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Article

A Greener, Efficient Approach to Michael Addition of Barbituric Acid to Nitroalkene in Aqueous Diethylamine Medium

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Abstract: An efficient method for the synthesis of a variety of pyrimidine derivatives **3a**–**t** by reaction of barbituric acids **1a**,**b** as Michael donor with nitroalkenes **2a**–**k** as Michael acceptor using an aqueous medium and diethylamine is described. This 1,4-addition strategy offers several advantages, such as using an economic and environmentally benign reaction media, high yields, versatility, and shorter reaction times. The synthesized compounds were identified by ^{1}H-NMR, ^{13}C-NMR, CHN, IR, and MS. The structure of compound **3a** was further confirmed by single crystal X-ray structure determination.

Keywords: Michael reactions; barbituric acid; aqueous media; green chemistry

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1. Introduction

The Michael reaction is one of the most powerful tools for the formation of carbon–carbon bonds in organic synthesis [1–6]. The addition of various active methines compounds to nitroalkenes has received increased attention since the conjugated addition products are aliphatic nitro compounds. These are recognized as versatile synthetic building blocks which can be either transformed into biologically active compounds such as tetrahydropyrans, amino acids, pyrrolidines and lactones [7–9], or readily converted into other functionalities such as ketones, amines, carboxylic acids, nitrile oxides, *etc.* [10–13]. Extensive studies have been devoted to the development of catalytic systems for Michael additions of various active methines such as pronucleophiles to nitroalkenes including cinchona organocatalysts [14], enzymes [15], various chiral amines [16,17], transition metal-free organocatalysts [18–20] and chiral metal complexes [21–25].

Recently, the utilization of water as a solvent has emerged as an extensively investigated topic in organic transformations for its environmental friendly character, low cost and properties conferring unique selectivity and reactivity [26]. For these reasons, the development of synthetically useful reactions that take place in water is of considerable topical interest.

Barbituric acids constitute an interesting family of pyrimidinetrione heterocycles [27–29]. They are well-known in medicinal chemistry as sedatives, hypnotics, anticonvulsants and anxiolytic agents [30–32]. Barbituric acids are also particularly utilized as nucleophiles. In continuation of our research program [33–37], we have investigated the reaction of barbituric acids, as nucleophiles with nitroalkenes as Michael acceptors in water using diethylamine to afford multifunctional pyrimidine systems for biological and pharmacological evaluation. To the best of our knowledge, this is the first successful method of this type using aqueous diethylamine as reaction medium.

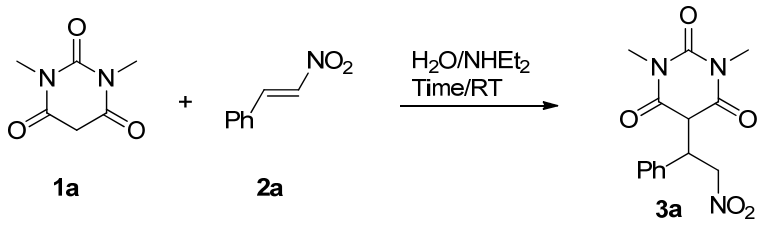
2. Results and Discussion

We initiated our investigations by using 1,3-dimethylbarbituric acid (**1a**) as C-based nucleophile and nitroalkene (**2a**) as a Michael acceptor for the 1,4-addition strategy in the presence of aqueous diethylamine at ambient temperature, as shown in Table 1. These are the optimal reaction conditions for the construction of Michael product by this strategy [38].

As expected, the Michael product **3a** was obtained in quantitative yield after 1 h (Table 1, entry 1). In addition, other secondary amines were examined. It was found that *i*Pr_2NH generated the Michael product in a significant yield of 85% (Table 1, entry 2). Additionally, $(cyclohexyl)_2NH$ and morpholine afforded the product in substantial yields of 82% and 78%, respectively (Table 1, entries 3, 4). NaOH was also examined and was found to be less efficient in the reaction. Only a moderate yield was obtained (Table 1, entry 5). In the absence of amine (entry 6) or water (entry 7), the reaction either could not be performed or proceeded very slowly. The best results, with respect to yield, were obtained by performing the reaction with the combined promoting effects of both H_2O and Et_2NH.

It is well known that the rate for organic reactions conducted in aqueous media require either hydrogen bonding activation of functional groups by water or the repulsive hydrophobic interactions of the reactants [39–41]. We thus envisioned that hydrogen bonding activation in the presence of amine as a base generates an enolate, the catalyst of choice for the Michael strategy (Scheme 1).

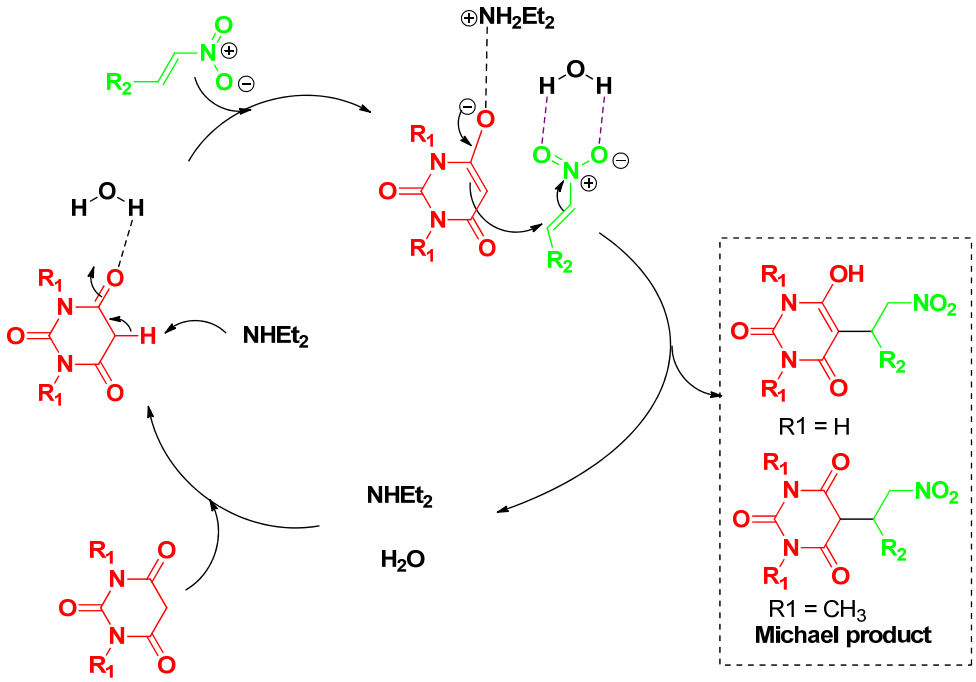
Table 1. Screening of conditions for the Michael addition reaction of the model substrate [a].



