Nano-MoO_3 as a highly efficient heterogeneous catalyst for a one-pot synthesis of tetrahydropyrimidine derivatives in water

Elham Zarenezhad[a]*, Mohammad Navid Soltani Rad[b], Mohammad Hossein Mosslemin[a], Masoumeh Tabatabaee[a] and Somayeh Behrouz[b]

[a]*Department of Chemistry, Yazd Branch, Islamic Azad University, PO Box 89195-155, Yazd, Iran*

[b]*Department of Chemistry, Shiraz University of Technology, 71555-313 Shiraz, Iran*

A green and highly efficient one-pot synthesis of 16 1,3,4,5-tetrasubstituted 1,2,3,6-tetrahydropyrimidines, four of which are new, using a three-component reaction involving an aniline, formaldehyde and a dialkyl acetylenedicarboxylate in aqueous media at room temperature catalysed by nano-MoO_3 has been achieved.

Keywords: three-component reaction, tetrahydropyrimidines, green synthesis, MoO_3-nanoparticle

The synthesis of polyfunctionalised heterocyclic compounds has received considerable attention in recent years owing to their known potential as drugs.[1] Although pyrimidine derivatives are a well-known, diverse and interesting group of heterocyclic drugs, largely owing to the presence of the heterocycle in the DNA and/or RNA scaffold,[2] dihydropyrimidine derivatives have also attracted increasing interest owing to their activities as antifungal,[3] anti-hypertensive,[4] and anti-tumour agents.[5]

Since multicomponent reactions (MCRs) yield complex products from readily available starting materials giving good yields in a single step process, they have emerged as green and powerful tools in organic synthesis and drug discovery.[6] Also, since MCRs can employ a large range of starting materials, many new classes of compounds can be synthesised which may show novel pharmaceutical properties.[7]

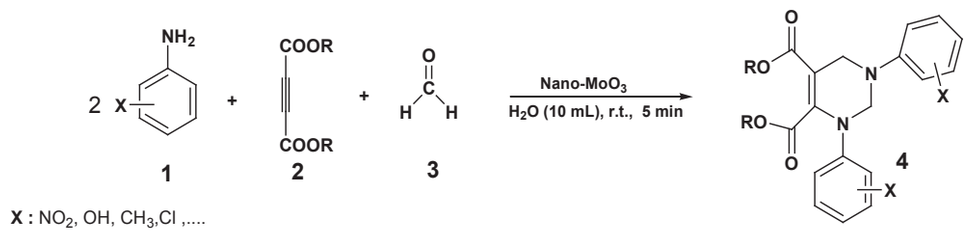
Metal oxide nanoparticles are known as useful heterogeneous catalysts which traditionally can catalyse MCRs. Development of such catalysts has resulted in more economical and environmentally friendly chemistry through replacing nonselective, unstable, or toxic catalysts.[8]

MoO_3-nanoparticles have received considerable attention as an inexpensive, eco-friendly and highly reactive catalyst. Furthermore, this catalyst is non-toxic and can be easily handled for various organic transformations, affording the corresponding products with high selectivity in excellent yields.[9] MoO_3 exhibits remarkable Lewis acid properties for various organic transformations in the liquid phase.[10] This catalyst can be recycled many times and in most cases its reactivity remains essentially intact; moreover, MoO_3-nanoparticles as a catalyst are quite active over a wide range of temperatures being resistant to thermal breakdown.[11] It Tetrahydropyrimidine derivatives can be synthesised using hazardous and toxic solvents,[12] as but the requirement for high temperatures, expensive organic solvents and long reaction times limits the use of these methods. Sun and coworkers have already reported the synthesis of some tetrahydropyrimidine derivatives in multi-step processes using organic media, but in low yields.[13] Recently, Darandale and coworkers reported a three-component reaction between formaldehydes, anilines and dialkyl acetylenedicarboxylate derivatives in boiling water using $ZrOCl_2$ as a catalyst to produce the corresponding 1,3,4,5-tetrasubstituted 1,2,3,6-tetrahydropyrimidine derivatives in moderate to good yields.[14] We have now found that the same reaction can be carried out more rapidly in good to excellent yields using MoO_3-nanoparticles as a catalyst at room temperature in H_2O (Scheme 1) and we now describe our successful synthesis of 16 1,3,4,5-tetrasubstituted 1,2,3,6-tetrahydropyrimidines, four of which are new. Since MoO_3-nanoparticles possess a high oxidation state of Mo (Mo^{+6}), they exhibit superior acid strength compared to $ZrOCl_2$ which we believe explains why they readily catalyse the highly efficient synthesis of the title products under very mild reaction conditions in a shorter reaction time.

