a step forward in this direction. In this expeditious and solvent free approach³ the adsorbed reactants over solid supports are exposed to microwave irradiation. The salient features of these high yield protocols are enhanced reaction rates, greater selectivity and experimental ease of manipulation.⁴ But this technique does not exactly meet the definition of 'no solvent'.⁵ The usage of solvent is only eliminated at the primary reaction stage whereas an appreciable amount of solvent is still required for the adsorption of reactants and elution of the product at the pre- and post- reaction stages respectively. A "neat reaction" is an alternative solvent free approach that eliminates the use of a solid support as well as solvent from the reaction. There has not been much advancement in this area as direct heating of the reactants in the absence of solvent and a solid support often leads to charring. But these no solvent reactions can prove to be advantageous for environmental reasons and can also offer the benefits of shorter reaction times especially when coupled with microwave radiation⁶ or ultrasound⁷ due to their uniform heating effect.

Pyrimidinones and their derivatives⁸ are medicinally important⁹ as calcium channel blockers, antihypertensive and anti-inflammatory agents and α 1-a antagonists. The first one pot synthesis of 3,4-dihydropyrimidine was reported by Biginelli¹⁰ in 1893. A serious drawback of the original procedure was low yield with substituted aliphatic and aromatic aldehydes.¹¹ Recently several improved procedures¹² have been reported using Lewis acids as well as protic acids as promoters. But these methods involve expensive reagents, stoichiometric amounts of catalyst, strong acidic conditions, longer reaction times, higher temperatures, unsatisfactory yields and incompatibility with other functional groups. However some microwave assisted Biginelli reactions have been reported with better yields but these involve the use of polyphosphate ester (PPE)¹³ or conc. HCl¹⁴ as catalysts or require sealed reaction vessels.¹⁵

In the present communication the Biginelli reaction (Scheme 1) was carried out with conventional heating by taking urea, ethyl acetoacetate and aldehydes **1a–e** in the presence of a few

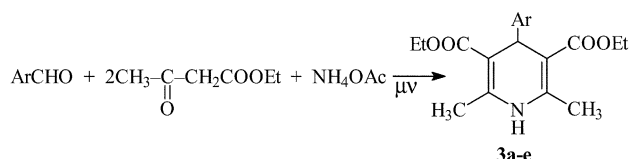


- 1a,** Ar = phenyl
1b, Ar = furyl
1c, Ar = indolyl
1d, Ar = piperonyl
1e, Ar = 2-chloro-7-methyl-3-quinolyl

Scheme 1

drops of conc. HCl for a few hours. The products were obtained in moderate yields but when the reaction was carried out over acidic alumina using microwave irradiation the products were obtained within several minutes in good yield (Table 1). The reaction was also carried out over neutral alumina, which gave appreciable yields within the same reaction times. An attempted reaction of ethyl acetoacetate, aldehyde and thiourea in ethanol to form **2a** in the absence of conc. HCl yielded no product while the same reaction in 20 ml of ethanol in the presence of conc. HCl yielded **2a** in low yield. This prompted us to carry out neat synthesis of dihydropyrimidinones without using solid support, solvent or acid. Equimolar amounts of neat reactants on exposure to microwave irradiation gave the required product after titrating with a few drops of MeOH. To our surprise, better yields with not much change in the reaction times were observed when compared with the solid support syntheses. Furthermore, the use of several heterocyclic aldehydes led to the synthesis of novel pyrimidine representatives belonging to the Biginelli series of condensation products.

The positive results obtained from the Biginelli reactions prompted us to synthesize well known pharmacologically important 1,4-dihydropyridines (1,4-DHP).¹⁶ Although various methods are reported for the synthesis of 1,4-DHP, the most prominent is the Hantzsch synthesis¹⁷ (Scheme 2) which



Scheme 2

involves the condensation of two moles of ethyl acetoacetate with one mole of aldehyde-NH₃ either in acetic acid or refluxing in alcohol for a longer time. A number of modified methods¹⁸ under improved conditions, reported for the Hantzsch synthesis have been found to be unsuccessful from an environmental point of view.

Extending the modifications of the Biginelli reaction to the Hantzsch synthesis gave excellent results (Table 1). The products were obtained in good yields when the reactions were

† Electronic supplementary information (ESI) available: General procedure for the synthesis of Biginelli tetrahydropyrimidines (**2b–e**) and 1,4-dihydropyridines **3a–e**. See <http://www.rsc.org/suppdata/p1/b2/b205539m/>

Table 1 Comparison of the reaction times and yields for the Biginelli and Hantzsch syntheses

Compound	R	Mp/°C	Solution phase (conventional)		Solid support (microwave) ^a		Neat (microwave) ^a	
			Yield (%)	Time/h	Yield (%)	Time/min	Yield (%)	Time/min
2a	C ₆ H ₅	205 ¹⁹	44	3	85	9	90	2.5
2b	2-Furyl	208–210	42	3	81	8.5	86	1.5
2c	Indolyl	>300	41	>24	82	10.0	84	4.0
2d	Piperonyl	158–160	46	5	84	9.5	89	2.0
2e	2-Chloro-7-methyl-3-quinolyl	>300	40	>24	80	10.5	82	6.5
3a	C ₆ H ₅	157–159 ^{18d}	50 ^b	12	85	3.0	90	2.5
3b	2-Furyl	164–165 ^{18d}	47 ^b	13	82	2.5	87	2.0
3c	Indolyl	184–185 ^{20a}	50 ^b	8	81	6.0	86	4.5
3d	Piperonyl	133–134 ^{20b}	77 ^b	24	83	6.5	88	5.0
3e	2-Chloro-7-methyl-3-quinolyl	178–180	40	>24	80	7.0	85	5.5

^a Microwave heating (800 W, 110–120 °C, 1 min). ^b Synthesized earlier conventionally using NH₃.

carried out over both acidic and neutral alumina, but better results were obtained when neat reactants (ethyl acetoacetate, aldehyde and ammonium acetate) were subjected to microwave irradiation.

Thus we have developed a simple, economical and environmentally benign synthesis. It is possible that in the future more drastic restrictions on 'solvent pollution' will require the adoption of no-solvent reaction conditions. Further investigations into the scope of such reactions are underway.

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