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Microwave-Mediated Facile Synthesis of Steroid-like 1,5-Diketones from Mannich Salts

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Abstract: A facile synthesis of some diketones that fit into a steroid motif was achieved from Mannich salts and cyclic ketones under microwave irradiation.

Keywords: 1,5-diketones, Mannich salt, microwave, steroids, 1,5,9-triketones

The A-ring aromatic steroids, for example, estrone **1** (Fig. 1), are an important group of hormones and drug molecules.[1] The steroids, in general, have a cyclopentaphenanthrene (Diels hydrocarbon) carbon framework with ABCD rings arranged as shown in structure **1**. The 1,5-diketones of type **2** (Fig. 1) having A and D rings fit well into the steroid motif, and therefore their synthesis assumes importance. The 1,5-diketones **2** can be prepared from phenyl vinyl ketones and cyclic ketones under thermal activation or by using a base.[2]

Austin and coworkers have shown that heating Mannich bases with cyclic ketones **4** furnishes 1,5-diketones **2** in moderate yields.[3] In this case, the Mannich bases were behaving as precursors for in situ generated phenyl vinyl ketones. We have previously reported that heating a mixture of Mannich bases and cyclic ketones at 155°C under solvent-free conditions furnished 1,5-diktones **2** and 1,5,9-triketones **5** in moderate yield.[4] The

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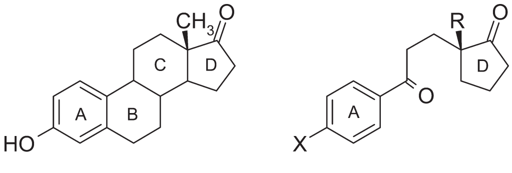
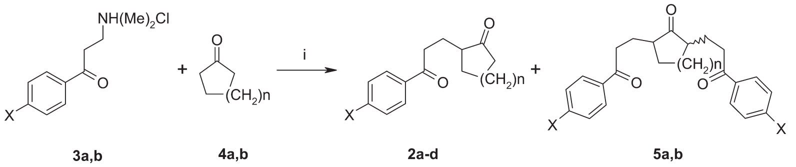


1 **2**

Figure 1. Structures of estrone and 1,5-diketones.

Mannich bases are generally prepared by neutralization of the Mannich salts, which in turn are prepared from aryl methyl ketones, formaldehyde, and dimethylamine hydrochloride.[5] We now report that the reaction of the Mannich salts **3** with cyclic ketones **4** can be achieved conveniently under microwave (MW) irradiation to furnish the diketones **2** in good yield (Scheme 1). Under the present reaction conditions, there is no need to employ either Mannich bases or phenyl vinyl ketones as one of the reacting partners to get diketones **2**.

The Mannich salt **3a**, prepared from acetophenone, formaldehyde, and dimethylammonium chloride, was mixed well with 1 molar equivalent of cyclopentanone **4a** in 5 equivalents of PEG-200 (polyethylene glycol-200) and irradiated in a MW oven at 370 W for 2 min to get a mixture of 1,5-diketone **2a** and 1,5,9-triketones **5a** in the ratio of 44:55 in 60% combined yield (Scheme 1 and Table 1, entry 1). The product ratio was estimated from integration of the relevant signals in the ^{13}C NMR spectra of the mixture. The 1,5,9-triketones **5a** were obtained as a mixture of *cis* and *trans* isomers formed in a 1:1 ratio. Compared to the reaction in PEG-200 reflux, the MW-mediated reaction was cleaner and faster. As anticipated, when 2 or 3 equivalents of the Mannich salt **3a** were employed, the yield of the 1,5,9-triketones **5a** increased at the cost of diketone **2a** (entries 3 and 4). On the other hand, when 2 or 3 equivalents of cyclopentanone **4a** were employed in the reaction, the diketone **2a** was obtained in higher yield



3a: X = H
3b: X = OMe

4a: n = 1
4b: n = 2

2a: X = H, n = 1
2b: X = OMe, n = 1
2c: X = H, n = 2
2d: X = OMe, n = 2

5a: X = H, n = 1
5b: X = OMe, n = 1
5c: X = H, n = 2
5d: X = OMe, n = 2

Scheme 1. Reagents and conditions: i) PEG-200, MW (370 W), 2 min, 63–78%.