Results and discussion

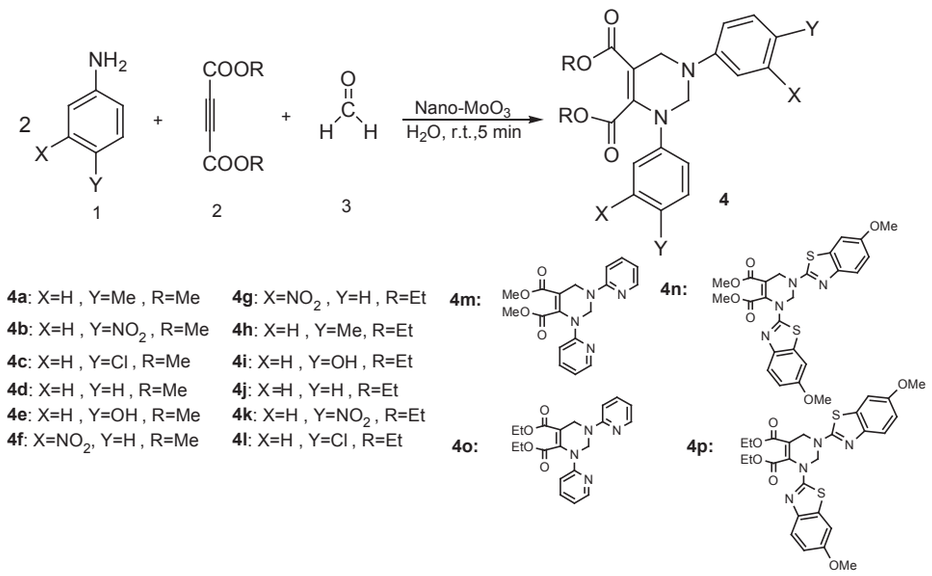
MoO_3-nanoparticles were previously synthesised[15] and their nano structures have been characterised and confirmed by the use of powder X-ray diffraction (PXRD) and scanning electron microscopy (SEM). Figure 1 shows the XRD pattern of nano-MoO_3 and Fig. 2 refers to the SEM micrograph. The crystal size structure was calculated from the Debye–Scherrer formula, $D = k\lambda/\beta\cos\theta$, where D is the crystallite size, k is a constant (=0.9 assuming that the particles are spherical), λ is the wavelength of the X-ray radiation, β is the line width (obtained after correction for the instrumental broadening) and θ is the angle of diffraction. The average particle size obtained from XRD data was ~50 nm.

Initially, to obtain the optimised reaction conditions, we selected the reaction of 4-methylaniline (**1**; X=H, Y=4-Me), dimethyl acetylenedicarboxylates **2**, and formaldehyde **3**



X : NO_2, OH, CH_3,Cl ,....
R: Me,Et

* Correspondent. E-mail: elham.zarenezhad2014@gmail.com



Scheme 1 Synthesis of 1,3,4,5-tetrasubstituted 1,2,3,6-tetrahydropyrimidines catalysed by nano-MoO_3.

(Scheme 1) in a molar ratio of 2 : 1 : 4 as a sample reaction, respectively. To this end, we tested the influence of different catalysts, solvents and temperatures on the reaction and the results are shown in Table 1.

When the reaction was carried out in the absence of catalyst, a longer reaction time was required (40 min) and in this case a low yield of product was attained (< 35%) even if the reaction time was prolonged (entry 1).

To obtain the desired product (**4a**), we tested the reaction using seven different homogeneous and heterogeneous Bronsted and/or Lewis acids (Table 1, entries 2–8). Among the tested acids, 10 mol% nano-MoO_3 gave the best yield of 95% in 5 min (entry 8) and was the catalyst of choice. We also investigated the effect of using a greater amount of MoO_3-nanoparticles. However, by increasing the molar percentage of catalyst to 11 or 12% no further improvement was observed for the model reaction (entries 9 and 10). A decrease in the amount of catalyst to less than 10% resulted in decreased yields (entries 11 and 12). Also for nano-MoO_3, it was demonstrated that H_2O was the best solvent in comparison with other solvents including EtOH, CH_3CN, MeOH and CH_2Cl_2 (entries 8 and 13–16). Therefore, H_2O was selected as the solvent of choice.

