

Green Synthesis of Tetraketones Using Barium Chloride

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Abstract

Carbon-carbon bond formation via condensation of acidic methylene containing compounds like dimedone with arylaldehydes is a reaction of great significance. The synthesis of tetraketones has been carried out via Knoevenagel condensations and Michael additions in aqueous medium under green chemistry conditions in presence of barium chloride at room temperature in high to moderate yields. This procedure proves to be very remarkable and efficient method due to use of water as a solvent which makes it environmentally benign, ecofriendly. Dimedone and arylaldehydes were taken in 2:1 ratio. The products were identified on the basis of their spectroscopic data and by comparison with authentic samples.

Keywords: 2,2'-aryl-methylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-ones), Dimedone, Knoevenagel Condensation, Organic synthesis

Introduction

C-C bond formation is the essence of organic synthesis and provides the foundation for generating more complicated organic compounds from simpler ones is a reaction of great significance in organic synthesis (Javed *et al* 1994, Li 2005). Global demand for eco-friendly chemical processes and products requires the development of novel and cost-effective approaches to pollution prevention (Jean *et al* 2004). Nowadays, the main objective is to avoid the use of toxic harmful and organic solvents which is included in goals of green chemistry (Anastas *et al* 1998; Anastas *et al* 2009). Therefore, commencing reactions in aqueous media from organic media is a challenging and striking task for organic chemists. Organic reactions in water without using harmful organic solvents have attracted a great deal of interest in both academic and industrial research because, in addition to environmental concerns, water being the most environmentally benign, cleanest, cheapest, nonflammable and naturally occurring solvent is the primary choice. Very few Knoevenagel condensations using water have been reported (Firouzeh *et al* 2011; Wang *et al* 2001; Ren *et al* 2002).

However, most of them involve high temperature, long reaction times, harsh reaction conditions, tedious work ups. In this context the choice of aqueous medium for carrying out organic reactions consumes great significance. (Li *et al* 2006).

Many of the reported methods for the formation of tetraketones have employed various catalysts such as

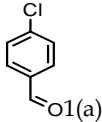
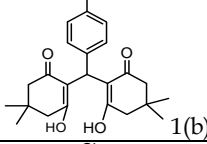
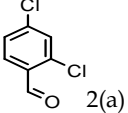
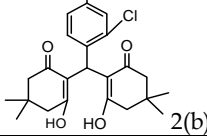
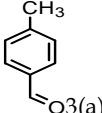
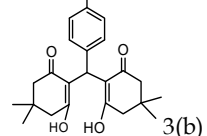
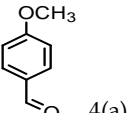
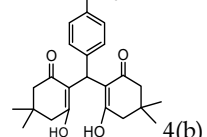
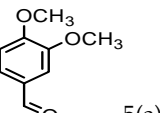
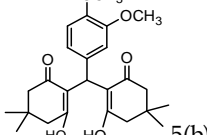
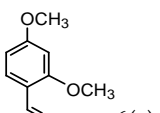
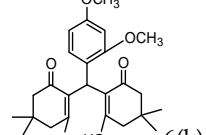
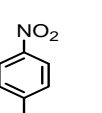
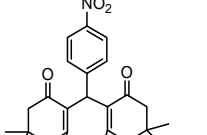
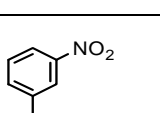
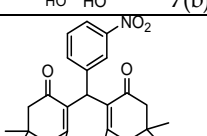
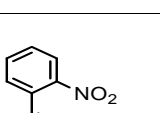
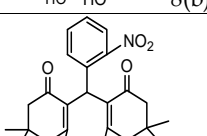
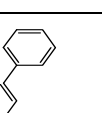
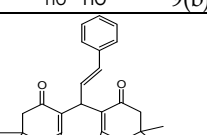
$\text{Ph}_3\text{P}=\text{CHCOCH}_3$ (Ramachary *et al* 2004), $\text{In}(\text{OTf})_3$ (Jung *et al* 2009), $\text{Yb}(\text{OTf})_3\text{-SiO}_2$, L-hystidine in ionic liquid, PPA-SiO_2 (Kantevari *et al* 2007).etc. Many of these involve traditional thermal heating or microwave irradiation and suffer from many limitations. Compared with existing methods for preparation of tetraketones or 2,2'-aryl-methylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-ones) we find a simple, convenient and time saving method in aqueous medium at room temperature using barium chloride as a catalyst. This proves to be an efficient method employing reusable green catalytical system and could reduce the time of reaction due to its appreciable solubility in water. Tetraketones are extensively used as important precursors for the synthesis of various acridinediones, xanthenediones, thioxanthenes which are structural unit in various natural products and shows significant lipoxygenase inhibitor activity and also exhibit wide spectrum of therapeutic and biological properties. (Rao *et al* 2011).

