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A New and Convenient Method for Synthesis of Barbituric Acid Derivatives

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In continuation of our current studies on the reaction between isocyanides and electron-defficient alkenes, we would like to report our recent reseaarch on synthesizing novel derivatives of barbituric acid. The reaction of alkylidene-substituted Meldrum's acid with alkyl isocyanides in the presence of urea led to the production of the corresponding 2-(hexahydro-2,4,6-trioxopyrimidin-5-yl)-*N*,2-dimethylpropanamide in good to high yields. The structure of the products was in agreement with their spectroscopic data .

Keywords: Isocyanide, Multi-component reaction, Barbituric acid, Alkylidene-substituted Meldrum's acid

INTRODUCTION

Among heterocyclic compounds, pyrimidines play an essential role in chemistry and biological systems. Barbituric acid (2,4,6-trioxohexahydropyrimidine) is one of the most interesting derivatives of pyrimidines [1-3]. The barbituric acid moiety is present in various synthetic compounds with pharmaceutical and industrial applications [4-7]. Owing to various pharmaceutical activities of 2,4,6-trioxohexahydro-pyrimidine and its derivatives, they have been used extensively in medicine and bioorganic researches. Barbituric acid itself, has been used as a reactant to form a large class of barbiturate drugs which are used as hypnotics, sedatives, anticonvulsants, anesthetics and as central nervous system depressants [2-3]. Due to the applications of barbiturates, exploration of new routes for the synthesis of these compounds is axiomatic.

Exploration of novel protocols for the synthesis of desirable organic compounds is a growing trend in organic synthesis. Among the new methodologies for a rapid access to the chemical diversity space, multi-component reactions (MCRs) are noteworthy tools for the quick and efficient synthesis of an extensive variety of organic compounds [8,9]. For the last two decades multi-component reactions have been exploited by combinatorial chemists, as a source of appendage diversity. The new possibilities for the development of the MCRs design took place with the introduction of diverse-oriented synthesis (DOS) [10,11]. Ideally, MCRs are suited for the creation of compounds having structural diversity in a combinatorial manner that ensures their leading position in DOS. Along with the various approaches to MCRs, isocyanide multi-component reactions (IMCRs) are very powerful condensations in DOS [12-14]. The classical representations of this class are Passerini and Ugi reactions [12]. In order to expand their utility and gain access to drug-like heterocyclic compounds, several research groups are currently developing modifications of these classical reactions [9,12-15].

Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione, isopropylidne malonate) and its derivatives are important molecules that are extensively used as intermediates in organic synthesis. Meldrum's acid is susceptible to electrophilic attack at C_5 and nucleophilic attack at C_4 and C_6. In addition, its

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unique ring-opening reactions make it a tremendously attractive and useful building block [13,14].

Among its derivatives, alkylidene-substituted Meldrum's acid has attractive features. There are a lot of examples reported for using them as dienophiles in hetero Diels-Alder reaction, as well as Michael acceptors [15-17]. One of the most interesting applications of Meldrum's acid and its derivatives is their application in MCRs especially in isocyanide-based multi-component reactions (IMCRs) [18-20].

As part of our current studies on the reaction between alkylidene-substituted Meldrum's acid and alkyl isocyanides in the presence of RXH as a proton source [18-20], here, we report a novel and one-pot three-component reaction of alkylidene-substituted Meldrum's acid **1**, alkyl isocyanide **2** and urea **3** that leads to the production of a new derivatative of 5-substituted barbituric acid **4** (Scheme 1).

