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The reaction of 1, 3-dicarbonyl compounds with various α-haloketones in the presence of ammonium acetate in aqueous ethanol

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Abstract: The reaction of 1, 3-dicarbonyl compounds with ethyl bromopyruvate thus led to dihydrofurans in good yields. Dihydrofurans were converted to the corresponding furan derivatives in the presence of *p*-toluenesulfonic acid (*p*-TSA). Under similar conditions, however, the reactions of α-haloketones 3-chloropentane-2, 4-dione and methyl 2-chloro-3-oxobutanoate with 1, 3-dicarbonyl compounds led directly to fused furan derivatives in good yields. While, the reaction of phenacyl bromides with 1, 3-dicarbonyl compounds led to either esters or α-substituted acetophenones in moderate yields.

Keywords: Furan, Dihydrofuran, Feist-Benary reaction, Ethyl bromopyruvate, Phenacyl bromide, 1, 3-Dicarbonyl compound.

Introduction

The Feist-Benary reaction involves condensation of 1, 3-dicarbonyl compounds with *α*-haloketones to produce substituted furans [1-2]. However, running the reaction under new conditions allowed the isolation of a dihydrofuran intermediate. Several groups studied the mechanism and scope of this "interrupted" Feist-Benary reaction [3-4]. [4]The most part of publications are aimed at studying of its catalytic asymmetric versions [5-8]. Dihydrofurans are constituents of many natural products arising from plants and marine organisms with promising biological activities [10-12].The use of water as a solvent for organic transformation offers several "green chemistry" benefits [13-14]. Water is a "green solvent" with much to contribute to this steadily growing field. However, for organic synthetic chemist to put components in solution and frequently approach organic reaction like-needs-like perspective, it is less important because water is traditionally not a popular choice of solvent.

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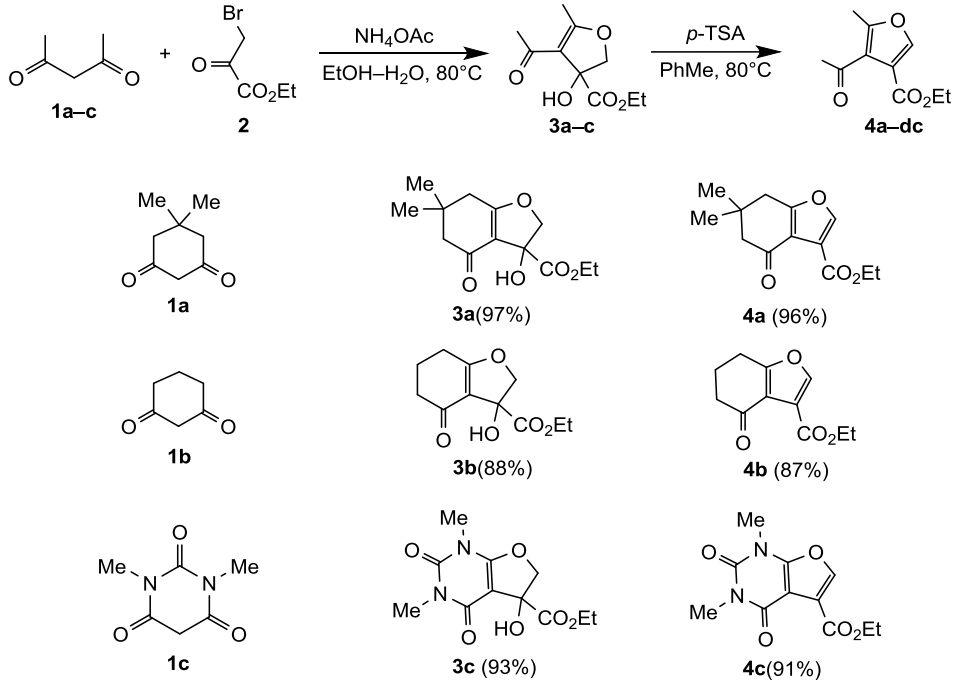
As a part of our current studies on the development of new routes to heterocyclic synthesis in water [15-17], we wish to report an efficient synthesis of functionalized dihydrofuranes and furans from the reaction of 1, 3-dicarbonyl compounds with *α*-haloketones in the presence of ammonium acetate in H_2O/EtOH (30:70). Under similar conditions, the reaction of phenacyl bromides with 1, 3-dicarbonyl compounds led to either esters or α-substituted acetophenones in moderate yields.

