A Green and Highly Efficient Protocol for Catalyst-free Knoevenagel Condensation and Michael Addition of Aromatic Aldehydes with 1,3-Cyclic Diketones in PEG-400

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A convenient, highly efficient and green approach for synthesis of tetraketones from aromatic aldehydes with dimedone and 1,3-indanedione at room temperature in PEG-400 is described. The use of PEG-400 as the reaction medium and avoiding the use of any catalyst makes the process environmentally benign. Seven new compounds are reported.

Keywords Michael addition, green chemistry, polyethelene glycol, Knoevenagel condensation, dimedone, 1,3-Indanedione

Introduction

The search for environmentally benign synthetic procedures is one of the major focus areas of green chemistry. Recently attention has been drawn to the replacement of volatile and often toxic solvents with alternative reaction media such as ionic liquids,[1] water,[2] supercritical media,[3] and polyethylene glycol.[4]

Polyethylene glycol promoted reactions have attracted organic chemists. This solvent possesses unique properties such as recyclability, ease of work up, thermal stability, no flammability and economical cost. In addition, numerous solvating ability of PEG-400, makes the system homogeneous so allowing molecular interactions to be more efficient.

The tetraketones and their enol forms, were commonly synthesized through the Knoevenagel condensations and Michael additions of aldehydes with dimedone or other types of 1,3-cyclic diketones. They are key intermediates for the preparation of some heterocylic compounds [5] and various acridindions as laser dyes.[6]

Several methods have already been reported for the preparation of tetraketones such as use of NaOH,[7] KOH,[8] piperidine,[5] proline,[9] SDS,[10] cetyltrimethyl ammonium bromide (CTMAB),[11] *L*-lysine in H_2O,[12] *L*-histidine in ionic liquid,[13] grinding,[14] and in solid state.[15] Very recently, the synthesis of tetraketones in water was reported, which produced 2,2'-(arylmethylene) dicyclohexane-1,3-diones in 64%—99% yields at room temperature for 0.5—4 h.[16] The protocol provides several features including use of water without any catalyst. Compared with the related procedure in water, PEG could reduce the time of the reaction. More importantly, 1,3-indanedione, which has little solubility in water, gave good results with different arylaldehydes in terms of yield and time under these conditions.

Experimental

General procedure for the synthesis of 2-((2,3-dihydro-1,3-dioxo-1*H*-inden-2-yl)(4-nitrophenyl)methyl)-2*H*-indene-1,3-dione (16B)

A mixture of 1,3-indanedione (0.292 g, 2 mmol) and 4-nitro benzaldehyde (0.151 g, 1 mmol) was taken in 5 mL of polyethylene glycol 400, and stirred for 45 min at room temperature (Table 2). After the completion of the reaction (monitored by TLC), the reaction mixture was poured into water. The precipitated solid was filtered and the crude product was crystallized with ethanol to afford the pure product (**16B**). Yellow crystals, yield 97%, 0.4 g, m.p. 197—199 ℃.

PEG-400 could be recycled by this procedure: after the completion of reaction, the reaction mixture was extracted with diethyl ether and the retained PEG-400 phase was reused. The ether layer was washed with water (2 mL) and dried over $MgSO_4$. The organic solvent was removed under reduced pressure to give the crude product. Crystallization from EtOH provided the pure product.

Spectral (IR, ^{1}H NMR, ^{13}C NMR) and analytical data for new compounds

2-((4-Fluorophenyl)(4,4-dimethyl-2,6-dioxocyclohexyl)methyl)-5,5-dimethylcyclohexane-1,3-dione (**13A**) (Entry 13, Table 2): Colorless crystals, yield 72%, 0.27 g, m.p. 185—187 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.11 (s, 6H), 1.23 (s, 6H), 2.50—2.18 (m, 8H), 5.49 (s,

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1H), 6.98—6.93 (m, 2H), 7.07—7.03 (m, 2H), 11.12 (s, br, 0.6H), 11.90 (s, br, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 27.39, 29.62, 29.70, 31.40, 32.22, 46.42, 47.04, 114.87, 115.15, 115.54, 128.21, 128.31, 133.59, 133.64, 159.40, 162.64, 189.41, 190.57; IR (KBr) *v*: 3047, 2962, 1589 cm^{-1}. Anal. calcd for $C_{23}H_{27}FO_4$: C 71.50, H 6.99; found C 71.43, H 6.81.

