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First application of hexaaquaaluminium(III) tetrafluoroborate as a mild, recyclable, non-hygroscopic acid catalyst in organic synthesis: a simple and efficient protocol for the multigram scale synthesis of 3,4-dihydropyrimidinones by Biginelli reaction

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ABSTRACT

For the first time hexaaquaaluminium(III) tetrafluoroborate has been used as a mild acid catalyst in organic synthesis. A simple method of its preparation based on the reaction of aluminium triisopropoxide and tetrafluoroboric acid in isopropanol afforded catalyst of high purity and activity. The three-component Biginelli condensation of acetoacetate esters, urea and aldehydes catalyzed by 10 mol % of $[Al(H_2O)_6](BF_4)_3$ in refluxing acetonitrile afforded 3,4-dihydropyrimidonones in good to high yields on multigram scales. The tolerance to acid sensitive reactants such as thienyl and furyl carbaldehydes, applicability to sterically hindered β-ketoesters and simple recyclability without losing catalytic activity make this catalyst as good replacement to literature methods. The mechanism of the reaction includes formation of the so called 'ureido-crotonate' rather than corresponding acylimino intermediate as found with Brønsted type catalysts.

1. Introduction

The Biginelli reaction[1] is a well-known, simple and straightforward procedure for the synthesis of 3,4-dihydropyrimidinones (3,4-DHPMs) by the three-component condensation of an aliphatic or aromatic aldehyde, β-ketoester and a urea. The original reaction was first reported by Pietro Biginelli in 1893[2] and was catalysed by mineral acids. This simple procedure has been successful in a number of Biginelli reactions involving substrates lacking sterically-demanded groups. By the three-component Biginelli condensation many 3,4-DHPMs have been synthesized to exhibit variety of pharmacological activity such as calcium channel modulation,[3] mitotic kinesin Eg5 inhibition (monastrol, Fig. 1),[4] antiviral,[5] antibacterial and antifungal activity,[6] anticancer[7] (MAL3-101, Fig. 1) etc.[8] 3,4-DHPMs are also used as starting material for the synthesis of so called 'superstatin' rosuvastatin selective and competitive inhibitor of HMG-CoA reductase,[9] the enzyme responsible for the biosynthesis of cholesterol. Moreover, the 3,4-DHPM motif is present in many products isolated from natural material such as several species of sponges. The representatives such as batzelladines, ptilomycalines and crambescidines[10] (Fig. 1) exhibit many biological activities such as anticancer, antifungal, anti HIV etc.

During the last few years, numerous catalytic methods have been developed in order to improve the reaction yield or the scope of the Biginelli reaction. A recent review article shows the interest of the synthetic chemists in order to find better and more selective catalysts for Biginelli 3,4-DHPM synthesis.[11] Most of the methods are based on employing Brønsted or Lewis acid type catalysts.[12–29] Probably the most effective methods involve the reagent(s), which are stoichiometric dehydrating agents in the presence of protic or Lewis acids: ethyl polyphosphate,[30] TMSCl,[31] TMSCl/NaI,[32] $FeCl_3$/$Si(OEt)_4$,[33] etc. However these methods suffer from cumbersome work-up of the reaction mixture and production of water waste and thus are suitable for the synthesis only on a small scale. In the recent years, catalysts, which are recyclable and capable of performing the reaction under mild condition have gained particular attention.[11,22,34,35] Those characteristics of the catalyst are essential in the case of the enantioselective version of Biginelli reaction.[36] From that point there is still need to find catalyst, which are capable to perform reaction under milder reaction conditions.

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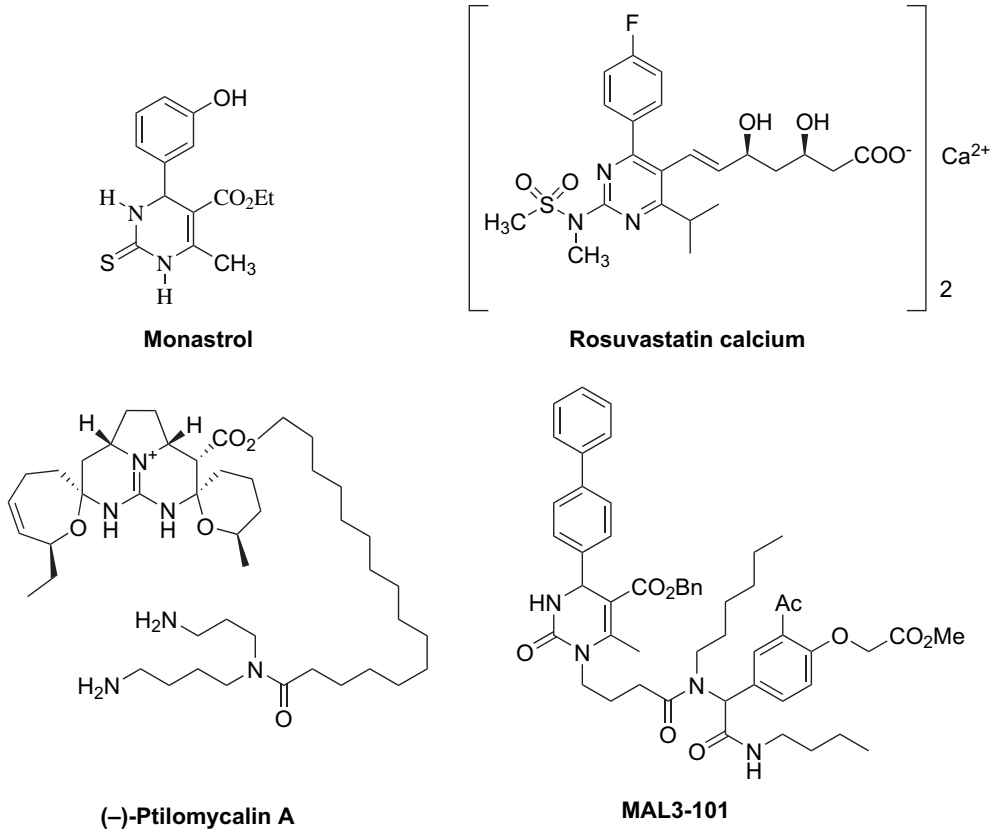


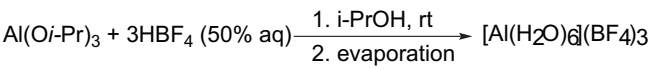
Figure 1.

Despite the plethora of different catalysts published so far and proved to be an efficient in Biginelli reaction the synthetic chemists may encounter the problem in finding the right one if reaction should be performed on larger scale. Moreover, most of them are exotic, expensive, complex, unavailable, harmful and sometimes ineffective in reaction with more complex reactants. Therefore, development of more selective and greener methods employing recyclable catalysts in Biginelli 3,4-DHPM synthesis is still demanded.