The heterogeneous nano-MoO_3 catalyst used in this experiment was recycled and reused several times by a simple filtration and washing with EtOAc. The catalytic activity of the nano-MoO_3 remained intact after two runs and even after 10 successive runs had decreased only to 87%.

Under the optimised reaction conditions, a series of 1,3,4,5-tetrasubstituted 1,2,3,6-tetrahydropyrimidines derivatives (**4b**–**p**) (Scheme 1) were synthesised in high yield (89–95%) and characterised by appropriate spectroscopic and physical methods (Table 2).

As can be seen in Table 2, this multi component approach can be used for the synthesis of such products (**4a**–**l**) from both aromatic amines with electron-withdrawing and electron-donating groups. Furthermore, several heteroaromatic amines were successfully used in this reaction producing products **4m**–**p** with excellent results. In this procedure, the products were easily separated from the reaction mixture by simple filtration, as they were virtually insoluble in water. Also for separating the catalyst from the crude product, the solid mixture was washed with excess of EtOAc to remove the product from the catalyst. We also attempted to use an aromatic aldehyde instead of formaldehyde in this method; but no product was obtained.

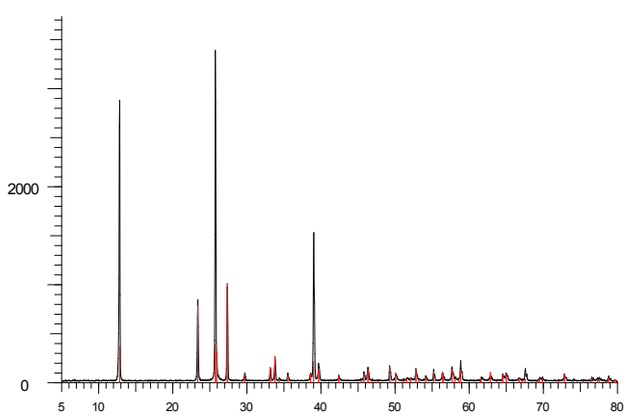


Fig. 1 PXRD patterns of the synthesised MoO_3 nano-crystal.

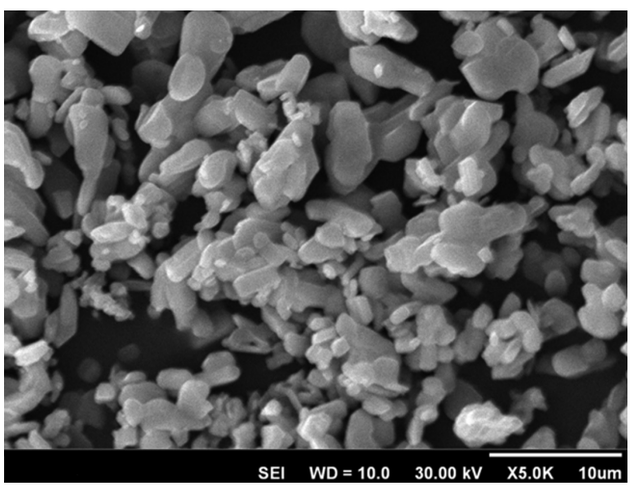


Fig. 2 Scanning electron micrographs for prepared nano-MoO_3.

Table 1 Optimisation of the three-component coupling reaction between 4-methylaniline **1** (X=4-Me) dimethyl acetylenedicarboxylate 1 (R=Me) and formaldehyde **3** in water (Scheme 1)[a]

Entry	Catalyst/mol%	Solvent	Time/min	Yield/%[b]
1	–	H_2O	40	35
2	SiO_2 (15)	H_2O	20	30
3	H_3PO_4 (15)	H_2O	50	35
4	CF_3CO_2H (10)	H_2O	50	35
5	CCl_3CO_2H (10)	H_2O	50	50
6	PTSA (10)	H_2O	50	40
7	$ZrOCl_2$ (10)	H_2O	50	55
8	MoO_3 (10)	H_2O	5	95
9	MoO_3 (11)	H_2O	5	95
10	MoO_3 (12)	H_2O	10	95
11	MoO_3 (8)	H_2O	10	75
12	MoO_3 (4)	H_2O	15	70
13	MoO_3 (10)	EtOH	20	53
14	MoO_3 (10)	CH_3CN	20	62
15	MoO_3 (10)	MeOH	20	62
16	MoO_3 (10)	CH_2Cl_2	20	50

[a]Reaction conditions: 4-methylaniline (2 mmol), dimethyl acetylenedicarboxylate (1 mmol), and formaldehyde (4 mmol) were left in contact with catalyst in water or an organic solvent at room temperature for various times.
[b]Isolated yield.