Entry	Condition	Time	Yield (%) [b]
1	Et_2NH/H_2O	1	99
2	iPr_2NH/H_2O	4	85
3	$(Cyclohexyl)_2NH/H_2O$	4	82
4	Morpholine/H_2O	3	78
5	$NaOH/H_2O$	6	65
6	Et_2NH	10	10
7	H_2O	10	0

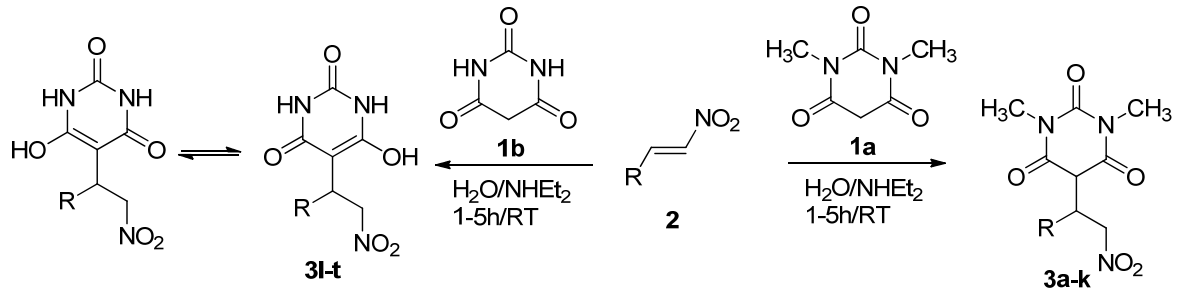
[a] All reactions were carried out with 1,3-dimethylbarbituric acid **1a** (1.5 mmol), nitroalkene **2a** (1.5 mmol) and amine (1.5 mmol) in water (1.5 mL) for the specified time. [b] Yield of isolated product.

Scheme 1. A possible mechanistic pathway.



With the optimal reaction conditions in hand, the substrate scope was then investigated. First, 1,3-dimethylbarbituric acid (**1a**) as C-based nucleophile was reacted with eight different phenyl-type substituted nitroalkenes as Michael acceptors (Table 2, entries 1–8). The reactions proved to work well with a range of nitroalkenes bearing either electron-withdrawing or electron-donating groups that produced the desired products with excellent yields (88%–99%).

Table 2. Michael addition reaction of barbituric acid derivatives **1** to nitroolefin **2** catalyzed by Et_2NH in water at room temperature [a].



Entry	3	R	Yield (%) [b]
1	**3a**	Ph	99
2	**3b**	*p*-CH_3Ph	96
3	**3c**	*p*-BrPh	92
4	**3d**	*p*-ClPh	91
5	**3e**	2,4-Cl_2Ph	90
6	**3f**	2,6-Cl_2Ph	91
7	**3g**	*p*-CH_3OPh	89
8	**3h**	*p*-NO_2Ph	88
9	**3i**	Ferrocene	93
10	**3j**	CH_3	96
11	**3k**	Thiophene	95
12	**3l**	Ph	97
13	**3m**	*p*-CH_3Ph	94
14	**3n**	*p*-BrPh	88
15	**3o**	*p*-ClPh	89
16	**3p**	2,4-Cl_2Ph	85
17	**3q**	2,6-Cl_2Ph	86
18	**3r**	*p*-CH_3OPh	88
19	**3s**	Ferrocene	92
20	**3t**	*p*-NO_2Ph	87

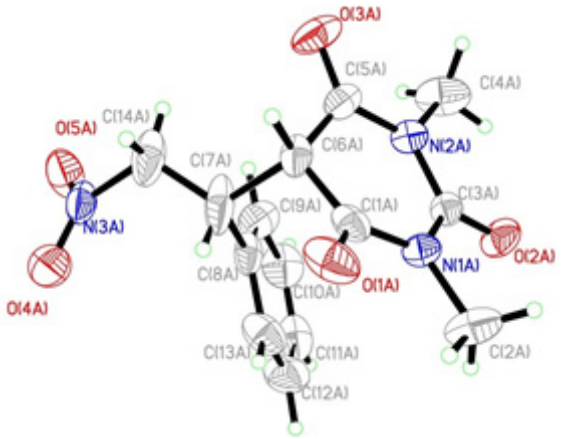
[a] All reactions were carried out with barbituric acid **1** (1.5 mmol), nitroalkene **2** (1.5 mmol) and amine (1.5 mmol) in water (1.5 mL) for the specified time. [b] Yield of isolated product.

Next, we applied the conditions to reactions of barbituric acid (**1b**) with eight different phenyl-type substituted nitroalkenes. Interestingly, the Michael product was separated in enol form and not in keto form in very good to excellent yields (Table 2, entries 13–20). Finally, to show the generality of the procedure, we tested ferrocene nitroalkene as Michael acceptor and the products were obtained in very good yields (Table 2, entries 9, 19). A further development has also been achieved by our group. Thus, Michael addition of barbiturate to either aliphatic nitroalkenes or heteroaromatic nitroalkenes affords the pyrimidine adduct (Table 2, entries 10, 11) with excellent yields (96% and 95%, respectively). Thus, the methodology not only suitable for aromatic nitroalkenes, but also aliphatic and heteroaromatic nitroalkenes.