2. Results and discussion

In continuation of our research on chemistry of 3,4-DHPMs we required multigram scale samples as a starting material for the study of their aromatization to the corresponding pyrimidines (similarly to chemistry of Hantzsch 1,4-dihydropyridines[37,38]). From our previous experience[12,33] we have found Lewis acids superior over Brønsted acids due to better selectivity and higher yields of the products. Thus we were guided to choose one suitable from the literature available on large scale, nonexpensive and recyclable. Interestingly, not many of them fulfilled the above requirements. Metallic triflates such as $Cu(OTf)_2$[35] $Zn(OTf)_2$[34] and $Yb(OTf)_3$ [22] as very efficient easily recyclable catalysts are not available in multigram quantities. Other, although readily available as laboratory chemicals such as $NiCl_2\cdot 6H_2O$,[13] $FeCl_3\cdot 6H_2O$,[13] $CuCl_2\cdot 2H_2O$,[14] $CeCl_3\cdot 7H_2O$,[15] $Mn(OAc)_3\cdot 2H_2O$[16] are not easily recyclable and thus not appropriate for our study. From basic organic synthesis it is known that aluminium halides such as $AlCl_3$ and $AlBr_3$ act as a strong Lewis acid catalyst in many organic transformations such as Friedel–Crafts acylations[39] and alkylations, rearrangements etc. A literature survey revealed that $AlCl_3$,[40] $AlBr_3$[40] and $Al(HSO_4)_3$[21] have already been used as a catalysts in Biginelli reaction. That encouraged us to find appropriate alternative to mentioned aluminium salt equally efficient but more water tolerant and recyclable.

One of the best alternative to aluminium halides is water tolerant and recyclable aluminium triflate ($Al(OTf)_3$), which has found its use as a catalyst for acetal formation,[41] ring opening of epoxides by alcohols,[42] synthesis of diethyl-1-aminophosphonates,[43] etc.[44] To the best of our knowledge $Al(OTf)_3$ has not been used as a catalyst in Biginelli 3,4-DHPM synthesis although it is expected to be at least equally active as other metallic triflates employed in the same reaction.[11,22,34,35] However, $Al(OTf)_3$ is not easily available and thus not appropriate as catalyst candidate for multigram scale synthesis of 3,4-DHPMs.[45] A much less expensive alternative to $Al(OTf)_3$ is the corresponding tetrafluoroborate salt. Literature survey revealed that aluminium tetrafluoroborate has been used as heterogenous catalyst[46] (impregnated to aluminosilicates or Al_2O_3) for isomerization of tricyclic naphthenes into adamantanes,[47] dealkylation of alkylphenols[48] or alkylaromatics[49] and recently as an additive in production of nonaqueous electrolyte batteries.[50] To our surprise aluminium tetrafluoroborate has not been prepared in pure form without a solid carrier and not used so far in classical organic synthesis. In order to test it in Biginelli reaction a few grams of catalyst was needed. The literature method of preparation was not convenient due to the difficult evaporation of the aqueous solution obtained by the treatment of $Al(OH)_3$ and boric acid in water with hydrofluoric acid.[47,48a] Therefore we developed new simple and practical method for preparation of pure $[Al(H_2O)_6](BF_4)_3$ according to Scheme 1.



Scheme 1.

By the treatment of commercial aluminium triisopropoxide dissolved in isopropanol at room temperature with stoichiometric amount of tetrafluoroboric acid (48% in water), evaporation of solvent and drying under vacuum, pure $[Al(H_2O)_6](BF_4)_3$ was prepared on 0.1 mol scale. The analysis of water content on dry catalyst by the Karl–Fisher method revealed that corresponding hexahydrate is obtained ($[Al(H_2O)_6](BF_4)_3$). The catalyst is non-hygroscopic and stable for a period of several months at room temperature. According to X-ray diffraction data (XRD) the $[Al(H_2O)_6](BF_4)_3$ is mainly amorphous substance characterized by the presence of broad background signal as depicted from Figure 2.[51] The recrystallization of $[Al(H_2O)_6](BF_4)_3$ ('hexahydrate') from water afforded a literature new salt $[Al(H_2O)_6](BF_4)_3\cdot 3H_2O$ ('nonahydrate') with presumably similar structure as corresponding hexaaquaaluminium(III) bromate trihydrate.[52] The FT-IR spectra of $[Al(H_2O)_6](BF_4)_3$ is characterized by the presence of strong water-stretching region (3200–3600 cm^{-1}) and low intensive bands at 1060 and 530 cm^{-1} characteristic for BF_4^- anion.[53]

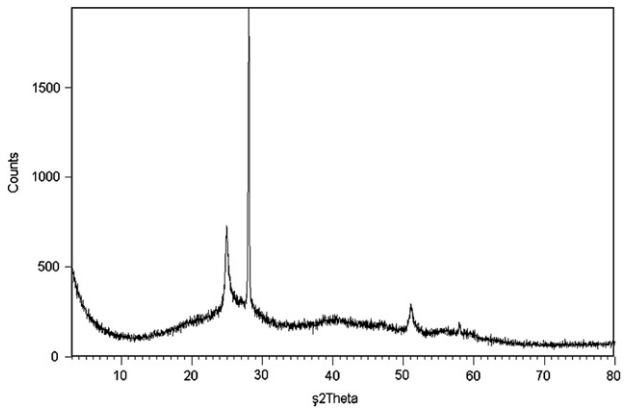
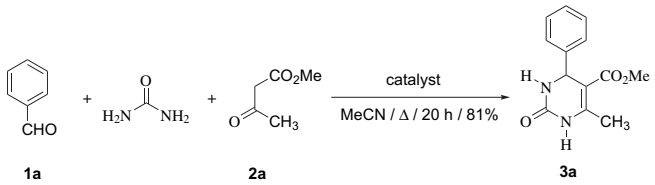


Figure 2. XRD pattern of $[Al(H_2O)_6](BF_4)_3$.

The thus obtained catalyst has been tested in the three-component condensation of benzaldehyde (**1a**), methyl-acetoacetate (**2a**) and urea in acetonitrile at reflux temperature according to Scheme 2.[54]



1a **2a** **3a**

Scheme 2.

After carrying out the reaction during 20 h and work-up of reaction mixture the product **3a** was isolated in 81% yield on a 10 mmol scale. For the comparison the same reaction has been performed with 16 different catalysts and the obtained results are outlined in Table 1. According to the obtained results $[Al(H_2O)_6](BF_4)_3$ is not only superior over other aluminium salts (Table 1, entries 1–3) but also to all other tested catalysts from the literature such as $CeCl_3\cdot 7H_2O$, $ZnCl_2$, $CuCl_2\cdot 2H_2O$, $FeCl_3\cdot 6H_2O$ etc. (Table 1, entries 5–13). The obtained results suggest that the non-coordinating counter ion BF_4^- plays an important role in activity of $[Al(H_2O)_6](BF_4)_3$ presumably by increasing acidity of $[Al(H_2O)_6]^{3+}$ cation.

Table 1
Catalyst effect (10 mol %) in the model Biginelli reaction (Scheme 1) on the yield of model 3,4-DHPM **3a** (10 mmol scale). Comparative study with literature catalysts

Entry	Catalyst	Reaction time[a]	Yield[b] (%)	Ref.
1	$AlCl_3\cdot 6H_2O$	24	48	—
2	$Al_2SO_4\cdot 16H_2O$	24	34	—
3	$AlCl_3$	20	64	38
4	$[Al(H_2O)_6](BF_4)_3$	20	81	This article
5	$NiCl_2\cdot 6H_2O$	20	73	13
6	$CeCl_3\cdot 7H_2O$	20	64	15
7	$ZnCl_2$	20	52	19
8	ZnI_2	20	60	55
9	$CuCl_2\cdot 2H_2O$	16	71	14
10	$CuSO_4\cdot 5H_2O$	24	69	14
11	$Mn(OAc)_3\cdot 2H_2O$	24	70	16
12	$FeCl_3$	18	73	—
13	$FeCl_3\cdot 6H_2O$	24	71	13

[a] Determined by TLC analysis.
[b] Isolated yield.

