Synthesis of Biginelli dihydropyrimidinone derivatives with various substituents on aluminium-planted mesoporous silica catalyst†

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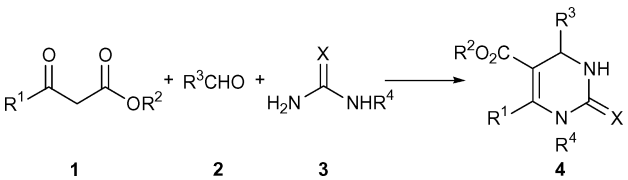
Biginelli reactions were well catalyzed on mesoporous silica MCM-41 (M41) whose activity was much greater than that of amorphous silica. Octane was the most suitable among 6 kinds of solvents examined. The addition of metal ions on M41 enhanced the catalytic activity in the order Al > Ti > Fe = In. Al-planted M41s with Si/Al ratios of 45–35 showed the highest catalytic activity and could be used repeatedly though a small loss of the activity was observed. The catalysis could widely be applied to obtain various substituted dihydropyrimidinones (DHPMs) with high yields, some of which were very difficult to prepare until now. In addition, Biginelli reactions were combined with formyl C–H insertion reactions of diazoester on mesoporous silica; that is, a tandem one-pot four-component DHPM synthesis was attempted. Acetaldehyde, ethyl diazoacetate, *p*-tolualdehyde, and urea could be condensed and the corresponding DHPM derivative was obtained with 50% yield on Al-planted M41.

Introduction

Dihydropyrimidinone (DHPM) derivatives are widely used as integral backbones of some biologically active compounds such as calcium channel blockers,[1] anti-cancer agents,[2] or anti-hypertensive agents.[3] The derivatives can be obtained through the Biginelli reaction, a three-component condensation of a β-keto ester, aldehyde, and urea derivative on acid catalyst under thermal conditions.[4,5] The reaction was first found by using HCl as the catalyst in ethanol,[5a–c] and then on various types of homogeneous[5d–k] and heterogeneous[5l–p] catalysts. $InCl_3$,[5e] $Yb(OTf)_3$,[5f] and $Ag_3PW_{12}O_{40}$[5l] gave 90% or more yields of many kinds of products. The TMSCl/NaI[5g] or TMSOTf[5h] system was reported to catalyze the reaction at room temperature. The reaction was also studied on substrates bound to polymers such as Wang resin[5r-t] and Rink-amide resin,[5u] or on the highly fluorinated substrates to develop the "fluorous chemistry".[5q] Some kinds of heterogeneous catalysts were investigated to prevent a troublesome separation process and realize the green chemical processes. Montmorillonite[5m,n] and HY zeolite[5o] showed high catalytic activity. $FeCl_3$-impregnated MCM-41[5p] was also active but microwave irradiation was essential. The yields of DHPMs on the heterogeneous catalysts were 95–70%.

One of the major drawbacks of the reported Biginelli reactions is the limitation of applicable β-keto esters.[4,5] The substituent R^1 in **1** (Scheme 1) is mostly limited to Me, Et, and Ph. The expansion of R^1 in **4** is very difficult; for example, Singh *et al.* first prepared DHPM with Me at R^1 by using methyl acetoacetate and then substituted the Me group by another alkyl group by lithiation with more than three equivalent of LDA and electrophilic substitution.[6] The undesirable production of the *N*-alkylated compound due to the excess amount of the base is another problem to be solved.



Scheme 1 The Biginelli reaction.

Only a few studies reported the direct syntheses of DHPMs with various alkyl substituents at R^1.[5j,7] The yields of the DHPMs, however, were not high and acceptable yields were attained in the presence of a stoichiometric or greater amount of Lewis acid. More efficient direct processes should be developed. The third point for improvement of the present Biginelli reaction is to modify the preparation method of β-keto esters. The compounds are generally produced *via* a non-catalytic Claisen condensation, which is accompanied with large amounts of waste and requires wasteful isolation steps.[8] If the production of β-keto esters and the subsequent Biginelli reaction could both be promoted on the same solid catalyst, the reaction efficiency would become much greater and we could establish greener reaction processes.

Mesoporous silica material MCM-41 (M41) possesses well-ordered hexagonal arrays of uniform channels and 1000 $m^2\ g^{-1}$ of high surface area. Recently, novel acidic properties of M41 were found by us, which catalyzed selective acetalization,[9a,b] Mukaiyama-aldol reaction,[9c] and Friedel–Crafts acylation.[9d] The following significant motives prompted us to investigate the Biginelli reaction. First is that the M41 catalyst was entirely stable against water produced in acetalization,[9a,b] and showed high catalytic activity for Friedel–Crafts acylation even at a high reaction temperature.[9d] These properties would be beneficial for the Biginelli reaction. In addition, we reported a convenient catalytic synthesis of β-keto esters on M41 by the insertion reaction of diazoesters to the formyl C–H bond of aldehydes.[9e] This might suggest the possibility of the consecutive reaction of β-keto ester synthesis and three-component Biginelli reaction,

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that is, the development of a novel four-component preparation of Biginelli DHPM derivatives. The present study was devoted to the development of metal-planted M41s active for the three-component Biginelli reaction with various substituents. Finally, the connection of the β-keto ester synthesis with the Biginelli reaction was tried.

Result and discussion

Catalytic activity of M41 for the Biginelli reaction

Most of the previous studies[4,5] employed acetoacetate giving 6-Me-substituted DHPMs to examine the catalytic activity for the Biginelli reaction. To the best of our knowledge, the synthesis 6-*n*-Pr-substituted DHPM by Biginelli reaction has been reported only twice in the literature.[7a,b] The reaction of 3-keto-*n*-hexanoic acid ethyl ester (**1c**), 4-nitrobenzaldehyde, and urea (**3a**) using 10 mol% of $Yb(OTf)_3$ gave the corresponding DHPM in 41% yield under microwave irradiation.[7a] The yield of 4-(4-fluorophenyl)-6-*n*-Pr-substituted DHPM using $(Bu_4N)HSO_4$ was 75% though an eight-fold amount of aldehyde was employed for the reaction.[7b] Clearly the 6-*n*-Pr-substituted DHPM synthesis is much more difficult than those of 6-Me-substituted DHPMs. We therefore studied the reaction of 3-keto-*n*-hexanoic acid ethyl ester (**1c**), *p*-tolualdehyde (**2a**), and urea (**3a**) to examine the catalytic activity of M41 (Table 1). The conversions of **1c** and **2a** were 43 and 45% in the presence of M41, and the targeted DHPM **4i** was obtained in 44% based on the amount of urea (**3a**) (Entry 1). The major by-product was the α-benzylidene-β-keto ester derivative **5a** produced through Knoevenagel condensation of **1c** and **2a**. The molar ratio of **1c**, **2a**, and **3a** was varied to improve the yield of **4i**, but it decreased greatly as shown in Entries 2 and 3. The catalysis of M41 was confirmed by the following experiments. Silica gel was separately prepared from the raw materials used in the preparation of M41 and confirmed to show small catalytic activity (Entry 4); the yield of **4i** was approximately one third of that on M41. Note that the total surface area of the silica gel applied in Entry 4 was equal to that of Entry 1. Without catalyst very small consumption of **1c** and **2a** and trace amount of **4i** production was observed (Entry 5). It follows that the ordered mesoporous structure of M41 is effective to generate the catalytic activity for Biginelli reaction.[9]

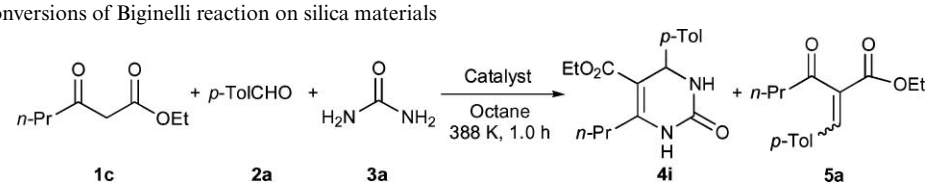
A recent report showed that urea (**3a**) catalyzed the Knoevenagel reactions with malononitrile[10] but the result in Entry 5 indicated no catalysis of urea (**3a**) in the present system. The product DHPM **4i** is a derivative of urea and could be another candidate for the catalyst of the Knoevenagel reaction, but the addition of **4i** into the reaction system did not result in the production of **5a** (Entry 6). Entries 1 and 5–7 suggested the progress in the Knoevenagel reaction only upon the coexistence of urea (**3a**) and M41.