The X-ray structure of **3a** (Figure 1) was obtained by single crystal structure determination from a single crystal grown from $CHCl_3/Et_2O$ as a solvent. The structure shows interesting characteristics and also the

hydrogen-bonding interactions are listed (see Supporting Information). The packing of the molecules in the crystal structure is stabilized by C–H· · ·O hydrogen bonds into a three-dimensional framework structure.

Figure 1. ORTEP representation of the structure of **3a**.



3. Experimental

3.1. General Information

All the chemicals were purchased from Sigma-Aldrich and Fluka (Seelze, Germany), and were used without further purification unless otherwise stated. All melting points were measured on a Gallenkamp melting point apparatus in open glass capillaries and are uncorrected. IR Spectra were measured as KBr pellets on a Nicolet 6700 FT-IR spectrophotometer (Madison, WI, USA). The NMR spectra were recorded on a Varian Mercury Jeol-400 NMR spectrometer (Tokyo, Japan).^{1}H-NMR (400 MHz), and ^{13}C-NMR (100 MHz) were run in either deuterated dimethylsulphoxide (DMSO-d_6) or deuterated chloroform ($CDCl_3$). Chemical shifts (δ) are referred in terms of ppm and *J*-coupling constants are given in Hz. Mass spectra were recorded on a Jeol JMS-600 H instrument (Tokyo, Japan). Elemental analysis was carried out on a Perkin Elmer 2400 Elemental Analyzer (Vernon Hills, Illinois, IL, USA); CHN mode.

3.2. General Procedure for Synthesis of Nitroalkenes **2a–k**

Equimolar amounts of aryl aldehyde and nitromethane (1 equiv.) were dissolved in 95% ethyl alcohol (100 mL) at room temperature and then a solution of sodium hydroxide (1 equiv.) in ethyl alcohol (30 mL) was added from a dropping funnel at a rate of 5 mL per minute. The solution of the nitromethane and aldehyde in alcohol was then vigorously stirred at room temperature for 1 h. As the reaction proceeded, the insoluble sodium salt of the condensation product precipitated. After all of the alkali had been added and with the temperature kept below 20 °C, ice water (about 30 mL) was slowly added until the precipitate just dissolved. This clear, cold solution was slowly added to a solution of 15% HCl (50 mL) and more cold water (300 mL) was added. A fine, light yellow precipitate was immediately formed and filtered with suction after standing for half an hour. The product thus formed was quite pure and was found to be satisfactory as a starting product for subsequent preparations without further purification.

3.3. General Procedure for Michael Addition for the Synthesis of **3a**–**t**

A mixture of nitroalkene **2a**–**k** (1.5 mmol), barbituric acid derivatives **1a**,**b** (1.5 mmol), and Et_2NH (1.5 mmol) in degassed H_2O (1.5 mL) was stirred at room temperature for 1 h until TLC showed complete disappearance of the reactants. The product either precipitated or was in an oily form. The reaction mixture was acidified using 1M HCl extract with DCM/10% EtOH then washed with brine and dried over $MgSO_4$ to afford **3a**–**t**.

1,3-Dimethyl-5-(2-nitro-1-phenylethyl)pyrimidine-2,4,6(1H,3H,5H)-trione (**3a**) According to the general procedure, **3a** was prepared from 1,3-dimethylbarbituric acid (**1a**) and (*E*)-(2-nitrovinyl)benzene (**2a**) as white crystals (453 mg, 1.48 mmol, 99%); m.p. 85 °C; IR (KBr) ν/cm^{-1} 1738, 1671, 1552, 1372, 1228; ^{1}H-NMR ($CDCl_3$) δ 7.29 (m, 3H, Ph), 7.03 (m, 2H, Ph), 5.28 (dd, 1H, J = 13.9, 5.8 Hz, CH_2NO_2), 5.02 (dd, 1H, J 13.9, 5.8, CH_2NO_2), 4.50 (m, 1H, CHPh), 3.84 (d, 1H, J = 3.6 Hz, COCHCO), 3.12(s, 3H, CH_3), 3.07(s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ 166.8, 150.5, 133.7, 129.4, 127.4, 76.5, 51.5, 45.5, 28.5, 28.3; LC/MS (ESI) *m/z* 305 $[M]^+$; Anal. for $C_{14}H_{15}N_3O_5$; calcd: C, 55.08; H, 4.95; N, 13.76; Found: C, 55.10; H, 4.95; N, 13.75.

The structure of **3a** was confirmed by X-ray crystal structure analysis (Bruker AXS GmbH, Karlsruhe, Germany). CCDC-933479 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. A colorless cubic crystal of the compound suitable for X-ray analysis was formed in $CHCl_3/Et_2O$ at room temperature after 2 days.

1,3-Dimethyl-5-(2-nitro-1-(p-tolyl)ethyl)pyrimidine-2,4,6(1H,3H,5H)-trione (**3b**) According to the general procedure, **3b** was prepared from 1,3-dimethylbarbituric acid (**1a**) and (*E*)-1-methyl-4-(2-nitrovinyl)benzene (**2b**) as an oily product (460 mg, 1.44 mmol, 96%). IR (KBr) ν/cm^{-1} 1738, 1671, 1552, 1372, 1228; ^{1}H-NMR ($CDCl_3$) δ 7.08 (d, 2H, J = 8.0 Hz, Ph), 6.91 (d, 2H, J = 8.0 Hz, Ph), 5.25 (dd, 1H, J = 13.9, 5.8 Hz, CH_2NO_2), 4.99 (dd, 1H, J = 13.9, 5.8 Hz, CH_2NO_2), 4.45 (m, 1H, CHPh), 3.82 (d, 1H, J = 3.6 Hz, COCHCO), 3.13 (s, 3H, CH_3), 3.08 (s, 3H, CH_3), 2.28 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ 166.9, 166.9, 150.6, 139.3, 130.5, 129.9, 127.3, 51.5, 45.3, 28.5, 28.3, 21.1; LC/MS (ESI): *m/z* 319 $[M]^+$; Anal. for $C_{15}H_{17}N_3O_5$; calcd: C, 56.42; H, 5.37; N, 13.16; Found: C, 56.41; H, 5.36; N, 13.17.