EXPERIMENTAL

Chemicals and Apparatus

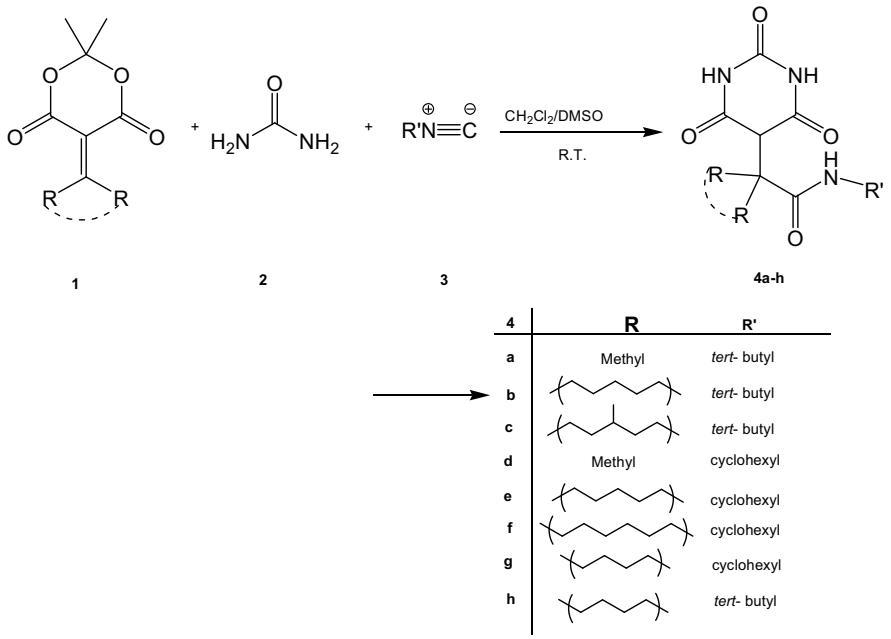
All chemicals and solvents were purchased from Fluka and Merck chemical company and used as received. Melting points were measured on an Electrothermal 9200 apparatus. IR spectra were recorded on a FT-IR 102MB BOMEM apparatus. Mass spectra were recorded on a AGILENT TECHNOLOGY (HP)-5973 mass spectrometer operating at an ionization potential of 70 eV (EI). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE-300 MHz spectrometer employing tetramethylsilane as an internal reference.

General Procedure for the Preparation of Compounds 4

To a stirred solution of alkylidene-substituted Meldrum's acid **1** (2 mmol) and urea **3** (2 mmol) in DMSO/CH_2Cl_2 (10 ml) was added a solution of alkyl isocyanide **2** (2 mmol) in 5 ml CH_2Cl_2 in over 10 min. The mixture was then allowed to stir for 24 h. The dichloromethane was removed under reduced pressure, and ice water was added to produce white precipitate. This crude product was purified by recrystalization with ethanol or petroleum benzene.

Spectra Data of the Products

***N-tert*-butyl-2-(hexahydro-2,4,6-trioxopyrimidin-5-yl)-2-methylpropanamide (4a).** Colorless powder (0.17 g, 68%), m.p.: 169 °C; IR (KBr) (ν_{max}/cm^{-1}): 1571 (NH bend, 1694 (4



Scheme 1. Multi-component reaction al kylidene Meldrum's acid, alkyl isocyanide and urea

C=O), 3139, 3325, 3431 (3 NH). ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.25 (3H, s, Me), 1.43 (3H, s, Me), 1.59 (9H, s, CMe_3) 3.37 (1H, s, CH), 5.55, 8.09, 10.20 (3H, s, 3NH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.18, 25.16 (2Me), 28.24 (C*Me*$_3$), 43.68 (*C*Me$_2$), 57.53 (*C*Me$_3$), 59.19 (CH), 153.96, 167.90, 173.95, 181.77 (4 C=O). MS *m/z* (%): 269 (M^+, 20.5), 214 (79.5), 171 (31), 154 (48), 149 (79.5), 83 (100), 61 (91). Anal. Calcd. for $C_{12}H_{19}N_3O_4$ (269.14): C, 53.52; H, 7.11; N, 15.60%. Found: C, 53.68; H, 7.02; N, 15.82%.