The effect of solvent on the Biginelli reaction is summarized in Table 2. Octane was the most suitable solvent for the reaction. In contrast toluene promoted the production of undesirable **5a** (Entry 2). Although ethanol and THF were conventionally used as the solvent in the Brønsted acid-catalyzed Biginelli reaction,[5a–d] they were not appropriate for the present reaction even at the reflux conditions (Entries 3 and 4). Dibutyl ether or 3-pentanol was also ineffective (Entries 5 and 6). Among the examined reaction temperatures (Entries 1, 7, and 8) the best temperature for the Biginelli reaction was 388 K and a higher temperature resulted in the progress in the side reaction. In the present study octane was employed as the solvent and the reaction temperature was set at 388 K unless otherwise stated.

Effect of metal ion planted on M41

The dependence of the catalytic activity for the Biginelli reaction on the metal ion planted on M41 was examined. It is widely known that the addition of Al or Ti improves or enhances the acidity of siliceous materials.[11,12] Kulkarni and co-workers synthesized Al-MCM-41 from Ludox colloidal silica and aluminium isopropoxide[5o] and examined the catalytic activity. On the basis of reports on the effectiveness of $FeCl_3$[5i] and $InCl_3$[5e] addition for the reaction, Choudhary *et al.* reported the catalysis of $FeCl_3$ supported Si-MCM-41 under the microwave irradiation.[5p] In the present work, therefore, we selected Al, Ti, Fe, and In as the candidates for improving the catalytic activity of M41 and

Table 1 Yields and conversions of Biginelli reaction on silica materials



1c **2a** **3a** **4i** **5a**

Entry	Catalyst	/mg	Surface area/m^2[a]	Reactants **1c**/mmol	**2a**/mmol	**3a**/mmol	Results[b] Conv. of **1c**/%	Conv. of **2a**/%	Yield of **4i**/%[c]	Yield of **5a**/%[d]
1	M41[e]	50	51	1.0	1.0	0.5	43	45	44	24
2	M41[e]	50	51	1.0	0.5	1.0	38	61	6	16
3	M41[e]	50	51	0.5	1.0	1.0	29	42	2	11
4	SiO_2-cs[f]	415	51	1.0	1.0	0.5	30	35	12	9
5	None	—	—	1.0	1.0	0.5	2	20	Trace	Trace
6[g]	None	—	—	1.0	1.0	0	16	17	[h]	Trace
7	M41[e]	50	51	1.0	1.0	0	27	25	—	Trace

Reaction conditions: octane 1.0 mL, reaction temperature 388 K, reaction time 1.0 h. [a] Whole surface areas of the silica catalysts applied for the respective experiments. [b] Determined by GC analysis. [c] Based on **3a**. [d] Based on **2a**. [e] BET surface area 1010 m^2 g^{-1}. [f] Prepared from colloidal silica and $C_{12}H_{25}NMe_3Br$ without hydrothermal synthesis. BET surface area 122 m^2 g^{-1}. [g] 0.2 mmol of **4i** was added in the reactants mixture. [h] **4i** added was recovered quantitatively.

Table 2 Effects of solvent and reaction temperature on the Biginelli reaction

Entry	Solvent	T/K	Conv. of **1c**/%[a]	Conv. of **2a**/%[a]	Yield of **4i**/%[a,b]	Yield of **5a**/%[a,c]
1	Octane	388	43	45	44	24
2	Toluene	388 (reflux)	50	52	14	41
3	Tetrahydrofuran	343 (reflux)	6	22	Trace	Trace
4	Ethanol	353 (reflux)	9	30	Trace	Trace
5	Di-*n*-butyl ether	388	55	66	Trace	25
6	3-Pentanol	388	57	56	Trace	19
7	Octane	353	21	25	2	1
8	Octane	398 (reflux)	88	77	28	42

Reaction conditions: M41 50 mg, **1c** 1.0 mmol, **2a** 1.0 mmol, **3a** 0.50 mmol, solvent 1.0 mL, reaction time 1.0 h.[a] Determined by GC analysis. [b] Based on **3a**. [c] Based on **2a**.

prepared the metal-planted M41s by the TIE method. Their catalytic activity is summarized in Table 3. The yields of **4i** on Al- and Ti-M41 were greater than that of parent M41, while Fe- and In-M41 did not show any enhancement effect. The catalytic activity of Al-M41 should here be compared with that of the reported catalysts, but various kinds of substrates were applied on a variety of catalysts and therefore the comparison will be made in the next section in detail.

Reusability of the present Al-M41 was investigated. The catalytic activity was measured in Table 4 as a function of the weight of catalyst recovered. The yield of **4i** gradually lowered with the number of recycles, while the conversions of **1c** and **2a** and the yield of **5a** were almost constant. This would indicate that the active site for the **4i** formation is different from those for activation of **1c** or **2a** or for the **5a** formation and that the formation site of **4i** alone gradually disappears.

The effect of the Al addition on M41 was studied in more detail. The yields of DHPM **4i** were plotted in Fig. 1(**A**) as a function of the Si/Al ratio. The plot at the right end is the result from the parent M41. The yield of **4i** showed a volcano-shaped dependence on the Si/Al ratio and the maximum yield was observed at Si/Al = 45–35. The intensity of the XRD (100) diffraction, the BET surface area, and the pore volume of each catalyst are summarized in Fig. 1(**B**). The changes in the physical properties with the Si/Al ratio could be divided into two parts, the ranges of Si/Al = 237–45 and 45–23. In the former range all of the parameters were almost constant or somewhat changed with the Si/Al ratio. The catalytic activity increased with decreasing the ratio as shown in Fig. 1(**A**). In contrast, in the latter range all of the physical properties were greatly reduced with decreasing ratio and the catalytic activity was also reduced. The partial collapse of the pore structure with the increment of Al content has been widely recognized on various types of mesoporous silica materials.[13] It follows that the pore structure is necessary for the progress in the Biginelli reaction and the higher Al contents result in a greater catalytic activity as far as the pore structure is maintained. It would be worthy to note that the yields of Knoevenagel product **5a** in Fig. 1(**A**) were almost constant independent of the Si/Al ratio. This is in contrast to the behavior in the Biginelli reaction, probably meaning that the pore structure is unnecessary in the Knoevenagel reaction. The Al-M41 was separately confirmed to be inert for the Knoevenagel reaction of **1c** and **2a** in the absence of urea (**3a**).

Table 3 Effect of metal-planting on the catalytic activity of M41 for the Biginelli reaction

Entry	M41s	[M]/mmol g^{-1}	Si/M	Conv. of **1c**/%[a]	Conv. of **2a**/%[a]	Yield of **4i**/%[a,b]	Yield of **5a**/%[a,c]
1	M41	[Al] 0.065	[Al] 237	81	88	53	47
2	Al-M41	0.24	45	86	80	75	42
3	Ti-M41	0.22	48	86	75	67	53
4	Fe-M41	0.19	55	94	83	51	39
5	In-M41	0.22	63	93	88	51	41

Reaction conditions: M41 50 mg, **1c** 1.0 mmol, **2a** 1.0 mmol, **3a** 0.50 mmol, octane 1.0 mL, reaction temperature 388 K, reaction time 10 h.[a] Determined by GC analysis. [b] Based on **3a**. [c] Based on **2a**.

Table 4 Repeated use of the Al-M41 (Si/Al = 33) catalyst for the Biginelli reaction

Entry	Run	Amount of Al-M41/mg[a]	Conv. of **1c**/%[b]	Conv. of **2a**/%[b]	Yield of **4i**/%[b,c]	Yield of **5a**/%[b,d]
1	1st	50	92	87	72	48
2	2nd	43	90	86	76	49
3	3rd	41	80	94	59	48
4	4th	40	88	95	46	44
5	5th	37	92	93	55	45

Reaction conditions: **1c** 20 mmol g^{-1}, **2a** 20 mmol g^{-1}, **3a** 10 mmol g^{-1}, octane 20 mL g^{-1}, reaction temperature 388 K, reaction time 10 h.[a] Amounts of reagents were adjusted based on the amounts of Al-M41 reused. [b] Determined by GC analysis. [c] Based on **3a**. [d] Based on **2a**.

