SOLVENT-FREE *C*-ALKYLATION OF BARBITURIC ACID IN THE NANOCRYSTALLINE MORDENITE MEDIA

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(Received: October 14, 2012 - Accepted: May 30, 2013)

ABSTRACT

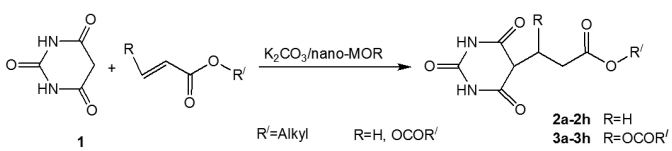
A simple, efficient and clean procedure has been developed for the *C*-alkylation of barbituric acid. The Michael addition of barbituric acid to α,β-unsaturated esters by employing K_2CO_3 in the nano-mordenite media (K_2CO_3/nano-MOR), as catalyst, gave *C*-alkylated barbituric acid in good to excellent yield. Nano-MOR showed good reusability. K_2CO_3/nano-MOR catalyst has been found to be an excellent catalyst for the reaction under solvent-free conditions at 80-90 ˚C.

Keywords: Solvent-free, *C*-Alkylation, Barbituric Acid, α,β-Unsaturated Esters, Nano-Mordenite (Nano-MOR),

INTRODUCTION

Barbiturates, that are derivatives of barbituric acid (pyrimidine-2,4,6-trione), belong to one of the most important classes of drug molecules.[1-7] These compounds were first introduced for medical use in 1911.[8] More than 2500 barbiturates have been synthesized and in the height of their popularity about 50 were marketed for human use.[9] Today, only about a dozen are still in use. Although barbituric acid itself is devoid of biological activity, its derivatives such as single or double *C*-alkylated barbituric acids have sedative, hypnotic, anesthetic and anticonvulsant activities.[10] Clinically important hypnotic-sedative barbiturates have substitutions at sites 1,2- and, especially, 5- of barbituric acid.[11-13] Side chains at position 5- (especially one of them is branched) is essential for hypnotic activity.[14]

Diverse routes have been reported for the synthesis of *C*-alkylated derivatives of barbituric acid the majority of them involving a condensation of urea and malonic esters derivatives.[15-18] But very little extent of work on the direct *C*-alkylation of barbituric acid is found in literature. Therefore, it is felt necessary to develop an efficient method for the performing of these reactions. In continuation of our studies on solvent-free organic reaction on solid supported reagents,[19-21] we report herein an efficient procedure for the synthesis of *C*-alkylated barbituric acids via Michael addition of barbituric acid to α,β-unsaturated esters in supported potassium carbonate on nano-MOR (K_2CO_3/nano-MOR) media under solvent-free conditions (Scheme 1). In this method, no dialkylation at position 5- was observed at all. To the best of our knowledge, there are only few reports on the addition reaction of barbituric acid on α,β-unsaturated carbonyl compounds.[22-24]



Scheme 1.

RESULTS AND DISCUSSION

The Michael addition of barbituric acid **1** to ethyl acrylate was investigated as model reaction in presence of K_2CO_3/nano-MOR, in the absence of solvent. It was found that when a mixture of ethyl acrylate (1 mmol), barbituric acid (1 mmol), and K_2CO_3 (1 mmol)/nano-MOR (0.5 gr)) was kept at 80-90 °C for 2 h the corresponding mono-*C*-alkylated barbituric acid was obtained in 90% yield as the sole product. The double Michael addition on this substrate was not successful even with addition excess Michael acceptor (2 mmol ethyl acrylate). Encouraged by these results we investigated the general applicability of this method on diverse α,β-unsaturated esters (Table 1). The reactions were completed in 1-3.5 h and the desired mono-*C*-alkylated barbituric acids were produced in good to excellent yields (Table 1, entries 1-16). It was observed that the steric hindrance of Michael acceptor did not influence negatively the yield of products (Table 1, entries 6-16).

Table 1. *C*-Alkylation of barbituric acid in the presence and absence of nano-MOR under solvent-free conditions.

