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A Practical and Green Approach towards Synthesis of Dihydropyrimidinones without Any Solvent or Catalyst

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Abstract:

A simple, efficient, green, and cost-effective procedure has been developed for the synthesis of dihydropyrimidinones by a solvent-free and catalyst-free Biginelli's condensation of 1,3-dicarbonyl compound, aldehyde, and urea. This approach of direct reaction in neat without solvent and catalyst shows a new direction in green synthesis.

The toxicity and volatile nature of many organic solvents, particularly chlorinated hydrocarbons, that are widely used in huge amounts for organic reactions have posed a serious threat to the environment.[1] Thus, design of solventless catalytic reaction has received tremendous attention in recent times in the area of green synthesis.[2] However, it has been observed that the catalysts employed are not always eco-friendly, and because of this severe environmental pollution often results during the process of waste disposal. This prompted us to initiate a systematic investigation to look into the feasibility of a solvent-free and catalyst-free reaction[3] under modified experimental conditions towards development of real green methodology for useful molecules.

Dihydropyrimidinone derivatives are of considerable interest in industry as well as in academia because of their promising biological activities as calcium channel blockers, antihypertensive agents, and anticancer drugs.[4] Thus, synthesis of this heterocyclic nucleus is of much importance, and quite a number of synthetic procedures based on the modifications of the century-old Biginelli's reaction[5] involving acid-catalyzed three-component condensation of 1,3-dicarbonyl compound, aldehyde, and urea, have been developed during past few years.[4,6] Basically, these methods are all similar, using different Lewis acid catalysts such as BF_3,[6a] $FeCl_3$,[6b] $InCl_3$,[6c] $BiCl_3$,[6d] $LaCl_3$,[6e] $LiClO_4$,[6f] $Mn(OAc)_3$,[6g] CAN,[6h] in a solvent such as CH_3CN, CH_2Cl_2, or THF. Recently, a number of procedures under solvent-free conditions using $Yb(OTf)_3$,[6i] montmorillonite[6j] and ionic liquid[6k] as catalysts have also been reported. Obviously, many of these catalysts and solvents are not at all acceptable in the context of green synthesis. Thus, as a part of our program towards green synthesis, we have discovered that Biginelli's reaction proceeds very efficiently by stirring a mixture of neat reactants at 100−105 °C for an hour, requiring no solvent and catalyst, and producing dihydropyrimidinones in high yields[7] (Scheme 1).

In a typical experimental procedure,[8] a mixture of 1,3-dicarbonyl compound, aldehyde, and urea was heated at

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(7) In a recent communication[6k] Peng and Deng reported that no desirable product was detected when a mixture of benzaldehyde, ethyl acetate, and urea (mol ratio 1:1:1.5) was heated at 100 °C for 30 min in the absence of ionic liquid, indicating a catalyst must be needed for the Biginelli reaction. However, when we found a very efficient reaction in neat without solvent and catalyst under similar reaction conditions, we communicated our observation to Professor Deng for his comments. We have not yet received a reply.

(8) **Representative Experimental Procedure: (a) Small-scale (milligram level) (Entry 5).** A mixture of 3-methoxybenzaldehyde (freshly distilled, 272 mg, 2 mmol), ethyl acetoacetate (freshly distilled, 260 mg, 2 mmol), and urea (180 mg, 3 mmol, Loba-chemie, India) was heated under stirring (magnetic stirrer) at 100−105 °C (oil bath). After few minutes with the progress of reaction the solid started to separate out and after completion (1 h, TLC) the resulting solid was crushed, washed with cold water, filtered, and dried under vacuum to give the crude product which is reasonably pure (>95% purity by ^{1}H NMR). However, recrystallization from hot ethanol provides the analytically pure product[6c] (476 mg, 82%), mp 207−208 °C; IR 3242, 1701, 1651, 1598 cm^{-1}; ^{1}H NMR δ 9.17 (s, 1H), 7.70 (s, 1H), 7.23 (t, $J = 7.8$ Hz, 1H), 6.79 (m, 3H), 5.09 (d, $J = 2.7$ Hz, 1H), 3.97 (q, $J = 6.9$ Hz, 2H), 3.70 (s, 3H), 2.22 (s, 3H), 1.09 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR δ 165.7, 159.5, 152.5, 148.8, 146.6, 129.9, 118.8, 112.7, 102.6, 99.4, 59.5, 55.3, 54.6, 18.1, 14.4. Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.25; N. 9.65. Found: C, 61.89; H, 6.18; N, 9.49. This procedure is followed for the preparation of all the dihydropyrimidinones listed in Table 1. All the products are reported earlier and are identified by comparison of their mp, IR, ^{1}H, and ^{13}C NMR spectral data with those reported.[6] **(b) Large-scale (1 kilogram level).** A mixture of benzaldehyde (530 g, 5 mol), ethyl acetoacetate (650 g, 5 mol), and urea (360 g, 6 mol) taken in a 2-L round-bottomed flask was stirred by a mechanical stirrer at room temperature for 2 min for uniform mixing, and then the temperature (oil bath) was raised to 100−105 °C. No exothermic reaction was observed during addition and mixing. Stirring was continued for another 1 h at that temperature. With the progress of reaction (approximately during the first 20 min all the urea dissolved, and solids started to appear) the reaction mixture became a thick slurry with the solids being deposited. At this stage, although no efficient stirring or agitation can be made, the reaction was not affected. After 1 h the reaction mixture was cooled in an ice−water bath (0−5 °C), and water (200 mL) was added. The solid was broken into pieces carefully with a spatula and filtered. The yellow solid was then washed with cold water (100 mL) followed by cold rectified spirit (50 mL) to provide a colorless solid (1.025 kg, 79%) which was practically pure, mp 201−202 °C (lit[6a] 202−204 °C). A portion of it was recrystallized from hot ethanol to give analytically pure sample.