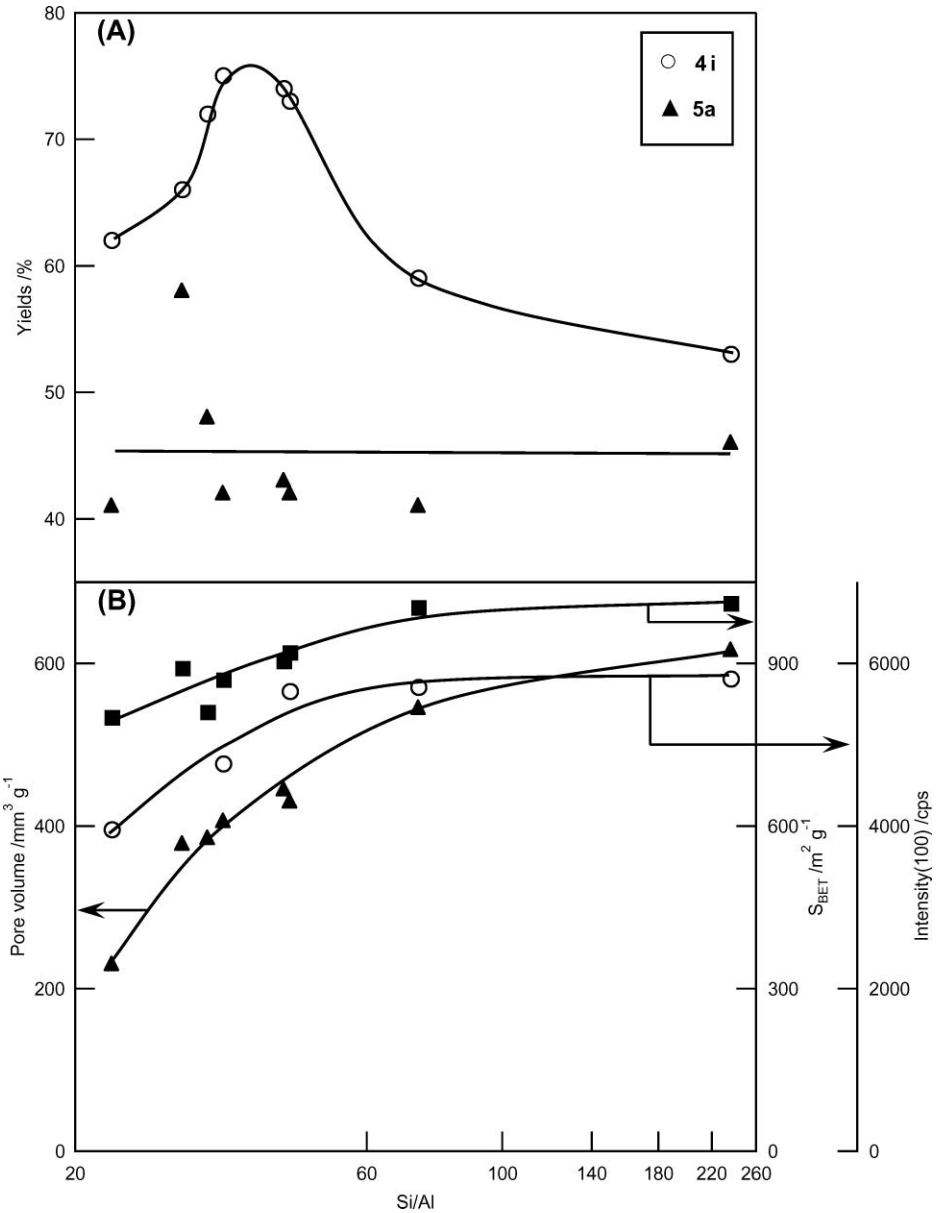


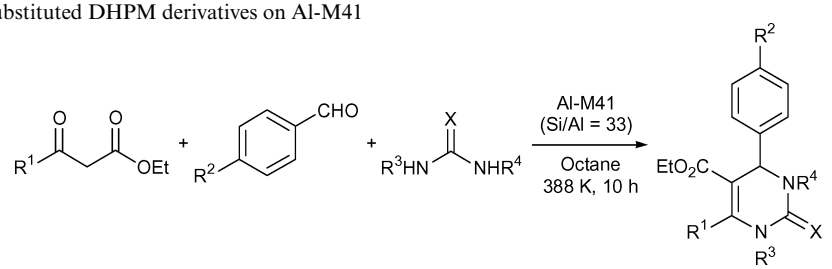
Fig. 1 Effect of Si/Al ratio on catalytic activity and physical properties of Al-M41s. (**A**) Yields of DHPM **4i** and α-benzylidene-β-keto ester derivative **5a**. (**B**) Pore volumes, BET surface areas, and XRD peak intensities of (100) diffraction of the catalysts. Reaction conditions: Catalyst 50 mg, **1c** 1.0 mmol, **2a** 1.0 mmol, **3a** 0.50 mmol, octane 1.0 mL, reaction temperature 388 K, reaction time 10 h. Yields were determined by GC analysis.

Syntheses of various substituted DHPMs

Under the reaction conditions determined above, many kinds of substrates were employed for the DHPM synthesis to reveal the potential of the Al-M41 catalyst and the results are shown in Table 5. Ethyl acetoacetate **1a** shows the great reactivity for various substrates and the corresponding products were obtained in high yields (Entries 1–5). In the literature, the reaction of **1a**, **2b**, and **3a** (the same as Entry 2) on Al- or Fe-modified MCM-41 yielded 38[5o] and 89%[5p], respectively, showing superiority of the present Al-M41 in catalytic activity.

The effect of the substituent R^1 for the reaction on Al-M41 is discussed split into alkyl and others. Entries 1, 6, 9, 16, 17, 19, and 20 showed that various types of β-keto ester were applicable in the present system. The yields of **4** in the reaction in octane were in the order Me (**4a**) > Et (**4f**) > *n*-Pr (**4i**) > $(CH_2)_2$Ph (**4q**) > *n*-Hex (**4p**) > *c*-Hex (**4s**) > *t*-Bu (**4t**), suggesting that steric effect of substituent R^1 affects the yield of the corresponding DHPM. The steric effect of alkyl substituents was evaluated by Taft's *E*s value,[14] which is plotted in Fig. 2 except for *n*-Hex (**4p**) due to there being no available *E*s value.[14] The figure clearly indicates that the bulkier substituents resulted in the lower yields of corresponding DHPMs. In the other substituents, β-keto ester **1f** ($R^1 = CH_2Cl$) did not give the desired DHPM **4r** under the present conditions (Entry 18), though it was reported as a good substrate.[15] Entries 21 and 22 showed the reactions with β-keto esters bearing unsaturated hydrocarbon groups. Although the yields were not high, these are the first examples of the preparation of Biginelli DHPMs with an unsaturated hydrocarbon at R^1. The yields of 6-Ph-substituted DHPMs were moderate. Note that the β-keto

Table 5 Yields of various substituted DHPM derivatives on Al-M41



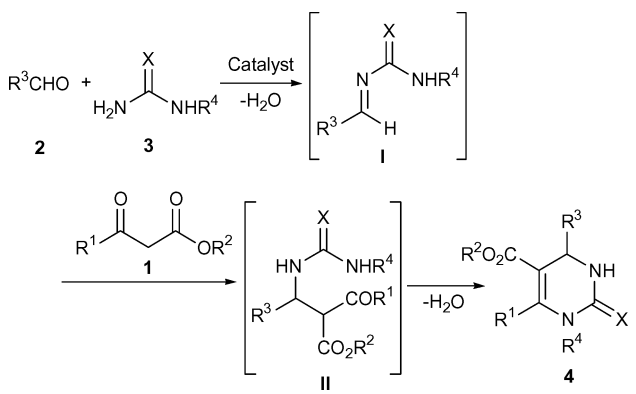
1 **2** **3** **4**

Entry	R^1 (**1**)	R^2 (**2**)	R^3	R^4	X (**3**)	Product	Yield of **4**/%[a]
1	Me (**1a**)	Me (**2a**)	H	H	O (**3a**)	**4a**	>99[b]
2	Me (**1a**)	H (**2b**)	H	H	O (**3a**)	**4b**	94[b]
3	Me (**1a**)	Me (**2a**)	Me	H	O (**3b**)	**4c**	86
4	Me (**1a**)	Me (**2a**)	H	H	S (**3c**)	**4d**	>99
5	Me (**1a**)	Cl (**2c**)	H	H	O (**3a**)	**4e**	87
6	Et (**1b**)	Me (**2a**)	H	H	O (**3a**)	**4f**	74
7	*n*-Pr (**1c**)	OMe (**2d**)	H	H	O (**3a**)	**4g**	74
8	*n*-Pr (**1c**)	OMe (**2d**)	H	H	S (**3c**)	**4h**	86
9	*n*-Pr (**1c**)	Me (**2a**)	H	H	O (**3a**)	**4i**	72[b]
10	*n*-Pr (**1c**)	Me (**2a**)	Me	H	O (**3b**)	**4j**	40
11	*n*-Pr (**1c**)	Me (**2a**)	Me	Me	O (**3d**)	**4k**	12
12	*n*-Pr (**1c**)	Me (**2a**)	H	H	S (**3c**)	**4l**	80
13	*n*-Pr (**1c**)	Cl (**2c**)	H	H	O (**3a**)	**4m**	49
14	*n*-Pr (**1c**)	Cl (**2c**)	H	H	S (**3c**)	**4n**	84
15	*n*-Pr (**1c**)	CF_3 (**2e**)	H	H	O (**3a**)	**4o**	37
16	*n*-Hex (**1d**)	Me (**2a**)	H	H	O (**3a**)	**4p**	41, 57[c]
17	$PhCH_2CH_2$ (**1e**)	H (**2b**)	H	H	O (**3a**)	**4q**	53, 67[c]
18	$ClCH_2$ (**1f**)	H (**2b**)	H	H	O (**3a**)	**4r**	Trace
19	*c*-Hex (**1g**)	Me (**2a**)	H	H	O (**3a**)	**4s**	28, 38[c]
20	*t*-Bu (**1h**)	H (**2b**)	H	H	O (**3a**)	**4t**	5, 20[c]
21	*n*-C_5H_{11} (**1i**)	Me (**2a**)	H	H	O (**3a**)	**4u**	10, 20[c]
22	*n*-C_5H_{11} (**1j**)	Me (**2a**)	H	H	O (**3a**)	**4v**	15, 28[c]
23	Ph (**1k**)	OMe (**2d**)	H	H	S (**3c**)	**4w**	73
24	Ph (**1k**)	Me (**2a**)	H	H	O (**3a**)	**4x**	35
25	Ph (**1k**)	Me (**2a**)	H	H	S (**3c**)	**4y**	62
26	Ph (**1k**)	H (**2b**)	H	H	O (**3a**)	**4z**	38
27	Ph (**1k**)	Cl (**2c**)	H	H	S (**3c**)	**4aa**	55