Materials And Methods

The melting points were measured on a perfit melting point apparatus and are uncorrected. $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectra were recorded on a Bruker Avance-400 MHz spectrometer in CDCl_3 as solvent and with TMS as internal standard. Chemicals were purchased from CDH and Fluka. Confirmation of product was done by comparing with authentic samples.

General procedure for synthesis of 2, 2'-(arylmethylene)bis(3- hydroxy- 5,5- dimethyl-2-

Table 1: Synthesis of Tetraketones via condensation of Dimedone and Arylaldehydes in 2:1 ratio in presence of barium chloride.

Entry	Arylaldehydes	Product	Time (min)	Yield (%)
1.	 1(a)	 1(b)	50	81
2.	 2(a)	 2(b)	55	83
3.	 3(a)	 3(b)	65	68
4.	 4(a)	 4(b)	70	84
5.	 5(a)	 5(b)	65	95
6.	 6(a)	 6(b)	60	93
7.	 7(a)	 7(b)	55	89
8.	 8(a)	 8(b)	60	87
9.	 9(a)	 9(b)	60	80
10.	 10(a)	 10(b)	75	86

cyclohexene-1-one) : Mixture of 5,5-Dimethylcyclohexane-1,3-dione (2mmol), 4-chlorobenzaldehyde (1.1 mmol) and BaCl₂ (250 mg) in water (3 mL) was taken in a 10 mL Borosil beaker and stirred on a magnetic stirrer for 50 min. The reaction was monitored with the help of TLC. The white color product was isolated by filtration, washed with water and dried. The product was pure enough and obtained in 81 % yield. Confirmation of product was done by spectral analysis and by comparison with authentic samples.

Spectroscopic data of the products

2,2'-(4-chlorophenylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one): 1(b);

M.P: 139-141 °C; R_f=0.46; ¹H NMR (CDCl₃): 1.06 (s, 6H), 1.58 (s, 6H), 2.30-2.50 (m, 8H), 5.48 (s, 1H), 7.0 (d, 2H, Ar), 7.2 (d, 2H, Ar), 11.90 (s, 1H, OH); ¹³C NMR (CDCl₃): δ 191, 189.5, 135.6, 131.3, 128.4, 128.2, 115.1, 46.9, 46.3, 32.3, 31.3, 29.4; IR (KBr): 3427, 1490 cm⁻¹.

2,2'-(2,4-dichlorophenylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one): 2(b); M.P: 169-171 °C; R_f=0.49; ¹H NMR (CDCl₃): δ 0.89 (s, 6H), 1.70 (s, 6H), 2.02-2.31 (m, 8H), 5.65 (s, 1H), 4.33 (s, 1H, Ar), 6.61 (d, 2H, Ar), 7.09 (d, 2H, Ar), 11.80 (s, 1H, OH); ¹³C NMR (CDCl₃): δ 191, 189.5, 135.6, 131.3, 128.4, 128.2, 115.1, 46.9, 32.3, 31.3, 29.4; IR (KBr): 3427, 1528 cm⁻¹.

2,2'-(4-methylphenylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one): 3(b); M.P: 128-130 °C; R_f=0.51; ¹H NMR (CDCl₃): δ 1.09 (s, 6H), 1.25 (s, 6H), 2.29 (s, 3H), 2.32-2.47 (m, 8H), 5.49 (s, 1H, CH), 6.98 (d, 2H, Ar), 7.26 (d, 2H, Ar), 11.91 (s, 1H, OH); ¹³C NMR (CDCl₃): δ 190.0, 189.4, 162.0, 157.1, 129.2, 129.1, 113, 111.2, 54, 46.2, 31.8; IR (KBr): 3016, 1450 cm⁻¹.