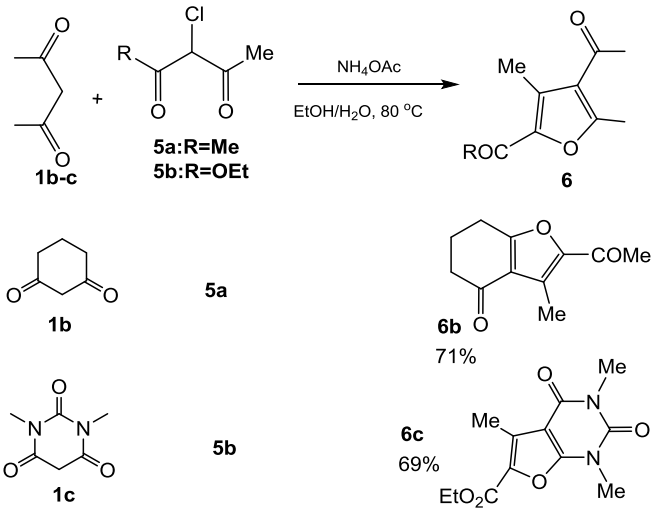
Results and discussion

The reaction of 1, 3-dicarbonyl compounds **1a-c** with ethyl bromopyruvate **2** in the presence of ammonium acetate in H_2O/EtOH (30:70) thus led to dihydrofurans **3** in good yields. Dihydrofurans **3a-c** were converted to the corresponding furan derivatives **4a-c** in the presence of *p*-toluenesulfonic acid (*p*-TSA), (Scheme **1**). Under similar conditions, the reactions of α-haloketones 3-chloropentane-2,4-dione and methyl 2-chloro-3-oxobutanoate **5** with 1,3-dicarbonyl compounds **1b-c** led directly to fused furan derivatives

6b-c in good yields, (Scheme **2**). And the reaction of phenacyl bromides **7** with 1,3-dicarbonyl compounds **1a-c** led to either esters **8a-a'-b-b'** or α-substituted acetophenones **9c-c'** in moderate yields, (Scheme **3**). The separation of compounds in this method are easier than in other described methods, and the reaction is more environment-friendly because of solvent (aqueous ethanol), in addition, the yields of the products are higher.



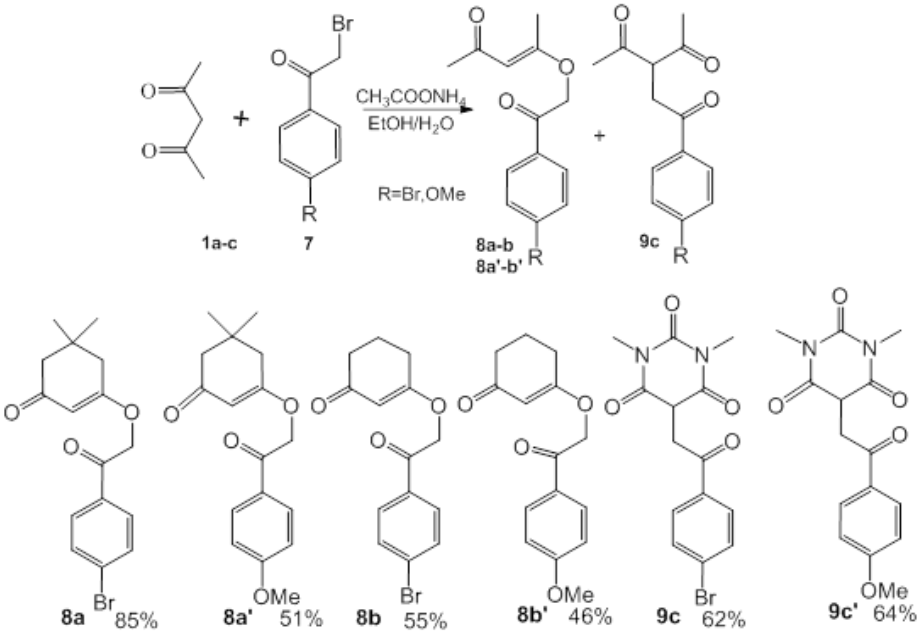
Scheme 1: Formation of compounds **3** and **4.**



