An Efficient Synthesis of *N*-Substituted-3-aryl-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)propanamides by Four-component Reaction in Aqueous Medium

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A mild and efficient synthesis of *N*-substituted-3-aryl-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)propanamides via four-component reaction of an aldehyde, amine, Meldrum's acid and 5,5-dimethylcyclohexane-1,3-dione in the presence of benzyltriethylammonium chloride (TEBAC) in aqueous medium is described. This method has the advantages of accessible starting materials, good yields, mild reaction conditions and eco-friendliness.

Keywords amide, four-component reaction, aqueous medium, synthetic method

Introduction

The amide bond plays an important role in the elaboration and composition of biological and chemical systems.[1] Amides are traditionally synthesized by the reaction of amines with activated carboxyl acid derivatives.[2] Recently there has been considerable interest in the synthesis of amides. The Staudinger reaction,[3] the Beckmann rearrangement,[4] Schmidt reaction,[5] aminocarbonylation of alkenes,[6] haloarenes[7] and alkynes,[8] oxidative amidation of alhydes,[9] hydrative amide synthesis with alkynes,[10] and the amidation of thio acids with azides[11] were used to synthesize amides. Jia *et al.*[12] recently reported Samarium-mediated facile method for the formation of amide bonds by the reaction of acyl chlorides and amines. However, although these methods have successfully led to a large library synthesis of amides, many of them still suffer from drawbacks such as using harmful organic synthesis, unsatisfactory yields and occurrence of side reactions. Therefore, a method with higher yield and environment-friendly manipulation needs to be developed.

Science Breslow demonstrated hydrophobic efforts could strongly enhance the rate of some organic reactions and rediscovered the use of water as solvent in organic synthesis in 1980s,[13] there has been a growing recognition that water has become an attractive medium for many organic reactions, such as Diels-Alder reactions,[14] Claisen rearrangement reactions,[15] Reformatsky reactions[16] and Pinacol-coupling reactions,[17] not only for the advantages concerning the avoidance of expensive drying reactions, catalysts and solvents, but also for some unique reactivity and selectivity.[18] On the other hand, organic reactions in water without using harmful organic solvents is one of the current focuses especially in the environmentally conscious society, because water is abundant, nontoxic and environment-friendly when compared with organic solvents used accordingly.

Multi-component reactions (MCRs), in which multiple reactions are combined into the synthetic operation have been used extensively to form carbon-carbon bonds in the synthetic chemistry.[19] Such reactions offer a wide range of possibilities for the efficient construction of highly complex molecules in a single procedural step, thus avoiding the complicated purification operations and allowing savings of both solvents and reagents. In the past decade, there has been tremendous development in three- and four-component reactions, and great efforts continue to be made to develop new MCRs.[20]

As a continuation of our interest in green synthesis and our previous work[21] on multi-component reaction in aqueous medium, herein we report a green, one-pot, efficient synthesis of novel propanamide derivatives in aqueous medium.

Results and discussion

When the four-component of aromatic aldehyde (**1**), Meldrum's acid (**2**), 5,5-dimethylcyclohexane-1,3-dione (**3**) and amines (**4**) were treated in water in the presence

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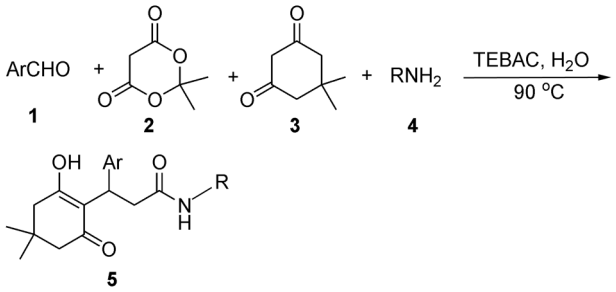
of TEBAC at 90 ℃ for 8—20 h, the desired product, *N*-substituted-3-aryl-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)propanamides (**5**) were obtained (Scheme 1).

Scheme 1



A range of novel valuable structures of **5** were synthesized in good to excellent yields by simply four-component reaction in aqueous media. The results are summarized in Table 1.