Next, we wanted to test the effect of the solvent on the reaction in order to find the optimal reaction condition. As presented in Table 2, acetonitrile emerged as the most convenient (entry 3) although in toluene the yield of **3a** (77%) is also high (entry 1). This is probably due to much higher boiling point of toluene (111 °C) compared to acetonitrile (82 °C).

Table 2
The influence of the solvent on the yield of model 3,4-DHPM **3a**

Entry	Solvent	Time	Yield[c] (%)
1	Toluene[a]	24	77
2	EtOH[a]	24	64
3	CH_3CN[a]	20	81
4	THF[a]	48	53
5	–[b]	24	61

[a] Reflux temperature.
[b] 100 °C, solventless media.
[c] Isolated yield.

Interestingly, the reaction performed under solventless media at 100 °C during 24 h (Table 2, entry 5) afforded product **3a** in only 61% yield. It seems that coordination of solvent at coordination sphere of cation determines the activity of catalyst, thereby improving the yield of the product. Finally, the last parameter needed to improve the reaction condition was the influence of the amount of the catalyst on the yield of **3a**, Table 3. The model reaction without a catalyst during 48 h at reflux in acetonitrile gives by TLC analysis only traces of the product (Table 3, entry 1). The incremental amount of catalyst from 1 to 50 mol % increases the conversion and yield of the product, (with shortening of the reaction times) from 32 to almost quantitative (Table 3, entries 2–5). However, 10 mol % of catalyst has been choosen for further studies because of satisfactory yield of the product (81%) in reasonably short time ('reflux overnight'). Moreover, the isolation of the product in case if reaction is carried out with 50 mol % of catalyst is somehow difficult due to coprecipitation of the catalyst and product.

Table 3
The influence of the amount of catalyst $[Al(H_2O)_6](BF_4)_3$ on the synthesis of model 3,4-DHPM **3a**

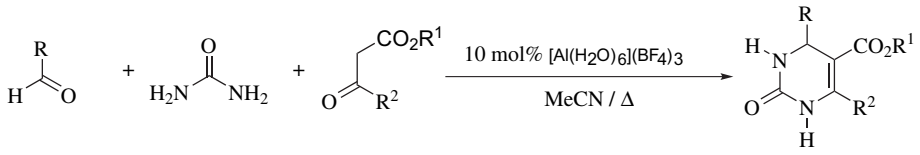
Entry	$[Al(H_2O)_6](BF_4)_3$[a] (mol %)	Time[a] [h]	Yield[b] (%)
1	No catalyst	48	Traces of the product
2	1	48	32
3	5	24	58
4	10	20	81
5	50	19	98

[a] Determined by TLC analysis.
[b] Isolated yield.

With optimized conditions in hand we decided to explore the scope and limitations of this method. Thus, series of Biginelli 3,4-DHPMs with significant steric, electron withdrawing and donating substituents, were synthesized and the obtained results are summarized in Table 4. While preliminary investigation (including optimization) has been performed on 10 mmol scale all preparative experiments were conducted on 200 mmol scale affording 40–50 g of the products depending on the molecular weights.

In order to provide a reasonable explanation of obtained results (tolerance to variety of substituted reactants) we performed a few experiments regarding determination of possible mechanistic pathways of the reaction.

Table 4
Three component synthesis of substituted 3,4-DHPMs **3a**–**q** catalyzed by $[Al(H_2O)_6](BF_4)_3$ (10 mol %) in acetonitrile at reflux temperature



1a-1n **2a-2g** **3a-3q**

Entry	3,4-DHPM	R	R^1; R^2	*t* (h)	Yield (%)[a,b]
1	**3a**	Ph	Me; Me	20	85
2	**3b**	*p*-FC_6H_4	Me; Me	22	84
3	**3c**	2,4-$(CH_3)_2C_6H_4$	Me; Me	18	93
4	**3d**	*o*-$OC_2H_5C_6H_4$	Me; Me	20	92
5	**3e**	2-Furyl	Me; Me	22	83 (92)[c]
6	**3f**	2-Thienyl	Me; Me	20	80 (89)[c]
7	**3g**	2-(5-Br-thienyl)	Me; Me	20	87
8	**3h**	*p*-ClC_6H_4	Me; *i*-Pr	21	81
9	**3i**	2-Thienyl	Me; *i*-Pr	20	83 (90)[c]
10	**3j**	*o*-ClC_6H_4	Et; Me	20	88
11	**3k**	*m*-ClC_6H_4	Et; Me	20	95
12	**3l**	*p*-ClC_6H_4	Et; Me	21	81
13	**3m**	*p*-$NO_2C_6H_4$	Et; Me	20	85
14	**3n**	Ph	Et; *n*-Pr	24	81
15	**3o**	Ph	Et; Ph	24	80
16	**3p**	*p*-$OCH_3C_6H_4$	*i*-Pr; Me	20	83
17	**3q**	*p*-$CH_3C_6H_4$	CH_2Ph; Me	21	82

[a] Isolated yield.
[b] All products were characterized by ^1H NMR, ^{13}C NMR, IR and MS spectra. Literature known compounds were compared with authentic samples.
[c] Yield obtained with freshly distilled aldehyde.

The main characteristics of the reaction are good to excellent yields (80–95%) of the products obtained after simple work-up, ability to tolerate the variation in all the two components (β-ketoesters and aldehydes), reuse of the catalyst without loosing of activity and most of all possibility of scale-up of reaction in order to prepare the products on multigram amounts. Both electronic withdrawing (F, Cl, NO_2) and donating substituents (CH_3, OCH_3) on the aldehyde reactant are well tolerated in reaction without significant impact on the yield of the product. Moreover, acid sensitive aldehydes such as thienyl (**1f**), 5-bromothienyl (**1g**) and furyl carbaldehydes (**1e**) furnished products in yields of 80%, 87% and 83%, respectively. Interestingly, freshly distilled **1e** and **1f** used in reaction have shown an improvement in yield of the products for almost 10% (Table 4, entries 5, 6 and 9). However, this was not the case for other usually stable aldehydes used in reaction. Most importantly, the reaction with sterically hindered methyl isobutyrylacetate (entries 8 and 9), ethyl butyrylacetate (entry 14) and ethyl benzoylacetate (entry 15) proceeded unexpectedly well and the valuable literature unknown products usually prepared with difficulty were isolated in excellent yield (>80%). As mentioned above, the catalyst as well as the excess of urea are easily recycled by extraction of residue obtained after evaporation of ethanolic mother liquor (see Experimental Section) with hot water and evaporation of thus formed catalyst solution. The recycled catalyst was used over four times without loss of activity when ethylacetoacetate (**2c**), *m*-chlorobenzaldehyde (**1k**) and urea were condensed in Biginelli reaction to give **3k**, Table 5. This feature provides a significant benefit (environmental and cost) over traditional Lewis and Brønsted acids.