***N*-*tert*-butyl-1-(hexahydro-2,4,6-trioxopyrimidin-5-yl) cyclohexane carboxamide (4b).** Colorless powder (0.22 g, 73%): m.p.: 178 °C; IR (KBr) (ν_{max}/cm^{-1}) 1567 (NH bend), 1693, 1779 (4 C=O), 3146, 3247, 3418 (3NH). ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.17-2.16 (10H, m, 5CH_2 of cyclohexyl), 1.57 (9H, s, CMe_3), 3.50 (1H, s, CH), 5.50, 8.16, 10.60 (3H, s, 3NH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.99, 22.17, 25.04, 27.32, 30.87 (5CH_2 of cyclohexyl), 28.19 (C*Me*$_3$), 35.80 (C of cyclohexyl), 48.2 (*C*Me$_3$), 58.7 (CH), 154.81, 169.27, 173.46, 182.17 (4C=O). MS *m/z* (%): 309 (M^+, 18), 253 (54), 241 (30), 211 (58), 197 (63.5), 184 (44), 83 (100), 61 (87). Anal. Calcd. for $C_{15}H_{23}N_3O_4$ (309.17): C, 58.24; H, 7.49; N, 13.58%. Found: C, 57.51; H, 7.82; N, 13.05%.

***N*-*tert*-butyl-1-(hexahydro-2,4,6-trioxopyrimidin-5-yl)-4-methylcyclohexane carboxamide (4c).** Colorless powder (0.14g, 45%): m.p.: 209 °C; IR (KBr) (ν_{max}/cm^{-1}) 1578 (NH bend), 1689, 1725, 1774 (4C=O), 3162, 3241, 3315, 3428 (3NH). ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 0.96 (3H, d, *J* = 6.26 Hz, Me), 1.58 (9H, s, CMe_3) 1.45-1.90 (9H, m, 4CH_2 and CH of cyclohexyl), 3.29 (1H, s, CH), 5.43, 8.12, 10.60 (3H, s, 3NH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.32 (Me), 28.27, 30.11 (4CH_2 of cyclohexyl), 29.78 (C*Me*$_3$), 30.68 (CH of cyclohexyl), 34.63 (C of cyclohexyl), 46.41 (*C*Me$_3$), 58.75 (CH), 154.81, 169.27, 173.46, 182.17 (4 C=O). MS *m/z* (%) = 323 (M^+, 26.5), 306 (17), 263 (41), 207 (90), 165 (33), 137 (43.3), 61 (75). Anal. Calcd. for $C_{16}H_{25}N_3O_4$ (323.18): C, 59.42; H, 7.79; N, 12.99%. Found: C, 58.60; H, 7.68; N, 12.29.

***N*-cyclohexyl-2-(hexahydro-2,4,6-trioxopyrimidin-5-yl)-2-methyl propanamide (4d).** Colorless powder (0.17g, 60%): m.p.: 167 °C, IR (KBr) (ν_{max}/cm^{-1}) 1585 (NH bend), 1695 (4C=O), 3161, 3430 (3NH). ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.14- 2.17 (16H, 5CH_2 of cyclohexyl and 2Me), 3.45 (1H, s, CH), 3.97 (1H, tt, *J* = 12.3, *J* = 3.75 Hz, CH-NH), 5.68, 8.10, 10.27 (3H, s, 3NH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.05 (2Me), 24.93, 25.41, 25.70, 28.58, 28.74 (5CH_2 of cyclohexyl), 43.63 (*C*Me$_2$), 52.21 (CH-NH), 57.59 (CH), 154.26, 167.92, 172.92, 180.92 (4C=O). MS *m/z* (%) = 295 (M^+, 4), 214 (100), 171 (40), 154 (60), 128 (70), 83 (85), 61 (90). Anal. Calcd. for $C_{14}H_{21}N_3O_4$ (295.15): C, 56.94; H, 7.17; N, 14.23%. Found: C, 58.07; H, 7.12; N, 13.53%.