2,2'-(4-methoxyphenylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one): 4(b); M.P: 146-148 °C; R_f=0.38; ¹H NMR (CDCl₃): δ 1.09 (s, 6H), 1.22 (s, 6H), 2.28-2.47 (m, 8H), 3.77 (s, 3H), 5.48 (s, 1H), 6.82 (d, 2H), 6.79 (d, 2H), 11.55, 11.92 (s, OH); ¹³C NMR (CDCl₃): δ 191.0, 190.4, 164.8, 155.3, 127.6, 128.0, 115.5, 54.9, 46.8, 46.2, 31.8, 29.3; IR (KBr): 2925, 1513 cm⁻¹.

2,2'-(3,4-dimethoxyphenylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one): 5(b); M.P:178-180 °C; R_f=0.41; ¹H NMR (CDCl₃): δ 1.22 (s, 12H), 2.55 (s, 8H), 3.64-3.87 (6H), 5.70 (s, 1H), 6.69-7.51 (m, 3H), 9.81; ¹³C NMR (CDCl₃): δ 187.5, 148.3, 146.5, 132.9, 118.3, 114.8, 55.5, 46.5, 31.3, 27.8; IR (KBr): 2962, 1589 cm⁻¹.

2,2'-(4-nitrophenylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one): 7(b); M.P: 177-179 °C; R_f=0.41; ¹H NMR (CDCl₃): δ 1.11 (s, 6H), 1.23 (s, 6H), 2.31-2.51 (m, 8H), 5.54 (s, 1H), 7.24-8.41 (m, 4H), 11.81 (s, 1H,

OH); ¹³C NMR (CDCl₃): δ 191.1, 189.3, 145.9, 127.5, 123.3, 114.8, 46.7, 32.9, 29.2, 27.4; IR (KBr): 3725, 1612 cm⁻¹.

2,2'-(2-nitrophenylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one): 9(b); M.P: 189-191 °C; ¹H NMR (CDCl₃): δ 1.01 (s, 6H), 1.15 (s, 6H), 2.17-2.47 (m, 8H), 6.03 (s, 1H), 7.23-7.55 (m, 4H), 11.58 (s, 1H, OH); ¹³C NMR (CDCl₃): δ 189.6, 149.4, 132.1, 131.2, 129.3, 126.9, 124.0, 114.3, 46.4, 31.6, 28.1; IR (KBr) 3261, 1455 cm⁻¹.

Results and Discussion

We report here a simple and efficient method for synthesis of tetraketones such as 2,2'-arylmethylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-ones). The present study started with the reaction between Dimedone i.e 5,5-dimethyl cyclohexane-1,3-dione and 4-chlorobenzaldehyde (molar ratio 2:1) using barium chloride as a catalyst in aqueous medium. The reaction mixture was stirred on a magnetic stirrer at room temperature and progress of the reaction monitored with the help of TLC. The product 1(b) was obtained in 81 % yield after 50 min. After completion of reaction solid product was isolated simply by filtration and washing with water. The products were characterized on the basis of spectroscopic data such as NMR and IR. Fig. 1 shows general reaction between Dimedone and arylaldehydes and resulting product tetraketones were formed via Knoevenagel condensation and Michael addition reactions.

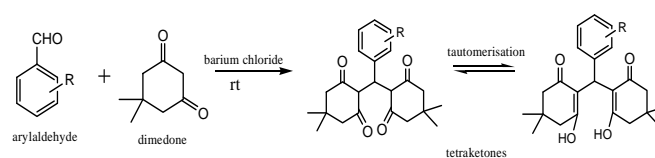


Fig.1 : General reaction between Dimedone and arylaldehydes

Replacing 4-chloro-benzaldehyde (1b) with a variety of other aromatic aldehydes containing electron-donating and electron attracting groups, viz., 2,4-dichlorobenzaldehyde(2b), 4-methylbenzaldehyde (3b), 4-methoxybenzaldehyde (4b), 3,4-dimethoxybenzaldehyde (5b), 3,4-dimethoxybenzaldehyde (6b), 4-nitrobenzaldehyde (7b), 3-nitrobenzaldehyde (8b), 2-nitrobenzaldehyde (9b), Cinnamaldehyde (10b), gave corresponding tetraketones as products as shown in Table 1. Reaction of dimedone with differently substituted arylaldehydes in presence of fairly water soluble catalyst i.e barium chloride proceeds via Knoevenagel condensation and Michael addition reactions at room temperature in aqueous medium. Mechanism for formation of desired products tetraketones was shown in Fig. 2.