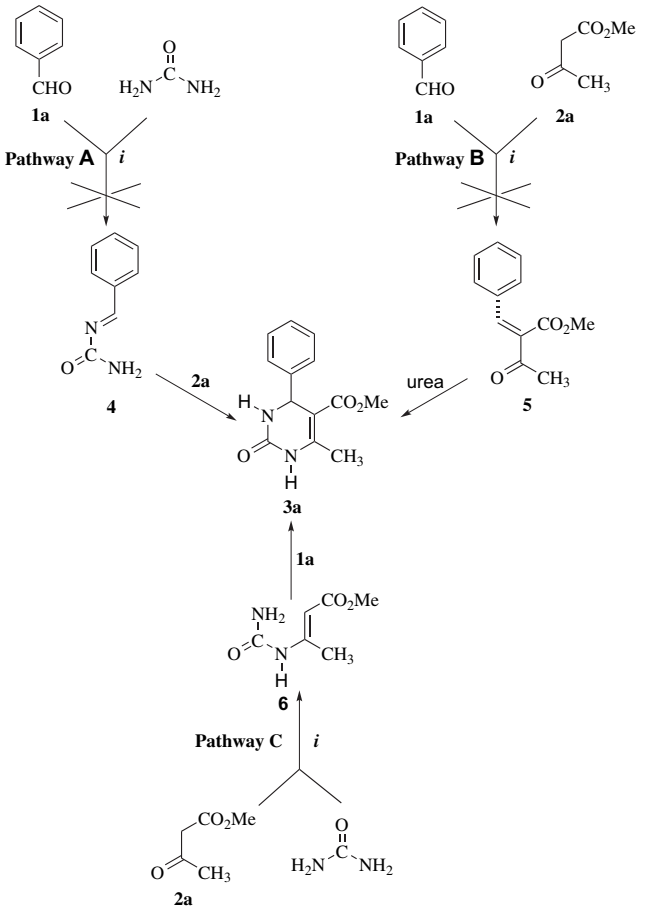
Table 5
$[Al(H_2O)_6](BF_4)_3$ recycling experiments on Biginelli **3k** synthesis

Run[a]	Yield[b] (%)
1	95
2	94
3	93
4	93

[a] The yield of isolated mixture of catalyst and unreacted urea is about 95% after each run.
[b] Isolated yield of **3k** on 10 mmol scale.

According to the literature three possible mechanisms are proposed but generally accepted Biginelli reaction mechanism includes the acid-catalysed formation of C=N bond from the benzaldehyde (**1a**) and urea, followed by addition of β-ketoester **2a** to the arylidene–urea **4** and cyclodehydration of intermediates yielding dihydropyrimidinone **3a** (Scheme 3, pathway A).[56–58]

However, this mechanism is probably characteristic only for protic acids but not for other types of acid catalysts including metallic salts. This conclusion comes from our results obtained with $SbCl_3$-catalysed synthesis of 3,4-DHPMs where pathway C (Scheme 3) is dominant to yield the product[12] while other two (pathway A and B) surprisingly do not participate in reaction at all. In order to clarify the role of $[Al(H_2O)_6](BF_4)_3$ three separated



i: 10 mol% $[Al(H_2O)_6](BF_4)_3$ / MeCN / reflux

Scheme 3.

reactions were conducted (Scheme 3, pathways A–C) under the optimized reaction condition (10 mol % of $[Al(H_2O)_6](BF_4)_3$ at reflux temperature during 24 h).

The prolonged heating of benzaldehyde (**1a**) and methyl acetoacetate (**2a**) did not undergo the expected reaction (pathway C) to yield a mixture (*E*/*Z*) of Knoevenagel products (**5**). The reaction of benzaldehyde (**1a**) and urea furnished only a trace (conversion <10%) of the arylidene–urea **4** (pathway A) whereas the condensation of methyl acetoacetate (**2a**) and urea smoothly furnished *N*-(1-ethoxycarbonyl-propen-2-yl)urea (**6**), which upon addition of benzaldehyde (**1a**) was easily converted to dihydropyrimidinone **3a** (Scheme 3, pathway C). The isolation of intermediate **6** is possible by the chromatographic method described in our previous article.[12] These findings clearly indicate that Biginelli reaction catalysed by $[Al(H_2O)_6](BF_4)_3$ proceeds predominately through ureido-crotonate intermediate **6** (pathway C), which somewhat supports prediction that Biginelli reaction catalysed by other types of acid catalysts such as metallic salts does not include formation of arylidene–urea **4** as in Brønsted type catalysis.[58] According to these results $[Al(H_2O)_6](BF_4)_3$ acts as a Lewis acid in reaction. Furthermore, this is also supported by the fact that ureido-crotonate intermediate **6** in Biginelli reaction catalysed by Brønsted type catalysts is regarded as unlikely.[58] Despite this observation, it is well-known from the literature that the $[Al(H_2O)_6]^{3+}$ cation in water solution acts as a weak proton donor (pK_a=4.97),[59] of comparable acidity to acetic acid (pK_a=4.76).[60] The dissociation of $[Al(H_2O)_6]^{3+}$ cation and possible action of a catalyst as Brønsted acid is presented in Scheme 4.

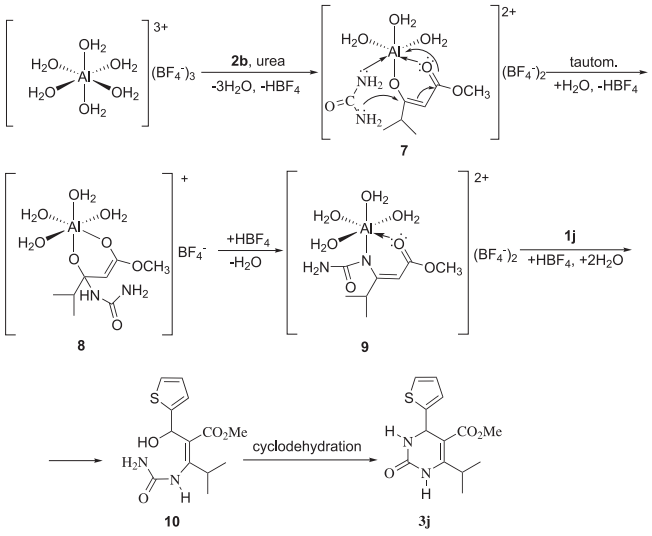
$$[Al(H_2O)_6]^{3+} \rightleftharpoons [Al(OH)(H_2O)_5]^{2+} + H^+$$

Scheme 4.

In order to determine whether the $[Al(H_2O)_6](BF_4)_3$ acts as a Lewis or Brønsted acid catalyst (or both) a series of experiments were carried out employing glacial acetic acid (Brønsted acid) and anhydrous $AlCl_3$ (Lewis acid) as a catalysts. The reactions were performed under the same reaction condition as outlined in Scheme 3. As expected, none of the catalysts was capable of performing the reaction between benzaldehyde (**1a**) and methyl acetoacetate (**2a**) to give **5** (pathway B). The condensation of urea and methyl acetoacetate (**2a**) catalysed by 10 mol % of glacial acetic acid did not undergo formation of **6**, which is in accordance to literature results for this type of reaction.[58] Interestingly, the condensation of urea and benzaldehyde (**1a**) even after 48 h at reflux in acetonitrile furnished only a traces of condensation product **4**, presumably as corresponding 'bisureide'[58] obtained by addition of second molecule of urea to **4**. As already mentioned $[Al(H_2O)_6](BF_4)_3$ with similar pK_a value as the acetic acid reached almost 10% conversion in the same reaction. Therefore, along with an activity as a Brønsted acid (proton donor) the coordination of the reactants on a coordination sphere of aluminium (Lewis acid activity) should not be neglected. The condensation of urea and methyl acetoacetate (**2a**) catalysed by 10 mol % of anhydrous $AlCl_3$ in acetonitrile at room temperature afforded **6** in 80% yield whereas urea and benzaldehyde (**1a**) did not react under the same reaction condition. If the latter reaction was carried out at reflux temperature roughly 15% conversion was reached, probably by the action of HCl released by decomposition of the catalyst with water formed in reaction. According to obtained results the pathway A (Scheme 3) is characteristic for the Brønsted type of catalysts whereas Lewis acid type of catalysts follow the pathway C (ureido-crotonate mechanism). Although without a free orbital (main characteristic of a Lewis acid) the aluminium in $[Al(H_2O)_6](BF_4)_3$ similarly to anhydrous $AlCl_3$ efficiently catalyzed reaction of urea and methyl acetoacetate (**2a**) to give **6** in high yield (Scheme 3, path C). To explain this observation the substitution of water molecules in coordination spheres of aluminium is required to allow satisfactory activity of the catalyst. Recently, Katakura and co-workers have published the one-step synthesis of aluminium(III) acetylacetonate from mineral Boehmite ($[AlO(OH)]_n$) and acetylacetone in water at room temperature.[61] They have shown how by simple mixing of reactants substitution of ligands such as hydroxide ions and oxygen bridges in mineral are replaced by organic bidentate ligand at mild reaction condition. We believe that substitution of two water molecules in $[Al(H_2O)_6](BF_4)_3$ by β-ketoester is even more facilitated at elevated temperature (reflux of acetonitrile).