***N*-cyclohexyl-1-(hexahydro-2,4,6-trioxopyrimidin-5-yl) cyclohexane carboxamide (4e).** Colorless powder (0.14 g, 40%): m.p.: 187 °C; IR (KBr) (ν_{max}/cm^{-1}) 1557 (NH bend), 1694, 1713, 1776 (4 C=O), 3145, 3410 (3NH). ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.22- 2.14 (20H, 10CH_2 of 2cyclohexyl), 3.51 (1H, s, CH), 3.96 (1H, tt, *J* = 12.2, *J* = 3.76 Hz, C*H*-NH), 5.40, 8.15, 10.45 (3H, s, 3NH).^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.99, 22.09, 24.93, 25.01, 25.73, 25.80, 27.52, 28.44, 28.83, 35.7 (10CH_2 of 2cyclohexyl), 48.17 (C of cyclohexyl), 52.06 (CH-NH), 58.15 (CH), 154.50, 168.91, 172.73, 181.02 (4 C=O). MS *m/z* (%) = 335 (M^+, 16), 254 (79), 211 (27), 194 (86), 84 (100), 61 (72). Anal. Calcd. for $C_{17}H_{25}N_3O_4$ (335.18): C, 60.88; H, 7.51; N, 12.53%. Found: C, 59.73; H, 8.11; N, 12.14%.

***N*-cyclohexyl-1-(hexahydro-2,4,6-trioxopyrimidin-5-yl) cycloheptane carboxamide (4f).** Colorless powder (0.14 g, 40%): m.p.: 187 °C; IR (KBr) (ν_{max}/cm^{-1}) 1571 (NH bend), 1696, 1777 (4C=O), 3146, 3329, 3424 (3NH). ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.21- 2.12 (22 H, 10CH_2 of cyclohexyl and cycloheptyl), 3.46 (1H, s, CH), 3.94 (1H, tt, *J* = 12.4, *J* = 3.3 Hz, CH-NH), 5.41, 8.13, 10.20 (3H, s, 3NH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 23.40, 23.54, 24.99, 25.76, 28.55, 28.71, 29.69, 29.97, 30.30, 31.69, 38.86 (5CH_2 of cyclohexyl and 6CH_2 of cycloheptyl), 50.77 (C of cycloheptyl), 52.04 (CH-NH), 59.96 (CH), 154.20, 168.56, 172.83, 181.73 (4C=O). MS *m/z* (%) = 349 (M^+, 21), 254 (79), 268 (38), 197 (86), 84 (100), 61 (52). Anal. Calcd. for $C_{18}H_{27}N_3O_4$ (349.2): C, 61.87; H, 7.79; N, 12.03%. Found: C, 61.53; H, 7.36; N, 12.04%.

***N*-cyclohexyl-1-(hexahydro-2,4,6-trioxopyrimidin-5-yl) cyclopentanecarboxamide (4g).** Colorless powder (0.21 g, 67%): m.p.: 178 °C; IR (KBr) (ν_{max}/cm^{-1}) 1575 (NH bend), 1695 (4C=O), 3127, 3332, 3440 (3NH). ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.22- 2.14 (18H, 5 CH_2 of 2cyclohexyl and 4CH_2 of cyclopentyl), 3.53 (1H, s, CH), 3.97 (1H, tt, *J* = 12.3, *J* = 3.7 Hz, CH-NH), 5.48, 8.12, 10.33 (3H, s, 3NH). ^{13}C NMR

(75.5 MHz, $CDCl_3$): δ = 24.98, 25.45, 25.75, 28.62, 28.74, 32.53, 38.97 (CH_2 of cyclohexyl and CH_2 of cyclopentyl), 52.21 (C of cyclopentyl), 53.62 (CH-NH), 58.54 (CH), 154.28, 168.68, 172.91, 181.44 (4 C=O). MS *m/z* (%) = 321 (M^+, 5), 240 (100), 197 (50), 180 (68.5), 152 (41), 109 (55), 61(90). Anal. Calcd. for $C_{16}H_{23}N_3O_4$ (321.17): C, 59.80; H, 7.21; N, 13.08%. Found: C, 59.87; H, 7.04; N, 13.07%.

