Cation Exchange Resin (Indion 130): An Efficient, Environment Friendly and Recyclable Heterogeneous Catalyst for the Biginelli Condensation

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Abstract: Ion exchange resin catalyzed multicomponent Biginelli reaction is studied for the synthesis of 3,4-dihydropyrimidin-2-ones. Among the various solid acid catalysts Indion-130 was found to be most efficient, recyclable and environmentally benign heterogeneous catalyst regarding reaction time, yield and ease of work up procedure.

Keywords: Biginelli reaction, 3,4-dihydropyrimidin-2-ones, Ion exchange resin, heterogeneous catalyst, Indion-130.

INTRODUCTION

Replacement of conventional, toxic and polluting Bronsted and Lewis acid catalysts with eco-friendly reusable solid acid heterogeneous catalysts like acidic zeolites, clays, sulfated zirconia and ion exchange resins is an area of current interest [1,2]. The use of solid acid catalyst instead of liquids includes many advantages, such as reduced equipment corrosion, ease of product separation, recycling of the catalyst and environmental acceptability. In the recent past ion exchange resins in general and styrene-DVB mattrixed resin sulfonic acid (Indion-130) in particular, which are strongly acidic and chemically as well as thermally stable have been found to be excellent catalysts for a variety of the major organic reactions like esterification, alkylation, acetalisation, acylation and condensation [3-8].

3,4-Dihydropyrimidinones are well known heterocyclic units in the realm of natural and synthetic organic chemistry due to their therapeutic and pharmacological properties including antiviral, antitumour, antibacterial and anti-inflammatory activities [9-12]. Biginelli in 1893 reported for the first time the synthesis of these compounds by the one-pot cyclocondensation of ethyl acetoacetate, benzaldehyde and urea in the presence of strong acid [13] however this method suffers from the drawbacks, such as the lower yields of the desired products (20-40%) particularly in case of substituted aldehydes and loss of sensitive functional groups during the reaction. Therefore, in the recent years several improved methodologies mainly using lewis acids [14-17], triflates [18,19], ionic liquids [20], natural HEU type zeolite [21], polyaniline–bismoclite complex [22], heteropoly acid [23-28], sulfated zirconia [29], L-proline [30], microwave assisted methodologies [31,32], and ultrasonic mediated methods [33] have been reported in the literature. However, inspite of their potential utility many of the existing methods suffers from the drawbacks, such as the use of strong acidic conditions, longer reaction times, tedious workup, environmental disposal problems and lower yields of the products, leaving scope for further development of an efficient and versatile method for Biginelli reaction.

Growing concern about environmental damage leads to an urgent requirement for the development of eco-friendly technology and economic processes. It is of great practical importance to synthesize DHPM derivatives by the Biginelli reaction by using a solid acid catalyst, because of the ability to modify the acid strength, ease of handling, recycling of the catalyst and environmental compatibility. In view of the above requirement, and as a part of our program towards green synthesis, we herein report a single-step and eco-friendly protocol for the synthesis of DHPM derivatives by the multicomponent reactions of β-dicarbonyl compound **1**, aldehydes **2** and urea **3** (Scheme **1**) over Indion-130 with good yields and selectivity.

RESULTS AND DISCUSSION

To evaluate the catalytic effect of various ion exchange resins we started with the model reaction of ethyl acetoacetate **1a** (10 mmol) with benzaldehyde **2a** (10 mmol) and urea **3** (12 mmol) in refluxing ethanol without and with use of various acidic ion exchange resins as catalysts to afforded dihydropyrimidine **4a** in various yields (Table **1**). It can be seen from Table **1** that Indion-130 was the most efficient (Table **1**, entries 2) among the three solid acidic ion exchange resins studied. It was found that 0.5 g of Indion-130 is sufficient to carry out the Biginelli reaction successfully. An increase in the amount of Indion-130 to more than 0.5 g showed no substantial improvement in the yield, whereas the yield is reduced by decreasing the amount of Indion-130.