As a result of a detailed experimental mechanistic investigation plausible simplified mechanism of $[Al(H_2O)_6](BF_4)_3$-catalysed Biginelli 3,4-DHPM synthesis is proposed to include activation of reactants by the dual action of the catalyst (Lewis and Brønsted acid) according to Scheme 5.

The presented mechanism on 3,4-DHPM **3j** having sterically-demanded groups is used to explain low sensitivity of reaction to electronic and sterical nature of substituents (Table 4). The catalytic cycle begins with a complexation of methyl isobutyrylacetate **2b** and urea on a catalyst to form **7** with elimination of three water molecules and HBF_4. The formation of more stable complex between catalyst and methyl isobutyrylacetate **2b** (bidentate ligand) than with aldehyde **1j** (monodentate ligand) allows intramolecular nucleophilic attack (Michael addition) of urea to activated C=C double bond followed by tautomerisation and elimination of HBF_4 to give a complexed hemiaminal **8**. The intramolecular tautomerization and elimination of water produce so



Scheme 5.

called 'ureido-crotonate' **9** in a complex with catalyst. The increased nucleophilicity of the carbon from the enamine group facilitates the addition to protonated thienyl carbaldehyde **1j** to form intermediate **10**, which with subsequent cyclodehydration yields product **3j**. The rate determining step of reaction is addition of urea to **2b** accelerated by chelation with aluminium cation, Scheme 5.

The reaction with aldehyde **1j** is facilitated by the precomplexation to **9** and/or protonation of carbonyl group by the action of HBF_4 released during the catalytical cycle. Therefore the reaction with aldehydes having both electron donating and withdrawing substituents gives similar results in reaction. As a result $[Al(H_2O)_6](BF_4)_3$ primarly acts as a Lewis acid catalyst in reaction but its Brønsted acid behaviour is particularly important during the activation of aldehyde component by protonation during catalytical cycle.

3. Conclusion

In conclusion, $[Al(H_2O)_6](BF_4)_3$ in an amount of 10 mol % has shown to be an excellent acid catalyst for one pot synthesis of 3,4-dihydropyrimidinones on multigram scales in good to high yields. The tolerance to acid sensitive reactants such as thienyl and furyl carbaldehydes, applicability to sterically hindered β-ketoesters and simple recyclability without losing catalytic activity making a catalyst as valuable addition to existing methods. The mechanism of the reaction includes formation of the so called 'ureido-crotonate' rather than corresponding acylimino intermediate as typical for Brønsted type catalysts. Further work is in progress to explore the catalytical activity of $[Al(H_2O)_6](BF_4)_3$ to other organic transformations such as Friedel–Crafts acylations, synthesis of other heterocyclic systems, rearrangements, etc.

4. Experimental

4.1. General

All IR spectra were recorded on a Perkin-Elmer Spectrum One spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a AV Bruker (600 MHz) spectrometer, and shifts are given in ppm downfield from TMS as an internal standard. TLC analyses were performed on Merck's (Darmstadt, Germany) DC-alufolien with Kieselgel 60F_{254}. Melting points were determined using a Büchi B-540 instrument. HPLC analyses were performed with a Thermo Separation Products (San Jose, USA) instrument equipped with vacuum degasser SCM 1000, quaternary gradient pump P 4000, autosempler AS 3000, scanning UV/vis detector UV 3000 HR and ChromQuest 251 software. Elemental analyses were done in Central Analytical Service (CAS) at Ruđer Bošković Institute. Karl–Fischer analysis was performed on Karl–Fischer Titrator Mettler Toledo DL31. HPLC MS analysis was performed on HPLC Waters Alliance 2795 with PDA detector Waters 996 (210–350 nm) and MS detector Micromass ZMD 4000 (ESI 3.50 kV). Powder X-ray data (XRD) were collected on Philips PW 3710 diffractometer, Cu Kα1 radiation, flat plate sample on a zero background in Bragg-Brentano geometry, tension 40 kV, current 40 mA. The literature known products were characterized by a comparison with authentic samples (melting point) and their NMR (^1H, ^{13}C), MS and IR spectra.[22,34,62–71]

4.2. Preparation of $[Al(H_2O)_6](BF_4)_3$

To a solution of aluminium triisopropoxide (20.4 g, 0.1 mol) in *i*-PrOH (240 mL), a commercial water solution of HBF_4 (39.2 mL, 0.3 mol, 48% in water) was added dropwise at room temperature during 30 min. The resulting solution after stiring at room temperature during 2 h was evaporated off to give gelatinous mass, which was slowly dried at 50 °C under vacuum during 24 h and additionally at 80 °C for 24 h to furnish $[Al(H_2O)_6](BF_4)_3$ as a white powder in almost quantitative yield (39 g), mp 100 °C (decomp.); [Found: H, 3.1. $AlB_3F_{12}H_{12}O_6$ requires Al, 6.82; B, 8.20; F, 57.65; H, 3.06%]; ν_{max}(KBr) 3431, 3249, 1637, 1477, 1305, 1300, 1194, 1083, 1069, 1063, 1040, 884, 771, 650, 534, 522.

4.3. General procedure for synthesis of 3,4-DHPMs

To a solution of corresponding aldehyde **1a**–**n** (0.2 mol, 1 equiv) in the acetonitrile (250 mL) urea (18.02 g, 0.3 mol, 1.5 equiv), β-ketoesters **2a**–**g** (0.2 mol, 1 equiv) and catalyst $[Al(H_2O)_6](BF_4)_3$ (10 mol %, 7.91 g) were added at once. The reaction mixture was stirred at reflux temperature for the time indicated in Table 4. After that acetonitrile was evaporated and the solid residue was recrystallized from hot 96% ethanol. The thus obtained product was filtered and dried in vacuum to constant weight to afford products **3a**–**q** of purities >99% (HPLC). Analytical results (IR, ^1H, ^{13}C NMR) of known products were identical to those reported in literature.[22,34,62–71]

4.3.1. 5-Methoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one ***3a****.* White needles (41.9 g, 85%); mp 208.0–210.0 °C (lit. Mp 208–210 °C[62]); [Found: C, 63.3; H, 5.7; N, 11.3. $C_{13}H_{14}N_2O_3$ requires C, 63.40; H, 5.73; N, 11.38%]; R_f (10% MeOH/CH_2Cl_2) 0.46; ν_{max}(KBr) 3246, 1732, 1664 cm^{-1}; δ_H (600 MHz, DMSO-d_6) 2.19 (s, 3H, CH_3), 3.87 (s, 3H, –COOCH_3), 5.02 (d, 1H, *J*=2.07 –C*H*), 7.25 (m, 5H, arom.), 7.64 (s, 1H, N*H*), 9.15 (s, 1H, N*H*); *m*/*z* 247 (MH^+).