***N- tert*-butyl -1-(hexahydro-2,4,6-tri oxopyrimidin-5-yl) cyclopentane carboxamide (4h).** Colorless powder (0.23 g, 78%): m.p.: 172 °C; IR (KBr) (ν_{max}/cm^{-1}): 1576 (NH bend), 1699 (4C=O), 3155, 3341, 3453 (3NH). ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.58 (9H, s, CMe_3), 1.62-2.09 (8H, m, $4CH_2$ of cyclopentyl), 3.48 (1H, s, CH), 5.68, 8.13, 10.48 (3H, s, 3NH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 25.33, 25.70, 31.98, 39.14 ($4CH_2$ of cyclopentyl), 28.22 (CMe_3), 53.76 (C of cyclopentyl), 58.93 (CMe_3), 59.53 (CH), 154.67, 169.12, 173.60, 182.42 (4 C=O). MS *m/z* (%) = 295 (M^+, 100), 235 (34), 208 (100), 61 (89). Anal. Calcd. for $C_{14}H_{21}N_3O_4$ (295.15): C, 56.94; H, 7.17; N, 14.23%. Found: C, 56.89; H, 7.35; N, 14.05%.

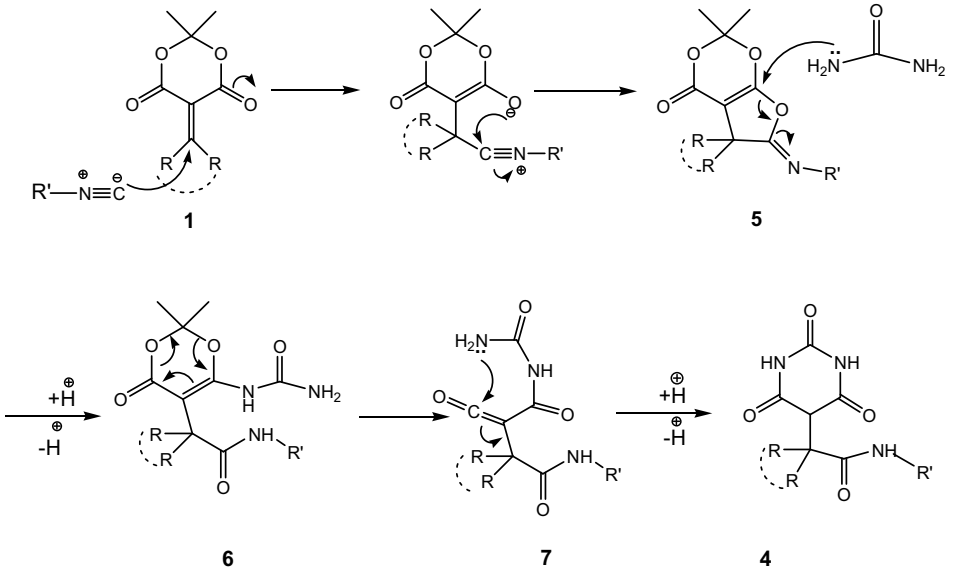
RESULTS AND DISCUSSION

Three-component reaction of alkylidene-substituted Meldrum's acid **1**, alkyl isocyanide **2** and urea **3** in DMSO/CH_2Cl_2 and at room temperature afforded new derivatives of barbituric acid **4**. The ^{1}H and ^{13}C NMR spectrum of the crude product clearly indicated the formation of **4**. No product other than **4** could be detected by NMR spectroscopy. The structures of these products were deduced from their elemental analyses and their IR, ^{1}H NMR, ^{13}C NMR and Mass spectra data.

The IR spectrum of **4a** showed three bands at 3431, 3325 and 3139 cm^{-1} arising from NH stretching. And also include C=O stretching that appeared at 1694 cm^{-1}. ^{1}H NMR spectrum of **4a** exhibited four singlet sharp lines readily recognized as arising from two methyl (δ = 1.25 and 1.43 ppm), *tert*-butyl (δ = 1.59 ppm) and methine (δ = 3.37 ppm) protons. Also, three broad singlets (δ = 5.55, 8.09 and 10.20 ppm) which belonged to three NH amide and imide groups.