5-(1-(4-Bromophenyl)-2-nitroethyl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (**3c**) According to the general procedure, **3c** was prepared from 1,3-dimethylbarbituric acid (**1a**) and (*E*)-1-bromo-4-(2-nitrovinyl) benzene (**2c**) as a yellow powder (530 mg, 1.38 mmol, 92%); m.p.: 99 °C; IR (KBr) ν/cm^{-1} 1738, 1668, 1552, 1375; ^{1}H-NMR (DMSO-d_6) δ 7.51 (d, 2H, J = 7.3 Hz, Ph), 7.07 (d, 2H, J = 7.3 Hz, Ph), 5.40 (dd, 1H, J = 13.9, 5.8 Hz, CH_2NO_2), 5.23 (dd, 1H, J = 13.9, 5.8 Hz, CH_2NO_2), 4.29 (bs, 1H, CHPh), 4.17 (bs, 1H, COCHCO), 3.06 (s, 3H, CH_3), 2.96 (s, 3H, CH_3); ^{13}C-NMR (DMSO-d_6) δ 167.8, 167.5, 166.4, 151.3, 135.0, 132.2, 132.1, 131.8, 130.3, 122.1, 76.6, 52.1, 44.0, 28.5, 28.3; LC/MS (ESI) *m/z* 384 $[M]^+$; Anal. for $C_{14}H_{14}BrN_3O_5$; calcd: C, 43.77; H, 3.67; Br, 20.80; N, 10.94;Found: C, 43.79; H, 3.65; Br, 20.81; N, 10.94.

5-(1-(4-Chlorophenyl)-2-nitroethyl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (**3d**) According to the general procedure, **3d** was prepared from 1,3-dimethylbarbituric acid (**1a**) and (*E*)-1-chloro-4-(2-nitrovinyl)benzene (**2d**) as an oily product (462 mg, 1.36 mmol, 91%). IR (KBr) ν/cm^{-1} 1738, 1669, 1552, 1423, 1238; ^{1}H-NMR (DMSO-d_6) δ 7.44 (d, 2H, J = 8.0 Hz, Ph), 7.13 (d, 2H, J = 8.0 Hz, Ph), 5.41 (dd, 1H, J = 13.9, 5.8 Hz, CH_2NO_2), 5.23 (dd, 1H, J = 13.9, 5.8 Hz, CH_2NO_2), 4.30 (bs, 1H, CHPh), 4.16 (bs, 1H, COCHCO), 3.06 (s, 3H, CH_3), 2.95 (s, 3H, CH_3); ^{13}C-NMR (DMSO-d_6) δ 167.8, 167.5, 166.4, 151.3, 135.0, 132.2, 132.1, 131.8, 130.3, 122.1, 76.6, 52.1, 44.0, 28.5, 28.3; LC/MS (ESI) *m/z* 339 [M]$^+$; Anal. for $C_{14}H_{14}ClN_3O_5$; calcd: C, 49.49; H, 4.15; Cl, 10.44; N, 12.37;Found: C, 49.50; H, 4.14; Cl, 10.43; N, 12.36.

5-(1-(2,4-Dichlorophenyl)-2-nitroethyl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (**3e**) According to the general procedure, **3e** was prepared from 1,3-dimethylbarbituric acid (**1a**) and (*E*)-2,4-dichloro-1-(2-nitrovinyl) benzene (**2e**) as a yellow powder (505 mg, 1.35 mmol, 90%); m.p.: 119 °C; IR (KBr) ν/cm^{-1} 1738, 1667, 1551, 1423, 1221;^{1}H-NMR (DMSO-d_6) δ 7.65 (s, 1H, Ph), 7.52 (d, 1H, J = 8.0 Hz, Ph), 7.45(d, 1H, J = 8.0 Hz, Ph), 5.31–5.22 (m, 3H, CH_2NO_2 and COCHCO), 4.83 (bs, 1H, CHPh); ^{13}C-NMR (DMSO-d_6): δ 167.3, 166.4, 151.7, 135.0, 130.9, 129.6, 127.9, 75.7, 51.6, 28.8, 28.7; LC/MS (ESI) *m/z* 374 [M]$^+$; Anal. for $C_{14}H_{13}Cl_2N_3O_5$; calcd: C, 44.94; H, 3.50; Cl, 18.95; N, 11.23; Found: C, 44.92; H, 3.51; Cl, 18.90; N, 11.25.

5-(1-(2,6-Dichlorophenyl)-2-nitroethyl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (**3f**) According to the general procedure, **3f** was prepared from 1,3-dimethylbarbituric acid (**1a**) and (*E*)-2,6-dichloro-1-(2-nitrovinyl)benzene (**2f**) as a white powder (510 mg, 1.36 mmol, 91%); m.p.: 140 °C; IR (KBr) ν/cm^{-1} 1738, 1670, 1551, 1423, 1228; ^{1}H-NMR (DMSO-d_6) δ 7.50 (d, 2H, J = 8.0 Hz, Ph), 7.36 (t, 1H, J = 8.0 Hz, Ph), 5.32 (d, 2H, J = 6.6 Hz, CH_2NO_2), 5.00 (m, 1H, CHPh), 4.11 (d, 1H, J = 11.0 Hz, COCHCO), 3.08 (s, 3H, CH_3), 3.03 (s, 3H, CH_3); ^{13}C-NMR (DMSO-d_6) δ 167.7, 166.8, 152.0, 134.7, 132.5, 131.2, 130.6, 129.3, 75.6, 50.47, 28.8, 28.7; LC/MS (ESI) *m/z* 374[M]$^+$; Anal. for $C_{14}H_{13}Cl_2N_3O_5$; calcd: C, 44.94; H, 3.50; Cl, 18.95; N, 11.23;Found: C, 44.92; H, 3.51; Cl, 18.90; N, 11.25.