4.3.2. 5-Methoxycarbonyl-6-methyl-4-(4-fluorophenyl)-3,4-dihydropyrimidin-2(1H)-one ***3b****.* White needles (44.4 g, 84%); mp 191.0–193.0 °C (lit. Mp 192–194 °C;[22] 193–194 °C[63]); [Found: C, 59.2; H, 4.8; F, 7.1; N, 10.7. $C_{13}H_{13}FN_2O_3$ requires C, 59.09; H, 4.96; F, 7.19; N, 10.60%]; R_f (10% MeOH/CH_2Cl_2) 0.48; ν_{max} (KBr) 3328, 3230, 3109, 2953, 1668, 1509, 1437, 1414, 1343, 1300, 1276, 1240, 1190, 1159, 1120, 1095, 1039, 1016 cm^{-1}; δ_H (600 MHz, DMSO-d_6) 2.26 (3H, s, CH_3), 3.53 (3H, s, OCH_3), 5.17 (1H, d, *J*=2.8, C*H*), 7.14 (2H, t, *J*=8.7, arom.), 7.25–7.30 (2H, m, arom.), 7.81 (1H, br s, N*H*), 9.32 (1H, s, N*H*); *m*/*z* 265 (MH^+).

4.3.3. 5-Methoxycarbonyl-6-methyl-4-(2,4-dimethylphenyl)-3,4-dihydropyrimidin-2(1H)-one ***3c****.* Pale yellow needles (51.1 g, 93%); mp 245.0–247.0 °C; [Found: C, 65.8; H, 6.4; N, 10.1. $C_{15}H_{18}N_2O_3$ requires C, 65.68; H, 6.61; N, 10.21%] R_f (10% MeOH/CH_2Cl_2) 0.44; ν_{max} (KBr) 3370, 3220, 3102, 2947, 1701, 1646, 1500, 1456, 1432, 1367, 1321,

1300, 1223, 1187, 1165, 1118, 1095 cm^{-1}; δ_H (600 MHz, DMSO-d_6) 2.22 (3H, s, CH_3), 2.29 (3H, s, CH_3), 2.37 (3H, s, CH_3), 3.45 (3H, s, OCH_3), 5.37 (1H, s, C*H*), 6.93–6.97 (2H, m, arom.), 7.07 (1H, d, J=7.7, arom.), 7.63 (1H, s, N*H*), 9.22 (1H, s, N*H*); δ_C (600 MHz, DMSO-d_6) 165.83, 151.83, 148.39, 140.34, 136.26, 134.53, 130.86, 127.13, 126.55, 99.27, 50.75, 50.17, 20.61, 18.62, 17.78; m/z 275 (MH^+), 200, 183.

4.3.4. 5-Methoxycarbonyl-6-methyl-4-(2-ethoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one ***3d***. White powder (53.4 g, 92%); mp 237.0–239.0 °C (lit. Mp not reported[64]); [Found: C, 62.2; H, 6.2; N, 9.7. $C_{15}H_{18}N_2O_4$ requires C, 62.06; H, 6.25; N, 9.65%]; R_f (10% MeOH/CH_2Cl_2) 0.54; ν_{max} (KBr) 3371, 3237, 3106, 2974, 2949, 1699, 1643, 1598, 1586, 1494, 1473, 1432, 1395, 1377, 1349, 1324, 1306, 1268, 1232, 1187, 1154, 1123, 1141, 1099, 1043 cm^{-1}; δ_H (600 MHz, DMSO-d_6) 1.37 (3H, t, J=6.8, OCH_2CH_3), 2.28 (3H, s, CH_3), 3.47 (3H, s, OCH_3), 4.02–4.06 (2H, m, OCH_2CH_3), 5.46 (1H, s, C*H*), 6.85 (1H, t, J=7.4, arom.), 6.97 (1H, d, J=8.2, arom.), 7.06 (1H, d, J=7.5, arom.), 7.18–7.24 (2H, m, N*H*+arom.), 9.18 (1H, s, N*H*); δ_C (600 MHz, DMSO-d_6) 165.8, 156.1, 152.2, 148.9, 131.4, 128.7, 127.6, 119.9, 111.9, 97.0, 63.3, 50.6, 50.1, 17.8, 14.5; m/z 291 (MH^+).

4.3.5. 5-Methoxycarbonyl-6-methyl-4-(2-furyl)-3,4-dihydropyrimidin-2(1H)-one ***3e***. Grey needles (39.2 g, 83%); mp 229.5–231.5 °C (lit. Mp 231–232 °C[34]); [Found: C, 55.8; H, 5.3; N, 11.8. $C_{11}H_{12}N_2O_4$ requires C, 55.93; H, 5.12; N, 11.86%]; R_f (10% MeOH/CH_2Cl_2) 0.60; ν_{max} (KBr) 3317, 3119, 2955, 1708, 1673, 1638, 1505, 1433, 1381, 1340, 1315, 1277, 1238, 1221, 1189, 1152, 1088, 1013 cm^{-1}; δ_H (600 MHz, DMSO-d_6) 2.23 (3H, s, CH_3), 3.57 (3H, s, OCH_3), 5.20 (1H, d, J=3.4, C*H*), 6.10 (1H, d, J=3.1, arom.), 6.34–6.36 (1H, m, arom.), 7.55 (1H, d, J=0.9, arom.), 7.78 (1H, br s, N*H*), 9.27 (1H, s, N*H*); m/z 237 (MH^+).

4.3.6. 5-Methoxycarbonyl-6-methyl-4-(2-thienyl)-3,4-dihydropyrimidin-2(1H)-one ***3f***. White needles (40.4 g, 80%); mp 225.5–227.0 °C (lit. Mp not reported[65]); [Found: C, 52.3; H, 4.7; N, 11.3; S, 12.6. $C_{11}H_{12}N_2O_3S$ requires C, 52.37; H, 4.79; N, 11.10; S, 12.71%]; R_f (10% MeOH/CH_2Cl_2) 0.50; ν_{max} (KBr) 3351, 3218, 3111, 2947, 2813, 1692, 1642, 1526, 1499, 1454, 1428, 1380, 1316, 1302, 1231, 1202, 1187, 1160, 1118, 1036 cm^{-1}; δ_H (600 MHz, DMSO-d_6) 2.24 (3H, s, CH_3), 3.60 (3H, s, OCH_3), 5.43 (1H, d, J=3.4, C*H*), 6.91–6.95 (2H, m, arom.), 7.35 (1H, dd, J_1=1.0, J_2=4.9, arom.), 7.93 (1H, br s, N*H*), 9.35 (1H, s, N*H*); δ_C (600 MHz, DMSO-d_6) 165.55, 152.30, 148.96, 148.78, 126.79, 124.68, 123.62, 99.64, 50.92, 49.37, 17.77; m/z 253 (MH^+).