Reaction conditions: Al-M41 (Si/Al = 33) 50 mg, **1** 1.0 mmol, **2** 1.0 mmol, **3** 0.50 mmol, octane 1.0 mL, reaction temperature 388 K, reaction time 10 h.[a] Isolated yields except for those of Entries 1, 2, and 9. [b] Determined by GC analysis. [c] Neat condition.

esters such as **1d**, **1e**, **1g**, **1i**, and **1j** could easily be prepared by using Al-M41 catalyst.[9e,16]

In the comparison of aldehyde derivatives (Entries 7, 9, 13, and 15), better yields were achieved in the reactions of aromatic aldehydes bearing electron-donating groups such as Me and OMe; that is, the reactivity order was OMe > Me > Cl > CF_3. Kappe suggested Scheme 2 in which the imine-type intermediate **I** is generated from aldehyde and urea in the first step.[17] The low electron density of intermediate **I** is usually favorable for the successive condensation with β-keto ester. This was indeed confirmed by the findings that the order of reactivity was 3,4-F_2 > Cl > NO_2 = H > OMe in H_2SO_4/EtOH.[5j] Clearly the present result was contrary to the previous one. The low yield in the reaction of electron-deficient aldehydes was possibly due to progress in undesirable Knoevenagel condensation between aldehyde and β-keto ester. The yields of Koevenagel products **5** were thus carefully investigated and found to be 48, 48, 45 and 42%, respectively, in the reactions of **2d** (R^2 = OMe), **2a** (R^2 = Me), **2c** (R^2 = Cl) and **2e** (R^2 = CF_3). The constant yields of **5** indicate that the low yields in the reactions of electron-deficient aldehydes were unconnected to the progress in Knoevenagel reaction. The



2 **3** **I** **1** **II** **4**

Scheme 2 Proposed mechanism of the Biginelli reaction.

reason for the present reaction order, the reaction mechanism, and the intermediates should be resolved in the near future.

Finally the effect of urea will be discussed. Substituents at the nitrogen atom significantly decreased the yield of the corresponding *N*-methyl- or *N*,*N*′-dimethyl-DHPM (Entries 9–11). The steric congestions of substituents strongly affected the

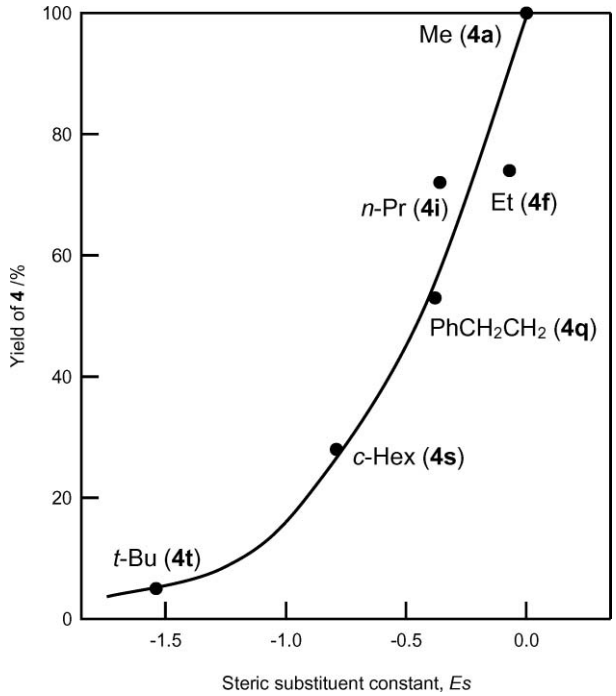


Fig. 2 Correlations between Taft's *Es* value of substituent R^1 and the yield of DHPM.

production of DHPM. Similar results were already reported on various catalysts.[4,5] Thiourea (**3c**) was a very good substrate for the present reaction, and the yields were greatly improved in the reaction using ethyl benzoylacetate (**1k**) or *p*-chlorobenzaldehyde (**2c**) (Entries 14, 23, 25, and 27).

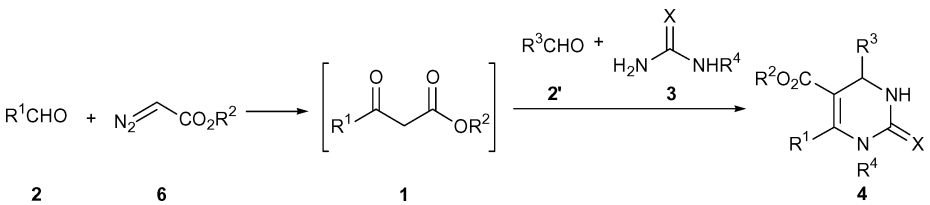
Novel tandem four-component DHPM synthesis

On the basis of the above results, the novel tandem four-component DHPM synthesis was tried here. In our program illustrated in Scheme 3, the β-keto ester will first be synthesized on Al-M41 and the product will be connected with the Biginelli reaction in one-pot. We examined the reaction to prepare **4i** from *n*-butanal (**2f**), ethyl diazoacetate (**6a**), *p*-tolualdehyde (**2a**), and urea (**3a**) in Table 6. The reaction of **2f** with **6a** on Al-M41 in 1,2,3-trichloropropane smoothly proceeded and gave **1c**, which was confirmed by GC analysis of reaction mixture. We then added the remaining two substrates, **2a** and **3a**, to the same reaction mixture but the amount of desired DHPM **4i** was trace as shown in Entry 1. 1,2,3-Trichloropropane was here selected as the solvent because it gave the best yield among the solvents employed for the β-keto ester synthesis on Al-M41,[9e] but it was not good. Octane, the optimum solvent for the Biginelli reaction on M41, was then employed in Entry 2. Although the yield of **1c** decreased to 48%, the desired DHPM **4i** was obtained in 22% yield. To increase the yield, the reaction without solvent, the neat reaction, was tried. The yield of **1c**, however, was only 34% and that of **4i** was 15% (Entry 3). There is the possibility that the mesoporous silica is a very bulky material, and therefore the reactions of the substrates might be prevented by the solid. The amount of Al-M41 used was thus reduced in Entry 4, which resulted in the better yield of **4i**, 35%.

Although the yield is not excellent, this is the first example to achieve the four-component DHPM synthesis on a single catalyst. Table 7 shows some combinations of the novel four-component condensation reaction. In the reaction of acetaldehyde (**2g**), the octane solvent gave higher yields than the neat reaction. The maximum yield of **4a** was 50% (Entry 2). *N*-Methyl urea (**3b**) was also applicable and **4c** was obtained in 34% (Entry 3). Unfortunately thiourea (**3c**) gave no advantage in the four-component reaction (22%, Entry 4).

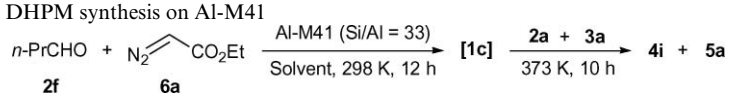
Conclusions

In the present study, Al-M41 was revealed to be catalytically active for the Biginelli reaction. Octane was the most effective among the tested solvents. 6-*n*-Pr substituted DHPM derivatives could be synthesized in up to 86% yields, which were rare reactions. The catalytic activity was greatly dependent on the Al



Scheme 3 Procedure for tandem-four component DHPM synthesis.

