Approach towards cost effective practical method for synthesis of 1-(substituted phenyl)-3-methyl propane 1,3-dione

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ABSTRACT: A simple, convenient and high yielding method for the synthesis of 1-(substituted phenyl)-3-methyl propane 1,3-dione from substituted acetophenones have been developed. This method provides several advantages such as shorter reaction time, high yields (78-90%) and simple work-up procedure.

Keywords: acetophenones; ethyl alcohol; sodium metal; ethylacetate; propane-1,3-dione

Introduction

1,3-Dione constitutes an important class of compounds. 1-(Substituted phenyl)-3-phenyl propane-1,3-diones are important compounds [1] of natural occurrence and are used as intermediates for synthesis of flavones [2], coumaran-3-ones [3], isoxazoles [4], pyrimidines [5], pyrazolines [6] and 1,5-benzodiazepines which have broad spectrum of pharmacological activities [7], β-diketone unit exhibit anti-inflammatory and antimitotic activities [8-11]. The most well known methods [12] for synthesis of 1,3-dicarbonyl compounds are acylation of ketone and Claisen condensation reaction. Acylation of ketone method involves use of acid chlorides or acid anhydrides, BF₃ and acetophenone. Reaction is carried out in a three naked round bottom flask, at a low temperature. Sodium acetate is added to decompose difluoride complex and solution is steam distilled to yield 1,3-dicarbonyl compound and further purified using copper salt.

Claisen condensation method involves the use of absolute ethanol and strong base such as sodium ethoxide in dry xylene/dry ether and acetophenone to yield carbanion.

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Carbanion react with ester to yield required 1,3-diketone. Both methods involve organic solvents, toxic reagents and special designed apparatus. Symmetrical and unsymmetrical 1,3-dicarbonyl compounds are prepared by these methods. 1-(Substituted phenyl)-3-phenyl propane-1,3-dione are synthesized from alpha aryloxyacetophenone [13], dibromostryl ketone [14].

1-(Substituted phenyl)-3-methylpropane-1,3-dione [15, 16] synthesized using metallic sodium and substituted acetophenones in absolute ethanol and reacting with ethyl acetate using solvent dry ether. Uekawa et al. [17] have prepared number of beta-diketones using ethyl acetate and selected methyl ketone using sodium methoxide base and diethyl ether solvent and reaction mixture is stirred for 48 h at room temperature. Zhen and Lin [18] reported synthesis of symmetrical beta-ketones by reacting substituted imidazolium salt with bis-Grignard reagent. Pond et al. [19] have synthesized bis-beta ketones, i.e. 3,3-(pyridine-2,6-diyl) bis-1-phenylpropane-1,3-dione monohydrate) and 3,3′(pyridine-2,6 diyl/bis pyridine-2yl) propane-1,3-dione by Claisen condensation of the appropriate ketone and dimethyl pyridine-2,6-dicarboxylate ester. 1-(2-Hydroxy-phenylpropane-1,3-dione) is synthesized by modified Baker-Venketraman transformation using microwave irradiation [20]; solid phase Baker-Venketraman rearrangement under solvent-free condition [21]. An efficient acetylation of the multiple anions of poly-beta-carbonyl compound is reported by Timothy et al. [22].

All these reported methods for synthesis of 1,3-diketones involves costly inflammable solvents, costly and hazardous toxic reagents, specific setup of apparatus and longer time period. In present communication, we report an efficient and simple procedure for the synthesis of 1-(substituted phenyl)-3-phenylpropane-1,3-diones.

Material and Methods

All melting points were determined in open capillary and are uncorrected. The IR spectra were recorded on Perkin-Elmer 157 and Shimadzu spectrometer. 1H NMR was recorded on Avenue-300 MHz instrument using CDCl3 as solvent and TMS as internal standard. The mass spectra were recorded on VG 7070H spectrometer using ionization energy of 70ev. Elemental analyses were performed on a Carlo Erba 106 Perkin-Elmer model 240 analyzer. The reactions were monitored on TLC and the spots were located in iodine chamber.

Typical procedure for synthesis of 1-(substituted phenyl)-3-methyl propane-1,3-dione. (2a-j)

Substituted acetophenones (0.01 mol) was dissolved in absolute ethanol (20 mL). Small pieces of sodium metal (0.011 mol) was added to it and stirred for 20 min. to obtain semisolid mass. Ethanol (5 mL) was added to obtain clear solution and ethyl
acetate (0.012 mol) was added drop wise with stirring within 10 min; stirring was continued for 20 min. and then acidified with acetic acid. The solid thus obtained was filtered and crystallized from ethyl alcohol.

Spectral and analytical data of 1-(Substituted phenyl)-3-methylpropane-1,3-diones

3 (a) 1-[(2-hydroxy-3,5-dichloro phenyl)]-3-methyl propane 1,3-dione: IR  $\nu_{\text{max}}$ cm$^{-1}$: 3450 (OH), 3048 (=CH), 1640 (C=O), 1608, 1510 (C=C Aromatic). $^1$H NMR: $\delta$ 2.04 (s, 3H, CH$_3$), 7.58 and 7.30 (s, 1H, Ar-H), 6.45 (s, 0.40 =CH), 12.40 (s, 1H, OH), 13.71 (s, .62, OH enol). Anal. Calcd. for C$_{10}$H$_8$O$_3$Cl$_2$: C, 48.61; H, 3.26; X (Cl), 28.70. Found: C, 48.60; H, 3.21; X (Cl), 28.28.