5-(1-(4-Methoxyphenyl)-2-nitroethyl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (**3g**) According to the general procedure, **3g** was prepared from 1,3-dimethylbarbituric acid (**1a**) and (*E*)-1-methoxy-4-(2-nitrovinyl) benzene (**2g**) as an oily product (447 mg, 1.33 mmol, 89%). IR (KBr) ν/cm^{-1} 1738, 1670, 1551, 1423, 1228; ^{1}H-NMR (DMSO-d_6) δ 6.96 (d, 2H, J = 8.0 Hz, Ph), 6.85 (d, 2H, J = 8.0 Hz, Ph), 5.41 (dd, 1H, J = 13.9, 5.8 Hz, CH_2NO_2), 5.16 (dd, 1H, J = 13.9, 5.8 Hz, CH_2NO_2), 4.21 (m, 1H, CHPh), 4.04 (d, 1H, J = 2.9 Hz, COCHCO), 3.69 (s, 3H, CH_3), 2.99 (s, 3H, CH_3), 2.93 (s, 3H, CH_3); ^{13}C-NMR (DMSO-d_6) δ 168.2, 167.7, 159.6, 151.3, 129.1, 126.6, 114.6, 77.0, 55.6,52.4, 44.7,28.4, 28.3 ; LC/MS (ESI) *m/z* 335[M]$^+$; Anal. for $C_{15}H_{17}N_3O_6$; calcd: C, 53.73; H, 5.11; N, 12.53; Found: C, 53.74; H, 5.10; N, 12.52.

1,3-Dimethyl-5-(2-nitro-1-(4-nitrophenyl)ethyl)pyrimidine-2,4,6(1H,3H,5H)-trione (**3h**) According to the general procedure, **3h** was prepared from 1,3-dimethylbarbituric acid (**1a**) and (*E*)-1-nitro-4-(2-nitrovinyl)benzene (**2h**) as a dark brown powder (462 mg, 1.32 mmol, 88%); m.p.: 170 °C; IR (KBr) ν/cm^{-1} 1738, 1646, 1551, 1366, 1217; ^{1}H-NMR (DMSO-d_6) δ 7.50 (d, 2H, J = 8.0 Hz, Ph), 7.38 (d, 2H, J = 8.0 Hz, Ph), 5.32 (d, 2H, J = 6.6 Hz, CH_2NO_2), 5.00 (m, 1H, CHPh), 4.11 (d, 1H,

J = 11 Hz, COCHCO), 3.08 (s, 3H, CH_3), 3.03 (s, 3H, CH_3); ^{13}C-NMR (DMSO-d_6) δ 167.7, 166.8, 152.0, 136.7, 134.7, 132.5, 131.2, 130.6, 129.3, 75.6, 50.4, 28.8, 28.7; LC/MS (ESI) *m/z* 350[M]$^+$; Anal. for $C_{14}H_{14}N_4O_7$; calcd: C, 48.00; H, 4.03; N, 15.99; Found: C, 48.01; H, 4.01; N, 16.01.

1,3-Dimethyl-5-(2-ferrocenyl)ethyl)pyrimidine-2,4,6(1H,3H,5H)-trione (**3i**) According to the general procedure, **3i** was prepared from 1,3-dimethylbarbituric acid (**1a**) and (*E*)-1-ferrocenyl-2-nitroethene (**2i**) as a dark purple powder (595 mg, 1.39 mmol, 93%); m.p.: 139 °C; IR (KBr) ν/cm^{-1} 1738, 1671, 1551, 1423, 1367, 1228; ^{1}H-NMR (DMSO-d_6) δ 5.17 (d, 2H, *J* = 7.3 Hz, CH_2NO_2), 4.21 (bs, 5H, ferrocene), 4.00 (m, 1H, CH-ferrocene), 3.92 (d, 1H, *J* = 2.9 Hz, COCHCO), 3.38 (bs, 4H, ferrocene), 3.03 (s, 3H, CH_3), 2.88 (s, 3H, CH_3), 2.93 (s, 3H, CH_3); ^{13}C-NMR (DMSO-d_6) δ 168.4, 167.6, 151.4, 83.2, 76.7, 69.4, 69.3, 68.7, 68.3, 67.7, 66.0, 52.2, 28.5, 28.2 ; LC/MS (ESI) *m/z* 427[M]$^+$; Anal. for $C_{19}H_{21}FeN_3O_5$; calcd: C, 53.41; H, 4.95; N, 9.84; Found: C, 53.42; H, 4.94; N, 9.85.

1,3-Dimethyl-5-(1-nitropropan-2-yl)pyrimidine-2,4,6(1H,3H,5H)-trione (**3j**) According to the general procedure, **3j** was prepared from 1,3-dimethylbarbituric acid (**1a**) and (*E*)-1-nitroprop-1-ene (**2j**) as a yellowish oily product (350 mg, 1.44 mmol, 96%). IR (KBr) ν/cm^{-1} 1745, 1665, 1325, 1225; ^{1}H-NMR (DMSO-d_6) δ 4.93 (dd, H, *J* = 11.2, 5.2 Hz, CH_2NO_2), 4.70 (dd, H, *J* = 11.2, 5.2 Hz, CH_2NO_2), 3.98 (d, 1H, *J* = 2.4, COCHCO), 3.23 (m, 1H, CH), 3.20 (s, 3H, CH_3), 3.02 (s, 3H, CH_3), 0.95 (d, 3H, *J* = 5.6, CH_3); ^{13}C-NMR (DMSO-d_6) δ 167.4, 167.3, 165.8, 151.4, 78.4, 50.3, 28.2, 27.7, 13.6; LC/MS (ESI) *m/z* 244[M]$^+$; Anal. for $C_9H_{13}N_3O_5$; calcd: C, 44.44; H, 5.39; N, 17.28; Found: C, 44.46; H, 5.40; N, 17.31.

