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"On Water" Organic Synthesis: One pot Facile Regioselective Synthesis of (1E,4E)-1,5-bis-aryl-penta-1, 4-dien-3-ones using an Alternative Precursor

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ABSTRACT

One-pot synthesis of a series of (1E,4E)-1,5-bis-arylpenta-1,4-dien-3-ones considering as curcumin analogs through the condensation of pentane-2,4-dione with aldehydes in water and base for the fast (5-8min) and high yielding (85- 95%)preparation of dienone systems such as **7a-g** are enclosed. The structures of the products were deduced from their elemental analyses and spectroscopic data.

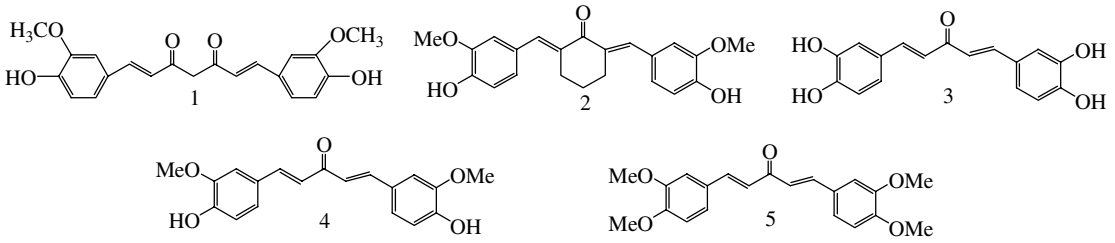
Key words: On water, One pot, regioselective, (1E,4E)-1,5-bis-aryl-penta-1,4-dien-3-ones.

INTRODUCTION

The use of water as a solvent for organic transformations offers several "green chemistry" benefits. Water is the *lingua franca* of life on our planet and is the solvent of choice for nature to carry out her syntheses. Water possesses many unique physical and chemical properties: a large temperature window in which it remains in the liquid state, extensive hydrogen bonding, high heat capacity, large dielectric constant, and optimum oxygen solubility to maintain aquatic life forms. These distinctive properties are the consequence of the unique structure of water. The structure and properties of water have been studied by scientists representing almost all fields of knowledge, and new theoretical models continue to emerge. Water is also known to enhance the rates and to affect the selectivity of a wide variety of organic reactions[1].

Curcumin, 1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione **1**, is a phytochemical obtained from *Curcuma longa*, frequently known as turmeric, a spice widely utilized in South-East Asia. It has attracted numerous attention due to its promising biological properties to treat cancer[2], alzheimer's disease[3], HIV[4,5], chronic inflammations[3], oxidative stress[6], and cystic fibrosis[7]. Curcumin underwent clinical trial for cancer owing to its prominent activity as an antitumor and chemopreventive agent[8]. However, this trial ceased due to poor bioavailability of the molecule[9,10]. Clinical

trials are ongoing to test the efficacy of curcumin against alzheimer's disease[11] and cystic fibrosis[12]. Intense research is also being undertaken to modify the structure of curcumin so as to increase the bioavailability and potency while maintaining the relative non-toxic nature of this natural product [5,13-18]. 2,6-bis((3-methoxy-4-hydroxyphenyl)-methylene)-cyclohexanone (BMHPC), 2 has been demonstrated to bind to nuclear type II sites on breast cancer cells with high affinity (Kd 1-7 nM) and to inhibit cell proliferation[19]. In the same study, a close relative of BMHPC, 2,6-bis(3,4-dihydroxyphenyl)-methylene)-cyclohexanone (BDHPC) 3 was shown to inhibit mouse mammary tumor growth in vivo[19]. Both curcumin and dibenzalketones as curcumin analogs have been shown to induce quinone reduction, quench super oxide radicals and stimulate Phase -2 enzyme transcription[20].