Reaction mechanism

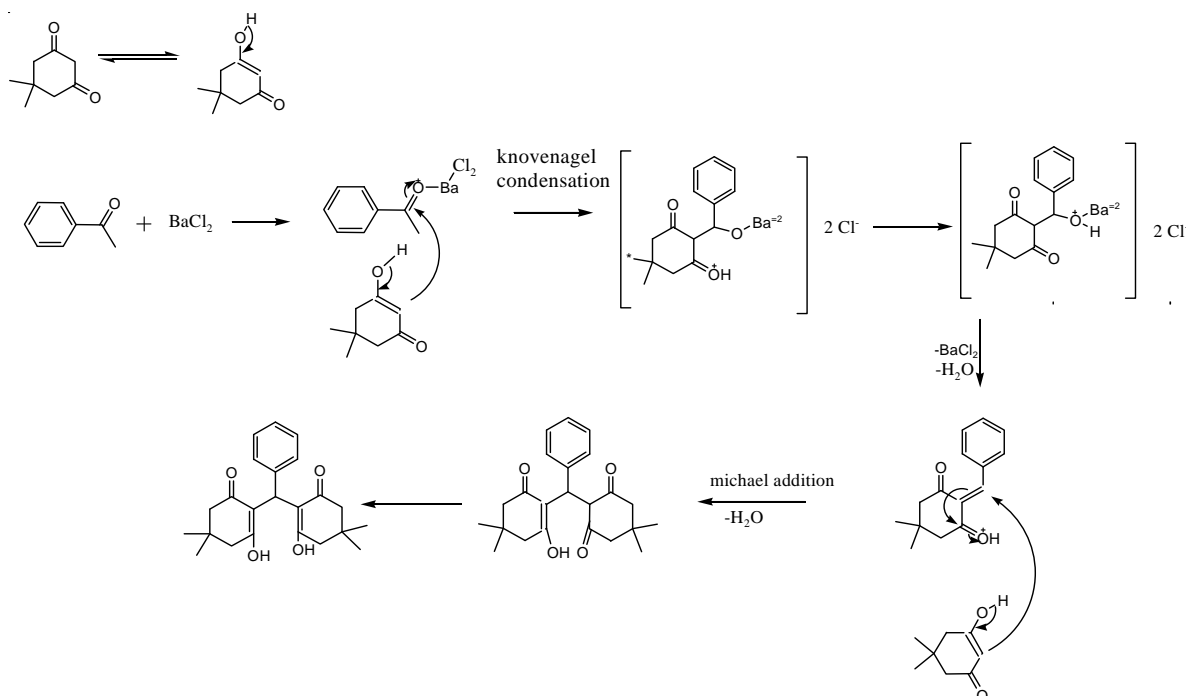


Fig. 2 : Mechanism for formation of tetraketones

The structure of products was confirmed by spectroscopic (IR, ^1H NMR and ^{13}C NMR) data. The IR spectra of compound 1 (b) shows characteristic absorption bands for OH and C=O at $3427, 1490\text{ cm}^{-1}$ and ^1H NMR spectrum of this product in CDCl_3 exhibit a singlet at δ 1.06 ppm corresponding to 6H, a singlet at δ 1.58 ppm due to 6H of methyl protons, a multiplet from δ 2.30–2.50 ppm for methine protons present in cyclohexane rings and a singlet at δ 5.48 ppm due to the C-H, in addition to a multiplet in the region δ 7.0–7.2 ppm which was assigned to the aromatic protons a singlet is observed for OH at δ 11.09 ppm. As it can be noticed from (Table-1) the products (1(b)-10(b)) were obtained in good to better yields.

Applications

The compounds synthesized are important structural precursors for synthesis of many natural products and organic compounds such as acridiediones, xanthenedione and thioxanthenes derivatives, used as laser dyes, shows antioxidant properties and also act as potential remedial source for inflammation and asthma (Khan et al 2007).

Conclusion

In conclusion, we have developed simple, efficient, reusable, economic and environmental friendly method without the use of any organic solvent for synthesis of

tetraketones or 2, 2'-arylmethylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-ones).

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