1,3-Dimethyl-5-(2-nitro-1-(thiophen-2-yl)ethyl)pyrimidine-2,4,6(1H,3H,5H)-trione (**3k**) According to the general procedure, **3k** was prepared from 1,3-dimethylbarbituric acid (**1a**) and (*E*)-2-(2-nitrovinyl)thiophene (**2k**) as a brown semisolid product (443 mg, 1.42 mmol, 95%). IR (KBr) ν/cm^{-1} 1767, 1680, 1558, 1343, 1225;^{1}H-NMR (DMSO-d_6) δ 7.45 (brs, 1H, thiophene), 6.95 (brs, 1H, thiophene), 6.89 (brs, 1H, thiophene), 5.45 (d, 1H, *J* = 10.8 Hz, CH_2NO_2), 5.20 (dd, 1H, *J* = 16.8, 8.8 Hz, CH_2NO_2), 4.66 (brs, 1H, COCHCO), 4.26 (brs, 1H, $CHCH_2NO_2$), 3.12 (s, 3H, CH_3), 3.05 (s, 3H, CH_3); ^{13}C-NMR (DMSO-d_6) δ 169.5, 168.7, 137.9, 135.9, 134.8, 129.8, 79.5, 29.1, 28.5, 27.5; LC/MS (ESI) *m/z* 312[M]$^+$; Anal. for $C_{12}H_{13}N_3O_5S$; calcd: C, 46.30; H, 4.21; N, 13.50; Found: C, 46.32; H, 4.22; N, 13.48.

6-Hydroxy-5-(2-nitro-1-phenylethyl)pyrimidine-2,4(1H,3H)-dione (**3l**) According to the general procedure, **3l** was prepared from barbituric acid (**1b**) and (*E*)-(2-nitrovinyl)benzene (**2a**) as a white powder (401 mg, 1.45 mmol, 97%); m.p.: 165 °C; IR (KBr) ν/cm^{-1} 3204, 3015, 2920, 1740, 1550, 1363, 1217;^{1}H-NMR (DMSO-d_6) δ 11.31 (s, 2H, NH), 7.40 (m, 3H, Ph), 7.13 (m, 2H, Ph), 5.44 (dd, 1H, *J* = 13.9, 5.8 Hz, CH_2NO_2), 5.28 (dd, 1H, *J* = 13.9, 5.8 Hz, CH_2NO_2), 4.33 (m, 1H, CHPh); ^{13}C-NMR (DMSO-d_6) δ 169.7, 169.5, 150.7, 135.8, 129.3, 128.8, 128.3, 79.7, 77.4, 51.3, 43.6; LC/MS (ESI) *m/z* 277 [M]$^+$; Anal. for $C_{12}H_{11}N_3O_5$; calcd: C, 51.99; H, 4.00; N, 15.16; Found: C, 52.01; H, 4.02; N, 15.15.

6-Hydroxy-5-(2-nitro-1-(p-tolyl)ethyl)pyrimidine-2,4(1H,3H)-dione compound with diethylamine (1:1) (**3m**) According to the general procedure, **3m** was prepared from barbituric acid (**1b**) and

(*E*)-1-methyl-4-(2-nitrovinyl)benzene (**2b**) as a white powder (513 mg, 1.41 mmol, 94%); m.p.: 210 °C; IR (KBr) ν/cm^{-1} 3210, 3015, 1738, 1686, 1574, 1374; ^{1}H-NMR (DMSO-d_6) δ 9.22 (s, 2H, NH), 7.27 (d, 2H, J = 8.0 Hz, Ph), 6.99 (d, 2H, J = 8.0 Hz, Ph), 5.35 (dd, 1H, J = 13.9, 5.8 Hz, CH_2NO_2), 5.09 (dd, 1H, J = 13.9, 5.8 Hz, CH_2NO_2), 4.74(m, 1H, CHPh), 2.92 (m, 1H and 4H, COCHCO and $CH_3CH_2NHCH_2CH_3$), 2.21 (s, 3H, CH_3), 1.14 (t, 6H, J = 7.3 Hz, $CH_3CH_2NHCH_2CH_3$); ^{13}C-NMR (DMSO-d_6) δ 164.7, 152.5, 141.2, 135.0, 128.7, 128.1, 85.0, 79.5, 41.9, 21.1, 11.5; LC/MS (ESI) *m/z* 364[M]$^+$; Anal. for $C_{15}H_{17}N_3O_5$; calcd: C, 56.03; H, 6.64; N, 15.38; Found: C, 56.05; H, 6.65; N, 15.39.

5-(1-(4-Bromophenyl)-2-nitroethyl)-6-hydroxypyrimidine-2,4(1H,3H)-dione (**3n**) According to the general procedure, **3n** was prepared from barbituric acid (**1b**) and (*E*)-1-bromo-4-(2-nitrovinyl) benzene (**2c**) as a yellow powder (566 mg, 1.32 mmol, 88%); m.p.: 130 °C; IR (KBr) ν/cm^{-1}: 3204, 3015, 2920, 1740, 1550, 1363, 1217; ^{1}H-NMR (DMSO-d_6) δ 9.22 (s, 2H, NH), 7.42 (d, 2H, J = 8.0 Hz, Ph), 7.18 (d, 2H, J = 8.0 Hz, Ph), 5.42 (dd, 1H, J = 13.9, 5.8 Hz, CH_2NO_2), 5.27 (m, 2H, CH_2NO_2 and CHPh); ^{13}C-NMR (DMSO-d_6) δ 169.5, 169.3, 150.7, 135.1, 133.4, 130.3, 129.3, 79.7, 77.1, 51.3, 33.2; LC/MS (ESI) *m/z* 356 [M]$^+$; Anal. for $C_{12}H_{10}BrN_3O_5$; calcd: C, 40.47; H, 2.83; Br, 22.44; N, 11.80; Found: C, 40.50; H, 2.85; Br, 22.45; N, 11.83.