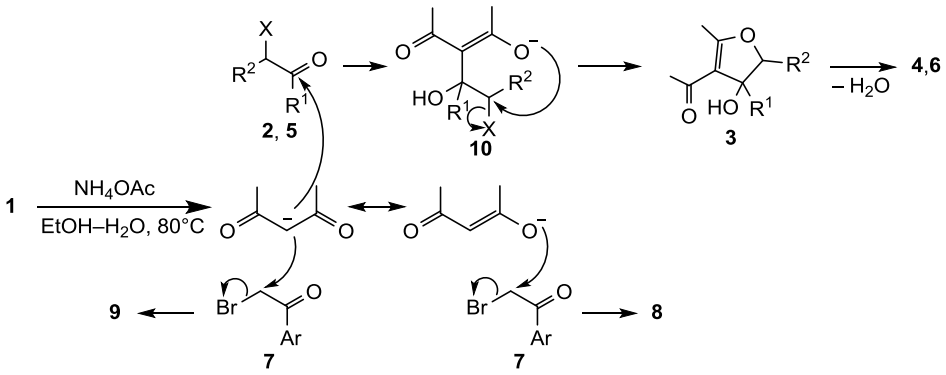
Scheme 2: Formation of compounds 6.

Structures **3a-c**, **4a-c** ,**6b-c**, **8a**–**b**, **8a'**–**b'**, **9a**,**b** were assigned to the isolated products on the basis of their elemental analyses, as well as, their IR, ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry data. The ^{1}H NMR spectrum of compound **8a** in $CDCl_3$ showed five sharp singlets arising from CMe_2 (δ 1.10 ppm), CH_2 (δ 2.23, 2.44 and 5.10 ppm), and methine (δ 5.20 ppm) protons. Mechanistically, the reaction starts with the formation of a 1:1 adduct **10** between the 1,3-dicarbonyl compound **1** and α-haloketones, which undergoes intramolecular cyclization reaction to produce dihydrofuranes of type **3**, which is converted to furans by elimination of H_2O (Scheme **4**).

When the reaction was performed in the presence of phenacyl bromides **7,** alkylation products at carbon or oxygen atoms (**8** or **9**, respectively) were obtained. In fact, In **1** compounds, the enolation form of 1, 3-diketons is dominate and the electron density is concentrated on O atom. Thus, O-alkylation was done, but in **1d** compound the electron density is concentrated on C atom between tow carbonyl groups, because of resonance of electrons of N atom with carbonyl group, thus C-alkylation was done. Also, carbonyl group in phenacyl bromide is involved by resonance with Ar-ring, thus the nucleopile will attack to C-α (connected to halogen).



Scheme 3: Formation of compounds 8 and 9.



Scheme 4: Proposed mechanism for the formation of compounds **4,6,8,9**.

Conclusion

The reaction between 1,3-dicarbonyl compounds and ethyl bromopyruvate, ethyl 2-chloroacetoacetate or 3-chloroacetylacetone in the presence of ammonium acetate in aqueous ethanol leads to highly substituted dihydrofurans and furans. and the reaction between 1,3-dicarbonyl compounds and phenacyl bromide, under similar conditions leads to carbon alkylation and oxygen alkylation of 1,3-dicarbonyl. This procedure has the advantage that not only the reaction is performed under environment-friendly conditions, but the reactants are readily available. The simplicity of the present procedure makes it an interesting alternative to complex multistep approaches.

Experimental

IR spectra were recorded on a Shimadzu IR-460 spectrometer in KBr. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AvanceDRX-300 instrument 300 and 75 MHz, respectively in $CDCl_3$ and acetone-d_6 with TMS as internal standard. Electron ionization mass spectra were recorded on a Finnigan MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were carried out on a Heraeus CHN-O-Rapid analyzer. Melting points were determined on an Electrothermal 9100 apparatus. Preparative column chromatography was performed on silica gel (Merck 230–400 mesh). All chemicals were purchased from Fluka and used without further purification.

*General procedure for synthesis of compounds **3:***

A mixture of the 1, 3-dicarbonyl compound **1a-c** (2 mmol) and ammonium acetate (0.14 g, 2 mmol) in of EtOH–H_2O, 7:3, (5 ml) was stirred at 80°C for about 1 h. Then, ethyl bromopyruvate (**2**) (0.23 g, 2 mmol) was added to the reaction mixture, and the stirring was continued for 3 h. The solvent was removed under reduced pressure, and the viscous residue was purified by column chromatography using *n*-hexane–AcOEt, 4:1, as eluent. 3a-b are reported Ref [4c].