5,5-Dimethyl-2-((4,4-dimethyl-2,6-dioxocyclohexyl)-(thiophen-2-yl)methyl)cyclohexane-1,3-dione (**14A**) (Entry 14, Table 2): White crystals, yield 71%, 0.26 g, m.p. 156—158 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 1.11 (s, 6H), 1.23 (s, 6H), 2.59—2.28 (m, 8H), 5.64 (s, 1H), 6.65 (d, br, *J*＝1.32 Hz, 1H), 6.88 (t, br, *J*＝3.75 Hz, 1H), 7.12 (d, br, *J*＝4.59 Hz, 1H), 11.62 (s, br, 0.6H), 12.34 (s, br, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 26.75, 29.99, 30.41, 31.17, 46.23, 47.00, 115.97, 123.50, 124.56, 126.37, 143.70, 189.51, 189.94; IR (KBr) *v*: 2592, 1589 cm^{-1}. Anal. calcd for $C_{21}H_{26}O_4S$: C 67.37, H 6.95; found C 67.29, H 6.71.

2-((2,3-Dihydro-1,3-dioxo-1*H*-inden-2-yl)(4-nitrophenyl)methyl)-2*H*-indene-1,3-dione (**16B**) (Entry 16, Table 2): Yellow crystals, yield 97%, 0.4 g, m.p. 197—199 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 4.03 (t, *J*＝7.41 Hz, 1H), 4.31 (d, *J*＝7.35 Hz, 2H), 7.60 (d, *J*＝8.61 Hz, 2H), 7.93—7.89 (m, 4H), 7.87—7.81 (m, 4H), 8.12 (d, br, 1H); ^{13}CNMR ($CDCl_3$, 75 MHz) *δ*: 41.22, 53.98, 123.38, 123.61, 123.68, 130.00, 134.25, 135.86, 136.02, 141.64, 142.68, 146.75, 147.07, 197.61, 198.53; IR (KBr) *v*: 1704, 1512, 1350 cm^{-1}. Anal. calcd for $C_{23}H_{27}NO_6$: C 66.82, H 6.53, N 3.38; found C 66.90, H 6.64, N 3.42.

2-((3-Bromophenyl)(2,3-dihydro-1,3-dioxo-1*H*-inden-2-yl)methyl)-2*H*-indene-1,3-dione (**17B**) (Entry 17, Table 2): Light brown crystals, yield 90%, 0.4 g, m.p. 169—170 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 3.86 (t, *J*＝7.31 Hz, 1H), 4.18 (dd, *J*＝7.22, 3.31 Hz, 2H), 7.38—7.11 (m, 3H), 7.57 (s, br, 1H), 7.93—7.80 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 41.30, 54.46, 122.40, 123.30, 127.65, 129.88, 130.54, 132.01, 135.62, 135.82, 141.73, 141.90, 197.68, 198.87; IR (KBr) *v*: 1743, 1704 cm^{-1}. Anal. calcd for $C_{23}H_{27}BrO_4$: C 61.74, H 6.04; found C 61.81, H 6.11.

2-((2,3-Dihydro-1,3-dioxo-1*H*-inden-2-yl)(*p*-tolyl)-methyl)-2*H*-indene-1,3-dione (**18B**) (Entry18, Table 2): Green crystals, yield 92%, 0.35 g, m.p. 172—174 ℃. ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 2.3 (s, 3H), 3.72 (d, *J*＝6.77, 1H), 3.85 (d, *J*＝6.92, 1H), 4.71 (t, *J*＝6.8 Hz, 1H), 7.41—7.20 (m, 3H), 7.97—7.82 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 24.3, 35.95, 54.82, 123.28, 123.38, 127.23, 128.50, 129.57, 129.92, 134.02, 135.48, 135.73, 138.35, 141.68, 141.74, 197.15, 198.75; IR (KBr) *v*: 1743, 1704 cm^{-1}. Anal. calcd for $C_{24}H_{30}O_4$: C 75.39, H 7.85; found C 75.44, H 7.71.

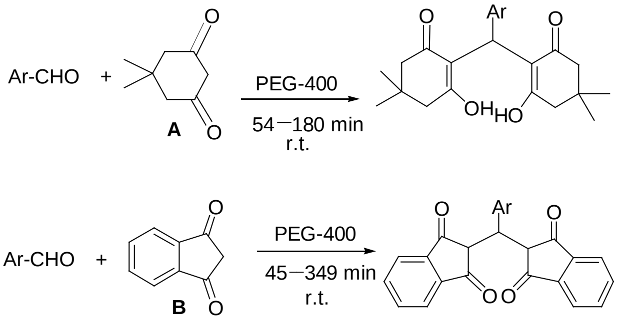
2-((4-Chlorophenyl)(2,3-dihydro-1,3-dioxo-1*H*-inden-2-yl)methyl)-2*H*-indene-1,3-dione (**19B**) (Entry 19, Table 2): Yellow crystals, yield 91%, 0.36 g, m.p. 153—155 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 3.90 (t, *J*＝7.40 Hz, 1H), 4.26 (d, *J*＝7.45 Hz, 2H), 7.21 (d, *J*＝8.45 Hz, 2H), 7.31 (t, *J*＝8.44 Hz, 2H), 7.85—7.79 (m, 4H), 7.93—7.89 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 41.55, 54.28, 123.30, 128.51, 130.38, 133.24, 135.38, 135.66, 135.83, 137.38, 141.82, 142.00, 198.087, 199.07; IR (KBr) *v*: 1743, 1704 cm^{-1}. Anal. calcd for $C_{23}H_{27}ClO_4$: C 68.57, H 6.70; found C 68.80, H 6.81.