5-(1-(4-Chlorophenyl)-2-nitroethyl)-6-hydroxypyrimidine-2,4(1H,3H)-dione (**3o**) According to the general procedure, **3o** was prepared from barbituric acid (**1b**) and (*E*)-1-chloro-4-(2-nitrovinyl) benzene (**2d**) as a white powder (512 mg, 1.33 mmol, 89%); m.p.: 80 °C; IR (KBr) ν/cm^{-1} 3208, 3018, 2980, 1740, 1699, 1555, 1363, 1217; ^{1}H-NMR (DMSO-d_6) δ 9.22 (s, 2H, NH), 7.55 (m, 4Ph), 5.37 (dd, 1H, J = 13.9 Hz, CH_2NO_2), 5.07 (dd, 1H, J = 13.9 Hz, CH_2NO_2), 4.73 (m, 1H, CHPh); ^{13}C-NMR (DMSO-d_6) δ 164.4, 152.3, 143.5, 132.2, 131.8, 131.4, 130.5, 119.2, 84.8, 78.9, 29.4; LC/MS (ESI) *m/z* 311 [M]$^+$; Anal. for $C_{12}H_{10}ClN_3O_5$; calcd:C, 46.24; H, 3.23; Cl, 11.37; N, 13.48; Found: C, 46.21; H, 3.22; Cl, 11.40; N, 13.45.

5-(1-(2,4-Dichlorophenyl)-2-nitroethyl)-6-hydroxypyrimidine-2,4(1H,3H)-dione compound with diethylamine (1:1) (**3p**) According to the general procedure, **3p** was prepared from barbituric acid (**1b**) and (*E*)-2,4-dichloro-1-(2-nitrovinyl)benzene (**2e**) as a beige powder (534 mg, 1.27 mmol, 85%); m.p.: 190 °C; IR (KBr) ν/cm^{-1} 3151, 2986, 1697, 1590, 1376; ^{1}H-NMR (DMSO-d_6) δ 9.18 (s, 2H, NH), 8.30 (bs, 1H, OH), 7.83 (d, 2H, J = 8.8 Hz, Ph), 7.44(s, 1H, Ph), 7.30 (d, 2H, J = 8.8 Hz, Ph), 5.35 (dd, 1H, J = 13.9, 5.8 Hz, CH_2NO_2), 5.14 (dd, 1H, J = 13.9, 5.8 Hz, CH_2NO_2), 4.90 (m, 1H, CHPh), 2.92 (m, 1H and 4H, COCHCO and $CH_3CH_2NHCH_2CH_3$), 2.21 (s, 3H, CH_3), 1.14 (t, 6H, J = 7.3 Hz, $CH_3CH_2NHCH_2CH_3$); ^{13}C-NMR (DMSO-d_6) δ 165.0, 152.5, 140.2, 134.1, 132.7, 131.7, 128.5, 127.3, 82.5, 77.3, 41.9, 21.1, 11.5; LC/MS (ESI) *m/z* 419 [M]$^+$; Anal. for $C_{16}H_{20}Cl_2N_4O_5$; calcd: C, 45.84; H, 4.81; Cl, 16.91; N, 13.36; Found: C, 45.87; H, 4.83; Cl, 16.90; N, 13.35.

5-(1-(2,6-Dichlorophenyl)-2-nitroethyl)-6-hydroxypyrimidine-2,4(1H,3H)-dione (**3q**) According to the general procedure, **3q** was prepared from barbituric acid (**1b**) and (*E*)-2,6-dichloro-1-(2-nitrovinyl) benzene (**2f**) as a yellow powder (540 mg, 1.29 mmol, 86%); m.p.: 130 °C; IR (KBr) ν/cm^{-1} 3155, 2986, 1740, 1670, 1551, 1423, 1228;^{1}H-NMR (DMSO-d_6) δ 11.38 (s, 2H, NH), 7.63 (d, 2H, J = 8.8 Hz, Ph), 7.46 (s, 1H, Ph), 7.36 (d, 2H, J = 8.8 Hz, Ph), 5.37 (dd, 1H, J = 13.9, 5.8 Hz, CH_2NO_2),

5.25 (dd, 1H, *J* = 13.9, 5.8 Hz, CH_2NO_2), 5.04 (m, 1H, CHPh); ^{13}C-NMR (DMSO-d_6) δ 169.6, 168.4, 151.3, 133.1, 130.9, 129.8, 129.2, 75.8, 49.2; LC/MS (ESI) *m/z* 419 $[M]^+$; Anal. for $C_{12}H_9Cl_2N_3O_5$; calcd: C, 41.64; H, 2.62; Cl, 20.49; N, 12.14; Found: C, 41.65; H, 2.61; Cl, 20.50; N, 12.13.