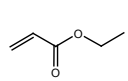
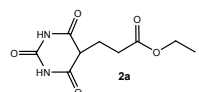
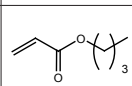
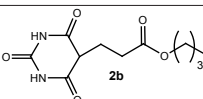
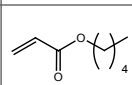
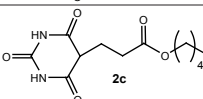
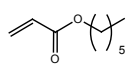
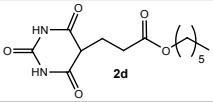
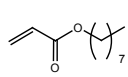
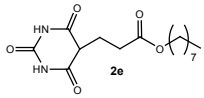
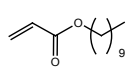
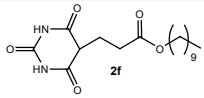
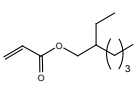
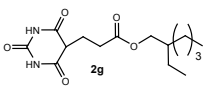
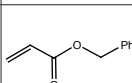
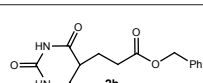
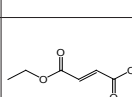
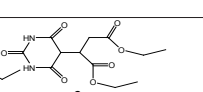
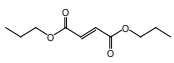
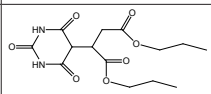
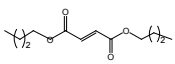
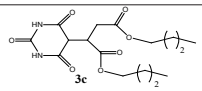
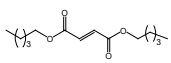
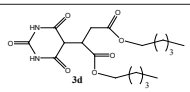
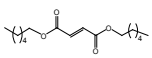
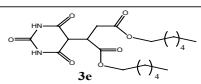
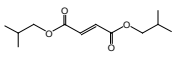
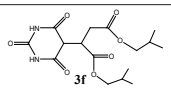
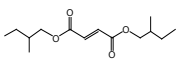
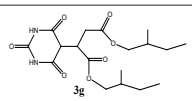
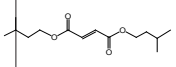
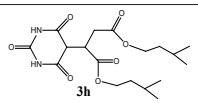
Entry	Ester	Product	Time (h)[a]	Yield (%)[b]
1		 **2a**	17:20 (2:00)	60 (90)
2		 **2b**	19:45 (2:00)	55 (87)
3		 **2c**	19:40 (1:55)	58 (87)
4		 **2d**	21:30 (2:10)	55 (85)
5		 **2e**	24:15 (2:15)	50 (80)
6		 **2f**	28:35 (3:00)	48 (78)
7		 **2g**	24:20 (2:30)	49 (79)
8		 **2h**	20:15 (1:50)	62 (88)
9		 **3a**	19:30 (2:00)	64 (89)

Table 1. Continued.

Entry	Ester	Product	Time (h)[a]	Yield (%)[b]
10		 **3b**	21:20 (2:45)	61 (87)
11		 **3c**	21:15 (2:50)	60 (85)
12		 **3d**	22:30 (3:00)	60 (85)
13		 **3e**	22:50 (3:00)	55 (80)
14		 **3f**	22:35 (3:00)	50 (87)
15		 **3g**	24:40 (3:30)	50 (76)
16		 **3h**	24:55 (0:25)	50 (78)

[a]In parentheses *C*-alkylation reaction times of barbituric acid in the presence of nano-MOR are given.

[b]Yield of isolated product (in parentheses *C*-alkylation reaction yields of barbituric acid in the presence of nano-MOR are given).

It was observed, from the results in Table 1, that although the reaction occurs without nano-mordenite, the reaction time is very long and the product is obtained in low yield. We believe that the presence of nano-mordenite acts as a media and provides a very effective heterogeneous surface area.

In order to evaluate the role of nano-mordenite in this reaction, we studied the model reaction in the presence of various solvents at 30 °C (Table 2). As Table 2 indicates, when K_2CO_3 was used in presence of nano-MOR, higher yield, as well as shorter reaction time, was observed (Table 2 entry 9).

Table 2. The effect of different solvents upon addition of barbituric acid to ethyl acrylate[a]

Entry	Base	Solvent	Time(h)	Yield(%)[b]
1	K_2CO_3	H_2O	24	-
2	K_2CO_3	EtOH	18	25
3	K_2CO_3	MeOH	18	28
4	K_2CO_3	CH_3COOEt	20	30
5	K_2CO_3	$CHCl_3$	22	25
6	K_2CO_3	CH_2Cl_2	24	25
7	K_2CO_3	n-Hexan	24	20
8	K_2CO_3	Solvent-free	17	35
9	K_2CO_3	Mor[c]	18	30
10	K_2CO_3	nano-Mor[d]	2	50

[a]Reaction condition: barbituric acid (1mmol), ethyl acrylate (1 mmol), K_2CO_3 (1 mmol), at 30 °C.

[b]Isolated yield.

[c]Ethyl acrylate (1 mmol), barbituric acid (1 mmol), and K_2CO_3 (1 mmol)/ MOR (0.5 gr), at 30 °C under solvent-free conditions.