Accordingly, a variety of reaction conditions were tried using Indion-130 as the catalyst to minimize side reactions and to improve the low yields that have been found even by using conc. HCl as the catalyst. By adapting a 1:1:1.2 mole ratio of ethyl acetoacetate, benzaldehyde and urea, the selective formation of **4a** can be achieved without the

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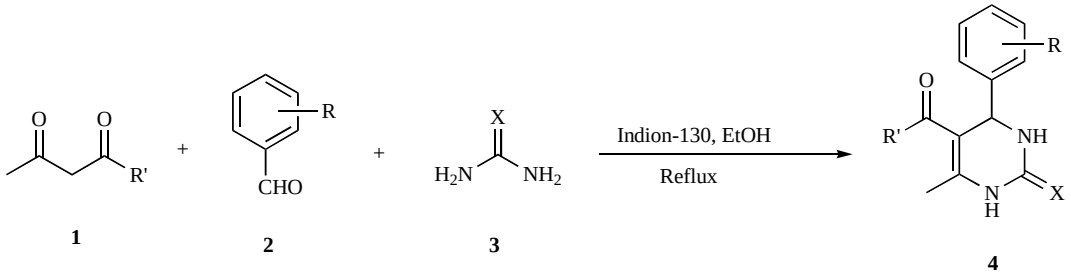


1 **2** **3** **4**

Scheme 1. Indion-130 resin catalyzed synthesis of various DHPMs.

Table 1. Catalytic Activity of Different Acidic Ion Exchange Resins in Biginelli Condensation[a]

Entry	Ion Exchange Resin	Reaction Time (h)	Yield[b] (%)
1	-	10	Trace
2	Indion-130	3	94
3	Amberlyst-15	5.5	92.5
4	Nafion-H	4.5	85

[a]Reaction Conditions: ethyl acetoacetate (10 mmol), benzaldehyde (10 mmol) and urea (12 mmol) in dry ethanol (10 ml), ion exchange resin (0.5 g) at refluxing temperature.
[b]Isolated yields.

formation of side products. The effect of solvent on the reaction was studied (Table **2**, entries 1-5) and ethanol was found to be the best solvent when considering the reaction yields and environmental damage.

The catalyst could be recovered easily by washing with ethyl acetate after filtration, and the remaining catalyst could be used for further runs. No obvious decrease of the yield was observed for four successive reactions (94, 93, 94 and 92%), demonstrating that the Indion-130 catalyst can be recycled without significant loss of activity.

Under this optimized reaction condition the scope of the reaction was then explored. A broad range of structurally diverse 1,3-dicarbonyl compounds, aldehydes and urea/thiourea were subjected under this protocol to produce the corresponding DHPMs (Table **3**). A variety of dicarbonyl compounds could be used successfully. Thiourea was also used with similar success. The results are presented in Table **3**. All the substrates were smoothly converted to their corresponding DHPMs in excellent yields.

The mechanism of this multicomponent reaction is not clear at this stage. Similar to the reports by Folkers and Johnson [34], and Kappe [35] for the Biginelli reaction, the formation of product **4** may involve an acyl imine intermediate, the addition of β-diketone to the iminium ion, and subsequent cyclodehydration (Scheme **2**).

CONCLUSION

In conclusion, we have developed a simple, efficient, environmentally benign and improved protocol for the synthesis of 3,4-dihydropyrimidin-2-ones/thiones over Indion-130 as the catalyst with excellent yields. The simplicity of the system, ease of separation/reuse of the catalyst due to its heterogeneous nature, excellent yields of the products and ease of work-up fulfill the triple bottom line philosophy of green chemistry and make the present methodology environmentally benign.

Table 2. Optimisation of the Reaction Conditions for the Synthesis of 4a[a]

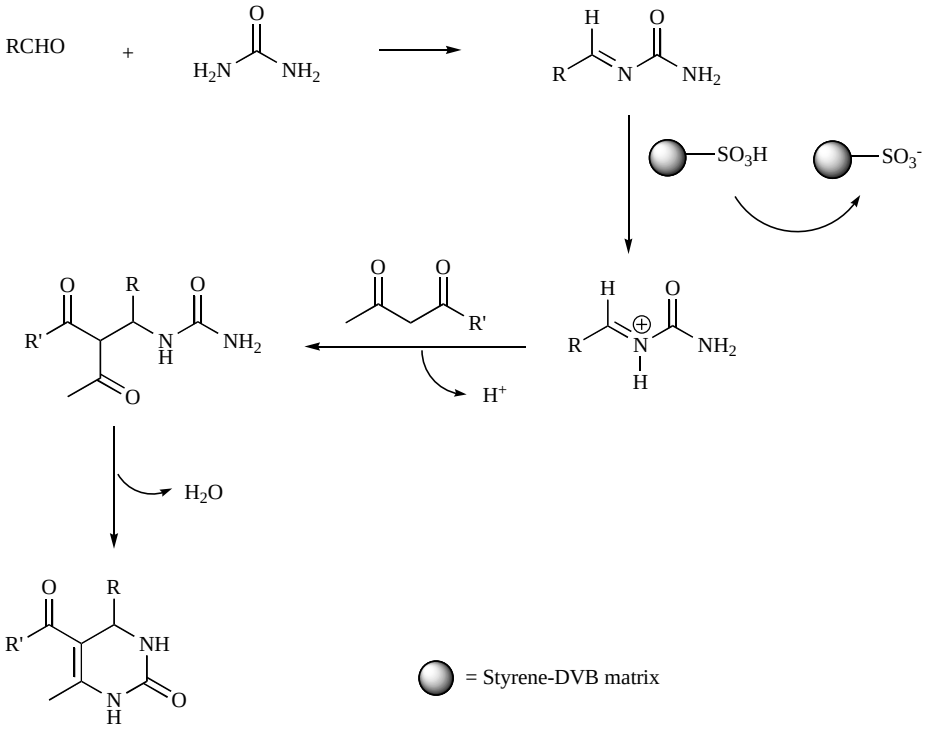
Entry	Catalyst	Solvent	Time (h)	Yield (%)
1	Indion-130	EtOH	3	94
2	Indion-130	CH_3CN	4.5	85
3	Indion-130	THF	6	87
4	Indion-130	Benzene	10	Trace
5	Indion-130	Toluene	10	Trace

