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GLYCOLIC ACID AS A NOVEL AND GREEN SOLVENT FOR THE PREPARATION OF 3, 4-DIHYDROPYRIMIDIN-2(1H)-ONES

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Abstract
Simple and improved conditions have been found to carry out the Biginelli reaction for the synthesis of 3, 4-dihydropyrimidin-2(1H)-one derivatives. This synthesis was performed using glycolic acid as a green acidic solvent. Compared with the classical Biginelli reaction conditions, this new method has the advantage of excellent yields and simple procedure.

Keywords: Multicomponent, Biginelli, 3, 4-dihydropyrimidin, Glycolic acid

Introduction

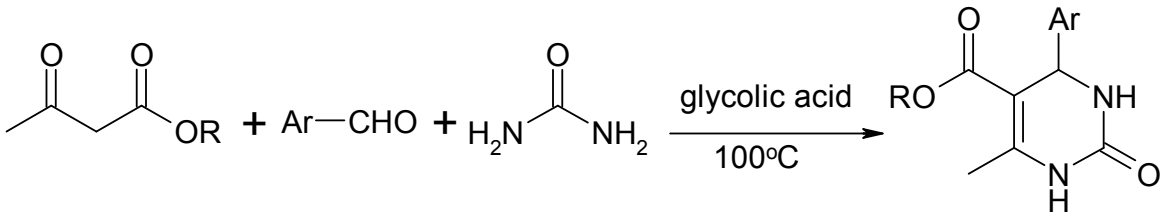
Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry for various reasons. One such important MCR that belongs in this category is the Biginelli dihydropyrimidine synthesis since its discovery by Biginelli in 1893.[i]

Dihydropyrimidinones (DHPMs) and their derivatives are well known heterocyclic units in the realm of natural and synthetic organic chemistry due to their therapeutic and pharmacological properties. They are medicinally important as calcium channel blockers, antihypertensive agents, alpha-la-antagonists and neuropeptide Y(NPY) antagonists.[ii] Moreover, several alkaloids containing the dihydropyrimidinones as a core unit have been isolated from marine source, which also showed biological properties.[iii, iv]

Although the original reaction conditions suffered from poor yields and a limited substrate scope, the recent discovery of dihydropyrimidine biological activity has led to a renewed exploration of the reaction conditions, revealing a variety of compatible solvents, acid catalysts, and an expanded substrate scope.

In order to improve the efficiency of Biginelli reaction, many acidic catalysts have been developed such as $Cu(OTf)_2$,[v] $FeCl_3$/Al-MCM,[vi] chloroacetic acid.[vii]

In this report an efficient and green synthetic protocol for the preparation of 3, 4-dihydropyrimidinones using glycolic acid as an acidic organic solvent is described (Scheme 1). Glycolic acid is a relatively strong organic acid, nontoxic, relative non-corrosive, safe to handle.

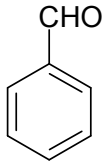
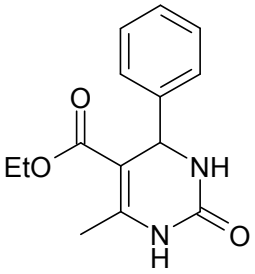
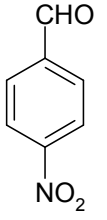
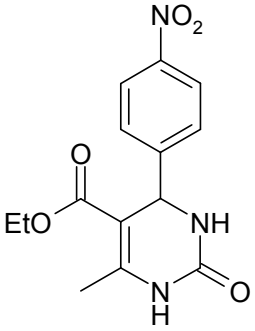


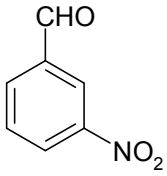
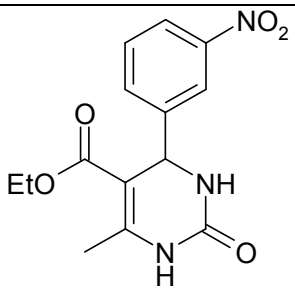
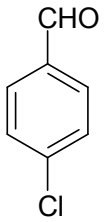
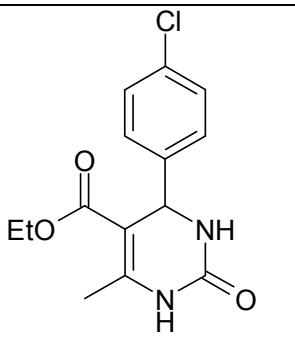
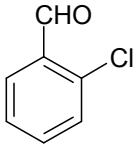
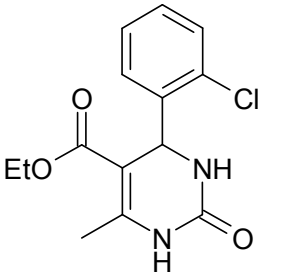
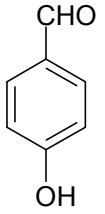
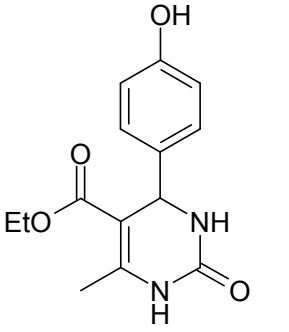
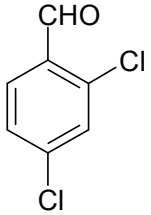
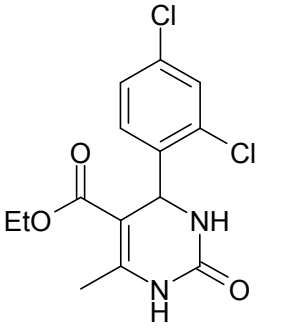
Scheme 1. Glycolic acid catalyzed synthesis of 3, 4-dihydropyrimidinones