Table 1 Synthesis of compounds **5** in aqueous media

Entry	Product	Ar	R	Time/h	Yield/%
1	**5a**	4-ClC_6H_4	4-$CH_3C_6H_4$	8	95
2	**5b**	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	12	97
3	**5c**	4-$CH_3OC_6H_4$	4-$CH_3C_6H_4$	20	97
4	**5d**	4-$CH_3C_6H_4$	4-$CH_3OC_6H_4$	15	93
5	**5e**	4-BrC_6H_4	4-$CH_3OC_6H_4$	17	92
6	**5f**	4-ClC_6H_4	C_6H_5	20	98
7	**5g**	4-$CH_3C_6H_4$	C_6H_5	12	97
8	**5h**	3,4-$(CH_3)_2C_6H_3$	C_6H_5	12	96
9	**5i**	3,4-$(CH_3O)_2C_6H_3$	C_6H_5	10	95
10	**5j**	4-ClC_6H_4	3-ClC_6H_4	20	95
11	**5k**	4-$CH_3OC_6H_4$	3-ClC_6H_4	20	94

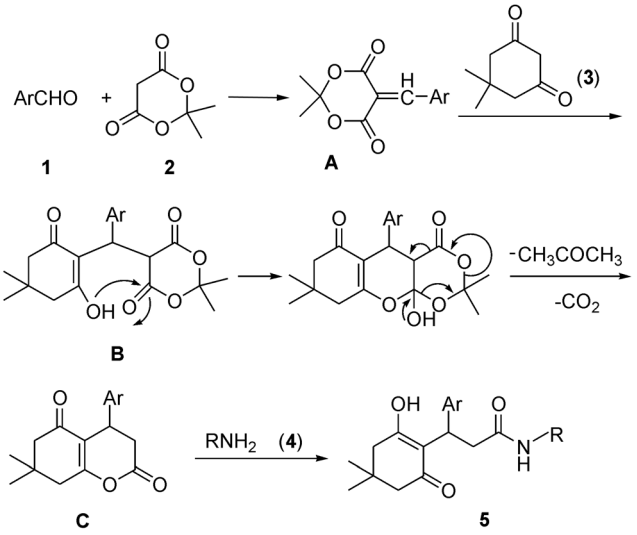
As shown in Table 1, we were pleased to find that the method was applicable to a broad substrate scope on both substituted aldehydes and amines. It can be seen that this protocol can be applied to weak electron-withdrawing groups (such as halide groups) or electron-donating groups (such as alkyl groups), which highlighted the wide scope of this reaction. So we concluded that no obvious effects from the electronic or nature of the aromatic ring substrates were observed in the above reactions.

All the products were characterized by ^{1}H NMR, IR and HRMS spectra.

Although the mechanism of the reaction has not yet been established, a possible explanation is proposed in Scheme 2.

The reaction might proceed via sequential condensation, addition, cyclization, and elimination. First, a Knoevenagel condensation between aldehydes **1** and Meldrum's acid **2** afforded intermediate **A**. The Michael addition of **A** with 5,5-dimethylcyclohexane-1,3-dione (**3**) would then furnish the intermediate product **B**, which subsequently underwent intramolecular cyclization and then released acetone and carbon dioxide to give intermediate product **C**. The intermediate product **C** was then attacked by amine **4** to give the product **5**.

Scheme 2 Possible mechanism for the formation of product **5**



In summary, a series of *N*-substituted-3-aryl-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)propanamides were synthesized via four-component reaction of aldehyde, amine, Meldrum's acid and 5,5-dimethylcyclohexane-1,3-dione in the presence of TEBAC in aqueous medium. This protocol has the advantages of accessible starting materials, high yield, mild reaction condensations and eco-friendliness.

Experimental

Commercial solvents and reagents were used as received. IR spectra were obtained on a Tensor 27 spectrophotometer. ^{1}H NMR spectra were recorded using Bruker DPX-400 MHz instrument, at 293 K unless otherwise noted, with residue peaks of the solvents DMSO-d_6 (δ=2.50) used for reference. HRMS were obtained on a microma GCT-TOF instrument.

Typical procedure for the synthesis of propanamides 5 in aqueous media

A mixture of the aldehyde **1** (2 mmol), Meldrum's acid **2** (2 mmol), 5,5-dimethylcyclohexane-1,3-dione **3** (2 mmol), amine **4** (2 mmol) and TEBAC (0.1 g) in water (10 mL) was stirred for 8—20 h at 90 ℃, then cooled to room temperature. The crystalline powder formed was collected by filtration, washed with water and recrystallized from ethanol to give pure **5**.