Table 2 Synthesis of 1,3,4,5-tetrasubstituted 1,2,3,6-tetrahydropyrimidines derivatives (**4a**–**p**) using nano-MoO_3 in water (Scheme 1)[a]

Yield/%[b]	Time/min	Product	Entry [ref.]
95	5	**4a**	1
92	7	**4b**	2
90	8	**4c**	3[14]
92	7	**4d**	4[14]
90	7	**4e**	5[14]
93	10	**4f**	6[14]
91	10	**4g**	7[14]
90	7	**4h**	8
90	8	**4i**	9[14]
92	5	**4j**	10[14]
92	5	**4k**	11[14]
90	7	**4l**	12[14]
91	9	**4m**	13[14]
93	10	**4n**	14[14]
90	10	**4o**	15[14]
89	8	**4p**	16[14]

[a]Reaction conditions: arylamine or heteroarylamine (2 mmol), dialkyl acetylenedicarboxylate (1 mmol), and formaldehyde (4 mmol) were left in contact with catalyst in water at room temperature for various times.
[b]Isolated yield.

A plausible mechanism has been suggested for the formation of 1,3,4,5-tetrasubstituted 1,2,3,6-tetrahydropyrimidines from similar reactants to the ones we used catalysed by $ZrOCl_2$ [14] and we assume that our procedure using MoO_3-nanoparticles proceeds similarly.

Experimental

Solvents were purified by standard procedures, and stored over 3Å molecular sieves. Reactions were followed by TLC using SILG/UV 254 silica-gel plates. Melting points were determined with an Electrothermal 9100 apparatus in open capillary tubes and are uncorrected. Elemental analyses were performed using a Heraeus CHN–O-Rapid analyser. IR spectra were recorded on a Shimadzu IR-470 spectrometer. NMR spectra were obtained on a Bruker DRX-400 Avance spectrometer (^{1}H NMR at 400 Hz, ^{13}C NMR at 100 Hz) in $CDCl_3$ or DMSO-d_6 using tetramethylsilane as internal standard. Chemical shifts (δ) are given in ppm and coupling constants (J) in Hz. Abbreviations used for ^{1}H NMR signals are: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, b=broad. The chemicals used in this work were purchased from Fluka or Merck and were used without further purification.

Synthesis of tetrahydropyrimidine derivatives; general procedure

In a round-bottomed flask (10 mL), a mixture of aromatic amine (2 mmol), dialkyl acetylenedicarboxylate (1 mmol), formaldehyde (4 mmol), MoO_3 (10 mol%) and H_2O (5 mL) was stirred for the appropriate times (Table 2). Progress of reactions was monitored by TLC. On completion, the reaction mixture was washed with H_2O (10 mL) and EtOAc (10 mL) to afford a crude product which was purified by recrystallisation in hot EtOH.

Dimethyl 1,3-di-p-tolyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**4a**): Creamy solid; yield 92%; m.p. 194–198 °C; IR (ν_{max}): 3365, 2929, 1722, 1603, 1615 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.50 (s, 6H, $2CH_3$) 3.33 (s, 3H, OCH_3) 4.71 (s, 2 H, CH_2) 5.35 (s, 2 H, CH_2) 6.58–6.81 (m, 4 H, arom.), 7.93–8.04 (m, 4 H, arom); ^{13}C NMR (DMSO-d_6) δ 23.4, 52.2, 53.4, 57.8, 85.8, 112.5, 117.5, 126.6, 128.9, 129.4, 129.9, 130.8, 141.6, 144.4, 147.2, 164.2, 166.4; ES-MS *m/z*: 380 (M+H). Anal. calcd for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36; found: C, 69.47; H, 6.40; N, 7.34%.