3 (b) 1-[(2-methoxy-3,5-diiodo phenyl)]-3-methyl propane 1,3-dione: IR  $\nu_{\text{max}}$ cm$^{-1}$: 3051 (=CH), 1647 (C=O), 1610, 1510, 1435 (C=C Aromatic). $^1$H NMR: $\delta$ 2.33 (s, 1H, CH$_3$), 12.75 (s, 1H, OH enol). Anal. Calcd. for C$_{11}$H$_{10}$O$_3$I$_2$: C, 29.76; H, 2.27; X (I), 57.16. Found: C, 29.59; H, 2.20; X (I), 57.30.

3 (c) 1-[(4'-hydroxy-3,5-diiodo phenyl)]-3-methyl propane-1,3-dione: IR  $\nu_{\text{max}}$ cm$^{-1}$: 3420 (OH), 3040 (=CH), 1640 (C=O), 1605, 1510, 1430 (C=C Aromatic). $^1$H NMR: $\delta$ 2.35 (s, 1H, CH$_3$), 6.50 (s, 0.34 =CH), 7.80 (s, 1H, 2 Ar-H), 8.04 (s, 1H, 6 Ar-H), 8.32 (s, 1H, 4 OH), 12.46 (s, 0.65 OH enol). Anal. Calcd. for C$_{10}$H$_8$O$_3$I$_2$: C, 29.93; H, 1.88; X (I), 59.03. Found: C, 30.09; H, 1.97; X (I), 58.93.

3 (d) 1-[(2-hydroxy-3-iodo-5-chloro phenyl)]-3-methyl propane-1,3-dione: IR  $\nu_{\text{max}}$ cm$^{-1}$: 3430 (OH), 3040 (=CH), 1640 (C=O), 1605, 1510, 1430 (C=C Aromatic). $^1$H NMR: $\delta$ 2.20 (s, 1H, CH$_3$), 7.67 and 7.69 (s, 1H, Ar-H), 6.75 (s, 0.36, =CH), 12.60 (s, 1H, 2 x OH), 13.9 (s, 1H, OH enol). Anal. Calcd. for C$_{11}$H$_{10}$O$_3$ClI: C, 27.90; H, 1.86; X (Cl + I), 47.96. Found: C, 27.88; H, 1.86; X (Cl + I), 47.87.

3 (e) 1-[(2-hydroxy-3,5-diiodo phenyl)]-3-methyl propane-1,3-dione: IR  $\nu_{\text{max}}$ cm$^{-1}$: 3430 (OH), 3070 (=CH), 1651 (C=O), 1552, 1422(C=C Aromatic). $^1$H NMR: $\delta$ 2.25 (s, 1H, CH$_3$), 4.82 (s, 1H, OH), 6.57 (s, 0.38, =CH), 8.09 (s, 1H, Ar-H), 12.51 (s, 1H, 2 x OH), 13.60 (s, 0.60, OH enol). MS m/z: 446 (M$^+$), 440, 413, 405, 361, 329, 307, 176, 154, 107, 95. Anal. Calcd. for C$_{11}$H$_{11}$O$_3$Br: C, 27.93; H, 1.88; X (Cl + I), 59.03. Found: C, 27.90; H, 1.88; X (Cl + I), 58.84.

3 (f) 1-[(2-hydroxy-3-bromo-5-methyl phenyl)]-3-methyl propane-1,3-dione: IR  $\nu_{\text{max}}$ cm$^{-1}$: 3455 (OH), 3070 (=CH), 1650 (C=O),1600, 1510, 1460 (C=C Aromatic). $^1$H NMR: $\delta$ 2.75 (s, 1H, CH$_3$), 8 and 8.06 (s, 1H, Ar-H), 6.5 (s, .35, =CH), 12.28 (s, 1H, 2 x OH), 13.50 (s, 1H, OH). Anal. Calcd. for C$_{11}$H$_{11}$O$_3$Br: C, 48.73; H, 4.09; X (Br), 29.47. Found: C, 48.71; H, 4.09; X (Br), 29.21.
Results and Discussion

Substituted acetophenones were dissolved in absolute ethanol and clean small pieces of sodium metal added and stirred for 20 minutes at room temperature. Acetophenones react with sodium metal and semisolid mass forms. Little more of absolute ethanol added to dissolve excess of sodium metal. Calculated amount of ethyl acetate added to the clear reaction solution and stirred for 10 minutes and then acidified with acetic acid up to the pH 5.5. Solid separated out. Separated solid filtered and crystallized from ethanol to gave 1-(substituted phenyl)-3-methyl propane-1,3-diones (Table 1). Structure of newly synthesized compounds confirmed by IR, $^1$HNMR and Mass. IR spectra of compounds (2a-j) gave a broad band at 3450 cm$^{-1}$ due to OH and a specific band appears at 3040-3068 cm$^{-1}$ due to =CH. $^1$HNMR gave signal at δ 6.4-6.6 due to =CH.

Reported methods involve the use of acetophenones and sodium hydride in ethanol or sodium metal and dry xylene. Further reported methods requires special
designed apparatus, dry ether/xylene as a solvent. We have used only absolute ethanol, sodium and acetophenone to give carbanion which react with ethyl acetate to yield 1,3-diketones, hence method is a cost effective.

![Scheme 1](image)

Scheme 1. Synthesis of 1-(substituted phenyl)-3-methyl propane-1,3-dione.

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<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
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<th>M.P (°C)</th>
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This modified method is quick, simple, cost effective, work up is easy, reaction completed within one hr. giving 75-90 % yield. No need of toxic, hazardous reagent such as HF, dry ether, typical set up of apparatus. Utilization of non-toxic hazardous chemicals, time saving and less cost can be a partial green synthetic strategy.

**Conclusion**

In summary we have developed a simple, efficient and easy methodology for synthesis of 1-(substituted phenyl)-3-methyl propane-1,3-dione. The notable merits offered by this methodology are mild reaction condition, simple procedure, cleaner reaction, short reaction time and excellent yields of products (75-90%).

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**References and Notes**


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