[d]Ethyl acrylate (1 mmol), barbituric acid (1 mmol), and K_2CO_3 (1 mmol)/ nano-MOR (0.5 gr), at 30 °C under solvent-free conditions.

In another experiment, we performed the model reaction in the presence of several organic and inorganic bases at 80-90 °C in the absence of solvent, and the results were summarized in Table 3. These results showed that supported potassium carbonate on nano-MOR gave the best results and produced the expected product in 90% yield (Table 3, entry 6).

Table 3. Influence of various bases on the addition of barbituric acid to ethyl acrylate under solvent-free conditions[a]

Entry	1	2	3	4	5	6
Base	Et_3N	DABCO	NaOH	KOH	K_2CO_3	K_2CO_3/ nano-MOR
Time(h)	24	18	18	20	15	2
Yield[b](%)	-	25	28	30	57	90

[a]Reaction condition: barbituric acid (1mmol), ethyl acrylate (1 mmol), base (1 mmol), at 80-90 °C.

[b]Isolated yield.

The recovery and reusability of the catalyst (nano-MOR) was studied on the model reaction. After completion of the reaction the product was extracted by chloroform. Un-dissolved nano-MOR was removed by simple filtration, dried at 200 °C and reused three times without significant loss of activity.

CONCLUSION

A convenient, simple and green process has been developed for the *C*-alkylation of barbituric acid using supported K_2CO_3 on nano-MOR type of zeolite under solvent-free conditions. The double Michael addition on this substrate was not successful even with excess Michael acceptor addition. This method is very simple, efficient, and environmentally friendly. It was demonstrated that among the organic and inorganic bases, potassium carbonate, as a cheap and green base, effectively catalyses this reaction in the presence of nano-MOR under solvent-free condition.

EXPERIMENTAL

α,β-Unsaturated esters were synthesized in our laboratory according to literature procedures.[25] The progress of the reactions was followed by TLC, using silica gel SILIG/UV 254 plates. Nano mordenite (nano-MOR) was synthesized in our laboratory.[26] ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker 300 MHz instrument. FT-IR spectra were recorded on a Perkin-Elmer RX-1 instrument. Mass spectra were recorded on a Shimadzu GC-MS-QP 1000PX. Elemental analysis for C, H, and N was performed using a Heraeus CHN-O-Rapid analyzer. The melting points were determined in open capillaries with a Stuart Melting Point Apparatus, and are uncorrected.

General procedure for addition of barbituric acid to α,β-unsaturated ester. The nano-MOR is ground together with K_2CO_3 (1 mmol K_2CO_3/0.5 gr nano-MOR) in a mortar and pestle for 15 minutes. Next, α,β-unsaturated esters (1 mmol) and barbituric acid (1 mmol) were added to this mixture and kept in the oil bath for the stipulated time (Table 1) at 80-90 ˚C. The progress of the reaction was monitored by TLC. After completion of reaction the resulting mixture was cooled to room temperature and suspended in chloroform (30 mL). Un-dissolved nano-MOR was separated by centrifugation and subsequent washing with chloroform. The chloroform layer was washed with water (2×10 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the resulting solid material was recrystallyzed from EtOH.

Physical and spectroscopic data of isolated products. *Ethyl 3-(hexahydro-2,4,6-trioxopyrimidin-5-yl)propanoate (**2a**):* White solid, m.p. 98-100 ˚C. FT IR (KBr): n 3378, 3328, 2941, 1732, 1675, 1396, 1378, 1254, 1193, 1094, 806, 734 cm^{-1}. ^{1}H NMR (DMSO, TMS, 400 MHz): δ 1.17 (t, J = 7.15 Hz, 3H); 2.21-2.24 (m, 4H); 4.03 (q, J = 7.05, 2H); 10.21 (s, 2H) ppm. ^{13}C NMR (DMSO, TMS, 100 MHz): δ 14.58; 31.26; 32.77; 60.01; 80.33; 154.42; 164.26; 174.50 ppm. MS (70 eV), m/e: 228 (M^+). Anal. calcd for $C_9H_{12}N_2O_5$: C, 47.37; H, 5.26; N, 12.28. Found: C, 47.53; H, 5.10; N, 12.56.