Dimethyl 1,3-bis(4-nitrophenyl)-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**4b**): Yellow solid; yield 92%; m.p. 222–224 °C; IR (ν_{max}): 3280, 2865, 1729, 1692, 1367 cm^{-1}; ^{1}H (DMSO-d_6) δ 3.63 (s, 6H, $2CH_3$) 4.75 (s, 2 H, CH_2) 5.70 (s, 2 H, CH_2) 6.57–6.68 (m, 4 H, arom.), 6.81–7.24 (m, 4 H, arom.); ^{13}C NMR (DMSO-d_6) δ 52.8, 53.1, 80.0, 112.8, 116.9, 122.5, 123.6, 124.2, 136.7, 137.5, 143.3, 150.5, 155.0, 165.0, 167.8; ES-MS *m/z*: 353 (M+H). Anal. calcd for $C_{20}H_{18}N_4O_8$: C, 54.30; H, 4.10; N, 12.66; found: C, 54.28; H, 4.13; N, 12.65%.

Dimethyl 1,3-bis(4-chlorophenyl)-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**4c**): Red solid; yield 90%; 260–263 °C (lit.[14] 262–264 °C); IR (ν_{max}): 3012, 2985, 1710, 1710 cm^{-1}; ^{1} H NMR ($CDCl_3$) δ 3.72 (s, 6H, $2CH_3$), 4.39 (s, 2H, CH_2), 5.40 (s, 2H, CH_2), 7.01–7.19 (m, 4H, arom.), 7.31–7.52 (m, 4H, arom.);^{13}C NMR ($CDCl_3$) δ 54.0, 55.9, 86.9, 115.2, 117. 0, 118.5, 126.5, 128.1, 131.0, 145.1, 146.3, 151.9, 168.1, 170.1;.ES-MS *m/z*: 422 (M+H). Anal. calcd for $C_{20}H_{18}Cl_2N_2O_4$: C, 57.02; H, 4.31, N, 6.65; found: C, 56.92; H, 4.55; N, 7.01%.

Dimethyl 1,3-diphenyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**4d**): Red-orange solid; yield 92%; (lit.[14] 197–199 °C); IR (ν_{max}): 3002, 2995, 1717, 1701 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.61 (s, 6H, $2CH_3$), 4.11 (s, 2H, CH_2), 5.10 (s, 2H, CH_2), 7.01–7.17 (m, 4H, arom.), 7.40–7.57 (m, 4H, arom.), 7.75–7.91 (m, 2H, arom.); ^{13}C NMR ($CDCl_3$) δ 53.0, 56.1, 86.2, 113.0, 115.2, 118.7, 120.9, 123.1, 130.9, 144.1, 142.2, 150.1, 161.9, 167.9;ES-MS *m/z*: 352 (M+H). Anal. calcd for $C_{20}H_{20}N_2O_4$:C, 68.17; H, 5.72; N, 7.95; found: C, 67.87; H, 6.02; N, 7.56%.

Dimethyl 1,3-bis(4-hydroxyphenyl)-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**4e**): Red solid; yield 90%; (lit.[14] 240–242 °C); IR (ν_{max}): 3012, 2995, 1713, 1705 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.49 (s, 6H, $2CH_3$), 4.43 (s, 2H, CH_2), 5.18 (s, 2H, CH_2), 5.49 (s, 2H, OH), 6.93–7.09 (m, 4H, arom.), 7.14–7.32 (m, 4H, arom.); ^{13}C NMR ($CDCl_3$) δ 51.8, 55.9, 87.9, 113.1, 113.8, 114.2, 115.1, 117.1, 118.2, 139.7, 142.9, 147.0, 167.1, 169.3. ES-MS *m/z*: 385 (M+H). Anal. calcd for $C_{20}H_{20}N_2O_6$: C, 62.49; H, 5.24; N, 7.29; found: C, 61.99; H, 5.90; N, 7.39%.

Dimethyl 1,3-bis(3-nitrophenyl)-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**4f**): Red-orange solid; yield 93%; (lit.[14] 251–253 °C); IR (ν_{max}): 3011, 2989, 1711, 1702 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.78 (s, 6H, $2CH_3$), 4.10 (s, 2H, CH_2), 5.54 (s, 2H, CH_2), 7.10–7.12 (m, 4H, arom.), 7.45–7.61 (m, 4H, arom.); ^{13}C NMR ($CDCl_3$) δ 52.2, 54.1, 86.4, 104.9, 112.1, 114.1, 116.9, 118.8, 120.9, 125.0, 130.0, 132.1, 142.1, 145.5, 148.4, 149.1, 168.2, 169.2. ES-MS *m/z*: 443 (M+H). Anal. calcd for

$C_{20}H_{18}N_4O_8$: C, 54.30; H, 4.10; N, 12.66; found C, 54.33; H, 4.15; N, 12.68%.