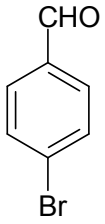
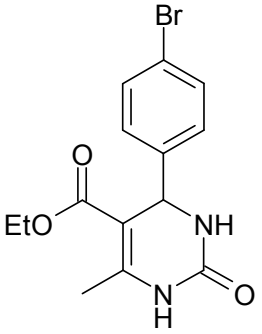
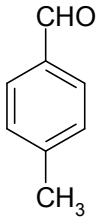
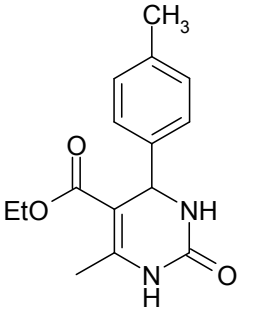
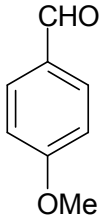
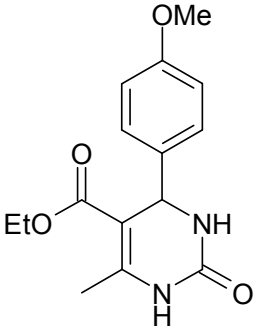
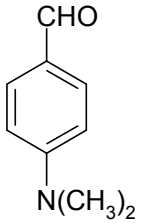
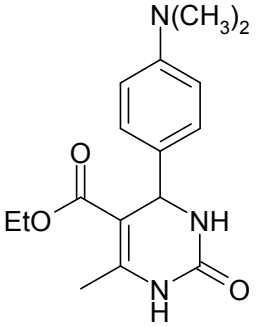
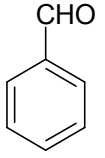
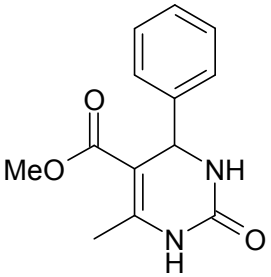
Results and discussion

To optimize the conditions, the reaction of benzaldehyde, ethyl acetoacetate and urea was selected as a model to investigate the effects of different amounts of glycolic acid and temperature on the yield. The best result was obtained by carrying out the reaction with 1mmol of benzaldehyde, 1 mmol of ethyl acetoacetate and 1.5 mmol of urea and 0.2 g of glycolic acid at 100°C. To investigate general scope and versatility of this procedure in the synthesis of a variety of substituted dihydropyrimidinones, we examined a number of differently substituted aryl aldehydes in the optimized conditions. The results are summarized in Table 1.

Table 1. Synthesis of 3, 4-dihydropyrimidinones in glycolic acid

Entry	aldehyde	product	Time (min)	Yield (%)	Mp (°C)	Ref.
1			20	90	200-202	viii
2			12	93	214-215	viii

3			16	94	230-231	x
4			14	88	210-213	viii
5			15	85	223-227	viii
6			22	87	200-204	viii
7			20	88	251-253	xi

8			15	90	215-218	x
9			20	90	214-217	ix
10			25	86	205-207	viii
11			20	89	233-236	viii
12			15	94	210-212	ix

Aromatic aldehydes containing both electron donating and electron withdrawing groups afforded high yields of the desired products with high purity.

Experimental

General

Aldehydes, ethylacetoacetate, urea and glycolic acid were purchased from Merck chemical company and used without further purification. All products are known and by comparison of their spectral data and physical properties with those of the authentic sample and all yields refer to isolated products. Melting points were determined in a capillary tube and are uncorrected. NMR spectra were recorded on a BRUKER DRX-500 AVANCE NMR spectrometer using DMSO-d_6 as solvent.

General procedure for synthesis of 3, 4-dihydropyrimidin-2(1H)-ones

A mixture of aldehyde (1 mmol), 1, 3-dicarbonyl compound (1 mmol), urea (1.5 mmol) and glycolic (0.2 g) was heated at 100 ◦C under stirring. The reaction was monitored by TLC. After completion, the reaction mixture was dissolved in 5 ml ethanol, poured into cold water and stirred for 5 min. The solid was filtered and the filtrate was recrystallized from ethanol to afford pure product.

*Ethyl-6-methyl-4-(4-nitrophenyl)-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate (**table 1, entry 2**)*

^{1}H NMR (DMSO-d_6) δ (ppm): 1.11 (t, J = 7.5 Hz, 3H), 2.29 (s, 3H), 4.00 (q, J = 7.5 Hz, 2H), 5.29 (d, J = 3.0 Hz, 1H), 7.51 (d, J = 10Hz, 2H), 7.91 (br s, 1H), 8.23 (d, J = 8.76 Hz, 2H, arom CH), 9.37 (s, 1H, NH).

Ethyl-6-methyl-4-(4-chlorophenyl)-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate (***table 1, entry 4***)

^{1}H NMR (DMSO-d_6) δ (ppm): 1.10 (t, J = 7.2, 3H), 22 (s, 3H), 3.96 (q, J = 7.2, 2H), 5.02 (s, J = 3.2, 1H), 6.64 (d, J = 8.4, 2H), 7.02 (d, J = 8.4, 2H), 7.57 (s, 1H), 9.07 (s, 1H).

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