Scheme 1

RESULTS AND DISCUSSION

A classical image of the hydrophobic effect relates to the formation of clathrates around a hydrophobic molecule in water, and the tendency of those hydrophobic droplets to merge so as to minimize the surface area of contact between hydrophobic molecules and water. Therefore, the acceleration of a reaction through the hydrophobic effect is expected to correlate with the hydrophobic surface area of the reactant(s). As discussed above, the influence of water on some reactions is very much like the influence of pressure, in which reactions that minimize volume along the reaction coordinate are accelerated. The cohesive energy density (c.e.d.) also bears units of pressure and water's c.e.d. has a magnitude that is comparable to pressures known to exert significant rate effects on reactions. Of course, distinguishing between surface area-related effects and volume-related effects is difficult because molecular surface area and volume tend to co-vary, at least for roughly spherical molecules. One aspect of that c.e.d. is potentially distinct from the hydrophobic effect is its temperature dependence. Because the density of water is temperature-dependent and is maximum at 4°C, at this temperature the c.e.d. is maximum, and therefore reactions whose acceleration is related to c.e.d. effects should show the greatest rate acceleration at 4°C. The regioselective condasation reaction in Scheme 2 was therefore examined at 4°C. The reaction rate speeds by 10% at the lower temperature. This inverse temperature dependence contravenes the conventional, $\Delta H^{\ddagger}$-based effect, faster reaction at higher temperature. This percentage change in reaction rate compares to a difference in c.e.d. of + 0.75% at 4 °C versus rt[21].

This study focused mainly on changes in the β-diketone structure and aryl substitution pattern of the molecule. Our intent was to explore monocarbonyl derivatives diarylpentanoids such as 7a-g (Table I). In contribution to these compounds synthesis of (1E,4E)-1,5-bis(4-hydroxy-3-methoxyphenyl)penta-1,4-dien-3-one 7a(using meal vaniline) and other analogues 7b-g as a follow-up, a number of novel mono-ketone analogs are reported (Table 1). In addition, compounds similar to those described herein have been probed recently as integrase inhibitors and blockers of herpes simplex virus1 [22].

Table 1: Synthesis of (1E,4E)-1,5-bis-aryl-penta-1,4-dien-3-ones (7a-g)

Entry	Product (7)	R_1	R_2	R_3	MP °C	Time(min)	Yield (%)[a,b]
1[c]	7a	H	OCH3	OH	110-111	7	85
2	7b	H	OCH3	OCH3	105-106	8	85
3	7c	H	H	Cl	168-169	5	90
4	7d	H	H	Br	195-197	5	95
5	7e	H	H	OCH3	121-122	5	85
6	7f	Cl	Cl	H	87-90	8	95
7	7g	Cl	H	H	100-102	8	85

[a] Isolated yields. [b] Identified by spectroscopic analyses (IR and ^1H, ^{13}C NMR). [c]using meal vaniline

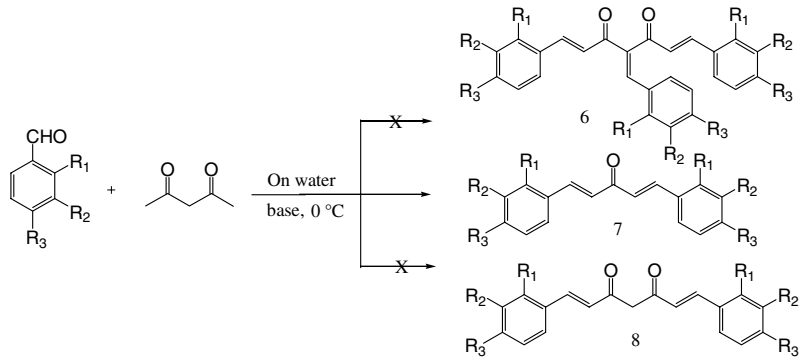
Table 2. Effect of various solvents in the synthesis of 7a under 0°C condition

Salvent	Time (min)	Yield (%)[a]
DMF	140	40
EtOH	60	65
CH_2Cl_2	120	45
1,4-dioxane	120	40
H_2O	7	85

[a]Isolated yields

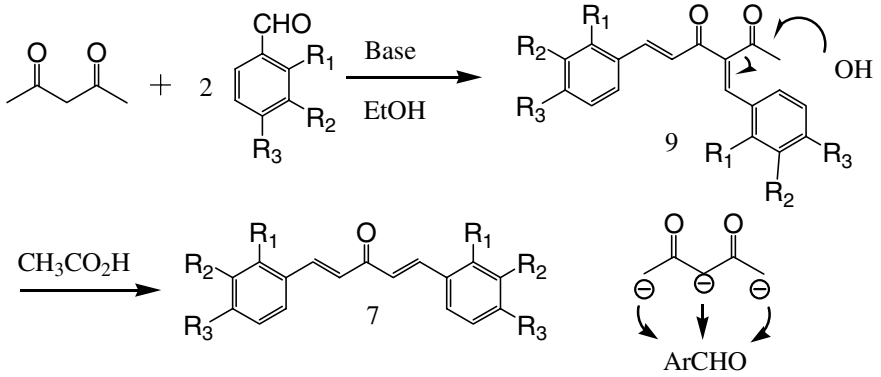
The effect of several solvents (1,4-dioxane, CH_3CN, DMF, EtOH, H_2O) on the efficiency of the reaction was also examined by using synthesis of 7a as model reaction. The results are presented in Table 2. This study revealed that H_2O is the solvent of choice.