Diethyl 1,3-bis(3-nitrophenyl)-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**4g**): Red-orange solid; yield 91%; (lit.[14] 235–238 °C); IR (ν_{max}): 3022, 2980, 1716, 1703, 1500.9, 1328.1 cm^{-1}; ^1H NMR ($CDCl_3$) δ1.48 (t, 6H, $2CH_3$), 4.20 (s, 2H, CH_2), 4.70 (q, *J*=7.1 Hz, 4H, $2CH_2$), 5.23 (s, 2H, CH_2),7.31–7.50 (m, 4H, arom.), 7.81–7.99 (m, 4H, arom.); ^{13}C NMR ($CDCl_3$) δ19.8, 54.4, 64.9, 83.2, 108.1, 112.2, 114.9, 115.8, 116.9, 120.9, 125.1, 136.9, 146.2 150.0, 164.9, 168.5; ES-MS *m/z*: 470 (M+H). Anal. calcd for $C_{22}H_{22}N_4O_8$: C, 56.17; H, 4.71; N, 11.91; found: C, 56.40; H, 5.01; N, 12.06%.

Diethyl 1,3-di-p-tolyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**4h**): Creamy solid; yield 90%; m.p. 201–203 °C. IR (ν_{max}): 3038, 2960, 1726, 1692 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.23 (t, *J*=8.0 Hz, 6H, $2CH_3$), 3.35 (s, 6H, $2CH_3$), 4.24 (q, *J*=8.0 Hz,4H, $2CH_2$) 4.70 (s, 2 H, CH_2) 5.73 (s, 2 H, CH_2) 6.58–6.81 (m, 4 H, arom.), 7.93–8.04 (m, 4 H, arom.); ^{13}C NMR (DMSO-d_6) δ15.4, 23.3, 55.6, 62.2, 85.2, 112.2, 117.2, 126.2, 128.5, 129.3, 130.1, 131.2, 142.3, 143.9, 146.2, 162.9, 165.6. Anal. calcd for $C_{24}H_{28}N_2O_4$: C, 70.57; H, 6.91; N, 6.86; found: C, 70.60; H, 6.94; N, 6.83%.

Diethyl 1,3-bis(4-hydroxyphenyl)-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**4i**): Red-orange solid; yield 90%;(lit.[14] 219–221 °C); IR (ν_{max}): 3010, 2998, 1719, 1706 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.54 (t, *J*=7.5 Hz, 6H, $2CH_3$), 4.20 (s, 2H, CH_2), 4.90 (q, *J*=7.5 Hz, 4H, $2CH_2$), 5.20 (s, 2H, CH_2), 5.56 (s, 2H, CH_2), 6.88–7.15 (m, 4H, arom), 7.33–7.65 (m, 4H, arom.); ^{13}C NMR ($CDCl_3$) δ 21.1, 55.4, 70.0, 87.1, 115.2, 119.2, 122.1, 123.1, 137.1, 140.7, 145.0, 146.0, 149.8, 166.1, 168.9.ES-MS *m/z*: 413 (M+H). Anal. calcd for $C_{22}H_{24}N_2O_6$: C, 64.07; H, 5.87; N, 6.79; found: C, 65.01; H, 5.57; N, 6.38%.

Diethyl 1,3-diphenyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**4j**): Yellow solid; yield 92%; (lit.[14] 84–86 °C); IR (ν_{max}): 3030, 2980.0, 1716.0, 1700.2 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (t, *J*=7.4 Hz, 3H, CH_3),1.42 (t, *J*=7.4 Hz, 3H, CH_3), 3.40 (s, 2H, CH_2), 4.00 (q, *J*=7.4 Hz, 2H, CH_2) 4.22 (q, *J*=7.4 Hz, 2H, CH_2), 5.36 (s, 2H, CH_2), 7.19–7.30 (m, 5H, arom.), 7.51–7.79 (m, 5H, arom.); ^{13}C NMR ($CDCl_3$) δ 21.0, 59.1, 70.2, 75.9, 88.2, 113.2, 119.1, 122.0, 124.9, 128.2, 128.6, 143.1, 150.5, 166.2, 170.1; ES-MS *m/z*: 381 (M+H). Anal. calcd for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36; found: C, 70.06; H, 6.01; N, 7.01%.