*Butyl 3-(hexahydro-2,4,6-trioxopyrimidin-5-yl)propanoate (**2b**):* White solid, m.p. 105-108 ˚C; FT IR (KBr): n 3390, 2961, 1720, 1693, 1475, 1393, 1310, 781, 550 cm^{-1}. ^{1}H NMR (DMSO, TMS, 400 MHz): δ 0.88 (t, J = 7.33

Hz, 3H); 1.31 (sex, *J* = 7.50 Hz, 2H), 1.53 (quin, *J* = 6.96 Hz, 2H); 2.24-2.38 (m, 4H); 3.97 (t, *J* = 6.60 Hz, 2H); 9.04 (s, 2H) ppm. ^{13}C NMR (DMSO, TMS, 100 MHz): δ 13.58; 18.63; 19.18; 30.26; 33.79; 63.01; 83.33; 151.50; 164.22; 173.47 ppm. MS (70 eV), m/e: 256 (M^+). Anal. calcd for $C_{11}H_{16}N_2O_5$: C, 51.56; H, 6.25; N, 10.94. Found: C, 51.81; H, 6.43; N, 10.55.

*Pentyl 3-(hexahydro-2,4,6-trioxopyrimidin-5-yl)propanoate (**2c**):* White solid, m.p. 112-116 ˚C. FT IR (KBr): n 3409, 3248, 2985, 1725, 1574, 1378, 1031, 755, 668 cm^{-1}. ^{1}H NMR (DMSO, TMS, 400 MHz): δ 0.89 (t, *J* = 7.05 Hz, 3H); 1.28-1.29 (m, 4H); 1.56 (quin, *J* = 7.00 Hz, 2H); 2.15 (q, *J* = 7.55, 2H); 2.40 (t, *J* = 7.40 Hz, 2H); 3.69 (t, *J* = 5.55 Hz, 1H); 3.98 (t, *J* =6.70 Hz, 2H); 11.16 (s, 2H) ppm. ^{13}C NMR (DMSO, TMS, 100 MHz): δ 13.79; 21.72; 21.96; 27.51; 27.71; 30.70; 46.84; 63.86; 150.84; 169.20; 172.59 ppm. MS (70 eV), m/e: 270 (M^+). Anal. calcd for $C_{12}H_{18}N_2O_5$: C, 53.33; H, 6.67; N, 10.37. Found: C, 53.63; H, 6.46; N, 10.21.

*Hexyl 3-(hexahydro-2,4,6-trioxopyrimidin-5-yl)propanoate (**2d**):* White solid, m.p. 117-120 ˚C. FT IR (KBr): n 3245, 2930, 1760, 1731, 1176, 1113, 1039, 754, 546 cm^{-1}. ^{1}H NMR (DMSO, TMS, 400 MHz): δ 0.87 (t, *J* = 7.2 Hz, 3H); 1.25-1.30 (m, 6H); 1.54 (quin, *J* = 6.50 Hz, 2H); 2.15 (q, *J* = 6.2 Hz, 2H); 2.40 (t, *J* = 7.25 Hz, 2H); 3.69 (t, *J* = 5.35 Hz, 1H); 3.98 (t, *J* = 6.55 Hz, 2H); 11.16 (s, 2H) ppm. ^{13}C NMR (DMSO, TMS, 100 MHz): δ 13.83; 21.94; 24.98; 27.97; 30.70; 30.82; 46.83; 63.87; 64.32; 150.83; 169.89; 172.19 ppm. MS (70 eV), m/e: 284 (M^+). Anal. calcd for $C_{13}H_{20}N_2O_5$: C, 54.93; H, 7.04; N, 9.86. Found: C, 54.75; H, 7.12; N, 9.76.

*Octyl 3-(hexahydro-2,4,6-trioxopyrimidin-5-yl)propanoate (**2e**):* White solid, m.p. 115-118 ˚C. FT IR (KBr): n 3234, 2976, 1760, 1577, 1525, 1393, 1175, 1037, 754, 546 cm^{-1}. ^{1}H NMR (DMSO, TMS, 400 MHz): δ 0.85 (t, *J* = 10.00 Hz, 3H); 1.25-1.26 (m, 10H); 1.53 (quin, *J* = 10.00 Hz, 2H); 2.08-2.21 (m, 2H); 2.39 (t, *J* = 6.50 Hz, 2H); 3.98 (t, *J* = 7.5 Hz, 2H); 11.09 (s, 2H) ppm. ^{13}C NMR (DMSO, TMS, 100 MHz): δ 13.95; 22.45; 23.15; 25.19; 27.31; 28.48; 30.29; 31.37; 33.98; 47.18; 64.37; 151.62; 169.97; 172.25 ppm. MS (70 eV), m/e: 312 (M^+). Anal. calcd for $C_{15}H_{24}N_2O_5$: C, 57.69; H, 7.69; N, 8.97. Found: C, 57.48; H, 7.55; N, 8.78.