3-(4-Chlorophenyl)-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-*N*-*p*-tolylpropanamide (5a) m.p. 239—240 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.93 (s, 6H, 2×CH_3), 2.35—2.20 (m, 7H, CH_3+2×

CH_2), 2.80 (dd, J=6.8, 14.8 Hz, 1H, CH), 3.24 (dd, J=8.4, 14.8 Hz, 1H, CH), 4.73 (t, J=7.6 Hz, 1H, CH), 7.04 (d, J=8.0 Hz, 2H, ArH), 7.29—7.24 (m, 4H, ArH), 7.41 (d, J=8.4 Hz, 2H, ArH), 9.80 (s, 1H, NH), 10.64 (s, 1H, OH); IR (KBr) v: 3293, 3125, 3068, 1668, 1602, 1559, 1514, 1491, 1449, 1377, 1309, 1281, 1249, 1092, 921, 816, 780, 757, 723 cm^{-1}. HRMS calcd for $C_{24}H_{26}{}^{35}ClNO_3$ 434.1499 (M+Na), found 434.1505.

3-(2-Hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-*N*,3-di(*p*-tolyl)propanamide (5b) m.p. 221—223 ℃ (Lit.[22] 218—220 ℃); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.92 (s, 6H, 2×CH_3), 2.35—2.00 (m, 10H, 2×CH_3+2×CH_2), 2.81 (dd, J=7.2, 14.8 Hz, 1H, CH), 3.21 (dd, J=8.4, 14.8 Hz, 1H, CH), 4.70 (t, J=7.6 Hz, 1H, CH), 6.98 (d, J=8.0 Hz, 2H, ArH), 7.04 (d, J=8.0 Hz, 2H, ArH), 7.15 (d, J=8.0 Hz, 2H, ArH), 7.42 (d, J=8.0 Hz, 2H, ArH), 9.77 (s, 1H, NH), 10.48 (s, 1H, OH); IR (KBr) v: 3297, 3195, 3029, 1670, 1618, 1601, 1550, 1513, 1446, 1379, 1262, 1249, 1046, 983, 936, 816, 752, 718 cm^{-1}. HRMS calcd for $C_{25}H_{29}NO_3$ 392.2226 (M+H), found 392.2230.

3-(2-Hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-3–(4-methoxyphenyl)-*N*-*p*-tolylpropanamide (5c) m.p. 204—206 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.92 (s, 6H, 2×CH_3), 2.04 (s, 2H, CH_2), 2.22 (s, 3H, CH_3), 2.33 (s, 2H, CH_2), 2.81 (dd, J=6.8, 14.8 Hz, 1H, CH), 3.19 (dd, J=8.4, 14.8 Hz, 1H, CH), 3.69 (s, 3H, CH_3O), 4.68 (t, J=7.6 Hz, 1H, CH), 6.75 (d, J=8.4 Hz, 2H, ArH), 7.04 (d, J=8.4 Hz, 2H, ArH), 7.19 (d, J=8.4 Hz, 2H, ArH), 7.42 (d, J=8.4 Hz, 2H, ArH), 9.76 (s, 1H, NH), 10.48 (s, 1H, OH); IR (KBr) v: 3297, 3196, 3058, 1668, 1615, 1560, 1513, 1448, 1379, 1247, 1150, 829, 815 cm^{-1}. HRMS calcd for $C_{25}H_{29}NO_4$ 430.1995 (M+Na), found 430.2008.

3-(2-Hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-*N*–(4-methoxyphenyl)-3-*p*-tolylpropanamide (5d) m.p. 227—229 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.93 (s, 6H, 2×CH_3), 2.05 (s, 2H, CH_2), 2.21 (s, 3H, CH_3), 2.35 (s, 2H, CH_2), 2.79 (dd, J=7.2, 14.8 Hz, 1H, CH), 3.19 (dd, J=8.4, 14.8 Hz, 1H, CH), 3.69 (s, 3H, CH_3O), 4.70 (t, J=7.6 Hz, 1H, CH), 6.82 (d, J=8.8 Hz, 2H, ArH), 6.98 (d, J=8.0 Hz, 2H, ArH), 7.15 (d, J=8.0 Hz, 2H, ArH), 7.44 (d, J=8.8 Hz, 2H, ArH), 9.71 (s, 1H, NH), 10.48 (s, 1H, OH); IR (KBr) v: 3202, 3139, 3082, 1664, 1615, 1558, 1512, 1465, 1379, 1246, 1108, 923, 824, 792, 750, 717 cm^{-1}. HRMS calcd for $C_{25}H_{29}NO_4$ 430.1995 (M+Na), found 430.2037.