[a]All reactions were conducted at reflux temperature of the solvent used.

Table 3. Indion-130 Catalyzed Synthesis of Dihydropyrimidin-2(1H)-ones and Thiones

Entry	R'	R	Product	X	Reaction Time (h)	Yield[a] (%)
1	OEt	H	**4a**	O	3.0	94
2	Me	H	**4b**	O	3.0	95
3	*t*-OBu	H	**4c**	O	3.0	91
4	*t*-OBu	H	**4d**	S	3.0	87
5	*n*-OBu	H	**4e**	S	3.5	87
6	*n*-OBu	4-OMe	**4f**	S	3.5	85
7	Ph	H	**4g**	O	3.25	90
8	Ph	4-Me	**4h**	O	3.25	92
9	Ph	4-OMe	**4i**	O	3.25	92
10	4-NO_2 PhNH	H	**4j**	O	3.75	84
11	4-NO_2 PhNH	4-OCH_3	**4k**	O	3.75	84
12	4-CF_3 PhNH	H	**4l**	O	3.5	86

[a]Isolated yields.



Scheme 2. The proposed mechanism for the formation of pyrimidine.

EXPERIMENTAL

All solvents and reagents were purchased from Aldrich and Merck with high-grade quality, and used without any purification. The Indion-130 was purchased from Ion Exchange India Ltd. Nafion-H and Amberlyst-15 were purchased from Aldrich. Melting points were determined on electro thermal apparatus by using open capillaries and are uncorrected. Thin-layer chromatography was accomplished on 0.2-mm precoated plates of silica gel G60 F_{254} (Merck). Visualization was made with UV light (254 and 365nm) or with an iodine vapor. IR spectra were recorded on a FTIR-8400 spectrophotometer using DRS prob. ^{1}H NMR spectra were recorded on a Bruker AVANCE II (400 MHz) spectrometer in $CDCl_3$. Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. Mass spectra were determined by using direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu). Solvents were evaporated with a BUCHI rotary evaporator.

General Experimental Procedure

A mixture of β-diketone (**1**, 10 mmol), aldehyde (**2**, 10 mmol), urea/thiourea (**3**, 12 mmol), and Indion-130 (500 mg)

in anhydrous ethanol (10 mL) were refluxed for an appropriate time as indicated by TLC. The catalyst was filtered and washed with ethyl acetate until free from organic material. The solvent was evaporated at reduced pressure and obtained solid was crystallised from ethanol to afford pure 3,4-dihydropyrimidin-2-one/thione **4** in excellent yields.

Ethyl 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxylate (4a)

White; mp 202–204 °C; IR (KBr, cm^{-1}): 3245, 3120, 3040, 1730, 1710; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (t, 3H, CH_3), 2.33 (s, 3H, CH_3), 4.04 (q, 2H, OCH_2), 5.20 (s, 1H, CH), 7.41-7.54 (m, 5H, Ar), 7.79 (s, 1H, NH), 8.57 (s, 1H, NH); MS: m/z = 260 (M^+).