*Decyl 3-(hexahydro-2,4,6-trioxopyrimidin-5-yl)propanoate (**2f**):* White solid, m.p. 120-123 ˚C. FT IR (KBr): n 3256, 2956, 1760, 1733, 1519, 1384, 1106, 755, 545 cm^{-1}.

^{1}H NMR (DMSO ,TMS, 400 MHz): δ 0.86 (t, *J* = 6.50 Hz, 3H); 1.23-1.27 (m, 14H); 1.55 (quin, *J* = 6.65 Hz, 2H); 2.15 (q, *J* = 6.2 Hz, 2H); 2.40 (t, *J* = 7.2 Hz, 2H); 3.69 (t, *J* = 5.35 Hz, 1H); 3.98 (t, *J* = 6.5 Hz, 2H); 11.16 (s, 2H) ppm. ^{13}C NMR (DMSO, TMS, 100 MHz): δ 13.90; 22.05; 25.31; 28.02; 28.62; 28.88; 30.70; 31.24; 46.83; 63.84; 150.81; 169.88; 172.19 ppm. MS (70 eV), m/e: 340 (M^+). Anal. calcd for $C_{17}H_{28}N_2O_5$: C, 60.11; H, 8.24; N, 8.24. Found: C, 60.21; H, 8.31; N, 8.53.

*2-ethylhexyl 3-(hexahydro-2,4,6-trioxopyrimidin-5-yl)propanoate (**2g**):* White solid, m.p. 116-118 ˚C. FT IR (KBr): n 3411, 3213, 2962, 1753, 1711, 1353, 1199, 807, 503, 483 cm^{-1}. ^{1}H NMR (DMSO, TMS, 400 MHz): δ 0.86 (t, *J* = 8.30 Hz, 6H); 1.24-1.31 (m, 8H); 2.08-2.13 (m, 1H); 2.14 (q, *J* = 7.55 Hz, 2H); 2.41 (t, *J* = 7.36 Hz, 2H); 3.69 (t, *J* = 5.35 Hz, 1H); 3.90-3.92 (dd, *J* = 1.88 Hz, *J* = 3.52 Hz, 2H); 11.17 (s, 2H) ppm. ^{13}C NMR (DMSO, TMS, 100 MHz): δ 10.78; 13.89; 21.94; 22.39; 23.20; 28.31; 29.77; 30.68; 30.76; 38.07; 46.86; 65.98; 150.87; 169.92; 172.26 ppm. MS (70 eV), m/e: 312 (M^+). Anal. calcd for $C_{15}H_{24}N_2O_5$: C, 57.69; H, 7.69; N, 8.97. Found: C, 57.39; H, 7.61; N, 8.66.

*Benzyl 3-(hexahydro-2,4,6-trioxopyrimidin-5-yl)propanoate (**2h**):* White solid, m.p. 148-152 ˚C. FT IR (KBr): n 3422, 3303, 3202, 3076, 1752, 1721, 1365, 1195, 1043, 731, 594, 506 cm^{-1}. ^{1}H NMR (DMSO, TMS, 400 MHz): δ 2.13 (t, *J* = 6.05 Hz, 2H); 2.46 (t, *J* = 6.50 Hz, 2H); 5.07 (s, 2H); 7.31-7.39 (m, 5H); 11.11 (s, 2H) ppm. ^{13}C NMR (DMSO, TMS, 100 MHz): δ 27.51; 34.87; 65.58; 73.22; 127.53; 127.98; 128.47; 136.15; 150.23; 172.32; 174.25 ppm. MS (70 eV), m/e: 290 (M^+). Anal. calcd for $C_{14}H_{14}N_2O_5$: C, 57.93; H, 4.83; N, 9.83. Found: C, 57.84; H, 4.69; N, 9.76.