Diethyl 1,3-bis(4-nitrophenyl)-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**4k**): Yellow solid; yield 92%; m.p. 189–192 °C; IR (ν_{max}): 3055, 2965, 1722, 1603, 1366 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.29 (t, *J*=8.0 Hz, 6H, $2CH_3$), 4.14–4.24 (m, 4H, $2CH_2$), 4.85 (s, 2 H, CH_2), 5.34 (s, 2 H, CH_2), 6.83–7.28 (m, 8 H, arom.); ^{13}C NMR (DMSO-d_6) δ 14.8, 55.3, 63.1, 63.4, 85.0, 112.8, 116.9, 123.1, 124.7, 125.0, 136.1, 137.2, 143.3, 150.5, 156.4, 164.4, 166.4; ES-MS *m/z*: 471 (M+H). Anal. calcd for $C_{22}H_{22}N_4O_8$: C, 56.17; H, 4.71; N, 11.91; found: C, 56.19; H, 4.74; N, 11.90%.

Diethyl 1,3-bis(4-chlorophenyl)-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**4l**): Red-orange solid; yield 90%; (lit.[14] 263–265 °C); IR (ν_{max}): 3030, 2994, 1722, 1701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (t, *J*=7.8 Hz, 6H, $2CH_3$), 4.09 (s, 2H, CH_2), 4.50 (q, *J*=7.7 Hz, 4H, $2CH_2$), 5.60 (s, 2H, CH_2), 7.19–7.30 (m, 4H, arom.), 7.68–7.99 (m, 4H, arom.); ^{13}C NMR ($CDCl_3$) δ 21.7, 56.2, 69.1, 86.5, 113.1, 120.1, 123.1, 125.5, 128.1, 129.1, 144.2, 151.9, 166.2, 169.0. ES-MS *m/z* (%): 450 (M+H). Anal. calcd for $C_{22}H_{22}Cl_2N_2O_4$: C, 58.81; H, 4.94; N, 6.23; found: C, 59.01; H, 4.82; N, 6.32%.

Dimethyl 1,3-di(pyridin-2-yl)-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**4m**): Red-orange solid; yield 91%; (lit.[14] 235–237 °C); IR (ν_{max}): 3018, 2978, 1715, 1712 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.70 (s, 6H, $2CH_3$), 3.98 (s, 2H, CH_2), 4.90 (s, 2H, CH_2), 6.81–7.15 (m, 4H, arom), 7.56–7.83 (m, 4H, arom); ^{13}C NMR ($CDCl_3$) δ 53.7, 56.0, 84.1, 108.1, 117.1, 117.9, 122.0, 137.1, 149.2 151.1, 150.8, 165.2, 167.1; ES-MS *m/z*: 355 (M+H). Anal. calcd for $C_{18}H_{18}N_4O_4$: C, 61.01; H, 5.132; N, 15.98; found C, 60.98; H, 5.34; N, 16.01%.

Dimethyl 1,3-bis(6-methoxybenzo(d)thiazol-2-yl)-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**4n**): Red solid; yield 93%; (lit.[14] 242–244 °C); IR (ν_{max}): 3017, 2975, 1713, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.65 (s, 6H, $2CH_3$), 3.85 (s, 6H, $2CH_3$), 3.98 (s, 2H, CH_2), 4.91 (s, 2H, CH_2), 6.92–7.07 (m, 4H, arom.), 7.40–7.60 (m, 4H, arom.); ^{13}C NMR ($CDCl_3$) δ 52.9, 57.5, 61.2, 86.1, 104.9, 114.9, 116.9, 119.1, 131.3, 147.4, 151.0, 158.1, 165.1, 164.9, 167.2, 170.4.ES-MS *m/z*: 527 (M+H). Anal. calcd for $C_{24}H_{22}N_4O_6S_2$: C, 54.74; H, 4.21; N, 10.64; S, 12.18. Found C, 55.09; H, 4.65; N, 10.32; S, 12.42%.