6-Hydroxy-5-(1-(4-methoxyphenyl)-2-nitroethyl)pyrimidine-2,4(1H,3H)-dione compound with diethylamine (1:1) (**3r**) According to the general procedure, **3r** was prepared from barbituric acid (**1b**) and (*E*)-4-methoxy-1-(2-nitrovinyl)benzene (**2g**) as a yellow powder (501 mg, 1.32 mmol, 88%); m.p.: 152 °C; IR (KBr) ν/cm^{-1} 3459, 3016, 2970, 1740, 1571, 1365; ^{1}H-NMR (DMSO-d_6) δ 9.07 (s, 2H, NH), 7.32 (d, 2H, *J* = 8.8 Hz, Ph), 6.75(s, 1H, Ph), 7.30 (d, 2H, *J* = 8.8 Hz, Ph), 5.31 (dd, 1H, *J* = 13.9, 5.8 Hz, CH_2NO_2), 5.06 (dd, 1H, *J* = 13.9, 5.8 Hz, CH_2NO_2), 4.68 (m, 1H, CHPh), 3.68 (s, 3H, OCH_3), 2.93 (m, 1H and 4H, COCHCO and $CH_3CH_2NHCH_2CH_3$), 1.15 (t, 6H, *J* = 7.3 Hz, $CH_3CH_2NHCH_2CH_3$); ^{13}C-NMR (DMSO-d_6) δ 164.6, 157.9, 152.5, 136.4, 129.3, 113.5, 85.0, 79.8, 55.4, 41.9, 11.6; LC/MS (ESI) *m/z* 380$[M]^+$; Anal. for $C_{17}H_{24}N_4O_6$; calcd: C, 53.68; H, 6.36; N, 14.73; Found: C, 53.68; H, 6.36; N, 14.73.

5-(2-Ferrocenyl)ethyl)6-Hydroxypyrimidine-2,4(1H,3H)-dione compound with diethylamine (1:1) (**3s**) According to the general procedure, **3s** was prepared from barbituric acid (**1b**) and (*E*)-1-ferrocenyl-2-nitroethene (**2i**) as a brown powder (550 mg, 1.38 mmol, 92%); m.p.: 190 °C; IR (KBr) ν/cm^{-1} 3449, 3016, 2970, 1738, 1546, 1365, 1217;^{1}H-NMR (DMSO-d_6) δ 8.98 (s, 2H, NH), 5.16 (t, 1H, *J* = 9.5 Hz, CH_2NO_2), 4.89 (dd, 1H, *J* = 13.9, 5.8 Hz, CH_2NO_2), 4.53(m, 1H, CHPh), 4.25-3.93 (m, 10H, ferrocene and COCHCO), 2.92 (bs, 4H, $CH_3CH_2NHCH_2CH_3$), 1.15 (bs, 6H, $CH_3CH_2NHCH_2CH_3$); ^{13}C-NMR (DMSO-d_6) δ 164.5, 152.5, 92.3, 84.7, 79.6, 69.3, 68.8, 67.8, 66.7, 66.4, 41.8, 34.7, 11.6; LC/MS (ESI) *m/z* 399 $[M]^+$; Anal. for $C_{17}H_{17}FeN_3O_5$; calcd: C, 51.15; H, 4.29; N, 10.53; Found: C, 51.17; H, 4.30; N, 10.54.

6-Hydroxy-5-(2-nitro-1-(4-nitrophenyl)ethyl)pyrimidine-2,4(1H,3H)-dione compound with diethylamine (1:1) (**3t**). According to the general procedure, **3t** was prepared from barbituric acid (**1b**) and (*E*)-4-nitro-1-(2-nitrovinyl)benzene (**2h**) as a yellow powder (515 mg, 1.3 mmol, 87%); m.p.: 185 °C; IR (KBr) ν/cm^{-1} 3445, 3015, 2970, 1738, 1575, 1373, 1216;^{1}H-NMR (DMSO-d_6) δ 9.18 (s, 2H, NH), 8.13(d, 1H, *J* = 7.3 Hz, Ph), 7.70(d, 1H, *J* = 8.0 Hz, Ph), 7.56(t, 1H, *J* = 8.0 Hz, Ph), 7.36(t, 1H, *J* = 7.3 Hz, Ph), 5.57(dd, 1H, *J* = 11.7, 8.0 Hz, CH_2NO_2), 5.11 (t, 1H, *J* = 8.0 Hz, COCHCO), 5.06 (dd, 1H, *J* = 11.7, 8.0 Hz, CH_2NO_2), 3.37 (bs, 1H, CHPh), 2.90 (q, *J* = 7.3 Hz, 4H, $CH_3CH_2NHCH_2CH_3$), 1.13 (t, 6H, *J* = 7.3 Hz, $CH_3CH_2NHCH_2CH_3$); ^{13}C-NMR (DMSO-d_6) δ 164.9, 152.5, 149.5, 138.6, 133.0, 131.4, 127.6, 123.6, 84.5, 78.0, 41.9, 35.1, 11.5; LC/MS (ESI) *m/z* 395$[M]^+$; Anal. for $C_{16}H_{21}N_5O_7$; calcd: C, 48.61; H, 5.35; N, 17.71; Found: C, 48.59; H, 5.34; N, 17.68.

4. Conclusions

A very convenient procedure for the syntheses of pyrimidine derivatives by Michael addition of cyclic 1,3-dicarbonyl compounds to a range of nitroalkenes using a simple $NHEt_2/H_2O$ medium has been developed. The reaction scope is substantial and a number of substituted barbituric acids and nitroalkenes could be successfully applied to give multifunctional pyrimidine derivatives. These reactions gave high yields of products in short periods of time. The study of the full scope of this

asymmetric transformation and its application in the synthesis of biologically active molecules are currently underway in our laboratory.

Supplementary Materials

Supplementary materials can be accessed at: http://www.mdpi.com/1420-3049/19/1/1150/s1.

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Author Contributions

A.B. proposed the subject, designed the study. H.J.A.-N. and M.W. carried out the synthesis of all the products. A.M.A.-M. and Y.N.M. monitor progress of the ongoing research of the proposed project, helped in the results and discussion. H.G. and H.-K.F. carried out the X-ray crystallography part. A.B. prepared draft the manuscript. All the authors read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Sample Availability: Samples of the compounds **3a**–**t** are available from the authors.