3-(4-Bromophenyl)-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-*N*–(4-methoxyphenyl)propanamide (5e) m.p. 217—219 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.07 (s, 6H, 2×CH_3), 2.15 (s, 2H, CH_2), 2.35 (s, 2H, CH_2), 2.92 (dd, J=6.8, 14.8 Hz, 1H, CH), 3.37 (dd, J=8.8, 14.8 Hz, 1H, CH), 3.84 (s, 3H, CH_3O), 4.86 (t, J=7.6 Hz, 1H, CH), 6.97 (d, J=8.8 Hz, 2H, ArH), 7.37 (d, J=8.4 Hz, 2H, ArH), 7.53 (d, J=8.0 Hz, 2H, ArH), 7.58 (d, J=8.8 Hz, 2H, ArH), 9.91 (s, 1H, NH), 10.80 (s, 1H, OH); IR (KBr) v: 3298, 3140, 3078, 1664, 1638, 1615, 1557, 1511, 1463, 1376, 1249, 1108, 921, 83, 756, 718 cm^{-1}. HRMS calcd for $C_{24}H_{26}{}^{79}BrNO_4$ 472.1123 (M+H), found 472.1118.

3-(4-Chlorophenyl)-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-*N*-phenylpropanamide (5f) m.p. 215—217 ℃ (Lit.[22] 208—210 ℃); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.93 (s, 6H, 2×CH_3), 2.30—2.05 (m, 4H, 2×CH_2), 2.82 (dd, J=6.8, 14.8 Hz, 1H, CH), 3.27 (dd, J=8.8, 14.8 Hz, 1H, CH), 4.74 (t, J=7.6 Hz, 1H, CH), 6.99 (t, J=7.2 Hz, 1H, ArH), 7.30—7.22 (m, 6H, ArH), 7.53 (d, J=8.4 Hz, 2H, ArH), 9.91 (s, 1H, NH), 10.67 (s, 1H, OH); IR (KBr) v: 3289, 3080, 1654, 1602, 1550, 1491, 1444, 1377, 1309, 1254, 1148, 1051, 821, 755, 727, 691 cm^{-1}. HRMS calcd for $C_{23}H_{24}{}^{35}ClNO_3$ 420.1343 (M+Na), found 420.1372.

3-(2-Hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-*N*-phenyl-3-*p*-tolylpropanamide (5g) m.p. 237—239 ℃ (Lit.[22] 233—235 ℃); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.92 (s, 6H, 2×CH_3), 2.05 (s, 2H, CH_2), 2.20 (s, 3H, CH_3), 2.28 (s, 2H, CH_2), 2.82 (dd, J=6.8, 14.8 Hz, 1H, CH), 3.24 (dd, J=8.8, 14.8 Hz, 1H, CH), 4.71 (t, J=7.6 Hz, 1H, CH), 7.00—6.97 (m, 3H, ArH), 7.16 (d, J=8.0 Hz, 2H, ArH), 7.24 (t, J=7.6 Hz, 2H, ArH), 7.54 (d, J=8.0 Hz, 2H, ArH), 9.87 (s, 1H, NH), 10.50 (s, 1H, OH); IR (KBr) v: 3297, 3197, 3049, 1654, 1602, 1551, 1514, 1498, 1488, 1442, 1376, 1254, 1176, 1116, 1095, 972, 795, 758, 723, 691 cm^{-1}. HRMS calcd for $C_{24}H_{27}NO_3$ 400.1889 (M+Na), found 400.1946.