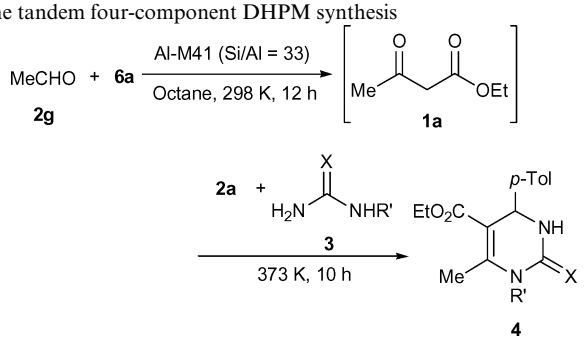
Table 6 Tandem four-component DHPM synthesis on Al-M41



Entry	Amount of Al-M41/mg	Solvent	/mL	Yield of **1c** (*in vitro*)/%[a]	Conv. of **2a**/%[a]	Yield of **4i**/%[a,b]	Yield of **5a**/%[a,b]
1	100	$CH_2ClCHClCH_2Cl$	5.0	88	11	Trace	26
2	100	Octane	2.0	48	66	22	17
3	100	Neat	—	34	98	15	16
4	20	Neat	—	52	70	35	23

Reaction conditions: **2f** 1.0 mmol, **6a** 1.5 mmol, **2a** 1.2 mmol, **3a** 1.0 mmol.[a] Determined by GC analysis. [b] Based on **2f**.

Table 7 Yields of DHPM derivatives in the tandem four-component DHPM synthesis



Entry	Amount of Al-M41/mg	Solvent	/mL	X	R′	Product	Yield of **4**/%
1	50	Neat	—	O	H (**3a**)	**4a**	39[a]
2	100	Octane	2.0	O	H (**3a**)	**4a**	50[a]
3	100	Octane	2.0	O	Me (**3b**)	**4c**	34[b]
4	100	Octane	2.0	S	H (**3c**)	**4d**	22[a]

Reaction conditions: **2g** 1.0 mmol, **6a** 1.5 mmol, **2a** 1.2 mmol, **3** 1.0 mmol.[a] Determined by GC. [b] Isolated yield.

content and the mesoporous structure of silica. In addition, a novel four-component DHPM synthesis was achieved through the connection of the β-keto ester synthesis and the Biginelli reaction. Acetaldehyde, ethyl diazoacetate, *p*-tolualdehyde, and urea gave the corresponding DHPM derivative in 50% yield on the Al-M41 catalyst.

Experimental

General experimental

Unless specified, all starting materials and solvents were purchased from commercial sources. Several β-keto esters (**1d**, **1e**, **1g**, **1i**, and **1j**)[9e] and ethyl diazoacetate (**6a**)[18] were prepared by the reported manners. Urea derivatives were recrystallized from MeOH, and other reagents and solvents were purified by standard literature procedures. GC analyses were performed on an HP model 6890 chromatograph equipped with an HP-5MS column (30 m × 0.25 mm × 0.25 μm) and an HP 5793 mass selective EI detector. NMR spectra were measured on an AVANCE-400 (Bruker) spectrometer. Chemical shifts were quoted in ppm from internal TMS or residual protic solvent (DMSO, $\delta_H = 2.49$, $\delta_C = 39.7$). High resolution mass spectra (HRMS) data were obtained on a JEOL JMS-700 spectrometer. Melting points were measured by using a DTG-60 (Shimadzu). Powder X-ray diffraction (XRD) patterns of silica materials were recorded on a RINT2000 diffractometer with Cu-Kα radiation (40 kV, 40 mA). N_2 sorption was analysed on a BELSORP 28SA volumetric adsorption analyzer at 77 K. An OPTIMA 3200XL ICP was used to determine the content of metal-ions in M41s.

Preparation of catalysts

M41 was prepared by hydrothermal synthesis in the reported manner.[19] $C_{12}H_{25}NMe_3Br$ and colloidal silica (Snow Techs 20, Nissan chemical Industries, Ltd.) were used as a template and a silica source. Planting of metal onto M41 was conducted by the TIE method.[20] Silica gel of colloidal silica (SiO_2-cs) was prepared with vigorous stirring at room temperature by using the same starting materials as those used in the preparation of M41. The resulting silica materials were calcined at 873 K for 6 h in air to remove organic compounds. All catalysts were characterized by XRD, ICP, and N_2 absorption measurements.

General procedure for the three-component Biginelli reaction

The appropriate amount of catalyst in a 40 mL test tube containing a magnetic stirrer bar was evacuated at 373 K for 1 h. The substrates, tetradecane (GC internal standard), and solvent were added to the catalyst and heated at the desired temperature under Ar atmosphere. After 1 or 10 h, the reaction mixture was diluted with MeOH, and the catalyst was removed by filtration and washed with AcOEt. The filtrate was evaporated and analyzed by GC. The produced DHPMs were purified by preparative TLC and their structures confirmed by ^{1}H- and ^{13}C-NMR spectra.

5-Pyrimidinecarboxylic acid, 1,2,3,4-tetrahydro-6-methyl-4-(4-methylphenyl)-2-oxo-, ethyl ester (4a)[5k]. (>99% yield); ^{1}H NMR (400 MHz, d_6-DMSO/TMS) δ_H 9.19 (br, 1H), 7.72 (br, 1H), 7.12 (br, 4H), 5.10 (d, $J = 3.3$, 1H), 3.98 (q, $J = 7.0$, 2H), 2.26 (s, 3H), 2.24 (s, 3H), 1.10 (t, $J = 7.1$, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ_C 165.83, 152.65, 148.62, 142.42, 136.84, 129.36, 126.61, 99.88, 59.63, 54.08, 21.11, 18.23, 14.56. Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.80; H, 6.57; N, 10.14%. Mp 209–212 °C

5-Pyrimidinecarboxylic acid, 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenyl-, ethyl ester (4b)[5f]. (94% yield); ^{1}H NMR (400 MHz, d_6-DMSO/TMS) δ_H 9.29 (d, $J = 1.6$, 1H), 7.85 (br, 1H), 7.16–7.39 (m, 5H), 5.24 (d, $J = 3.6$, 1H), 3.70 (q, $J = 7.2$, 2H), 2.27 (s, 3H), 0.71 (t, $J = 7.2$, 3H). ^{13}C NMR (100 MHz, d_6-DMSO): δ_C 165.14, 152.33, 148.67, 141.52, 136.53, 135.13, 129.08, 128.28, 126.96, 125.40, 100.68, 59.04, 54.56, 15.24, 13.90. Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.33; H, 6.54; N, 10.59%. Mp 205–208 °C.

5-Pyrimidinecarboxylic acid, 1,2,3,4-tetrahydro-1,6-dimethyl-4-(4-methylphenyl)-2-oxo-, ethyl ester (4c). (86% yield); ^{1}H NMR (400 MHz, d_6-DMSO): δ_H 7.92 (d, $J = 4.0$, 1H), 7.11 (d, 4H,

$J = 2.0$), 5.13 (d, 1H, $J = 3.6$), 4.03 (dq, 2H, $J = 7.2, 3.2$), 3.10 (s, 1H), 2.50–2.52 (m, 1H), 2.48 (s, 3H), 2.26 (s, 3H), 1.13 (t, $J = 7.2$, 3H). ^{13}C NMR (100 MHz, d_6-DMSO): δ_C 165.53, 153.06, 150.31, 141.03, 136.36, 128.88, 125.87, 102.51, 59.42, 51.96, 29.60, 20.55, 15.92, 13.98. Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.50; H, 7.11; N, 9.51%. Mp 107–111 °C.

5-Pyrimidinecarboxylic acid, 1,2,3,4-tetrahydro-6-methyl-4-(4-methylphenyl)-2-thioxo-, ethyl ester (4d)[21a]. (>99%); ^{1}H NMR (400 MHz, d_6-DMSO): δ_H 10.29 (s, 1H), 9.61 (br, 1H), 7.08–7.16 (m, 4H), 5.13 (d, $J = 3.6$, 1H), 4.00 (q, $J = 7.2$, 2H), 2.28 (s, 3H), 2.27 (s, 3H), 1.11 (t, $J = 7.2$, 3H). ^{13}C NMR (100 MHz, d_6-DMSO): δ_C 173.66, 164.65, 144.36, 140.54, 136.38, 129.33, 127.82, 126.68, 125.02, 100.18, 78.47, 59.65, 53.43, 16.16, 12.92. HRMS (FAB) Calcd for $[C_{15}H_{19}N_2O_2S^+]$ 291.1167, Found 291.1165. Mp 190–193 °C.