4.3.7. 5-Methoxycarbonyl-6-methyl-4-(5-bromo-2-thienyl)-3,4-dihydropyrimidin-2(1H)-one ***3g***. Pale yellow needles (57.6 g, 87%); mp 185.0–187.5 °C; [Found: C, 39.8; H, 3.5; Br, 24.1; N, 8.6; S, 9.6. $C_{11}H_{11}BrN_2O_3S$ requires C, 39.89; H, 3.35; Br, 24.13; N, 8.46; S, 9.68%]; R_f (10% MeOH/CH_2Cl_2) 0.58; ν_{max} (KBr) 3240, 3115, 2953, 1712, 1678, 1655, 1528, 1463, 1433, 1386, 1343, 1286, 1241, 1229, 1189, 1154, 1094, 1049 cm^{-1}; δ_H (600 MHz, DMSO-d_6) 2.23 (3H, s, CH_3), 3.62 (3H, s, OCH_3), 5.34 (1H, d, J=3.4, C*H*), 6.73 (1H, d, J=3.7, arom.), 7.05 (1H, d, J=3.8, arom.), 7.96 (1H, br s, N*H*), 9.42 (1H, s, N*H*); δ_C (600 MHz, DMSO-d_6) 165.4, 152.2, 150.5, 149.6, 130.1, 124.4, 109.9, 99.9, 51.1, 49.6, 17.8; m/z 333 (MH^+), 290, 258.

4.3.8. 5-Methoxycarbonyl-6-isopropyl-4-(4-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one ***3h***. Pale yellow needles (50.0 g, 81%); mp 176.0–177.5 °C; [Found: C, 58.2; H, 5.7; Cl, 11.6; N, 9.2. $C_{15}H_{17}ClN_2O_3$ requires C, 58.35; H, 5.55; Cl, 11.48; N, 9.07%]; R_f (10% MeOH/CH_2Cl_2) 0.51; ν_{max} (KBr) 3444, 3313, 3128, 2970, 1629, 1490, 1456, 1435, 1343, 1314, 1277, 1227, 1191, 1144, 1100, 1014 cm^{-1}; δ_H (600 MHz, DMSO-d_6) 1.13 (3H, d, J=5.7, $CH_2(CH_3)_2$), 1.15 (3H, d, J=5.9, $CH_2(CH_3)_2$), 3.53 (3H, s, OCH_3), 4.08–4.18 (1H, m, CH(CH_3)$_2$), 5.14 (1H, d, J=3.5, C*H*), 7.23–7.26 (2H, m, arom.), 7.39–7.42 (2H, m, arom.), 7.80 (1H, br s, N*H*), 8.95 (1H, s, N*H*); δ_C (600 MHz, DMSO-d_6) 165.7, 157.1, 152.2, 143.5, 131.9, 128.5, 128.1, 97.6, 53.1, 51.0, 27.1, 19.2, 19.0; m/z 309 (MH^+), 266, 234.

4.3.9. 5-Methoxycarbonyl-6-isopropyl-4-(2-thienyl)-3,4-dihydropyrimidin-2(1H)-one ***3i***. Pale yellow needles (46.5 g, 83%); mp 235.0–237.0 °C; [Found: C, 55.8; H, 5.6; N, 9.8; S, 11.2. $C_{13}H_{16}N_2O_3S$ requires C, 55.70; H, 5.75; N, 9.99; S, 11.44%]; R_f (10% MeOH/CH_2Cl_2) 0.56; ν_{max} (KBr) 3467, 3280, 3112, 2961, 1683, 1626, 1526, 1448, 1434, 1409, 1370, 1344, 1312, 1278, 1233, 1221, 1192, 1174, 1138, 1122, 1098, 1031 cm^{-1}; δ_H (600 MHz, DMSO-d_6) 1.10 (3H, d, J=2.3, CH_3), 1.13 (3H, d, J=2.4, CH_3), 3.59 (3H, s, OCH_3), 4.08–4.17 (1H, m, CH(CH_3)$_2$), 5.41 (1H, d, J=3.7, C*H*), 6.73–6.97 (2H, m, arom.), 7.35 (1H, dd, J_1=1.2, J_2=5.0, arom.), 7.89 (1H, d, J=1.7, N*H*), 9.02 (1H, s, N*H*); δ_C (600 MHz, DMSO-d_6) 165.44, 157.11, 152.74, 148.69, 126.79, 124.71, 123.75, 98.56, 51.05, 49.17, 26.97, 18.98, 18.85; m/z 281 (MH^+), 206, 163.

4.3.10. 5-Ethoxycarbonyl-6-methyl-4-(2-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one ***3j***. Bright yellow needles (51.9 g, 88%); mp 212.5–214.5 °C (lit. Mp 214–216 °C[34]); [Found: C, 57.1; H, 5.2; Cl, 12.2; N, 9.6. $C_{14}H_{15}ClN_2O_3$ requires C, 57.05; H, 5.13; Cl, 12.03; N, 9.50%]; R_f (10% MeOH/CH_2Cl_2) 0.43; ν_{max} (KBr) 3479, 3325, 3252, 3125, 2962, 1718, 1703, 1652, 1606, 1583, 1557, 1463, 1377, 1349, 1319, 1287, 1223, 1173, 1142, 1089, 1014 cm^{-1}; δ_H (600 MHz, DMSO-d_6) 0.74 (3H, t, J=6.0, CH_2CH_3), 2.31 (3H, s, CH_3), 3.69–3.80 (2H, m, CH_2CH_3), 5.29 (1H, d, J=3.3, C*H*), 7.52 (1H, d, J=8.7, arom.), 7.58–7.61 (1H, m, arom.), 7.90 (1H, br s, N*H*), 8.21–8.24 (2H, m, arom.), 9.38 (1H, s, N*H*); m/z 295 (MH^+).

4.3.11. 5-Ethoxycarbonyl-6-methyl-4-(3-chloro-phenyl)-3,4-dihydropyrimidin-2(1H)-one ***3k***. White needles; mp 216.0–218.0 °C (lit. Mp 217–219 °C[66]); (56.0 g, 95%); [Found: C, 57.0; H, 5.3; Cl, 12.0; N, 9.6. $C_{14}H_{15}ClN_2O_3$ requires C, 57.05; H, 5.13; Cl, 12.03; N, 9.50%]; R_f (10% MeOH/CH_2Cl_2)=0.53; ν_{max} (KBr) 3368, 3228, 3118, 2982, 2927, 1706, 1651, 1594, 1574, 1476, 1431, 1390, 1379, 1365, 1331, 1286, 1268, 1227, 1187, 1149, 1122, 1112, 1091, 1023 cm^{-1}; δ_H (600 MHz, DMSO-d_6) 1.10 (3H, t, J=7.1, OCH_2CH_3), 2.28 (3H, s, CH_3), 3.93–4.08 (2H, m, OCH_2CH_3), 5.18 (1H, d, J=3.2, C*H*), 7.21–7.27 (2H, m, arom.), 7.30–7.40 (2H, m, arom.), 7.81 (1H, d, J=2.2, N*H*), 9.23 (1H, s, N*H*); m/z 295 (MH^+).

4.3.12. 5-Ethoxycarbonyl-6-methyl-4-(4-chloro-phenyl)-3,4-dihydropyrimidin-2(1H)-one ***3l***. White needles; mp 230.0–232.0 °C (lit. Mp 231–232 °C[22]); (47.7 g, 81%); [Found: C, 57.3; H, 5.0; Cl, 12.1; N, 9.4. $C_{14}H_{15}ClN_2O_3$ requires C, 57.05; H, 5.13; Cl, 12.03; N, 9.50%]; R_f (10% MeOH/CH_2Cl_2)=0.46; ν_{max} (KBr) 3243, 3118, 2981, 1702, 1648, 1575, 1490, 1461, 1422, 1367, 1323, 1292, 1220, 1182, 1170, 1088, 1026, 1011 cm^{-1}; δ_H (600 MHz, DMSO-d_6) 1.09 (3H, t, J=7.0, CH_2CH_3); 2.24 (3H, s, CH_3); 3.95 (2H, q, J=14.1, CH_2CH_3), 5.13 (1H, d, J=2.8, C*H*); 7.23 (2H, d, J=8.5, arom.); 7.37 (2H, d, J=8.5, arom.); 7.77 (1H, br s, N*H*); 9.24 (1H, br s, N*H*); m/z 295 (MH^+).