5-Acetyl-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1H)-one (4b)

White; mp 219–221 °C; IR (KBr, cm^{-1}): 3256, 3056, 1701, 1664; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.11 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 5.19 (s, 1H, CH), 7.28-7.43 (m, 5H, Ar), 7.90 (s, 1H, NH), 8.69 (s, 1H, NH); MS: m/z = 230 (M^+).

tert-Butyl 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxylate (4c)

White; mp 215–216 °C; IR (KBr, cm^{-1}): 3234, 3089, 1707, 1694, 1645; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (s, 9H, t-Bu), 2.18 (s, 3H, CH_3), 5.10 (s, 1H, CH), 6.87–7.21 (m, 5H, Ar), 7.74 (s, 1H, NH), 9.05 (s, 1H, NH); MS: m/z = 288 (M^+).

tert-Butyl 1,2,3,4-tetrahydro-6-methyl-4-phenyl-2-thioxopyrimidine-5-carboxylate (4d)

Pale-Yellow; mp 206–207 °C; IR (KBr, cm^{-1}); 3185, 3050, 1710, 1554; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (s, 9H, t-Bu), 2.22 (s, 3H, CH3), 5.09 (s, 1H, CH), 7.24-7.48 (m, 5H, Ar), 9.57 (s, 1H, NH), 10.19 (s, 1H, NH); MS: m/z = 304 (M^+).

n-Butyl 1,2,3,4-tetrahydro-6-methyl-4-phenyl-2-thioxopyrimidine-5-carboxylate (4e)

Pale-yellow; mp 206-208 ˚C; IR (KBr, cm^{-1}): 1180, 1427,1456, 1707, 2868, 2976, 3215; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84 (t, 3H, CH_3), 1.20 (m, 2H, CH_2), 1.47 (m, 2H, CH_2), 2.34 (s, 3H CH_3), 4.02 (m, 2H, CH_2), 5.35 (s, 1H, CH), 7.29 (m, 5H, Ph), 8.17 (s, 1H, NH), 8.76 (s, 1H, NH); MS: m/z = 304 (M^+).

n-Butyl 1,2,3,4-tetrahydro-4-(4-methoxyphenyl)-6-methyl-2-thioxopyrimidine-5-carboxylate (4f)

Pale-yellow; mp 186-188 ˚C; IR (KBr, cm^{-1}): 1462, 1560, 1599, 2877, 2955, 3319; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 0.85 (t, 3H, CH_3), 1.21 (m, 2H, CH_2), 1.50 (m, 2H, CH_2), 2.35 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 4.01 (m, 2H, CH_2), 5.28 (s, 1H, CH), 6.83 (d, 2H, Ph), 7.20 (d, 2H, Ph), 8.91 (s, 1H, NH), 9.54 (s, 1H, NH); MS: *m/z* = 334.

5-Benzoyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (4g)

White; mp 202-203 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 2.27 (s, 3H, CH_3), 5.17 (s, 1H, CH), 6.86 (s, 1H, NH), 7.00 (s, 1H, NH), 7.02-7.15 (m, 5H, Ar), 7.24-7.33 (m, 5H, Ar); MS: *m/z* = 292.

5-Benzoyl-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1H)-one (4h)

White; mp 211-213 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 2.16 (s, 3H, CH_3), 2.32 (s, 3H, CH_3) 5.02 (s, 1H, CH), 6.40 (s, 1H, NH), 6.71 (s, 1H, NH), 6.96-7.09 (m, 5H, Ar), 7.18-7.46 (m, 4H, Ar); MS: *m/z* = 306.

5-Benzoyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (4i)

White; mp 218-220 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 2.33 (s, 3H, CH_3), 3.66 (s, 3H, OCH_3) 5.01 (s, 1H, CH), 6.04 (s, 1H, NH), 6.47 (s, 1H, NH), 6.67-7.10 (m, 4H, Ar), 7.20-7.47 (m, 5H, Ar); MS: *m/z* = 322.

6-Methyl-N-(4-nitrophenyl)-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4j)

White; mp 216-217 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.68 (s, 3H, CH_3), 4.96 (s, 1H, CH), 6.96-7.24 (m, 4H, Ar), 7.33-7.89 (m, 5H, Ar), 8.16 (s, 1H, NH), 8.19 (s, 1H, NH), 9.97 (s, 1H, CONH); MS: *m/z* = 352.

4-(4-Methoxyphenyl)-6-methyl-N-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4k)

White; mp 210-212 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.74 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 4.89 (s, 1H, CH), 6.85 (d, 2H, Ar), 7.19 (d, 2H, Ar), 7.87 (m, 2H, Ar), 8.17 (m, 2H, Ar), 8.54 (s, 1H, NH), 8.90 (s, 1H, NH), 10.21 (s, 1H, CONH); MS: *m/z* = 382.

6-Methyl-2-oxo-4-phenyl-N-[4-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4l)

White; mp 208-210 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.64 (s, 3H, CH_3), 5.46 (s, 1H, CH), 7.22-7.50 (m, 4H, Ar), 7.67-8.09 (m, 5H, Ar), 8.45 (s, 1H, NH), 9.98 (s, 1H, NH), 10.14 (s, 1H, CONH); MS: *m/z* = 375.

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