Ethyl 5-hydroxy-1,3-dimethyl-2,4-dioxo-1, 2, 3, 4, 5,6-hexahydrofuro [2,3-d] pyrimidine-5-carboxylate (**3c**):

Yield: 0.51 g (93%), white powder, mp.164-167˚C. IR (KBr): 3438, 2924, 2359, 1644, 1463, 1388, 1114. ^{1}H-NMR: 1.34 (*t*, ^3J = 6.9, Me), 3.30 (*s*, Me), 3.40 (*s*, Me), 4.19 (br *s*, OH), 4.36-4.39 (*m*, CH_2O), 4.84 (*d*, ^2J = 9.9, CH_2), 5.12 (*d*, ^2J = 9.9, CH_2). ^{13}C-NMR: 14.4, 28.2, 29.8 (3 Me), 63.7 (OCH_2), 80.2 (CH_2), 84.4, 91.7, 151.7 (3 C), 159.3, 164.2, 171.9 (3 C=O). Anal. Calcd. For $C_{11}H_{14}N_2O_6$: C, 48.89; H, 5.22; N, 10.37. Found: C, 48.05; H, 5.32; N, 10.89%.

*General procedure for synthesis of compounds **4**:*

To a stirred solution of **3a-c** (2 mmol) in 10 mL of toluene was added (0.34 g, 0.5 mmol) of p-toluenesulfonic acid and stirred at 80 ˚C for 6 h. The solvent was removed under reduced pressure, and the residue was separated by silica gel (Merck 230–400 mesh) column chromatography using hexane:AcOEt (6:1) mixture as eluent to give compound **4a-c**. 4a-b are reported Ref [4c].

Ethyl 1,3-dimethyl-2,4-dioxo-1, 2, 3,4-tetrahydrofuro [2,3-d] pyrimidine-5-carboxylate (**4c**)*:*

Yield: 0.46 g (91%), white powder, mp.140-142˚C. IR (KBr): 3434, 2925, 1747, 1671, 1524, 1260, 1101, 1017. ^{1}H-NMR: 1.40 (*t*, ^3J = 7.1, Me), 3.43 (*s*, Me), 3.58 (*s*, Me), 4.39 (*q*, ^3J = 7.1, OCH_2), 7.80 (*s*, CH). ^{13}C-NMR: 14.6, 29.0, 29.9 (3 Me), 61.8 (OCH_2), 94.9, 119.0, 150.6 (3 C), 143.7 (CH), 156.8, 156.9, 161.3 (3 C=O). EI-MS, *m/z* (%): 252 (M^+, 100), 195 (91), 167 (77), 123 (28), 95 (46), 66 (46). Anal.Calcd. For $C_{11}H_{12}N_2O_5$: C, 52.38; H, 4.80; N, 11.11. Found: C, 52.32; H, 4.71; N, 11.21%.

*General procedure for synthesis of compounds **6:***

A mixture of the 1, 3-dicarbonyl compound **1b-c (**2 mmol) and ammonium acetate (0.14 g, 2 mmol) in 5 mL of H_2O/EtOH (30:70) was stirred at 80 °C for 1 h. Then, α-haloketone **5a-b (**2 mmol) was added to the reaction mixture was stirred at 80 ˚C for 3 h. The solvent was removed under reduced pressure and the viscous residue was purified by column chromatography on silica gel (Merck 230–400 mesh) using hexane-AcOEt (4:1) as eluent to give the product **6b-c**.

2-Acetyl-3-methyl-6, 7-dihydrobenzofuran-4(5H)-one (**6b**):

Yield: 0.32 g (%71), white powder, mp.114-116˚C. IR: (KBr): 2922, 1734, 1677, 1218, 766. ^{1}H-NMR: 2.20 (*m*, CH_2), 2.42 (*s*, Me), 2.47 (*t*, ^3J = 7.5, CH_2), 2.50 (*s*, Me), 2.97 (*t*, ^3J = 6.0, CH_2). ^{13}C-NMR: 9.9, 22.3 (2 Me), 23.6, 26.9, 38.4 (3 CH_2), 123.1, 128.9, 154.6, 169.2 (4 C), 188.3, 194.0 (2 C=O). EI-MS, *m/z* (%): 192 (M^+, 53), 149 (64), 71 (53), 57 (100), 43 (75). Anal.Calcd. For $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 66.89; H, 6.39%.