5-Pyrimidinecarboxylic acid, 1,2,3,4-tetrahydro-4-(4-chlorophenyl)-6-methyl-2-oxo-, ethyl ester (4e)[5]. (87% yield); ^{1}H NMR (400 MHz, d_6-DMSO/TMS): δ_H 9.26 (br, 1H), 7.79 (br, 1H), 7.40 (d, $J = 8.2$, 2H), 7.25 (d, $J = 8.2$, 2H), 5.14 (d, $J = 3.2$, 1H), 3.98 (q, $J = 7.0$, 2H), 2.25 (s, 3H), 1.09 (t, $J = 7.0$, 3H). ^{13}C NMR (100 MHz, d_6-DMSO/TMS): δ_C 165.10, 151.83, 148.63, 143.67, 131.67, 128.30, 128.08, 98.69, 59.17, 53.28, 17.69, 13.96. Anal. Calcd for $C_{14}H_{15}ClN_2O_3$: C, 57.05; H, 5.13; Cl, 12.03; N, 9.50. Found: C, 57.00; H, 5.15; Cl, 11.93; N, 9.40%. Mp 214–217 °C.

5-Pyrimidinecarboxylic acid, 1,2,3,4-tetrahydro-6-ethyl-4-(4-methylphenyl)-2-oxo-, ethyl ester (4f). (74% yield); ^{1}H NMR (400 MHz, d_6-DMSO/TMS): δ_H 9.21 (br, 1H), 7.72 (br, 1H), 7.12 (br, 4H), 5.12 (d, $J = 3.2$, 1H), 3.98 (q, $J = 7.2$, 2H), 2.59–2.73 (m, 2H), 2.25 (s, 3H), 1.22 (t, $J = 7.2$, 3H), 1.10 (t, $J = 7.2$, 3H). ^{13}C NMR (100 MHz, d_6-DMSO/TMS): δ_C 164.95, 153.65, 152.49, 141.91, 136.37, 128.87, 126.11, 98.56, 59.17, 53.55, 24.05, 20.58, 13.95, 12.93. Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.36; H, 7.24; N, 9.55%. Mp 154–155 °C.

5-Pyrimidinecarboxylic acid, 1,2,3,4-tetrahydro-4-(4-methoxyphenyl)-6-propyl-2-oxo-, ethyl ester (4g)[6]. (74% yield); ^{1}H NMR (400 MHz, d_6-DMSO/TMS): δ_H 9.15 (br, 1H), 7.67 (br, 1H), 7.15 (d, $J = 8.4$, 2H), 6.88 (d, $J = 8.8$, 2H), 5.10 (br, 1H), 4.00 (q, $J = 7.2$, 2H), 3.72 (s, 3H), 2.60–2.64 (m, 2H), 1.48–1.56 (m, 2H), 1.11 (t, $J = 7.2$, 3H), 0.87 (t, $J = 7.2$, 3H). ^{13}C NMR (100 MHz, d_6-DMSO/TMS): δ_C 165.09, 158.39, 152.36, 152.02, 137.00, 127.33, 113.65, 99.29, 59.18, 54.99, 53.27, 32.29, 21.63, 13.99, 13.66. Anal. Calcd for $C_{17}H_{22}N_2O_4$: C, 64.13; H, 6.97; N, 8.80. Found: C, 63.66; H, 6.81; N, 8.66%. Mp 120–124 °C.

5-Pyrimidinecarboxylic acid, 1,2,3,4-tetrahydro-4-(4-methoxyphenyl)-6-propyl-2-thioxo-, ethyl ester (4h). (86% yield); ^{1}H NMR (400 MHz, d_6-DMSO/TMS): δ_H 10.30 (s, 1H), 9.61 (br, 1H), 7.03 (dd, $J = 8.8$, 86, 4H), 5.14 (d, $J = 3.6$, 1H), 4.01 (q, $J = 7.2$, 2H), 3.72 (s, 3H), 2.67–2.72 (m, 2H), 1.48–1.59 (m, 2H), 1.13 (t, $J = 7.2$, 3H), 0.92 (t, $J = 7.2$, 3H). ^{13}C NMR (100 MHz, d_6-DMSO/TMS): δ_C 174.18, 164.87, 158.69, 148.79, 135.66, 127.54, 113.80, 100.68, 59.55, 55.00, 53.35, 31.58, 21.78, 13.91, 13.63. HRMS (FAB) Calcd for $[C_{17}H_{23}N_2O_3S^+]$ 335.1429, Found 335.1430. Mp 91–94 °C.

5-Pyrimidinecarboxylic acid, 1,2,3,4-tetrahydro-4-(4-methylphenyl)-2-oxo-6-propyl-, ethyl ester (4i). (72% yield) ^{1}H NMR (400 MHz, d_6-DMSO): δ_H 9.14 (br, 1H), 7.68 (br, 1H), 7.11 (d, $J = 1.5$, 4H), 5.12 (d, $J = 3.3$, 1H), 3.97 (q, $J = 7.0$, 2H), 2.63 (t, $J = 7.3$, 2H), 2.24 (s, 3H), 1.49–1.62 (m, 2H), 1.09 (t, $J = 7.0$, 3H), 0.90 (t, $J = 7.1$, 3H). ^{13}C NMR (100 MHz, d_6-DMSO): δ_C 165.56, 152.86, 152.64, 142.47, 136.83, 129.36, 126.59, 99.66, 59.66, 54.08, 32.78, 22.10, 21.10, 14.50, 14.15. HRMS (FAB) Calcd for $[C_{17}H_{23}N_2O_3^+]$ 303.1709, Found 303.1701. Mp 140–144 °C.

5-Pyrimidinecarboxylic acid, 1,2,3,4-tetrahydro-1-methyl-4-(4-methylphenyl)-2-oxo-6-propyl-, ethyl ester (4j). (40% yield); ^{1}H NMR (400 MHz, d_6-DMSO/TMS): δ_H 7.97 (d, $J = 3.6$, 1H), 7.07–7.12 (m, 4H), 5.09 (d, $J = 3.6$, 1H), 3.99–4.07 (m, 2H), 3.10 (s, 3H), 2.81–2.90 (m, 2H), 2.51 (s, 3H), 2.25 (s, 3H), 1.45–1.56 (m, 2H), 1.13 (t, $J = 7.2$, 3H), 0.96 (t, $J = 7.4$, 3H). ^{13}C NMR (100 MHz, d_6-DMSO/TMS): δ_C 165.13, 153.74, 153.30, 140.93, 136.32, 128.88, 125.82, 102.49, 59.43, 51.64, 30.21, 29.26, 21.53, 20.55, 13.96, 13.80. Anal. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 68.22; H, 7.60; N, 8.76%. Mp 140–141 °C.

5-Pyrimidinecarboxylic acid, 1,2,3,4-tetrahydro-1,3-dimethyl-4-(4-methylphenyl)-2-oxo-6-propyl-, ethyl ester (4k). Yellow oil. (12% yield); ^{1}H NMR (400 MHz, d_6-DMSO/TMS): δ_H 7.11 (dd, $J = 8.4, 6.8$, 4H), 5.15 (s, 1H), 4.02 (q, $J = 7.2$, 2H), 3.19 (s, 3H), 2.78–2.94 (m, 2H), 2.75 (s, 3H), 2.26 (s, 3H), 1.42–1.54 (m, 2H), 1.15 (t, $J = 7.2$, 3H), 0.95 (t, $J = 7.2$, 3H). ^{13}C NMR (100 MHz, d_6-DMSO/TMS): δ_C 164.82, 152.86, 153.03, 137.91, 136.91, 129.08, 126.36, 102.39, 59.52, 59.42, 33.76, 30.19, 30.11, 21.41, 20.57, 13.92, 13.77. HRMS (FAB) Calcd for $[C_{19}H_{26}N_2NaO_3^+]$ 353.1841, Found 353.1851.

5-Pyrimidinecarboxylic acid, 1,2,3,4-tetrahydro-4-(4-methylphenyl)-6-propyl-2-thioxo-, ethyl ester (4l). (80% yield); ^{1}H NMR (400 MHz, d_6-DMSO/TMS): δ_H 10.29 (s, 1H), 9.61 (br, 1H), 7.08–7.16 (m, 4H), 5.13 (d, $J = 3.6$, 1H), 4.01 (q, $J = 7.2$, 2H), 2.68 (m, 2H), 2.26 (s, 3H), 1.54 (m, 2H), 1.10 (t, $J = 7.2$, 3H), 0.91 (t, $J = 7.4$, 3H). ^{13}C NMR (100 MHz, d_6-DMSO/TMS): δ_C 174.25, 164.81, 148.83, 140.51, 136.82, 128.98, 126.16, 100.52, 59.53, 53.57, 31.49, 21.70, 20.57, 13.87, 13.57. HRMS (FAB) Calcd for $[C_{17}H_{23}N_2O_2S^+]$ 319.1480, Found 319.1486. Mp 123–125 °C.