*Diethyl 2-(hexahydro-2,4,6-trioxopyrimidin-5-yl)succinate (**3a**):* White solid, m.p. 135-139 ˚C. FT IR (KBr): n 3224, 3099, 2988, 1717, 1429, 1351, 1261, 1207, 1029, 796, 529 cm^{-1}; ^{1}H NMR (DMSO, TMS, 400 MHz): δ 1.11 (t, *J* = 8.90 Hz, 3H); 1.21 (t, *J* = 8.90 Hz , 3H); 2.71 (dd, *J* = 10.81 Hz, *J* = 7.50 Hz, 1H); 2.92 (dd, *J* = 10.81 Hz, *J* = 8.70 Hz, 1H); 3.82 (ddd, *J* = 7.50 Hz, *J* = 8.70 Hz *J* = 2.21 Hz, 1H); 3.97 (q, *J* = 8.90 Hz, 2H); 4.05 (q, *J* = 8.90 Hz, 2H); 4.12 (d, *J* = 2.21 Hz, 1H); 11.34 (s, 1H); 11.39 (s, 1H) ppm. ^{13}C NMR (DMSO, TMS, 100 MHz): δ 13.99; 14.09; 34.05; 34.05; 49.16; 61.06; 61.14; 150.68; 168.93; 169.65; 171.34; 171.53 ppm. MS (70 eV), m/e: 301 (M^++1). Anal. calcd for $C_{12}H_{16}N_2O_7$: C, 48.12; H, 5.23; N, 9.33. Found: C, 48.21; H, 5.42; N, 9.54.

*Dipropyl 2-(hexahydro-2,4,6-trioxopyrimidin-5-yl)succinate (**3b**):* White solid, m.p. 146-149 ˚C. FT IR (KBr): n 3226, 3102, 2964, 2940, 2879, 1720, 1429, 1352, 1205, 802, 502 cm^{-1}. ^{1}H NMR (DMSO, TMS, 400 MHz): δ 0.67 (t, *J* = 7.41 Hz, 3H); 0.70 (t, *J* = 7.42 Hz , 3H); 1.35 (m, 4H); 2.71 (dd, *J* = 10.23 Hz, *J* = 7.93 Hz, 1H); 2.90 (dd, *J* = 10.23 Hz, *J* = 6.84 Hz, 1H); 3.58 (ddd, *J* = 7.93 Hz, *J* = 6.84 Hz, *J* = 1.77 Hz, 1H); 3.78 (t, *J* = 6.74 Hz, 2H); 3.81 (t, *J* = 6.26 Hz, 2H); 3.82 (d, *J* = 1.77 Hz, 1H); 10.89 (s, 1H); 10.94 (s, 1H) ppm. ^{13}C NMR (DMSO, TMS, 100 MHz): δ 10.57; 10.63; 21.93; 22.08; 33.90; 33.90; 48.72; 66.57; 67.44; 150.83; 168.65; 169.45; 171.80; 172.00 ppm. MS (70 eV), m/e: 329 (M^++1). Anal. calcd for $C_{14}H_{20}N_2O_7$: C, 51.12; H, 6.10; N, 8.54. Found: C, 51.27; H, 6.25; N, 8.78.

*Dibutyl 2-(hexahydro-2,4,6-trioxopyrimidin-5-yl)succinate (**3c**):* White solid, m.p. 141-143 ˚C. FT IR (KBr): n 3223, 3106, 2961, 2936, 2874, 1722, 1428, 1352, 1258, 1202, 804, 502 cm^{-1}. ^{1}H NMR (DMSO, TMS, 400 MHz): δ 0.85 (t, *J* = 7.00 Hz, 3H); 0.90 (t, *J* = 7.20 Hz , 3H); 1.25 (m, 2H); 1.35 (m, 2H); 1.42 (m, 2H); 1.54 (m, 2H); 2.71 (dd, *J* = 11.45 Hz, *J* = 6.54 Hz, 1H); 2.90 (dd, *J* = 11.45Hz, *J* = 8.51 Hz, 1H); 3.87 (ddd, *J* = 8.51 Hz, *J* = 8.51 Hz, *J* = 1.93 Hz, 1H); 3.96 (t, *J* = 6.55 Hz, 2H); 4 (t, *J* = 6.27 Hz, 2H); 4.15 (d, *J* = 2.93 Hz, 1H); 11.39 (s, 1H); 11.44 (s, 1H) ppm. ^{13}C NMR (DMSO, TMS, 100 MHz): δ 13.50; 13.60; 18.49; 18.63; 29.95; 30.15; 34.13; 34.13; 49.33; 63.95; 64.74; 150.63; 168.81; 169.60; 171.35; 171.60 ppm. MS (70 eV), m/e: 357 (M^++1). Anal. calcd for $C_{16}H_{24}N_2O_7$: C, 53.93; H, 6.74; N, 7.86. Found: C, 53.48; H, 6.55; N, 7.78.