The ^{1}H decoupled ^{13}C NMR spectrum of **4a** showed ten distinct resonances in agreement with the suggested structure. The mass spectra of **4a** showed molecular ion peaks at appropriate *m/z* values. The ^{1}H and ^{13}C NMR spectra of **4b-i** have similar signals to **4a** except for the differences in the proton or carbon-13 resonances of the substituent.

On the basis of what we know about the chemistry of isocyanide [1-3], and according to our previous reports [18-20], a plausible mechanism of the three-component reaction between alkylidene-substituted Meldrum's acid **1**, isocyanide **2**, and urea **3** is presented in Scheme 2. The first step of the



Scheme 2. Proposed mechanism for the reaction

mechanism involves the [4+1] cycloaddition reaction of the electron-deficient heterodiene moiety of alkylidene-substituted Meldrum's acid with the isocyanide, producing an iminolactone intermediate **5**. Then, conjugate addition of urea to enone moiety of **5**, results in the opening of a five-membered ring to form intermediate **6**, which eliminates acetone to form ketene **7** by well-precedented [21] electrocyclic ring opening of *O*-alkylated Meldrum's acids. Nucleophilic attack of urea through the second nitrogene atom to the ketene intermediate **7** produces the final product **4**.

CONCLUSIONS

We have introduced an efficient and simple method for the synthesis of new barbituric acid derivatives. This method enjoys a mild reaction condition, moderate to good yield, a fast and convenient one-pot three-component reaction which make it offer a better alternative to the conventional methods.

REFERENCES

[1] R. Rastaldo, C. Penna, P. Pagliaro, Life Sci. 69 (2001) 729.

[2] M.E. Wolff, Burger's Medicinal Chemistry and Drug Discovery, Wiley, New York, 1997.

[3] A. Oliva, G. Zimmermann, H.-W. Krell, Barbituric Acid Derivatives with Antimetastatic and Antitumor Activity, Intetnational Patent WO 98/58925.

[4] M. Gleason, R. Gosselin (Eds.), Clinical Toxicology of Commercial Products, Williams & Wilkins Co, Baltimore, MA, 1963, pp. 26-27.

[5] R. Acheson, Introduction to the Chemistry of Hetero-Cyclic Compounds, Interscience Publishers, New York, 1967, pp. 339-342.

[6] D. Brown, R. Evans, T. Batterham, The Pyrimidines Supplement I, Wiley Interscience, New York, 1970, pp. 199-201.

[7] W. Zhou, M.J. Kurth, Polymer 42 (2000) 345.

[8] J. Zhu, H. Bienaymé (Eds.), Multicomponent Reactions, Wiley-VCH, Verlag GmbH & Co. KGaA, Weinheim, 2005.

[9] A. Dömling, Chem. Rev. 106 (2006) 17.

[10] D.S. Tan, Nature Chemical Biology 1 (2005) 74.

[11] M.D. Burke, S.L. Schreiber, Angew. Chem. Int. Ed. Engl. 43 (2004) 46.

[12] I. Ugi, Isonitrile Chemistry, Academic Press, London, 1971.

[13] H. McNab, Chem. Soc. Rev. 7 (1978) 345.

[14] B.C. Chen, Heterocycles 32 (1991) 529.

[15] A.S. Ivanov, Chem. Soc. Rev. 37 (2008) 789.

[16] J. Gerencser, G. Dorman, F. Darvas, QSAR Comb. Sci. 5-6 (2006) 439.

[17] A.-A.M. Gaber, H. McNab, Synthesis 14 (2001) 2059.

[18] I. Yavari, A. Habibi, M.R. Hosseini-tabatabaei, Monatshe. Chem. (2003) 1.

[19] I. Yavari, A. Habibi, Synthesis 7 (2004) 989.

[20] A. Habibi, E. Sheikhosseini lory, A. Shockravi, Tetrahedron Lett. 50 (2009) 1075.

[21] M. Sato, H. Ban, C. Kaneko, Tetrahedron Lett. 38 (1997) 6689.