Table 1. Reaction of the Mannich salt **3a** with cyclopentanone **4a**/cyclohexanone **4b**

Entry	Reactants and their ratio	Solvent[a]	Yield[b] (%)	Products and their ratio
1	**3a**:**4a** = 1:1	PEG 200	60	**2a**:**5a** = 45:55
2	**3a**:**4a** = 1:1	EG	36	**2a**:**5a** = 55:45
3	**3a**:**4a** = 2:1	PEG 200	66	**2a**:**5a** = 28:72
4	**3a**:**4a** = 3:1	PEG 200	68	**2a**:**5a** = 26:74
5	**3a**:**4a** = 1:2	PEG 200	84	**2a**:**5a** = 72:29
6	**3a**:**4a** = 1:3	PEG 200	87	**2a**:**5a** = 80:20
7	**3b**:**4a** = 1:1	PEG 200	84	**2b**:**5b** = 95:05
8	**3a**:**4b** = 1:1	PEG 200	90	**2c**:**5c** = 40:60
9	**3a**:**4b** = 1:1	EG	45	**2c**:**5c** = 55:45
10	**3a**:**4b** = 2:1	PEG 200	80	**2c**:**5c** = 30:70
11	**3a**:**4b** = 3:1	PEG 200	85	**2c**:**5c** = 25:75
12	**3a**:**4b** = 1:2	PEG 200	90	**2c**:**5c** = 60:40
13	**3a**:**4b** = 1:3	PEG 200	92	**2c**:**5c** = 60:40
14	**3b**:**4b** = 1:1	PEG 200	80	**2d**:**5d** = 75:25
15	**3a**:**6** = 1:1	PEG 200	67	**7a**
16	**3b**:**6** = 1:1	PEG 200	72	**7b**

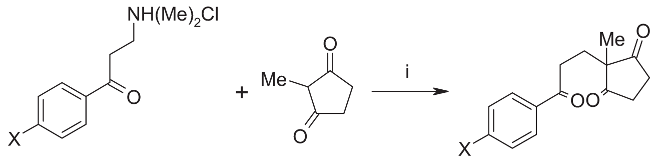
[a] PEG-200 = polyethylene glycol of average molecular weight of 200, EG = ethylene glycol.

[b] Combined yield of diketone **2** and triketone **5**.

(entries 5 and 6). Generality of the reaction was established by reacting Mannich salt **3b** with cyclopentanone **4a** to furnish 1,5-diketone **2b** and 1,5,9-triketones **5b** in the ratio of 95:5, 84% yield (entry 7). The diketone **2b** has a carbon skeleton that fits into estrone framework. The MW-mediated reaction of the Mannich salts **3a** with cyclohexanone **4b** furnished 1,5-diketone **2c** and the 1,5,9-triketone **5c** in good yield (entry 8). Employment of excess Mannich salt **3a** improved the yield of the triketone **5c** (entries 10 and 11), whereas when excess cyclohexanone was used, diketone **2c** was the major product (entry 12 and 13). The condensation reaction of the Mannich salt **3b** with cyclohexanone **4b** furnished diketone **2d** and triketone **5d** in good yield (entry 14). The diketone **2d** forms structure motif on A-ring aromatic D-homosteroids. The condensation reactions of cyclopentanone/cyclohexanone also took place in ethylene glycol (EG) medium, however, in lower yield (entries 2, 9).

After establishing a facile synthesis of diketones **2a–d**, Mannich salt **3a** was reacted with 2-methyl-1,3-cyclopentanedione **6** under MW irradiation. The reaction provided the triketone **7a** in good yield (Scheme 2, Table 1, entry 15). Similarly, the reaction of the Mannich salt **3b** with the diketone **6** provided **7b** in good yield.[6] The triketone **7b** has structural similarities with estrone **1**.