Our efforts toward the design of novel curcumin analogues have focused on the synthesis of the general structure to dienone system 7a-g (Scheme 2) (Table 1). The traditional Claisen-Schmidt condensation procedure utilizing ketone, NaOH or KOH and aqueous alcohols for one pot preparation of diarylethenes such as 7a-g while applied to synthesis of (1E,4E)-1,5-bis-aryl-penta-1,4-dien-3-one 7a (utilizing meal vaniline), 7b and 7g was not successful even in a variety of conditions. The workup procedure for separation and purification of the final diarylenones was either difficult or the yields was too low. Here we report, Claisen-Schmidt condensation for one-pot preparation of curcumin analogs replacing acetylacetone as an alternative precursor to acetone in the presence of NaOH in aqueous media (Scheme 2). Initially we explore the synthesis of novel compounds such as di-, and tri-condensation products 6 and 8, however none of these compounds was recovered. The dienones 7a-g was individually isolated. These results suggest that intermediate 9 probably underwent deacethylation fast to provide 7a-g and other by-products.



Scheme 2: General synthetic scheme for the preparation of dienone analogues of curcumin

The deacethylated products were subsequently partially oxidized and converted into insoluble compounds. The diarylketones were obtained presumably via intermediate **9** (Scheme 3).



Scheme 3: Mechanism of formation of (1E,4E)-1,5-bis-aryl-penta-1,4-dien-3-ones 7a-g

All reagents were obtained from commercial suppliers and used without further purification. Reaction progress was monitored through thin layer chromatography (TLC) on coated glass plates (silicagel 60F 254, ~ 0.25-30 mm thickness). Flash chromatography was carried out with silica gel 60 (230–400 mesh ASTM). ^{1}HNMR and ^{13}CNMR spectra were recorded on a Brucker DRX 500 MHz Avance spectrometer. Unless otherwise specified, all NMR spectra were obtained in deuterated chloroform ($CDCl_3$) or DMSO-d_6 and referenced to the TMS or residual solvent peak; chemical shifts are reported in parts per million, and coupling constants in hertz (Hz). Melting points were determined on a Mettler Fp5 capillary melting point apparatus and are uncorrected. IR spectra were obtained on a Shimadzu IR-470.

General procedure for the base catalyzed synthesis of (1E,4E)-1,5-bis-aryl-penta-1,4-dien-3-ones (7a-g).

To a solution of appropriate benzaldehyde (4mmol) in water (10 mL), acetylacetone (0.2 g, 2 mmol) was added. The reaction mixture was stirred at 0°C on ice bath. To this solution was added 15 mL 10 % aqueous NaOH solution dropwise during 5-10 min. After addition was completed the resulting reaction mixture was allowed to stir at that temperature over 10 min. The process of reaction was monitored by TLC. The reaction mixture was quenching with dilute HCl. The yellow precipitate was washed with 60: 40 mL 96% EtOH: H_2O ûltered off, washed with distd H_2O, and dried under vacuum. The products were purified by recrystallization from the indicated solvents. Preparation of (1E,4E)-1,5-bis(4-hydroxy-3-methoxyphenyl)penta-1,4-dien-3-one 4 the similar procedure as used for 7a-g was applied, but instead of 15 mL solution of 10 % aqueous NaOH, 10 mL 30 % aqueous NaOH solution was slowly added over period of 10 min. for Physical properties see Table 1.

CONCLUSION

In this procedure acetylacetone was utilized in presence of appropriate aldehyde, aqueous media and base for preparation of dibenzalketones such as (1E,4E)-1,5-bis-aryl-penta-1,4-dien-3-one 7a(utilizing meal vaniline) and 7b. The products were purified from preparative TLC using EtOAc: ligroin 1:5. Our attempt for synthesis of 7a and 7b utilizing regular Claisen-Schmidt condensation method was unsatisfactory[23]. Recently, several papers on the synthesis of variety of novel compounds containing condensation reactions have been published[24].