*Dipentyl 2-(hexahydro-2,4,6-trioxopyrimidin-5-yl)succinate (**3d**):* White solid, m.p. 123-126 ˚C. FT IR (KBr): n 3224, 3105, 2961, 2935, 2875, 1732, 1428, 1352, 1260, 1205, 802, 502 cm^{-1}. ^{1}H NMR (DMSO, TMS, 400 MHz): δ 0.82 (t, *J* = 6.54 Hz, 3H); 0.87 (t, *J* = 6.55 Hz , 3H); 1.17 (m, 8H); 1.48 (m, 2H); 1.54 (m, 2H); 2.71 (dd, *J* = 11.52 Hz, *J* = 5.23 Hz, 1H); 2.90 (dd, *J* = 11.52 Hz, *J* = 5.71 Hz, 1H); 3.86 (ddd, *J* = 5.71 Hz, *J* = 5.23 Hz *J* = 2.50 Hz 1H); 3.92 (t, *J* = 6.00 Hz, 2H); 4.02 (t, *J* = 5.27 Hz, 2H); 4.15 (d, *J* = 2.50 Hz, 1H); 11.41 (s, 1H); 11.43 (s, 1H) ppm. ^{13}C NMR (DMSO, TMS, 100 MHz): δ 13.77; 13.83; 21.67; 21.76; 27.37; 27.53; 27.56; 27.75; 34.13; 34.13; 49.34; 64.19; 64.99; 150.57; 168.72; 169.53; 171.29; 171.55 ppm. MS (70 eV), m/e: 385 (M^++1). Anal. calcd for $C_{18}H_{28}N_2O_7$: C, 56.25; H, 7.29; N, 7.29. Found: C, 56.38; H, 7.58; N, 7.54.

*Dihexyl 2-(hexahydro-2,4,6-trioxopyrimidin-5-yl)succinate (**3e**):* White solid, m.p. 119-122 ˚C. FT IR (KBr): n 3226, 3106, 2963, 2935, 2877, 1722, 1427, 1350, 1258, 1231, 1205, 800, 501 cm^{-1}. ^{1}H NMR (DMSO, TMS, 400 MHz): δ 0.82 (t, *J* = 7.41 Hz, 3H); 0.87 (t, *J* = 7.44 Hz , 3H); 1.07 (m, 2H); 1.18 (m, 2H); 1.23 (m, 2H); 1.31 (m, 2H); 1.38 (m, 2H); 1.45 (m, 2H); 1.54 (m, 2H); 1.65 (m, 2H); 2.71 (dd, *J* = 10.24 Hz, *J* = 7.25 Hz, 1H); 2.90 (dd, *J* = 10.24 Hz, *J* = 8.51 Hz, 1H); 3.90 (ddd, *J* = 7.25 Hz, *J* = 8.51 Hz *J* = 2.24 Hz 1H); 4.01 (t, *J* = 5.91 Hz, 2H); 4.05 (t, *J* = 5.89 Hz, 2H); 4.15 (d, *J* = 2.24 Hz, 1H); 11.38 (s, 1H); 11.43 (s, 1H) ppm. ^{13}C NMR (DMSO, TMS, 100 MHz): δ 11.09; 11.49; 13.59; 13.91; 18.49; 18.63; 25.16; 25.45; 29.96; 30.15; 33.59; 34.14; 49.34; 63.95; 64.74; 150.62; 168.98; 169.58; 171.35; 171.61 ppm. MS (70 eV), m/e: 413 (M^++1). Anal. calcd for $C_{20}H_{32}N_2O_7$: C, 58.12; H, 7.77; N, 6.80. Found: C, 58.41; H, 7.81; N, 6.75.

*Diisobutyl 2-(hexahydro-2,4,6-trioxopyrimidin-5-yl)succinate (**3f**):* White solid, m.p. 136- 138 ˚C. FT IR (KBr): n 3224, 3105, 2961, 2935, 2874, 1721, 1428, 1351, 1257, 1202, 804, 502 cm^{-1}. ^{1}H NMR (DMSO, TMS, 400 MHz): δ 0.88 (d, *J* = 6.61 Hz, 6H); 0.95 (d, *J* = 6.92 Hz , 6H); 2.1 (m, 2H); 2.71 (dd, *J* = 11.26 Hz, *J* = 7.43 Hz, 1H); 2.90 (dd, *J* = 11.26 Hz, *J* = 8.62 Hz, 1H); 3.85 (ddd, *J* = 7.43 Hz, *J* = 8.62 Hz *J* = 2.19 Hz 1H); 4.01 (d, *J* = 6.55 Hz, 2H); 4.08 (d, *J* = 6.82 Hz, 2H); 4.15 (d, *J* = 2.19 Hz, 1H); 11.38 (s, 1H); 11.43 (s, 1H) ppm. ^{13}C NMR (DMSO, TMS, 100 MHz): δ 17.92; 18.29; 23.93; 24.29; 34.09; 34.25; 49.16; 66.06; 66.54; 150.68; 168.93; 169.65; 171.34; 171.53 ppm. MS (70 eV), m/e: 357 (M^++1). Anal. calcd for $C_{16}H_{24}N_2O_7$: C, 53.93; H, 6.74; N, 7.86. Found: C, 53.81; H, 6.29; N, 7.89.