It is possible that under MW irradiation the Mannich salts decompose to aryl vinyl ketones, which react with enolates of cyclic ketones to provide the



3a,b **6** **7a,b**

3a: X = H
3b: X = OMe

7a: X = H
7b: X = OMe

Scheme 2. Reagents and conditions: i) PEG-200, MW (370 W), 2 min, 67–72%.

diketones **2**. Presence of hydrochloric acid given out by the salt in the reaction medium could facilitate enolate generation from ketones **4**. In conclusion, we have shown that MW irradiation of the Mannich salts **3** with cyclic ketones **4**/**6** provide diketones of type **2** in a facile manner. Some of the compounds generated in this study fit well into a steroid carbon framework. We are presently working on the reductive amination–cyclization of ketones **2**/**7** to generate 8-azasteroids.[7]

EXPERIMENTAL

General

Polyethylene glycol-200 (PEG-200) and ethylene glycol were used as solvents. The IR spectra were recorded with KBr using an ABB BOMEM 104 FT-IR spectrometer. The ^{1}H and the ^{13}C NMR spectra were recorded in $CDCl_3$ or $CDCl_3$–CCl_4 (1:1) mixture on Jeol 400-MHz or Brucker 300-MHz NMR spectrometers using TMS (0 ppm) or the center line of the chloroform-D triplet (77.0 ppm) as the internal standard, respectively. Melting points were recorded using a Gallenkamp melting-point apparatus. The microwave reactions were carried out using a BPL-Sanyo (India) microwave oven (monomade, multipower source, 230 V, 50 Hz) with operating microwave frequency of 2450 MHz.

General Procedure for Michael Addition Reaction

A mixture of Mannich salt **3** and cyclic ketone **4** (see Table 1) suspended in PEG medium (2 mL) was irradiated in a domestic microwave oven at 370 W for the time indicated. The GC analysis was used to monitor progress of the reaction. The cooled reaction mixture was poured on crushed ice (50 g), and the product was extracted with dichloromethane (3 × 20 mL). The organic layer, dried over anhydrous sodium sulfate, was evaporated under reduced pressure. The crude product was subjected to column chromatography (silica gel) to separate and purify diketones **2** and triketones **5**. The products **2a–d** and **5a–d** isolated in the present study are known compounds.[2,3] Similarly, the reaction of Mannich salts **3a** and **b** with diketone **6** furnished triketones **7a** and **b**, whose spectral data are given next.

Data

2-Methyl-2-(3-oxo-3-phenylpropyl)-1,3-cyclopentanedione **7a**: Mp 80–82°C; IR (KBr) ν_{max}: 1721, 1688, 1598, 1449, 1404 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.16 (s, 3H), 2.06 (t, $J = 7.2$ Hz, 2H), 2.72–2.88 (m, 4H), 2.98 (t, $J = 7.2$ Hz, 2H), 7.44 (td, $J = 7.5, 6.9$ Hz, 2H), 7.55 (t, $J = 7.5$ Hz, 1H), 7.88 (d, $J = 6.9$ Hz, 2H) ppm; ^{13}C NMR (75 MHz CDCl$_3$) δ 19.0, 28.3, 32.4, 34.6, 55.2, 127.9, 128.5, 133.2, 136.3, 199.2, 215.7 ppm. Anal. calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.48; H, 6.53.

2-[3-(4-Methoxyphenyl)-3-oxopropyl]-2-methyl-1,3-cyclopentanedione **7b**: Mp 96–98°C; IR ν_{max}: 1770, 1725, 1675, 1615, 1580 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.07 (s, 3H), 1.96 (t, $J = 7.2$ Hz, 2H), 2.71 (t, $J = 4.4$ Hz, 2H), 2.84 (t, $J = 7.2$ Hz, 4H), 3.77 (s, 3H), 6.83 (d, $J = 8.8$ Hz, 2H), 7.86 (d, $J = 8.8$ Hz, 2H) ppm; ^{13}C NMR (100 MHz CDCl$_3$) δ 19.1, 28.6, 32.0, 34.7, 55.2, 55.3, 113.4, 129.4, 130.2, 163.5, 197.7, 215.8 ppm. Anal. calcd. for $C_{16}H_{18}O_4$: C, 69.98; H, 6.86. Found: C, 70.05; H, 6.61.

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