4.3.13. 5-Ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one ***3m***. White needles; mp 216.0–217.5 °C (lit. Mp 208–210 °C[67]); (51.9 g, 85%); [Found: C, 55.2; H, 5.0; N, 13.9. $C_{14}H_{15}N_3O_5$ requires C, 55.08; H, 4.95; N, 13.76%]; R_f (10% MeOH/CH_2Cl_2)=0.60; ν_{max} (KBr) 3353, 3228, 3113, 2979, 1697, 1639, 1572, 1454, 1369, 1321, 1299, 1255, 1227, 1145, 1096, 1027 cm^{-1}; δ_H (600 MHz, DMSO-d_6) 0.99 (3H, t, J=7.1, CH_2CH_3), 2.31 (3H, s, CH_3), 3.89 (2H, q, J=14.1, CH_2CH_3), 5.64 (1H, d, J=2.7, C*H*), 7.08–7.33 (3H, m, arom.), 7.40 (1H, d, J=7.6, arom.), 7.71 (1H, br s, N*H*), 9.28 (1H, s, N*H*); m/z 306 (MH^+).

4.3.14. 5-Ethoxycarbonyl-6-n-propyl-4-(phenyl)-3,4-dihydropyrimidin-2(1H)-one ***3n***. Colourless needles; mp 138.0–140.0 °C (lit. Mp 162–165 °C[68]); (46.7 g, 81%); [Found: C, 66.4; H, 6.8; N, 9.8.

$C_{16}H_{20}N_2O_3$ requires C, 66.65; H, 6.99; N, 9.72%]; R_f (7.5% MeOH/CH_2Cl_2)=0.51; ν_{max} (KBr) 3443, 3347, 3248, 3116, 3037, 2983, 2961, 2930, 2903, 2870, 1703, 1649, 1598, 1464, 1425, 1362, 1347, 1324, 1311, 1289, 1269, 1229, 1214, 1181, 1172, 1155, 1144, 1129, 1097, 1018 cm^{-1}; δ_H (600 MHz, DMSO-d_6) 0.91 (3H, t, J=7.3, $CH_2CH_2CH_3$), 1.10 (3H, t, J=7.1, CH_2CH_3), 1.50–1.62 (2H, m, $CH_2CH_2CH_3$), 2.63 (2H, t, J=7.5, $CH_2CH_2CH_3$), 3.98 (2H, q, J=14.1, CH_2CH_3), 5.15 (1H, d, J=3.3, CH), 7.22–7.25 (m, 2H, arom.), 7.30–7.34 (m, 3H, arom.), 7.27 (br s, NH), 9.17 (s, NH); m/z 289 (MH^+).

4.3.15. 5-Ethoxycarbonyl-6-phenyl-4-(phenyl)-3,4-dihydropyrimidin-2(1H)-one ***3o***. Colourless needles; mp 157.0–159.0 °C (lit. Mp 158 °C[69]); (51.6 g, 80%); [Found: C, 70.9; H, 5.8; N, 8.8. $C_{19}H_{18}N_2O_3$ requires C, 70.79; H, 5.63; N, 8.69%]; R_f (7.5% MeOH/CH_2Cl_2)=0.52; ν_{max} (KBr) 3384, 3309, 3224, 3116, 3058, 3031, 3006, 2988, 2979, 2960, 2934, 2902, 1703, 1667, 1637, 1600, 1494, 1473, 1456, 1445, 1413, 1396, 1372, 1350, 1335, 1291, 1281, 1267, 1247, 1187, 1159, 1130, 1099, 1030, 1014 cm^{-1}; δ_H (600 MHz, DMSO-d_6) 0.71 (3H, t, J=7.1, CH_2CH_3), 3.71 (2H, q, J=14.2, CH_2CH_3), 5.24 (1H, d, J=3.4, CH), 7.27–7.31 (3H, m, arom.), 7.36–7.43 (7H, m, arom.), 7.85 (1H, d, J=2.2, NH), 9.28 (1H, s, NH); m/z 323 (MH^+).

4.3.16. 5-Isopropyloxycarbonyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one ***3p***. Bright yellow powder; mp 223.0–225.0 °C (lit. Mp not reported[70]); (50.5 g, 83%); [Found: C, 63.0; H, 6.6; N, 9.1. $C_{16}H_{20}N_2O_4$ requires C, 63.14; H, 6.62; N, 9.20%]; R_f (10% MeOH/CH_2Cl_2)=0.46; ν_{max} (KBr) 3243, 3115, 2983, 2834, 1723, 1702, 1650, 1615, 1584, 1515, 1461, 1461, 1440, 1385, 1348, 1309, 1277, 1257, 1224, 1178, 1147, 1109, 1031 cm^{-1}; δ_H (600 MHz, DMSO-d_6) 1.00 (3H, d, J=6.2, CH_3), 1.16 (3H, d, J=6.2, CH_3), 2.24 (3H, s, CH_3), 3.72 (3H, s, OCH_3), 4.77–4.87 (1H, m, $CH(CH_3)_2$), 5.08 (1H, d, J=2.9, CH), 6.87 (2H, d, J=8.6, arom.), 7.15 (2H, d, J=8.6, arom.), 7.64 (1H, br s, NH), 9.12 (1H, s, NH); m/z 305 (MH^+).

4.3.17. 5-Benzyloxycarbonyl-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1H)-one ***3q***. White powder; mp 168.0–170.0 °C (lit. Mp 170–171 °C[71]); (55.2 g, 82%); [Found: C, 71.3; H, 6.1; N, 8.2. $C_{20}H_{20}N_2O_3$ requires C, 71.41; H, 5.99; N, 8.33%]; R_f (10% MeOH/CH_2Cl_2)=0.50; ν_{max} (KBr) 3389, 3222, 3090, 2934, 2819, 1692, 1638, 1511, 1497, 1452, 1429, 1374, 1321, 1293, 1265, 1223, 1183, 1139, 1094, 1024 cm^{-1}; δ_H (600 MHz, DMSO-d_6) 2.26 (3H, s, CH_3), 2.27 (3H, s, CH_3), 5.00 (1H, d, J=12.8, CH_2Ph), 5.06 (1H, d, J=12.8, CH_2Ph), 5.16 (1H, d, J=3.1, CH), 7.10–7.17 (6H, m, arom.), 7.27–7.30 (3H, m, arom.), 7.71 (1H, br s, NH), 9.24 (1H, s, NH); m/z 337 (MH^+).

4.4. Regeneration of $[Al(H_2O)_6](BF_4)_3$ and synthesis of 3k with recycled catalyst (10 mmol scale)

The ethanolic mother liquor obtained after crystallization of products (Table 4) was evaporated to dryness and the residue was triturated with three portions of hot distilled water (50 mL). The combined water extracts if necessary were extracted with ethylacetate to remove the traces of organic compounds and colouration residues were evaporated to dryness to afford a mixture of excess of urea (0.5 equiv) and regenerated catalyst (yield ~95%). Thus obtained catalyst was used in four successive reaction with *m*-chlorobenzaldehyde (**1k**, 10 mmol), urea (10 mmol, 1 equiv) and ethylacetoacetate (**2c**, 10 mmol) and the results are summarized in Table 5.

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