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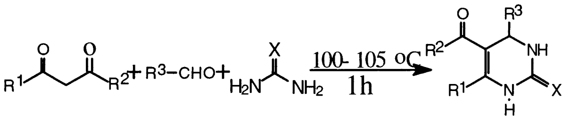
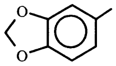
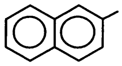
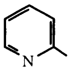
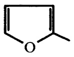
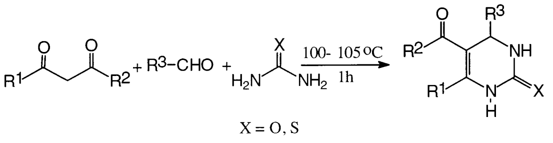
Table 1. **Synthesis of dihydropyrimidinones without any solvent and catalyst**



entry	R^1	R^2	R^3	X	yield (%)[a]
1	Me	OEt	Ph	O	81
2	Me	OEt	4-(NO_2)-C_6H_4	O	85
3	Me	OEt	4-(Cl)-C_6H_4	O	85
4	Me	OEt	4-(OMe)-C_6H_4	O	83
5	Me	OEt	3-(OMe)-C_6H_4	O	82
6	Me	OEt	PhCH=CH	O	78
7	Me	OEt	4-(OH)-3-(OMe)-C_6H_3	O	85
8	Me	OEt		O	85
9	Me	OEt		O	83
10	Me	OMe	Ph	O	80
11	Me	OMe	4-(Cl)-C_6H_4	O	83
12	Et	OEt	Ph	O	81
13	Et	OEt	4-(NO_2)-C_6H_4	O	85
14	Et	OMe	4-(Cl)-C_6H_4	O	85
15	Et	OMe	4-(NO_2)-C_6H_4	O	83
16	Me	OEt	*n*-Pr	O	78
17	Me	OEt	*i*-Pr	O	80
18	Me	OEt	*n*-C_6H_{13}	O	80
19	Me	Me	Ph	O	85
20	Me	Me		O	81
21	Me	Me		O	80
22	Me	Ph	Ph	O	83
23	Me	Ph	4-(OMe)-C_6H_4	O	82
24	Me	OEt	3-(OMe)-C_6H_4	S	82
25	Me	Me	Ph	S	81
26	Me	Ph	Ph	S	80

[a] Yields refer to those of recrystallized pure products characterized by mp and spectral data (IR, ^1H, and ^{13}C NMR).

Scheme 1



100−105 °C in neat without any solvent or catalyst. The reactions are complete by an hour, and the solid products were filtered and recrystallized. It has also been observed that under identical reaction conditions (without an acid catalyst) the reaction did not progress at all in refluxing dichloromethane, dichloroethane, THF, and toluene during 1 h, although refluxing for 5 h in toluene furnished 15−20% yields. This indicates the special advantage of the solventless reaction and the negative role of solvent at least in this case.

A broad range of structurally diverse 1,3-dicarbonyl compounds, aldehydes, and urea are subjected under this procedure to produce the corresponding dihydropyrimidinones. The results are reported in Table 1. A wide variation of alkyl groups in 1,3-dicarbonyl compound as well as in aldehyde are tolerated in this procedure to provide a library of dihydropyrimidinones with a variety of substituents. Thiourea also works well to give the corresponding thioderivatives which are also of much interest with regard to biological activity.[4]

In general, the reactions are very clean, and no side product was obtained in any run. In fact, the crude products obtained are of high purity (>95% by ^1H NMR) and do not require any chromatographic separation. Recrystallization from hot ethanol provides analytically pure sample. Most significantly, the whole operation does not involve any organic solvent[7] at any stage and can be scaled up to the level producing 1 kg of product in the laboratory (not optimized) without any problem. In addition, the reaction condition is mild enough to tolerate a variety of sensitive functionalities such as NO_2, Cl, OH, OMe, conjugated C−C double bond, and heterocyclic moieties.

In conclusion, the present procedure of the synthesis of dihydropyrimidin-2(1H)-ones by a solvent-free and catalyst-free condensation of 1,3-dicarbonyl compound, aldehyde, and urea provides a simple, efficient, cost-effective, and 100% green modification of the Biginelli's reaction. Most significantly, this solvent-free and catalyst-free process of three-component condensation throws a challenge to the existing procedures[4,6] which use volatile and hazardous solvents and toxic catalysts, and in general, leads to a new direction in organic synthesis. We believe this will find useful applications as a practical alternative for the synthesis of dihdropyrimidinones to cater the need of industry as well as acedmia.

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