3-(2-Hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-3-(3,4-dimethylphenyl)-*N*–phenylpropanamide (5h) m.p. 218—220 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.93 (s, 6H, 2×CH_3), 2.35—2.05 (m, 10H, 2×CH_3+2×CH_2), 2.83 (dd, J=6.8, 14.8 Hz, 1H, CH), 3.22 (dd, J=8.4, 14.8 Hz, 1H, CH), 4.89 (t, J=7.6 Hz, 1H, CH), 6.92—6.99 (m, 3H, ArH), 7.04 (s, 1H, ArH), 7.24 (t, J=7.6 Hz, 2H, ArH), 7.56 (d, J=8.0 Hz, 2H, ArH), 9.86 (s, 1H, NH), 10.47 (s, 1H, OH); IR (KBr) v: 3279, 3139, 3053, 1641, 1597, 1558, 1499, 1485, 1456, 1376, 1249, 1096, 971, 927, 891, 814, 749, 718 cm^{-1}. HRMS calcd for $C_{25}H_{29}NO_3$ 414.2045 (M+Na), found 414.2107.

3-(2-Hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-3-(3,4-dimethoxyphenyl)-*N*–phenylpropanamide (5i) m.p. 223—224 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.94 (s, 6H, 2×CH_3), 2.07 (s, 2H, CH_2), 2.34 (s, 2H, CH_2), 2.83 (dd, J=6.8, 14.8 Hz, 1H, CH), 3.23 (dd, J=8.8, 14.8 Hz, 1H, CH), 3.66 (s, 3H, CH_3O), 3.67 (s, 3H, CH_3O), 4.70 (t, J=8.0 Hz, 1H, CH), 6.77 (s, 2H, ArH), 6.91 (s, 1H, ArH), 6.98 (t, J=7.6 Hz, 1H, ArH), 7.24 (t, J=8.0 Hz, 2H, ArH), 7.55 (d, J=8.0 Hz, 2H, ArH), 9.88 (s, 1H, NH), 10.52 (s, 1H, OH); IR (KBr) v: 3275, 3136, 3089, 1640, 1612, 1555, 1517, 1501, 1489, 1465, 1455, 1381, 1269, 1229, 1048, 1025, 970, 850, 766, 701 cm^{-1}. HRMS calcd for $C_{25}H_{29}NO_5$ 446.1944 (M+Na), found 446.1972.

***N*-(3-Chlorophenyl)-3-(4-chlorophenyl)-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl) propanamide (5j)** m.p. 237—238 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.92 (s, 6H, 2×CH_3), 2.04 (s, 2H, CH_2),

2.31 (s, 2H, CH_2), 2.88 (dd, J=6.8, 14.8 Hz, 1H, CH), 3.26 (dd, J=8.4, 14.8 Hz, 1H, CH), 4.73 (t, J=7.6 Hz, 1H, CH), 7.05 (d, J=8.0 Hz, 1H, ArH), 7.29—7.25 (m, 5H, ArH), 7.38 (d, J=8.0 Hz, 1H, ArH), 7.77 (s, 1H, ArH), 10.11 (s, 1H, NH), 10.69 (s, 1H, OH); IR (KBr) v: 3279, 3241, 3071, 1656, 1608, 1536, 1492, 1477, 1374, 1276, 1251, 1095, 960, 876, 849, 780, 729, 691 cm^{-1}. HRMS calcd for $C_{23}H_{23}{}^{35}Cl_2NO_3$ 454.0953 (M+Na), found 454.0972.

***N*-(3-Chlorophenyl)-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-3-(4-methoxyphenyl)propanamide (5k)** m.p. 227—229 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.92 (s, 6H, 2×CH_3), 2.30—2.02 (m, 4H, 2×CH_2), 2.89 (dd, J=7.6, 14.8 Hz, 1H, CH), 3.21 (dd, J=8.8, 14.8 Hz, 1H, CH), 3.68 (s, 3H, CH_3O), 4.69 (t, J=8.0 Hz, 1H, CH), 6.76 (d, J=8.4 Hz, 2H, ArH), 7.04 (d, J=8.0 Hz, 1H, ArH), 7.19 (d, J=8.4 Hz, 2H, ArH), 7.28 (t, J=8.0 Hz, 1H, ArH), 7.40 (d, J=8.4 Hz, 1H, ArH), 7.79 (s, 1H, ArH), 10.08 (s, 1H, NH), 10.52 (s, 1H, OH); IR (KBr) v: 3242, 3183, 3066, 1656, 1583, 1544, 1511, 1477, 1453, 1425, 1370, 1265, 1185, 1027, 970, 881, 787, 733, 706 cm^{-1}. HRMS calcd for $C_{24}H_{26}{}^{35}ClNO_4$ 450.1448 (M+Na), 450.1445.

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