Diethyl 1,3-di(pyridin-2-yl)-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**4o**): Red-orange solid; yield 90%; (lit.[14] 255–259 °C); IR (ν_{max}): 3022, 2981, 1716, 1703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60 (t, *J*=7.9 Hz, 6H, $2CH_3$), 3.89 (s, 2H, CH_2), 4.30 (q, *J*=7.9 Hz, 4H, $2CH_2$), 4.69 (s, 2H, CH_2),7.50–7.72 (m, 4H, arom.), 7.88–8.19 (m, 4H, arom.); ^{13}C NMR ($CDCl_3$) δ 19.9, 54.0, 62.5, 83.0, 108.2, 116.8, 117.96, 121.9, 137.2, 150.7 151.9, 156.9, 166.1, 169.0; ES-MS *m/z*: 383 (M+H). Anal. calcd for $C_{20}H_{22}N_4O_4$: C, 62.82; H, 5.80; N, 14.65; found: 63.02; H, 5.38; N, 14.97%.

Diethyl 1,3-bis(6-methoxybenzo(d)thiazol-2-yl)-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**4p**): Red-orange solid; yield 89%;(lit.[14] 273–275 °C); IR (ν_{max}): 3021, 2984, 1712, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (t, *J*=7.6 Hz 6H, $2CH_3$), 3.70 (s, 2H, CH_2), 3.93 (s, 6H, $2CH_3$), 4.42 (s, 2H, CH_2), 4.55 (q, *J*=7.7 Hz, 4H, $2CH_2$), 7.02–7.11 (m, 2H, arom.), 7.41–7.56 (m, 4H, arom.); ^{13}C NMR ($CDCl_3$) δ 21.0, 54.1, 58.1, 64.2, 83.1, 107.1, 116.3, 118.1, 119.9, 134.1, 148.0, 158.4, 165.7, 167.0, 167.9, 169.2; ES-MS *m/z*: 555 (M+H). Anal. calcd for $C_{26}H_{26}N_4O_6S_2$: C, 56.30; H, 4.72; N, 10.10; S, 11.56; found: C, 57.00; H, 4.31; N, 10.12; S, 12.08%.

Received 31 July 2014; accepted 13 September 2014
Paper 1402797 doi: 10.3184/174751914X14115772243815
Published online: 17 October 2014

References

1 A. Dömling, W. Wang and K. Wang, *Chem. Rev.*, 2012, **112**, 3083.
2 K.K. Pasunooti, H. Chai, C.N. Jensen, B.K. Gorityala, S. Wang and X.W. Liu, *Tetrahedron Lett.,* 2011, **52**, 80.
3 G. Regnier, L. Canevar, R.J. Le, J.C. Douarec, S. Halstop and J. Daussy, *J. Med. Chem*., 1972, **15**, 295.
4 Y. Kotaiah, K.N. Hari, K. Naga Raju, C.V. Rao, S.B. Jonnalagadda and M. Suresh, *J. Korean Chem. Soc.,* 2012, **56**, 1.
5 M.B. Deshmukh, S.M. Salunkhe, D.R. Patil and P.V. Anbhule, Eur. *J. Med. Chem*., 2009*,* **44**, 2651.
6 J. Zhu and H. Bienaymé, *Multicomponent reactions*, Wiley-VCH: Weinheim., **2005**.
7 Z.I. Akritopoulou and S.W. Djuric, *Synthesis of heterocycles via multicomponent reactions II*, R.V.A. Orru and E. Ruijter, eds.; Springer: New York, 2010, pp. 231–287.
8 F.M. Matloubi and H. Saeidian, *Mater. Sci. Eng. B,* 2007, **139**, 265.
9 Z. Peng *Nanofibers – production, properties and functional applications*, T. Lin, ed. 2011; Vol. 1, pp. 135–151.
10 B.M. Reddy and V.R. Reddy. *J. Mater. Sci. Lett.,* 2000, **19**, 763.
11 M. Liqiang, H. Bin, C. Wen, Q. Yanyuan, L. Changshi, Y. Rusen, D. Ying and L.W. Zhong, *Adv. Mater*., 2007, **19**, 3712.
12 Q. Zhu, H. Jiang, J. Li, M. Zhang, X. Wang and C. Qi, *Tetrahedron*, 2009, **65**, 4604.
13 C.W. Sun, T. Fang, J. Wang, Z. Hao and S. Nan *J. Agric. Food Chem*., 2012, **60**, 9553.
14 S.N. Darandale, N.D. Pansare, A.N. Mulla and B.D. Shinde, *Bioorg. Med. Chem, Lett*., 2013, **23**, 2632.
15 X. Tian, Qin, L.; L. Xiangdong, M. Jian and C. Xueqiang *J. Phys. Chem., B*, 2006, **110**, 2006.

Copyright of Journal of Chemical Research is the property of Science Reviews 2000 Ltd. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.