Tetrahydrobenzofuro[2,3-d]pyrimidine-6-carboxylate (**6c**):

Yield: 0.37 g (%69), white powder, mp.158-161˚C. IR: 2924, 1683, 1636, 1344, 770. ^{1}H-NMR: 1.41 (*t*, ^3J = 7.1, Me), 2.65 (*s*, Me), 3.40 (*s*, Me), 3.62 (*s*, Me), 4.39 (*q*, ^3J = 7.1, CH_2O). ^{13}C-NMR: 10.8, 14.7, 28.5, 31.8 (4 Me), 61.5 (OCH_2), 131.6, 137.0, 150.9, 156.1 (4 C), 158.8, 158.9, 170.2 (3 C=O). EI-MS, *m/z* (%): 266 (M^+, 100), 209 (91), 181 (77), 137 (28), 109 (46), 80 (46). Anal.Calcd. For $C_{12}H_{14}N_2O_5$: C, 54.13; H, 5.30; N, 10.52. Found: C, 55.16; H, 5.51; N, 10.21%.

*General procedure for synthesis of compounds **8** and **9:***

A mixture of 1,3-diketon **1a-c (** 2 mmol) and ammonium acetate (0.14 g, 2 mmol) in H_2O/EtOH (30:70) (3 mL) was stirred at 80 °C for about an hour.

Upon completion, monitored by TLC, Phenacyl bromide **7 (**2 mmol) was added to the reaction mixture and completed within 3 h. The solvent was removed under reduced pressure and the viscous residue was purified by column chromatography on silica gel (Merck 230–400 mesh) using n-hexane-EtOAc (6:1) as eluent to give the product **8a-a'-b-b'** and **9c-c'**.

2-(2-(4-Bromophenyl)-2-oxoethyl)-3-hydroxy-5,5-dimethylcyclohex-2-enone (**8a**):

Yield: 0.57 g (85%), white powder, mp.177-179˚C. IR (KBr): 1709, 1601, 1383, 1208. ^{1}H-NMR: 1.10 (*s*, 2 Me), 2.23 (*s*, CH_2), 2.44 (*s*, CH_2), 5.10 (*s*, CH_2O), 5.20 (*s*, CH), 7.65 (*d*, ^3J = 8.5, 2 CH), 7.77 (*d*, ^3J = 8.5, 2 CH). ^{13}C-NMR: 28.6 (2 Me), 33.0 (C), 42.9, 51.1 (2 CH_2), 70.2 (OCH_2), 102.8 (CH), 129.7, 132.7 (4 CH), 129.9, 133.1, 175.4 (3 C), 191.3, 199.6 (2 C=O). EI-MS, *m/z* (%): 338 (M^++ 2, 19), 336 (M^+, 17.8), 323 (43), 321 (41), 185 (100), 183 (98), 157 (13), 155 (12.5). Anal. Calcd. For $C_{16}H_{17}BrO_3$: C, 57.33; H, 5.01. Found: C, 56.99; H, 5.08%.

3-Hydroxy-2-(2-(4-methoxyphenyl)-2-oxoethyl)-5, 5-dimethylcyclohex-2-enone (**8a'**):

Yield: 0.29 g (51%), white powder, mp.165-168˚C. IR (KBr): 1741, 1708, 1600, 1316, 1172. ^{1}H-NMR: 1.05 (*s*, 2 Me), 2.23 (*s*, CH_2), 2.30 (*s*, CH_2), 3.88 (*s*, OMe), 5.15 (*s*, CH), 5.30 (*s*, OCH_2), 6.97 (*d*, ^3J = 8.8, 2 CH), 7.90 (*d*, ^3J = 8.8, 2 CH). ^{13}C-NMR: 28.7 (2 CH_3), 32.1 (C), 43.7, 50.7 (2 CH_2), 55.9 (OCH_3), 69.9 (OCH_2), 107.2 (CH), 114.5, 132.9 (4 CH), 128.4, 165.2, 175.4 (3 C), 196.7, 202.5 (2 C=O). EI-MS, *m/z* (%): 288 (M^+, 25), 273 (41), 136 (100), 108 (18). Anal. Calcd. For $C_{17}H_{20}O_4$: C, 70.81/71.21; H, 6.99/6.91. Found: C, 71.21; H, 6.91%.