5-Pyrimidinecarboxylic acid, 1,2,3,4-tetrahydro-4-(4-chlorophenyl)-2-oxo-6-propyl-, ethyl ester (4m). (49% yield); ^{1}H NMR (400 MHz, d_6-DMSO/TMS): δ_H 9.25 (br, 1H), 7.78 (br, 1H), 7.40 (d, 2H, $J = 8.2$), 7.25 (d, 2H, $J = 8.2$), 5.15 (d, $J = 3.2$, H1), 3.99 (q, $J = 7.0$, 2H), 2.63 (m, 2H), 1.58 (m, 2H), 1.10 (t, $J = 7.0$, 3H), 0.91 (t, $J = 7.6$, 3H). ^{13}C NMR (100 MHz, d_6-DMSO/TMS): δ_C 164.87, 152.65, 152.10, 143.73, 131.71, 128.33, 128.05, 99.45, 98.55, 59.24, 53.30, 32.25, 21.57, 13.92, 13.60. Anal. Calcd for $C_{16}H_{19}ClN_2O_3$: C, 59.54; H, 5.93; Cl, 10.98; N, 8.68. Found: C, 59.51; H, 6.15; Cl, 11.15; N, 8.61%. Mp 125–127 °C.

5-Pyrimidinecarboxylic acid, 1,2,3,4-tetrahydro-4-(4-chlorophenyl)-6-propyl-2-thioxo-, ethyl ester (4n). (84% yield); ^{1}H NMR (400 MHz, d_6-DMSO/TMS): δ_H 10.39 (br, 1H), 7.68 (br, 1H), 7.34 (dd, $J = 8.4$, 69.6, 4H), 5.19 (d, $J = 3.6$, 1H), 4.00–4.05 (m, 2H), 2.66–2.73 (m, 2H), 1.52–1.59 (m, 2H), 1.12 (t, $J = 7.0$, 3H), 0.91 (t, $J = 7.0$, 3H). ^{13}C NMR (100 MHz, d_6-DMSO/TMS): δ_C 174.44, 164.68, 149.35, 142.34, 132.21, 128.53, 128.18, 100.06, 59.65, 53.32, 31.56, 21.74, 13.87, 13.60. HRMS (FAB) Calcd for $[C_{16}H_{20}ClN_2O_2S^+]$ 339.0934, Found 339.0932. Mp 74–78 °C.

5-Pyrimidinecarboxylic acid, 1,2,3,4-tetrahydro-4-[(4-trifluoromethyl)phenyl]-6-propyl-2-oxo-, ethyl ester (4o). (37% yield); ^{1}H

NMR (400 MHz, d_6-DMSO/TMS): δ_H 9.32 (br, 1H), 7.87 (br, 1H), 7.60 (dd, J = 8.0, 96, 4H), 5.25 (d, J = 3.2, 1H), 4.00 (q, J = 7.2, 2H), 3.72 (s, 3H), 2.59–2.72 (m, 2H), 1.53–1.60 (m, 2H), 1.11 (t, J = 7.2, 3H), 0.92 (t, J = 7.4, 3H). ^{13}C NMR (400 MHz, d_6-DMSO/TMS): δ_C 164.94, 153.13, 152.19, 149.35, 127.13, 125.49, 98.37, 59.40, 53.76, 32.41, 21.70, 13.99, 13.95, 13.70, 13.68. Anal. Calcd for $C_{17}H_{19}F_3N_2O_3$: C, 57.30; H, 5.37; F, 15.99; N, 7.86. Found: C, 57.09; H, 5.63; F, 15.76; N, 7.65%. Mp 141–144 °C.

5-Pyrimidinecarboxylic acid, 1,2,3,4-tetrahydro-6-hexyl-4-(4-methylphenyl)-2-oxo-, ethyl ester (4p). (41% yield); ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ_H 8.52 (br, 1H), 7.13 (dd, J = 8.0, 30.8, 4H), 6.23 (br, 1H), 5.33 (d, J = 2.8, 1H), 4.06 (q, J = 7.0, 2H), 2.67 (t, J = 7.2, 2H), 2.31 (s, 3H), 1.55–1.62 (m, 2H), 1.21–1.38 (m, 6H), 1.17 (t, J = 7.2, 3H), 0.86 (t, J = 6.8, 3H). ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ_C 164.31, 152.81, 149.68, 139.87, 136.25, 128.10, 125.29, 99.66, 58.73, 54.05, 30.65, 30.37, 27.96, 27.11, 21.37, 19.92, 12.94, 12.86. HRMS (FAB) Calcd for [$C_{20}H_{29}N_2O_3^+$] 345.2178, Found 345.2173. Mp 105–108 °C.

5-Pyrimidinecarboxylic acid, 1,2,3,4-tetrahydro-4-phenyl-6-(2-phenylethyl)-2-oxo-, ethyl ester (4q)[6]. (53% yield); ^{1}H NMR (400 MHz, d_6-DMSO): δ_H 9.36 (br, 1H), 7.96 (s, 1H), 7.18–7.37 (m, 10H), 5.18 (d, J = 3.6, 1H), 4.01 (q, J = 7.0, 2H), 2.81–2.96 (m, 4H), 1.10 (t, J = 7.0, 3H). ^{13}C NMR (100 MHz, d_6-DMSO): δ_C 165.51, 152.83, 151.95, 128.89, 128.81, 128.75, 127.76, 126.76, 126.50, 99.74, 59.83, 54.48, 34.54, 32.24, 14.54. HRMS (FAB) Calcd for [$C_{21}H_{23}N_2O_3^+$] 351.1709, Found 351.1709. Mp 162–164 °C.

5-Pyrimidinecarboxylic acid, 1,2,3,4-tetrahydro-6-cyclohexyl-4-(4-methylphenyl)-2-oxo-, ethyl ester (4s). (28% yield); ^{1}H NMR (400 MHz, d_6-DMSO): δ_H 8.78 (br, 1H), 7.68 (s, 1H), 7.11 (br, 4H), 5.09 (d, J = 3.6, 1H), 3.94–3.99 (m, 2H), 3.76–3.85 (m, 1H), 2.26 (s, 3H), 1.51–1.74 (m, 6H), 1.17–1.25 (m, 4H), 1.09 (t, J = 7.2, 3H). ^{13}C NMR (100 MHz, d_6-DMSO): δ_C 165.87, 155.96, 153.05, 142.26, 136.87, 129.40, 126.58, 98.92, 59.77, 53.95, 38.08, 29.05, 28.75, 26.57, 26.41, 25.36, 21.11, 14.46. HRMS (FAB) Calcd for [$C_{20}H_{27}N_2O_3^+$] 343.2022, Found 343.2028. Mp 211–212 °C.

5-Pyrimidinecarboxylic acid, 1,2,3,4-tetrahydro-6-*tert*-butyl-4-phenyl-2-oxo-, ethyl ester (4t)[5j]. Colorless oil. (5% yield); ^{1}H NMR (400 MHz, d_6-DMSO): δ_H 8.02 (br, 1H), 7.76 (s, 1H), 7.30–7.40 (m, 5H), 4.98 (d, J = 3.2, 1H), 3.50–4.50 (m, 2H), 1.29 (s, 9H), 1.10 (t, J = 7.0, 3H). ^{13}C NMR (100 MHz, d_6-DMSO): δ_C 168.32, 153.56, 148.99, 143.86, 128.82, 127.95, 126.99, 102.06, 60.50, 56.44, 35.95, 28.63, 14.19. HRMS (FAB) Calcd for [$C_{17}H_{23}N_2O_3^+$] 303.1709, Found 303.1705.

5-Pyrimidinecarboxylic acid, 1,2,3,4-tetrahydro-6-(1-heptenyl)-4-(4-methylphenyl)-2-oxo-, ethyl ester (4u). (10% yield); ^{1}H NMR (400 MHz, d_6-DMSO): δ_H 9.00 (br, 1H), 7.75 (br, 1H), 7.11–7.19 (m, 5H), 6.56–6.63 (td, J = 6.8, 16.4, 1H), 5.16 (d, J = 3.2, 1H), 3.97–4.05 (m, 2H), 2.27 (s, 3H), 2.17 (q, J = 7.2, 2H), 1.38–1.45 (m, 2H), 1.28–1.31 (m, 4H), 1.13 (t, J = 7.2, 2H), 0.88 (t, J = 7.2, 3H). ^{13}C NMR (100 MHz, d_6-DMSO): δ_C 165.60, 153.03, 145.00, 141.96, 139.04, 136.97, 129.43, 126.57, 121.76, 100.84, 60.04, 53.92, 33.07, 31.18, 28.18, 22.44, 21.11, 14.50, 14.37. HRMS (FAB) Calcd for [$C_{21}H_{29}N_2O_3^+$] 357.2178, Found 357.2181. Mp 145–148 °C.