2-((2-Chlorophenyl)(2,3-dihydro-1,3-dioxo-1*H*-inde-n-2-yl)methyl)-2*H*-indene-1,3-dione (**20B**) (Entry 20, Table 2): Crystals, yield 80%, 0.32 g, m.p. 165—167 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 3.95 (d, *J*＝6.96 Hz, 2H), 4.70 (t, *J*＝6.99 Hz, 2H), 7.40—7.19 (m, 3H), 7.96—7.79 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 35.81, 54.75, 122.92, 123.23, 123.33, 127.19, 128.45, 129.50, 129.84, 133.93, 135.45, 135.70, 138.29, 141.58, 141.64, 197.11, 198.73; IR (KBr) *v*: 1743, 1704, 1589, 1342, 756 cm^{-1}. Anal. calcd for $C_{23}H_{27}ClO_4$: C 68.57, H 6.70; found C 68.69, H 6.59.

Results and discussion

In our pursuit of improved synthetic method for the preparation of organic compounds[17] here in we want to report a simple, mild and highly efficient procedure for the synthesis of tetraketones that employs only PEG-400 as a solvent at room temperature (Scheme 1).

Scheme 1 Knoevenagel condensation and Michael addition of aromatic aldehydes with dimedone and 1,3-indanedione in PEG-400 at room temperature



When benzaldehyde and dimedone in different solvents, were allowed to react at room temperature, the expected product was obtained whose ratio depends on the nature of the solvent (Table 1). As can be seen in Table 1, the most satisfactory result was obtained in PEG-400 at room temperature.

Based on the above results, we examined the substrate scope of this reaction. First the reaction was carried out using various substituted arylaldehydes and dimedone. The results are presented in Table 2 (Entries 1—15).

A variety of arylaldehydes including both electron-deficient and electron-rich groups were employed and participated well to give the corresponding products in good to excellent yields and no undesirable side reactions were observed, although the yield and the time of the reaction were dependent on the substituent.

PEG-400 is a sufficient solvent and helps in the eno-

Table 1 Synthesis of 2,2'-[(phenyl)methylene]bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) in different conditions

Entry	Solvent	Time/min	T/℃	Yield/%
1	PEG-400	60	r.t.	81
2	PEG-400	80	r.t.	85
3	PEG-400	100	r.t.	97
4	PEG-400	100	50	91
5	PEG-400	100	70	84
6	H_2O	240	r.t.	96[16]
7	EtOH	240	r.t.	80[16]
8	EtOH/H_2O (1∶1)	240	r.t.	94[16]

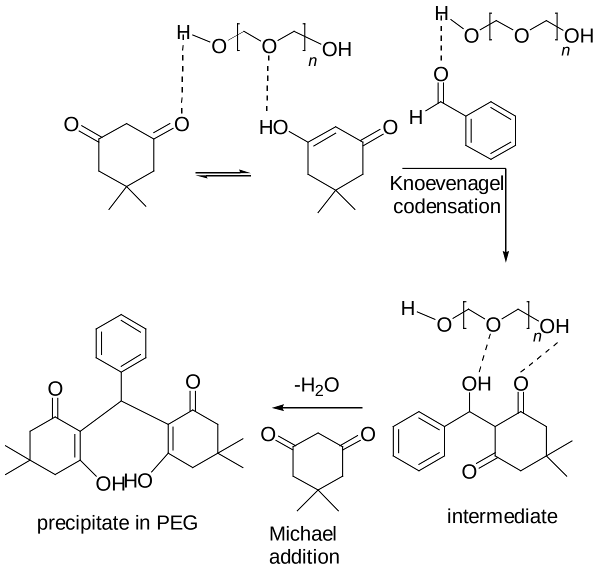
Table 2 The reaction of dimedone or 1,3-indanedione and arylaldehydes in PEG-400 at room temperature