3-(2-(4-Bromophenyl) -2-oxoethoxy) cyclohex -2-enone (**8b**)*:*

Yield: 0.34 g (55%), white powder, mp.179-181˚C. IR (KBr): 1701, 1637, 1392, 1222. ^{1}H-NMR: 2.04 (*m*, CH_2), 2.38 (*t*, ^3J = 7.6, CH_2), 2.50 (*t*, ^3J = 6.2, CH_2), 5.14 (*s*, CH_2O), 5.28 (*s*, CH), 7.67 (*d*, ^3J = 7.7, 2 CH), 7.79 (*d*, ^3J = 7.7, 2 CH). ^{13}C-NMR: 21.5, 29.1, 37.1 (3 CH_2), 70.1 (OCH_2), 104.1 (CH), 129.7, 132.8 (4 CH), 130.0, 132.6, 177.2 (3 C), 191.3, 199.8 (2 C=O). EI-MS, *m/z* (%): 310 (M^++2, 25), 308 (M^+, 27), 185 (98), 183 (100), 157 (13), 155 (16). Anal. Calcd. For $C_{14}H_{13}BrO_3$: C, 54.39; H, 4.24. Found: C, 55.21; H, 4.38%.

3-(2-(4-Metoxyphenyl) -2-oxoethoxy) cyclohex -2-enone (**8b'**):

Yield: 0.24 g (46%), white powder, mp.128-130˚C. IR (KBr): 1722, 1683, 1591, 1380, 1179 cm^{-1}. ^{1}H-NMR: 1.92-194 (*m*, CH_2), 2.34 (*t*, ^3J = 5.8, CH_2), 2.39 (*t*, ^3J = 5.5, CH_2), 3.85 (*s*, OCH_3), 5.15 (*s*, CH_2O), 5.28 (*s*, CH), 6.86 (*d*, ^3J = 8.8, 2 CH), 7.70 (*d*, ^3J = 8.8, 2 CH). ^{13}C-NMR: 20.3, 33.1, 40.1 (3 CH_2), 55.7 (OCH_3), 70.0 (OCH_2), 100.2 (CH), 113.5, 130.0 (4 CH), 115.6, 132.4, 164.8 (3 C), 191.1, 202.0 (2 C=O). EI-MS, *m/z* (%) = 260 (M^+, 23), 136 (100), 108 (20). Anal. Calcd. For $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found: C, 69.11; H, 6.08%.

5-(2-(4-Bromophenyl)-2-oxoethyl)-1,3-dimethylpyrimidine-2, 4,6(1H, 3H, 5H)-trione (**9c**)*:*

Yield: 0.44 g (62%), white powder, mp.178-180˚C. IR (KBr): 1660, 1588, 1381. ^{1}H-NMR: 3.37 (*s*, 2 Me), 3.61 (*t*, ^3J = 2.4, CH), 4.01 (*d*, ^3J = 2.4, CH_2), 7.64 (*d*, ^3J = 7.5, 2 CH) ,7.81 (*d*, ^3J = 7.5, 2 CH). ^{13}C-NMR: 29.2 (2 Me), 38.0 (CH_2), 44.8 (CH), 129.7, 134.4 (4 CH), 130.1, 132.5 (2 C), 152.0 (C=O), 168.2 (2 C=O), 196.3 (C=O). EI-MS, *m/z* (%): 354 (M^++2, 35), 352 (M^+, 34), 185 (97), 183 (100), 157 (14), 155 (17). Anal. Calcd. For $C_{14}H_{13}BrN_2O_4$: C, 47.55; H, 3.70; N, 7.45. Found: C, 46.61; H, 3.71; N, 7.93%.

5-(2-(4-Methoxyphenyl)-2-oxoethyl)-1,3-dimethylpyrimidine-2, 4,6(1H, 3H, 5H)-trione (**9c'**):

Yield: 0.44 g (64%), white powder, mp 167-169˚C. IR (KBr):1682, 1600, 1455, 1170. ^{1}H-NMR: 3.37 (*s*, 2 Me), 3.56 (*t*, ^3J = 3.6, CH), 3.89 (*s*, OCH_3), 4.01 (*d*, ^3J = 3.6, CH_2), 6.94 (*d*, ^3J = 8.5, 2 CH), 7.89 (*d*, ^3J = 8.5, 2 CH). ^{13}C NMR: 29.3 (2 Me), 37.0 (CH_2), 47.9 (CH), 55.9 (OMe), 114.3, 130.9 (4 CH), 128.5, 164.0 (2 C), 164.8 (C=O), 169.7 (2 C=O), 196.1 (C=O). EI-MS, *m/z* (%): 304 (M^+, 33), 136 (100), 108 (19). Anal. Calcd. For $C_{15}H_{16}N_2O_5$: C, 59.20; H, 5.30; N, 8.88. Found: C, 59.21; H, 5.30; N, 9.21%.

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