5-Pyrimidinecarboxylic acid, 1,2,3,4-tetrahydro-6-(1-heptynyl)-4-(4-methylphenyl)-2-oxo-, ethyl ester (4v). Yellow oil. (15% yield); ^{1}H NMR (400 MHz, d_6-DMSO): δ_H 9.53 (br, 1H), 7.63 (br, 1H), 7.12 (dd, J = 2.8, 14.0, 4H), 6.29 (s, 1H), 5.32 (d, J = 3.2, 1H), 4.15–4.25 (m, 2H), 2.47 (t, J = 7.0, 2H), 2.24 (s, 3H), 1.55–1.60 (m, 2H), 1.55–1.60 (m, 2H), 1.24–1.32 (m, 4H), 1.19 (t, J = 7.0, 3H), 0.82 (t, J = 7.0, 3H). ^{13}C NMR (100 MHz, d_6-DMSO): δ_C 159.26, 159.14, 153.36, 146.28, 142.02, 136.91, 129.30, 126.55, 102.52, 100.16, 61.34, 52.38, 37.50, 31.34, 28.82, 22.44, 21.10, 14.92, 14.35. HRMS (FAB) Calcd for [$C_{21}H_{27}ClN_2O_3^+$] 355.2022, Found 355.2027.

5-Pyrimidinecarboxylic acid, 1,2,3,4-tetrahydro-4-(4-methoxyphenyl)-6-phenyl-2-thioxo-, ethyl ester (4w). (73% yield) ^{1}H NMR (400 MHz, d_6-DMSO/TMS): δ_H 10.47 (s, 1H), 9.74 (br, 1H), 6.95–7.45 (m, 9H), 5.21 (d, J = 3.6, 1H), 3.75 (s, 3H), 3.73 (q, J = 7.2, 2H), 0.73 (t, J = 7.0, 3H). ^{13}C NMR (100 MHz, d_6-DMSO/TMS): δ_C 174.17, 164.81, 158.74, 145.49, 135.09, 133.96, 128.97, 128.55, 127.60, 127.56, 113.91, 101.93, 59.33, 55.01, 53.42, 13.25. Anal. Calcd for $C_{20}H_{20}N_2O_3S$: C, 65.20; H, 5.47; N, 7.60; S, 8.70. Found: C, 64.81; H, 5.10; N, 7.60; S, 8.49%. Mp 171–174 °C.

5-Pyrimidinecarboxylic acid, 1,2,3,4-tetrahydro-4-(4-methylphenyl)-2-oxo-6-phenyl-, ethyl ester (4x)[21b]. (35% yield); ^{1}H NMR (400 MHz, d_6-DMSO/TMS): δ_H 9.29 (br, 1H), 7.84 (br, 1H), 7.16–7.41 (m, 9H), 5.20 (d, 1H, J = 3.6), 3.70 (q, J = 7.1, 2H), 2.29 (s, 3H), 0.71 (t, J = 7.0, 3H). ^{13}C NMR (100 MHz, d_6-DMSO/TMS): δ_C 165.04, 152.10, 148.66, 141.44, 136.46, 135.03, 128.95, 128.75, 128.24, 127.63, 126.36, 126.13, 100.52, 58.96, 53.76, 20.59, 18.83, 13.69, 13.29. Anal. Calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.20; H, 5.72; N, 8.26%. Mp 173–175 °C.

5-Pyrimidinecarboxylic acid, 1,2,3,4-tetrahydro-4-(4-methylphenyl)-6-phenyl-2-thioxo-, ethyl ester (4y). (62% yield); ^{1}H NMR (400 MHz, d_6-DMSO/TMS): δ_H 10.49 (s, 1H), 9.76 (br, 1H), 7.19–7.42 (m, 9H), 5.25 (d, J = 3.6, 1H), 3.73 (q, J = 7.2, 2H), 2.29 (s, 3H), 0.72 (t, J = 7.2, 3H). ^{13}C NMR (100 MHz, d_6-DMSO/TMS): δ_C 174.34, 164.83, 145.60, 140.08, 136.97, 133.95, 129.12, 128.56, 127.61, 126.25, 101.87, 59.37, 53.76, 20.63, 13.26. Anal. Calcd for $C_{20}H_{20}N_2O_2S$: C, 68.16; H, 5.72; N, 7.95; S, 9.10. Found: C, 67.78; H, 5.62; N, 7.94; S, 8.89%. Mp 177–180 °C.

5-Pyrimidinecarboxylic acid, 1,2,3,4-tetrahydro-2-oxo-4,6-diphenyl-, ethyl ester (4z)[5l]. (38% yield); ^{1}H NMR (300 MHz, d_6-DMSO/TMS): δ_H 9.40 (s, 1H), 7.90 (s, 1H), 7.30–7.40 (m, 10H), 5.25 (s, 1H), 3.72 (q, J = 6.5, 2H), 0.70 (t, J = 6.4, 3H). ^{13}C NMR (75 MHz, d_6-DMSO): δ_C 165.19, 152.33, 152.24, 149.04, 135.14, 129.64, 129.49, 128.59, 127.51, 126.73, 125.41, 100.42, 55.19, 53.29, 14.27. HRMS (EI) Calcd for [$C_{19}H_{18}N_2O_3^+$] 322.1317, Found 322.1317. Mp 171–174 °C.

5-Pyrimidinecarboxylic acid, 1,2,3,4-tetrahydro-4-(4-chlorophenyl)-6-phenyl-2-thioxo-, ethyl ester (4aa). (55% yield); ^{1}H NMR (400 MHz, d_6-DMSO/TMS): δ_H 10.59 (s, 1H), 9.81 (br, 1H), 7.30–7.50 (m, 9H), 5.28 (d, J = 4.0, 1H), 3.75 (q, J = 7.0, 2H), 0.73 (t, J = 7.0, 3H). ^{13}C NMR (100 MHz, d_6-DMSO/TMS): δ_C 174.45, 164.74, 146.03, 141.83, 133.74, 132.32, 129.10, 128.63, 128.57, 128.22, 127.62, 101.31, 59.46, 53.37, 13.22. Anal. Calcd for $C_{19}H_{17}ClN_2O_2S$: C, 61.20; H, 4.60; Cl, 9.51; N, 7.51; S, 8.60. Found: C, 60.75; H, 4.48; Cl, 9.57; N, 7.42; S, 8.33%. Mp 185–188 °C.

Hexanoic acid, 2-[(4-methylphenyl)methylene]-3-oxo-, ethyl ester (5a). Yellow oil. *Ca.* 55/45 *E*/*Z* mixture of diastereoisomers. Data for *E*/*Z* mixture; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ_H 7.66 (s, 1.1H), 7.56 (s, 0.9H), 7.15–7.36 (m, 4H), 4.34 (q, $J = 7.2$, 0.9H), 4.28 (q, $J = 7.2$, 1.1H), 2.70 (t, $J = 7.4$, 0.9H), 2.55 (t, $J = 7.4$, 1.1H), 2.37 (s, 1.35H), 2.36 (s, 1.65H), 1.62–1.76 (m, 2H), 1.32 (t, $J = 7.6$, 1.65H), 1.30 (t, $J = 7.6$, 1.35H), 0.98 (t, $J = 7.4$, 1.35H), 0.91 (t, $J = 7.4$, 1.65H). ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ_C 205.97, 196.84, 168.31, 164.84, 141.24, 140.93, 140.53, 140.40, 133.50, 133.11, 130.28, 130.26, 129.81, 129.69, 129.63, 129.60, 61.63, 61.40, 45.47, 40.58, 21.50, 21.45, 17.53, 16.86, 14.18, 13.93, 13.76, 13.54. HRMS (EI) Calcd for [$C_{16}H_{20}O_3^+$] 260.1412, Found 260.1417.

Typical procedure of four-component DHPM synthesis

100 mg of Al-M41 in a 40 mL test tube containing a magnetic stirrer bar was evacuated at 373 K for 1 h. Tetradecane (0.40 mmol, GC internal standard) in 1.5 mL of octane was added to the catalyst, and then the mixture of acetaldehyde **2f** (44 mg, 1.0 mmol) and ethyl diazoacetate **6a** (170 mg, 1.5 mmol) was added slowly over 30 min. The resulting suspension was stirred at 298 K for 12 h, and then *p*-tolualdehyde **2a** (140 mg, 1.2 mmol) and urea **3a** (60 mg, 1.0 mmol) in octane (0.50 mL) were added. The mixture was heated at 373 K and stirring continued for 10 h. The reaction mixture was diluted with MeOH and filtered to remove the catalyst. The filtrate was evaporated and analyzed by GC to determine the yield of **4a** (50%).

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