NMR spectral data IR, ^{1}HNMR, ^{13}CNMR (DMSO, 300MHz, δppm)

Compound *7a*

yellow solid; mp = 110-111 °C; IR (KBr, cm^{-1}): 3200, 3025, 2850, 1675, 1655, 1590, 1510,

1465, 1260, 1150, 1025 ^{1}HNMR (DMSO, 500MHz): δ, 4.00 (s, 6H), 5.95 (s, br, 2H), 6.96-7.00 (d, J = 15.80 Hz, 2H), 6.98-7.01 (d, J = 8.00 Hz, 2H), 7.162-7.165 (d, J = 1.51 Hz, 2H), 7.22-7.24 (dd, J = 8.18 Hz, 2H), 7.70-7.24 (d, J = 15.80 Hz, 2H) PPm.

Compound *7b*

yellow solid; mp = 105-106 °C; IR (KBr, cm^{-1}): 3025, 2950, 1655, 1635, 1595, 1515, 1460, 1260, 1012 ^{1}HNMR (DMSO, 500MHz): δ, 3.96 (s, 6H), 3.98 (s, 6H), 6.92-6.93 (d, J = 8.02 Hz, 2H), 6.98-7.01 (d, J = 15.77, 2H), 7.18 (s, 2H), 7.23-7.25 (d, J = 7.65, 2H), 7.71-7.75 (d, J = 15.74 , 2H); ^{13}CNMR ($CDCl_3$, DMSO-d_6); 56, 78, 110, 115, 123.47, 123.95, 128, 143, 149.52, 151.63, 188.88 PPm.

Compound *7c*

yellow solid; mp = 168-169ÚC[23]; IR (KBr, cm^{-1}): 3050, 1647, 1627, 1588, 1564, 1489, 1087 ^{1}HNMR (DMSO, 500MHz): δ, 7.06 -7.09 (d, J = 15.91 Hz , 2H), 7.42 - 7.44 (d, J = 8.27Hz , 4H), 7.58 - 7.60 (d, J = 8.50 Hz , 4H), 7.71 - 7.74 (d, J = 15.92 Hz, 2H); ^{13}CNMR 126.17, 129.70, 130, 133.67 , 137, 142.43, 188.71 PPm.

Compound *7d*

yellow solid; mp = 195-198 °C; IR (KBr, cm^{-1}): 3025, 1645, 1635, 1590, 1580, 1480, 1070 ^{1}HNMR (DMSO, 500MHz): δ, 7.07 -7.10 (d, J = 15.92Hz , 2H), 7.50 - 7.52 (d, J = 8.46Hz, 4H), 7.58 - 7.60 (d, J = 8.45Hz , 4H), 7.70 - 7.72 (d, J = 16.00 Hz, 2H); ^{13}CNMR: 125.21, 126.36, 130.05, 132.64 , 134.20, 142.37, 188.58 PPm.

Compound *7e*

yellow solid; mp = 121-122 °C; IR (KBr, cm^{-1}): 3050, 2950, 1645, 1625, 1590, 1510, 1460, 1245, 1025 ^{1}HNMR (DMSO, 500MHz): δ, 3.90 (s, 6H), 6.96 - 6.98 (d, J = 8.85 Hz , 4H), 6.98 - 7.01(d, J = 16 Hz , 2H), 7.60 -7.62(d, J = 8.60 Hz, 4H), 7.72 - 7.76 (d, J = 15.85 Hz, 2H) ^{13}CNMR: 55.76, 114.83, 123.88, 127.99 , 130.53, 143.03, 161.96, 189 PPm.

Compound *7f*

yellow solid; mp = 87-90 °C; IR (KBr, cm^{-1}): 3050, 1655,1590, 1550, 1469, 1106, 1046 ^{1}HNMR (DMSO, 500MHz): δ, 7.06-7.09 (d, J = 15.98 Hz, 2H), 7.34 – 7.36 (dd, J = 8.45, 1.77 Hz, 2H), 7.52 (d, J = 1.96, 2H), 7.68 - 7.70 (d, J = 8.47 Hz , 2H), 8.07 - 8.10 (d, J = 16.02 Hz, 2H) PPm.

Compound *7g*

yellow solid; mp = 100-102 °C; IR (KBr, cm^{-1}): 3025, 1670, 1650, 1615, 1580, 1555, 1095 ^{1}HNMR (DMSO, 500MHz): δ, 7.10-7.13 (d, J = 16.07 Hz , 2H), 7.35-7.40 (m, 4H), 7.48 - 7.50 (dd, J = 8.88, 1.74 Hz, 2H), 7.76 -7.78 (dd, J = 7.30, 1.96 Hz, 2H), 8.17- 8.20 (d, J = 16.20 Hz, 2H) PPm.

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