*Bis(2-methylbutyl) 2-(hexahydro-2,4,6-trioxopyrimidin-5-yl)succinate (**3g**):* White solid, m.p. 116-119 ˚C. FT IR (KBr): n 3227, 3107, 2963, 2935, 2877, 1721, 1422, 1351, 1258, 1205, 802, 501 cm^{-1}. ^{1}H NMR (DMSO, TMS, 400 MHz): δ 0.81 (t, *J* = 7.21 Hz, 3H); 0.83 (t, *J* = 7.00 Hz , 3H); 0.85 (d, *J* =

6.25 Hz, 3H); 0.88 (d, *J* = 6.20 Hz, 3H); 1.11 (m, 2H); 1.21 (m, 2H); 1.45 (m, 1H);1.56 (m, 1H); 2.71 (dd, *J* = 10.22 Hz, *J* = 7.65 Hz, 1H); 2.90 (dd, *J* = 10.22 Hz, *J* = 7.51 Hz, 1H); 3.81 (ddd, *J* = 7.51 Hz, *J* = 7.65 Hz *J* = 2.53 Hz 1H); 3.85 (dd, *J* = 10.51 Hz, *J* = 5.22 Hz, 1H); 3.91 (dd, *J* = 10.51 Hz, *J* = 6.2 Hz, 1H); 3.97 (dd, *J* = 10.55 Hz, *J* = 6.14 Hz, 1H); 4.05 (dd, *J* = 10.55 Hz, *J* = 6.14 Hz, 1H); 4.15 (d, *J* = 2.53 Hz, 1H); 11.38 (s, 1H); 11.45 (s, 1H) ppm. ^{13}C NMR (DMSO, TMS, 100 MHz): δ 13.58; 13.90; 18.48; 18.62; 25.15; 25.44; 30.14; 30.89; 33.57; 34.13; 49.32; 63.93; 64.72; 150.61; 168.89; 169.57; 171.33; 171.59 ppm. MS (70 eV), m/e: 385 (M^++1). Anal. calcd for $C_{18}H_{28}N_2O_7$: C, 56.25; H, 7.29; N, 7.29. Found: C, 56.45; H, 7.69; N, 7.78.

Diisopentyl 2-(hexahydro-2,4,6-trioxopyrimidin-5-yl)succinate ***(3h)****:* White solid, m.p. 135-137 ˚C. FT IR (KBr): n 3227, 3108, 2960, 2872, 1720, 1428, 1352, 1258, 1206, 804, 502 cm^{-1}. ^{1}H NMR (DMSO, TMS, 400 MHz): δ 0.83 (d, *J* = 6.54 Hz, 6H); 0.89 (d, *J* = 6.83 Hz, 6H); 1.36 (m, 2H); 1.48 (m, 2H); 1.58 (m, 1H); 1.65 (m, 1H); 2.71 (dd, *J* = 11.61 Hz, *J* = 5.22 Hz, 1H); 2.91 (dd, *J* = 11.61 Hz, *J* = 8.62 Hz, 1H); 3.81 (ddd, *J* = 8.62 Hz, *J* = 5.22 Hz, *J* = 2.51 Hz, 1H); 3.98 (t, *J* = 6.54 Hz, 2H); 4.04 (t, *J* = 6.51 Hz, 2H);, 4.15 (d, *J* = 2.51 Hz, 1H); 11.38 (s, 1H); 11.43 (s, 1H) ppm. ^{13}C NMR (DMSO, TMS, 100 MHz): δ 22.11; 22.25; 24.18; 24.49; 33.54; 34.08; 36.56; 36.78; 49.32; 62.67; 63.37; 150.52; 168.67; 169.47; 171.22; 171.51 ppm. MS (70 eV), m/e: 385 (M^++1). Anal. calcd for $C_{18}H_{28}N_2O_7$: C, 56.25; H, 7.29; N, 7.29. Found: C, 56.73; H, 7.43; N, 7.60.

ACKNOWLEDGMENT

Authors are grateful to, University of Mohaghegh Ardabili for the financial support and the laboratories of Tehran University for the product analysis.

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