Entry[a]	Ar-CHO	Time/min	Yield[b]/%	m.p. (Lit.)/℃
1A	C_6H_5	100	97	194—195 (194—195)[16]
2A	4-Br-C_6H_4	118	77	172—173 (172—174)[13]
3A	3-Br-C_6H_4	71	90	197—198 (184—186)[13]
4A	4-MeO-C_6H_4	54	98	183—185 (185—186)[16]
5A	2-MeO-C_6H_4	81	96	185—186 (181—183)[16]
6A	4-NO_2-C_6H_4	71	97	190—191 (188—190)[15]
7A	3-NO_2-C_6H_4	150	98	196—198 (196—198)[16]
8A	4-Me-C_6H_4	130	74	141—142 (141—142)[14]
9A	4-Cl-C_6H_4	102	79	144—146 (145—146)[15]
10A	2-Cl-C_6H_4	54	98	204—205 (203—205)[14]
11A	2,4-Cl_2-C_6H_3	75	91	202—204 (203—204)[14]
12A	2-OH-C_6H_4	116	95	208—209 (205—206)[14]
13A	4-F-C_6H_4	108	72	185—187
14A	2-Thiophen	94	71	156—158
15A	4-(Me_2N)-C_6H_4	180	59	193—194 (194—195)[16]
16B	4-NO_2-C_6H_4	45	97	197—199
17B	3-Br-C_6H_4	349	90	169—170
18B	4-Me-C_6H_4	322	92	172—174
19B	4-Cl-C_6H_4	250	91	153—155
20B	2-Cl-C_6H_4	338	80	165—167
21B	C_6H_5	186	93	163—164 (162)[16]

[a] Reaction condition: aldehyde (1 mmol), **A**: Dimidone (2 mmol) or **B**: 1,3-indanedion (2 mmol) and PEG (5 mmol) at r.t. [b] Isolated yield.

lization and increase of nucleophilic character of the methylene carbon of 1,3-cyclic diketone by making hydrogen bonds with OH groups. In addition, it could increase the electrophilic character of the carbonyl carbon of arylaldehydes. After the Knoevenagel condensation, the intermediate is transformed to the product (Scheme 2).[16]

Scheme 2 A plausible mechanism



To check the versatility of this method we had also studied the reaction of 1,3-indanedione with variety of arylaldehydes. Interestingly, 1,3-indanedione was also effective for this reaction. However, reaction of 1,3-indanedion needs longer time due to lower activity than dimedone (Table 2, Entries 16—21). The *ortho*- and *para*-methoxy benzaldehydes only produced the Knoevenagel condensation products with 1,3-indanedione. Spectroscopic data support the chemical structure of this intermediates.[18]

We have also successfully applied this new methodology on a larger scale. For example up to 20 mmol benzaldehyde could produce 5,5-dimethyl-2-((4,4-dimethyl-2-oxocyclohexyl)(phenyl)methyl)cyclohexanone with yield up to 80%.

Conclusions

In summary, we have established a green and simple method for the preparation of tetraketones. The procedure offers several merits including high reaction yields, broad application scope, simple experimental process and avoidance of any catalyst and volatile organic solvents. On the other hand, these advantages could make this process available on an industrial scale.

Supporting information

Supporting information for this article is available on the www under http://dx.doi.org/10.1002/cjoc.201100005 or from the author.

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18 2-(4-Methoxybenzylidene)-2*H*-indene-1,3-dione: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.9 (dd, J＝7.89, 1.57 Hz, 1H), 8.5 (s, 1H), 8.0—7.96 (m, 2H), 7.81—7.77 (m, 2H), 7.52 (td, J＝7.13, 1.66 Hz, 1H), 7.07 (t, J＝7.44 Hz, 1H), 6.94 (d, J＝8.35 Hz, 1H), 3.93 (s, 3H); ^{13}CNMR ($CDCl_3$, 75 MHz) δ: 190.60, 189.25, 160.51, 142.37, 141.33, 140.05, 135.40, 135.17, 135.01, 133.96, 128.24, 123.17, 123.15, 122.00, 120.38, 110.66, 55.76.

19 2-(2-Methoxybenzylidene)-2*H*-indene-1,3-dione: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.91 (dd, J＝7.89 Hz, 1.42 Hz, 1H), 8.5 (s, 1H), 8.02—7.98 (m, 2H), 7.83—7.78 (m, 2H), 7.53 (td, J＝7.84, 1.58 Hz, 1H), 7.08 (t, J＝7.65 Hz, 1H), 6.95 (d, J＝8.36 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 190.62, 189.27, 160.52, 142.38, 141.37, 140.07, 135.39, 135.17, 135.01, 133.96, 128.26, 123.18, 123.17, 122.02, 120.39, 110.66, 55.76.

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